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Editorial

Current Themes and Controversies in the Alzheimer's Disease Field: Looking Ahead to the CTAD Meeting in San Francisco, November 29-December 2, 2022

M.W. Weiner

Professor of Radiology and Biomedical Imaging, Medicine, Psychiatry, and Neurology, University of California, San Francisco, Principal Investigator: Alzheimer's Disease Neuroimaging Initiative (ADNI)

Corresponding Author: Michael W. Weiner, Professor of Radiology and Biomedical Imaging, Medicine, Psychiatry, and Neurology, University of California, San Francisco, USA, Michael.Weiner@ucsf.edu

Key words: Alzheimer, drug, clinical trials, Alzheimer therapy, biomarkers.

After reviewing all the abstracts and final program for the upcoming CTAD meeting, several major themes have emerged.

Phase 3 trials of disease modifying monoclonal antibodies (mAbs) against amyloid plaques

During the 23 years since Dale Schenk demonstrated that injection of amyloid beta into mice generated anti-amyloid antibodies which removed amyloid plaques (1), there have been many efforts to demonstrate the effectiveness of this approach in humans. There have been numerous negative trials, often associated with serious adverse effects, leading many to say that this approach is doomed to failure and that the "amyloid hypothesis" (2) has little merit. The experience with Biogen's Aducanumab (Aduhelm), a mAb that significantly lowered amyloid plaques in humans (3) was mixed for several reasons. First, they halted their two Phase 3 trials early (apparently because of futility) only then to show that one (but not both) of the trials demonstrated significant slowing of progression. Additionally there were significant side effects, mostly ARIA. Second, the FDA advisory panel strongly recommended not to approve Aducanumab, but the FDA granted accelerated approval based on amyloid plaque removal. Finally, the Center for Medicare Services (CMS) declined to reimburse for Aduhelm, leading to extremely little clinical use.

Then, a press release from Eisai last month reported that their single Phase 3 study of Lecanemab, another plaque clearing mAb, met its primary and secondary endpoints, with a significant 27% slowing of the decline in CDR sum of boxes. We have few details of this study, but Eisai is scheduled to present at CTAD and we eagerly await the data. Furthermore, Roche has completed its Phase 3 study of Gantenerumab, and they have informed the CTAD that they also wish to present their results. As of this writing these have not been announced. The Eisai and Roche presentations alone will make this CTAD meeting very informative and exciting. There will be panel discussions of the data, and there will be opportunities for panelists and speakers from the audience to voice their enthusiasm, questions, and concerns about these studies. There are some (including myself) who believe that the cognitive decline associated with plaque clearing mAbs has clinical significance and affirms the amyloid hypothesis, but others disagree and all voices will be heard.

Other clinical trial results

In addition to the above, the CTAD program is rich with results of Phase 1 to Phase 3 clinical trials of all types of therapies including mAbs and small molecules, as well as risk reduction studies. Some of these will be platform presentations and there will be many outstanding poster presentations as well.

Biomarkers, especially plasma biomarkers

Twenty years ago, the major biomarkers used in AD research were MRI (to measure brain atrophy), FDG PET (to measure brain metabolism), and amyloid/tau analysis of cerebrospinal fluid from lumbar punctures. Chet Mathis's invention of the amyloid PET tracer, 11C-Pittsburgh compound B, revolutionized our diagnostic approach, because this facilitated diagnosis of amyloid plaques in life. Subsequently, fluorinated PET tracers made by several manufacturers have allowed widespread distribution of both amyloid and tau PET tracers. These tracers are currently widely used in many clinical trials, but they are not reimbursed by Medicare in the USA, and thus they have had little practical impact on clinical practice. The demonstration that plasma assays can detect a lowering of the $A\beta_{42}/A\beta_{40}$ ratio (4, 5) launched the era of plasma testing. Shortly thereafter it was shown that plasma ptau181 is elevated in AD (6). More recently ptau217 appears to have even better diagnostic performance (7). Many academic laboratories, diagnostic companies and pharmaceutical companies have been exploring the use of both immune- and

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mass spectroscopy-based assays. Thus far, almost all studies have been "retrospective studies" using batches of plasma samples banked from participants who had amyloid PET scans and clinical evaluations in the past. Most of the cut points have been derived from the batch samples and the AUC values presented are from the same batch, which is not ideal. Some comparison studies of different methods have been published (8, 9) and more of these are needed. What is needed is for validation data to be obtained where cut points are first determined and then applied prospectively to samples which are analyzed over time. Some prospective studies of this type will be presented at CTAD. We expect that plasma assays will come into the clinic (10). In addition, the plasma biomarkers have been shown to change after mAb treatment removes amyloid plaques. More data concerning the therapeutic effects on biomarkers will be shown at CTAD.

CTAD is unique in our field in that there is only one platform presentation at a time, resulting in a very limited number of oral platform presentations over the three day meeting, We expect that all these talks will be extremely interesting and high quality. This year we had a record number of submissions, and many deserving abstracts which would be platform presentations at other meetings with simultaneous sessions will be posters at CTAD. We strongly encourage a tour of the poster sessions.

This is a beautiful time of the year in San Francisco. Due to our drought, we pray for rain but it is not expected. There are many wonderful places to see, great restaurants, and great beauty. We look forward to seeing you in San Francisco at the Hilton for CTAD this year.

Conflicts of interest: Dr. Weiner received funding from NIH grant U19-AG024904. He has consulted for Cerecin, BioClinica, Nestlé, and Roche/Genentech, and received honoraria from the Buck Institute for Research on Aging, and China Association for Alzheimer's disease. He has patents at the University of Southern California, NerveGen, and CTAD Congress. He has served on the Internal Review Board of the University of California San Francisco and the Roche Advisory Board, and owns stock in Anven, Alzecal, and Alzheon.

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Editorial

We Have Turned the Corner

P.S. Aisen[1], *B. Vellas*[2]

1. Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA; 2. Toulouse Gerontopole University Hospital, Universite Paul Sabatier, INSERM U 1295, Toulouse, France

Corresponding Author: Paul S. Aisen, Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA, paisen@usc.edu

Key words: Alzheimer, drug, clinical trials, Alzheimer therapy.

The decades-long effort to develop disease-slowing therapy for Alzheimer's disease has been littered with failure and frustration. Academic investigators have debated the reasons, reaching starkly different conclusions. Some companies have abandoned their efforts. Most of the clinical trials have focused on targeting amyloid. The rationale has been compelling, but the number of negative trials has led many to urge abandoning the strategy.

Contentious debate peaked over the aducanumab development program. Aducanumab was the first anti-amyloid monoclonal antibody to demonstrate substantial reduction in brain fibrillar amyloid associated with apparent slowing of clinical progression (1). But the Phase 3 program was interrupted based on a flawed interim futility analysis, yielding two incomplete datasets with conflicting results (2). U.S. Food and Drug Administration (FDA) reviewers drew different conclusions about the overall submission, while the external advisory committee voted against approval. The final FDA decision was accelerated approval based on the view that amyloid reduction, clearly demonstrated in both pivotal trials, was reasonably likely to predict clinically meaningful benefit; this conclusion was supported by Phase 2 trial data for two other amyloid-lowering antibodies, lecanemab and donanemab (3). The accelerated approval required an additional study post-marketing that supported a clinical benefit.

Debate raged on in the field and in the media, with many urging that AD drug development efforts be re-directed to other therapeutic strategies. The U.S. Centers for Medicare & Medicaid Services (CMS) decided that apart from approved trials aducanumab therapy would not be reimbursed. The sponsor discontinued marketing aducanumab while pursuing the follow-up study mandated by the FDA.

Now the topline results of the Phase 3 lecanemab trial in early symptomatic AD have been released. This completed large international study met its primary endpoint: lecanemab treatment of individuals with early AD slowed by 27% clinical progression as measured by change in the Clinical Rating Scale Sum-of-Boxes (CDR-SB) score at 18 months. All key secondary outcomes were also positive, confirming a slowing of progression on cognitive and functional scales. Lecanemab is now on the path to a full approval in the U.S. and elsewhere, the first for a disease-slowing therapy for AD. We have achieved a major milestone.

In contrast, topline results just released indicate that the Phase 3 gantenerumab studies missed their primary endpoint, showing only minimal, non-significant slowing of clinical decline and lower than expected reduction in brain amyloid. These disappointing results may be related to subcutaneous rather than intravenous administration and/or the long dose titration period in these studies.

Controversy will continue. How important is the 27% slowing of progression seen with lecanemab? What is the clinical importance of a treatment effect of less than one half of a point on an 18 point scale? Arguments supporting the importance of the beneficial effect point to the face-validity of the CDR-SB as a measure of clinically meaningful benefit (even at a magnitude of one half point), the likelihood of increasing benefit with continued therapy and the substantial delay to feared events such as loss of independence that may be anticipated. Ongoing consideration of this issue should contribute to the development of improved measures of clinically meaningful benefit for future trials.

The more important question concerns our best path to building on this success and enlarging the clinical benefit. We will soon learn the results of other amyloid-reducing antibodies in similar early AD populations, potentially presenting new options. Perhaps earlier intervention, at the pre-symptomatic stage of disease before the accumulation of irreversible neurodegeneration, will yield more dramatic benefits. This reasonable hypothesis is now being tested in trials of lecanemab, donanemab and gantenerumab that are still years from completion.

For greater benefit in symptomatic AD, a combination therapy approach may be required. Other strategies abound, from anti-tau therapies to neuroprotective, vascular, anti-inflammatory, and neuroendocrine approaches, though none yet has yielded convincing evidence of clinical benefit. Adding on to amyloid reduction may improve the likelihood of success of alternative strategies. We must continue to rigorously pursue the most plausible approaches. Rapid progress will require collaboration and sharing of data and methodologies, and the generous participation of

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representative populations in our trials. The success of lecanemab in early AD may complicate future trial designs, but should invigorate worldwide efforts to continue the advance toward disease control. Advances in trial methodology, particularly the development of accurate plasma biomarkers of AD neuropathology, will accelerate further progress. The outlook for effective interventions against the neurobiology of AD is bright indeed.

Conflict of interest: PSA has received research support from Biogen, Eli Lilly, Janssen, Eisai, the Alzheimer's Association, the National Institutes of Health, and the Foundation for the National Institutes of Health; he has consulted for Merck, Roche and ImmunoBrain Checkpoint. BV is an investigator in clinical trials sponsored by Biogen, Lilly, Roche, Eisai Pharmaceuticals, and the Toulouse University Hospital (Inspire Geroscience Program). He has served as SAB member for Biogen, Alzheon, Green Valey, Norvo Nordisk, Longeveron, but received no personal compensation. He has served as consultant and/or SAB member for Roche, Lilly, Eisai, TauX , Cerecin with personal compensation.

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15th Clinical Trials on Alzheimer's Disease Conference

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ABSTRACTS

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Symposia

S1- CTAD 2022 FLUID BIOMARKER SYMPOSIUM: RECENT ADVANCES IN PLASMA AND CSF ALZHEIMER BIOMARKERS TO IMPROVE CLINICAL PRACTICE AND TRIALS.

R. Bateman[1], M. Mielke[2], O. Hansson[3], K. Blennow[4] *(1. Washington University School Of Medicine - St. Louis (United States), 2. Wake Forest University School Of Medicine - Winston-Salem (United States), 3. Lund University - Lund (Sweden), 4. University Of Gothenburg - Gothenburg (Sweden))*

Presentation 1: *Relationship between blood plasma and CSF measures of Aβ 42/40, tau, and NfL species for tracking drug effects in clinical trials of Alzheimer's disease*, Randall J. Bateman (Washington University School of Medicine, St. Louis, MO, (United States))

Background: Recent advances in the development of novel Alzheimer's disease (AD) measures of amyloid, tau, and neurodegeneration in blood have enabled the ability to track drug effects in clinical trials of AD. The discoveries of novel tau species in brain, CSF, and blood, such as specific phospho-tau (p-tau) and truncated species including the microtubule binding region (MTBR) region that comprises tangles, have greatly expanded our understanding of tau biology, target development, and drug effect tracking. Longitudinal Aβ, tau, and neurofilament light chain (NfL) changes previously measured in CSF are now being measured accurately in blood, enabling the ability not only to screen and enroll much larger and diverse populations, but also to design secondary and primary prevention trials and measure drug effects. These advances promise to accelerate treatment and prevention development for AD. **Methods:** We analyzed blood plasma measures of Aβ42/40, multiple p-tau species, and NfL in sporadic AD and dominantly inherited AD cohorts and determined concordance with CSF, amyloid and tau aggregation measures by Positron Emission Tomography (PET) scans, and clinical and cognitive measures in local and international clinical cohorts. Some of these measures were also used to measure plaque-removing drug effects. **Results:** The findings indicate that CSF and blood plasma Aβ42/Aβ40 ratio and phosphorylation of specific tau species (e.g., p-tau217, p-tau181) mirror decreases in amyloid plaques with anti-amyloid antibody treatments as measured by amyloid PET. Further, findings from CSF suggest that quantitative measures of tau aggregation can be made with specific tau MTBR fragment species, enabling tracking tau aggregation effects separately from amyloid effects. **Conclusions:** Our results demonstrate that biomarkers to track soluble or aggregated amyloid, and now tau aggregation, are highly precise measures of brain amyloidosis, tauopathy, and neurodegeneration. Use of these novel biomarkers can enable larger and more diverse AD studies and improve the understanding of drug impacts on pathophysiology in clinical trials.

Presentation 2: *Consideration and use of AT(N) blood-based biomarkers for community screening*, Michelle M. Mielke, Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, NC (United States))

A major benefit of the use of blood-based biomarkers in screening for Alzheimer's disease pathology, or diagnosis, is that collection of blood is less invasive and costly than cerebrospinal fluid or neuroimaging markers, and more feasible at the primary care levels where most individuals will present with cognitive symptoms. Blood-based biomarkers of amyloid (A), phosphorylated tau (T), and neurofilament light (N) are already clinically available or nearing clinical use. This talk will highlight some next steps needed before the biomarkers can be implemented for screening or diagnosis at the population level: 1) the identification of factors that may affect the interpretation of the biomarkers (e.g., sex, race/ethnicity, co-morbidities), 2) further discussion regarding how to include the biomarkers in clinical care (e.g., measurement of all 3 biomarkers, development of algorithms or 1 biomarker suitable), and 3) disclosure and ethical considerations.

Presentation 3: *Implementation of plasma biomarkers into clinical practice and trials*, Oskar Hansson (Lund University, (Sweden))

Plasma biomarkers for Alzheimer's disease (AD) have already been started to be used in clinical practice and trials. In this presentation I will summarize the Alzheimer's Association appropriate use recommendations for plasma AD biomarkers, and the key steps needed to be taken before widespread use in e.g. primary care. I will show head-to-head comparisons of different p-tau assays, revealing the high performance of certain mass spectrometry-based assays. I will also show how plasma p-tau217 can be used to drastically lower the need for CSF and PET assessments in the clinical diagnostic work-up of patients with cognitive impairment and still retain a very high diagnostic accuracy. Further, I will describe high-performing plasma-based algorithms for detection of preclinical AD, as well as prediction of cognitive decline in such an early AD population. Longitudinal analyses show that especially plasma p-tau217 is a promising marker for detecting change in AD pathology during the preclinical disease stages. Finally, the effects of potential confounding factors (such as kidney disease) on plasma AD biomarkers will be described, and their effects on the clinical performance will be shown. In summary, plasma AD biomarkers, especially certain p-tau assays, seem to be able to revolutionize the clinical practice and trials in the coming years.

S2- DECENTRALIZED APPROACHES FOR CLINICAL TRIALS ON ALZHEIMER'S DISEASE.

H. Massett[1], J. Langbaum[2], P. Maruff[3], R. Lee[4], E. Lee[4], A.M. Wessels[5], K.C. Holdridge[5], M.B. Ferguson[5], R. Yaari[5] *(1. National Institute on Aging - Baltimore, MD (United States), 2. Banner Alzheimer's Institute - Phoenix, AZ (United States), 3. Cogstate Ltd - Melbourne, VIC (Australia), 4. Irvine Clinical Research - Irvine, CA (United States), 5. Eli Lilly and Company - Indianapolis, IN (United States))*

Introduction: Decentralized trials (DCTs) offer flexibility typically limited in traditional trial design, which may increase geographical and ethnic/racial diversity in trial populations, improve participant engagement and retention, and reduce trial cost. The first DCTs were conducted in the early 2000s and trials with remote designs have exponentially increased within the past 5 years. The need for DCTs was further intensified by the COVID-19 pandemic when trial participants were unable to visit or access facilities for clinical trial assessments, which prompted the FDA to suggest draft guidance on DCT methods to clarify best practices for remote data collection methods. Research utilizing DCT approaches continues to identify both potential benefits and challenges of decentralizing trial

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research. Clinical trials focused on Alzheimer's disease (AD) pose specialized challenges to remotely assessing cognitive outcomes. This symposium will feature presentations focused on examples of DCTs addressing AD and cognitive health measures, including benefits and limitations of DCTs in the AD population.

Presentation 1: *Remote assessments in a follow-on study from TRAILBLAZER-ALZ*, Jessica Langbaum (Banner Alzheimer's Institute, Phoenix, AZ, (United States))

The comparison of remote, at-home to in-clinic administration of cognitive and functional assessments most often used in clinical trials remains a gap in the literature. To address this, the TRAILBLAZER-EXT (NCT04640077) study Part A was conducted as a multicenter, randomized, non-drug, multiple crossover design that evaluated the reliability of at-home, video teleconferencing (VTC) assessments of cognitive and functional abilities. Participants with AD underwent alternating at-home and in-clinic visits. The reliability of VTC compared with on-site administration of the ADAS-Cog13, ADCS-ADL, MMSE, and CDR-SB was assessed by estimating the intraclass correlation coefficient between the two test modalities. The results from these comparisons will be presented.

Presentation 2: *Effects of supervision on cognitive and functional assessment outcomes*, Paul Maruff (Cogstate Ltd, Melbourne, VIC, (Australia))

Clinical and cognitive outcomes validated for their sensitivity to early AD must be altered slightly for their administration in telehealth settings. Performance on various cognitive and functional tests were compared between in-clinic and telehealth assessment contexts in a sample of community dwelling, cognitively unimpaired (CU, N=31; mean age (SD)= 67 (9); 16 females) or MCI (CDR 0.5, N=23, mean age (SD)= 69 (13); 16 females) adults recruited from the Australian Dementia Network (ADNET) online registry and the Australian Imaging Biomarkers and Lifestyle (AIBL) study. Recruited participants completed the CDR, Cogstate PACC tests [International Shopping List Test (ISLT), Continuous Paired Associate Learning Test (CPAL), International Digit Symbol Substitution test-Medicines (IDSSTm)], the C3 battery, and the MOCA in-clinic and telehealth assessment contexts with context order randomized and CDR raters blinded to clinical status. For the CDR, there was high agreement in clinical classification between in-clinic and telehealth contexts (Kappa=0.93). Associations between scores on the individual neuropsychological tests in the two assessment contexts were also high (R-value range: 0.87-0.92). Magnitudes of impairment in the MCI group compared to the CU group on the neuropsychological tests ranged between -1 to -1.8 and were not significantly different when derived from in-clinic or telehealth contexts. Based on the results, clinical and neuropsychological tests commonly used to assess adults with early AD (preclinical and MCI) are valid for administration using telehealth contexts.

Presentation 3: *Decentralized approaches in TRAILBLAZER-ALZ 3*, Roy Yaari (Eli Lilly and Company, Indianapolis, IN (United States))

The TRAILBLAZER-ALZ 3 (TB3) (NCT05026866) study is an ongoing Phase 3 research trial with a decentralized design, testing donanemab in preclinical AD. This talk will provide an overview of key decentralized design characteristics utilized in the study. The remote screening process, which includes mobile research units and health fairs, uses the modified Telephone Interview for Cognitive status (TICS-m) to help select for cognitively unimpaired individuals. Plasma AD assays assess an AD biomarker as part of the inclusion screening criteria and minimize participant burden. Optional remote genetic counseling for APOE disclosure is offered as well as two optional sub-studies testing amyloid PET and tau PET. Clinical outcomes are assessed throughout the study using central raters who administer the Clinical Dementia Rating scale (CDR) to study partners and participants, and psychometric examinations to study participants. Self-administered tests are proctored remotely by a centralized study coordinator who also helps coordinate and facilitate all remote appointments for the participant and study partner. Infusion and imaging centers outside of traditional study «sites» are available in order to improve participant convenience and access throughout the study. In addition to key DCT design elements, screening data influenced by the DCT design will be presented.

Presentation 4: *Investigator experience in a decentralized clinical trial on Alzheimer's disease*, Ralph Lee (Irvine Clinical Research, Irvine, CA (United States))

The investigator experience is particularly valuable when it comes to identifying and addressing practical considerations with DCTs. An experienced brick and mortar site, Irvine Clinical Research, will share challenges and opportunities faced in participating in its first DCT conducted within the TRAILBLAZER-ALZ 3 study design. The site conducted in-person trial screening events using mobile research units (MRUs) off-site in the community. A fully site investigator-staffed outreach model and an outsourced model were both tested. The outcomes, effect on diversity of participants, and operational challenges of this decentralized approach will be discussed and may help to identify key approaches to further refine future DCT designs.

READOUTS

TOPLINE RESULTS OF PHASE III GRADUATE I & II PIVOTAL TRIALS WITH SUBCUTANEOUS GANTENERUMAB. R. Bateman[1], J. Smith[2], M.C. Donohue[3], P. Delmar[4], R. Abbas[4], S. Salloway[5], J. Wojtowicz[4], K. Blennow[6,7], T. Bittner[4,8], S.E. Black[9,10], G. Klein[11], M. Boada[12], T. Grimmer[13], A. Tamaoka[14], R.J. Perry[15], R.S. Turner[16], D. Watson[17], M. Woodward[18], A. Thanasopoulou[4], C. Lane[2], M. Baudler-Klein[4], N.C. Fox[19,20], J.L. Cummings[21], P. Fontoura[4], R.S. Doody[4]
(1. Department of Neurology, Washington University School of Medicine - St. Louis, MO (United States), 2. Roche Products Ltd - Welwyn Garden City (United Kingdom), 3. Alzheimer's Therapeutic Research Institute, Keck School of Medicine, University of Southern California - San Diego, CA (United States), 4. F. Hoffmann-La Roche Ltd - Basel (Switzerland), 5. Butler Hospital and Warren Alpert Medical School of Brown University - Providence, RI (United States), 6. Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg - Mölndal (Sweden), 7. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 8. Genentech, Inc. - South San Francisco, Ca (United States), 9. Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre - Toronto, Ontario (Canada), 10. LC Campbell Cognitive Neurology Research Unit, Dr Sandra Black Centre for Brain Resilience and Recovery, Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, University of Toronto - Toronto, Ontario (Canada), 11. F. Hoffmann-La Roche Ltd, Basel, Switzerland - Basel (Switzerland), 12. Ace Alzheimer Center Barcelona, Universitat Internacional de Catalunya - Barcelona (Spain), 13. Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar, School of Medicine, Technical University of Munich - Munich (Germany), 14. Department of Neurology, Faculty of Medicine, University of Tsukuba - Tsukuba (Japan), 15. Department of Brain Sciences, Faculty of Medicine, Imperial College London - London (United Kingdom), 16. Department of Neurology, Georgetown University School of Medicine - Washington, DC (United States), 17. Alzheimer's Research and Treatment Center - Wellington, FL (United States), 18. Medical and Cognitive Research Unit, Heidelberg Repatriation Hospital, Austin Health - Melbourne, Victoria (Australia), 19. Dementia Research Centre, Department of Neurodegenerative Disease, Queen Square Institute of Neurology, University College London - London (United Kingdom), 20. UK Dementia Research Institute, Queen Square Institute of Neurology, University College London - London (United Kingdom), 21. Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV) - Las Vegas, NV (United States))

Objectives: GRADUATE I and II are two identically designed ongoing global Phase III parallel-group, placebo-controlled, randomized trials investigating the efficacy and safety of subcutaneous gantenerumab in people with early AD (i.e., mild cognitive impairment [MCI] due to AD or mild AD dementia), as well as its effect on biomarkers of AD pathology and neurodegeneration. **Methods:** Eligible participants (50–90 years) were diagnosed with MCI due to AD or mild AD dementia; demonstrated abnormal memory using the Free and Cued Selective Recall Test; met criteria for the Mini-Mental State Examination (MMSE≥22) and the Clinical Dementia Rating –Global Score (0.5 or 1); with evidence of amyloid positivity confirmed by Aβ positron emission tomography (PET) scan or cerebrospinal fluid (CSF) analysis. Participants were randomized 1:1 to subcutaneous gantenerumab or placebo, administered at the study site or at home using home nursing. Gantenerumab was up-titrated over a 36-week period to a target dosage of 510 mg every 2 weeks (Q2W), irrespective of apolipoprotein E ε4 (APOE ε4) genotype. The primary endpoint was the change from baseline to Week 116 in Clinical Dementia Rating scale – Sum of Boxes (CDR-SB). Secondary confirmatory efficacy endpoints evaluated the change from baseline to Week 116 in cognition and function, including the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog 13), Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) and Functional Activities Questionnaire (FAQ). In addition to the safety assessments, the studies also included further secondary and exploratory efficacy measures, as well as Tau and amyloid PET, and cerebrospinal fluid (CSF) and plasma biomarker assessments. **Results:** In total, 1,965 participants (n = 985 for GRADUATE I; n = 980 for GRADUATE II) from 288 sites across 30 countries were enrolled. Data will be presented on baseline demographics and disease characteristics for both GRADUATE I and II studies. The presentation will focus on the top-line efficacy, safety and biomarker results of the two studies. **Conclusion:** Results of GRADUATE I and II will build on evidence from previous studies and provide a robust dataset informing the overall benefit:risk profile of subcutaneous gantenerumab in early AD. **References:** Klein G, et al. J Prev Alzheimers Dis 2021;8:3–6. Roche.com. Roche's anti-amyloid beta antibody gantenerumab granted FDA Breakthrough Therapy Designation in Alzheimer's disease. Accessed online at: https://www.roche.com/investors/updates/inv-update-2021-10-08 on 6 October 2022. **Acknowledgement:** «GRADUATE I and GRADUATE II participants, their families, clinical investigators and the gantenerumab study group»

TACKLING AGITATION IN ALZHEIMER'S DEMENTIA: BREXPIPRAZOLE PHASE III TRIAL RESULTS. G. Grossberg[1], D. Lee[2], M. Slomkowski[2], N. Hefting[3], D. Chen[2], K. Larsen[3], E. Kohegyi[2], M. Hobart[2], J. Cummings[4]
(1. Department of Psychiatry and Behavioral Neuroscience at Saint Louis University School of Medicine - St. Louis, Missouri (United States), 2. Otsuka Pharmaceutical Development & Commercialization Inc. - Princeton, New Jersey (United States), 3. H. Lundbeck A/S - Valby, Copenhagen (Denmark), 4. Chambers-Grundy Center for Transformative Neuroscience at School of Integrated Health Sciences University of Nevada Las Vegas (UNLV) - Las Vegas, Nevada (United States))

Background: Agitation is highly prevalent among patients with Alzheimer's dementia, in community and long-term care settings (1, 2). The presence of agitation in Alzheimer's dementia (AAD) increases the risk of institutionalization (3), negatively impacts patient quality of life, and increases caregiver distress (4). Currently, there are no FDA-approved pharmacological treatments for the management of AAD. Brexpiprazole, which acts on noradrenergic, serotonergic, and dopaminergic neurotransmitter systems (5), has been investigated as a potential AAD therapy. **Objectives:** To assess the efficacy, safety, and tolerability of brexpiprazole in patients with AAD based on results of a recently completed Phase III trial, together with two previously completed Phase III trials. **Methods:** The first two trials (NCT01862640, NCT01922258), completed in 2017, were 12-week, randomized, double-blind, placebo-controlled, parallel-arm trials of brexpiprazole versus placebo in patients with AAD (6). Patients were required to have a baseline Neuropsychiatric Inventory (NPI) Agitation/Aggression domain score of ≥4. One trial investigated fixed

doses of brexpiprazole (0.5, 1 or 2 mg/day [0.5 mg/day arm discontinued]), whereas the other investigated a flexible dose (0.5–2 mg/day). The third trial (NCT03548584), completed in 2022, also had a 12-week, randomized, double-blind, placebo-controlled, parallel-arm design, but differed in terms of the dose administered (2 or 3 mg/day), and agitation requirements, which comprised the NPI criterion, the International Psychogeriatric Association (IPA) provisional definition, and a criterion based on Cohen–Mansfield Agitation Inventory (CMAI) Factor 1. In all three trials, change in CMAI Total score was the primary endpoint, and change in Clinical Global Impression – Severity of illness (CGI-S) score, as related to agitation, was the key secondary endpoint. Safety was also assessed. **Results:** In the first fixed-dose trial, the highest brexpiprazole dose (2 mg/day) demonstrated statistically significant improvement versus placebo in CMAI Total score change from baseline to Week 12 (least squares mean difference [LSMD], -3.77; p=0.040); the 1 mg dose did not separate from placebo. In the flexible-dose trial, although brexpiprazole 0.5–2 mg/day was not superior to placebo on CMAI Total score, a post hoc analysis of patients titrated to the 2 mg dose showed reduced agitation versus placebo (LSMD, -5.06; p=0.012). A post hoc analysis of both trials indicated that patients who did not meet CMAI Factor 1 criteria at baseline had insufficient baseline agitation severity to show measurable change over time. Hence, the third trial investigated higher doses (2 or 3 mg/day [3 mg tested for efficacy and safety, per FDA request]) in an enriched sample who met CMAI Factor 1 criteria at baseline. In the third trial, brexpiprazole 2 or 3 mg/day demonstrated statistically significant improvement versus placebo from baseline to Week 12 in CMAI Total score (LSMD, -5.32; p=0.0026) and CGI-S score as related to agitation (LSMD, -0.27; p=0.0078). Pooled response rate across the three trials (CMAI criteria) was higher with brexpiprazole versus placebo. Across all three trials, the incidence of treatment-emergent adverse events (TEAEs) was 51.1% with brexpiprazole (all doses pooled) and 45.9% with placebo. Across all three trials (pooled), no single TEAE had an incidence >5% with brexpiprazole (all doses pooled) and more than in placebo-treated patients. TEAEs that occurred in ≥2% of patients receiving brexpiprazole and more than in placebo-treated patients were insomnia (3.7% versus 2.8%), somnolence (3.4% versus 1.8%), nasopharyngitis (2.7% versus 2.6%), and urinary tract infection (2.6% versus 1.5%). The incidence of falls was 1.7% (brexpiprazole) versus 2.6% (placebo). Overall, 6.3% of patients receiving brexpiprazole discontinued treatment due to TEAEs, versus 3.4% receiving placebo. Six brexpiprazole-treated patients (0.9%) and one placebo-treated patient (0.3%) died during double-blind treatment; no deaths were considered related to brexpiprazole treatment. **Conclusion:** Across three Phase III trials in patients with AAD, brexpiprazole doses of 2 or 3 mg/day showed a statistically significant improvement versus placebo on agitation in Alzheimer's dementia. Brexpiprazole was generally well tolerated, which is of critical importance in this vulnerable patient population. **References:** 1. Halpern et al. Using electronic health records to estimate the prevalence of agitation in Alzheimer disease/dementia. Int J Geriatr Psychiatry 2019;34(3):420–431. 2. Fillit et al. Impact of agitation in long-term care residents with dementia in the United States. Int J Geriatr Psychiatry 2021;36(12):1959–1969. 3. Cloutier et al. Institutionalization risk and costs associated with agitation in Alzheimer's disease. Alzheimers Dement (N Y) 2019;5:851–861. 4. Khoo et al. The impact of neuropsychiatric symptoms on caregiver distress and quality of life in persons with dementia in an Asian tertiary hospital memory clinic. Int Psychogeriatr 2013;25(12):1991–1999. 5. Maeda et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin–dopamine activity modulator. J Pharmacol Exp Ther 2014;350(3):589–604. 6. Grossberg et al. Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. Am J Geriatr Psychiatry 2020;28(4):383–400.

ROUNDTABLES

ROUNDTABLE 1- INVESTMENTS IN INNOVATION: ADVANCING THE PATH FORWARD TO NEW ALZHEIMER'S TREATMENTS. N. Bose[1], H. Fillit[2], L. Barker[3], P. Scheltens[4] *(1. Gates Ventures, Seattle, WA (United States), 2. Alzheimer's Drug Discovery Foundation (ADDF), New York City, NY (United States), 3. Dementia Discovery Fund (DDF), London (United Kingdom), 4. LSP Dementia Fund at EQT Life, Alzheimer Centre Amsterdam (University Medical Centre Amsterdam, Amsterdam (The Netherlands))*

Topline summary: Over six million people in the United States and 55 million globally are living with Alzheimer's and related dementias, and that number is expected to grow substantially with an aging population. There is a large global unmet medical need with few effective treatments available for patients, creating an urgency to accelerate efforts to develop novel and effective therapies that target a whole host of underlying pathologies that contribute to Alzheimer's. It is important to foster collaboration across various sectors – government, academia, industry, and philanthropy – combine resources and capital, and utilize innovative and creative approaches to successfully conquer this disease. This roundtable will pull expertise from four influential global investment organizations – all with a venture-minded approach that span across drug discovery and development to commercialization – focused on identifying and investing in innovative, impactful therapies. The will panel will discuss where we are now in the field and where we want to be 10 years from now and more importantly, the path forward, which is only possible when leading scientists and entrepreneurs are connected and have access to capital. The panel will cover their interests, approach, resources, and funding opportunities to support and accelerate research of new drugs, technologies, and breakthrough innovations. Lastly, they will discuss recommendations and provide evidence where these have been used in practice. Recommendations include: • Leveraging the modern era of Alzheimer's research to explore drugs beyond amyloid and tau proteins and focusing the next phase of research, based on the biology of aging, which is centered on promising drugs that target a host of underlying pathologies that contribute to Alzheimer's. • Highlighting the need for more rigorously designed clinical trials enabling the field to more rapidly and efficiently evaluate whether a drug should move to the next stage of clinical development. • Emphasizing the importance of biomarkers as it relates to drug development and precision medicine, with an emphasis on the need for new biomarkers that can measure the impact of each biology of aging target, and the drugs designed to treat them

ROUNDTABLE 2- THE ALZHEIMER'S DISEASE PATIENT PATHWAY FROM A SEX AND GENDER LENS.

F.C. Quevenco[1,2], M.C. Tartaglia[3], M. Carrillo[4], P. Ferrell[5], P. Poulsen[6], A. Santuccione Chadha[2,7], M.T. Ferretti[2], M.F. Iulita[2,8] *(1. Roche (Switzerland), 2. Women's Brain Project (Switzerland), 3. University Of Toronto (Canada), 4. Alzheimer's Association (United States), 5. Eli Lilly (United States), 6. Novo Nordisk (Denmark), 7. Altoida (United States), 8. Memory Disorders Unit, Hospital Sant Pau - Barcelona (Spain))*

The topic of sex differences is now positioned as a top priority in neurology research, particularly in the context of precision medicine and personalized care. There is a growing literature about sex differences in Alzheimer's disease manifestations, highlighting sex and gender-specific factors that are not captured in a standard patient pathway. A patient pathway takes a patient-centric approach to describe an individual's journey from symptom onset to treatment completion. It is a crucial resource for persons living with Alzheimer's disease, physicians, and clinical trial sponsors. When considering sex and gender differences, there are likely deviations between a male and female patient journey. To address this, an ongoing study led by the Women's Brain Project and collaborators is mapping a comprehensive patient pathway that is able to capture these differences. The goal of this symposium is to discuss the importance of why this patient pathway is needed in Alzheimer's disease and why it is relevant for clinical trials by inviting different stakeholders.

Oral Communications

OC1- ACI-35.030 AND JACI-35.064, TWO NOVEL ANTI-PHOSPHO-TAU VACCINES FOR THE TREATMENT OF ALZHEIMER'S DISEASE: INTERIM PHASE 1B/2A DATA ON SAFETY, TOLERABILITY AND IMMUNOGENICITYE.

J. Streffer[1,2], J. Mermoud[1], O. Sol[1], M. Vukicevic[1], E. Fiorini[1], E. Gollwitzer[1], V. Hliva[1], D. Hickman[1], J. Gray[1], P. Donati[1], M.P. Lopez Deber[1], J. Rongère[1], A. Pfeifer[1], M. Kosco-Vilbois[1], P. Scheltens[3] *(1. AC Immune SA - Lausanne (Switzerland), 2. University of Antwerp - Antwerp (Belgium), 3VUMC - Amsterdam (Netherlands))*

Background: Tau deposition is a key pathological feature of Alzheimer's disease (AD) and other neurodegenerative disorders. The spreading of Tau neurofibrillary tangles across defined brain regions is associated with cognitive decline in AD. It is hypothesized that Tau spreading throughout the brain involves extracellular phosphorylated Tau (pTau). Immunotherapy offers the potential to interfere with the spreading of Tau neuropathology and prevent or reduce cognitive impairment. In particular, active vaccination targeting pTau species that seed pathological aggregation, represents an attractive strategy for long-term treatment and potentially prevention of AD as well as other Tauopathies. **Objectives:** This Phase 1b/2a clinical trial, NCT04445831, aims to evaluate two first-in-class anti-pTau vaccine candidates, ACI-35.030 (i.e., liposome-based) and JACI-35.054 (i.e., conjugate-based) for the treatment of AD. We report here interim results of immunogenicity as well as safety and tolerability. **Methods:** This currently ongoing multicenter, double-blind, randomized, placebo-controlled study evaluates the safety, tolerability and immunogenicity of different doses of two anti-pTau vaccines, ACI-35.030 and JACI-35.054, in subjects with early AD. The antibody response is evaluated using ELISAs and measuring binding of the antibodies generated over time to the immunizing peptide, i.e., pTau, as well as against brain derived paired helical filaments (ePHF) and non-phosphorylated Tau. Epitope profiling is also employed using a specifically developed assay to cover phosphorylated and nonphosphorylated epitopes. Each dose-level sub-cohort comprises 8 subjects randomized in a 3:1 active/placebo ratio with the option to expand sub-cohort(s) up to 24 subjects to enlarge the assessment of safety, tolerability and immunogenicity. The study population is characterized as 50-75 year-old, male and female subjects with a diagnosis of mild AD or MCI due to AD according to NIA-AA criteria, CSF Aß42 levels consistent with AD pathology, a CDR global score of 0.5 or 1 and a MMSE score ≥ 22. Subjects receive injections of ACI-35.030 (Cohort 1), JACI-35.054 (Cohort 2) or placebo (Cohorts 1 and 2) at weeks 0, 8, 24 and 48. **Results:** 41 subjects have been randomized in the 3 dose-levels of cohort 1, and 16 subjects in the 2 dose-levels of cohort 2. Both vaccines are considered safe and well tolerated as no clinically relevant safety concerns associated related to the study vaccines have been observed at the time of abstract submission. Subjects immunized with the liposomal vaccine, ACI-35.030, show a high, specific and sustained anti-pTau and anti-ePHF IgG response, with an apparent dose-response between the low- and mid-dose with evidence of immunoglobulin class switch from IgM to IgG. Individual responder rates were high and consistent, especially for anti-pTau and ePHF antibodies. Over time, the data demonstrates that the IgG response matures towards a stronger preference for binding ePHF, the more pathologic species while concomitantly lowering antibody titers towards the non-pathological, non-phosphorylated Tau. Subjects immunized with the conjugate vaccine, JACI-35.054, display a high anti-ePHF and anti-pTau IgG response with no apparent dose-effect observed between the low- and mid-dose. The IgG response shows maintained binding capacity to both pTau and the non-pathological, non-phosphorylated Tau. To further profile the antibody response for breadth and selectivity towards pathological pTau, epitope mapping was performed on the subjects' sera after 3 vaccinations. For ACI-35.030, the IgG response of the subjects was relatively homogenous displaying a broad epitope coverage as binding occurred across the pTau sequences tested and importantly, without end terminal specificity or substantial binding to nonphosphorylated sequences. The subjects vaccinated with JACI-35.054 demonstrated a more heterogeneous response with a strong disproportional binding to end terminal antibodies. These results further elucidate the differences produced by the two vaccines as well as the conclusion of IgG maturation with ACI-35.030 and not JACI-35.054 over time. Finally, as expected, no antibody responses are observed in placebo-treated subjects. **Conclusions:** The clinical study is successfully ongoing despite the challenges of being performed during the restrictions of the Covid-19 pandemic demonstrating that vaccination with either ACI-35.030 or JACI-35.054 is safe and well tolerated, inducing IgG responses to the immunizing peptide as well as ePHF. However, overall ACI-35.030 emerges as the superior vaccine candidate in terms of responder rate, number of immunizations to achieve the initial antibody titer, homogeneity of the antibody response across subjects, epitope coverage, with evidence of antibody maturation towards pathologic forms of Tau. As both vaccines contain the same antigenic peptide sequence, the differences observed so far in antibody response can be ascribed to the different technologies used to present the antigenic peptide to the immune system.

OC02- RESULTS OF A PHASE 2/3 PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL-GROUP, RANDOMIZED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF 12 WEEK TREATMENT WITH THE PHOSPHODIESTERASE 9 (PDE9) INHIBITOR IRSENONTRINE (E2027) IN SUBJECTS WITH DEMENTIA WITH LEWY BODIES. M. Irizarry[1], R. Lai[2], S. Hersch[1], K. Pinner[2], S. Dhadda[1], L. Kramer[1] *(1. Eisai Inc. - Nutley (United States), 2. Eisai Ltd. - Hattfield (United Kingdom))*

Objectives: To assess the safety and efficacy of irsenontrine for treatment of cognition in patients with Dementia with Lewy Bodies (DLB). **Methods:** Study 201 was a phase 2/3, 12-week study in subjects with DLB (N=196) randomized 1:1 to irsenontrine 50 mg or placebo. The co-primary endpoints were change from baseline in the electronic Montreal Cognitive Assessment (eMoCA) and the electronic Clinician's Interview Based Impression of Change Plus Caregiver Input (eCIBIC-plus) at 12 weeks. Secondary outcomes included the Neuropsychiatric Inventory (NPI), Mini-Mental State Examination (MMSE), Cognitive Function Inventory (CFI), and the Clinician's Global Impression of Change – Dementia with Lewy Bodies (CBIC-DLB). **Results:** The study did not meet its primary objective of determining the superiority of irsenontrine compared with placebo on both the cognitive endpoint of MoCA and the global clinical endpoint of CIBIC-Plus after 12 weeks of treatment in the overall population. The irsenontrine group tended to show less decline from Baseline to Week 12 in the MoCA total score in the overall population compared with the placebo group, but the difference between treatment groups was not statistically significant (MMRM analysis: least square (LS) mean difference [95% CI] of 0.181 [-0.716, 1.078], p=0.69). Subjects in the irsenontrine group showed minimal improvement in the CIBIC-Plus compared with the placebo group at Week 12; the difference between treatment groups was not statistically significant (GLMM analysis: odds ratio [95% CI] of 1.018 [0.695, 1.492]; p=0.83). Secondary efficacy endpoints did not show a significant treatment difference between irsenontrine and placebo in the overall population. Exploratory post-hoc analyses suggested that irsenontrine performed better than placebo on the primary efficacy endpoints in a key subgroup of subjects without amyloid copathology (identified by plasma amyloid Aβ42/40 ratio ≥0.092 [C2N assay], N=26 and 30 for the placebo and irsenontrine groups, respectively): For subjects without amyloid copathology ("pure DLB"), irsenontrine treatment resulted in an improvement from Baseline to Week 12 MoCA compared with a decline in the placebo group. The difference approached statistical significance (LS mean difference [95% CI] of 1.567 [-0.024, 3.157]; p=0.05). For subjects without amyloid copathology, the irsenontrine group tended to show greater improvement in CIBIC-Plus at Week 12 compared with the placebo group, with more subjects showing improvement in the irsenontrine group compared with the placebo group: odds ratio (95% CI) of 1.596 [0.753, 3.386]; p=0.47. In the small number of subjects for whom data were available (n=4), 9 weeks of irsenontrine treatment resulted in an average of 168% increase in cGMP in the CSF. Irsenontrine was generally well-tolerated with similar incidence rates of Serious Adverse Events (SAEs) and Treatment Emergent Adverse Events (TEAEs) between the irsenontrine and placebo groups. Worsening DLB, dizziness, somnolence, orthostatic hypotension, and aggression occurred with a higher incidence in the irsenontrine group (3.0% to 5.1%) compared with the placebo group (0% to 1.0%). **Conclusions:** In the overall DLB population, 12 weeks treatment with irsenontrine 50 mg daily did not improve cognition relative to placebo. The suggestion of efficacy in the "pure" DLB subgroup, lacking AD co-pathology, generated the hypothesis that irsenontrine preferentially increases CSF cGMP in pure DLB relative to mixed DLB due to relative preservation of synapses (the site of action of PDE9 inhibition) in patients lacking amyloid co-pathology. This hypothesis is explored in the translational medicine Study 203.

OC03- HMTM TOPLINE RESULTS OF PHASE 3 LUCIDITY – THE FIRST TAU AGGREGATION INHIBITOR. B. Schelter[1,2] *(1. TauRx Therapeutics Ltd - Aberdeen (United Kingdom), 2. University of Aberdeen - Aberdeen (United Kingdom))*

LUCIDITY interim data are currently being analysed and this symposium will provide an opportunity to present new data analysis not yet in the public domain. **Part 1:** History of HMTM and its development (Prof Claude Wischik). Hydromethylthionine mesylate (HMTM) is a tau aggregation inhibitor shown to have exposure-dependent pharmacological activity on cognitive decline and brain atrophy in two completed Phase 3 trials in mild/moderate Alzheimer's disease (AD). The role of tau pathology in AD and the mode of action of HMTM will be presented. Context will be provided using data from 2 completed Phase 3 clinical trials in AD. **Part 2:** Update on the interim data, including safety, key endpoints and biomarkers (Prof Bjoern Schelter). The ongoing Phase 3 LUCIDITY trial (NCT03446001) investigates 16 mg/day as monotherapy as the optimal treatment regime compared to placebo. The trial comprises a 12-month double-blind, placebo-controlled phase followed by a 12-month modified delayed-start open-label treatment phase. The trial is being conducted across 76 clinical research sites in North America and Europe. It recruited 598 subjects in total with probable AD or MCI-AD with 545 in the final version of the protocol. Participants were assigned randomly to receive HMTM at doses of 16 mg/day, 8 mg/day or placebo at a 4:1:4 ratio during the double-blind phase. All participants in the open-label phase receive the 16 mg/day dose. The study has co-primary clinical outcomes comprising the 11-item Alzheimer's Disease Assessment Scale (ADAS-cog11) and the 23-item Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL23). Secondary biomarker measures include whole-brain atrophy measured by MRI and temporal lobe 18F-fluorodeoxyglucose positron emission tomography. 470 participants completed the 12-month placebo-controlled phase by April 2022. During this symposium updates will be provided from ongoing interim data analysis of the double blind and open label phases of LUCIDITY. **Part 3:** What does this mean for the AD landscape? (Dr Richard Stefanacci). LUCIDITY is the only late-stage clinical trial targeting tau pathology. The trial is novel in design as it includes individuals with mild – moderate AD and MCI under the same protocol. A unique feature among tau- and amyloid-targeting approaches in development is that HMTM is an oral drug which has a proven benign safety profile including lack of ARIA risk. The possibility for a medication to come to market to treat a broad range of AD severity and be accessible to patients presents a significant opportunity to transform the AD treatment landscape. This presentation will consider the extent of the potential transformation of the patient pathway that HMTM could provide.

OC04- JANSSEN SIMOA PLASMA P217+TAU ASSAY AS A PRECISION PRESCREENING TOOL IN AUTONOMY PH2 ANTI-TAU MONOCLONAL AB TRIAL IN EARLY ALZHEIMER'S DISEASE. G. Triana-Baltzer[1], Z. Saad[1], S. Moughadam[1], R. Slemmon[1], M. Quiceno[1], D. Henley[1], H. Kolb[1] *(1. Janssen Research & Development - San Diego (United States))*

Background: It is hypothesized that anti-amyloid or anti-tau therapies should be most effective in Alzheimer's Disease (AD) when initiated early in disease. CSF and PET-based measures have proven utility in identifying subjects with AD pathology even prior to clinical symptom manifestation, however they are burdensome to the patient and costly. Phosphorylated tau (p-tau) as measured in CSF, and most recently plasma, has emerged as one of the most sensitive and specific biomarkers for AD pathology and appears to predict amyloid and tau PET positivity as well as gross cognitive state. Janssen has developed a highly sensitive and precise assay for measuring p217+tau in plasma, with good ability to predict amyloid and tau PET status with a cutoff of ≥0.1 pg/ml. This assay is unique from others specific for phosphorylated T217 in that it has enhanced signal when tau is phosphorylated at neighboring amino acids as well, as is often found in pathological tau species. We have studied the utility of this non-invasive assay for clinical trial enrollment with confirmation of performance via comparison to tau PET. **Objectives:** The Autonomy trial (63733657ALZ2002) seeks to enroll early AD (MCI/mild AD dementia) patients who are tau PET positive (standardized uptake value ratio (SUVR) Z-score > 1 in bilateral inferior temporal cortex) but without having widespread tau tangles [SUVR Z-score > 5 in each of Braak 4, 5, and 6 regions of interest (ROI)]. Patients within this range are further stratified into high and low groups based on SUVR in the Braak 4 ROI. We report on the performance of the Janssen Simoa plasma p217+ tau assay as a prescreening tool for identifying patients who are likely tau PET positive. **Methods:** The plasma p217+tau assay developed on Simoa platform was validated at Quanterix (Billerica, MA) and performed on screening samples from participants presenting with early AD in weekly batches. Technical performance across the initial 55 batches was evaluated. Participants presenting with plasma p217+tau levels ≥ a pre-specified cutoff of 0.1 pg/ml progressed to tau PET (18F-MK6240) screening. Concentrations of plasma p217+tau in this population and prevalence of tau PET positivity in the plasma p217+tau positive participants was studied. To assess the assay's ability to predict participant stratification, we performed a post-hoc ROC analysis using one year's worth of screening data. **Results:** From February 2021 to April 2022, 55 batches of plasma p217+tau screening were performed at Quanterix. A panel of 3 peptide Quality Control (QC) samples (0.1, 0.4, and 1.6 pg/ml) were run in duplicate in each batch revealing excellent intra-run precision (average CV = 6.0, 4.5, and 5.5%, respectively) and inter-run precision (7.6, 6.6, and 13.3% CV, respectively). Precision was also acceptable with clinical trial samples, as amongst N=725 plasma samples the mean CV was 7.9% (0-120% range), with an estimated LLOQ of 0.030 pg/ml (based on mean concentration where CV>20%). Of the 787 early AD patients in which plasma p217+tau was measured, 72% had levels ≥0.1 pg/ml, and hence were slated to have tau PET imaging performed. Of the 346 patients imaged to date, 86% were tau PET positive and 64% satisfied the trial tau PET eligibility criteria of intermediate tau burden. While assay screening performed as expected, 59% of eligible patients were in the high stratum. ROC analysis shows the plasma p217+tau assay can predict patient stratum with an AUC of 0.8, making it possible to use the assay for further patient enrichment for a desired stratification profile. **Conclusion:** Accurate, sensitive, and precise measurement of p-tau isoforms in plasma has emerged as the most promising non-invasive method for detecting aberrant amyloid and tau processes. Longer fragments of multi-phosphorylated tau, containing at least phosphorylation at amino acid 217, have been reported as one of the isoforms most associated with AD pathology and may begin accumulating in CSF and plasma 10-20 years before cognitive decline. Janssen has developed a robust and highly sensitive assay to measure plasma p217+tau which can quantify signal in all early AD participants, suggesting utility for pre-screening participants for anti-tau trials such as Autonomy. Pressure testing of the plasma p217+tau assay in the Autonomy phase-2 clinical trial has shown good precision within and between batches, and demonstrated the ability to enrich populations for tau PET positivity. This "low friction" tool should enable faster and more efficient AD clinical trial enrollment now, and due to its ability to quantify signal in even preclinical AD could potentially be used in the future as a tool to identify the earliest stages of disease in the general population. Additional work should focus on refining cutoffs to stage AD subjects based on time to onset of clinical symptoms and/or amyloid and tau PET progression. **Conflicts of Interest:** GTB, ZSS, SM, RS, MQ, DH, and HCK are employees of Janssen R&D.

OC05- LONG TERM AND ECONOMIC OUTCOMES FOR MIRTAZAPINE AND CARBAMAZEPINE VERSUS PLACEBO: NEW DATA FROM THE SYMBAD RCT. S. Banerjee On Behalf Of The Symbad Group[1] *(1. University Of Plymouth - Plymouth (United Kingdom))*

Background: Agitation is common in people with dementia and impacts negatively on the quality of life of both people with dementia and carers. Non-drug patient-centred care is the first-line treatment, but there is a need for other treatment when this fails. Current evidence is sparse on safer and effective alternatives to antipsychotics. We assessed efficacy and safety of mirtazapine (an antidepressant) and carbamazepine (an anticonvulsant) prescribed for agitation in dementia. Here we present new data from the SYMBAD trial including those on carbamazepine and long-term and economic outcomes. **Objectives:** To assess the safety, clinical and cost effectiveness of mirtazapine and carbamazepine in the treatment of agitation in dementia (Cohen Mansfield Agitation Inventory (CMAI) score), with 12 weeks follow up the primary outcome, and long-term follow up at 6 and 12 months. Registered ISRCTN17411897 and ClinicalTrials.gov NCT03031184, funded by UK National Institute for Health Research. **Methods:** Pragmatic, phase III, multi-centre, double blind, superiority, randomised, placebo-controlled trial of the clinical and cost-effectiveness of mirtazapine and carbamazepine over 12 weeks. Approved by Hampshire A South Central Research Ethics Committee (15/SC/0606) and MHRA (58810/0001/001-0001). Eligible participants randomised to receive either mirtazapine (target dose 45mg), carbamazepine (target 300mg), or placebo. Participants eligible if the following criteria were met: (i) clinical diagnosis of probable or possible Alzheimer's disease; (ii) co-existing agitated behaviours; (iii) evidence the agitated behaviours have not responded to management; (iv) CMAI score of 45+; (v) written informed consent from participant or consultee if capacity lacking; and (vi) availability of suitable informant. Exclusion criteria: (i) currently on antidepressants, anticonvulsants, or antipsychotics; (ii) contraindications

to mirtazapine or carbamazepine; (iii) second degree atrioventricular block; (iv) bone marrow depression or hepatic porphyria; (v) case too critical for randomisation (eg suicide risk or risk of harm to others); and (vi) females of childbearing potential. Participants were drawn from 26 UK sites, allocated in a 1:1:1 ratio to receive placebo or carbamazepine or mirtazapine, each with treatment as usual. Random allocation block stratified by centre and type of residence with random lengths. The trial was double-blind, with drug and placebo identically encapsulated. Analyses were based on intention-to-treat, the primary outcome (CMAI at 12 weeks) was analysed using a general linear regression model including baseline CMAI score as a covariate. General linear regression models were created for secondary outcomes. The primary outcome for the economic evaluation was the incremental cost per 6-point difference in CMAI score at 12 weeks, from a health and social care system perspective. Due to slower than expected recruitment the carbamazepine arm was discontinued in August 2018 with 1:1 randomisation to mirtazapine or placebo thereafter. **Results:** Between January 2017 and February 2020, 244 participants were recruited and randomised to either the mirtazapine (n=102), the placebo (n=102), or the carbamazepine arm (n=40). Mean CMAI scores at 12 weeks were not significantly different between participants allocated to receive mirtazapine and placebo (adjusted mean difference -1.74, 95% CI -7.17 to 3.69, p=0.53). The number of controls with adverse events (65/102 [64%]) was similar to that in the mirtazapine group (67/102 [66%]). There were more deaths in the mirtazapine group (n=7) by week 16 than in the control group (n=1), with post-hoc analysis suggesting this was of marginal statistical significance (p=0.065), but this difference did not persist at 6- and 12-month follow-up. At 12-week follow-up, the costs of unpaid care by the dyadic carer over the prior 6 weeks were significantly higher in the mirtazapine than placebo group (difference: £1,120 (95% CI £56, £2,184)). In the cost-effectiveness analyses mean raw and adjusted outcome scores and costs of the complete cases samples showed no differences between groups. The cost effectiveness analyses showed no evidence of benefit of mirtazapine over placebo. The carbamazepine arm had only 40 randomisations, we therefore lack the statistical power for the planned comparisons with placebo, however exploratory analyses using the same modelling as for mirtazapine versus placebo showed there was also no evidence of any benefits compared to placebo at 12 weeks (adjusted mean difference 2.46, 95% CI -5.01 to 9.93, p=0.52) or at long-term follow-up, with similar levels of adverse events reported. **Conclusions:** This is a trial with negative findings and clinical implications. The data suggest that mirtazapine is not clinically effective or cost-effective (compared to placebo) for clinically significant agitation in dementia. Our findings suggest that there is no reason to use mirtazapine for people with dementia who experience agitation. The data also provide no signal that carbamazepine might have any positive effect on agitation in dementia above that seen in the placebo group and no evidence of long-term benefit of either drug. These data bring into question the use of antidepressants for agitation in dementia.

OC06- COMBINATION OF REGIONAL FLORTAUCIPIR QUANTIFICATION AND EVENT-BASED MODELING IN CLINICAL TRIAL ANALYSES.

I. Higgins[1], A. Morris[1], J. Sims[1], M. Mintun[1], S. Shcherbinin[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Background: Positron emission tomography (PET) imaging of brain tau burden, topography, and propagation is used to evaluate Alzheimer's disease (AD) progression and treatment response. Regions of interest (ROIs) brain analysis for tau levels may be more sensitive than global whole brain tau estimates (Leuzy et al, Molecular Psychiatry, 2019). Topographic PET staging methods can incorporate a priori established ROI sequences (e.g. Braak staging and Lobar Classification, Schwarz et al, Alzheimer's & Dementia, 2018) and data-driven methodologies, such as an Event-Based Model (EBM, Fonteijn et al, Neuroimage, 2012, Young et al, Brain, 2014, Berron et al, Brain, 2021) that can deliver an ordering scheme in a discrete-event dynamic system to determine a sequence from which a set of ROIs transition to abnormally high tau burden. **Objectives:** Assess an ordered sequence of cortical atlas-based brain regions reflecting tau propagation across the Alzheimer's disease spectrum. Examine data from an interventional trial with donanemab (Mintun et al, NEJM, 2021) for the potential utility of EBM in the efficacy measurements on tau PET. **Methods:** Baseline flortaucipir PET scans from 1238 participants from observational and interventional trials were combined to develop and validate the model. Analyzed images were collected in 1) observational phase 2/3 18F-AV-1451-A05 study (NCT02016560); 2) EXPEDITION 3 phase 3 solanezumab trial (NCT01900665); 3) NAVIGATE-AD phase 2 trial with BACE inhibitor (NCT02791191); 4) AMARANTH phase 2/3 trial with lanabecestat (NCT02245737); and 5) DAYBREAK-ALZ phase 3 trial with lanabecestat (NCT02783573). Flortaucipir images pertaining to 57 elderly cognitive normal participants, 229 participants with mild cognitive impairment (MCI), and 936 participants with AD were included in the consolidated cross-sectional dataset. As regional outputs, standardized uptake value ratios (SUVRs) were calculated with respect to a reference signal intensity in white matter (PERSI, Southekal et al, JNM, 2018) and to an average signal in cerebellar gray matter region (Pontecorvo et al, Brain, 2017). Bilateral cortical ROIs from the Automated Anatomical Labeling (AAL, Tzourio-Mazoyer et al, Neuroimage, 2002) brain atlas were utilized as targets. The EBM assessed each brain region in our consolidated cross-sectional dataset as either "tau unburdened" or "tau burdened", where Gaussian probability density functions governed the distribution of tau SUVRs under these two settings. A brain region experienced "an event" when it switched from normal/unburdened to abnormal tau levels. The ordered sequence of regions was determined from the regional tau SUVR dataset. The EBM ran for 250,000 iterations, where at each step the algorithm swapped the positions of two brain regions and accepted the new sequence if the data fit improved. A simple subject-level resampling scheme permitted estimation of numerous ordered sequences from which regional variation about the characteristic sequence was evaluated. A permutation test was used to determine whether the characteristic sequence was better supported by data than a randomly ordered sequence. To assess the robustness of EBM performance, sensitivity analyses were conducted by varying the reference signal utilized in SUVR measurements. The sequence was also applied to post hoc exploratory analyses of tau PET data from 172 participants with baseline PET scans collected in the multicenter, randomized, double-blind, placebo-

controlled phase 2 TRAILBLAZER-ALZ trial (NCT03367403), to assess the efficacy of donanemab in early, symptomatic patients with AD (Mintun et al, NEJM, 2021). **Results:** EBM-generated sequences for temporal, parietal, and frontal lobe AAL ROIs were generally consistent with previously reported staging schemes (Schwarz et al, A&D, 2018), in that tau largely propagated along the temporal-parietal-frontal axis as AD progressed. Specifically, EBM placed the inferior temporal region at the beginning of the tau spread sequence followed by lateral temporal and parietal regions. All nine frontal ROIs were positioned at the end. The characteristic sequence was largely unchanged when the cerebellar crus was used as the reference region rather than PERSI. In TRAILBLAZER-ALZ post hoc exploratory analyses, regional SUVR values using cerebellar gray as a reference suggested that SUVR values showed more pronounced separation between placebo and donanemab-treated participants in regions identified later in the EBM sequence. Specifically, a significant separation was observed in frontal, temporal, and parietal ROIs ($p<0.05$), but there was no significant difference in tau change in "earlier" inferior temporal ROIs ($p>0.05$). Overall, more slowing in tau was observed ($p<0.001$) across the EBM sequence in participants treated with donanemab relative to placebo. **Conclusions:** Our analyses suggest that EBM can provide useful information in multi-regional analyses of flortaucipir images by ordering brain regions according to the pathologic sequence of tau progression. The EBM approach may better illustrate the therapeutic effect of AD treatment on tau PET by providing evidence of tau spread (Schwarz, Neurotherapeutics, 2021) to complement global tau measures. Larger trial data can further confirm these observations. **Conflict of Interest:** Ixavier A. Higgins is an employee and stockholder of Eli Lilly and Company.

OC07- LONGITUDINAL TAU PET INCREASE IS HIGHEST IN BRAIN REGIONS WITH STRONGEST FUNCTIONAL CONNECTIVITY TO REGIONS WITH MOST NFT AT BASELINE: AN INDEPENDENT VALIDATION.

Z.S. Saad[1], R. Datta[1], C. Rowe[2], H.C. Kolb[1] *(1. Janssen R&D, Johnson & Johsnon - San Diego (United States), 2. Austin Health and University of Melbourne - Melbourne (Australia))*

Background: Tau PET is the gold standard for in-vivo quantification of tau Neuro Fibrillary Tangles (NFT), which along with amyloid plaques and neurodegeneration, constitute the pathological hallmarks of Alzheimer's Disease (AD). Since NFT presence and accumulation is heterogenous across patients and brain regions, assessments need to be individualized. Identifying regions most likely to show NFT progression can improve detection of treatment effects and result in smaller trials. **Objectives:** Franzmeier et al. (1) showed based on Flortaucipir PET that future NFT increases were highest in brain regions with the strongest functional connectivity to regions with the highest NFT levels at baseline. We have performed an independent validation of this work using MRI and Tau PET data obtained with a different tracer, MK6240, and an in-house implementation of the analysis pipeline. **Methods:** NFT levels were quantified using MK6240 SUVR in 232 brain regions (reference region: cerebellar gray). Longitudinal tau PET data was analyzed from 18 amyloid positive MCI patients who fit the profile for inclusion in Janssen's Autonomy trial, and 36 Cognitively Normal (CN), amyloid negative subjects as controls. Quantification pipeline was implemented using FreeSurfer (2) and AFNI (3) software. For each subject, NFT epicenter consisted of regions with the top 10% of NFT levels that are at least one standard deviation above uptake in CN controls. All remaining regions were assigned a rank based on the strength of their average functional connectivity to the epicenter. Functional connectivity matrix for 232 cortical and sub-cortical regions (4, 5) was derived using resting state FMRI data from 500 healthy subjects available from the Human Connectome Project ((6, 7). Rank of connectivity to the epicenter was used to group regions into four quartiles Q1 to Q4, with Q1 having the strongest connectivity. **Results:** In the CN amyloid negative cohort, average annualized SUVR changes were close to 0 across quartiles with means and standard deviations of: Q1=-0.02 (0.04), Q2=-0.01 (0.04), Q3=-0.01 (0.04), Q4=-0.01 (0.03). In contrast, SUVR change for the MCI cohort was highest at Q1 and progressively lower across the four quartiles: Q1=0.05 (0.07), Q2=0.04 (0.07), Q3=0.03 (0.07), Q4=0.01 (0.09). Epicenter SUVR change of 0.01 (0.06) was comparable to that in Q4. In the MCI cohort, SUVR changes in Q1 and Q2 were nominally significantly greater than 0 ($p<0.05$) with effect sizes of 0.74 and 0.53, respectively. **Conclusions:** We have validated a patient-centered approach (1) for predicting future NFT increases using the patient's specific pattern of Tau NFT at BL and whole brain functional connectomics. This validation, conducted using independent pipelines, patient cohorts, and a different PET tracer, confirms that NFT increases are largest in brain regions with the strongest functional connectivity to the epicenter at BL. This precision approach may increase the efficiency of AD clinical trials. **References & Acknowledgements:** 1. Franzmeier et al., Nat Commun. 2020; 2. Reuter et al., Neuroimage. 2012; 3. Cox RW, Comput Biomed Res. 1996; 4. Schaefer et al., Cereb Cortex. 2018; 5. Tian et al., Nat Neurosci. 2020; 6. Glasser et al., Neuroimage. 2013; 7. Smith et al., Neuroimage. 2013. The authors would like to acknowledge the following institutions for contributing the imaging data to the Cerveau consortium: University of Wisconsin, Massachusetts General Hospital, Biogen Inc. Author conflicts of interest statements: ZSS, RD, and HCK are employed by Janssen Pharmaceuticals and may hold stock or stock options. Author CR has received research grants from NHMRC, Enigma Australia, Biogen, Eisai and Abbvie. He is on the scientific advisory board for Cerveau Technologies and consulted for Prothena, Eisai, Roche and Biogen Australia.

OC08- INDIVIDUALISED TAU-PET MEASURES MIGHT BE SUPERIOR TO GROUP LEVEL MEASURES WHEN DETERMINING CHANGE IN TAU DEPOSITION OVER TIME IN ALZHEIMER'S DISEASE.

A. Leuzy[1], A. Pichet-Binette[1], J. Vogel[2], G. Klein[3], E. Borroni[3], M. Tonietto[3], O. Strandberg[1], N. Mattsson-Carlgren[1], S. Palmqvist[1], E. Stomrud[1], R. Ossenkoppele[1], R. Smith[1], O. Hansson[1] *(1. Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden - Lund (Sweden), 2. Penn/CHOP Lifespan Brain Institute, University of Pennsylvania, Philadelphia, PA, USA - Philadelphia (United States), 3. F. Hoffmann-La Roche Ltd, Basel, Switzerland - Basel (Switzerland))*

Background: Though clinical trials in Alzheimer's disease (AD) typically use change in cognition as a primary outcome, the use of longitudinal tau positron emission tomography (PET) as a (secondary) outcome is becoming increasingly more common. Regions of interest (ROIs) are typically used to summarize change in tau-PET signal over time. To date, most ROIs have been based on neuropathological studies or data-driven approaches where the same ROI is used for each subject (i.e., group-level ROI). However, given the inter-individual heterogeneity in spatial patterns of tau-PET, a key question is whether the use of subject-specific (i.e., individualized) ROIs might offer any advantages over group-level ROIs in AD clinical trials. **Objectives:** To i) compare longitudinal change

in tau-PET estimated using group-level vs. individualized ROIs; ii) assess the number of patients required to detect a 25% reduction in the rate of change of either regional tau-PET or cognition across the different clinical stages of AD using group-level or individualized ROIs. **Methods:** Our sample consisted of 215 participants from BioFINDER-2 with longitudinal (baseline, 2-year) tau-PET using [18F]RO948 and longitudinal cognition. This included 97 Aβ-positive cognitively unimpaired individuals (preclinical AD), 77 Aβ-positive MCI patients (prodromal AD) and 41 patients with mild AD dementia (Mini-Mental State Examination [MMSE] ≥ 22). Longitudinal cognitive measures included MMSE and the modified Preclinical Alzheimer's Cognitive Composite (mPACC). Annual change in [18F]RO948 standardized uptake value ratio (SUVR) was calculated ROI-wise as the difference between follow-up and baseline, divided by baseline uptake and multiplied by the time interval between scans in years: ([follow-up SUVR – baseline SUVR] / baseline SUVR) × 100 / Δtime. Group-level ROIs included i) five ROIs reflecting event-based modelling stages (data-driven stages) and ii) six ROIs reflecting Braak stages; iii) a temporal meta-ROI and iv) a whole-brain composite-ROI. Individualized ROIs included i) epicenter (top 10% of regions with highest tau at baseline), ii) Q1 (top quartile of regions closest to subject-specific epicenter based on functional connectivity), iii) probability-based approach (Gaussian mixture modelling was performed on cross-sectional data to extract probabilities of being tau-positive across individual FreeSurfer ROIs; percent change in SUVR was then calculated for different probability intervals, with selection based on the interval that provided the highest annual percent change in SUVR). A final individualized approach was used based on calculating change in tau-PET in iv) highest data-driven stage that showed abnormal tau-PET signal at baseline using Gaussian mixture modelling-based cut-offs. Change in MMSE and mPACC were calculated as slopes derived from linear mixed models. Power calculations were performed using group-wise analyses (preclinical AD, prodromal AD, mild AD dementia) of tau-PET and cognition data to determine sample size estimates for an intervention with a hypothetical intervention effect of 25%. **Results:** Using the group-level ROIs, the greatest changes in tau-PET SUVR were seen using the data-driven stage I (preclinical AD, 5.14%), II (prodromal AD, 6.23%) and IV (mild AD dementia, 8.90%), which encompassed medial temporal, temporal and frontal lobe regions, respetively. In comparison to group-level ROIs, higher annual change in tau-PET SUVR was seen using individualized ROIs, with the approach iv ("highest data-driven stage approach") performing best in all groups (preclinical AD, 6.4%; prodromal AD, 8.67%; mild AD dementia, 10.72%). In comparison to longitudinal cognition as an outcome, tau-PET using best-performing group-level ROIs as an outcome resulted in greater sample size reductions (preclinical AD: data-driven stage I, 58% fewer subjects compared to mPACC and 63% compared to MMSE; prodromal AD: data-driven stage II, 54% fewer subjects compared mPACC and 65% compared to MMSE; mild AD dementia: data-driven stage IV, 64% fewer subjects compared mPACC and 51% compared to MMSE). Using the best performing individualized ROI (highest data-driven stage) resulted in even greater differences compared to cognitive measures (74% for preclinical AD compared to mPACC, 71% for prodromal AD and 67% for mild AD dementia compared to MMSE). **Conclusion:** Using longitudinal tau-PET as an outcome in early phase trials require fewer participants when compared to cognitive decline in AD clinical trials. If using longitudinal tau-PET as outcome, individualized ROIs appear to carry an advantage over group-level ROIs.

OC09- PREVALENCE AND LONGITUDINAL CLINICAL OUTCOMES OF VISUALLY 18F-FLORTAUCIPIR PET-POSITIVE INDIVIDUALS ACROSS THE ALZHEIMER'S DISEASE SPECTRUM.

A. Moscoso[1], F. Heeman[1], V. Camacho[2], M. Van Essen[3], M.J. Grothe[4], L. Lin[5], I. Mainta[6], F. Ribaldi[7], M.D. Devous[8], M.J. Pontecorvo[8], G.B. Frisoni[7], V. Garibotto[7], M. Schöll[1] *(1. Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg - Gothenburg (Sweden), 2. Department of Nuclear Medicine, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain. - Barcelona (Spain), 3. Department of Clinical Physiology, Sahlgrenska University Hospital, 413 45 Gothenburg, Sweden. - Gothenburg (Sweden), 4. Movement Disorders Group, Institute of Biomedicine of Seville-IBiS, Seville, Spain. - Sevillla (Spain), 5. Department of radiology, the third affiliated hospital of sun yat-sen university. - Guangzhou (China), 6. Division of Nuclear Medicine, Geneva University Hospitals, Geneva, Switzerland. - Genève (Switzerland), 7. Geneva Memory Center, Department of Rehabilitation and Geriatrics, Geneva University Hospitals, Geneva, Switzerland - Genève (Switzerland), 8. Avid Radiopharmaceuticals, Philadelphia, PA, USA - Philadelphia (United States))*

Background: The advent of positron emission tomography (PET) imaging with [18F]flortaucipir has allowed in-vivo visualization of aggregated tau in Alzheimer's disease (AD). Recently, a visual interpretation method for [18F]flortaucipir was developed and validated using neuropathological data, showing that tau-PET positivity can be regarded as a marker of advanced Braak stages (V-VI). This led to the approval of [18F] flortaucipir by the US Food and Drug Administration (FDA) as the first PET radiopharmaceutical indicated to 'estimate the density and distribution of aggregated neurofibrillary tangles'. In the clinical trials realm, this visual tau-PET positivity is one of the key eligibility criteria for inclusion in Donanemab trials. Yet, despite the relevance of this novel visual interpretation method, relevant variables for trialists such as the prevalence of visual tau-PET positivity across the AD spectrum or the longitudinal outcomes associated to visual tau-PET-positivity have not been investigated before. **Objectives:** 1) To estimate the prevalence of visual tau-PET positivity across the AD spectrum. 2) To establish the longitudinal clinical course of visually tau-PET-positive individuals across the AD spectrum. **Methods:** We included cognitively unimpaired individuals and patients with mild cognitive impairment (MCI) and AD dementia from five observational cohort studies — Alzheimer's Disease Neuroimaging Initiative (ADNI), Harvard Aging Brain study (HABS), A4 study, AVID's A05 study and Geneva Memory Clinic cohort — all of which had available FTP PET scans (n=1828, 1219 unimpaired, 425 MCI, and 184 AD dementia). Furthermore, Aβ status, established with Aβ-PET, was available in 1724 participants (94%), and longitudinal clinical and cognitive data was obtained for 523 unimpaired (median follow-up: 2 years) and 372 impaired (median follow-up: 1.5 years) participants. A trained reader (AM), blinded to clinical and imaging information, scored each [18F]flortaucipir PET scan as either negative or positive, and additionally classified positive [18F]flortaucipir PET scans as either moderate or advanced AD patterns. Multinomial generalized additive models (GAM) were fitted to obtain prevalence estimates of each [18F]flortaucipir AD pattern. Linear mixed models were used to estimate cognitive decline trajectories across Aβ- and visual tau-PET groups (A±vTAU±). **Results:** Among all cognitively unimpaired individuals, the prevalence of visual tau-PET positivity was 13.4%, with similar prevalence of moderate and advanced AD patterns (6.1% and 7.3%, respectively). The prevalence

of tau-PET-positivity increased non-linearly with age from ~5% at 65 years to 17% at 90 years. Tau-PET positivity was strongly dependent on Aβ status, showing high specificity (97.8%) for Aβ pathology. In the Aβ-positive unimpaired cohort of the A4 study, 24% of the participants were tau-PET-positive. In longitudinal analyses, A+vTAU+ unimpaired individuals showed the fastest rates of cognitive decline (Aβ+/vTAU+: ΔPACC3 = -0.34/y, p=0.02; Aβ+/vTAU-: ΔPACC3 = -0.16/y, p=0.06; Aβ-/vTAU- as reference). In cognitively impaired individuals, the overall prevalence of tau-PET positivity was 38.1% for MCI and 71.2% for AD dementia, with a much higher relative prevalence of the advanced pattern compared to the moderate (only 8.0% of MCI and 5.4% of AD dementia participants showed a moderate pattern). For both MCI and AD dementia participants, the prevalence of the advanced pattern decreased with age while that of the moderate pattern increased with age. As for unimpaired individuals, tau-PET positivity was highly specific for Aβ pathology (95%). In the longitudinal analysis, only the advanced AD pattern was significantly associated with faster clinical deterioration in MCI or AD dementia patients as measured by longitudinal MMSE, CDR-SB or ADAS-Cog 11. There were no significant differences between the clinical trajectories of A-vTAU- and A+vTAU- individuals. **Conclusion:** Our large-scale study provides the first robust estimates of the prevalence and longitudinal clinical outcomes of tau-PET positive individuals as defined using a clinically applicable, FDA-approved method. These estimates indicate that a non-negligible fraction of the cognitively unimpaired elderly population is tau-PET positive, indicative of advanced Braak stages. This prevalence increases even more among Aβ-positive unimpaired persons, with approximately 1 out of 4 unimpaired Aβ-positive being tau-PET-positive in the A4 study. Together with the fact that tau-PET-positive subjects show the fastest rates of clinical decline, this relatively high prevalence of unimpaired individuals in advanced Braak stages may be relevant for prevention trials using anti-amyloid therapies. The fact that A-vTAU- and A+vTAU- impaired individuals had similar longitudinal clinical outcomes suggests that the advanced AD pattern, and not amyloid pathology, is the main driver for AD-related clinical symptoms.

OC10- CONCORDANCE OF VISUAL AND QUANTITATIVE ANALYSIS FOR AMYLOID PET IMAGING WITH THREE 18F TRACERS IN THE CHARIOT-PRO SUBSTUDY.

G. Novak[1], Z. Saad[2], D. Scott[3], C. Udeh-Momoh[4], L. Bracoud[5], C. Ritchie[6], L. Middleton[7] *(1. Janssen R&D - Titusville, Nj (United States), 2. Janssen R&D - La Jolla, Ca (United States), 3. Clario (formerly Bioclinica) - San Mateo, CA (United States), 4. Imperial College - London (United Kingdom), 5. Clario (formerly Bioclinica) - Lyon (France), 6. University of edinburgh - Edinburgh (United Kingdom), 7. Imperial College - Edinburgh (United Kingdom))*

Background: Assessment of amyloid burden has been essential in the selection of patients most likely to be informative of safety and efficacy in clinical trials of amyloid-directed therapy. Three 18F PET tracers are approved for assessment of amyloid status through visual interpretation; quantitative thresholds of Standard Uptake Value Ratios (SUVR) have been defined for each, and a common centiloid (CL) scale has been derived from the linear relationship among the SUVRs of each tracer. While it may be desirable to choose a specific tracer for use within a single clinical trial, the long duration of these studies and their geographic range may require one to use 2 or more approved tracers, and the potential impact of this on consistency of performance needs to be explored. **Objectives:** To compare the performance of three 18F amyloid tracers in an observational trial, the CHARIOT-PRO Substudy (CPSS). **Methods:** The CPSS aims to assess the rate of longitudinal cognitive change in equal numbers of cognitively unimpaired elders with and without biomarker evidence of increased cerebral amyloid burden (A+ and A-, respectively). Participants were recruited at 2 centers in the UK, Imperial College London and the University of Edinburgh; the majority had amyloid assessment via PET. PET exams were acquired using a uniform scanning protocol that minimizes between-site differences in PET systems, as characterized with a Hoffman phantom exam. All exams were acquired in 3D mode, with correction for attenuation (CT-based), scatter and random coincidence. Visual assessments of the scans were performed by one of 3 neuroradiologists in a central laboratory, according to the prescribing information for each tracer, blinded to SUVR. Quantitative analysis involved coregistration of the image to each participant's baseline 3DT1 MRI. A composite SUVR was calculated as the volume-weighted average across FreeSurfer target and reference subregions derived from native-space MRI. The thresholds for amyloid positivity for each tracer were: Florbetapir, > 1.14 referred to whole cerebellum; Florbetaben, > 1.20 referred to cerebellar gray matter; and Flutemetamol > 1.21 referred to whole cerebellum. Composite SUVRs were then re-scaled to centiloid units, using linear regression derived by the central laboratory. PET positivity was determined using a hybrid approach. Concordant visual and quantitative assessments were accepted as A+ or A-, respectively. A negative visual read with an above threshold SUVR was considered A+. In case the visual read was positive and SUVR was below threshold, a second reader considered both results and made a final determination via consensus with the first reader. In case the SUVR was deemed unreliable, results were determined by consensus of 2 visual readers. Agreement between the visual read and SUVR were quantified by the kappa statistic. The sensitivity and specificity of the SUVR threshold defined for each tracer was calculated with respect to the results of the visual read, and an optimized SUVR cutpoint for predicting visual reads was determined by ROC analysis. Similarly, sensitivity and specificity were derived for a CL value of > 22 relative to the visual read, and this was compared to the optimized CL values resulting from ROC analysis. **Results:** A total of 1170 participants had amyloid PET, of whom 1112 had complete visual reads and SUVR (207 A+, 905 A-). Overall concordance was 95.5% and kappa = 0.837, indicating good agreement, but 49 of the 50 discordant cases were visual positive (V+) and SUVR negative (SUVR-). Thus, the visual read identified a higher proportion of participants as A+ (18.6%) than did SUVR (14.3%). Concordance was nominally higher for Florbetapir (n=178, A+=20.8%, concordance=98.3%, kappa=0.948) than for Florbetaben (n=615, A+=17.7%, concordance=95.1%, kappa=0.812) and Flutemetamol (n=319, A+=18.6%, concordance=94.7%, kappa=0.807). With respect to the visual read, the defined cutpoints yielded a sensitivity/specificity of 94.6%/99.3% for Florbetapir, 67.9%/100% for Florbetaben, and 70.1%/100% for Flutemetamol. These observations suggested that the defined SUVR cutoffs for the latter 2 tracers, derived from limited data available in 2015 and 2014 respectively, were too conservative. ROC analysis identified less stringent SUVR thresholds for each tracer (> 1.115 for Florbetapir and Florbetaben, and > 1.08 for Flutemetamol).; in the pooled population, sensitivity/specificity were 94.7%/96.6%. Using a defined threshold CL value > 22, 20.1% of the pooled population was identified as A+, with a sensitivity/specificity of 94.2%/96.7%. ROC analysis yielded an

identical CL threshold of > 22. **Discussion:** Use of a universal CL threshold of 22 units allowed for a consistent mapping of quantitative to qualitative assessments in a study that used 3 different amyloid tracers for participant selection. While there was no direct within-subject tracer comparison in this study, the concordance of the visual assessment with a CL cutoff of 22 across tracers suggests their performance is comparable and supports the use of multiple tracers for patient selection in clinical trials. ZSS, GN, and SB are employed by Janssen and may hold stock or stock options; LB and DS are employees of Clario but declare no conflicts.

OC11- AMYLOIDIQ QUANTIFICATION STRONGLY AGREES WITH BOTH HISTOPATHOLOGY AND VISUAL READS ACROSS MULTIPLE AMYLOID TRACERS.

A. Whittington[1], S. Bullich[2], L. Porat[1], R.N. Gunn[1] *(1. Invicro - London (United Kingdom), 2. Life Molecular Imaging - Berlin (Germany))*

Background: Neuritic plaques formed predominantly of misfolded Amyloid-β (Aβ) are one of 2 pathological hallmarks of Alzheimer's Disease (AD). Amyloid PET imaging with one of the FDA approved amyloid PET radiotracers provides a method to detect Aβ pathology in vivo. Scans are routinely classified as either positive (Aβ+) or negative (Aβ-) by visual assessment (often with a majority read from multiple independent reads). With the advance of quantitative algorithms such as AmyloidIQ, which has shown strong performance in cross-sectional and longitudinal studies, it now becomes possible to provide an automated quantitative assessment of Aβ pathology in the brain. **Objectives:** In this work, we assess the performance of AmyloidIQ against gold-standard post-mortem histopathology data and against visual assessment performed by trained readers for the PET tracers [18F]Florbetaben and [18F]Florbetapir. Within these analyses we also compared the performance of AmyloidIQ with a PET only pipeline and also with an associated structural MRI image available. **Methods:** There were 3 distinct analyses performed on different datasets in this work. In the first, histopathology (either Bielschowsky silver staining (BSS) or Immunohistochemistry (IHC)) was compared to AmyloidIQ quantification of ante-mortem [18F] Florbetaben scans for both PET-MR and PETOnly AmyloidIQ pipelines (PET-MR: n = 80, 25 Aβ-, 35 Aβ+ and PETOnly: n = 88, 35 Aβ-, 54 Aβ+). The second and third were comparisons of AmyloidIQ quantification with visual reads with [18F] Florbetaben (PET-MR: n = 345, 173 Aβ-, 172 Aβ+ and PETOnly: n = 439 , 246 Aβ-, 193 Aβ+) and [18F]Florbetapir (PET-MR and PETOnly: n=610, 313 Aβ-, 297 Aβ+) respectively. The visual reads for both analyses were performed by 5 experienced independent readers. The AmyloidIQ algorithm models spatially normalised SUVR images as the linear combination of two canonical images (carrying capacity image K and non-specific image NS) to produce a single continuous outcome measure, Amyloid Load (AβL), which quantifies the global amyloid burden. AmyloidIQ was successfully run on all scans from all 3 datasets with the only difference between PET-MR and PETOnly pipeline being the spatial normalisation algorithm (PET-MR: nonlinear using DARTEL, PETOnly: affine). Histopathology and visual reads provided a classification of the presence or absence of amyloid pathology (Aβ pathology was considered present, if any of the 6 regions sampled had moderate or frequent neuritic plaques either by BSS or IHC or both) and Aβ+/Aβ- respectively. ROC curve analyses produced optimum thresholds for AβL for classification for both PET-MR and PETOnly pipelines. The accuracy of each methodology was evaluated at these optimum thresholds using both histopathology and visual reads as a gold standard. **Results:** The comparison of AmyloidIQ against post-mortem data yielded a strong agreement (PET-MR: Accuracy 95.0% with sensitivity 94.5% and specificity 96.0% and PETOnly: Accuracy 95.5% with sensitivity 94.4% and specificity 97.1%) at the optimum thresholds (PET-MR: 35.6% and PETOnly: 42.3%). Visual reads also exhibited a strong agreement with AmyloidIQ regardless of the tracer used. More specifically, in the [18F]Florbetapir data, the accuracy of the PET-MR pipeline was 93.4% and the accuracy of the PETOnly pipeline was 93.1%. The optimum AβL thresholds for the two pipelines were similar (PET-MR: 32.5% and PETOnly: 35.6%). The [18F]Florbetaben results were remarkably similar. The accuracy of the PET-MR pipeline was 94.5% at the optimum AβL threshold of 35.6% and the accuracy of the PETOnly pipeline was 93.2% and cut-off at the optimum AβL threshold of 42.3%. **Conclusion:** AmyloidIQ analysis of [18F]Florbetaben scans exhibits a very strong agreement with both histopathology (IHC/BSS) data and visual assessment. Further, AmyloidIQ analysis of [18F]Florbetapir also showed a very strong agreement with visual assessment. AmyloidIQ classification was unaffected without an associated MRI scan which paves the way for the straightforward deployment in the clinical setting. The optimum thresholds found in all circumstances were extremely similar and the carrying capacity image can be calibrated to produce a standardised threshold of 33% across all tracers and pipelines hence providing a global and easily interpretable scale for AβL. This extensive assessment of AmyloidIQ against the gold-standard measures of post-mortem data and visual reads shows that its quantification can be used to both detect amyloid burden in the brain and automate the visual assessment of amyloid PET scans.

OC12- TOPLINE RESULTS OF EXERT: CAN EXERCISE PROTECT AGAINST COGNITIVE DECLINE IN MCI?

C. Cotman[1], H. Feldman[2], A. Lacroix[2], A. Shadyab[2], D. Jacobs[2], D. Salmon[2], R. Thomas[2], S. Jin[2], J. Pa[2], J. Katula[3], R. Rissman[4], J. Brewer[2], Y. Jung[5], J. Zhang[2], L. Baker[6] *(1. UCI (United States), 2. UCSD (United States), 3. Wake Forest University (United States), 4. USC (United States), 5. UC Davis (United States), 6. Wake Forest University School of Medicine (United States))*

Background: There are currently no effective therapeutic options to delay the progression of Alzheimer's disease (AD). The potential benefits of exercise on brain health in older adults at risk for AD are supported by preliminary studies and warrant further investigation. The EXERT trial (NCT02814526) was a Phase 3, multicenter, randomized single-blind study that examined the effects of regular exercise on cognition and other measures of brain function in a planned sample of 300 older adults with amnestic mild cognitive impairment (MCI). **Objective:** To test whether 12 months of supervised moderate intensity aerobic exercise versus an active control of stretching and balance protected against cognitive decline and other measures of AD progression in adults with MCI. **Methods:** EXERT was conducted at 14 sites and coordinated by the Alzheimer's Disease Cooperative Study (ADCS), in partnership with Wake Forest School of Medicine and the YMCA of the USA (Y-USA) for oversight of intervention delivery. Participants were randomized to complete aerobic exercise (AX) training or stretching, balance, and range of motion (SBR) activities for 18 months. For the first 12 months, exercise was completed with supervision of YMCA trainers twice per week, and independently twice per week. In the final 6 months (Months

13-18), participants completed exercise without supervision. The AX group completed moderate intensity exercise indicated by elevated heart rate (65-70% of heart rate reserve) and ratings of exertion. The SBR group exercised at a lower heart rate (<35% heart rate reserve) and ratings of exertion. Objective measures of adherence were tracked and monitored regularly by exercise specialists (Wake Forest, Y-USA). Outcomes assessments were completed in the clinic at baseline, and at Months 6, 12, and 18. The primary endpoint included outcomes obtained at Months 6 and 12. A modified version of the ADAS-Cog13 that included select subtests with additional measures of executive function (referred to as the ADAS-Cog-Exec) was validated and used as the primary outcome. Additional tests of executive function and memory were administered, blood was collected for AD biomarker analysis, and brain MRI was completed. In addition, 12-month changes in the ADAS-Cog-Exec and Clinical Dementia Rating Sum of Boxes (CDR-SB) were compared for both EXERT intervention groups relative to propensity-matched samples from other cohorts (e.g., ADNI-1) to estimate treatment effects relative to no intervention (i.e., "Usual Care"). **Results:** A total of 296 participants were enrolled from September 2016 to March 2020. Over 31,000 exercise sessions were completed in the 12-month supervised phase of the study, 18,045 of which (58.2%) were supervised by a trainer. For the AX group, 81% of expected supervised sessions were completed; for the SBR group, 87% of expected supervised sessions were completed. During the COVID-19 pandemic when the study was paused, >60% of participants reported continued exercise. The AX and SBR groups were balanced in baseline characteristics; 13.2% represented communities of color, and 40% did not have a college degree. Baseline MMSE and CDR-SB scores indicated that EXERT participants had mild cognitive impairments (mean MMSE=27.9; mean CDR-SB=1.5), and 25% of the sample were APOE4 carriers. Using a modified ITT approach (i.e., ppts must have initiated exercise and completed at least 1 follow-up assessment) to data analysis, neither the AX group nor the SBR group showed cognitive decline on either the ADAS-Cog-Exec or the CDR-SB over 12 months of follow-up. There were no significant treatment differences between AX and SBR on these outcomes. In the Usual Care analysis comparing ADNI-1 and EXERT participants matched on several key variables (demographics, baseline cognitive function, APOE4), ADNI-1 participants showed the expected 12-month decline on the ADAS-Cog-Exec but the EXERT AX and SBR groups did not (ADNI-1: vs. AX: p=0.012; vs. SBR: p=0.00049). **Conclusions:** In past smaller trials, exercise-related benefits were observed showing relative 'protection against decline' vs. the control group that showed expected rates of decline for adults with MCI. In EXERT, the expected 12-month declines for the control group did not occur. Our findings suggest that both exercise interventions stalled cognitive decline for adults with MCI. EXERT is the longest exercise trial in MCI conducted to date, and it is possible that greater 'volume' of exercise provided more protection, regardless of exercise intensity. In addition, both groups were provided with equal amounts of socialization, which may have also protected against decline. These results are particularly noteworthy given that the trial was conducted during the COVID-19 pandemic. **Funding:** NIH/NIA U19 AG010483

OC13- SENOLYTIC THERAPY TO MODULATE THE PROGRESSION OF ALZHEIMER'S DISEASE (STOMP-AD) – PILOT STUDY RESULTS ON CENTRAL NERVOUS SYSTEM PENETRANCE AND ALZHEIMER'S DISEASE BIOMARKERS.

M. Gonzales[1], V. Garbarino[1], T. Kautz[1], R. Petersen[2], T. Tchkonia[2], J. Kirkland[2], S. Craft[3], S. Seshadri[1], N. Musi[1], M. Orr[3] *(1. Ut Health San Antonio - San Antonio (United States), 2. Mayo Clinic - Rochester (United States), 3. Wake Forest School Of Medicine - Winston-Salem (United States))*

Objectives: Cellular senescence, a hallmark of biological aging, is a novel therapeutic target for neurodegenerative disease, which leverages the geroscience approach to disease prevention and treatment. Accumulation of senescent cells across tissues, including the brain, increases with aging. Senescent cells can produce a noxious secretome of cytokines and chemokines, which propagates inflammation and induces tissue dysfunction if not efficiently cleared by immune system. In the brain, senescent cells frequently colocalize with neuropathology. Preclinical studies have demonstrated that pharmacological ablation of senescent cells dampens inflammation, reduces ventricular enlargement, preserves neuronal and synaptic density, attenuates neuropathological burden, and improves cognitive behavior. However, the safety and efficacy of this novel therapeutic approach, referred to as "senolytics", in humans with cognitive impairment remains unestablished. Herein, we conducted a vanguard open-label clinical trial of senolytic therapy for Alzheimer's disease. The primary objectives were to evaluate the safety profile of intermittent orally-administered dasatinib and quercetin and determine central nervous system penetrance of the compounds. We also aimed to gain preliminary data into treatment effects on cognitive function, fluid biomarkers of AD pathogenesis, and senescence-associated inflammation. **Methods:** Participants with a clinical diagnosis of early-stage AD (CDR Global = 1) were enrolled in an open-label twelve-week pilot trial of intermittent orally-delivered dasatinib (100 mg) and quercetin (1000 mg). Safety was continuously monitored with adverse event reporting, vitals, and laboratory work. Plasma and cerebrospinal fluid (CSF) levels of dasatinib and quercetin were assessed before treatment and within four hours after final study drug administration using HPLC with tandem mass spectroscopy. CSF levels of Ab40, Ab42, phosphorylated tau 181 (p-tau 181), p-tau 231, neurofilament light (NFL), and glial fibrillary acidic protein (GFAP) were assayed using the Simoa HD-X Analyzer. For purposes of rigor, we also used Lumipulse to measure Ab40, Ab42, total tau, and p-tau 181; and capillary electrophoresis for measuring total and phosphorylated tau. Target engagement was assessed by investigating treatment-related changes in plasma and CSF markers of senescence and the senescence-associated secretory phenotype by Meso Scale Discovery Immunoassays. Paired t-tests were used to examine differences in biomarker levels pre- and post-treatment. **Results:** Five participants (40% female) with a mean age of 76±4 years completed the open-label trial. The treatment was well-tolerated with no significant changes in vitals, complete blood counts, and comprehensive metabolic panels (all p>0.05). The primary cognitive endpoints, the CDR Sum of Boxes (CDR SOB, t(4)=2.449, p=0.070) and the Montreal Cognitive Assessment (MoCA, t(4)=-0.196, p=0.854) were stable from pre- to post-treatment. Dasatinib was detected in plasma (t(4)=3.612, p=0.023) and CSF (t(4)=3.123, p=0.035) following treatment. Plasma quercetin levels were higher post-treatment (t(4)=2.847, p=0.047), whereas quercetin levels in CSF were undetectable across timepoints. Simoa results demonstrated

that in four out of five participants, CSF levels of p-tau 181 and the p-tau 181/Ab1-42 ratio decreased from pre- to post-treatment. There was a significant increase in CSF GFAP levels across timepoints (t(4)=3.354, p=0.028). Mean treatment-related changes in all other AD biomarkers did not reach statistical significance (Ab40: t(4)=0.274, p=0.797, Ab1-42: t(4)=-0.092, p=0.931, p-tau 181: t(4)=-1.521, p=0.203, p-tau 181/Ab1-42: t(4)=-0.869, p=0.434, p-tau 231: t(4)=-0.152, p=0.887, NFL: t(4)=-0.096, p=0.928). Lumipulse data indicated that in four out of five participants, Ab1-42 increased and the tau/Ab1-42 ratio decreased, although the results for the whole sample did not reach statistical significance (Ab1-42: t(4)=2.338, p=0.0795, p-tau 181/Ab1-42: t(4)=1.606, p=0.1835). Capillary electrophoresis demonstrated that high molecular weight p-tau 181 significantly decreased in all subjects with treatment (t(4)=2.941, p=0.0424) though the lower molecular weight tau did not change (t(4)=0.8199, p=0.4583). Assays of senescence in plasma and CSF are underway. **Conclusion:** Results from the first clinical trial of senolytic therapy in older adults with AD indicates that the treatment was well-tolerated. Preliminary data from our open-label pilot supports central nervous system penetration of dasatinib. While early results are promising, fully powered, double-blinded, placebo-controlled studies are needed to evaluate the potential of disease modification with the novel approach of targeting cellular senescence in AD.

OC14- A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, PHARMACODYNAMICS AND PHARMACOKINETICS OF TW001 IN ALZHEIMER PATIENTS. R. Van Der Geest[1], A. Lili[1], O. Van Loosbroek[1], A. Almeida[1], M. Oosthoek[2], C. Teunissen[2], S. Sikkes[3], E. Vijverberg[2] *(1. Treeway TW001AD BV - Tilburg (Netherlands), 2. Neurochemistry Laboratory, Department of Clinical Chemistry, Vrije Universiteit Amsterdam, Amsterdam UMC - Amsterdam (Netherlands), 3. Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC - Amsterdam (Netherlands))*

Background: The pathological hallmarks of Alzheimer's disease (AD) are the amyloid-beta (Aβ) plaques and the tau neurofibrillary tangles. Recent failures in phase 3 studies of anti-amyloid agents and tau aggregation inhibitors in patients with early stage, mild or mild to moderate AD suggest that novel approaches to drug development are urgently needed. Oxidative stress has been reported to be a prominent early event in the pathogenesis of AD. Reactive oxygen species (ROS) can alter the physical structures of proteins and accompanied by reactive nitrogen species (RNS) can induce cell membrane lipids to undergo peroxidation under oxidative stress conditions. All these oxidative stress products accumulate and trigger AD development. Accumulated in vitro and in vivo evidence has demonstrated that edaravone, a free radical scavenger with the ability to cross the blood brain barrier, can be effective in AD. In particular, edaravone can reduce oxidative stress in animal models of AD, measured by a reduction of pro-oxidants or products of lipid peroxidation or an increase in antioxidants in different brain regions. Moreover, the studies indicate that there is a neuroprotective effect of edaravone on several other levels that could reduce the rate of AD progression. This is indicated by the effect of edaravone on pro-inflammatory cytokines and on the cholinergic system, the latter being the main system targeted by current medication in the treatment of AD dementia. The intravenous formulation of edaravone is already on the market in a variety of countries (including the US and Japan) initially to reduce neuronal damage caused by Acute Ischemic Stroke (AiS) and later in the treatment of Amyotrophic Lateral Sclerosis (ALS). Treeway B.V. has developed an oral formulation for edaravone (TW001) to overcome the challenges related to intravenously administered edaravone for the treatment of ALS. This formulation is currently being tested in a Pivotal Phase 3 Clinical Trial in Europe. **Objectives:** It is hypothesized that an antioxidant therapy, such as edaravone, might also be a promising treatment strategy for AD, as oxidative stress plays a pivotal role in the development and progression of the disease. Current treatment options for AD, however, do not target oxidative stress. This is the first study that aims to investigate the effect of an antioxidant treatment for early AD. In light of this, Treeway B.V., supported by ADDF, has planned to initiate a Phase IIA clinical trial in AD patients in collaboration with the VU Medical Center and the Brain Research Center in Amsterdam. **Methods:** This is a double-blind, randomized, placebo-controlled, phase IIA proof-of-concept study to evaluate the safety, pharmacodynamics and pharmacokinetics of TW001 in mild AD patients. Although the primary objective of this highly innovative study design is to investigate the effect of oral edaravone on a series of disease and target engagement (e.g., oxidative stress) biomarkers, the study will also explore the early effect of edaravone on a variety of individual biomarkers and surrogate endpoints such as EEG, to define a potential composite biomarker that can be used in subsequent long-term clinical studies. In addition, a newly developed and highly sensitive clinical assessment tool (Cognitive-Functional Composite - CFC), developed by the Alzheimer Center of Amsterdam, will be tested in the study as a clinical outcome measure to potentially detect early changes in cognitive function. **Conflict of interest:** Treeway TW001AD B.V. has received a research grant in November 2019 sponsored by ADDF (reference GC-2013807) for the development of this project.

OC15- PROTEIN BIOMARKERS IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE CEREBROSPINAL FLUID IDENTIFY EARLY CHANGES IN BRAIN GLUCOSE METABOLISM AND THE MATRISOME. S. Bian[1], E.K. Carter[1], R. Haque[1], C. Watson[1], B. Gordon[2], L. Ping[1], D. Duong[1], M. Epstein[1], J. Lah[1], B. Roberts[1], A. Fagan[2], N. Seyfried[1], A. Levey[1], E. Johnson[1] *(1. Emory University - Atlanta (United States), 2. Washington University - St. Louis (United States))*

Background: Alzheimer's disease (AD) is characterized by multiple pathological brain alterations beyond amyloid-β (Aβ) and tau dyshomeostasis. How these pathological changes evolve over the course of the disease and are reflected by current AD biomarkers is currently unknown. **Objectives:** To better understand the natural history of AD pathology, we analyzed cerebrospinal fluid (CSF) from autosomal dominant AD (ADAD) mutation carriers and family member controls by targeted mass spectrometry to measure the levels of multiple proteins related to disease. The proteins were mapped to different AD brain pathologies as recently described in a consensus proteomic brain co-expression network of late-onset AD. **Methods:** 59 proteins were measured in 284 ADAD mutation carriers and 183 non-carriers in the Dominantly Inherited Alzheimer Network (DIAN). Measurements were obtained from baseline visits, and protein levels for each subject were placed in a longitudinal framework by the estimated year of disease onset (EYO). To better approximate protein levels sampled at a discrete set of EYO time points, we modeled EYO using a restricted cubic spline transformation with three knots

at the 0.10, 0.50, and 0.90 quantiles. To achieve uncertainty estimates and to account for random effects imposed by shared genetic background, the Bayesian regression model was built using a Markov Chain Monte Carlo algorithm and was applied to model the relationship between protein levels and fixed effects including mutation status, EYO, and the interaction effect. Differences in protein levels between mutation carriers and non-carriers at the 99% confidence interval were inferred using the posterior coefficient estimates from the Bayesian regression model at discrete EYO 0.5 year intervals between -36 and 26. The time at which protein biomarker levels in carriers were noted to diverge from non-carriers was compared to other biomarker changes measured in DIAN. **Results:** 29 proteins out of the 59 targeted for measurement were found to be different between mutation carriers and non-carriers at any EYO time point, with most proteins increased in mutation carrier CSF. Proteins derived from the brain matrisome co-expression module associated with Aβ deposition were among the earliest to change in mutation carriers—earlier than the absolute decreased levels of Aβ42 and nearly 30 years prior to symptom onset—followed by synaptic proteins and proteins associated with glucose metabolism. Markers of glucose metabolism were elevated at approximately the same time point as tau phosphorylated at residues 217 and 181 (pTau217 and pTau181). Multiple proteins associated with inflammation were noted to increase concomitantly with decreases in brain tissue and metabolism as assessed by MRI and metabolic imaging. Decreased levels of proteins from the granin family were found to be associated with cognitive impairment and functional decline. **Conclusion:** Proteomic approaches are able to identify novel brain-based biomarkers for AD. Measurement of these AD biomarkers in DIAN provides insight into the natural history of AD pathophysiology, which begins approximately three decades prior to the onset of cognitive symptoms in ADAD. The authors declare no competing interests. On behalf of the Dominantly Inherited Alzheimer Network.

OC16- LEVERAGING NOVEL TECHNOLOGIES TO DESIGN AND IMPLEMENT MORE PATIENT FOCUSED CLINICAL TRIALS.

D. Miller[1] *(1. Unlearn.AI - Berkeley (United States))*

Late-stage Alzheimer's disease (AD) randomized controlled trials (RCTs) are typically characterized by enrolling a large number of participants, high screen failures, and a trial duration commonly ranging from 2 to 4 years. It is then critical to bring efficiency to these late-stage AD clinical trials to accelerate the drug development process while maintaining the reliability of the evidence being generated. Unlearn's novel clinical trial participant-focused approach, called TwinRCTs, enables reducing the number of participants in the control arm for a desired power while maintaining a strict control of type I error rate as with the traditional RCT. Unlearn's approach has received a draft qualification opinion from the European Medicines Agency (EMA) novel methodologies program for a 3-step procedure called PROCOVA, the foundation of our TwinRCTs. The PROCOVA procedure consists of 3 steps: Step 1 is to build and evaluate a prognostic machine learning model for use in a particular planned trial (the Target Trial); Step 2 is to estimate the sample size and plan the Target Trial using PROCOVA for the primary analysis. Step 3, taking place after Target Trial database lock, is to estimate the treatment effect using a linear model while adjusting for the prognostic score. For the Step 1 of the PROCOVA procedure, Unlearn has developed machine learning methods to build models trained with historical data that are highly suitable to be used with the PROCOVA procedure. Among our current models, we have developed an AD model leveraging historical AD data that has been used in collaboration with a number of pharmaceutical companies for determining potential use cases in their existing AD clinical programs. We have shown that for a completed Phase 2 AD clinical trial, Unlearn's approach could enable the reduction of the control arm by more than 20%. TwinRCTs, including the PROCOVA procedure, are faster, participant-focused, and more efficient RCTs that generate regulatory-suitable clinical evidence.

OC17- AMYLOID AND TAU PET POSITIVE COGNITIVELY UNIMPAIRED INDIVIDUALS: DESTINED TO DECLINE?

R. Ossenkoppele[1], A. Pichet Binette[1], C. Groot[1], R. Sperling[2], C. Masters[3], W. Van Der Flier[4], W. Jagust[5], P. Ronald[6], C. Jack[6], O. Hansson[1] *(1. Lund University - Lund (Sweden), 2. Mgh - Boston (United States), 3. The Florey Institute Of Neuroscience And Mental Health Melbourne Victoria Australia - Parkville (Australia), 4. Amsterdam University Medical Center - Amsterdam (Netherlands), 5. Uc Berkeley - Berkeley (United States), 6. Mayo Clinic - Rochester (United States))*

Background: A major unanswered question in the dementia field is whether cognitively unimpaired individuals who harbor both Alzheimer's disease (AD) neuropathological hallmarks (i.e., amyloid-beta plaques and tau neurofibrillary tangles) can preserve their cognition over time or are destined to decline. Consequently, there is fundamental disagreement between the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria and the International Working Group (IWG) criteria about the nomenclature for cognitively unimpaired individuals who harbor one or both AD hallmark neuropathological features. For example, a cognitively unimpaired individual with positive Abeta (A+) and tau (T+) biomarkers is classified as "preclinical AD" by the NIA-AA criteria, while the IWG criteria would label such an individual "at risk for progression to AD". **Objective:** In this large multi-center amyloid and tau-PET study (n=1325), we examined the risk for future progression to mild cognitive impairment and the rate of cognitive decline over time among cognitively unimpaired individuals who were amyloid-PET-positive (A+) and tau-PET positive (T+) in the medial temporal lobe (A+TMTL+) and/or in the neocortex (A+TNEO+) and compared them with A+T- and A-T- groups. **Methods:** Participants were recruited from the Mayo Clinic Olmsted Study of Aging (n=680), the Swedish BioFINDER-1 (n=56) and BioFINDER-2 (n=228) studies, the Berkeley Aging Cohort study (n=109), the Harvard Aging Brain Study (n=162), the Australian Imaging Biomarkers and Lifestyle Study of Ageing (n=48) and the Amsterdam Dementia Cohort (n=42). All participants were i) cognitively unimpaired at baseline defined by neuropsychological test scores within the normative range given an individuals' age, sex and educational background, ii) had amyloid-PET available to determine Abeta-status, iii) underwent a tau-PET scan before January 1, 2019, to allow for sufficiently long follow-up duration, and iv) had at least one clinical follow-up visit available. Follow-up data was collected until April 1st, 2022. Abeta-status was determined using center-specific cut-offs or visual read metrics using [18F] flutemetamol, [11C]Pittsburgh compound-B, [18F]florbetapir or [18F]NAV4694 PET. Tau-PET was performed using [18F] flortaucipir across all cohorts, except BioFINDER-2 where [18F]RO948 was used. We computed tau-PET status for a medial temporal lobe (MTL; unweighted average of bilateral

entorhinal cortex and amygdala) and a neocortical (NEO; weighted average of bilateral middle temporal and inferior temporal gyri) region-of-interest. The threshold was determined for each cohort separately, based on the mean+2*standard deviation across all Abeta-negative participants within each cohort. Based on amyloid and tau-PET status we generated four different biomarker groups: A-T-, A+T-, A+TMTL+ (defined as tau-PET positive in the MTL but not in the neocortex) and A+TNEO+ (defined as tau-PET positive in the neocortex and/or in the MTL). First, we examined progression from cognitively unimpaired to mild cognitive impairment (MCI) using Cox proportional hazard models, adjusting for age, sex, education and cohort using A-T- as the reference group. Second, we examined differences in cognitive trajectories between groups on the modified preclinical Alzheimer cognitive composite 5 (mPACC5) and the Mini-Mental State Examination (MMSE) using linear mixed effect models with random intercepts and slopes, adjusting for age, sex, education and cohort. Statistical significance for all models was set at p<0.05 two-sided. **Results:** We included 1325 cognitively unimpaired participants, of whom 843 (63.6%) were A-T-, 328 (24.8%) A+T-, 55 (4.2%) A+TMTL+ and 65 (4.9%) A+TNEO+. During clinical follow-up, 26/781 (3.3%) of A-T-, 26/292 (8.9%) of A+T-, 25/51 (49.0%) of A+TMTL+ and 32/60 (53.3%) of A+TNEO+ participants progressed to MCI. Cox proportional hazard models, adjusted for age, sex, education and cohort, showed an increased risk for future progression to MCI in the A+TNEO+ (Hazard ratio [HR]=19.2[95% confidence interval: 10.9-33.7], p<0.001), A+TMTL+ (HR=14.6[8.1-26.4], p<0.001) and A+T- (HR=2.4[1.4-4.3], p=0.002) groups compared to the A-T- (reference) group. Pairwise log-rank tests showed that the A+TMTL+ and A+TNEO+ groups (both p<0.001) had steeper survival curves compared to the A+T- group, while the A+TMTL+ and A+TNEO+ groups did not differ from each other (p=0.19). Fifty percent of the A+TNEO+ and A+TMTL+ groups had progressed to MCI after 42.8 and 43.6 months, respectively. Linear mixed effect models adjusting for age, sex, education and cohort indicated that the A+TNEO+ (standardized b [stb] of interaction with time in months ± standard error=-0.020±0.002, T=-10.14, p<0.001), A+TMTL+ (stb=-0.017±0.002, T=-8.84, p<0.001) and A+T- (stb=-0.005±0.001, T=-5.26, p<0.001) groups showed faster decline over time on the mPACC5 compared to the A-T- (reference) group. On the MMSE, the A+TNEO+ (b=-0.056±0.005, T=-11.55, p<0.001), A+TMTL+ (b=-0.024±0.005, T=-4.72, p<0.001) and A+T- (b=-0.008±0.002, T=-3.46, p<0.001) groups showed faster decline over time compared to the A-T- (reference) group. The A+TNEO+ (T=-9.51, p<0.001) and A+TMTL+ (T=-3.04, p=0.002) groups progressed faster than the A+T- group, and the A+TNEO+ group declined faster than the A+TMTL+ group (T=-4.82, p<0.001). **Conclusion:** Evidence of advanced AD pathological changes provided by amyloid and tau-PET is strongly associated with short-term (i.e., 3-5 years) cognitive decline in cognitively unimpaired individuals and is therefore of high clinical relevance. This supports the NIA-AA criteria-based classification of A+T+ cognitively unimpaired individuals as "preclinical AD", especially when "T" is defined by PET.

OC18- PLASMA NT1-TAU CORRELATES WITH AGE AND COGNITIVE DECLINE IN TWO LARGE DOWN SYNDROME COHORTS. A.M. Stern[1], K.L. Van Pelt[2], L. Liu[1], A.K. Anderson[1], B. Ostaszewski[1], D.J. Selkoe[1], F. Schmitt[2], E. Head[3] *(1. Ann Romney Center For Neurologic Diseases, Brigham And Women's Hospital, Harvard Medical School - Boston, Ma (United States), 2. Sanders-Brown Center For Aging, Department Of Neurology, University Of Kentucky - Lexington, Ky (United States), 3. Department Of Pathology And Laboratory Medicine, University Of California, Irvine - Irvine, Ca (United States))*

Background: New plasma biomarker assays can predict cognitive decline and pathology in patients with or at risk for Alzheimer disease (AD). There is a need to expand upon novel plasma biomarker profiles in people with Down syndrome (DS), who nearly universally develop AD pathology. We previously found the NT1-tau assay can predict cognitive decline and imaging biomarker changes in sporadic non-DS AD. We have also recently developed plasma assays for Aβ37, Aβ40, and Aβ42. **Objectives:** To determine whether plasma Aβ isoforms and the ratios between them, and NT1-tau, predict cognitive decline in people with DS. **Methods:** The discovery cohort from the University of Kentucky (UKY) consisted of 104 participants with 416 longitudinal plasma samples. After excluding outliers and missing data, 85 participants with 220 observations were included in the analysis. The validation cohort from the Alzheimer's Biomarker Consortium Down Syndrome (ABC-DS) consisted of 297 cross-sectional plasma sample. The NT1-tau assay was run on the Quanterix Simoa HD-X instrument, and the Aβ isoform assays on the SP-X instrument. Linear mixed models first assessed change in biomarkers in the discovery cohort over time, with covariates including baseline age, sex, level of intellectual disability (ID), and consensus diagnosis. No longitudinal effect of time was observed in the linear mixed models, so individual regressions for each biomarker were used in a cross-sectional manner for baseline discovery cohort samples to correlate with age, sex, performance on the Dementia Scale for People with Learning Disabilities (DLD), or consensus diagnosis. The regression models developed in the discovery cohort were evaluated in the validation cohort by comparing the model-predicted vs actual values. **Results:** In the discovery cohort, the Aβ42 and NT1-tau linear regression models demonstrated significant main effects of baseline age (Aβ42: $F(6, 78) = 3.37$, $p = 0.005$, R2adj = 0.14, RMSE = 18.18, $\beta = -0.70$; NT1-tau: ($F(6, 78) = 4.98$, $p < 0.001$, R2adj = 0.22, RMSE = 1.32, $\beta = 0.05$). NT1-tau was not independently associated with DLD-Total or DLD subscores when controlling for age, sex, ID, and clinical diagnosis. However, NT1-tau was significantly associated with DLD-Cognitive ($\beta = 1.76$, R2adj = 0.095, $p = 0.003$), DLD-Social ($\beta = 1.45$, R2adj = 0.11, $p = 0.002$), and DLD-Total ($\beta = 3.20$, R2adj = 0.12, $p = 0.001$) scores when Aβ40, Aβ42, Aβ37 were the only covariates. The linear regression model for NT1-tau developed in the discovery UKY cohort predicted the NT1-tau level in the validation ABC-DS cohort (correlation between actual and predicted NT1-tau $r = 0.38$, $p < 0.001$). **Conclusions:** Plasma NT1-tau and Aβ42 correlate with age in people with DS. Plasma NT1-tau correlates with cognitive decline, and its predictive power holds across two large independent cohorts. **Conflicts of Interest:** DJS is a director of Prothena Biosciences and a consultant to Eisai. KLVP is now an employee of Synaptek, LLC.

OC19- SPECIFIC ASSOCIATIONS BETWEEN PLASMA BIOMARKERS AND POST-MORTEM AMYLOID PLAQUE AND NEUROFIBRILLARY TAU TANGLE BURDEN.

G. Salvadó[1], R. Ossenkoppele[1,2], N.J. Ashton[3,4,5], T.G. Beach[6], G.E. Serrano[6], G. Kollmorgen[7], H. Zetterberg[3,8,9,10], S. Janelidze[1], K. Blennow[3], O. Hansson[1,11] *(1. Clinical Memory Research Unit, Department Of Clinical Sciences, Malmö, Lund University - Lund (Sweden), 2. Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam University Medical Center - Amsterdam (Netherlands), 3. Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy, University Of Gothenburg - Gothenburg (Sweden), 4. Institute of Psychiatry, Psychology and Neuroscience, Maurice Wohl Institute Clinical Neuroscience Institute, King's College London - London (United Kingdom), 5. NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia at South London and Maudsley, NHS Foundation - London (United Kingdom), 6. Banner Sun Health Research Institute - Sun City (United States), 7. Roche Diagnostics GmbH - Penzberg (Germany), 8. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 9. Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square - London (United Kingdom), 10. UK Dementia Research Institute at UCL - London (United Kingdom), 11. Memory Clinic, Skåne University Hospital - Malmö (Sweden))*

Background: Multiple plasma biomarkers have been recently developed and have shown promise as diagnostic and prognostic tools for Alzheimer's disease (AD). However, their specific relationship with post-mortem pathological burden is still not fully understood. **Objectives:** We aimed to investigate the specific associations between multiple plasma biomarkers (phosphorylated tau217 [p-tau217], p-tau181, p-tau231, amyloid-β42/40 [Aβ42/40] ratio, glial fibrillary acidic protein [GFAP], and neurofilament light [NfL]) and core pathological measures of AD pathology (amyloid plaques and neurofibrillary tau tangles) assessed at autopsy. **Methods:** We included 132 participants from the Banner Sun Health Research Institute with a post-mortem neuropathological exam and available plasma biomarkers. Plasma p-tau217 and p-tau181 were measured using immunoassay developed by Lilly Research Laboratories (IN, USA); plasma p-tau231 was analysed using in-house single molecular arrays (Simoa) developed at the University of Gothenburg and; Aβ42, Aβ40, GFAP and NfL were analyzed using in-house Elecsys prototype plasma immunoassays (not commercially available, Roche Diagnostics International Ltd). We created a global measure for both plaques and tangles, which were measured in a semi-continuous scale (0–3) in five different regions (hippocampus, entorhinal cortex, and frontal, temporal, and parietal lobes). To assess specific associations between plasma makers and each of the two AD pathological measures, we performed linear regression models with plasma biomarkers as dependent variables and measures of both plaques and tangles as independent variables. The relevance of AD pathology was also assessed using the AD neuropathological change level (ADNC) based on the NIA-AA criteria, which considers presence of both plaques and tangles. We then investigated the diagnostic accuracy of plasma biomarkers in predicting presence (intermediate/high) of ADNC using receiver operating characteristic (ROC) curve analysis. The most parsimonious models for predicting pathological measures were selected based on the corrected Akaike criterion (AICc). We inverted the Aβ42/40 ratio from the usual practice, so that higher standardized betas would represent higher pathology for an easier comparison with the other markers. **Results:** We included 54 participants with none/low ADNC and 78 participants with intermediate/high ADNC. Participants had a mean(SD) age of 84.5(8.6) years at death and 52 (39.4%) were women. In univariate analyses, all markers except NfL were associated with plaques ($0.35 \leq \beta \leq 0.67$, $p<0.001$) and tangles ($0.25 \leq \beta \leq 0.60$, $p<0.011$). When both plaques and tangles were included in the same model, the Aβ42/40 ratio and p-tau231 were associated with plaques (βinverted Aβ42/40[95%CI]=0.57[0.36,0.77]; βp-tau231[95%CI]=0.33[0.10,0.55], both $p<0.001$), while GFAP was associated with tangles (βGFAP[95%CI]=0.34[0.15,0.53], $p=0.001$). In contrast, p-tau217 and p-tau181 were associated with both plaques (βp-tau217[95%CI]=0.51[0.37,0.65]; βp-tau181[95%CI]=0.48[0.32,0.64], both $p<0.001$) and tangles (βp-tau217[95%CI]=0.32[0.17,0.47], $p<0.001$; βp-tau181[95%CI]=0.23[0.06,0.40], $p=0.008$), with p-tau217 showing a significantly higher correlation coefficient with tangles than p-tau181 (βdiff[95%CI]=0.09[0.00,0.18], $p=0.038$). A model combining p-tau217 and the Aβ42/40 ratio showed the highest accuracy for predicting presence of ADNC (AUC[95%CI]=0.89[0.82,0.96], R2=0.62) as semi-quantitative measures of plaques (R2=0.55), while p-tau217 alone showed the highest accuracy to predict semi-quantitative measures of tau tangles (R2=0.45). **Conclusion:** We observed that some plasma biomarkers are strictly associated with only amyloid pathology (the Aβ42/40 ratio and p-tau231) or only tau pathology (GFAP), whereas p-tau181 and, particularly, p-tau217 are independently associated with both pathologies. These results may have important applications for clinical trials targeting one or both hallmarks of AD as they reveal specific associations with actual pathology. We suggest that the combined use of the Aβ42/40 ratio and p-tau217 may be useful in selecting participants for trials targeting amyloid-b pathology, whereas the use of plasma p-tau217 alone may be sufficient for participant selection in trials targeting tau pathology. **Conflicts of interest:** GK is a full-time employee of Roche Diagnostics GmbH. Work at the authors' research center was supported by the Swedish Research Council (2016-00906), the Knut and Alice Wallenberg foundation (2017-0383), the Marianne and Marcus Wallenberg foundation (2015.0125), the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, the Swedish Alzheimer Foundation (AF-939932), the Swedish Brain Foundation (FO2021-0293), The Parkinson foundation of Sweden (1280/20), the Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, the Skåne University Hospital Foundation (2020-O000028), Regionalt Forskningsstöd (2020-0314) and the Swedish federal government under the ALF agreement (2018-Projekt0279). The funding sources had no role in the design and conduct of the study; in the collection, analysis, interpretation of the data; or in the preparation, review, or approval of the abstract.

OC20- SYSTEMIC INFLAMMATION AND REDUCED CEREBRAL AB CLEARANCE TRIGGERED BY PANCREATIC AMYLIN.

F. Despa[1], N. Verma[1], E. Winford[1], P. Nelson[1], G. Jicha[1], L. Goldstein[1], C. Troakes[2], H. Zetterberg[3], J. Hardy[3], T. Lashley[3] *(1. University Of Kentucky - Lexington (United States), 2. King's College London - London (United Kingdom), 3. Dementia Research Institute At Ucl - London (United Kingdom))*

Background: Overexpression or/and impaired clearance of amyloidogenic proteins such as islet amyloid polypeptide (amylin) and β-amyloid (Aβ) are critical pathological pathways

in both type-2 diabetes and Alzheimer's disease (AD). Data from different research teams (including our own) show cerebral amylin deposits in humans with both sporadic and familial AD; however, a potential relationship between blood amylin concentrations and AD pathology remains unclear. **Objectives:** Because amylin deposits can be detected within the cerebral blood vessels in humans with AD, we hypothesized that amylin secreted from the pancreas disturbs cerebral Aβ clearance. To test this hypothesis, we measured blood amylin concentrations in humans with and without AD and assessed the relationships with brain parenchymal and vascular Aβ; transgenic rats were used to determine how pancreatic amyloid-forming human amylin affects cerebral Aβ clearance. **Methods:** Blood and brain tissue were collected as part of the University of Kentucky (UK) prospective cohort study (n=172). Additional formalin fixed temporal cortex tissues from familial AD (fAD) mutation carriers were provided by the Queen Square Brain Bank for Neurological Disorders at UCL Queen Square Institute of Neurology and King's College London. Observer-masked analyses were conducted on blood samples from cohort participants spanning the continuum of being cognitively unimpaired (CU; n=42) to mild cognitive impairment (MCI; n=19) and dementia (DEM; n=19) using amylin ELISA and flow cytometry. The results were communicated to UK-AD Research Center to assess the relationship between blood amylin concentrations and cognitive function. To assess the brain amylin-Aβ relationship, we measured amylin and Aβ42 concentrations in temporal cortex homogenates from persons with sporadic (sAD) (n=42) and CU individuals (n=18) by ELISA. Both plasma and frozen brain tissue were available from 20 participants. Histological evidence of cerebrovascular amylin-Aβ co-localization was tested in fAD (n=27) and sAD (32) brain slices by immunohistochemistry (IHC), confocal microscopy and proximity ligation assay (PLA) with anti-amylin and anti-Aβ antibodies. **Results:** CU, MCI and DEM groups had similar blood glucose concentrations (112.9 ± 5.71 mg/dL vs. 119.1 ± 9.43 mg/dL vs. 113.2 ± 5.10 mg/dL; one-way ANOVA, P = 0.79) and age (79.35 ± 2.18 years vs. 81.35 ± 1.78 years vs. 77.60 ± 0.66 years; one-way ANOVA, P = 0.14). Blood amylin concentrations were higher in DEM vs. CU groups with estimated medians of 4.33 (2.84-6.56, interquartile range) and 1.53 (1.12-3.43, interquartile range) (Kruskal-Wallis one-way analysis of variance, P < 0.001). Blood samples with amylin concentrations in the upper quartile contained increased fractions of CD14+ monocytes positive for amylin, with an estimated mean rank difference of difference of 38 (Kruskal-Wallis one-way analysis of variance, P < 0.0001). Confocal microscopic imaging confirmed amylin inclusions in circulating CD14+ monocytes. Brain amylin concentrations were higher in sAD vs. control groups with an estimated difference between medians of 4.653 (unpaired t test, P<0.01). Increased brain amylin concentrations were associated with greater Aβ42 concentrations (r = 0.34; P < 0.05), consistent with the amylin-Aβ42 relationship recently reported in fAD brains. The point estimate of the pairwise correlation coefficient suggests a possible relationship between blood amylin levels and brain amylin accumulation (r = 0.40; P = 0.09) (potential outliers were excluded from the analysis). The IHC analysis detected amylin in approximately 2/3 of the total blood vessels staining positive for Aβ in AD brains. Aβ deposits were present in perivascular spaces and blood vessel walls, whereas amylin accumulated within the lumen and on the luminal side of blood vessel walls. Confocal microscopic analysis of brain section triple stained with anti-amylin, anti-Aβ, and anti-α smooth muscle cell actin antibodies showed co-localization patterns in which Aβ was present in perivascular areas and amylin within the blood vessel wall. The PLA signal showed an overall consistency with amylin-Aβ colocalization within the arteriolar wall. In rats, pancreatic expression of human amylin indeed induced systemic inflammation, cerebrovascular amylin deposits and local perivascular inflammation. LRP1-mediated Aβ transport across the blood-brain barrier (BBB) and Aβ clearance through interstitial fluid drainage along vascular walls were impaired, as indicated by Aβ deposition in perivascular spaces. At the molecular level, cerebrovascular amylin deposition altered immune and hypoxia-related brain gene expression. **Conclusions:** Three interdependent factors underlie amylin-induced impairment of cerebral Aβ clearance: blood amylin concentrations are increased in dementia vs. cognitively unimpaired individuals; chronically increased concentrations of amyloid-forming amylin in blood promote amylin accumulation in circulating monocytes reflecting systemic inflammation and leading to cerebrovascular amylin deposition; and cerebrovascular amylin deposition disturbs LRP1-mediated Aβ transport across BBB and Aβ clearance through interstitial fluid drainage along vascular walls, as indicated by amylin-Aβ co-localization in blood vessel walls and perivascular spaces. Future studies are needed to clarify these relationships and test whether screening for pancreatic amylin dysregulation could identify people at increased risk for brain microvascular and AD pathologies. Altering pancreas-derived amylin in blood could potentially reduce cerebrovascular amylin deposits, Aβ pathology, and the risk of diabetic brain injury and cognitive impairment.

OC21- PRAZOSIN FOR AGITATION IN ALZHEIMER'S DISEASE: PEACE-AD. E. Peskind[1], M. Raskind[2], R. Thomas[3], G. Jicha[4], N. Patel[5], A. Pierce[6], S. Brangman[7], M. Sano[8], J. Kaye[6], M. Lim[6], M. Au-Yeung[6], M. Herman[9], G. Leger[9], K. Messer[9], H. Feldman[9] *(1. VA Northwest Mental Illness Research, Education and Clinical Center (MIRECC), Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine - Seattle (United States), 2. VA Northwest Mental Illness Research, Education and Clinical Center (MIRECC) and Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine - Seattle (United States), 3. Departments of Family Medicine and Neurosciences, University of California San Diego - La Jolla (United States), 4. Department of Neurology, University of Kentucky - Lexington (United States), 5. Department of Family and Community Medicine, UT Health San Antonio - San Antonio (United States), 6. Department of Neurology, OHSU School of Medicine - Portland (United States), 7. Department of Geriatrics, SUNY Upstate Medical University - Syracuse (United States), 8. Department of Psychiatry, Mount Sinai School of Medicine - New York (United States), 9. Department of Neurosciences, University of California San Diego - La Jolla (United States))*

Background: To evaluate the efficacy and safety of prazosin for the treatment of disruptive agitation in Alzheimer's disease participants residing at home or in a long-term care facility in a national multicenter randomized controlled trial conducted by the NIA-funded Alzheimer's Disease Cooperative Study (ADCS). **Methods:** In this multi-site randomized controlled trial (RCT) in which recruitment was substantially handicapped by the COVID-19 pandemic, participants were randomized to prazosin or placebo using a 2:1 permuted block randomization. Prazosin was titrated over 4 weeks to a maximum possible dose of 4 mg mid-morning and 6 mg at bedtime based on tolerability and persistent agitation. Adverse events and orthostatic blood pressure and heart rate were monitored. Primary outcome

measure was the ADCS-Clinical Global Impression of Change-Agitation (CGIC-A) targeting disruptive agitated behaviors. Secondary outcomes were the 17-item Neuropsychiatric Inventory (NPI), Cohen Mansfield Agitation Inventory (CMAI), ADCS-Activities of Daily Living (ADCS-ADL) for severe dementia, and total number study days completed. An exploratory outcome was the NPI 5-item subscale reflecting agitation. Due to COVID-19 restrictions, methods were adapted to allow for remote consent, participant screening, and outcome and safety assessments. In addition, caregivers were trained to measure blood pressure and heart rate using the Omron automated blood pressure machine. **Results:** Thirty-five participants were randomized 2:1 to prazosin or placebo for 12 weeks. Mixed Models Repeated Measures analysis was performed. There were no significant differences in the CGIC-A or total NPI scores. In the prazosin group, 7 of 18 participants were moderately or markedly improved on the CGIC-A compared to 1 of 4 participants in the placebo group (NS). Change from baseline in CMAI score significantly favored prazosin (-5.5 ± 4.1 [mean ± SEM] in the prazosin group vs. +10.0 ± 6.0 in the placebo group, p=0.04) and the 5-item NPI Agitation subscale numerically favored prazosin (NS). Kaplan-Meier Survival Analysis numerically favored prazosin with 63% of prazosin participants completing all 12 weeks compared to 38% of placebo participants (NS). The adverse event (AE) profile was as anticipated for prazosin; AEs that occurred in >5% of prazosin participants and >2X the occurrence in the placebo group included syncope, dizziness, nausea, and somnolence. Remote consenting, screening, and assessments allowed continuation of the study without the necessity of in-person clinic visits. **Conclusion:** PEACE AD provides some additional evidence of the potential efficacy in this small RCT testing of prazosin in the treatment of disruptive agitation in AD. While the assessment of both efficacy and safety were limited by the small number of participants, particularly in the placebo group, there was some benefit with prazosin seen across measures of behavioral assessment over 12 weeks of treatment, with the expected safety profile. PEACE AD was successfully conducted during COVID 19 using fully remote visits with home dwelling participants and technology support. It demonstrates the feasibility and significant advantages of performing a randomized controlled trial for disruptive agitation in AD using remote technology in home dwelling participants. This approach permitted the inclusion of severely agitated AD outpatients for whom attendance at frequent clinic visits would itself have been extremely challenging. A larger multi-center study of prazosin for moderate-severe disruptive agitation in AD is necessary and warranted to extend these results with lessons from this trial applied in its design and methods. The PEACE-AD study was funded by the National Institute on Aging via the Alzheimer's Disease Cooperative Study (U19 AG010483) with additional support from the Alzheimer's Association (SG-20-690388).

OC22- DEMOGRAPHIC ANALYSIS OF INDUSTRY SPONSORED ALZHEIMER'S DISEASE TRIAL POPULATIONS IN THE UNITED STATES.

S. Peroutka[1]
(1. Ppd, Part Of Thermo Fisher Scientific - Carmel (United States))

Background: The Food and Drug Administration (FDA) stated in 2020 that "sponsors should enroll participants who reflect the characteristics of clinically relevant populations with regard to age, sex, race, and ethnicity". Moreover, the FDA Guidance recommended that sponsors include a plan for inclusion of clinically relevant populations no later than the end of the Phase 2 meeting for all drugs and biological investigational therapeutics. In view of the significant amount of clinical trial research in Alzheimer's Disease, a comprehensive demographic evaluation of the study populations used in Alzheimer's disease trials seems prudent. **Objectives:** Although it has been noted for at least 30 years that Alzheimer's Disease trials have enrolled predominantly White subjects, a thorough analysis of industry-sponsored, US-based Alzheimer's trials has yet to be performed. The present study therefore evaluated all available demographic data on industry-sponsored Alzheimer's trials of 100 or more subjects, performed solely in the United States. Global Alzheimer trials were excluded since sponsors rarely report demographics on a country by country basis. The objective was to determine if the gender and racial distributions of the trial subjects were representative of the known epidemiological characteristics of Alzheimer's Disease. **Methods:** A search of the ClinicalTrials.Gov website (https://clinicaltrials.gov/) for "Alzheimer's Disease, Industry-sponsored" clinical trials was made on March 31, 2022. A total of 1,145 trials were identified. The trials data were then screened for US only trials with at least 100 enrolled Alzheimer's Disease subjects. Finally, the analysis dataset included all trials that had gender and/or racial demographic results available on either the ClinicalTrials.Gov website or in an associated publication identified via a PubMed search. **Results:** There were 35 identified trials with gender and/or racial demographic results, comprised of nearly 13,000 enrolled Alzheimer's Disease subjects. These trials were completed between 1997 and 2019. The subject enrollment per trial ranged from 100 to 1,649 individuals. The gender distribution was available from 35 trials involving 12,912 subjects. There were 6,970 (54%) females and 5,942 (46%) males in these trials. The racial distribution was available from 24 trials, involving 10,872 Alzheimer's Disease subjects. There were 10,017 (92%) Whites, 341 (3.1%) Black or African Americans, 49 (0.5%) Asians and 464 (4.3%) Others (e.g., Mixed, Unknowns, etc.). The percentage of White subjects per study in the 24 trials ranged from 84%-99%. **Conclusion:** The analysis of 35 industry-sponsored Alzheimer's trials, performed solely in the US, showed an increased frequency of female vs. male participation in the trials. This observation is consistent with the known epidemiology of Alzheimer's Disease. By contrast, the analysis of 24 US only, industry sponsored trials identified a major discrepancy between the racial distribution in the trial subjects compared to the known epidemiology of Alzheimer's Disease in the United States. Large scale epidemiological studies in Alzheimer's Disease across the entire US population have not been performed. However, 92% of Alzheimer's Disease trial subjects have been White over the past 25 years in the United States. This fact is clearly a significant deviation from the known racial demographics of Alzheimer's Disease. These data suggest that significant modifications of subject recruitment methods are needed to increase the enrollment of underrepresented populations into Alzheimer's Disease trials. The consistently high percentage of White subjects per trial, in all 25 studies analyzed, suggests that these racial disparities are a likely result of a recruitment process that has not focused on subject diversity. The result is that an immediate need exists to increase the enrollment of multiple underrepresented populations of Alzheimer's patients in US clinical trials. Based on a review of clinical trial participation barriers in underrepresented populations (e.g., Black or African-America, Hispanic and American Indian), two consistent themes have emerged that limit research participation: mistrust and lack of information. These obstacles can be overcome, but they require a significant and long-term investment in community outreach

programs. In the short-term, information about ongoing trials needs to be communicated effectively to underrepresented communities via local health centers, senior community centers, neighborhood association meetings, pharmacies, churches, etc. Although limited research has suggested that this approach can be successful, more research is needed to determine the optimal ways to inform underrepresented populations about clinical trial research opportunities. A more challenging need is to determine the optimal ways to build trust between the medical research community and historically underrepresented populations in Alzheimer's Disease clinical trials.

OC23- PLASMA BIOMARKER FINDINGS FROM THE ALZHEIMER'S PREVENTION INITIATIVE AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE COLOMBIA TRIAL.

E.M. Reiman[1], F. Lopera[2], S. Rios-Romenets[2], C. Schiffman[3], D. Hibar[3], G. Kollmorgen[4], M. Giraldo[2], N. Acosta[2], A. Espinosa[2], G. Villegas[2], C. Muñoz[2], L. Serna[2], K. Herrera[2], Y. Su[1], R. Alexander[1], Y.T. Quiroz[5], R.S. Doody[3], J.B. Langbaum[1], P.N. Tariot[1], K.M. Sink[3], T. Bittner[1] *(1. Banner Alzheimer's Institute - Phoenix, Arizona (United States), 2. Neurosciences Group of Antioquia, University of Antioquia - Medellín (Colombia), 3. Genentech, Inc., - South San Francisco, Ca (United States), 4. Roche Diagnostics GmbH - Mannheim (Germany), 5. Massachusetts General Hospital and Harvard University - Boston, MA (United States))*

Background: Crenezumab is an anti-amyloid monoclonal antibody that binds to beta-amyloid (Aβ) oligomers and is hypothesized to prevent the buildup of pathogenic Aβ plaques and to modify Alzheimer's disease (AD) progression with a low risk of amyloid-related imaging abnormalities (ARIA). The Alzheimer's Prevention Initiative (API) Autosomal Dominant AD (ADAD) Colombia trial evaluated crenezumab using clinical and biomarker endpoints in cognitively unimpaired presenilin 1 (PSEN1) E280A mutation carriers recruited from the world's largest ADAD kindred (NCT01998841). Blood-based biomarkers (BBBMs) of amyloid and tau pathophysiology, neurodegeneration, and neuroinflammation have the potential to inform the development of AD-modifying and prevention therapies. **Objectives:** To describe baseline and change from baseline treatment-related BBBM findings from participants of the API ADAD Colombia trial. **Methods:** This randomized, double-blind, placebo-controlled, parallel-group trial evaluated the efficacy, safety, and tolerability of crenezumab in cognitively unimpaired 30–60-year-old Colombian PSEN1 E280A kindred members whose median age of mild cognitive impairment onset is 44 years. The 252 trial participants included mutation carriers who were randomized to crenezumab, mutation carriers who were randomized to placebo, and non-carriers who received placebo distributed in an approximately 1:1:1 ratio. Participants and researchers were blinded to mutation status. While participant inclusion in the trial was independent of baseline amyloid positron emission tomography (PET) findings, 40% of the carriers were found to have a negative amyloid PET scan prior to treatment. While dosing started with 300 mg subcutaneously every 2 weeks, it evolved over time and participants were eventually treated with either crenezumab (up to 720 mg subcutaneously every 2 weeks or 60 mg/kg intravenously every 4 weeks) or placebo for 5–8 years using a common close design. The primary endpoint family included the change in the API ADAD Cognitive Composite Test score and the Free and Cued Selective Reminding Test score. Most of the participants had serial amyloid PET, tau PET, 18F-FDG PET, magnetic resonance imaging, cerebrospinal fluid (CSF) and BBBM measurements and other assessments. Blood samples collected annually were measured using Elecsysâ robust prototype immunoassays. Biomarkers tested included plasma phosphorylated tau (p-tau)181 and p-tau217, which provide information about Aβ plaque burden and Aβ-related tau pathophysiology; plasma neurofilament light (NfL), which provides information about neuronal injury and neurodegeneration; and plasma glial fibrillary acid protein (GFAP), chitinase 3-like 1 (YKL-40) and soluble triggering receptor expressed on myeloid cells 2 (TREM2), which provide information about neuroinflammation. **Results:** After summarizing trial aims and design, participant characteristics, and treatment-related clinical, cognitive, imaging and CSF biomarker findings, we will describe the participants' baseline BBBM and treatment-related BBBM findings, including in mutation carriers with positive and negative baseline Aβ PET scans, and relationships between BBBM and clinical effects. **Conclusion:** The API ADAD Colombia Trial was intended to characterize the efficacy, safety, and tolerability of crenezumab in the prevention of AD; explore the treatment's differential biomarker effects in amyloid-positive and amyloid-negative participants at virtually certain AD risk; clarify relationships between the treatment effects on biomarker and clinical outcomes; provide a shared resource of data and samples for the field; help to establish a new era in AD prevention research; and advance the role of emerging BBBMs in these endeavors. **Conflict of interest statement:** Our work on this particular study was supported by NIH grants, F. Hoffmann-La Roche, philanthropic donations to Banner Alzheimer's Foundation, and grants from the state of Arizona. Eric. M. Reiman is a Co-Founder & Advisor of ALZPath. He is a scientific advisor to Alzheon, Aural Analytics, Denali, Retromer Therapeutics, Vaxxinity and has Institutional Research Agreements with F. Hoffmann-La Roche/Genentech, Avid/Lilly.

OC24- NEUROIMAGING DATA FROM A PHASE 2, OPEN-LABEL STUDY OF NE3107 IN PATIENTS WITH COGNITIVE DECLINE DUE TO DEGENERATIVE DEMENTIAS.

K. Jordan[1], K. Mahdavi[1,2], J. Haroon[1], E. Rindner[1], M. Zielinski[1], V. Venkatraman[1,2], S. Becerra[2], D. Goodenowe[3], C. Ahlem[4], C. Reading[4], J. Palumbo[4], B. Pourat[5], S. Jordan[1,2] *(1. The Regenesis Project - Santa Monica (United States), 2. Synaptec Network - Santa Monica (United States), 3. Prodrome Sciences USA LLC - Temecula (United States), 4. Biovie Inc. - Carson City (United States), 5. Pourat MD - Beverly Hills (United States))*

Background: Alzheimer's disease (AD) affects more than 6 million Americans and is associated with substantial healthcare costs and suffering. Unfortunately, therapies targeting neurodegenerative and abnormal protein deposits in the brain, including amyloid beta (Aβ) and phosphorylated tau (P-tau), have shown unclear clinical benefit, and more effective therapies are urgently needed. AD is associated with imbalances or deficiencies in neuronal glutathione levels and significant synapse and dendritic spine loss in parts of the brain, among other neurophysiological deficiencies. During the past decade, chronic inflammation and impaired glucose metabolism have been recognized as important contributors to the pathophysiology of AD. Neuroinflammation, insulin resistance (IR), and Aβ and P-tau pathologies form a feed-forward loop in AD progression. Therefore, targeting neuroinflammation and IR are attractive strategies in the treatment of AD. NE3107 is a well-tolerated, blood-brain permeable oral agent that selectively inhibits several inflammatory mediators and improves insulin signaling. Across several clinical studies, NE3107 increased insulin sensitivity and restored metabolic

homeostasis in patients with type 2 diabetes and inflammation. It was also shown to alter inflammatory biomarkers that have been associated with cognitive decline. Multimodal imaging in patients with dementia has demonstrated certain qualities that would reflect associated changes in brain structure and function. These include change in regional neural dysfunction as shown in arterial spin labeling (ASL), change in interstitial free water and neurite density as found in diffusion tensor imaging - neurite orientation dispersion and density imaging (DTI-NODDI), change in redox stress as reflected in glutathione magnetic resonance spectroscopy (MRS), and change in seed-based functional connectivity of the nucleus basalis of Meynert as found in blood oxygen level dependent (BOLD) imaging. **Objectives:** This is a Phase 2, open-label study to evaluate the potential efficacy of NE3107 in patients with mild cognitive impairment (MCI) or mild dementia using advanced neuroimaging endpoints, AD and inflammatory biomarkers, changes in glucose metabolism, and cognitive performance testing. The primary objective of this study is to evaluate changes in neurophysiological health using multi-modal brain MRIs obtained at baseline and treatment termination (3 months). Secondary objectives of this study include a longitudinal comparison of glucose homeostasis, cognitive impairment as defined by neuropsychological testing, and AD and inflammatory markers. **Methods:** Twenty-three participants were enrolled and received 20-mg oral NE3107 twice daily for 3 months. Participants were between 50-89 years old with MCI or mild dementia (Quick Dementia Rating Scale [QDRS] cutoff range: 1.5-12.5; Clinical Dementia Rating [CDR] score range: 0.5-1). AD markers (Aβ and P-tau) were evaluated at baseline and treatment termination. Primary endpoints evaluated neurophysiological health using multi-modal brain MRIs at baseline and treatment termination, including stabilization or increase in glutathione levels (measured by MRS), enhancement of arterial perfusion (quantified by ASL), increased functional connectivity of the nucleus basalis of Meynert (visualized by seed analysis of BOLD imaging), and improvements in dendritic density and interstitial free water (measured by DTI-NODDI). Secondary endpoints evaluated changes in serological inflammatory markers, glucose and insulin homeostasis, and cognitive functioning—including changes in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 12) from baseline at treatment termination. **Results:** Participants had a mean age of 71.6 (SD = 9.63) years and 15 (65%) were females. At baseline, the mean QDRS score was 5.07, 18 (78%) participants had a CDR score of 0.5, and 5 (22%) participants had a CDR score of 1. Results of neuroimaging analyses will be presented at the conference. **Conclusion:** Using an array of advanced neuroimaging techniques to ascertain changes in participants' neurophysiological health before and after treatment with NE3107, this study aimed to demonstrate the potential therapeutic efficacy associated with NE3107 treatment in patients with MCI. Funded by: BioVie Inc. **Disclosures:** ER, KM, KJ, JH, MZ, VV, SB, and SJ have received grant support from BioVie Inc. DG has nothing to disclose. BP has nothing to disclose. CA, CR, and JP are employees of BioVie Inc.

OC25- HOPE4MCI TRIAL TARGETING HIPPOCAMPAL OVERACTIVITY FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE WITH AGB101: BASELINE TAU AND MRI IMAGING CHARACTERISTICS. R. Mohs[1], S. Rosenzweig-Lipson[1], A. Bakker[2], E. Chang[2], N. Rani[2], R. Barton[1], M. Gallagher[1,2] *(1. AgeneBio, Inc - Baltimore (United States), 2. Johns Hopkins University - Baltimore (United States))*

Background: No effective therapies exist to halt or reverse Alzheimer's Disease (AD). With a predicted prevalence of AD cases rising to over 100 million worldwide by 2050, the need for such therapy is urgent. Novel therapies are primarily focused on patients with amnestic mild cognitive impairment (aMCI) due to AD, recognized as a prodromal phase between normal aging and a clinical diagnosis of dementia, as interventions will likely confer the greatest clinical benefit during the early phases of the disease. In addition to tau and amyloid accumulation, hippocampal hyperactivity has been recognized as a characteristic feature of aMCI with strong evidence from both studies of animal models and humans observing that hyperactivity in neuronal circuits contributes to the accumulation and spread of AD pathology and forecasts subsequent cognitive decline. Clinical studies in patients with aMCI have demonstrated that treatment with low dose levetiracetam normalizes hippocampal hyperactivity and improves memory function in these patients (Bakker et al., 2012). The HOPE4MCI trial is a randomized placebo-controlled study of AGB101, a once daily extended-release formulation containing 220 mg of levetiracetam (NCT03486938). **Objectives:** The objective of the HOPE4MCI study is to examine the efficacy of AGB101 compared to placebo in patients with aMCI due to AD using the Clinical Dementia Rating Scale Sum of Boxes score as well as secondary functional and cognitive measures. In addition, the HOPE4MCI trial includes several cutting-edge biomarker measures including longitudinal structural magnetic resonance imaging (MRI), and longitudinal FMK-6240 PET measures of tau in a subset of participants. **Methods:** The HOPE4MCI trial is a multicenter randomized, double-blind placebo-controlled 78-week, fixed dose study of AGB101. Participants are between 55-85 years old, meeting NIA-AA criteria for MCI due to AD based on a corroborated subjective memory complaint, objective memory impairment, and amyloid positivity by PET scan. **Results:** The HOPE4MCI trial is fully enrolled with 164 participants meeting criteria for aMCI due to AD and is expected to complete data collection by the end of 2022. A subgroup of 49 participants completed both structural MRI and FMK-6240 tau PET at baseline. Image analysis of the structural MRI data was completed using Freesurfer generating volumetric measures of the hippocampus, entorhinal cortex, and amygdala and measures of cortical thickness of the entorhinal cortex, areas that show neurodegeneration as a function of disease progression in aMCI. In addition, volume and cortical thickness were obtained for control areas where primary disease related neurodegeneration has not been observed. FMK-6240 Tau PET analysis was similarly completed using Freesurfer, generating measures of tau accumulation in the hippocampus, entorhinal cortex, and amygdala. Previous work using the FMK-6240 tau marker has shown that tau accumulation in these regions can be used to assess disease progression consistent with Braak staging (Pascoal et al., 2020). Results will be presented to show convergence of biomarkers with associations between regional tau accumulation and localized neurodegeneration particularly in the entorhinal cortex. These results will be presented in the context of cognitive and functional measures obtained from these participants

establishing a richly characterized sample of patients with aMCI. **Conclusion:** The current study includes multiple measures relevant to dementia due to AD in a prodromal condition recognized as transitional between normal aging and progression to a clinical AD diagnosis. The use of additional biomarkers in the subset of patients is informative for further characterization of MCI due to AD. The association between structural MRI and FMK-6240 Tau PET in this sample will also be informative bridging to the full dataset of 164 enrollees in which structural MRI was obtained in all participants. In addition, the imaging biomarkers were also obtained within-subject at the end of the 78 week protocol providing additional opportunities to examine change in these measures as a function of treatment (AGEB 101 compared to placebo). **References:** Bakker A, Krauss GL, Albert MS, Speck CL, Jones LR, Stark CE, Yassa MA, Bassett SS, Shelton AL, Gallagher M. Reduction of hippocampal hyperactivity improves cognition in amnestic mild cognitive impairment. Neuron. 2012 May 10;74(3):467-74. Pascoal TA, Therriault J, Benedet AL, Savard M, Lussier FZ, Chamoun M, Tissot C, Qureshi MNI, Kang MS, Mathotaarachchi S, Stevenson J, Hopewell R, Massarweh G, Soucy JP, Gauthier S, Rosa-Neto P. 18F-MK-6240 PET for early and late detection of neurofibrillary tangles. Brain. 2020 Sep 1;143(9):2818-2830.

OC26- DESIGN OF THE ABCA1 AGONIST CS6253 PHASE 1 SAD AND MAD STUDY IN MALE AND FEMALE, APOE4 AND NON-APOE4 CARRIERS TO ASSESS SAFETY, PK AND BIOMARKER EFFICACY.

J. Johansson[1], H. Yassine[2], D. Michaelson[3], H. Zetterberg[4], J. Cummings[5], B. Winblad[6] *(1. Artery Therapeutics, Inc. - San Ramon (United States), 2. USC - Los Angeles (United States), 3. Tel Aviv University - Tel Aviv (Israel), 4. U of Gothenburg - Gothenburg (Sweden), 5. U Nevada Las Vegas - Las Vegas (United States), 6. Karolinska Insitute - Stockholm (Sweden))*

Background: Apolipoprotein E (APOE) ε4 genotype, the main genetic late-onset Alzheimer's disease (AD) risk factor, is characterized by the apoE4 protein (as opposed to apoE3) having impaired interaction with astrocyte's ATP-binding cassette transporter A1 (ABCA1). The ABCA1 agonist CS6253 appears to correct this deficit. Current anti-amyloid AD-therapies in development have ARIA side effects in the APOE4 carriers and development of alternative therapies is warranted. The CS6253 IND is now open and a Phase 1 Single Ascending dose (SAD) and Multiple Ascending Dose (MAD) study has been designed to assess safety, PK and efficacy in male and female subjects with and w/o APOE4. Efficacy assessment will be guided by results from mice pharmacology studies and cynomolgus monkey studies showing CS6253 effects on lipoprotein and AD variables related to neuron protection and cognition. **Methods:** SAD: In 4-6 cohorts of 8 subjects (6 active: 2 placebo) CS6253 starting with 1 mg/kg will be administered and plasma and CSF collected simultaneously over 24 hours to assess PK and effect markers. MAD: In 3-4 cohorts of 8 subjects (6 active: 2 placebo) CS6253 will be administered starting with 75% of the SAD maximum tolerated dose. Prior to dosing and in conjunction with the 4th/last dose, plasma and CSF will be collected simultaneously over 24 hours. PK will be analyzed by LC-MS. Plasma and CSF will be analyzed by ELISA for ApoE and Ab42/40 (Simoa). **Results:** In APOE4 targeted replacement mice CS6253 20 mg/kg QOD ip for 6 weeks increased plasma apoE 37% ($p<0.05$). In cynomolgus monkeys CS6253 10 mg/kg IV single and repeat 4 doses increased plasma apoE with concomitant increase in plasma Ab42/40-ratio (all $p<0.05$). Human SAD results are expected the summer of 2023 and human MAD data the fall of 2023. **Conclusion:** The Phase 1 SAD and MAD study of the ABCA1 agonist CS6253 treatment will evaluate safety, PK and biomarker efficacy in male and female subjects with and w/o APOE4. Simultaneous collection and analysis in plasma and CSF of PK and of PD markers including apoE and Ab42/40-ratio will assess clinical potential for this cholesterol-targeting treatment of hereditary APO4-associated AD.

OC27- SIGNIFICANT EFFECTS OF ORAL ALZ-801 ON PLASMA BIOMARKERS OF ALZHEIMER'S DISEASE: 12-MONTH INTERIM ANALYSIS OF PHASE 2 BIOMARKER STUDY IN APOE4 CARRIERS WITH EARLY AD.

S. Abushakra[1], J. Hey[1], K. Blennow[2], P. Scheltens[3], J. Hort[4], K. Sheardova[5], N. Prins[6], S. Rutgers[6], P. Dautzenberg[7], L. Pazdera[8], P. Kesslak[1], A. Power[1], M. Tolar[1] *(1. Alzheon Inc. - Framingham, Ma (United States), 2. Gothenburg University, Institute of Neuroscience & Physiology - Molndal (Sweden), 3. Amsterdam University Medical Center - Amsterdam (Netherlands), 4. Charles University Dept. of Neurology - Prague (Czech Republic), 5. St. Anne University Hospital & International Clinical Research Center - Brno (Czech Republic), 6. Brain Research Center - Amsterdam (Netherlands), 7. Brain Research Center - Den Bosch (Netherlands), 8. Vestra Research Clinic - Rychnov Nad Kněžnou (Czech Republic))*

Background: ALZ-801 (valiltramiprosate) is in development as an oral disease-modifying treatment for Alzheimer's disease (AD). ALZ-801 is a brain-penetrant, small molecule inhibitor of amyloid oligomer formation. A fully enrolled Phase 2 study is ongoing in APOE4 carriers with Early AD to evaluate ALZ-801 effects on core AD neuropathologies, including plasma biomarkers of beta amyloid (Aβ) and hyperphosphorylated tau (p-tau). A pivotal APOLLOE4 Phase 3 placebo-controlled study is currently enrolling APOE4/4 homozygotes with Early AD. Advances in blood-based biomarker assays of AD support their use to assess efficacy in drug trials. Plasma p-tau, a marker of Aβ-induced neuronal stress and injury, is elevated in AD, and can be detected using new sensitive assays. Agents that inhibit Aβ toxicity in brain are expected to reduce p-tau release into blood. Indeed, the amyloid antibodies lecanemab and aducanumab, at doses that demonstrate clinical efficacy, both showed significant plasma p-tau181 reduction at 18 months. **Objectives:** To evaluate effect of oral ALZ-801 on core AD pathologies including fluid biomarkers (p-tau181, Aβ42, Aβ40), hippocampal volume (HV), and on clinical outcomes over 2 years of treatment. **Methods:** The Phase 2 biomarker study of ALZ-801 is an ongoing, open-label study at 7 sites in the Czech Republic and the Netherlands. Enrolled subjects (MMSE 22-30, CDR-G 0.5 or 1) have either APOE4/4 or APOE3/4 genotype and prior positive amyloid-PET or CSF biomarkers fulfilling A+/T+ criteria. CSF criteria are ratio of CSF Aβ42/40 ≤ 0.061, and p-tau181 ≥ 61 pg/ml. Subjects receive oral ALZ-801 as 265 mg BID tablets over 2 years and undergo serial assessments of plasma, CSF, volumetric MRI (vMRI), cognitive and functional tests. All fluid biomarker analyses are conducted at the Neurochemistry Laboratory of Dr. Blennow (Molndal, Sweden), and blinded to subject's demographics or genotype. CSF biomarker assays are analyzed using Lumipulse (Fujirebio) and plasma assays utilized Simoa platform. vMRI analyses of HV are conducted at Bioclinica/Clario. Cognitive tests include the Rey Auditory Verbal Learning Test (RAVLT: immediate, delayed and recognition memory) and Digit Symbol Substitution Tests (DSST), and

a composite cognitive Z-score is calculated (3-item RAVLT + DSST). Change from baseline analyses performed on the modified intent-to-treat population (mITT) population includes all observed data, using paired t-tests and 2-sided p-values. The primary biomarker outcome is p-tau181 and total HV is the primary imaging outcome. HV atrophy rate on MRI using tensor-based morphometry is measured on each side, and total HV (left + right) atrophy compared to external control subjects from the ADNI database, who are matched for genotype and disease stage. Interim analyses to detect early biomarker effects of ALZ-801 were pre-specified. **Results:** A total of 84 APOE4 carriers enrolled and received ALZ-801, and 80 and 75 subjects completed 26 and 52 weeks, respectively. The mITT population baseline demographics were mean age 69 years, 51% female, MMSE 26.0, CDR-G 0.6, 70% MCI and 30% Mild AD. Plasma p-tau181 reduction was significant at 13 and 26 weeks and reached -41% at 52 weeks (p=0.016). Plasma Aβ42 and Aβ40 showed significant elevation at 13-26 weeks followed by significant reduction at 52 weeks (both -5%, p =0.002 & p=0.005). Reductions of p-tau181/Aβ42 were significant at each time point (-37%% at 52 weeks, p=0.032). Bilateral HV atrophy at 1 year was reduced by 25% compared to the matched ADNI subjects. The composite cognitive test (RAVLT memory scores + DSST) Z-score improved significantly at 13 and 26 weeks (p=0.002, 26 weeks), and remained numerically above baseline at 52 weeks. The effects on the 3-item RAVLT memory test showed significant correlations to effects on left HV (correlation coefficient 0.3, p=0.01). Most common adverse events were mild nausea and COVID infection, with no drug-related serious events and no events of ARIA-E in 75 subjects at 52 weeks. **Conclusions:** This 1-year interim analysis of ALZ-801 in APOE4 carriers with Early AD shows significant, progressive, and sustained reduction of plasma p-tau181, reaching a robust 41% reduction at 52 weeks. The time course of Aβ42 and Aβ40 changes in plasma suggests clearance of soluble Aβ monomers from brain to plasma, with significant reduction at 52 weeks. These effects are consistent with the molecular mechanism of ALZ-801, namely preventing the formation of soluble toxic amyloid oligomers. The cognitive composite outcome showed initial symptomatic improvement over 26 weeks followed by stability at 1 year compared to baseline. Reduction of hippocampal atrophy compared to matched controls suggests a neuroprotective effect on brain volume and showed significant correlation to memory benefits. The convergence of positive effects on plasma biomarkers, hippocampal volume and clinical benefits supports the disease modifying profile of ALZ-801. These data strengthen the case for a Phase 3 study in APOE4 carriers. The favorable safety, low risk of ARIA-E, and convenience of a simple oral regimen, make ALZ-801 an attractive potential disease-modifying treatment with wide access for AD patients, and very suitable for future AD prevention trials.

OC28- MEASURES OF CORTICAL MICROSTRUCTURE ARE LINKED TO AMYLOID PATHOLOGY IN ALZHEIMER'S DISEASE. N. Spotorno[1], O. Strandberg[1], G. Vis[2,3], E. Stomrud[1], M. Nilsson[2,4], O. Hansson[1] *(1. Clinical Memory Research Unit, Department Of Clinical Sciences, Lund University - Lund (Sweden), 2. Diagnostic Radiology, Institution For Clinical Sciences, Lund University - Lund (Sweden), 3. Memory Clinic, Skåne University Hospital - Malmö (Sweden), 4. Memory Clinic, Skåne University Hospital - Malmö (Sweden))*

Background: Markers of downstream events are a key component of clinical trials of disease-modifying therapies for Alzheimer's disease, especially during later stages to monitor the response of the participants to the treatment. Clinical and cognitive scores are the most obvious primary outcome measures at this point. However, when targeting upstream pathological events, such as Aβ misfolding and accumulation, therapies will likely be more effective during pre-symptomatic or prodromal disease stages before overt and irreversible neurodegeneration become more evident. In this context, clinical readout might become more challenging and putative makers will be of critical importance. Morphological metrics like cortical thickness are established measures of atrophy but are not sensitive enough to detect Aβ-related changes that occur before overt atrophy become visible. Objectives. We aimed to investigate to what extent diffusion MRI can provide sensitive markers of cortical microstructural changes and to test their associations with multiple aspects of the Alzheimer's disease pathological cascade, including both Aβ and tau accumulation, astrocytic activation and cognitive deficits. **Methods:** We applied the mean apparent diffusion propagator model (MAP-MRI) to diffusion MRI data from 492 cognitively unimpaired elderly and patients with mild cognitive impairment from the Swedish BioFINDER-2 cohort. Participants were stratified in Aβ-negative/tau-negative, Aβ-positive/tau-negative, and Aβ-positive/tau-positive based on Aβ- and tau-PET uptake. Cortical regional values of MAP-MRI metrics and cortical thickness were compared across groups. Associations between regional values of MAP-MRI metrics and both Aβ- and tau-PET uptake were also investigated along with the association with plasma level of glial fibrillary acidic protein (GFAP), a marker of astrocytes activation (available in 292 participants). **Results:** Mean square displacement (MSD) from MAP-MRI revealed widespread microstructural differences already between Aβ-negative/tau-negative and Aβ-positive/tau-negative participants with a spatial distribution that closely resembled the pattern of Aβ accumulation, including retrosplenial regions extending to the precuneus, neocortical temporal regions, as well as rostral anterior cingulate and rostral middle frontal cortex (p-values FDR corrected, $p < 0.05$, standardized-β coefficients range: 0.18 – 0.30). In contrast, differences in cortical thickness were clearly more limited (only entorhinal cortex, parahippocampal gyrus and temporal pole p-values FDR corrected, $p < 0.05$). MSD was also highly correlated with both Aβ- and tau-PET uptake even independently from one another and independently from cortical thickness. Further, analysis focusing on a composite ROI encompassing regions that accumulate Aβ early in the disease process confirmed MSD exhibited significantly stronger correlations with Aβ-PET uptake than cortical thickness (significant difference between the β coefficients of MSD and cortical thickness: $p < 0.01$). Similar results were found when focusing on a temporal meta-ROI where MSD was more strongly associated to tau-PET uptake than cortical thickness ($p<0.01$). Regional MSD values were also positively correlated with the glial marker GFAP with a pattern that resemble Aβ accumulation (standardized-β coefficients range: 0.14 – 0.20), and GFAP partially mediated the association between Aβ accumulation and MSD. Further, impairments in executive functions were significantly more associated with MSD extracted from the early-Aβ meta-ROI than with cortical thickness ($p<0.05$). Similarly, impairments in memory functions were significantly more associated with MSD extracted from the temporal meta-ROI, than with cortical thickness ($p<0.05$). Further longitudinal analyses to investigate the possible use of diffusion MRI for tracking disease changes over time are undergoing and the results will be presented at the conference. **Conclusions:** Metrics of cortical microstructural

alteration derived from diffusion MRI are highly sensitive to multiple aspects of the Alzheimer's disease pathological cascade. Of particular interest is the link between MSD, Aβ-PET and GFAP which suggests that MSD might reflect microstructural changes related to the astrocytic response to Aβ aggregation. Therefore, MSD might be an important outcome measure in anti-Aβ treatments clinical trials for detecting drug-induced changes in early Aβ-related microstructural changes. **Competing interest:** The corresponding author has no competing interests to report.

OC29- A BRIEF, AUTOMATED SPEECH-BASED SCREENER FOR MILD COGNITIVE IMPAIRMENT TO SUPPORT ONLINE RECRUITMENT AT SCALE. C. Skirrow[1], J. Weston[1], M. Meszaros[1], U. Meepegama[1], E. Fristed[1] *(1.Novoic - London (United Kingdom))*

Background: Cognitive changes occurring during the early stages of Alzheimer's disease (AD) are reflected in how someone speaks, where sensitive patterns can be extracted using audio- and text-based machine learning models. Automated speech-based testing makes an excellent candidate for at-scale screening and recruitment into larger research projects and clinical trials. Participants can self-administer tests at home in a few minutes using a range of personal mobile devices. Recorded speech samples can be automatically analysed to produce sensitive diagnostic screening data, which can facilitate onward referral for further clinical evaluation in key participant groups. **Objectives:** Develop a short, automated speech-based AI system to screen for MCI based on automatically transcribed speech alone. **Methods:** Data was taken from the AMYPRED-UK (NCT04828122) and AMYPRED-US (NCT04928976) studies, comprising 200 participants age 54-85 with established amyloid beta (Aβ) and clinical diagnostic status (MCI, mild AD or cognitively unimpaired). Participants engaged in optional remote once-daily speech-based assessments for up to 8 days using their own smart devices. Assessments included the Automatic Story Recall Task (ASRT). Responses were recorded and then transcribed manually and using an out-of-the-box Automatic Speech Recognition (ASR) system. Data was extracted from two immediate and one delayed recall of two short ASRT stories administered in the same test session, to emulate a brief screening set-up. Differences in the original story source text and transcribed participant retelling were evaluated via a generalized matching score ("G-match"). G-match is computed in Python as the weighted sum of the cosine similarity between the embeddings of ASRT source text and the transcribed retellings. G-match was evaluated separately for manual and ASR transcribed speech data, in the full sample and after restriction of the cognitively impaired group to those with MCI only. Logistic regression models were trained to predict clinical labels (MCI/mild AD vs. cognitively unimpaired) using 5-fold cross-validation, producing Receiver Operating Curve (ROC) outputs. 95% confidence intervals for Area Under the Curve (AUC) were computed using the standard error of the 5-fold AUC samples. The ASRT models were evaluated relative to a demographic comparison (combining age, gender and years in education), and the Preclinical Alzheimer's Clinical Composite with semantic processing (PACC5), a more extensive supervised clinical assessment battery. The reduction in in-person clinical assessment required with pre-screening using G-match was evaluated in a simulated US population sample age 65+ (MCI prevalence 15.4%), using the sensitivity and specificity of the G-match model for differentiating MCI and cognitively unimpaired participants. **Results:** The participant sample completing the abbreviated test battery, and included in the current analysis comprised 96 adults (N=55 cognitively unimpaired, N=34 MCI, N=7 mild AD; N=48 Aβ positive, N=48 Aβ negative; 51 female, 45 male). The abbreviated assessment battery collected an average of 2.4 minutes of speech per participant. G-match of the brief test battery showed good prediction of MCI/mild AD status using ASR transcripts with AUC=0.87 +/- 0.03. Results remained consistent when restricting analyses to comparisons between MCI and cognitively unimpaired participants alone with AUC=0.82 +/- 0.04. Differences between ASR and manually transcribed data were not statistically significant ($p \geq 0.33$). G-match models were significantly superior to random performance ($p \leq 0.001$), and outperformed the demographic comparison ($p \leq 0.01$). PACC5, a longer, multi-task battery evaluated in-person during a clinical assessment, outperformed G-match for the analysis restricted to the MCI and cognitively healthy group alone (AUC=0.91 +/-0.04, p=0.02), but not for the combined MCI/mild AD group (p=0.26). Screening based on G-match (ASR transcription; sensitivity 0.94 and specificity=0.54 at Youden's index) was simulated in a population sample age 65+. For a targeted sample of MCI patients for research, the ASRT system screening is estimated to reduce the number of in-depth clinical assessments required by 43.2%, but require 5.9% more participants at the recruitment and screening stage. **Conclusion:** Combined with an advanced AI language model, brief speech-based testing offers simple and accessible screening for MCI. Such testing could be used at scale to screen for appropriate patients for treatment, research and clinical trials. The ASRT system does not require trained personnel or specialist equipment and could help to reduce the costs of clinical trials by enriching recruited samples. The ASRT system has potential to reduce the quantity of more in-depth clinical assessments required, reducing clinical resource bottlenecks and costs of research and clinical trials. **Funding and competing interests:** All authors are employees of Novoic and option holders or shareholders of Novoic.

OC30- AB-STRUCTURE AS PRECISE RISK PLASMA BIOMARKER FOR FUTURE CONVERSION TO ALZHEIMER´S DISEASE 17 YEARS IN ADVANCE. K. Gerwert[1,2] *(1. Ruhr-University Bochum - Bochum (Germany), 2. Center for Protein Diagnostics (ProDi) - Bochum (Germany))*

Background: The identification and validation of early-stage biomarkers is coming into focus. Especially, early stage diagnosis in a symptom-free stage before significant amyloid plaques have been formed might provide the best therapy response. In recent years, the development of highly sensitive analytical methods enabled the identification of non-invasive and low costs blood-based biomarkers. Blood-based biomarkers allow beside expensive PET scans and invasive CSF measurements pre-screening of the elder population. In contrast to the widely studied concentration-based analyses of Aβ and P-tau biomarkers in body fluids we have examined Aβ and tau misfolding as structure biomarkers. The misfolding of Aβ from a monomeric/unstructured to a β-sheet enriched isoform is one of the earliest events in AD pathogenesis. With the patented infrared-immuno-sensor (iRIS) we are able to measure the secondary structure distribution of all Aβ isoforms as structure biomarker (1). Initial misfolding of Aβ takes place about 15-20 years before AD is clinically diagnosed and is followed by β-sheet oligomerization and aggregation to much larger fibrils on the nanometer scale. After several years, this Aβ misfolding

becomes visible at the macroscopic scale as deposits in large amyloid plaques. We have shown in a discovery study that the structure biomarker indicates probable Alzheimer's disease in a prospective cohort (1). We extended this to prodromal AD in the BioFINDER cohort (2). Furthermore, we have shown that the structure biomarker is prognostic and predicts the conversion to AD in older adults in the population based ESTHER cohort 14 years in advance (2). There was an added value when including APOEe4 as risk factor for identifying preclinical AD states 14 years before disease onset increasing the AUC over 0.87 (3). Additionally, the combination of other biomarkers such as tau misfolding in CSF or plasma Aβ42/40 showed added values as well. Analyzing tau misfolding in CSF and Aβ misfolding in plasma increases the sensitivity to 89% and specificity up to 97% as compared to clinical diagnosis (4). Beside the general threshold <1644 cm-1 indicating abnormal misfolding in diseased individuals, a second threshold >1646 cm-1 was introduced indicating a normal Aβ secondary structure distribution as observed in individuals without AD (4). Frequencies between both thresholds indicate low misfolding. This analysis enables the risk stratification by means of the misfolding status as already proven on SCD subjects from the Amsterdam dementia cohort (5). **Objectives:** We investigated the performance of Aβ misfolding as a prescreening plasma biomarker for AD development in a population based cohort up to 17 years before clinical manifestation. Additionally, the performance was compared to the concentration biomarkers GFAP, NfL and P-tau181 measured with SIMOA (6). **Methods:** Baseline plasma samples of 308 subjects taken between 2000-2002 were analyzed using the infrared-immuno sensor (iRIS). The obtained structure biomarker results were compared with GFAP, P-tau181 and NfL levels obtained by the SIMOA platform. **Results:** Baseline plasma analysis revealed significant differences for all plasma biomarkers in AD subjects compared to the controls. Additionally, the misfolding biomarker showed the best prognostic performance at 17-year follow-up relative to all concentration biomarkers. Furthermore, a biomarker panel of Aβ misfolding and GFAP levels showed an added value. Interestingly, the prognostic performance of P-tau181 was limited to 8 years before symptom onset. It could not predict AD conversion more than 8 years in advance. **Conclusions:** Aβ misfolding allows the identification of individuals who will develop AD up to 17 years before clinical manifestation. This highlights the potential of the misfolding biomarker as a simple blood biomarker and as a screening method for the aging population, analyzing symptom-free stages and determining the risk of future AD development. Thus, prevention and early intervention of Alzheimer's can be achieved. **References:** 1. Nabers A, et al. J.Biophotonics. 2016;9(3):224-34. 2. Nabers A, et al. EMBO.Mol.Med. 2018May;10(5). 3. Stocker H, et al. Alzheimer's and Dementia. 2020;16:283–91. 4. Nabers A, et al. Alzheimer's and Dementia (Amst). 2019 Mar 12;11:257-263. 5. Stockmann J and Verberk I et al. Alz Res and Ther. 2020, 6. Beyer L and Stocker H, et al. Alzheimer's and Dementia. 2022, in press

OC31- NVG-291 PHASE 1 RESULTS AND PHASE 1B/2A STUDY DESIGN IN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT OR MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE.

D. Mikol[1], J. Toews[1], M. Farlow[2], B. Lamb[2], G. Perry[3], R. Sperling[4], M. Weiner[5], H. Zetterberg[6], J. Cummings[7] *(1. Nervgen - Vancouver (Canada), 2. Indiana University School Of Medicine - Indianapolis (United States), 3. University Of Texas, San Antonio - San Antonio (United States), 4. Harvard Medical School - Cambridge (United States), 5. University Of California, San Francisco - San Francisco (United States), 6. University Of Gothenburg - Gothenburg (Sweden), 7. University Of Nevada, Las Vegas - Las Vegas (United States))*

Background: Chondroitin sulfate proteoglycans (CSPGs) are increased at sites of central nervous system (CNS) damage, including regions with beta-amyloid plaques and neurofibrillary tangles of Alzheimer's disease (AD). CSPGs inhibit neural repair mechanisms, in part through their interaction with the receptor protein tyrosine phosphatase sigma (PTPσ). NVG-291 is a subcutaneously (SC) administered peptide that modulates PTPσ. In various animal models of CNS damage, NVG-291 treatment resulted in functional improvements due to enhanced axonal regeneration, plasticity, and remyelination. It is hypothesized that NVG-291 treatment of individuals with impaired cognition due to AD will lead to improved function of CNS neurons as a result of enhanced plasticity and strengthened synaptic connections, which may be measured using functional brain imaging techniques. **Objectives:** Present Phase 1 results (healthy subjects) and Phase 1b/2a study design (subjects with mild cognitive impairment or mild dementia due to Alzheimer's disease). **Methods:** The single ascending dose (SAD) portion of the Phase 1 trial in healthy subjects enrolled 37 subjects in 6 dose cohorts of NVG-291 or placebo. The multiple ascending dose (MAD) portion of the study is dosing up to 18 subjects randomly assigned into 3 dose cohorts to receive NVG-291 or placebo SC once-daily for 14 days. Additional subjects treated with open-label NVG-291 are undergoing cerebrospinal fluid (CSF) analysis to measure NVG-291 concentration. NVG-291 doses being investigated in the MAD portion of the study exceed human equivalent levels that showed efficacy in animal models. The primary objective of the multicenter Phase 1b/2a trial is to assess the safety, tolerability and pharmacokinetic profile of NVG-291 in subjects with AD. Secondary objectives are to investigate the biological effects of NVG-291 by assessing change in the standardized uptake value ratio of 18F-fluorodeoxyglucose (18FDG) in a pre-specified region of interest and by voxel-based subtraction analysis using 18FDG-positron emission tomography; and to assess change in cognition using the AD Assessment Scale-Cognitive Subscale (ADAS-Cog) 13 and Clinician Interview-Based Impression of Change, plus caregiver interview (CIBIC-plus). Exploratory objectives include assessment of cerebral resting state functional connectivity using functional magnetic resonance imaging Blood Oxygenation Level Dependent (BOLD) sequences and to assess episodic/working memory, reaction time, learning, executive function and activities of daily living using additional cognitive instruments. The Phase 1b/2a trial will enroll ~80 subjects aged 55-85 with mild cognitive impairment or mild dementia due to AD, mini-mental state exam score 22-28, abnormal paragraph recall, and evidence of AD biology. Subjects will be randomized 1:1 to NVG-291 or placebo administered by daily SC injection x 12 weeks, followed by no intervention for 12 weeks. **Results:** NVG-291 has been safe and well-tolerated through 6 completed SAD cohorts and two completed MAD cohorts. In the SAD cohorts, all adverse

events (AEs) were mild and transient; the most common AE was injection site related. Blinded analysis of safety in the MAD (dose cohorts 1 and 2) has shown that AEs were mild except for a single event of moderate migraine; the most common AE was injection site related. There were no serious AEs, and no effect on vital signs or ECGs in any subjects, and NVG-291 has shown promising pharmacokinetic characteristics. **Conclusion:** NVG-291 appears well tolerated after administration of multiple ascending doses in healthy subjects. Upon completion this year, the Phase 1 study will establish the safety/tolerability/pharmacokinetics of NVG-291 to support advancement to the Phase 1b/2a clinical trial in subjects with mild cognitive impairment or mild dementia due to AD. The Phase 1b/2a study in AD will assess change in functional and advanced structural imaging measures and cognition following treatment, with the trial expected to initiate in late 2022. **Disclosures:** DM and JT are employees of NervGen. MF, BL, GP, RS, MW, HZ, and JC are paid consultants of NervGen

OC32- INTRODUCTION TO THE VERI-T TRIAL: A PHASE 1 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER TRIAL OF VERDIPERSTAT IN PATIENTS WITH SVPPA DUE TO FTLD-TDP. P. Ljubenkov[1], A. Staffaroni[1], L. Vandevrede[1], J. Rojas-Martinez[1], M. Koestler[1], A. Porsteinsson[2], M.B. Pascual[3], J. Masdeu[3], I. Grant[4], D. Irwin[5], D. Knopman[6], R. Bowser[7], M. Grossman[5], I. Qureshi[8], A. Boxer[1] *(1. UCSF Memory and Aging Center - San Francisco (United States), 2. University of Rochester - Rochester (United States), 3. Houston Methodist - Houston (United States), 4. Northwestern University - Chicago (United States), 5. University of Pennsylvania - Philadelphia (United States), 6. Mayo Clinic Rochester - Rochester (United States), 7. Barrow Neurological Institute - Phoenix (United States), 8. Biohaven Pharmaceuticals - New Haven (United States))*

Background: Nuclear depletion and cytoplasmic accumulation of TAR DNA-binding protein 43 (TDP-43) is a major cause of dementia, present in about 20% of patients with Alzheimer's disease and about half of patients with frontotemporal dementia. There is currently an unmet need for dementia clinical trials targeting sporadic TDP-43 pathology, but TDP-43 mislocalization is typically difficult to diagnose prior to autopsy. The semantic variant of primary progressive aphasia (svPPA) is over 80% predictive of frontotemporal lobar degeneration with TDP-43 mislocalization (FTLD-TDP) and is thus an ideal cohort in which to conduct the first wave of therapeutic trials targeting sporadic TDP-43 pathology. Potential therapeutic targets in FTLD-TDP include oxidative stress, which promotes mislocalization of TDP-43 in neurons. Verdiperstat is a potent, oral, CNS-penetrant, myeloperoxidase inhibitor that reduces production of oxidative species from microglia. The Veri-T trial (NCT05184569) will explore the therapeutic potential of verdiperstat in the first clinical trial to focus on patients suffering from svPPA. The Veri-T trial is also the first clinical trial to leverage the recruitment resources of the ARTFL LEFFTDS Longitudinal FTLD (ALLFTD) research network of clinical centers. **Objectives:** The primary objective of this study is to determine the safety and tolerability of verdiperstat in patients svPPA due to FTLD-TDP. The secondary objective of this study is to determine the pharmacokinetic (PK) profile of verdiperstat in patients with svPPA. Exploratory objectives will include investigation of verdiperstat's effects on candidate pharmacodynamic markers and candidate markers of efficacy for future trials in patients with FTLD-TDP. Exploratory endpoints include plasma myeloperoxidase activity, cerebrospinal fluid (CSF) biomarkers of glial activity (chitinase-family proteins), neurodegeneration (neurofilament light chain), and unbiased CSF proteomics (via SOMAmer reagent assays), as well as volumetric MRI changes unique to svPPA, and cognitive and language impairment measures assessed via ALLFTD's Smartphone app. **Methods:** This is a multisite, phase 1, randomized, double-blind, placebo-controlled trial. N=64 participants with svPPA will be randomized 1:3 to placebo or oral verdiperstat (titrated to a dose of 600mg BID) for 6 months of double-blind therapy. Neuropsychological assessments, plasma and CSF, and volumetric brain imaging will be collected prior to and upon conclusion of treatment. Recruitment will occur at 5 ALLFTD research network clinical centers. **Results:** The first participant was randomized April 19th, 2022 and recruitment remains ongoing. To date, no dose-limiting toxicities have occurred. **Conclusion:** The Veri-T trial examines the safety, tolerability and pharmacokinetic properties of verdiperstat in svPPA and explores novel pharmacodynamic biomarkers and outcome measures that could be employed in future efficacy studies targeting sporadic FTLD-TDP.

OC33- A PHASE 1, OPEN-LABEL, 52-WEEK, MULTICENTER STUDY TO EVALUATE THE SAFETY AND BIOCHEMICAL EFFICACY OF AAV GENE THERAPY (LX1001) IN PATIENTS WITH APOE4 HOMOZYGOTE ALZHEIMER'S DISEASE – INTERIM DATA. M. Kaplitt[1], P. Leopold[2], E. Noch[3], J. Ivanidze[4], L. Chazen[4], R. Crystal[2], S. Kaminsky[2], H. Bowe[2], M. Wang[2], D. Ballon[4], J. Dyke[4], D. Sondhi[2], S. Gandy[5], G. Giannantoni-Ibelli[6], J. Barth[6] *(1. Department of Neurological Surgery, Weill Cornell Medical College - New York (United States), 2. Department of Genetic Medicine, Weill Cornell Medical College - New York (United States), 3. Department of Neurology, Weill Cornell Medical College - New York (United States), 4. Department of Radiology, Weill Cornell Medical College - New York (United States), 5. Departments of Neurology and Psychiatry, Icahn School of Medicine at Mt Sinai - New York (United States), 6. LEXEO Therapeutics, Inc. - New York (United States))*

Background: Alzheimer's disease (AD), a progressive neurodegenerative disorder, is associated with a strong genetic risk resulting from polymorphisms of the apolipoprotein E (APOE) gene. The APOE4 allele is a well-recognized genetic risk factor for late-onset AD. While this allele increases risk and reduces the age of AD onset, the E2 allele decreases risk and delays the age of AD onset. APOE4 homozygotes have a 15-fold greater risk of developing AD compared with the APOE3 homozygotes, the most common genotype. The marked reduction in AD risk among APOE2/E4 heterozygotes suggests a potential protective effect of APOE2, yet only 5% of the population carry an APOE2 allele. LX1001 is an adeno-associated viral vector (AAV) investigational gene therapy (AAVrh.10hAPOE2) designed to deliver the protective apolipoprotein E2 (APOE2) gene into the central nervous system of APOE4 homozygous AD subjects in order to halt or slow the disease progression, mediated by the APOE4 allele. **Objectives:** The primary objective of this first-in-human trial is to evaluate the safety of LX1001 administered into the cerebrospinal fluid (CSF) at the craniocervical junction (via CT-guided C1-C2 or intracisternal route), given the equipoise regarding the potential effects of both overexpressing APOE2 in the AD brain and of widespread CSF delivery of AAV vectors in the degenerating human brain. This trial is also designed to evaluate the feasibility of converting CSF from the APOE4 homozygous profile to an APOE4/E2 profile as a biomarker

of successful gene delivery. Additional secondary endpoints include analysis of other CSF AD biomarkers, including Aß42, total tau (T-tau), and phosphorylated tau (P-tau) along with amyloid-targeted PET, structural MRI imaging, and cognitive tests. **Methods:** This is a Phase 1, open label, dose-finding study evaluating the safety and tolerability of LX1001 in AD. LX1001 is being evaluated in three ascending single-dose cohorts (5.0E10, 1.6E11 and 5.0E11 gc/ml CSF), with the dose for each subject determined based on CSF volume measured by MRI. Each of 3 dose cohorts consists of ~5 APOE4 homozygotes. Enrollment criteria include APOE4 homozygous genetic profile, age 50 years or older, positive amyloid-targeted PET, CSF biomarkers consistent with AD, and mild cognitive impairment to mild or moderate dementia due to AD. After completing this study, subjects are invited to enroll into an extension study for evaluation of long-term safety and efficacy for an additional 4 years post gene transfer. **Results:** A total of five subjects were dosed in the low-dose (5E10 gc/ml CSF) cohort. Based on data available to date, among all subjects in cohort 1 (n=5, age 59-73 years, with MCI or moderate dementia due to AD), treatment with LX1001 was well-tolerated with no serious adverse events reported to date. Follow-up data for evaluation of efficacy are available for 4 subjects, aged 59-73 years, with MCI or moderate dementia due to AD. Preliminary data for cohort 1 demonstrated that post-vector administration APOE2 was expressed in CSF in all 4 subjects with follow-up data ≥ 3 months. Both subjects with 12-month data demonstrated a decline in the CSF T-Tau and P-Tau. One subject showed a CSF T-Tau reduction from baseline over 12-months of ~20% and CSF P-Tau reduction of ~9%. The other subject showed a CSF T-Tau reduction from baseline over 12-months of ~4% and CSF P-Tau reduction of ~14%. **Conclusion:** LX1001 is the first investigational gene therapy to directly address APOE, a well-recognized genetic risk factor of AD. Initial data in the low-dose cohort supports technical feasibility of conferring APOE2 expression in the CNS of human APOE4 homozygotes and indicates that there were no serious adverse events from either CSF delivery of LX1001 or from documented expression of APOE2 in these subjects. These data support further exploration of APOE2 gene therapy as a potential therapeutic for APOE4 homozygous AD patients. **Conflicts of Interest:** None at this time.

OC34- PRELIMINARY EVIDENCE FOR RELIABILITY AND VALIDITY OF THE INTERPERSONAL FUNCTIONING AND DAILY ACTIVITIES QUESTIONNAIRE (IFDAQ) IN THE A4/LEARN PRE-RANDOMIZATION SAMPLE.

C.J. Edgar[1], R. Amariglio[2], J.M. Barbone[3], J.M. Chandler[4], S.J. Coons[5], M. Donohue[6], W.R. Lenderking[7], R. Sperling[8]
(1. Cogstate - London (United Kingdom), 2. Departments of Neurology, Brigham and Women's Hospital and Massachusetts General Hospital, Harvard Medical School - Boston (United States), 3. Cogstate - New Haven (United States), 4. Eli Lilly and Company - Indianapolis (United States), 5. Clinical Outcome Assessment Program, Critical Path Institute - Tucson (United States), 6. Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego (United States), 7. Patient-centered Research, Evidera - Bethesda (United States), 8. Department of Neurology, Brigham and Women's Hospital - Boston (United States))

Introduction: There is an unmet need for patient-reported measures reflecting relevant domains of treatment benefit in early Alzheimer's disease (AD) that have been developed using best practices, including appropriate input from persons with Mild Cognitive Impairment (MCI) and caregivers. The Cognition Working Group (WG) of the Critical Path Institute's Patient-Reported Outcome (PRO) Consortium developed a new PRO instrument, intended as a "fit-for-purpose" efficacy endpoint measure in clinical trials in prodromal AD or MCI due to AD. Using a targeted literature review, focus groups, and interviews, concepts of importance for complex activities of daily living (cADLs) and interpersonal functioning (IF) were identified. Using FDA feedback, advice from clinical experts, and concept elicitation interviews in 79 MCI, probable AD and non-impaired controls, and 65 informants, a conceptual framework was developed for a draft measure (the Interpersonal Functioning and Daily Activities Questionnaire (IFDAQ)) that included both cADL (16 items e.g., managing finances and planning skills) and IF domains (10 items e.g., conversational skills) (Gordon et al., 2016). Each item had response options of "Never" (0), "Rarely" (1), "Sometimes" (2), "Often" (3), and "Always" (4) to measure the frequency with which people with early AD experience difficulties in each domain. **Objectives:** To provide initial evidence for the reliability and validity of the IFDAQ using a large dataset derived from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's study (A4) and the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) studies' pre-randomization data. The A4 Study is a secondary prevention trial in preclinical AD and has a companion observational study called LEARN. The A4 study aims to prevent or slow the onset of AD symptoms in healthy adults with amyloid-beta plaque to see if treatment can show a benefit in preventing or slowing cognitive decline i.e., progression from clinical stages 1 and 2 (preclinical) to clinical stage 3 (prodromal or MCI). **Methods:** The IFDAQ was included in A4/LEARN and is part of the assessment schedule for two pre-randomization visits conducted within 90 days of each other (Screening Visits 1 and 3 (Note: Amyloid PET imaging occurred at Screening Visit 2, followed by disclosure of amyloid status)). Analyses were performed on the total score (26 items, range 0-104) and the IF (10 items, range 0-40) and cADL (16 items, range 0-64) subscales. Reliability was evaluated using Cronbach's alpha for internal consistency and ICC (A,1) for test retest. Validity was evaluated using known groups validity (t-test and Cohen's d) at Visit 1 comparing between the group with CDR Global =0 and that with CDR Global =0.5. **Results:** Data were available for a total of N=6203 participants (mean age 71.5 (SD 4.8); 58% female; mean years of education 16.5 (SD 2.93), with IFDAQ data available for N=5402 participants at Visit 1 and N=4264 participants at Visit 3. Item level missing data increased marginally over the length of instrument with a maximum of 4.3% of data missing for the final item (#26). Internal consistency reliability was high for the cADL and IF subscales (α=0.90 (95% CI 0.89, 0.90) and α=0.87 (95% CI 0.87, 0.88), respectively), and the total score (α=0.93 (95% CI 0.93, 0.93)). Test-retest reliability was adequate for the cADL and IF subscales (ICC=0.76 (95% CI 0.75, 0.77) and ICC=0.75 (95% CI 0.74, 0.76), respectively), and the total score (ICC=0.78 (95% CI 0.77, 0.79)). Known groups validity analyses showed statistically significant differences between CDR Global =0 (N=5230) and CDR Global =0.5 (N=101) groups at Visit 1 (unequal variances t-test p<0.001). Higher scores indicating worse participant reported function were seen in the CDR 0.5 group for cADL (Cohen's d=1.06; mean 12.6 (SD 6.79) and mean 16.7 (SD 7.72) respectively), IF (Cohen's d=0.68; mean 10.3 (SD 5.34 and mean 12.4 (SD 6.10) respectively), and the total score (Cohen's d=0.97; mean 22.9 (SD 11.20) and mean 29.2 (SD 12.66) respectively). **Conclusion:** Initial analyses of the IFDAQ in a largely cognitively normal population undergoing screening for the A4 secondary prevention trial in

preclinical AD and the companion observational study LEARN, support its validity and reliability as a PRO measure assessing interpersonal function and complex ADLs. In the know groups validity analyses a larger difference was evident for cADL items versus IF items, which may suggest cADL difficulties were more prominent and/or reflect concept coverage in the CDR. The IFDAQ has potential utility for the measurement of early changes in the frequency with which people with predementia/prodromal AD (clinical stages 1-3) experience difficulties in complex ADLs and interpersonal functioning. **References:** Gordon, M. F. et al. (2016) 'Development of a patient-reported outcome instrument to assess complex activities of daily living and interpersonal functioning in persons with mild cognitive impairment: The qualitative research phase', Alzheimer's and Dementia. doi: 10.1016/j.jalz.2015.04.008. **Disclosures:** Chris J Edgar is a fulltime employee of Cogstate.

OC35- APOE-TARGETED EPIGENOME THERAPY FOR ALZHEIMER'S DISEASE. B. Kantor[1,2], O. Chiba-Falek[1,3] *(1. Duke University - Durham (United States), 2. CLAIRIgene LLC - Durham (United States), 3. CLAIRIgene - Durham (United States))*

Background: There is an urgent need to refocus Alzheimer's disease (AD) drug discovery on new targets and shifting the paradigm of AD drug development towards precision medicine. Apolipoprotein E gene (APOE) is the strongest and most reproducible genetic risk factor for late-onset Alzheimer's disease (LOAD). Moreover, 50% reduction in APOE levels showed beneficial effects in AD cellular and mouse models. Thus, APOE gene holds promise as a potential therapeutics target for LOAD. **Objectives:** In this study we developed an epigenome therapy platform to reduce APOE expression generally and APOEe4 allele specifically by targeted modification of the epigenome landscape within APOE locus. **Methods:** Our gene therapy strategy is based on CRISPR/deactivated (d)Cas9 editing technology fused with an effector molecule and delivered by viral-based vehicles. Our gRNAs were designed to target regulatory elements within the APOE promoter/intron 1 region and in exon 4 sequence overlapping the SNP that defines the APOEe4 allele. We evaluated our epigenome therapy platform in vitro using human hiPSC-derived neurons and in vivo by stereotactic injection of reporter gene into the hippocampus of mice. **Results:** The viral dCas9-repressor vector showed decreased APOE-mRNA and protein overall levels in hiPSC-derived neuronal model. To specifically target the APOEe4 allele we utilized the VRER-dCas9 protein. Evaluation of the system specificity showed a reduction in APOE-mRNA levels in the hiPSC-derived neurons with the e4 allele while there was no effect in the isogeneic hiPSC-derived neurons homozygous for the e3 allele. Moving onto in vivo studies in mice, administration of the viral dCas9-repressor vector and the green fluorescent protein (GFP) reporter gene into the hippocampus showed a significant decrease in GFP expression with strong repression effect, demonstrating promising preliminary data. Collectively, our results provided in vitro and in vivo proof-of-concept for the utility and efficacy of the APOE-targeted epigenome therapy. **Conclusions:** Our epigenome therapy strategy for fine-tuning of APOE expression based on dCas9 technology is translational toward the development of a therapeutics approach to prevent and/or delay LOAD onset. Furthermore, the technology offers the opportunity to refine the platform for the development of gene-specific and even allele- and cell-type- specific therapies, and by that enables the advancement of strategies for precision medicine in LOAD.

OC36- CONFOUNDING FACTORS OF ALZHEIMER'S DISEASE PLASMA BIOMARKERS AND THEIR IMPACT ON CLINICAL PERFORMANCE. A. Pichet Binette[1], S. Janelidze[1], N. Cullen[1], J.L. Dage[2], R.J. Bateman[3], H. Zetterberg[4,5], K. Blennow[1], E. Stomrud[1], N. Mattsson-Carlgren[1], O. Hansson[1] *(1. Clinical Memory Research Unit, Faculty Of Medicine, Lund University - Lund (Sweden), 2. Department Of Neurology, Indiana University School Of Medicine - Indianapolis (United States), 3. Department Of Neurology, Washington University School Of Medicine - St. Louis (United States), 4. Department Of Psychiatry And Neurochemistry, The Sahlgrenska Academy, University Of Gothenburg - Gothenburg (Sweden), 5. UK Dementia Research Institute, University College London - London (United Kingdom))*

Background: Plasma biomarkers will likely revolutionize the diagnostic work-up of Alzheimer's disease (AD). However, before widespread clinical use, it is important to determine which, if any, confounding factors might affect the levels of these biomarkers, and their clinical utility. Here we studied whether common comorbidities, as well as proxies of kidney function (plasma creatinine) and blood volume (body mass index [BMI]) confounded the levels of several state-of-the-art plasma biomarkers for AD and neurodegeneration. **Objectives:** First, we investigated associations between plasma biomarkers levels and comorbidities/medication use, creatinine, and BMI, which allowed us to identify key potential confounding factors. Second, we studied whether the performance of plasma biomarkers was improved when adjusting for such potential confounding factors in two contexts: i) associations between individual plasma biomarkers and their CSF counterparts, and (ii) the ability of plasma biomarkers to predict conversion to AD dementia or all-cause dementia in non-demented individuals. **Methods:** Participants with plasma and CSF biomarkers, creatinine, BMI, and medical history data from the Swedish BioFINDER-1 (n=748) and BioFINDER-2 (n=421) cohorts were included. Beta-amyloid (Ab42, Ab40), phosphorylated tau (p-tau217, p-tau181), neurofilament light (NfL), and glial fibrillary acidic protein (GFAP) were measured in plasma and CSF, using high-performing assays (mass-spectrometry [MS], Meso Scale Discovery or Sioma for plasma and all Elecsys assays for CSF, apart from p-tau217). For plasma Ab, results were validated across three assays, including the WashU-IP-MS. Linear regression models first assessed associations for plasma biomarkers with BMI, creatinine, and comorbidities. Next, we used bootstrapping to assess if models with or without confounding factors as covariates (linear regressions for plasma-CSF correspondence and logistic regressions for progression to dementia) were significantly different. **Results:** In both cohorts, creatinine and BMI, but not comorbidities or medication use, were the main factors associated with plasma biomarkers. Creatinine was positively correlated with NfL and GFAP in both cohorts (average standardized coefficients of 0.2, all $p<0.05$). In BioFINDER-1, creatinine was also positively correlated with p-tau217 and p-tau181 (average standardized coefficients of 0.14, all $p<0.05$). BMI was negatively correlated with NfL, GFAP, and to a lesser extent with p-tau217 and p-tau181 in both cohorts (average standardized coefficients of -0.15, all $p<0.05$). No associations were found with the Ab42/Ab40 ratio. Adjustment for BMI and creatinine had minor effects in models predicting either the corresponding levels in CSF or subsequent development of dementia. In both cohorts, NfL was the main biomarker for which accounting for confounding factors consistently improved the plasma coefficient (by 6 to 10%) in relation to

CSF. Smaller improvements (2-3%) were seen when accounting for confounding factors with the Ab42/Ab40 ratio, only on MS-based assays. Regarding progression to subsequent dementia, plasma p-tau217 and NfL odds ratio were improved by 4.5% to discriminate between stable participants and those progressing to AD dementia or all-cause dementia respectively. However, the discriminative accuracies between models (AUC of 0.82 for p-tau217 and 0.71 for NfL) were virtually the same, with a maximum change in AUC of 0.01. **Conclusion:** In two large cohorts, creatinine and BMI were related to certain plasma biomarkers levels. Still, the improvements in models were modest when including these two confounding factors, suggesting their limited clinical relevance for the majority of individuals.

OC37- ADUCANUMAB AND LECANEMAB LABEL INSOLUBLE, FIBRILLAR, DIFFUSIBLE AB AGGREGATES IN AQUEOUS EXTRACTS OF HUMAN ALZHEIMER DISEASE BRAIN. A.M. Stern[1], A.L. Meunier[1], W. Liu[1], M. Ericsson[2], D.J. Selkoe[2] *(1. Ann Romney Center For Neurologic Diseases, Brigham And Women's Hospital, Harvard Medical School - Boston (United States), 2. Harvard Medical School Electron Microscopy Core - Boston (United States))*

Background: Monoclonal antibodies that bind aggregated forms of Aβ are FDA-approved or are completing confirmatory phase 3 trials, and some may enter the clinic in common use in the next few years. Detailed studies have described their binding to synthetic Aβ and in vitro-derived aggregates thereof, but less is known about the nature of aggregates these antibodies bind in human brain. Binding and removing small aqueously soluble "oligomers" has been proposed to be one mechanism of action for these antibodies and an attractive target for future generations. Lecanemab has been shown to bind small oligomeric synthetic Aβ species aggregated in vitro, but in human subjects it reduces amyloid PET signal, which measures large fibrillar forms of Aβ. **Objectives:** We sought to describe the quantity, size and shape of aggregates bound by clinical antibodies in the aqueous fraction of extracts from human AD brain tissue. **Methods:** Aqueous extracts of postmortem AD and control cortical tissue were prepared by mincing and then soaking in TBS buffer followed by ultracentrifugation, retaining the supernatant. Immunoprecipitation followed by denaturation and detection with an Aβ42-specific ELISA were used to quantify Aβ species in the extracts reactive to therapeutic antibodies. Extracts were adsorbed onto carbon-coated grids, and immuno-electron microscopy with protein A-gold was used to study binding of therapeutic antibodies to Aβ fibrils found in the aqueous extracts. **Results:** Aducanumab, lecanemab, and bapineuzumab all immunoprecipitated the majority of Aβ detectable in aqueous AD brain "soaking" extracts. Negative staining and immunogold transmission EM revealed the presence of pelletable, fibrillar Aβ species in aqueous "soaking" extracts of all thirteen human AD brains examined. Aducanumab, lecanemab, and bapineuzumab all decorated these Aβ fibrils. Lecanemab immunoprecipitation of Aβ did not occur from the supernatants of very high ultracentrifugation speeds (250,000 - 475,000 g) but did occur from supernatants prepared at lower speeds (20,000 – 100,000 g). **Conclusions:** At least some oligomers present in aqueous diffusible extracts of AD brain are fibrillar and can bind therapeutic monoclonal antibodies. The fibrils are lost with very high-speed ultracentrifugation. The results suggest that the mechanism of action of therapeutic anti-amyloid antibodies may in part be due to binding insoluble Aβ aggregates. This agrees with the observation of robust clearance of amyloid PET by these antibodies, including lecanemab. **Disclosures:** DJS is a director of Prothena Biosciences and a consultant to Eisai.

OC38- A MULTIMODAL CLINICAL AND LIFESTYLE INTERVENTION INDUCES MULTIOMIC SYSTEMIC EFFECTS AND IMPROVES COGNITIVE OUTCOMES IN ALZHEIMER'S DISEASE. J.C. Roach[1], L.E. Edens[1], S. Rajbhandari[1], J. Hara[2], J. Bramen[3,4], M.K. Rapozo[5], C. Funk[1], W.R. Shankle[2,6,7,8], L. Hood[1] *(1. Institute For Systems Biology - Seattle, Washington (United States), 2. Pickup Family Neurosciences Institute, Hoag Memorial Hospital Presbyterian - Newport Beach, California (United States), 3. Pacific Brain Health Center, Pacific Neuroscience Institute - Santa Monica, California (United States), 4. Department of Translational Neurosciences and Neurotherapeutics, Saint John's Cancer Institute - Santa Monica, California (United States), 5. Providence St. Joseph Health - Renton, Washington (United States), 6. Shankle Clinic - Newport Beach, California (United States), 7. Department of Cognitive Sciences, University of California - Irvine, California (United States), 8. EMBIC Corporation - Newport Beach, California (United States))*

Background: The Coaching for Cognition in Alzheimer's (COCOA) trial was a prospective randomized clinical trial (RCT) to test the effect of a multimodal intervention on individuals in the early stages of cognitive decline. Participants met criteria for at least one definition of either Alzheimer's disease (AD) or a condition on the AD spectrum. AD and other dementias result from the interplay of multiple interacting dysfunctional biological systems. The motivation for COCOA was to test the hypothesis that personalized multimodal lifestyle and clinical interventions could ameliorate cognitive decline in this population. Coached interventions in COCOA were tailored to personal, clinical, and molecular data for each individual – representing a form of precision medicine. Standard of care, including pharmaceutical combination therapy, was available to all individuals enrolled in the trial; the intervention arm received personalized coaching for combination lifestyle interventions and cognitive training in addition to this standard of care. **Objectives:** Our overarching objective is to establish (or disprove) causal paths connecting specific interventions (or combinations of them) through intermediate molecular subsystems to neurological subsystems that promote cognition. Parts of this epistemological argument should include: (i) evidence that multimodal interventions improve cognition, such as a significant change in an RCT primary outcome measure, (ii) evidence that multimodal interventions impact particular endophenotypes, including description of the particular molecular analytes comprising these endophenotypes, and (iii) evidence connecting these endophenotypes to beneficial neurological and cognitive outcomes. Our goal for the resulting knowledge is to enhance the design of future clinical trials, tweak or overhaul recommendations for multimodal interventions, and stimulate broader adoption of lifestyle interventions already suspected or known to ameliorate cognitive decline. **Methods:** COCOA's trial design is as described (1). COCOA's primary outcome measure is the Memory Performance Index (MPI), a measure of cognition. The MPI is a summary statistic of the MCI Screen (MCIS). Secondary outcome measures include the Functional Assessment Staging Test (FAST), a measure of function. In addition to testing a hypothesis of improvement in a primary cognitive outcome endpoint, COCOA was also designed to produce dense omics data to enable epistemological analyses

and exploration (2). We analyzed an interim data freeze from COCOA spanning a full year of trial participation for all participants. These data included cognitive outcome measures, clinical labs, targeted serum proteomics, and comprehensive serum metabolomics. We integrated these data into a combined omics dataset and analyzed them as a connected system, using both pre-existing knowledge graphs and connections learned from the data. Dimensionality reduction techniques included multidimensional scaling, principal components analysis, and force-directed network layout. Gene set and metabolite set enrichment analyses were performed on connected subsystems. Significance was computed for subsystems as well as for individual analytes. New results were contextualized and integrated with prior knowledge using knowledge graphs summarizing existing biomedical knowledge. **Results:** In aggregate, both the primary cognitive outcome measure (MPI) and the functional outcome measure (FAST) significantly improved in cases compared to controls. Omics data from the 42 participants with at least two omic timepoints were considered. The multimodal intervention impacted (significantly different between cases and controls) analytes spanning overlapping systems including metabolic, immune, cardiovascular, and neurologic function. The most significant of these subsystems had functions related to protein and amino acid metabolism. A subset of the most significant proteins had neurotrophic function. A distinct set of analytes, particularly cardiovascular proteins, were correlated with better cognitive outcomes across all individuals (both cases and controls). **Conclusion:** Multimodal lifestyle interventions have broad impacts on many physiological systems; these impacts are reflected in hundreds of serum analytes. In aggregate, individuals receiving these interventions have better cognitive outcomes than those who do not. One possible interpretation is that some single aspect of the multimodal intervention, potentially different in each person, may convey the bulk of causal benefit. However, it is more likely that improving general health across a wide variety of connected organ systems improves multiple functions that work synergistically to improve cognitive health. These functions appear to include cardiovascular health and neurotrophic support. More generally, improved overall energetics and protein synthesis may fundamentally enable systems in the body that have been degraded by other processes, have become underpowered to maintain homeostasis, and have allowed the body to veer towards a path of cognitive decline and dementia. Revitalization of these basic metabolic processes may enhance allostasis and improve cognitive outcomes. Progression of AD may be delayed, halted, or reversed (ameliorated) in some individuals. These insights may be generalizable to other conditions of aging. Additional work remains for the analysis of this and future COCOA data freezes. Our existing results facilitate design of future clinical trials and may guide refinements to personalized multimodal interventions. **References:** 1. Roach et al. The Coaching for Cognition in Alzheimer's (COCOA) Trial: Study Design. Alzheimers Dement. In Press. 2. Roach et al. 2022. Dense data enables twenty-first century clinical trials. Alzheimers Dement. e12297.

OC39- ADVANTAGES OF NEXT GENERATION SUPRAANTIGEN® PLATFORM LIPOSOMAL VACCINES TO IMMUNIZE AGAINST PATHOLOGICAL TARGETS OF ALZHEIMER'S DISEASE. M. Vukicevic[1], E. Fiorini[1], D. Hickman[1], R. Carpintero[2], M. Rincon[2], P. Lopez-Deber[2], M. Ayer[2], S. Siegert[2], C. Babolin[2], E. Gollwitzer[2], S. Delpretti-Anex[2], P. Donati[2], J. Streffer[2,3], A. Pfeifer[2], M. Kosco-Vilbois[2] *(1. Ac Immune SA - Lausanne (Switzerland), 2. AC Immune SA - Lausanne (Switzerland), 3. University of Antwerp - Antwerpen (Belgium))*

Background: Alzheimer's disease (AD) and certain related neurodegenerative diseases are silent pandemics that are expanding in step with our ageing global population. Amyloid plaques, composed of misfolded Abeta species such as neurotoxic pyroGlu-Abeta and oligomeric Abeta, are one of the early hallmarks of AD, appearing when people are pre-symptomatic and proliferating as disease progresses. In addition, early in the disease, Tau forms neurofibrillar tangles, rich in aggregated phosphorylated (p)Tau, the deposition of which tracks with loss of cognition and neurodegeneration. For over a decade, we have been evolving our liposome-based SupraAntigen® vaccine platform, comparing it to commonly used approaches, such as protein-conjugate-based vaccines, to create best-in-class vaccines that can slow disease progression as well as delay or prevent disease onset. **Objectives:** Development of vaccines that safely generate sustained, conformation-specific antibody titers with preferences for the pathological species of Abeta and Tau. Evaluation of these vaccines in mice, non-human primates (NHP) and AD patients. **Methods:** For Abeta, several vaccines were generated as follows: a liposome-based SupraAntigen® vaccine (i.e., optimized ACI-24) containing the antigenic peptide Abeta 1-15, an adjuvant and a universal T-helper cell peptide; and CRM-conjugated vaccines containing various antigenic Abeta peptides (e.g., ACC-001) or full-length Abeta (i.e., AN1792) mixed with adjuvant. Mice and NHPs were vaccinated as follows: mice, 3 times every 2 weeks and plasma collected one week post immunization; cynomolgus monkeys, 5 times monthly and serum collected one week post immunization. ELISA-based assays assessed the binding to various forms of Abeta. Epitope mapping was carried out assessing the binding to 8 amino acid long peptides of Abeta. For Tau, various vaccines were generated as follows: a liposomal-based SupraAntigen® vaccine (i.e., ACI-35.030) containing an antigenic phosphorylated peptide pTau, adjuvants and a universal T-helper cell peptide: and a CRM-conjugated vaccine containing an antigenic phosphorylated Tau peptide. NHPs were immunized at 0, 1, 3 and 6 months and serum collected one and three weeks after each immunization. ELISA-based assays assessed the binding to various forms of Tau. Epitope mapping was carried out assessing the binding to the peptides of non-phospho- and phospho-Tau. **Results:** When immunizing mice and NHPs with vaccines containing the various Abeta peptides, all animals developed anti-Abeta 1-42 titers. However, only the liposomal-based optimized ACI-24 induced a homogenous and robust response to the Abeta-toxic species, pyroglutamate (pyroGlu-Abeta). Furthermore, this protective IgG response was maintained over time and could be consistently boosted. Additional profiling of the antibody response by epitope mapping revealed the superior broad coverage of the repertoire, as only optimized ACI-24 induced antibody responses to different short peptides including the mid-domain of Abeta 1-15, while the other vaccines generated antibodies that bound mainly to the very N-terminal sequence

of Abeta. For the Tau targeting vaccines, ACI-35.030 and the CRM-conjugated vaccine induced similar IgG titers to the immunizing peptide, as well as ePHF. However, ACI-35.030 induced antibodies with a strong preference towards the phospho peptide and low binding to the non-phospho peptide, while the CRM-conjugated vaccine induced a strong response to the non-phospho peptide. This was in line with the epitope mapping data, which demonstrated strong binding to the phosphorylated residues for the ACI-35.030-induced antibodies. In contrast, the CRM-conjugated vaccine induced limited coverage mainly recognizing a truncation-specific open end amino acid of the Tau peptide sequence. Importantly, both vaccines showed a favorable safety profile and did not induce Tau-specific T-cell activation. Further evaluation of the 2 Tau targeted vaccines in AD patients confirmed similar specificity of the induced antibodies observed in the NHPs. **Conclusions:** For both Abeta and Tau targeting vaccines, the liposome-based SupraAntigen® vaccines demonstrated a superior quality of the IgG repertoire generated post-immunization. The responses in NHPs were well tolerated, homogenous, robust and boostable over time, while broadly engaging relevant pathological epitopes. For Abeta, the liposome-based SupraAntigen® vaccine generated the highest titers of antibodies specifically targeting pyroGlu-Abeta. For Tau, only the liposome-based SupraAntigen® vaccine matured a repertoire of antibodies that broadly recognized species containing the pathological pTau. Taken together, the SupraAntigen® vaccine technology platform, using carefully chosen target peptides combined with adjuvants and universal T-helper cell peptides, creates a broad and safe antibody response to the key pathological species which translates to best-in-class clinical vaccine candidates.

OC40. U-P53AZ IN PROGNOSTICATION OF EARLY ONSET ALZHEIMER'S DISEASE UP TO 6 YEARS IN ADVANCE OF THE CLINICAL DIAGNOSIS. S. Piccirella[1], L. Van Neste[2], C.H.R.I.S. Fowler[3], C.M.A.S. Masters[3], J.U.R.G.E. Fripp[4], J.D. Doecke[4], C. Xiong[5], D. Uberti[6], P. Kinnon[1]
(1. Diadem SpA - Brescia (Italy), 2. Halixo BV - Hoegaarden (Belgium), 3. The Florey Institute of Neuroscience and Mental Health - Parkville (Australia), 4. The Australian e-Health Research Centre, CSIRO - Herston (Australia), 5. Washington University School of Medicine, Division of Biostatistics - St. Louis (United States), 6. Department of Molecular and Translational Medicine, University of Brescia - Brescia (Italy))

Background: The unfolded conformational variant of the p53 protein is a potential prognostic biomarker of Alzheimer's dementia (AD) (U-p53AZ), previously observed in individuals in the prodromal and clinical AD stages. Diadem have developed AlzoSure® Predict (Piccirella et al, 2022), a simple, non-invasive, rapid blood-based test that allows the assessment of cognitive decline to AD-dementia up to 6 years in advance of any clinical symptoms by detecting the concentration of a specific sequence peptide, AZ284®, from U-p53AZ. **Objectives:** This study aims to confirm the prognostic performance of U-p53AZ in the onset of AD and to compare this with other AD biomarkers. **Methods:** In this retrospective study, we evaluate the prognostic performance U-p53AZ (detected by AlzoSure® Predict) in plasma samples from individuals participating in the Australian Imaging, Biomarkers and Lifestyle (AIBL) cohort. AlzoSure® Predict is a LC-MS/MS based method that detects a specific peptide belonging to the U-p53AZ protein, called AZ284®. AlzoSure® Predict is a CE-IVD marked test, recently designated as breakthrough device by the FDA. At baseline, this cohort consists of 237 cognitively normal subjects, including both those without and with subjective memory complaints (NMC/SMC), 98 individuals with mild cognitive impairment (MCI), 141 patients with AD, and 3 other dementia patients that were followed up every 18 months. The performance of U-p53AZ was compared with other AD biomarkers, i.e. amyloid status assessed by calibrated centiloid, tau protein, ApoE4 allele status, age, and gender. To evaluate the prognostic potential , Cox proportional hazards regression models were developed for the beforementioned markers. **Results:** The prognostic value of U-p53AZ was evaluated in the longitudinal AD patient subset of the AIBL cohort, removing all individual that were already diagnosed with AD at baseline. The value of AZ284® relative to other biomarkers was evaluated by fitting Cox proportional hazards models. The other risk factors that were explored include centiloid, ApoE4, tau, age, and gender, in addition to combinations of these. While AZ284® data is available for a total of 338 men and women, comparisons can only be made on subjects with a complete marker profile. Because information on tau is lacking for many, this biomarker is addressed separately. First, AZ284® was compared with 294 subjects for which amyloid, age, gender, and ApoE4 are available, of which 36 develop AD over time. In terms of individual risk factors, AZ284® clearly outperforms the other risk factors with a concordance (C) index of 95.3% ± 0.9% (standard error) (all $p < .0016$). The best multi-risk factor model includes AZ284® ($p<.0001$), amyloid ($p<.0001$), and age ($p=.0096$), resulting in a C-index of 94.3% ± 1.6%. Gender and ApoE4 were not significant and did not result in any improvement of the model and were hence not included. Similarly, the best model that does not include AZ284® consists of amyloid ($p<.0001$) and age ($p=.0007$), with a C-index of 86.4% ± 3.1%. This model has a significantly lower performance compared to the model with AZ284® ($p<.0001$), demonstrating the significance and synergistic performance of AZ284®. The comparison with tau protein was more difficult, since this biomarker was only available for a limited subset of the subjects. When the maximum difference in sample collection for AZ284® and tau protein was limited to 1 year, only 29 subjects were eligible, of which only 2 developed AD over time. To increase the patient number, in particular those that develop AD, AZ284® and tau were compared without time restriction. It is important to note that the lead time for AZ284® is significantly larger compared to that of the tau sample, i.e. samples were taken significantly longer before the final diagnosis ($p < .0001$), which is also the case for those subjects that develop AD ($p=.0418$), creating a slight bias in favor of tau since the time-to-event of the AZ284® was used for all. This allowed to compare both biomarkers on a set of 64 subjects, of which 6 developed AD over time. In this subset, AZ284® performs similarly compared to the larger population, with a C-index of 95.7% ± 2.1%. Total tau and p-tau 181 were assessed, both as binary marker (positive vs negative) or using the actual concentration. For both, the actual concentration performed better than the binary marker, with C-indices 88.3% ± 4.6% vs .65.8% ± 10.1% and 77.7% ± 8.8% vs 63.6% ± 10.2%, respectively. Except for total tau concentration ($p=.0841$), AZ284® significantly outperformed tau protein (total tau binary: $p=.0024$; p-tau binary: $p=.0013$; p-tau concentration: $p= .0303$). **Conclusion:** The present study confirms the prognostic performance of U-p53AZ for AD. Despite the small sample size, the trend clearly indicates that AZ284® is the strongest performing biomarker and would be recommended as an integral part of any biomarker-based model. More details are available on: https://link.springer.com/article/10.14283/jpad.2022.52.

OC41- IWHELD: AN RCT OF A NOVEL DIGITAL NON-PHARMACOLOGICAL INTERVENTION TO IMPROVE QUALITY OF LIFE AND REDUCE ANTIPSYCHOTICS IN 741 PEOPLE LIVING IN NURSING HOMES DURING THE COVID-19 PANDEMIC. C. Ballard[1], J. Mcdermid[1], A. Sweetnam[1] *(1. University of Exeter - Exeter (United Kingdom))*

Background: Inconsistent quality of care in nursing homes has long been recognised as a challenging area that requires urgent action and its impact on quality of life in people living with dementia. These enduring issues have been compounded by the emergence of and ongoing pressures of the COVID-19 pandemic on nursing home settings. People living in nursing homes and long-term care facilities are often frail and have complex needs, many with dementia, neuropsychiatric symptoms, and/or other physical conditions and have been disproportionately impacted by the pandemic, affecting not only residents but also their families and the care workforce. Whilst high prescribing rates of antipsychotics in the early 2000s for people living with dementia in nursing homes had significantly reduced in recent years, the pandemic has seen a rebound increase in use. Implementation of evidence-based training and support for nursing staff into real world practice in nursing home settings is a major challenge. Digital approaches provide real potential to addressing the barriers, particularly over the difficult period of the COVID-19 pandemic. **Objectives:** In response to the COVID-19 crisis, to rapidly develop and implement a nursing home intervention programme to include virtual coaching, peer networking and solution sharing, alongside evidence-based elements focussing on person-centred care, personalised activities, and reduction of unnecessary antipsychotic medications. **Method:** iWHELD is a first-of-its-kind digital programme evolving the principles of the WHELD intervention combining person centred care, social interaction, movement, and antipsychotic review with virtual coaching and a digital resource for nursing homes. The entirely remote intervention utilising a Dementia Champion model supported by live virtual coaching set within a digital resource hub and peer networking platform was compared to usual care in a 16-week randomised control cluster study of 741 people with dementia across 149 nursing homes in the UK. The primary outcome evaluated quality of life (using the DEMQOL-Proxy) and secondary outcomes included the use of antipsychotic drugs and neuropsychiatric symptoms (using the Neuropsychiatric Inventory NH). **Result:** The average age of residents was 84.5 years (71% female). 64% of participating nursing homes had experienced a COVID-19 outbreak. At baseline, 28% of residents were prescribed an antipsychotic (a significant 55% increase compared to pre pandemic in previous WHELD RCT trial in 2014). 36/72 (53%) of nursing homes allocated to the active treatment arm engaged successfully with the digital intervention, with 563 residents completing the treatment period. There was significant benefit in quality of life for residents receiving the iWHELD intervention compared to those in the control group (DEMQOL-Proxy 4.76 ± 15.03 point advantage, p=.006, Cohen's D effect size 0.32). There was also a significant reduction in antipsychotic use in the iWHELD treatment group from 49% to 31% compared to no change in the group receiving usual care (p=0.046). Analysis of neuropsychiatric symptoms indicates a significant benefit for the treatment group with respect to delusions (p= .01) with no significant differences in hallucinations or agitation in the intervention group compared to those receiving usual care indicating no significant worsening of these symptoms in the context of a significant reduction in antipsychotic prescriptions. **Conclusion:** For this current large scale RCT, we successfully designed, recruited, and delivered a novel digital programme in 149 nursing homes with 741 residents and over 200 staff as part of a rapid response COVID-19 initiative. The iWHELD intervention with live virtual coaching delivered through a Dementia Champion achieved better than 50% engagement, which compares favourably with previous studies of digital interventions in other therapeutic areas. The iWHELD intervention conferred significant benefit in quality of life as well as significant reductions in antipsychotic use without any worsening of neuropsychiatric symptoms and significant benefit with respect to delusions. This study provides an important potential approach to both improving wellbeing and quality of life and to safely reducing the rise in antipsychotic use in nursing home residents with dementia that has become a major challenge during the COVID-19 pandemic. The iWHELD digital format provides a potential solution for wide-scale rollout into real world settings.

OC42- MAKING DIGITAL MEASURES FIT-FOR-PURPOSE IN ALZHEIMER'S TRIALS. F. Cormack[1], J. Sorinas[2], C. Meunier[3] *(1. Cambridge Cognition - Cambridge (United Kingdom), 2. Novartis - Basel (Switzerland), 3. DiMe - San Francisco (United States))*

Background: Developing novel cognitive tasks or adapting existing cognitive tasks to novel technology requires an iterative and cumulative approach to validation in order to develop measures which are fit for purpose, particularly in the context of virtual clinical trials, where scalable, robust and repeatable testing are needed. Three key aspects of this are considered here: 1) the technical feasibility across device, which encompasses the accuracy of automated scoring 2) participant acceptability 3) analytical validation, focused on psychometric properties. Here we illustrate these three aspects of task development. We conducted a series of large (a total of 2,868 participants) home-based feasibility studies deploying a device-agnostic web-based technology for administering and scoring verbal neuropsychological tests (Verbal Paired Associates and Digit Span Forwards and Back and Serial Subtraction). We describe the methods developed to support automated stimulus generation to enable repeated longitudinal assessment and robust automated scoring in home settings. Technical feasibility and robustness of these methods were assessed through manual review of responses. Participant acceptability was assessed through post-test questionnaires, and the suitability of the tasks for repeat remote administration, was assessed through repeated administration of parallel forms. Qualitatively, participants reported that the automated instructions were clear and easy to understand, and that the tasks were challenging but enjoyable. We observed expected effects of task difficulty and demographic variables on task performance. We also present data on the psychometric properties of assessments, supporting the psychometric properties of the tasks and the suitability of the tests for repeat, remote administration. Together, these results illustrate developing cognitive assessment technology for use in decentralised clinical trials. Specifically, the constraints of scalable, repeatable, and robust testing were met through a combination of specifically designed algorithms to generation stimuli, and score responses, together with iterative refinements to the user interactions to ensure ease of use for participants in the absence of trained raters.

Late Breaking

LB1: TAU PET ASSOCIATED WITH PLASMA P-TAU217 AND COGNITIVE TESTING IN PRECLINICAL AD: SCREENING DATA FROM THE AHEAD STUDY A3 AND A45 TRIALS. K. Johnson[1], A. Schultz[1], R. Rissman[2], O. Langford[2], E. Thibault[1], M. Meyer[3], K. Kirmess[3], M. Irizarry[4], J. Zhou[4], M. Donohue[2], R. Raman[2], P. Aisen[2], R. Sperling[1,5], A.3.4.S. Team[6] *(1. Massachusetts General Hospital - Boston (United States), 2. University of Southern California - San Diego (United States), 3. C2N Diagnostics - St. Louis (United States), 4. Eisai - Nutley (United States), 5. Brigham and Women's Hospital - Boston (United States), 6. ACTC - Many Sites (United States))*

Background: The emergence of more accurate plasma AD biomarkers will substantially improve screening efficiency for prevention trials. Our work in the AHEAD 3-45 Study screening cognitively unimpaired participants has recently demonstrated that plasma Aβ42/40 and p-tau217 are highly predictive of positive amyloid PET status (18F-NAV4694 PET > 20CL eligibility). In addition, plasma p-tau measures could also enable prediction of tau deposition on Tau PET, subsequent cognitive decline, response to specific therapeutic mechanisms, or as a trial inclusion criterion. **Objective:** In this study, we investigated the ability of plasma p-tau measures to predict level of tau deposition estimated with 18F-MK6240 Tau PET in cognitively unimpaired individuals who were eligible (>20CL on amyloid PET) for the AHEAD Study A3 and A45 trials. **Methods:** The AHEAD Study has a shared screening platform for both the A3 (20-40 CL) and the A45 (>40CL) trials. Only individuals who showed >20CL on NAV PET and were otherwise eligible for the AHEAD trials moved forward in screening and underwent tau PET imaging with MK6240. Samples with both plasma and PET data available in the U.S. as of March 2022 (prior to the introduction of plasma measures to determine eligibility to continue in AHEAD screening) were sent to C2N Diagnostics for batch analysis of Aß42/40, and both the phosphorylated (p-tau) and non-phosphorylated (np-tau) forms of tau181 and tau217 using C2N's mass spectrometry platform. A concentration ratio of p-tau to np-tau was calculated to normalize for differing np-tau concentrations at each epitope (p-tau181r and p-tau217r). We tested two Tau PET aggregate regions representing tau deposition at the early and mid-stages of AD tauopathy: the medial temporal allocortex (MTL: amygdala, entorhinal, parahippocampal) and inferolateral temporal/parietal neocortex (NEO: inferior temporal, fusiform, middle temporal, inferior parietal). Tau PET was quantified with the standardized uptake value ratio (SUVr; 4mm eroded cerebral white matter reference). InVicro generated NAV4694 centiloid values for global amyloid PET quantification. Pearson correlations and multivariate linear models were calculated to predict baseline Tau PET composites and the subsample z-scored Preclinical Alzheimer's Cognitive Composite score (PACC-5). None of the p values are adjusted for multiple comparisons in these exploratory analyses. **Results:** There were 303 AHEAD 3-45 amyloid eligible (>20CL) participants with plasma and screening Tau PET data available: age 69.5±5.5 years, 66% female, 75% APOE ε4 carriers, and education 16.4+2.7 years. Across the full Tau PET sample, p-tau217r showed consistently stronger associations with both Tau PET composite regions than p-tau181r. The p-tau217r correlated with Tau PET SUVr in both MTL (r=0.35; p<0.0001) and NEO (r=0.43;p<0.0001) composites. The NAV amyloid PET also correlated with MTL (r=0.33; p>0.0001) and NEO (r=0.27;p<0.0001). Interestingly, in a multivariate model with age and APOE ε4 included, p-tau217r and amyloid NAV CL were significant independent predictors of both Tau PET composites, with stronger associations observed for ptau217r over NAV CL: MTL (ptau217r estimated β=0.088, t=4.49, p<0.0001; NAV CL β=0.003, t=2.89, p=0.004); and NEO (p-tau217r β=0.104; t=6.49, p<0.0001; NAV β=0.002, t=2.13, p=0.034). Among the full Tau PET sample, 93 individuals were eligible for the A3 trial (20-40 NAV CL) and 210 were eligible for A45 (>40 NAV CL). Among the A3 subset, p-tau217r was correlated with both MTL (r=0.27, p=0.0088) and NEO (r=0.30, p=0.0035). NAV CL was marginally correlated with MTL (r=0.20, p=0.054) but not with NEO (r=0.13, p=NS). Among the A45 subset, p-tau217r was correlated with MTL (r=0.28, p<0.001) and NEO (r=0.42, p<0.0001) Tau PET composites. NAV CL was also correlated with Tau PET MTL (r=0.20, p=0.003) and NEO (r=0.23, p=0.001) composites in the A45 subset. Finally, we evaluated the association of amyloid NAV, Tau PET composites, and p-tau plasma measures with screening PACC-5 score, with age, sex, and education covaried. Across the full Tau PET sample and within the A45 subsample alone, only the NEO Tau PET composite was associated with screening PACC-5 (β= -0.18; p=0.0006). No association with cognition at screening was observed with NAV CL, MTL Tau PET, p-tau181r, or p-tau217r. **Conclusions:** In this sample of cognitively unimpaired participants who were all amyloid eligible for the AHEAD 3-45 Study, p-tau217r predicts tau deposition as measured by Tau PET imaging, above and beyond amyloid levels. Neocortical Tau PET burden was associated with screening cognitive testing, even within the restricted range of normal cognition required for eligibility in the AHEAD Study. These results suggest that plasma p-tau217r measures may be useful in identifying those preclinical AD individuals with evidence of Tau pathology, whereas Tau PET may be valuable for tracking cognitive outcomes. In particular, these markers should enable efficient screening and sensitive outcomes for upcoming trials targeting tau mechanisms at very early stages of AD.

LB2- PLASMA LEVELS OF ABETA42/40 AND P-TAU217 RATIOS INCREASE ACCURACY OF AMYLOID PET PREDICTION IN PRECLINICAL AD. R.A. Rissman[1,2], O. Langford[2], M. Donohue[2], R. Raman[2], S. Abdel-Latif[2], M. Meyer[3], K. Kirmess[3], J. Braunstein[3], M. Irizarry[4], K. Johnson[5], P. Aisen[2], R. Sperling[6], T. Ahead 3-45 Study[7] *(1. UC San Diego - La Jolla, Ca (United States), 2. University of Southern California - San Diego, Ca (United States), 3. C2N Diagnostics - St. Louis, Mo (United States), 4. Eisai - Indianapolis, In (United States), 5. Massachusets General Hospital, Harvard University - Boston, Ma (United States), 6. Brigham and Woman's Hospital, Harvard - Boston, Ma (United States), 7. ACTC - San Diego, Ca (United States)*

Background: Our prior data from the A4 and AHEAD Study, and that from other groups demonstrates that plasma Aβ42/40 quantification by mass spectrometry can serve as a reliable biomarker for predicting elevated brain amyloid detected by PET. We studied the value of adding plasma p-tau measures to our plasma Aβ42/40 algorithm to further streamline identification of eligible participants and reduce burden and trial cost. **Objective:** To determine if the addition of plasma p-tau181 and/or p-tau217 concentrations can improve plasma Aβ42/40 algorithms to correctly identify participants with amyloid burden of >20 centiloids with the NAV4694 tracer among individuals screening for participation in the AHEAD preclinical AD trial. **Methods:** Plasma amyloid and tau measures were quantified by C2N Diagnostics using mass spectrometry-based analytical platforms. Participant plasma

samples (N=1085) collected prior to the introduction of plasma Aβ42/40 testing during screening were used. Plasma samples for these analyses consisted of those with sufficient amyloid PET levels (n = 364; 33%) to be eligible for AHEAD and those who screen failed (n = 747; 67%). C2N quantified Aβ (Aβ42/40) and various tau species, including both the phosphorylated (p-tau) and non-phosphorylated (np-tau) forms of tau181 and tau217. A ratio of p-tau to np-tau was also calculated for each epitope (p-tau181r and p-tau217r) to normalize for inter-individual differences in np-tau concentrations. We conducted Receiver Operating Characteristic (ROC) curve analyses for each of these biomarkers against amyloid status defined by amyloid PET status (>20 centiloids). We also fit a Mixture of Experts model to assess the value of including p-tau181r and p-tau217r in the existing predictive algorithm (Aβ42/40, Age and APOE) for amyloid PET status using NAV4694. **Results:** This sample of N =1085 contained 67% Female, 13.5% Hispanic, 3.7% Black or African American with a mean age of 67.6 (SD = 6.1) years. 45% of the participants had at least one APOE4 allele. The Area Under the Curve (AUC) for plasma Aβ42/40 was 0.87 (95% CI; 0.84, 0.89), consistent with prior reports. For plasma tau markers, we observed AUCs of 0.74 (95% CI; 0.71, 0.77) with p-tau181, to 0.91 (95% CI; 0.90, 0.93) with p-tau217r. The model including covariates p-tau217r, Aβ42/40, Age and APOE improved AUC to 0.95 (95% CI; 0.93, 0.96). **Conclusions:** These findings demonstrate that the addition of plasma p-tau/np-tau concentration ratios for tau181 and tau217 species greatly improved the utility of plasma testing for amyloid PET positivity, with p-tau217r conferring the greatest improvement. Our data suggests that consideration of plasma p-tau217r in addition to Aβ42/40 ratio can dramatically improve anti-amyloid clinical trial screening burden and timelines for participant recruitment. In addition to determining how our results can be applied to other amyloid tracers and varying levels of neuropathology as informed by Aβ and tau PET, our current priorities involve expanding these findings to underrepresented populations to determine whether the specific levels and cutoffs of plasma Aβ and p-tau species and their relation to PET amyloid positivity are similar across different racial, ethnic and other underrepresented groups.

LB3- TRAILBLAZER-ALZ 4: TOPLINE STUDY RESULTS DIRECTLY COMPARING DONANEMAB TO ADUCANUMAB ON AMYLOID LOWERING IN EARLY, SYMPTOMATIC ALZHEIMER'S DISEASE.

S. Salloway[1], E. Lee[2], M. Papka[3], A. Pain[4], E. Oru[4], M.B. Ferguson[4], H. Wang[4], M. Case[4], M. Lu[4], E.C. Collins[4], D. Brooks[4], J. Sims[4]
(1. Department of Neurology and Department of Psychiatry, Alpert Medical School of Brown University, Providence, RI, USA; Butler Hospital - Providence (United States), 2. Irvine Clinical Research - Irvine (United States), 3. The Cognitive and Research Center of New Jersey LLC - Springfield (United States), 4. Eli Lilly and Company - Indianapolis (United States))

Background: The amyloid cascade in Alzheimer's disease (AD) involves the production and deposition of amyloid beta (Aβ) as an early and necessary event in the pathogenesis of AD (1). Both donanemab and aducanumab have demonstrated the ability to reduce brain amyloid plaque burden and potentially slow clinical decline (2, 3). Recently, the FDA provided accelerated approval for aducanumab for the treatment of early symptomatic AD based on its ability to reduce Aβ plaques (4) as a surrogate biomarker reasonably likely to predict a clinical benefit to AD patients. **Objectives:** The primary outcome of TRAILBLAZER-ALZ 4 (NCT05108922) evaluated the potential superiority of donanemab treatment compared to aducanumab on the percentage of participants with amyloid plaque clearance (≤24.1 Centiloids (CL)) at 6 months in the overall study population and subpopulation of participants with intermediate tau deposition. **Methods:** TRAILBLAZER-ALZ-4 is a multicenter, phase 3, open-label, active comparator study of participants with early symptomatic AD (n=148), randomized 1:1 to receive donanemab (700 mg IV Q4W for first 3 doses, then 1400 mg IV Q4W for subsequent doses) or aducanumab (per USPI4: 1 mg/kg IV Q4W for first 2 doses, 3 mg/kg IV Q4W for next 2 doses, 6 mg/kg IV Q4W for next 2 doses and 10 mg/kg IV Q4W for subsequent doses). The overall study duration is 18 months with the primary endpoints assessed at 6 months. Eligible participants are considered to have early symptomatic AD with a mini-mental state examination score of 20-30 (inclusive) and Clinical Dementia Rating-global score of 0.5 or 1.0. Other eligibility criteria included elevated Aβ as detected by florbetapir F18 PET scan, age 50-85 years; and consent to apolipoprotein E (APOE ε4) genotyping. Magnetic resonance imaging (MRI)-based exclusions included >4 microhemorrhages, superficial siderosis, and severe white matter changes; use of anti-coagulation agents was not permitted. Participant randomization was stratified by amyloid burden at baseline and APOE ε4 status. A flortaucipir F18 PET scan was also performed to identify a subpopulation with an intermediate tau level. Intermediate tau deposition was defined as an initial flortaucipir scan with moderate AD patterns based on visual assessment and neocortical standardized uptake value ratio (SUVR) between 1.10 and 1.46, inclusive, or advanced AD patterns and neocortical SUVR ≤ 1.46. Key secondary objectives include assessment of the superiority of donanemab treatment compared to aducanumab brain amyloid plaque levels percent and mean change at 6 months. Beyond standard safety assessments, MRI assessments monitored amyloid-related imaging abnormalities (ARIA) occurrence. **Results:** The analysis set was defined as those with at least one dose of donanemab (N=71) or aducanumab (N=69). There were N=27 participants defined as having intermediate tau in the donanemab group compared to N=28 in the aducanumab group. Baseline demographics and characteristics were well-balanced across treatment groups. Upon assessment of florbetapir F18 PET scans at 6 months, 37.9% of donanemab-treated participants achieved amyloid clearance compared to 1.6% of aducanumab-treated participants (p<0.001). In the intermediate tau subpopulation, 38.5% of donanemab-treated participants achieved amyloid clearance compared to 3.8% of aducanumab-treated participants (p=0.008). Percent change and mean change in brain amyloid levels for participants on donanemab were -65.2% +/- 3.9% (baseline: 98.29 +/- 27.83 CL, change: -62.10 +/- 3.69 CL), and -17.0% +/- 4.0% (baseline: 102.40 +/- 35.49 CL, change: -16.41 +/- 3.77 CL) for participants on aducanumab (p<0.001). In the intermediate tau subpopulation, percent and mean change in brain amyloid levels for participants on donanemab were -63.9% +/- 7.4% (baseline: 104.97 +/- 25.68 CL, change: -64.08 +/- 7.34 CL) and -25.4% +/- 7.8% (baseline: 102.23 +/- 28.13 CL, change: -23.82 +/- 7.70 CL) for participants on aducanumab (p≤0.001). 62.0% of participants treated with donanemab reported an adverse event (AE) and there were no serious AEs due to ARIA. In the aducanumab group, 66.7% of participants reported an AE, and there were 1.4% serious AEs (one event) due to ARIA. The incidence of ARIA-E in the donanemab group was 21.1%, with 2.8% symptomatic ARIA-E (13.3% of those with ARIA-E). In the aducanumab group, ARIA-E incidence was 23.2%, with 4.3% symptomatic ARIA-E of all participants in the aducanumab group (18.8% of those with ARIA-E). The

incidence of ARIA-H in the donanemab group was 19.7% and in the aducanumab group was 17.4%. Infusion-related reactions (IRRs) were reported by 7.0% of the donanemab group; in the aducanumab group, 2.9% of participants reported IRRs. **Conclusions:** The TRAILBLAZER-ALZ 4 study provides the first active comparator data on amyloid plaque clearance in patients with early symptomatic AD. There were significantly more participants reaching amyloid clearance and significantly greater amyloid plaque reductions with donanemab compared to aducanumab at 6 months. Both agents showed similar safety profiles to their previous studies. **References:** 1. Selkoe DJ. JAMA. 2000;283(12):1615-1617. 2. Mintun MA, et al. NEJM. 2021;384(18):1691-1704. 3. Budd Haeberlein S, et al. JPAD. 2022;9(2):197-210. 4. Aducanumab-avwa prescribing information. ADUHELM (fda.gov).

LB4- CSF MTBR-TAU243 IS A NON-AMYLOID SPECIFIC BIOMARKER OF NEUROFIBRILLARY TANGLES OF ALZHEIMER'S DISEASE. K. Horie[1,2], G. Salvadó[3], N. Barthélemy[1], Y. Li[1], B. Saef[1], C. Chen[1], H. Jiang[1], B. Gordon[1], T. Benzinger[1], D. Holtzman[1], S. Schindler[1], O. Hansson[3,4], R. Bateman[1] *(1. Washington University School of Medicine - St. Louis (United States), 2. Eisai Inc. - Nutley (United States), 3. Lund University - Lund (Sweden), 4. Skåne University Hospital - Malmö (Sweden))*

Background: Neurofibrillary tangles (NFTs) are a key pathological hallmark of Alzheimer's disease (AD) and are comprised of hyper-phosphorylated tau (p-tau) and microtubule binding region of tau (MTBR-tau) species. While the levels of soluble p-tau species such as p-tau181, 217, and 231 in cerebrospinal fluid (CSF) and blood are widely used as indicators of AD tau tangles, recent studies indicate that these soluble p-tau species are more strongly associated with amyloid plaques than tau tangles. We previously discovered that CSF MTBR-tau species containing the residue of 243 (MTBR-tau243) located in the upstream region of the MTBR was the fluid biomarker most highly correlated with tau tangles as measured by positron emission tomography (PET) in a small cohort (Horie et al., Brain, 2021). **Objectives:** We aimed to establish a non-amyloid dependent CSF biomarker to specifically quantify NFTs in AD. We measured the novel biomarker, MTBR-tau243, in CSF samples from two cohorts: 1. The Swedish BioFINDER-2 study and 2. The Knight Alzheimer Disease Research Center (Knight ADRC). Furthermore, we compared CSF MTBR-tau243 and p-tau as predictors of amyloid pathology, tau pathology and cognitive function. **Methods:** BioFINDER-2 (n=448) and Knight ADRC (n=219) participants underwent a lumbar puncture within two years of an amyloid PET (Flutemetamol or Florbetapir/Pittsburgh Compound-B, respectively) and/or tau PET (RO6958948 or Flortaucipir, respectively) scan. CSF was subjected to sequential immunoprecipitation with anti-N-terminal to mid-domain antibodies for p-tau analyses (p-tau181, 205, 217, and 231) and a specific antibody targeting the upstream region of MTBR for MTBR-tau243 analyses, then evaluated via mass spectrometry. Spearman correlations were used to evaluate the relationships of CSF biomarkers with amyloid PET, tau PET measures, and the Mini-Mental State Examination (MMSE). To identify the combination of CSF biomarkers that best predicted amyloid and tau PET measures, linear regression with the Least Absolute Shrinkage and Selection Operator (LASSO) variable selection method was used. The longitudinal rates of changes for the CSF tau species were compared among groups that were amyloid and tau positive vs. negative groups at baseline. **Results:** The majority of participants were amyloid positive (A+, 59% for BioFINDER-2 and 62% for the Knight ADRC); 70% of BioFINDER-2 and 35% of Knight ADRC were cognitively impaired. Longitudinal CSF collected 2 years after the baseline CSF was available for 223 participants from BioFINDER-2. In both the BioFINDER-2 and Knight ADRC cohorts, CSF MTBR-tau243 concentration was the biomarker most strongly correlated with NFTs as measured by tau PET even in the amyloid-positive group (Spearman Rho=0.83 and 0.70, respectively) and was the least correlated with amyloid plaques as measured by amyloid PET in the same group (Rho=0.49 and 0.48, respectively). CSF p-tau205 occupancy was also highly correlated with NFTs even in the amyloid-positive group (Rho=0.78 and 0.70, respectively) but had a stronger association with brain amyloidosis in the same group (Rho=0.67 and 0.60, respectively) than MTBR-tau243. Linear regression with LASSO selection suggested that the combination of MTBR-tau243 level and p-tau205 occupancy was the best predictor of tau PET (adjusted R2=0.75 and 0.65, respectively), while the combination of p-tau217, 205 occupancies and Aβ42/40 was the best predictor of amyloid PET (adjusted R2=0.77 and 0.69, respectively). Notably, CSF MTBR-tau243 was the most highly correlated with the MMSE (Rho=-0.62 and -0.53, respectively) across all CSF tau measures. Linear regression with LASSO selection suggested that the combination of MTBR-tau243 level and p-tau205 occupancy was the best predictor of MMSE (adjusted R2=0.41 and 0.35, respectively), which was only slightly inferior to tau PET (adjusted R2=0.43 and 0.44, respectively). In longitudinal analyses of the BioFINDER-2 cohort, MTBR-tau243 exhibited the most significant increase in rate of change according to disease progression between amyloid-positive tau-positive (A+T+) and the other two groups (A-T-: Cohen's d=1.48, p<0.001; A+T-: Cohen's d=1.13, p<0.001), while p-tau205 and the other p-tau species (i.e., 181, 217, and 231) exhibited no significant change and even decreases in the rates of changes between A+T- and A+T+ groups. **Conclusion:** These findings suggest that CSF MTBR-tau243 reflects changes in tau pathology that occur at a later stage in AD progression than brain amyloidosis and could be used to stage AD tauopathy and track the effects of tau-targeting therapies independent of amyloid effects. The combination of CSF MTBR-tau243 and p-tau205 occupancy explained most of the total variance in tau PET and predicted MMSE almost as accurately as tau PET, which suggests high clinical utility of a biomarker panel containing MTBR-tau243. The mechanisms underlying these findings add to the growing understanding of AD pathophysiology and strategies for novel tau-targeting AD therapies.

LB5- TOP-LINE RESULTS FROM THE 2-YEAR SYSTEMATIC MULTI-DOMAIN ALZHEIMER'S RISK REDUCTION TRIAL (SMARRT). K. Yaffe[1], E. Vittinghoff[1], S. Dublin[2], C. Peltz[1], L. Fleckenstein[2], D. Rosenberg[2], D. Barnes[1], B. Balderson[2], E. Larson[3] *(1. University of California, San Francisco - San Francisco, Ca (United States), 2. Kaiser Permanente Washington Health Research Institute - Seattle, Wa (United States), 3. University of Washington - Seattle, Wa (United States))*

Background: Modifiable risk factors account for 30-40% of dementia; yet, few trials, especially multi-domain, have demonstrated that risk reduction interventions can improve these risk factors and in turn, cognitive outcomes. We conducted the NIH-funded Systematic Multi-domain Alzheimer's Risk Reduction Trial (SMARRT), a 2-year randomized pilot trial to test a personalized, pragmatic, multi-

domain dementia risk reduction intervention in an integrated healthcare delivery system. (NCT03683394). **Objective:** To determine whether a 2-year personalized multi-domain risk reduction intervention benefits cognition and behavioral risk factors compared to a health education group. **Methods:** We recruited 172 older adults at higher risk for dementia (age 70-89, subjective cognitive complaints, low-normal performance on a brief telephone cognitive screen, and ≥ two targeted modifiable risk factors) from primary care clinics of Kaiser Permanente Washington (KPWA). Modifiable risk factors that counted towards eligibility and were targeted by the intervention included poorly controlled diabetes or hypertension, use of risky prescription medications, physical inactivity, social isolation, poor sleep, smoking, and depression. Participants were randomly assigned to the SMARRT intervention or to a Health Education (HE) control. The intervention consisted of personalized risk reduction goals with health/nurse coaching for those target goals. Personalized intervention was based on the prevalence of risk factors as well as personal preference for risk reduction priority and strategy. The primary outcome was change in a composite cognition score (initially assessed in person and then due to the COVID-19 pandemic, by phone); pre-planned secondary outcomes were change in risk factors and quality of life measures. Participants were evaluated at baseline, 6, 12, 18, and 24 month assessments. Analyses of all outcomes were by intention-to-treat and used linear mixed models to compare changes from baseline, averaged across the four follow-up visits. **Results:** The mean age of participants was 75.7 years (sd 4.8), 63% were women and 19% were non-White; the mean number of risk factors at enrollment was 2.5 (0.6). Intervention participants had a mean of 20 (sd 3.8) contacts with the health coach or study nurse during the 2-year intervention. The trial recently was completed, and we will present top-line results on the primary and secondary outcomes. We will also present data on safety and adherence. **Conclusion:** The recently completed SMARRT study is the first NIH-funded personalized multi-domain trial testing a risk reduction intervention with cognitive and behavioral outcomes among high-risk older adults. Results from this trial will be critical for guiding risk reduction strategies for cognitive aging.

LB6- TWO-YEAR PROGNOSTIC UTILITY OF PLASMA P217+TAU IN THE ALZHEIMER CONTINUUM.

A. Feizpour[1,2], V. Doré[2,3], J.D. Doecke[4], Z.S. Saad[5], G. Triana-Baltzer[5], N. Krishnadas[1,2], C. Fowler[1], L. Ward[1], R.N. Martins[6,7], C.L. Masters[1], V.L. Villemagne[2,8], J. Fripp[4], H.C. Kolb[5], C.C. Rowe[1,2,9] *(1. The Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia - Melbourne (Australia), 2. Department of Molecular Imaging & Therapy, Austin Health, Melbourne, Victoria, Australia - Melbourne (Australia), 3. The Australian e-Health Research Centre, CSIRO, Melbourne, Victoria, Australia - Melbourne (Australia), 4. The Australian e-Health Research Centre, CSIRO, Brisbane, Queensland, Australia - Brisbane (Australia), 5. Neuroscience Biomarkers, Janssen Research and Development, La Jolla, CA, USA - San Diego (United States), 6. Edith Cowan University - Perth (Australia), 7. McCusker Alzheimer's Research Foundation, Nedlands, - Perth (Australia), 8. Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA - Pittsburgh (United States), 9. Florey Department of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Victoria, Australia - Melbourne (Australia))*

Background: Plasma p217+tau is a novel biomarker that detects tau phosphorylation at threonine 217 and is augmented by phosphorylation at threonine 212. P217+tau has shown high predictive accuracy for CSF and PET amyloid-β (Aβ) and tau status. However, the association of p217+tau with longitudinal cognition and its comparative performance to neuroimaging biomarkers of Aβ and tau in predicting prospective cognitive decline has not yet been investigated. **Objectives:** We examined whether p217+tau can 1) predict prospective cognitive decline on multiple well-established measures of cognition; 2) be a better predictor of cognitive decline than neuroimaging biomarkers of Aβ (18F-NAV4694) and tau (18F-MK6240); 3) provide a (pre)screening strategy to decrease sample size, and therefore cost, of therapeutic trials aiming to slow cognitive decline. All objectives were investigated in a cognitively unimpaired and a cognitively impaired cohort to assess performance of p217+tau in early and later stages of the Alzheimer's Disease (AD) continuum. **Methods:** 134 cognitively unimpaired (CU) participants and 41 age-matched patients with cognitive impairment (CI: i.e., mild cognitive impairment or mild dementia) were included. Participants underwent blood sampling, 18F-MK6240 tau PET, and 18F-NAV4694 Aβ-PET at baseline. PET were quantified in Centiloid (CL) for Aβ scans and SUVR in the mesial temporal (Me), temporo-parietal (Te), and meta-temporal (MetaT) regions for tau scan using CapAIBL. Clinical and neuropsychological assessments (MMSE, CDR-SB, AIBL-PACC) were performed at baseline and follow-up (2 ± 0.6 years). Multivariable linear models were used to evaluate the association of baseline biomarkers with change in cognition (individual cognitive slopes calculated via robust linear models), after adjusting for baseline age, sex, APOE ε4, and years of education. Standardised beta coefficients (β) and their corresponding p values are reported. Binary p217+tau (pT-/pT+), Aβ (A-/A+), and tau (T-/T+) groups were created using 80% sensitivity thresholds to identify cognitive decliners. Power analysis was performed in CI to estimate sample size required to detect a 30% slope reduction on CDR-SB, with 90% power. Sample size and associated screening cost for the pT+ group was compared to those for A+ and T+ PET groups. **Results:** In the CI group, plasma p217+tau was a significant predictor of change in MMSE ($\beta = -0.51$, $p = 0.002$) and CDR-SB ($\beta = 0.57$, $p < 0.001$), with the effect size larger than Aβ-PET CL (MMSE $\beta = -0.43$, $p = 0.021$; CDR-SB $\beta = 0.37$, $p = 0.045$) but lower than MetaT tau SUVR (MMSE: $\beta = -0.59$, $p < 0.001$; CDR-SB: $\beta = 0.64$, $p < 0.001$). In the CU group, plasma p217+tau did not correlate with decline in AIBL-PACC score over two years ($\beta = -0.08$, $p = 0.36$;), similar to Aβ-PET CL ($\beta = -0.05$, $p = 0.58$) while MetaT tau SUVR was associated with cognitive decline ($\beta = -0.19$, $p = 0.031$). In CI, the biomarker thresholds based on 80% sensitivity to detect positive CDR-SB slope were 131.1 fg/ml for pT+, 1.12 SUVR for T+Me, 1.2 SUVR for T+Te, 1.18 SUVR for T+MetaT and 62 CL for A+ group. Screening pT+ CI participants into a therapeutic trial — aiming at slowing cognitive decline— led to 29% reduction in sample size compared to screening with PET for A+ and 4-16% reduction compared to screening with PET for T+ (for different ROIs). Using plasma p217+tau for trial selection rather than a PET scan would translate to a >75% test cost saving assuming a blood test cost one fifth of a PET scan, owing to both the lower cost of the test and the smaller cohort size required for the trial. In a therapeutic trial recruiting PET T+MetaT, p217+tau pre-screening followed by PET would save 4% of the PET cost in the CI group, compared to 38% in the CU group. **Conclusion:** This data suggests that substantial cost reduction can be achieved using plasma p217+tau alone to select participants with MCI or mild dementia for a clinical trial designed to slow cognitive decline by 30% over two years, compared to participant selection by PET. Cognitive decline in

CI participants that were pT+ was slightly steeper than that in PET T+ or A+; therefore, savings would result from the lower cost of the test and the smaller cohort size required for the trial. Cost-effectiveness of using p217+tau for pre-screening in MCI and mild dementia can only be achieved if the plasma p217+tau test costs far less than one fifth of the PET scan but increases the number needed to screen and this may negate any saving from lower test cost. In contrast, in the cognitively unimpaired population, p217+tau was not able to predict cognitive decline over two years, but it provided significant cost-saving if used as a pre-screening measure for PET A+ or T+. In CU, only tau PET predicted two-year cognitive decline. These findings require replication in larger cohorts.

LB7- ALZ-NET: USING REAL WORLD EVIDENCE TO DEFINE THE FUTURE OF ALZHEIMER'S TREATMENT AND CARE. M. Carrillo[1], G. Rabinovici[2], M. Rafii[3] *(1. Alzheimer's Association - Chicago (United States), 2. Memory and Aging Center, Departments of Neurology, Radiology & Biomedical Imaging, University of California, San Francisco - San Francisco (United States), 3. Alzheimer's Therapeutic Research Institute, Keck School of Medicine of the University of Southern California - San Diego (United States))*

Background: There are over 100 therapies being tested in clinical trials for Alzheimer's disease (AD) today. With potential therapies undergoing regulatory review and a growing drug development pipeline, the field is in a new phase of treatment. Once approved and used in the community, it will be important to track longitudinal clinical and safety outcomes of novel therapies in large numbers of diverse patients being cared for in real-world clinical practice. **Methods:** The Alzheimer's Association, American College of Radiology, American Society of Neuroradiology, the Department of Biostatistics, Brown University School of Public Health and the Critical Path Institute, along with international clinical, research and imaging experts, have launched the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET). ALZ-NET builds on successes of networks developed in other neurologic and systemic diseases, and leverages the groundwork from the IDEAS and New IDEAS studies. These have demonstrated large-scale, real-world data collection in dementia practice is feasible for addressing critical research questions regarding dementia care. Networks of dementia clinics and imaging facilities will provide ALZ-NET's foundation and will expand over time to include a variety of clinical practices. Patients about to start or already receiving treatment with a novel FDA-approved AD therapy will be eligible to enroll in ALZNET. ALZ-NET is structured to collect a data set that aligns with patient care, agnostic of therapy and care setting, including, baseline demographic, medical, neurologic, genetic and biomarker data. Every 6-12 months, patients will be followed longitudinally with MMSE or MoCA (required), AD8 (optional), FAQ (required) and NPI-Q (optional). Trajectories for cognition, function and behavior over time will be evaluated, assessing the patient-specific predictors of response, including clinical response to individual drugs or combination of drugs. ALZ-NET will track all adverse events (CTCAE grade≥3), unexpected and serious adverse events. A central repository will collect baseline and longitudinal neuroimaging (MRI, PET). Existing databases will track health outcomes and resource utilization. Patients will be followed until withdrawal of consent, death or lost to follow-up. All data collection and sharing will be fully compliant with research participant protections, privacy and patient/provider autonomy. **Results:** ALZ-NET will collect longitudinal clinical and safety data for enrolled patients treated with novel FDA-approved AD therapies and will track long-term health outcomes (effectiveness and safety), associated with use in real-world settings. ALZ-NET aims to assess the clinical course of people from a variety of backgrounds and communities, to achieve representativeness beyond the populations historically enrolled in clinical trials. ALZ-NET has partnered with clinical sites providing care in diverse practice settings to serve as the network's initial vanguard sites. These clinical sites are the first to enroll patients into the network and provide clinical and imaging data on the use of currently approved FDA therapy for AD. ALZ-NET continues to invite sites who already, or will, offer these therapies to their patients. Participating sites have multi-disciplinary clinical expertise and an infrastructure to support the use of novel FDA-approved AD therapies consistent with the safety monitoring outlined in applicable FDA approved labels. Aspects of a qualified participating site include: access to accredited and appropriate radiological services for diagnostic and safety brain imaging; access to infusion services; access to emergency services; and access to standard cognitive, behavioral, and functional assessments used in dementia care. Efforts have been made to minimize patient and site burden while still ensuring collection of a rigorous core dataset that can be used to answer critical research questions. ALZ-NET is designed to work collaboratively and in conjunction with affiliated studies conducted by academia, industry, federal or ALZ-NET project teams. Affiliated studies could be designed to answer broad or specific questions regarding treatment. Data are being collected in a regulatory grade manner to maximize the potential for how data can be used and applied for all stakeholders. **Conclusions:** ALZ-NET is actively engaging and expanding the network of sites, allowing for the collection of real-world data from enrolled patients receiving novel FDA-approved AD therapies. It is designed to answer questions for therapies available now and those on the horizon including: tracking longitudinal change of treatment (or treatments); identifying responders and non-responders or predictors of response and non-response to specific therapeutics; and comparing aggregated data on outcomes across mechanisms of action and within classes of therapeutics. Over time, ALZ-NET will be used to study clinical outcomes and resource utilization using claims and EHR. ALZ-NET will be a resource for evidence gathering, information sharing, and education across clinical and research communities, encouraging innovative, inclusive research and supporting opportunities to improve care. **Note:** This abstract is submitted on behalf of the ALZ-NET Project Team: Ali Atri, Banner Sun Health Research Institute; Jerome Barakos, Sutter Health California; Sharon Brangman, SUNY Upstate Medical University; Kirk Daffner, Harvard Medical School; Rebecca M. Edelmayer, Alzheimer's Association; Constantine Gatsonis, Brown University School of Public Health; Gregory Jicha, University of Kentucky; John Jordan, American College of Radiology / American Society of Neuroradiology / Providence Little Company of Mary Medical Center-Torrance; Jennifer Lingler, University of Pittsburgh School of Nursing; Oscar Lopez, University of Pittsburgh School of Medicine; Andrew W. March, American College of Radiology; Anton P. Porsteinsson, University of Rochester School of Medicine; Katherine Possin, Memory and Aging Center, University of California, San Francisco; Klaus Romero, Critical Path Institute; Stephen Salloway, Butler Hospital / Warren Alpert Medical School of Brown University; Mary Sano, Mount Sinai School of Medicine; Sudhir Sivakumaran, Critical Path Institute; Heather Snyder, Alzheimer's Association; Rade B. Vukmir,

Alzheimer's Association; Christopher Whitlow, Wake Forest School of Medicine / American College of Radiology; Consuelo Wilkins, Vanderbilt University Medical Center; Charles Windon, Memory and Aging Center, University of California, San Francisco. **Disclosures:** Maria C. Carrillo is a full-time employee of the Alzheimer's Association. She has a daughter that is a full-time graduate student in the USC Neuroscience program. Gil Rabinovici receives research support from Avid Radiopharmaceuticals, GE Healthcare, Genentech, and Life Molecular Imaging; served on SAB for Eli Lilly, Genentech, and Roche; serves on DSMB for Johnson & Johnson; is an Associate Editor for JAMA Neurology. Michael Rafii receives research support from Eli Lilly and Eisai Inc.; chairs DSMBs for Alzheon and Biohaven; serves on the SAB for Embic; provides consultation to AC Immune SA and Keystone Bio.

LB8- TOP LINE DATA OF ANAVEX®2-73 (BLARCAMESINE) RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED PHASE 2B/3 IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE (AD). S. Macfarlane[1], T. Grimmer[2], T. O'brien[3], E. Hammond[4], W. Kaufmann[4], E. Fadiran[4], C. Missling[4] *(1. Hammoncare - Melbourne (Australia), 2. THU Munich - Munich (Germany), 3. Monash University, Alfred Health - Melbourne (Australia), 4. Anavex Life Sciences - New York (United States))*

Background: ANAVEX®2-73 (blarcamesine) is a novel, oral, investigational sigma-1 receptor (SIGMAR1) agonist with multimodal activity with previously demonstrated dose-dependent target engagement by positron emission tomography (PET) imaging as well as reduction of pathological inflammation, amyloid beta, and tau. A prior Phase 2a ANAVEX®2-73 study in patients with Alzheimer's disease (AD) (1) demonstrated reduction in rates of cognitive (MMSE) and functional (ADCS-ADL) decline in participants with higher ANAVEX®2-73 plasma concentration (doses up to 50 mg once daily). This effect was also observed in the cohort carrying the common SIGMAR1 wild type (WT) gene variant (80-84% of worldwide population), which would be an additional confirmation of the biological relevance of the SIGMAR1 activation (2). Furthermore, in a transcriptomics analysis (RNAseq) of a randomized, placebo-controlled dementia study in patients with Parkinson's Disease Dementia (PDD), levels of pathways and genes, which are down-regulated in AD pathology were significantly increased by the therapeutic effect of ANAVEX®2-73 ($p<0.005$) (3). **Objectives:** The ANAVEX®2-73-AD-004 study was an international, randomized, double-blind, multicenter, placebo-controlled Phase 2b/3 clinical study in participants with early AD, which included biomarkers of both drug response and AD pathology (4). Here we report efficacy over 48 weeks of ANAVEX®2-73 administration on reduction in cognitive (ADAS-Cog) and functional (ADCS-ADL) decline as well as the effect of the common SIGMAR1 wild type (WT) gene variant on efficacy outcome measures. **Methods:** 509 patients with early AD were randomized 1:1:1 to oral target doses of 30 mg, 50 mg ANAVEX®2-73 or placebo, once daily. The primary endpoint was reduction in cognitive and functional decline, assessed from baseline, over the 48-week period as evaluated by co-primary efficacy endpoints ADAS-Cog and ADCS-ADL in participants receiving ANAVEX®2-73 compared to placebo. Key secondary efficacy endpoint was reduction in cognitive decline as measured by the CDR-SB from baseline to end of treatment (48 weeks). Safety of ANAVEX®2-73 in this study was also evaluated. **Results:** The top line results of the study are expected to be available around the time of the CTAD 2022 conference. **Conclusions:** The conclusions of the study are expected to be available around the time of the CTAD 2022 conference. **References:** 1. Hampel et al. A precision medicine framework using artificial intelligence for the identification and confirmation of genomic biomarkers of response to an Alzheimer's disease therapy: Analysis of the blarcamesine (ANAVEX2-73) Phase 2a clinical study. Alzheimer's Dement. 2020;00:1–14; 2. Excluding the cohort carrying the SIGMAR1 rs1800866 gene variant (16%-20%): https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=rs1800866; 3. https://www.anavex.com/_files/ugd/79bcf7_c5813c517d9f4ca5aacbeb719508827a.pdf; 4. ClinicalTrials.gov Identifiers: NCT03790709, NCT02756858.

LB9- HIGHER SENSITIVITY AMYLOID-PET DETECTION OF THE EARLIEST FOCAL BETA-AMYLOID ACCUMULATION USING SPATIAL EXTENT. M.E. Farrell[1], E.G. Thibault[1], J.A. Becker[1], J.C. Price[1], K. Gong[1], A.P. Schultz[1], M.J. Properzi[1], R.F. Buckley[1,2], H.I.L. Jacobs[1], B.J. Hanseeuw[1,3], R.A. Sperling[1,2], K.A. Johnson[1,2] *(1. Massachusetts General Hospital - Boston, Ma (United States), 2. Brigham & Women's Hospital - Boston, Ma (United States), 3. Cliniques Universitaires Saint-Luc, Université Catholique de Louvain - Brussels (Belgium))*

Background: The key to the prevention of Alzheimer's disease may lie with intervening at the earliest possible point in the pathological cascade, before neurodegeneration at the earliest signs of beta-amyloid (Aβ). The current gold standard for measuring Aβ deposits in the brain relies on average measures of global neocortical burden using PET, which fails to detect earlier focal Aβ deposits and likely leaves a limited time window before neurodegeneration. Importantly, it may be possible to reliably measure Aβ below global AbPET thresholds by changing two key aspects of Aβ-PET measurement: where we look and how we measure. Prior studies indicate focusing on early-accumulating regions can aid detection of early focal Aβ, but heterogeneity across studies in where Aβ begins accumulating has impeded the development of a reliable and generalizable early Aβ PET aggregate. In the present study, we sought to allow greater flexibly by incorporating more early Aβ regions, aggregating across all regions that are reliably associated with future Aβ-PET accumulation using longitudinal PIB-PET from initially globally Aβ- adults from the Harvard Aging Brain Study (HABS). However, while an expanded early Aβ aggregate may allow greater flexibility, doing so may also dilute the early focal signals we aim to detect. To avoid this dilution, we shifted our summary Aβ from the standard measure of average burden to a measure of the spatial extent of Aβ deposits. We hypothesized that measuring the number of regions with elevated Aβ within a larger set of reliable early Aβ regions would allow for greater sensitivity to focal early Aβ deposits than requiring the average burden across the entire aggregate to surpass a detection threshold. **Objective:** To demonstrate the improved sensitivity and specificity of measuring spatial extent within a set of reliable early Aβ regions to predict which individuals will progress to global Aβ positivity in the future and assess its potential for improved targeting of individuals with early Aβ in clinical trials. **Methods:** Longitudinal Pittsburgh Compound B (PIB)-PET data from 160 clinically normal (CN) older adults from HABS with globally Aβ- PET scans at baseline were used to identify all regions for which baseline elevated PIB was not significantly associated with future local decline (a sign of vulnerability to signal noise) and was significantly associated with increasing future global PIB slope. The mean burden and spatial extent in different potential aggregates based on these results were tested for their ability to predict progression to global Aβ+ in 3 years

using receiver operate characteristic (ROC) curve analysis and beyond (up to 8 years) using survival analysis. The replicability and generalizability of these results were validated in an external sample of 208 initially globally Aβ- CN older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Power analyses determined the number of the individuals that would need to be screened to enroll 200 participants to detect a 50% change in Ab burden over 1 year with 80% power based on 4 possible approaches to defining the lower bound for early Aβ deposits: 1) the current global Aβ threshold, 2) a lowered global Aβ threshold, 3) mean burden in the optimized early Aβ aggregate, and 4) spatial extent in the global Aβ burden. **Results:** A large aggregate of reliable and predictive regions (bilateral medial frontal/parietal, cingulate, lateral parietal/occipital and left lateral frontal/parietal) developed within HABS provided high sensitivity in predict progression to global positivity while maintaining high specificity in HABS (SE=.88, SP=.97) and ADNI (SE=1.00, SP=.91), though its slight advantage in specificity over other large aggregates is small compared with the 2.5x increased rate of early detection conferred by switching from a measure of mean burden to extent (SEextent=.88, SEmean=.35). Using Spatial extent in the early Aβ aggregate resulted in a 73% reduction in the number of individuals that would need to the screened relative to a standard global Aβ threshold (nstandard=4340, nextent=1193), a 44% reduction relative to a lowered global threshold (n = 2146) and 51% relative to using the mean burden in the early Aβ aggregate (n=2543). **Conclusion:** Our findings demonstrate that measures of spatial extent across a broad set of neocortical regions are far more sensitive to detect early Aβ than traditional measures of average burden in two independent samples. These extent measures display great potential for improved targeting of early Aβ in both clinical trials and research into the earliest stages of amyloidosis and AD pathogenesis.

LB10- SAMPLE SIZE ESTIMATES FOR PRECLINICAL AD INTERVENTION TRIALS BASED ON WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION LONGITUDINAL PET AMYLOID, PLASMA P-TAU217, AND COGNITIVE ASSESSMENT DATA.

R. Langhough Koscik[1], D. Norton[1], T. Betthauser[1], L. Du[1], E. Jonaitis[1], K. Cody[1], B. Hermann[1], K. Mueller[1], R. Chappell[1], B. Christian[1], S. Janelidze[1], N. Mattsson-Carlgren[1], O. Hansson[1], S. Johnson[1]
(1. University of Wisconsin SMPH - Madison (United States))

Background: Data increasingly show that progression from amyloid onset to Alzheimer's disease (AD)-dementia spans many years. Our study and others have demonstrated that preclinical cognitive decline is related to brain amyloid burden and how long amyloid has been present. Thus, an ideal intervention window for amyloid therapies may be at the earliest signs of amyloid accumulation, before cognitive decline has reached clinical impairment. This study uses longitudinal data from the Wisconsin Registry for Alzheimer's Prevention (WRAP) to inform sample size estimates for preclinical AD trial designs aiming to slow amyloid accumulation and slow or delay tau accumulation and cognitive decline. **Methods:** WRAP, a longitudinal cohort study of persons who were without dementia at cognitive baseline (mean(sd) age=54(6)), is enriched for AD risk via oversampling for parental AD history (~72%). WRAP participants complete biennial cognitive assessments and blood draws; a subset complete positron emission tomography (PET) amyloid scans. PET amyloid burden was quantified from eight bi-lateral ROI's using the tracer 11C-Pittsburgh Compound B to obtain a global PiB DVR value from each scan; DVR was then used to get estimated amyloid onset age and imputed DVR's corresponding to ages at cognitive and plasma sampling (Betthauser et al, 2022). Longitudinal plasma P-tau217 was assayed in a PET subset (Meso Scale Discovery platform). To assess the effect of baseline amyloid on expected progression on various trial-relevant outcomes, we stratified observations into groups defined by PiB DVR at each assessment age. Groups (and corresponding DVR ranges) included amyloid negative (Aneg; DVR<1.13), sub-threshold-to-low-amyloid-positive (subApos; DVR≈[1.13, 1.2); and amyloid-positive (Apos; Global PiB DVR≥1.2). Visit-level data were included in estimates for each group if: the DVR was in that group's range; the participant was between 50-80 years and cognitively unimpaired (CU) at first visit in that group; and the participant had at least two visits for the outcome of interest. A single participant could in this way contribute in more than one group. We used linear mixed effects models to estimate group-specific slope and error for Global PiB DVR, plasma P-tau217 and a set of cognitive composites and individual tests considered sensitive to AD-related change (fixed effect: years since baseline measurement; random within-person intercepts and slopes). The fixed effects slope estimates were then used to estimate sample sizes needed to detect a range of possible treatment effects for PiB, plasma and cognitive outcomes for trials targeting CU subApos samples and CU Apos samples (power=80%; assuming 3-year PiB and plasma follow-up and 6-year cognitive follow-up). Treatment effects were calculated as percent change relative to slope estimates within the subApos and Apos groups (i.e., representing attenuation towards 0 in treatment group); for the subApos group, we also calculated sample sizes for treatment effects relative to the Aneg slopes (representing attenuation to normal preclinical age-related change in the treatment group). We report samples sizes needed per treatment arm (25% treatment effect) for the five cognitive outcomes with lowest estimates from a set that included three cognitive composites and eight individual tests. **Results:** In the Aneg sample, longitudinal data from 109, 93, and 330 participants, respectively, contributed to slope estimates for PiB, plasma, and cognitive outcomes (median baseline ages by outcome:62, 62, and 55). In the subApos sample, longitudinal data from 13, 28, and 68 participants contributed to PiB, plasma, and cognitive estimates (median baseline ages: 65, 65, and 61). Sample sizes needed per treatment arm to detect a 25% reduction in worsening relative to 0/aNeg are, by cognitive outcome: Digit Symbol Substitution test, 441/2697; Harvard Aging Brain Study processing speed composite (HABS-PS, Trails A and Digit Symbol), 1373/2573; WRAP 3-test preclinical Alzheimer's Cognitive composite (PACC3; RAVLT learning, Logical Memory II, Digit Symbol Substitution), 1903/8716; WRAP 5-test PACC (PACC3 plus MMSE and CFL fluency), 2015/3242; and log(Trails B) time, 6738/5206. In the Apos sample, longitudinal data from 20, 46, and 61 participants, contributed to estimates for PiB, plasma, and cognitive outcomes (median baseline ages 66, 64, 59). Sample size needed per treatment arm to detect a 25% reduction in worsening relative to 0 are, by outcome: PiB, 117; plasma p-tau217, 377; Digit Symbol, 190; PACC5, 843; PACC3, 905; Logical Memory II, 1545; and HABS-PS, 1960. For both target samples, powering to detect such cognitive change corresponds to >80% power to detect PiB and plasma p-tau217 effects of ~10% or higher. **Conclusion:** Sample size requirements for cognitive outcomes vary widely depending on the cognitive measure, the baseline amyloid range of trial participants and whether treatment effects are based on attenuation to zero or to trajectory estimates of those who are amyloid negative (i.e., presumably healthy

controls). Our estimates suggest that a processing speed composite or the Digit Symbol task contributing to it may out-perform more commonly used preclinical AD composites. Studies that are adequately powered to detect slowing in preclinical cognitive decline will be adequately powered to detect clinically meaningful PiB and plasma P-tau217 treatment effects.

LB11- CEREBROSPINAL FLUID BIOMARKER EFFECTS FROM A FIXED-DOSE COMBINATION OF SODIUM PHENYLBUTYRATE AND TAURURSODIOL IN ALZHEIMER'S DISEASE: RESULTS FROM THE PEGASUS TRIAL. S.E. Arnold[1,2], N. Knowlton[3], V.J. Williams[4], J.M. Burns[5], M. Crane[6], A.J. Mcmanus[1], S.N. Vaishnavi[7], Z. Arvanitakis[8], J. Neugroschl[9], K. Bell[10], B.A. Trombetta[1], B.C. Carlyle[11], P. Kivisäkk[2,12], R.E. Tanzi[13,14], K. Leslie[15,16] *(1. Department of Neurology, Massachusetts General Hospital, Boston, MA, USA - Boston (United States), 2. Harvard Medical School, Boston, MA, USA - Boston (United States), 3. Pentara Corporation, Millcreek, UT, USA - Millcreek (United States), 4. Department of Medicine, University of Wisconsin-Madison, School of Medicine and Public Health, Madison, WI, USA - Madison (United States), 5. University of Kansas Alzheimer's Disease Center, Kansas City, KS, USA - Kansas City (United States), 6. Genesis Neuroscience Clinic, Knoxville, TN, USA - Knoxville (United States), 7. Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA - Philadelphia (United States), 8. Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA - Chicago (United States), 9. Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA - New York (United States), 10. Department of Neurology, Columbia University, New York, NY, USA - New York (United States), 11. Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, England, United Kingdom - England (United Kingdom), 12. Department of Neurology, Massachusetts General Hospital, Boston, MA, USA; Harvard Medical School, Boston, MA, USA - Boston (United States), 13. Harvard Medical School, Boston, MA, USA - Boston (United Kingdom), 14. Department of Neurology, Genetics and Aging Research Unit, McCance Center for Brain Health, Massachusetts General Hospital, Harvard University, Boston, MA, USA - Boston (United States), 15. Amylyx Pharmaceuticals, Inc., Cambridge, MA, USA - Cambridge (United States), 16. Present address: Division of Biology and Biological Engineering Graduate Program, California Institute of Technology, Pasadena, CA, USA - Pasadena (United States))*

Background: An oral, fixed-dose combination of sodium phenylbutyrate and taurursodiol (PB and TURSO) is hypothesized to simultaneously mitigate endoplasmic reticulum stress and mitochondrial dysfunction, pathways relevant in neurodegenerative diseases. Oral PB and TURSO was shown to significantly slow functional decline and prolong survival in a randomized, placebo-controlled trial in amyotrophic lateral sclerosis (ALS). Preclinical studies have shown activity of PB and TURSO individually and in combination in animal models of Alzheimer's disease (AD). PEGASUS (NCT03533257) was the first-in-indication clinical trial designed to evaluate the safety and biologic activity of PB and TURSO in AD, with an aim of informing the design of future studies of PB and TURSO in AD and other neurodegenerative diseases. **Objective:** Report final safety and full biomarker results from PEGASUS. **Methods:** PEGASUS was a phase 2, multicenter, randomized, double-blind, placebo-controlled trial enrolling adults aged 55 to 89 years with mild cognitive impairment or mild to moderate dementia (baseline Montreal Cognitive Assessment [MoCA] score ≥8) with supporting biomarkers of AD pathology. Participants were randomized to receive oral PB and TURSO or matching placebo for 24 weeks and were permitted to continue on stable dosing regimens of standard-of-care AD medications. The primary outcome of the study was safety and tolerability of PB and TURSO. The secondary outcome was efficacy assessed using a global statistical test for change from baseline to week 24 combining 3 univariate end points: Mild/Moderate Alzheimer's Disease Composite Scale (MADCOMS), Functional Activities Questionnaire, and hippocampal volume on volumetric magnetic resonance imaging. Exploratory outcome measures consisted of cerebrospinal fluid (CSF) biomarkers, namely, changes from baseline in core AD biomarkers (amyloid beta species [Aβ42, Aβ40, and Aβ42/Aβ40 ratio], total tau [t-tau], and phospho-tau 181 [p-tau]) as well as biomarkers of neurodegeneration (neurofilament light chain, fatty acid binding protein-3 [FABP3]), synaptic integrity (neurogranin), inflammation and immune modulation (interleukin [IL]-6, IL-8, IL-15, monocyte chemoattractant protein-1, glial fibrillary acidic protein, chitinase 3–like protein 1 [YKL-40]), neurovascular/neuropil remodeling (matrix metalloproteinase-10), oxidative stress (8-hydroxy-2′-deoxyguanosine [8-OHdG]), and metabolic dysregulation in the brain (24S-hydroxycholesterol, leptin, soluble insulin receptor). Based on feasibility, a sample size of approximately 100 participants was chosen. Mean between-group differences in change from baseline at week 24 were compared between active and placebo arms for all efficacy outcomes and declared significant if P<.05 without multiplicity adjustment. No hypothesis testing was performed for safety variables. **Results:** A total of 95 participants with an average age of 70.7 years were randomized (PB and TURSO, n=51; placebo, n=44). Approximately 67% of participants were receiving donepezil and 37% participants were receiving memantine at baseline for cognitive impairment. Baseline demographics and biomarker values were generally well matched between the groups; however, participants randomized to PB and TURSO had evidence of greater baseline cognitive impairment based on mean Alzheimer's Disease Assessment Scale–Cognitive Subscale, MoCA, and MADCOMS scores (all P≤.007 vs placebo). No new safety signals were observed compared to the previous study in ALS, despite the older participant population in PEGASUS. Adverse events were predominantly gastrointestinal. This study was not powered to see differences in clinical efficacy end points, and no significant between-group differences were observed for the primary or secondary clinical end points. However, mean (SD) changes from baseline to week 24 directionally favored PB and TURSO versus placebo for the core AD biomarkers Aβ42/Aβ40 ratio (+0.004 [0.004] vs –0.005 [0.004]; P=.005), t-tau (–64.9 [15.5] vs +8.82 [15.2] pg/mL; P<.0001), and p-tau (–14.6 [3.0] vs –0.27 [2.9] pg/mL; P=.0002), as well as FABP3 (–344.6 [85.9] vs +102.9 [80.6] pg/mL; P=.0004), neurogranin (–81.2 [16.5] vs –8.3 [15.9] pg/mL; P= .0003), IL-15 (–0.02 [0.08] vs +0.25 [0.07] pg/mL; P=.01), YKL-40 (–14,635.4 [3954.0] vs +1507.9 [3776.8] pg/mL; P=.004), and 8-OHdG (+0.31 [0.16] vs –0.13 [0.15]; P=.006). Other biomarkers did not show significant mean between-group differences. **Conclusions:** Compared with placebo, PB and TURSO significantly improved CSF amyloid, tau, and neurodegeneration markers and other biomarkers relevant to AD pathophysiology. Results from PEGASUS provide the first-in-human evidence for a treatment effect of PB and TURSO on AD pathology and pathways of inflammation, synaptic function, oxidative stress, and neurodegeneration, complementing preclinical studies that showed a biologic effect for PB and TURSO both individually and in combination in AD

models. Taken together, these findings may be used to inform the design of subsequent trials and provide support for further clinical development of PB and TURSO for AD and other neurodegenerative diseases. **Disclosures:** Conflicts of interest will be listed in the presentation at CTAD.

LB12- USE OF A BLOOD-BASED BIOMARKER TEST IMPACTS CLINICAL DECISION MAKING AMONG NEUROLOGISTS EVALUATING PATIENTS WITH SYMPTOMS OF COGNITIVE IMPAIRMENT. J. Braunstein[1], M. Monane[1], K. Johnson[2], B.J. Snider[3], R. Scott Turner[4], J. Drake[5], D. Jacobs[6], J. Ortega[1], J. Henderson[1], T. West[1] *(1. C2N Diagnostics - St Louis (United States), 2. Duke University - Durham (United States), 3. Washington University - St Louis (United States), 4. Georgetown University - Washington (United States), 5. Lifespan - Providence (United States), 6. Neurological Services of Orlando - Orlando (United States))*

Background: A critical need exists for early, accurate diagnosis of Alzheimer's disease (AD) to guide patients to current and emerging anti-AD therapies as well as to rule out AD to allow for other diagnostic considerations. There is also a need for safe, less resource-intensive, easily accessible, and broadly available tests that identify the presence or absence of brain amyloid plaques, a pathologic hallmark of AD. Blood-based biomarkers (BBMs) offer advantages over imaging and cerebrospinal fluid (CSF) measurements, potentially fulfilling these unmet needs. The PrecivityAD™ blood test quantifies plasma concentrations of amyloid beta 42 and 40 (Aβ42 and Aβ40) and determines the presence of apolipoprotein E (ApoE)-specific peptides to establish the APOE genotype. The Aβ42/40 ratio + APOE genotype + patient's age are used to calculate the Amyloid Probability Score (APS), which is the test result, by way of a validated regression model. The PrecivityAD blood test has demonstrated 92% sensitivity and 77% specificity in a large trial incorporating patients from the Plasma Test for Amyloidosis Risk Screening (PARIS) study (NCT02420756), a prospective add-on to the Imaging Dementia–Evidence for Amyloid Scanning study, as well as the MissionAD study (BCT02956486). While clinical validity for the PrecivityAD blood test has been demonstrated, this study focuses on clinical decision making associated with results of BBM testing. **Objectives:** The study objective is to assess patient selection and score interpretation of the PrecivityAD blood test and the APS as well as post-test changes in diagnostic certainty and management of symptomatic patients being evaluated for AD or other causes of cognitive decline. **Methods:** The Quality Improvement PrecivityAD (QUIP I) Clinician Survey (NCT05477056) is a prospective, single cohort study conducted at outpatient sites among patients 60 years and older presenting to a neurologist with signs or symptoms of mild cognitive impairment (MCI) or dementia. All patients received PrecivityAD blood testing and an APS result. The APS reflects the likelihood that a patient, on a scale of 0-100, will be amyloid positive on an amyloid PET scan, with low APS (0-35), intermediate APS (36-57), and high APS (58-100) as established score categories representing low, intermediate, and high likelihood of amyloid PET positivity, respectively. Physician surveys focused on quality improvement were conducted after receipt of the test results. Collected data included subject demographics, APS result, diagnostic certainty pre- and post-blood testing, and planned drug therapy. **Results:** Participating clinicians from 13 sites submitted 272 surveys between March 2021 and July 2022. The surveys reflected patients with a median age of 73 years old, 56% female, and 90% white. The mean APS was 45 (range 0-100): 46% (n=125) patients had low scores, 14% (n=39) had intermediate scores, and 40% (n=108) had high scores. The mean probability of AD diagnosis was rated by physicians as 63% pre-test and 52% post-test ($p<0.0001$). The mean probability of physicians' estimates of AD changed pre-test to post-test from 56% to 20% (low APS group), 63% to 47% (intermediate APS group), and 70% to 89% (high APS group) ($p<0.0001$). Anti-AD drug therapy was noted in 50% of patients pre-test and 57% of patients post-test; however, 25% (69/272) of patients had planned changes in anti-AD drug therapy. Of note, 85% (33/39) of patients with increased drug therapy were in the high APS group, and 93% (28/30) of patients with decreased drug therapy were in the low APS group ($p<0.0001$). **Conclusions:** In summary, the PrecivityAD blood test showed clinical utility in its association with physician decision-making around diagnostic certainty and drug therapy management in patients evaluated for mild cognitive impairment or dementia, with 86% of patients deriving clinically useful low or high APS results. Low APS patients were evaluated by neurologists to have lower AD likelihood post-test and were less likely to be managed with anti-AD drugs, consistent with ruling out AD. High APS patients were judged by neurologists to have higher AD likelihood post-test and were more likely to be managed with anti-AD drugs, consistent with ruling in AD. While previous studies have demonstrated that the use of amyloid PET and CSF biomarkers have been associated with changes in diagnostic confidence of AD as well as changes in anti-AD drug therapy, this study is one of the first to show clinical management changes using a BBM test assessing the presence or absence of brain amyloidosis among symptomatic patients being evaluated for AD or other causes of cognitive decline.

LB13- PHASE 1 PHARMACOKINETIC AND CNS TARGET ENGAGEMENT PROPERTIES OF THE ORALLY ADMINISTERED O-GLCNACASE INHIBITOR ASN51 IN HUMANS. R. Schubert[1], R. Pokorny[1], B. Permanne[1], P. Fang[1], V. Teachout[1], M. Nény[1], S. Ousson[1], J. Hantson[1], A. Sand[1], R. Ahmed[1], M. Schneider[1], J.F. Stallaert[1], A. Quattropani[1], E. Yuen[1], D. Beher[1] *(1. Asceneuron - Lausanne (Switzerland))*

Background: Inhibition of the O-linked-β-N-acetylglucosaminidase (OGA) enzyme blocks the removal of O-linked GlcNAc carbohydrate moieties from the hydroxyl groups of serine and threonine residues on target proteins. One protein that is markedly O-GlcNAcylated in response to OGA inhibition is the microtubule associated protein tau. Tau is best known for its central role in the onset and progression of neurofibrillary tangle (NFT) pathology in Alzheimer's disease (AD) and related forms of dementia. The O-GlcNAcylation of tau proteins prevents their incorporation into insoluble NFTs and maintains tau in a soluble state (O-tau). The ability of orally administered OGA inhibitors to slow the development of neurofibrillary tangle pathology in vivo across multiple preclinical tauopathy models has raised the visibility and potential of this new therapeutic class. Recent work has further shown that O-GlcNAcylation slows the aggregation of α-synuclein proteins by increasing the amount of O-synuclein, with therapeutic implications for Parkinson's disease and related disorders. ASN51 is a novel, oral, brain-penetrant, active-site-directed, reversible OGA inhibitor that is being evaluated as a clinical candidate for the treatment of Alzheimer's and Parkinson's disease. **Objectives and Methods:** Two Phase 1 studies examined the human safety, tolerability, pharmacokinetic, pharmacodynamic and CNS target engagement properties of ASN51 in healthy volunteers. The first study, ASN51-101, was a randomized, double-blind,

placebo-controlled safety, tolerability, pharmacokinetic and pharmacodynamic study of oral ASN51 in healthy young volunteers administered single doses of 20 mg and 50 mg and in healthy elderly volunteers administered ten daily doses of 20 mg. The second study, ASN51-102, was an open-label OGA positron emission tomography (PET) study in healthy adult volunteers administered two single doses of 5 to 15 mg, to determine the relationship between plasma concentration and brain target engagement of ASN51. **Results:** ASN51 was safe and well tolerated throughout the two clinical studies, reaching meaningful plasma and CSF concentrations. Exposures increased in proportion to dose with plasma half-lives in the multiple dose healthy elderly cohort ranging from 38 to 48 hours in steady state. The O-GlcNAcylation of PBMC proteins after ASN51 administration was measured as a surrogate biomarker of O-tau and was >2-fold the baseline value 8 hours after administration of a single 20 mg dose. The OGA PET study indicated that single daily doses of 10 mg can yield OGA enzyme occupancies >95% occupancy at trough. **Conclusions:** Altogether, the Phase 1 data suggest that daily doses of 10 mg or lower will maintain a therapeutic level of OGA inhibition with elevated O-tau and O-synuclein throughout the entire day. ASN51 thus demonstrates safety, pharmacokinetic and pharmacodynamic target engagement properties that are ideal for a once-daily, low dose CNS therapy. Based on ASN51's optimal safety and human pharmacology profile in Phase 1, ASN51 is being advanced to a Phase 2A tau PET proof of mechanism biomarker study in early symptomatic AD patients.

LB14- ANALYSIS OF 15 SOFTWARE PIPELINES FOR VALIDATION OF [18F]FLORBETABEN PET QUANTITATION. A. Jovalekic[1], N. Roe-Vellve[1], N. Koglin[1], M. Lagos Quintana[1], A. Nelson[2], M. Diemling[3], J. Lilja[3], J.P. Gomez Gonzalez[4], V. Dore[5], P. Bourgeat[5], A. Whittington[6], R. Gunn[6], A. Stephens[1], S. Bullich[1] *(1. Life Molecular Imaging - Berlin (Germany), 2. MIM Software - Cleveland (United States), 3. Hermes Medical Solutions - Stockholm (Sweden), 4. QuBiotech - A Coruna (Spain), 5. CSIRO - Brisbane (Australia), 6. Invicro - London (United Kingdom))*

Background: Amyloid positron emission tomography (PET) with [18F]florbetaben is an established tool for detecting Aβ deposition in the brain in vivo and has been approved for routine clinical use since 2014 as Neuraceq® based on visual assessment (VA) of PET scans. Quantitative measures are however commonly used in the research context, with many of the available PET software packages capable of calculating amyloid burden both on a regional and a composite level, allowing continuous measurement of amyloid burden in addition to the approved dichotomous VA. **Objectives:** This study aimed to provide scientific evidence of the robustness and additional value of florbetaben PET quantification, with a focus on Centiloid-based analysis. The diagnostic performance (i.e., sensitivity and specificity) of quantification against the histopathological confirmation of Aβ load was estimated and compared to the effectiveness of the approved VA method. Additionally, the concordance between visual and quantitative evaluation of florbetaben PET scans was assessed. The reliability and comparability of the different analytical pipelines was further tested. **Methods:** This is a retrospective analysis of florbetaben PET images that had been acquired in previous clinical trials. The study population consisted of 589 subjects with at least one available florbetaben PET scan. Florbetaben PET scans were quantified with 15 analytical pipelines using nine software packages (MiMneuro, Hermes BRASS, Neurocloud, Neurology Toolkit, statistical parametric mapping (SPM8), PMOD Neuro, CapAIBL, non-negative matrix factorization (NMF), AmyloidIQ (Whittington et al., 2019)) that used several metrics to estimate Aβ load (SUVR, Centiloid, amyloid load and amyloid index). Six analytical methods reported Centiloid (MiMneuro (Piper et al., 2014), standard centiloid pipeline (Klunk et al., 2015, Rowe et al., 2017), Neurology Toolkit, SPM8 (PET-only), CapAIBL (Bourgeat et al., 2018), NMF (Bourgeat et al., 2021). For some software packages, different analytical methods were tested using different reference regions, for example, without using the T1-weighted MRI scan. All the scans were quantified in batch mode to minimize operator intervention. The operators were different for each software package and blinded to the diagnosis of subjects, demographics, visual PET assessment, histopathology results and all other clinical data. All results were quality controlled. **Results:** The mean sensitivity, specificity and accuracy was 96.1±1.6%, 96.9±1.0% and 96.4±1.1%, respectively, for all quantitative methods tested. Centiloid-based approaches yielded a comparable mean sensitivity, specificity and accuracy of 96.1±1.6%, 97.4±1.2% and 96.7±1.2%, respectively. The mean percentage of agreement between binary quantitative assessment across all 15 pipelines and visual majority assessment was 92.4±1.5%. For the Centiloid-based sub-analysis the mean percentage of agreement with visual majority assessment was 93.2±0.4%. Substantial agreement was observed across software packages using different measures. Intra-software reliability based on re-analysis of selected scans (n=84) ranged between R2=0.98 and 1.00. **Conclusion:** Results from this retrospective analysis demonstrate that software quantification methods, for example Centiloid analysis, can complement visual assessment of florbetaben PET images. Such robust, validated methods could enable readers to augment their visual analysis with optional quantitative tools. Adjunct use of quantification software tools could be beneficial for newly trained or inexperienced operators in instances when images are visually assessed with relatively low confidence, or when amyloid levels of patients are close to «pathology» thresholds, or in longitudinal studies for studying amyloid accumulation or removal. Based on this study, quantification of [18F]florbetaben PET as an adjunct to visual assessment was recently approved by the European Medicines Agency (EMA) in the EU for Neuraceq®. **References:** Bourgeat, P., et al., Implementing the centiloid transformation for (11)C-PiB and beta-amyloid (18)F-PET tracers using CapAIBL. Neuroimage, 2018. 183: p. 387-393. Bourgeat, P., et al., Non-negative matrix factorisation improves Centiloid robustness in longitudinal studies. Neuroimage, 2021. 226: p. 117593. Klunk, W.E., et al., The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement, 2015. 11(1): p. 1-15 e1-4. 27. Piper, J., A. Nelson, and A. Javorek. Evaluation of a Quantitative Method for Florbetaben (FBB) PET Using SUVR. in EANM. 2014. Rowe, C.C., et al., (18)F-Florbetaben PET beta-amyloid binding expressed in Centiloids. Eur J Nucl Med Mol Imaging, 2017. 44(12): p. 2053-2059. Whittington A, and Gunn RN. Amyloid Load: A More Sensitive Biomarker for Amyloid Imaging. J Nucl Med. 2019. 60(4):536-540.

LB15- RESULTS FROM A CLINICAL STUDY OF AN ANTI-GALECTIN-3 MONOCLONAL ANTIBODY IN PATIENTS WITH MODERATE TO SEVERE ALZHEIMER'S DISEASE.

D. Sun[1], G. Haig[1], S. Rasool[1] *(1. Truebinding Inc - Foster City (United States))*

Background: Galectin-3 has been reported to be highly expressed in Alzheimer's disease (AD) brain tissues. Our studies elucidated its intrinsic ability of acting as glue to promote oligomerization of Abeta, pTAU and other amyloid proteins in vitro. It's antagonist monoclonal antibodies showed dramatic cognition improvement and plaque reduction in AD mice after only two-week treatment Inhibition of Galectin-3 is a novel approach to the treatment of AD. The hypothesis is disease reversal, not halting disease progression. Gal-3 is a ubiquitous endogenous protein involved the pathology of certain neurodegenerative, metabolic, and immunologic disorders. TB006 is a humanized IgG4 type monoclonal antibody with high affinity and selectivity for Gal-3. Preclinical studies in Tg mice demonstrated dramatic cognitive improvement and plaque reduction with only two weeks of treatment. In a SAD study in healthy volunteers, doses of up 5000 mg (~70 mg/kg) were safe and well tolerated. Dosing of the clinical lead antibody TB006 in a single ascending dose (SAD) study in healthy volunteers up to 5000mg (70mg/kg) was safe and well tolerated. This phase 1b/2a study was conducted in moderate to severe AD patients to assess the safety, tolerability, PK and efficacy of five weekly TB006 doses. **Methods:** This was a seamless Ph 1b/2a double-blinded, placebo controlled, multicenter study. AD patients with a screening MMSE <24 and without confounding neurologic or psychiatric disease were eligible. In Ph 1b, 3 groups (140 mg, 420 mg, 1000 mg) of 8 patients in sequential ascending fashion received either weekly TB006 (6) or placebo (2) infusions for 5 doses. In Ph 2a, 1 participants16 were to be randomized (1:1) to receive either TB006 (1000mgthe highest safe and tolerated dose from Part 1) or placebo weekly for 5 doses. Ph 2a used the clinical dementia rating -sum of boxes (CDR-SB) score as the primary endpoint. Other endpoints were the mini-mental state examination (MMSE), neuropsychiatric inventory (NPI), CDR battery and plasma and imaging (MRI/PET) biomarkers. Cognition testing was done at baseline and on Days 15, 364, 64, and 104. Safety assessments were conducted at each visit. The sample size provided 80% power to detect a mean difference between TB006 and placebo of 0.25 point at Day 104 on the CDR-SB. **Results:** 157 patients, including 24 in Part 1, were randomized at 15 US sites. ; Nine9 subjects prematurely discontinued. TB006 was safe and well tolerated at all dose levels. There were 9 severe adverse events (SAEs), including 1 death. None were related to TB006 treatment. Most other AEs were mild, sporadic and self-limiting. Patients in Group 3 (1000 mg), as well as all placebo patients in Ph 1a were included in the efficacy analysis. The primary endpoint was met. Patients receiving TB006 showed a dramatic0.9 point reduction on the CDR-SB score compared with placebo ($p<0.015$). Secondary efficacy endpoints were equally robust. Mean efficacy endpoint scores in the placebo group remained consistent throughout the observation period. **Conclusion:** TB006 demonstrated evidence of AD reversal in this short-term treatment study. TB006 was safe and well tolerated.

LB16- PHASE 1 PREVENTIVE ADJUVANTED TAU VACCINE, AV-1980R.

S. Schneider[1], A. Ghichikyan[2], R. Alexander[3], H. Zetterberg[3], E. Reiman[3], D. Tosun[4], M. Agadjanyan[2] *(1. USC - Los Angeles (United States), 2. Institute for Molecular Medicine - Huntington Beach (United States), 3. Banner Alzheimer's Institute - Phoenix (United States), 4. University of California San Francisco - San Francisco (United States))*

Objectives: Results from active and passive immunotherapy in early Alzheimer's patients demonstrate that monoclonal antibodies decrease Aβ and tau pathology. A recent report stated that treatment with anti-amyloid mAb lecanemab reduced cognitive decline by 0.45 CDR-SB points. This facilitates the shift from treatment to prevention, and aligns with a long-standing tenet that safe and immunogenic preventive Aβ and/or tau vaccines should be initiated in cognitively unimpaired participants with preclinical AD. **Methods:** GMP grade AV-1980R was manufactured. Edematous changes, meningeal changes, micro-hemorrhages and meningoencephalitis, and brain atrophy assessed by MRI will be analyzed. Anti-tau cellular and humoral responses will be assessed by ELISPOT and ELISA, respectively. Plasma Aβ42/40, P-tau181, P-tau217, and P-tau231, neurofilament light chain, GFAP will be measured by SIMOA technology. **Results:** This is a randomized, multicenter, double-blind, placebo-controlled, multiple ascending dose trial consisting of 64 cognitively unimpaired individuals at risk of MCI due to AD (preclinical) determined by PET scan and blood biomarkers to determine the safety and tolerability of AV-1980R/A at 20, 100, and 300 μg, i.m. doses. Participants are injected four times at 0, 4, 12, 36 weeks and followed up for a 44-week period. to determine the safety and tolerability of AV-1980R/A at 20, 100, and 300 μg, i.m. doses. Participants will be injected four times and followed up for 44-weeks. Primary outcome is Treatment-Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs). Secondary outcomes are humoral and cellular immune responses and blood biomarkers. **Conclusion:** Passive mAb immunotherapy for cognitively unimpaired people is impractical due to the complexity and need for frequent administration of very high doses. Safe and immunogenic active vaccines are suitable candidates for preventing the accumulation of tau pathology and potentially delaying onset of illness. We are evaluating for the first-time preventive vaccine, AV-1980R/A targeting the phosphatase-activating domain (PAD) of pathological tau.

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Posters

CLINICAL TRIALS: METHODOLOGY

P1- FEASIBILITY OF VIRTUAL AMYLOID PET DISCLOSURE WITH COGNITIVELY UNIMPAIRED RESEARCH PARTICIPANTS.

C. Erickson[1], N. Chin[1], H. Rosario[1], A. Peterson[1], S. Johnson[1], L. Clark[1] *(1. University Of Wisconsin-Madison - Madison (United States))*

Background: Sharing AD biomarker results with older adult cognitively unimpaired research participants is safe and has been effective at educating individuals about the meaning of their results. As biomarkers become more widely available, more cognitively unimpaired older adults may learn their results through clinical trial enrollment and participation in observational cohort studies. Many prior studies, however, have been conducted in-person. Pushes towards telemedicine accelerated during the COVID-19 pandemic and presented opportunities to research virtual return of results. **Objectives:** We virtually returned beta-amyloid PET results to cognitively unimpaired older adults enrolled in a longitudinal observational cohort study (Wisconsin Registry for Alzheimer's Prevention; WRAP). One of the primary goals of the WRAP Amyloid Disclosure Study was to assess protocol feasibility for virtual beta-amyloid PET results disclosure. **Methods:** The study consists of three virtual visits conducted via televideo (education, disclosure, and brain health counseling) and three telephone follow-ups over a 9-month period. Participants are given the option to complete visits at home or onsite over televideo in a separate room from study staff. Feasibility was assessed by measures of participation, retention, adherence to meeting brain health goals, clinician competence in including intervention elements, and safety. Additionally, we assessed participant satisfaction and preparedness for the study visits. Safety was measured through assessment of mood, anxiety, and suicidality using Patient Health Questionnaire (PHQ-9), Geriatric Anxiety Scale 10-item form (GAS-10), and Columbia Suicide Severity Rating Scale (C-SRRS), respectively. Severe depression was indicated by PHQ-9 scores ≥20. Severe anxiety was indicated by GAS-10 scores ≥18. Participant Preparedness and Satisfaction was measured through separate questionnaires assessing usefulness of study materials, utility of visit, and qualitative feedback for study improvement for both the disclosure and brain health counseling visits. We assessed distributions of study materials usefulness and visit utility. We compiled themes of participant feedback for study improvement. **Results**: Data collection is ongoing and will include approximately 100 participants upon study completion in December 2022. The measures reported are current as of March 3rd, 2022. 72.6% of participants contacted chose to enroll. Three enrolled participants withdrew themselves prior to disclosure based on clinician interviewing of participant and reported hesitance to learn results (96.9% retention). 32 participants completed all study procedures. The sample was predominantly female (69.1%), college-educated (72.7%), White (96.4%), has a family history of dementia (69%), and the average age was 71.2+/-4.6. Approximately 30% of participants had elevated amyloid PET results. 83.3% of follow-up scores indicated participants made progress on their brain health SMART goals. Study clinicians leading disclosure on average hit 23.4 of 24 essential visit components (>97%) and reported that the visit went "very well" (average quality rating: 4.1). Participants reported an average satisfaction rating of 3.9 for the disclosure visit (median: 4, "very much satisfied"). Clinicians leading the brain health counseling on average hit 23.1 of 24 essential visit components (>96%) and reported that the visit went "very well" (average quality rating: 4.2). Participants reported an average satisfaction rating of 3.3 for counseling visit (median: 4, "very much satisfied"). Only 2 participants expressed suicidality and they were withdrawn before disclosure. No participants endorsed severe depression or anxiety, or suicidality after disclosure. To date, all participants have denied regretting learning their beta-amyloid result. Overall, participants endorsed that the disclosure visit was useful (96% reported the visit was "very" or "somewhat" useful) and they were satisfied with the visit (98% were "very" or "somewhat" satisfied). All participants recommended we continue with the disclosure visits. 86.4% of participants reported that the brain health counseling visit was "very" or "somewhat" useful, with 81.8% reporting they were "very" or "somewhat" satisfied. 81.8% of participants also recommended that we continue with the brain health counseling visit. Upon asking participants to share any feedback on the study, the most common responses included requesting a more detailed result (as opposed to a binary elevated/non-elevated result), showing a visual image of the PET result, and more check-ins about their brain health goal progress. Many participants reported enjoying the virtual visits, though 24.5% reported a preference for in-person disclosure. To date, 37.6% of participants came onsite for televideo visits due to technological inaccessibility. **Conclusion:** Eligible participants were interested, enrolled, and remained in the study. Virtual data collection has been successful and streamlined the data entry process. Both study clinicians/staff and participants report that the disclosure and brain health counseling visits have gone well. Participants shared that being in their homes provided them comfort and a sense of safety when learning amyloid PET results; however about one-third of participants needed to complete the visit onsite due to technological inaccessibility for an at-home televideo visit. Most importantly, virtual disclosure has been safe and not resulted in increased depression, anxiety, or suicidality. Overall, the Amyloid Disclosure Study has demonstrated that virtual return of beta-amyloid PET results to cognitively unimpaired research participants is feasible.

P02- USING COMMON-CLOSE TRIAL DESIGNS FOR EFFICIENTLY DETECTING SLOWING OF PROGRESSION IN ALZHEIMER'S DISEASE.

L.L. Raket[1], J. Cummings[2] *(1. Novo Nordisk - Søborg (Denmark), 2. Chambers-Grundy Center For Transformative Neuroscience, Pam Quirk Brain Health And Biomarker Laboratory, Department Of Brain Health, School Of Integrated Health Sciences, University Of Nevada Las Vegas (unlv) - Las Vegas (United States))*

Background: The combination of slow clinical progression and great heterogeneity of early Alzheimer's disease (AD) makes it very difficult to detect disease-modifying treatment effects that manifest as slowing of disease progression. While longer trial duration can address this problem, the variability in measurement endpoints increases with time since baseline as greater divergence of patient trajectories occurs. Furthermore, longer follow-up leads to greater trial drop-out and increases development timelines and associated time for new drugs becoming available to patients. **Objectives:** To explore if a

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common-close trial design where patients have variable degree of follow-up combined with disease progression modeling improves detection of disease-modifying treatment effects. **Methods:** We modeled a common-close design where all patients stayed on randomized treatment until the last randomized patient had the opportunity to complete 24 months of treatment. The follow-up time of individual patients depended on when they were recruited and how long trial recruitment took. We assumed that clinical endpoints were assessed every 6 months until the 24-month visit (0, 6, 12, 18, and 24 months since baseline) and yearly after that (36 and 48 months since baseline) for the subjects having the opportunity to do so before the common close. We evaluated several methods for estimating the treatment effects and how including data collected beyond the 24-month visit affected the power to detect a slowing of disease progression. We simulated trials in subjects with mild cognitive impairment due to Alzheimer's disease (clinical diagnosis of MCI; amyloid positivity [CSF/PET]; MMSE ≤28) with the 13-item ADAS-cog as the outcome measure. Subject-level trajectories were simulated based on modeling of 356 subjects in the Alzheimer's Disease Neuroimaging Initiative meeting our inclusion criteria: A baseline-constrained mixed model for repeated measures (MMRM) of the ADAS-cog scores was used to estimate the mean trajectory and covariance matrix using data collected at the baseline visit and visits 6, 12, 18, 24, 36 and 48 months after baseline. Placebo group subject-level trajectories were simulated from the estimated model and active treatment group trajectories were simulated the same way except the mean parameters were modified to reflect an average 20% slowing of disease progression. A 5% cumulative drop-out rate for every additional post-baseline visit was implemented and recruitment time (first to last patient randomized) was assumed to be 30 months with recruitment rate assumed to follow a quadratic pattern (4%, 16%, 36%, 64%, 100% recruited after 6, 12, 18, 24, and 30 months respectively). On average, this meant that at study completion, 81% of patients had data at 24 months, 28% had data at 36 months and 3% had data at 48 months. Trials with 300 to 1000 subjects per arm were simulated. The trial data both with and without post-24-month data were analyzed using a conventional MMRM and two different Progression Model for Repeated Measures (PMRMs) with assumptions of proportional reduction in decline and proportional slowing of disease progression. Using the MMRM, the treatment effects were quantified in two ways: treatment difference at 24 months and difference in area under the curve (AUC) between active therapy and placebo across the entire study duration. For each method and scenario, significance cut offs were re-calibrated based on simulations under the null hypothesis of no effect to ensure a comparable 2.5% one-sided significance level across methods. **Results:** Without post-24-month data, trials would require approximately 920 patients per arm to achieve 80% power to detect a 20% slowing of progression using a conventional MMRM analysis with the treatment effect quantified as the treatment difference at 24 months. For the difference in AUC more than 1000 patients per arm were needed. For the proportional decline PMRM, 650 patients per arm were needed, while the slowing PMRM needed 440. Including post-24-month data that would be collected as part of the common-close design did not change the 920 patients needed to achieve 80% power with the 24-month MMRM treatment difference. The patients needed with AUC difference was reduced to 680 per arm. The proportional decline PMRM needed 460 patients per arm to achieve 80% power and the slowing PMRM needed 400 patients per arm. **Conclusion:** Compared to conventional clinical trial designs and statistical methods such as the MMRM, a common-close design where double-blind longer-term follow up data is available for a subset of patients can greatly increase power to detect slowing of AD progression when paired with statistical models that quantify treatment effects across multiple visits.

P03- EVALUATING KARXT (XANOMELINE–TROSPIUM) AS A TREATMENT FOR PSYCHOSIS ASSOCIATED WITH ALZHEIMER'S DISEASE DEMENTIA: DESIGN OF THE PHASE 3, ADEPT-1, RELAPSE PREVENTION STUDY.

C. Watson[1], J. Cummings[2], G. Grossberg[3], M. Kang[1], R. Marcus[1]
(1. Karuna Therapeutics - Boston (United States), 2. University Of Nevada Las Vegas School Of Integrated Health Sciences - Las Vegas (United States), 3. Saint Louis University School Of Medicine - Saint Louis (United States))

Background: Psychosis is a common, serious unmet medical need in patients with Alzheimer's disease (AD) dementia. There are presently no approved pharmacologic treatments for psychosis in AD dementia. Current treatment includes off-label use of antipsychotics with modest efficacy and significant safety concerns. Xanomeline, a brain-penetrant M1/M4 preferring muscarinic receptor agonist, previously showed antipsychotic efficacy in placebo-controlled trials in subjects with AD in a completers analysis [Bodick NC et al. 1997; DOI: 10.1001/archneur.1997.00550160091022]. Despite promising efficacy, further clinical development of xanomeline was limited by cholinergic adverse events. The investigational antipsychotic KarXT combines xanomeline with trospium, an FDA-approved nonspecific muscarinic receptor antagonist that does not measurably cross the blood-brain barrier. Trospium acts to mitigate the peripheral procholinergic side effects of xanomeline, providing a strategy for using xanomeline to stimulate brain muscarinic receptors with a decreased side effect burden. The decrease in adverse events was observed in KarXT pharmacokinetic studies in normal healthy volunteers as well as a phase 2 inpatient efficacy trial (EMERGENT-1) for the treatment of schizophrenia in which KarXT met the primary endpoint of reduction in Positive and Negative Syndrome Scale total score as well as other secondary efficacy endpoints. Unlike currently available antipsychotics, KarXT has no direct dopamine D2-blocking activity, and as such, its safety and tolerability profile differs from conventional and atypical antipsychotics. In the phase 2 trial there were no differences in weight gain, metabolic parameters, or changes on extrapyramidal symptom scales between active treatment and placebo. **Objectives:** To evaluate relapse prevention in subjects with psychosis associated with AD dementia treated with KarXT compared with placebo. A key secondary objective is to evaluate the time from randomization to discontinuation for any reason. Additional secondary objectives are to evaluate the safety and tolerability of KarXT in this patient population. **Methods:** The phase 3 ADEPT-1 trial is a double-blind, flexible-dose, placebo-controlled randomized withdrawal study to evaluate the safety and efficacy of KarXT in decreasing the risk of relapse in subjects with psychosis (with or without symptoms of agitation or aggression) associated with AD dementia. Subjects aged 55-90 years with moderate to severe psychosis associated with mild to severe AD dementia (Mini-Mental State Exam score range 8-22) will be enrolled into the study. Subjects will receive single-blind KarXT for 12 weeks during the single-blind treatment period. Each subject will be flexibly titrated to the maximum dose of KarXT 200 mg xanomeline/20 mg trospium/day. At the end of the single-blind treatment period,

eligible responders will be randomized to either continue KarXT or be switched to matched placebo for a 26-week double-blind treatment period. The total study treatment duration is 38 weeks. A responder is defined as a subject with a ≥40% decrease (improvement) on the Neuropsychiatric Inventory-Clinician: Hallucinations + Delusions (NPI-C: H+D) score compared with baseline (day 1) and a Clinician Global Impression–Change (CGI-C) score of 1 or 2 (very much improved or improved). The primary endpoint of the study, time from randomization to relapse during the double-blind, randomized withdrawal treatment period, will be evaluated by survival analysis using Kaplan-Meier methodology. A key secondary endpoint is the time to discontinuation for any reason. Additional secondary endpoints are the safety and tolerability of KarXT compared with placebo. The study is planned to start mid-2022 and will enroll approximately 400 subjects to randomize approximately 200 subjects with psychosis associated with AD dementia into the double-blind randomized discontinuation period of the trial. Subjects completing the study will be offered the opportunity to receive KarXT in a 1-year, open-label safety extension study. **Conclusion:** The trial design of the ADEPT-1 study is an efficient way to assess the potential for KarXT to provide clinically meaningful benefit in preventing the return of psychosis associated with AD dementia in patients who have responded and have been stabilized on KarXT. If ADEPT-1 is successful, KarXT has the potential to be the first in a new class of treatments based on muscarinic receptor agonism for psychosis in patients with AD dementia.

P04- NUMBER OF DAYS BETWEEN INITIAL CONTACT AND IN-PERSON VISIT PREDICT ATTENDANCE RATES FOR POTENTIAL ALZHEIMER'S DISEASE TRIAL PARTICIPANTS. S. Starling[1], G. Munoz[1], M. Evans[1], J. Engler[1], S. Rutrick[1] *(1. Adams Clinical - Watertown (United States))*

Background: Alzheimer Disease (AD) clinical trials can be challenging in regard to recruitment and retention of participants, including high no-show or cancellation rates for screening visits. Identifying strategies to increase attendance rates will speed up enrollment in AD trials1. The lag time between the site's first contact with a potential participant and their scheduled in-person prescreening visit date is one factor that impacts attendance rates in psychiatry clinical trials2, yet it has not been explored in AD trials. We examined if shorter scheduling lag time was associated with higher attendance rates for AD trial prescreening visits. **Methods:** Our sample includes prospective AD trial participants recruited from April 2021 through April 2022 by advertising with Facebook and Google. After potential subjects submitted contact information online, a recruiter called them to conduct a remote interview. The recruiter then scheduled potentially eligible subjects for an in-person prescreening visit with a clinician, with scheduling lag ranging from the same day as the phone screen to up to 6 weeks later. This analysis examined the impact of scheduling lag (number of days between phone screen and date of scheduled prescreening visit) on prescreening visit attendance. **Results:** From April 2021 to April 2022, 5,816 individuals applied to participate in AD trials at our site through online advertisements. Of those, 16% (956) completed a phone screen interview and of those interviewed, 46% (436) were scheduled for an in-person prescreening visit. Scheduling lag ranged from 0 days to 42 days (M=7.6, SD=6.6). The overall attendance rate was 55%. Scheduling lag was found to be a significant predictor of prescreening visit attendance, with subjects who were scheduled sooner (i.e., fewer days between their phone screen and scheduled prescreening visit) being more likely to attend their visit (β=-.052, p=.001). Age was also correlated with attendance, with older participants being more likely to show (β=1.03, p=.015); however, scheduling lag remained a significant predictor of prescreening visit attendance, even when controlling for subjects' age. **Conclusions:** In line with findings from psychiatry trial recruitment data, our results suggest that scheduling prescreening visits sooner could result in improved attendance rates in AD trials as well. Encouraging potential participants to come in sooner for their prescreening visits could be an effective way to speed up enrollment. Anecdotally, although AD trial-seekers often prefer to schedule prescreening appointments weeks out, our results suggest encouraging subjects to come in sooner may be more effective for recruitment. **References:** 1. Puffer, S., & Torgerson, D. (2003). Recruitment difficulties in randomized controlled trials. Controlled Clinical Trials, 24, 214-215; 2. Evans, M., Sauder, C., Thorpe, D., Engler, J., & Domilici, D. (May 2020). Increasing show rates for major depressive disorder clinical trial screening visits: The impact of scheduling speed on screening visit attendance. [Poster presentation]. American Society of Clinical Psychopharmacology Conference, Virtual. The authors have no conflicts of interest to report.

P05- POWER ANALYSIS OF A PROGNOSTIC ENRICHMENT PROCEDURE BASED ON AD COURSE MAP, A SIMULATION STUDY. E. Maheux[1], I. Koval[1], J. Ortholand[1], C. Birkenbihl[2], V. Bouteloup[3], S. Durrleman[1] *(1. Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM, CNRS, Inria, Inserm, AP-HP, Hôpital de la Pitié Salpêtrière, F-75013 - Paris (France), 2. Fraunhofer Institute for Algorithms and Scientific Computing SCAI - Sankt Augustin (Germany), 3. Université de Bordeaux, Inserm 1219, CIC1401-EC - Bordeaux (France))*

Background: Many longitudinal studies have demonstrated the large heterogeneity of progression encountered by patients suffering from Alzheimer's disease (AD). While knowledge improved a lot and trials shifted to enrolling biomarker-confirmed patients at earlier stage of their disease, the heterogeneity remains. This heterogeneity is dramatically hardening the drug development for AD and it calls for precision drug development, as advocated by Cummings and colleagues. Today, the emergence of trial-ready cohorts together with the broad availability of retrospective AD data and the development of disease progression models, is providing the means to effectively implement the triptych of selecting the right patient, at the right time, in a right trial. **Objective:** To evaluate a new enrichment technique, based on a prognostic biomarker automatically computed from multimodal screening data. **Methods:** We trained a disease progression model called AD Course Map using all available visits of amyloid positive subjects from ADNI. We used the open-source software Leaspy (https://gitlab.com/icm-institute/aramislab/leaspy). The model summarizes the distribution of trajectories of the following endpoints from asymptomatic to symptomatic stages of AD: cognitive and functional assessments (MMSE, ADAS-Cog13, CDR-SB), CSF biomarkers, whole-brain amyloid PET SUVR, normalized volumes of the hippocampus and the lateral ventricles. From three external cohorts (AIBL, J-ADNI, MEMENTO) and held-out ADNI subjects, we selected the 828 subjects with 1) an early AD, 2) high levels of brain amyloid according to PET or CSF, 3) 50 to 85 years old at baseline, 4) a follow-up visit 18 months after their baseline visit. We disclosed the multimodal data of those selected individuals at

their baseline visit only. We personalized our AD Course Map to those data, that is to say we estimate the random effects of our model per individual. We were then able to forecast all endpoints, per individual, at any timepoint. We defined our prognostic biomarker as the predicted primary outcome of our simulated trial, chosen to be the change from baseline of CDR-SB after 18 months. Finally, we constructed an enriched population of our trial by considering subjects above a clinically meaningful cutoff for this prognostic biomarker. We then split the enrolled individuals into two arms: a placebo and a treated arm. The placebo arm is supposed to follow the natural disease history (e.g. no placebo effect); the treated arm is simulated by applying a given treatment effect on the observed progression. We computed the sample size required to adequately power the trial for a hypothetical 25% treatment effect (two-sided t-test with 5% significance, 80% power, no drop-out included). We bootstrapped the procedure to get empirical confidence intervals. We also compared our data-driven enrichment strategy with a genetic enrichment consisting in restricting to APOE-e4 carriers. **Results:** When using our enrichment technique, the sample size is reduced by 41.5% (95% confidence interval: [39.0%, 44.3%]), while targeting 52.6% of initial subjects as compared to no enrichment. In comparison, the sample size reduction when selecting only APOE-e4 carriers is only of 12.2% ([8.2%, 16.3%]), while targeting 62.9% of initial subjects. **Conclusion:** From a pool of trial candidates, AD Course Map is able to identify the ones at risk of experiencing a significant progression of the outcome. The selected progressors show a greater and more homogenous progression, thus resulting in a more powered trial. Our enrichment procedure leads to more than 40% sample size reduction, outperforming enrichment based on the APOE genotype. These findings demonstrate the benefits of such a companion software tool for patient recruitment in trials and, in the future, for supporting clinicians in prescribing the right treatment to the right patient at the right time. **References:** 1. Cummings, J., Feldman, H. H. & Scheltens, P. The "rights" of precision drug development for Alzheimer's disease. Alzheimers Res. Ther. 11, 76 (2019); 2. Jutten, R. J. et al. Finding Treatment Effects in Alzheimer Trials in the Face of Disease Progression Heterogeneity. Neurology 96, e2673–e2684 (2021); 3. Schiratti, J.-B., Allassonnière, S., Colliot, O. & Durrleman, S. A Bayesian Mixed-Effects Model to Learn Trajectories of Changes from Repeated Manifold-Valued Observations. J. Mach. Learn. Res. 18, 1–33 (2017); 4. Koval, I. et al. AD Course Map charts Alzheimer's disease progression. Sci. Rep. 11, 8020 (2021).

P06- IMPLEMENTING NOVEL CLINICAL TRIAL DESIGNS IN DEMENTIA WITH LEWY BODIES: A ROADMAP TO PERSONALIZED MEDICINE. C. Abdelnour[1], J.B. Toledo[2], D. Ferreira[3], F. Rodríguez-Porcel[4], P. Choudhury[5], M. Okafor[6], S. Scholz[7], B. Boeve[5], I. Litvan[8], J. Leverenz[9], L. Bonanni[10], J.P. Taylor[11], S.J.G. Lewis[12], D. Aarsland[13], K. Poston[1] *(1. Neurology And Neurological Sciences Department, Stanford University - Palo Alto (United States), 2. Department Of Neurology University Of Florida College Of Medicine - Gainesville (United States), 3. Division Of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society, Karolinska Institutet - Stockholm (Sweden), 4. Department Of Neurology, Medical University Of South Carolina - Charleston (United States), 5. Department Of Neurology, Mayo Clinic - Rochester (United States), 6. Department Of Neurology, Emory University School Of Medicine - Atlanta (United States), 7. Neurodegenerative Diseases Research Unit, National Institute Of Neurological Disorders And Stroke. Laboratory Of Neurogenetics, National Institute On Aging - Bethesda (United States), 8. Parkinson and Other Movement Disorders Center, Department of Neurosciences, University of California San Diego - La Jolla (United States), 9. Lou Ruvo Center for Brain Health, Neurological Institute, and Department of Neurology. Cleveland Clinic - Cleveland (United States), 10. Department of Neuroscience Imaging and Clinical Sciences and CESI, University G d'Annunzio of Chieti-Pescara - Chieti (Italy), 11. Translational and Clinical Research Institute, Newcastle University - Newcastle (United Kingdom), 12. Forefront Parkinson's Disease Research Clinic, Brain And Mind Centre, University Of Sydney - Camperdown Nsw 2050 (Australia), 13. Institute of Psychiatry, Psychology, & Neuroscience, King's College London - London (United Kingdom))*

Background: Dementia with Lewy Bodies (DLB) is a heterogeneous disorder. Clinically, patients can present with a wide variety of cognitive, neuropsychiatric, motor, sleep, and autonomic symptoms that may be differentially expressed throughout the course of the disease. From the neuropathological standpoint, the typical α-synucleinopathy is commonly found in combination with features of Alzheimer's disease (AD) neuropathologic change, cerebrovascular disease, and TDP-43 proteinopathy. These co-pathologies are likely to influence the clinical presentation and disease progression. Several prodromal presentations have been proposed in DLB including: isolated REM-sleep behavior disorder (iRBD), mild cognitive impairment, delirium-onset, and a psychiatric-onset. The prodromal stage is a potential target window for disease-modifying treatments, but little is known about predicting the disease course of these prodromal entities. For example, iRBD patients can phenoconvert to Parkinson's disease (PD), multiple system atrophy, or DLB with differing lag times from symptom onset. Thus, the natural history of DLB poses challenges for the design of clinical trials. Adaptive methodologies and master protocols provide opportunities to address these challenges and may be a roadmap to personalized medicine. **Objectives:** To analyze the potential benefit of adaptive methodologies and master protocols in DLB. **Methods:** In this review, we discuss the specific characteristics of DLB that justify the potential benefit of new clinical trial designs. Also, we discuss the concepts of adaptive methodologies and master protocols, and their potential advantages and pitfalls in DLB trials. Finally, we present illustrative examples where platform trials have been utilized in AD, PD, and ALS. **Results:** Adaptive methodologies in clinical trials are innovative designs that allow pre-specified modifications to a clinical trial protocol during the period of data collection. These modifications may include: sample

size re-estimation, changes to eligibility criteria, endpoints, dosage or patient allocation; as well as the addition or termination of treatment arms. Alternatively, master protocols are a type of clinical trial design that use a single protocol to test multiple therapies (separately or in combination), and/or multiple diseases in parallell. They are classified as basket, umbrella, and platform trials. It is envisaged that adaptive methodologies and master protocols could be implemented in DLB to improve cost-efficacy and enable the detection of clinical benefit. Specific benefits of new designs for DLB trials include improving operational efficiency, the inclusion of diverse patient populations, sharing a single common control group for multiple therapies (thus requiring fewer participants), facilitating comparison across sub-studies, cycling between therapies, and increasing the number of treatments tested. Nevertheless, clinical trial design in DLB poses some challenges. Firstly, there are no specific validated outcome measures for monitoring DLB accurately, and the current evaluation of potential therapeutic benefit relies on tools developed for AD and PD. Secondly, there is lack of disease-specific diagnostic and prognostic biomarkers. Finally, patients are often under- and/or misdiagnosed leading to very slow recruitment rates in clinical trials. Adaptive methodologies and master protocols have been implemented in several neurodegenerative diseases, including AD, PD, and amyotrophic lateral sclerosis (ALS). Some examples are the DIAN-TU platform, a secondary prevention trial in participants with dominantly inherited AD mutations; the Australian Parkinson's Mission clinical platform (APM001), a phase II clinical trial of three repurposed drugs in patients with moderate PD; and the HEALEY ALS Platform Trial, a multicenter adaptive platform trial investigating multiple treatments in parallel for ALS patients. It is hoped that lessons learned from these clinical trials could be adapted to enhance clinical trial design in DLB. **Conclusion:** New clinical trial designs are needed in DLB due to its heterogeneous clinical presentation, presence of co-pathologies, and variable clinical trajectory. Platform trials in AD, ALS an PD fields have shown promise. Although the implementation these type of trials in DLB will face some challenges, innovative clinical trial designs are required to address the specific characteristics of DLB and improve the efficacy and efficiency of drug development. **Conflicts of interest:** none.

P07- ADULT-ONSET LEUKOENCEPHALOPATHY WITH AXONAL SPHEROIDS AND PIGMENTED GLIA (ALSP) IS COMMONLY MISDIAGNOSED AS ALZHEIMER'S DISEASE (AD) AND FRONTOTEMPORAL DEMENTIA (FTD). S. Papapetropoulos[1], A. Pontius[2], S. Zappia[1], M. Brennan[2], L. Leahy[2] *(1. Vigil Neuroscience - Cambridge (United States), 2. Consultant To Vigil Neuroscience - Cambridge (United States))*

Background: ALSP is a progressive, fatal autosomal dominant neurodegenerative disease caused by CSF1R gene mutations that result in microglial dysfunction and lead to profound white matter changes primarily affecting the corpus callosum and periventricular regions of the frontal and parietal lobes. The prevalence of ALSP is estimated to be 10,000 in the US alone. The predominant phenotype associated with ALSP is cognitive impairment and is believed to be frequently misdiagnosed as AD or FTD. Diagnostic accuracy of ALSP has modestly improved due to publication of diagnostic criteria but the rate of initial misdiagnosis remains high. Disease awareness and correct diagnosis of ALSP are critical to avoid inclusion of such patients in dementia clinical trials and for initiation of early therapy of this debilitating and lethal disorder. **Methods:** A systematic literature review of clinical and genetic features of ALSP was conducted with published case studies (January 1,1980 through March 22, 2022) from a MEDLINE search using prespecified selection criteria. The search identified 87 published case reports with data extracted from 292 ALSP patients and is currently the largest case series of ALSP. Data were extracted, entered electronically into a Master Excel table under specific demographic and clinical characteristic headings, independently reviewed and examined for accuracy. Categorical variables were stratified by initial diagnosis, dichotomized by ALSP versus dementia and presented as frequency distribution. P-values for differences in frequency distribution between stratification factors were generated by the Chi-square test. **Results:** Demographic data revealed the mean (SD) age (years) of patients was 43.2 (11.6) with a median (minimum, maximum) of 42.0 (18.0, 86.0). Family history of ALSP was identified in 58.9% of patients with a greater frequency of females (48.3%) compared to males (42. 5%). A slightly greater percentage of patients with ALSP was found in Asia (34.2%) compared to Europe (32.2%) and North America (28.1%). Misdiagnosis of ALSP involved a broad spectrum of neurodegenerative, neuroimmune and vascular disorders. Due to phenotypic heterogeneity at disease onset, accurate initial diagnosis was detected in only 31.5% of ALSP patients. Frontotemporal dementia (11.6%), and Alzheimer's disease (4.5%) were common misdiagnoses. Cognitive impairment (45.9%) and behavioral and psychiatric dysfunction (26.4%) were the most common initial symptoms. Comparison of patients with a correct diagnosis of ALSP to a diagnosis of patients with dementia (FTD, AD, other) revealed interesting observations. Dementia-diagnosed patients were significantly older with mean (SD) years 50.7 (9.05) vs 43.5 (12.2) ($p<0.001$) and reported family history more frequently (73.9% vs 53.8%), $p=0.0048$) compared to patients with ALSP. **Conclusions:** This systematic review confirms that ALSP is commonly misdiagnosed as a cognitive disorder, AD or FTD. To avoid misdiagnosis and inclusion of patients with ALSP in dementia clinical trials, screening patients for family history, white matter MRI lesions and early-onset cognitive impairment with behavioral and/or motor dysfunction should be considered. This combination of symptoms should trigger suspicion for ALSP and initiate early genetic testing. Larger prospective studies are warranted to further investigate presenting symptoms of ALSP. Increased disease awareness and genetic testing should improve diagnostic accuracy. **Disclosures:** This systematic review was financially supported by Vigil Neuroscience, Inc. S. Papapetropoulos and S. Zappia are full-time employees of Vigil Neuroscience, Inc and hold stock or stock options in Vigil Neuroscience. A. Pontius and M. Brennan are consultants for Vigil Neurosciences and hold stock or stock options in Vigil Neuroscience. L. Leahy is consultant for Vigil Neuroscience.

P08- UPDATE ON THE TOGETHER STUDY: A PATIENT- AND INVESTIGATOR-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY, SAFETY AND TOLERABILITY OF BEPRANEMAB, UCB0107, IN PRODROMAL-TO-MILD ALZHEIMER'S DISEASE. M.E. Barton[1], B. Van Den Steen[2], H.L.G. Van Tricht[2], W. Byrnes[1], F.E. Purcell[3], S.A. Southcott[1], D. Raby[3], Y.I. Starshinov[3], C. Ewen[2] *(1. UCB Pharma - Raleigh, North Carolina (United States), 2. UCB Pharma - Brussels (Belgium), 3. ICON plc - Dublin (Ireland))*

Background: Bepranemab (formerly known as UCB0107) is a recombinant, humanized, full-length IgG4 monoclonal antibody

that binds to a central tau epitope (amino acids 235–250). Here, we provide an update on the progress of the TOGETHER study (AH0003; NCT04867616) with bepranemab in people living with early Alzheimer's disease (AD). **Objective:** The objective of the TOGETHER study is to evaluate the efficacy, safety and tolerability of bepranemab in patients living with prodromal-to-mild AD. **Methods:** TOGETHER is a global, multicenter, patient- and investigator-blind, placebo controlled, parallel-group study investigating the efficacy, safety and tolerability of bepranemab versus placebo. Patients with prodromal (National Institute on Aging-Alzheimer's Association [NIA-AA] Stage 3) or mild (NIA-AA Stage 4) AD (target N=450) will be randomized (1:1:1) to receive one of two doses of bepranemab or placebo (intravenous, every 4 weeks), over an 80-week treatment period, followed by an optional 48-week open-label-extension period. Participants will have a global Clinical Dementia Rating (CDR) score of 0.5 (prodromal AD) or 0.5–1.0 (mild AD) and a CDR-Memory Box score ≥0.5 at screening and baseline, a score of ≤85 for the delayed recall domain of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), mini-mental state examination (MMSE) ≥20 at screening and must meet the NIA-AA 2018 definition of cerebral beta-amyloid (Aβ) accumulation, by either a positive centrally read positron emission tomography (PET) scan or a positive cerebrospinal fluid (CSF) pTau181/Aβ1-42 ratio. The primary endpoint is change from baseline to Week 80 in CDR scale Sum of Boxes total score. Secondary endpoints include: pharmacokinetics; safety and tolerability; tau PET imaging and change from baseline in AD Assessment Scale-Cognitive Subscale 14, Amsterdam Instrumental Activities of Daily Living questionnaire and MMSE at Weeks 56 and 80. **Results:** As of June 1, 2022, 101 planned centers have enrolled participants across 10 countries: Belgium, Canada, France, Netherlands, Poland, Spain, Italy, Germany, UK and USA. Of the 1,079 participants who entered screening, 173 have been randomized so far and 693 failed screening. Predominant reasons for screen failure include not meeting RBANS, MMSE or Aβ positivity (measured by CSF or PET) criteria. **Conclusion:** This proof-of-concept study employs clinical outcome measures, imaging, pharmacokinetics, and biomarkers to assess the ability of bepranemab to slow progression of AD when administered in the early stages of disease. Enrollment and randomization of participants are well on the way, with over half of the study centers active. Conflicts of interest: Matthew Barton, Bart Van Den Steen, Hans L.G Van Tricht, William Byrnes and Colin Ewen are employees of UCB Pharma and may hold/have access to stock options. The full disclosure of conflicts of interest will be detailed in our presentation. **Funding:** This study is funded by UCB Pharma.

P09- THE IMPACT OF ERRATIC CHANGES ON 1 YEAR CHANGE IN CDR-SB. AN EXPLORATORY ANALYSIS. A. Kott[1], X. Wang[2], D. Miller[2] *(1. Signant Health - Prague (Czech Republic), 2. Signant Health - Blue Bell (United States))*

Background: Erratic changes represent large opposite changes in scale scores at a minimum of 3 consecutive visits. We have previously demonstrated the detrimental impact of erratic changes on placebo response and drug placebo separation in schizophrenia clinical trials. **Objectives:** In this analysis, we assessed the impact of erratic changes in the CDR-SB over 1-year post-baseline in a pooled dataset of early Alzheimer's Disease (AD) clinical trial data. The goal was to see whether the pattern found in schizophrenia also existed in AD. **Methods:** Blinded data were pooled from 6 clinical trials in early AD. We defined as erratic those CDR-SB changes where the visit-to-visit change exceeded 1 point and these changes were in opposite direction at consecutive visits. A generalized linear model estimating the 1-year CDR-SB change from baseline was fitted with the presence of erratic ratings, baseline CDR-SB score and protocol as predictors. **Results:** Our dataset consisted of a total of 4,023 subjects, where the presence or absence of erratic changes could be established and 1-year change values were available. Compared to baseline, the CDR-SB in the whole sample worsened at 1-year on average by 1.25 points (SD=1.97). Erratic changes were identified in a total of 210 subjects (5.2%). The presence of erratic ratings significantly decreased the CDR-SB change by 0.55 points (CI = 0.28 – 0.82; $p < 0.001$). Subjects not affected by erratic changes worsened by 1.35 points (CI = 1.27 – 1.43), while subjects affected by erratic changes worsened by 0.80 points (CI = 0.53 – 1.07). **Conclusions:** Our results indicate that when present, erratic changes on the CDR-SB over 1-year had a substantial impact on the data. Specifically, the presence of erratic changes reduced the 1-year worsening by over 40%. Based on our prior analyses in schizophrenia, subjects affected by erratic changes failed to separate drug from placebo. It is thus important to replicate this analysis in unblinded datasets in AD trials as well. While it is possible that some erratic changes are driven by an unusual group of subjects, in the vast majority erratic changes likely represent a number of measurement errors that result into the zig-zag pattern of disease severity fluctuation over time. Identifying the raters at increased risk of having erratic changes and remediating these raters may positively translate into an increased signal. **Conflict of interest:** All authors are full-time employees of Signant Health.

P10- EARLY ENGAGEMENT WITH THE ALZHEIMER'S DISEASE COMMUNITY TO GAIN INSIGHTS INTO DESIGNING THE SKYLINE TRIAL FOR PRE-SYMPTOMATIC ALZHEIMER'S DISEASE. F. Rose[1], N. Lynn[2], J.B. Langbaum[3], C. Langlois[3], E.L. Dodd[1], J. Roeser[4], G. Respondek[4], S. Ostrowitzki[4] *(1. Roche Products Ltd - Welwyn Garden City (United Kingdom), 2. BrightFocus Foundation - Clarksburg (United States), 3. Banner Alzheimer's Institute - Phoenix (United States), 4. F. Hoffmann-La Roche Ltd - Basel (Switzerland))*

Background: Recruiting cognitively healthy older adults at risk for developing Alzheimer's disease (AD) is challenging. Preemptively seeking to understand the needs and concerns of these individuals, as well as their motivations for participation in clinical trials, could help inform how best to identify and engage them and determine what will improve their experience and retention within a clinical trial setting. Collecting and incorporating feedback from the targeted participant population during the protocol development stage is critical to improving participants' experiences during the trial, thereby aiding in retention. In addition, it is anticipated that such a protocol would be more accessible and sensitive to a broad variety of prospective volunteers, thus making recruitment easier. **Objectives:** To gather insights from global representatives within the AD community to help customize the design of clinical trials to improve participants' trial experience. **Methods:** Advisory boards were held with two groups made up of individuals with diverse backgrounds from multiple countries. These groups included CareRing, comprising five Roche employees who all care for people living with AD, and a group of representatives from twelve global AD advocacy organizations. Feedback was gathered on participant and study partner perceptions of the draft protocol design for SKYLINE:

a global Phase III, multicenter study to evaluate the efficacy and safety of gantenerumab in participants at risk for or in the earliest stages of AD (NCT05256134). Groups were asked to share recommendations for the holistic and individualized support required to enable a positive trial experience. Feedback was then assessed and implemented into the SKYLINE protocol design and supporting materials. **Results:** Feedback highlighted the importance of tailoring study materials and design to specifically engage with a cognitively healthy, at-risk, or asymptomatic AD population and their study partners. Feedback also identified that flexibility of dosing options was seen as an essential part of the SKYLINE trial design in order to maintain personal lifestyle choices. Varied and tailored supporting materials were highlighted as a requirement to ensure successful trial participation, such as those to explain the trial expectations and what would be required for home administration. Furthermore, having a sensitive and supportive disclosure process managed by professionals for both brain amyloid status and APOE genotype was seen as crucial. This highlights the importance of tailoring materials specific to unique participant population needs, and providing guidance and training for trial site staff, to ensure suitable support measures are available for participants and their families. **Conclusion:** This collaboration with the wider AD patient advocacy community demonstrates the importance of early dialogue with participant and study partner representatives to build a patient-centric study design to ensure holistic supporting materials and processes are implemented for this unique study population. **Conflict of interest:** Fiona Rose is an employee and shareholder of F. Hoffmann-La Roche Ltd.

P11- CONTRASTING THE NIH TOOLBOX EMOTIONAL BATTERY OUTCOMES BETWEEN CAUCASIANS AND AFRICAN AMERICAN OLDER ADULT PARTICIPANTS IN A RANDOMIZED CLINICAL TRIAL: I-CONECT STUDY.

K. Yu[1], L. Silbert[1,2], L. Struble[3], H.H. Dodge[1] *(1. NIA-Layton Aging and Alzheimer's Disease Center, Department of Neurology, Oregon Health & Science University, Portland, Oregon, USA - Portland (United States), 2. Portland Veterans Affairs Health Care System, Portland, OR, USA - Portland (United States), 3. Department of Health Behavior and Biological Sciences, School of Nursing, University of Michigan Ann Arbor, Michigan, USA - Ann Arbor (United States))*

Background: Challenges in recruiting minority older adults for clinical trials have been widely documented. However, the sample selection bias within minority groups has not been sufficiently addressed. The more difficult it is to recruit participants, the less likely they are to be representative of the group. **Objectives:** This study compared the emotional wellbeing of Caucasian and African American (AA) participants recruited for a year-long behavioral intervention study which aimed to enhance cognitive functions by increasing social interactions among socially isolated participants with normal cognition or mild cognitive impairment (MCI). **Methods:** We used data from the baseline of the Internet-Based Conversational Engagement Clinical Trial (I-CONECT, ClinicalTrial.gov: NCT02871921). Individuals were eligible to participate if they aged 75 and older and met the operational definition of social isolation (Yu et al., 2022). Emotional characteristics of participants were assessed with the NIH toolbox emotion battery (NIHTB-EB) collected at baseline before the intervention started. NIHTB-EB includes three domains that consist of 17 subscales. The three domains are negative affect, psychological wellbeing, and social satisfaction. We ran linear regression models comparing the NIHTB-EB outcomes between Caucasian and AA participants, controlling for age, sex, years of education, marital status, depressive symptoms, and cognitive status (MCI vs. normal). MCI status were diagnosed with National Alzheimer's Coordinating Center Uniform Data Set Version 3 (UDS V3). **Results:** Out of 1139 individuals screened over phone calls,186 participants were randomized (9% of the screened AA, 20% of the screened Caucasian). The 163 participants who completed the NIHTB-EB at baseline were included in this study. The mean age of the sample is 81.22 (SD=4.65), 70.99% were female, 53.09% with MCI diagnosis, and 20.73% (n=34) self-identified as AA. The AA participants scored higher in psychological wellbeing (B=5.67, SE=1.59, p<.001) and social satisfaction (B=7.92, SE=1.80, p<.001) than Caucasians. In terms of subscales, AA participants had lower sadness (B=-5.39, SE=1.97, p<.01), higher positive affect (B=4.74, SE=1.58, p<.01), and higher meaning and purpose (B=7.70, SE=1.55, p<.001) scores than their Caucasians counterparts. **Conclusion:** Individuals who live in isolation are a "hidden" population and are rarely included in clinical trials. The findings comparing NIBTB-EB outcomes show that AA participants were better off than their Caucasian counterparts in psychological wellbeing and social satisfaction. This finding might suggest possible selection biases: individuals enrolled in trials could be different from those who declined the opportunity, especially when the recruitment was challenging. Merely increasing the proportion of minority participants might introduce some unexpected bias in trial results.

P12- DEVELOPMENT AND FEASIBILITY OF A DATA-DRIVEN APPROACH TO PRECLINICAL ALZHEIMER'S DISEASE CLINICAL TRIAL RECRUITMENT THROUGH CENTRALIZED PRE-SCREENING DATA COLLECTION.

D. Kirn[1], J. Grill[2], P. Aisen[3], K. Ernstrom[3], S. Gale[4], J. Heidebrink[5], G. Jicha[6], G. Jimenez-Maggiora[3], L. Johnson[7], E. Peskind[8], R.S. Turner[9], D. Sultzer[2], S. Wang[3], R. Sperling[4], R. Raman[3] *(1. Department of Neurology, Massachusetts General Hospital - Boston (United States), 2. Institute for Memory Impairments and Neurological Disorders, Department of Psychiatry and Human Behavior, University of California Irvine - Irvine (United States), 3. Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego (United States), 4. Department of Neurology, Brigham and Women's Hospital, Harvard Medical School - Boston (United States), 5. Department of Neurology, University of Michigan - Ann Arbor (United States), 6. Sanders-Brown Center on Aging, University of Kentucky - Lexington (United States), 7. Institute for Translational Research, University of North Texas Health Science Center - Fort Worth (United States), 8. VA Northwest Mental Illness Research, Education, and Clinical Center (MIRECC), VA Puget Sound Health Care System - Seattle (United States), 9. Department of Neurology, Georgetown University Medical Center - Washington D.c. (United States))*

Background: Recruiting to multi-site preclinical Alzheimer's Disease (AD) trials is challenging, particularly when striving to ensure the randomized sample is demographically representative of the larger population at risk. Though Black or African American and Hispanic or Latino individuals are at increased risk for AD, they are underrepresented in trials. While previous studies have reported disparities by race and ethnicity in enrollment and randomization, they do not investigate whether disparities exist in the recruitment process prior to consent. Sites may include a participant prescreening process (pre-consent) for trials to conserve resources by limiting in-person consent and screening to participants most likely to

be eligible. Capturing these prescreening data centrally has been rare in multi-site clinical trials, as data collected prior to formal consent is typically not included in trial databases. Better understanding of the pipeline of participants who do and do not continue past the prescreening phase of trials could aid efforts to improve recruitment of groups traditionally underrepresented in clinical trials research. **Objective:** The Alzheimer's Clinical Trials Consortium (ACTC) Recruitment Unit developed infrastructure to centrally collect a subset of prescreening variables for the AHEAD 3-45 study (NCT NCT04468659). By collecting these data, we aim to evaluate potential selection bias and improve our understanding of recruitment initiative effectiveness, particularly related to participants from historically underrepresented groups. **Methods:** A vanguard phase captured participant-level prescreening data from seven sites actively recruiting for the AHEAD 3-45 study. The AHEAD 3-45 study is examining the safety and efficacy of Lecanemab (BAN2401, Eisai Inc.) in a cohort of cognitively unimpaired participants aged 55-80, at increased biological risk of developing AD dementia. The following variables, a subset of the variables used for the study, were collected in this phase for each participant prescreened at the site: age, biological sex, race, ethnicity, education, occupation, zip code, recruitment source, prescreening eligibility, reason for pre-screen ineligibility, and study ID for those who continued to an in-person screening visit. Sites had the option of providing the data by direct entry or through bi-weekly batched upload. This study received a Waiver of HIPAA and Waiver of Consent from the central IRB (Advarra, Columbia, MD). **Results:** All seven vanguard sites provided prescreening data on 1029 participants. The total number of prescreened participants varied widely by site (range 3-611), with the differences in numbers driven mainly by the time to receive site approval for the main study. The study website consistently produced meaningful proportions (range: 36-75%) of prescreen activity across sites. Hispanic participants more often were identified from recruitment registries (14%) and local recruitment efforts (37%), compared to non-Hispanic participants (6% and 30%, respectively). At these sites, a higher proportion of American Indian and Alaska Natives (56%) and lower proportion of Blacks (9.1%) were eligible for an in-person screening compared to non-Hispanic Whites (22%), though many participants remained in the prescreening process. **Conclusion**: We demonstrated that it is feasible for multi-center trials to successfully collect prescreening data across vanguard sites for an ongoing multi-site preclinical AD trial. Measuring the impact of recruitment interventions, even before participants sign consent, has the potential to identify and address selection bias, instruct resource use, contribute to effective trial design, accelerate evaluation timelines, and inform the science of recruitment. This initiative has now been expanded to include all interested U.S. based study sites in the study.

P13- DESIGN OF PRAGMATIC TRIALS FOR INTERVENTIONS TARGETING COGNITIVE DECLINE: BENCHMARKS FROM THE COCOA SUPPLEMENT AND MULTIVITAMIN OUTCOMES STUDY OF THE MIND (COSMOS-MIND).

M. Espeland[1], J. Manson[2], S. Rapp[1], H. Sesso[2], S. Gaussoin[1], S. Shumaker[1], L. Baker[1] *(1. Wake Forest School of Medicine - Winston-Salem (United States), 2. Brigham and Women's Hospital - Boston (United States))*

Background: COSMOS-Mind (NCT03035201) was a large, pragmatic clinical trial that examined whether daily treatment with 500 mg/day cocoa extract (CE) versus placebo (primary) or standard multivitamin-mineral (MVM; Centrum Silver) versus placebo (secondary) for 3 years in 2262 older adults (>65 years) protected cognitive function and attenuated the cognitive decline associated with normal and pathological aging, including Alzheimer's disease (AD). CE was not found to affect cognitive function. MVM produced a mean [95% confidence interval] relative benefit in a global cognitive composite score of 0.07 [0.02, 0.12] SDs, p=0.007, which corresponded to a 60% slowing of expected cognitive decline in the cohort over 3 years. **Objectives:** We present findings from COSMOS-Mind that provide support for the conduct of future pragmatic trials with cognitive outcomes. We use benchmark data from the trial to inform 1) choices and parametric models for outcomes, 2) trial duration, 3) sampling targets for special populations, and 4) targeted effect sizes. **Methods:** We used COSMOS-Mind data -- cognitive outcomes (composite scores of global cognition, executive function, memory), retention, subgroup analyses -- to guide simulation-based comparisons of differing design options for future pragmatic trials. **Results:** The COSMOS-Mind cognitive test battery of telephone-based assessments provided a high degree of statistical efficiency based on their repeatability over time and, in general, higher efficiency (and statistical power) projected for a global composite than for subdomains (e.g., executive function) or single tests (e.g., Digit Symbol). The primary outcome chosen for COSMOS-Mind, the average difference from baseline in test scores over 3 annual assessments, provided better overall statistical power than alternative choices for outcomes based on slopes or scores at close-out. To achieve comparable statistical power for the COSMOS-Mind primary outcome, a 2-year trial would have required 32%-72% more enrollees than our 3-year trial. Enrolling participants with more diversity in baseline cognitive function, education, and ethnicity may yield greater statistical power than cohorts with less diversity: participants with lower baseline cognitive test scores, less formal education, and from minoritized communities had qualitatively (although not significantly) greater benefits from MVM in COSMOS-Mind. To achieve sufficient power to replicate COSMOS-Mind findings, it is important to target clinically significant effect sizes smaller than what were observed to allow for imprecision in estimated benefits: a future sufficiently targeted trial of MVM will require a larger sample size. **Conclusions:** COSMOS-Mind demonstrates that pragmatic randomized clinical trials can be designed and implemented to identify approaches to slow cognitive decline and potentially reduce risk for Alzheimer's disease and other dementias. **Funding:** COSMOS-Mind: NIH/NIA 5R01AG050657-02; NIH/NIA P30AG049638-01A1; COSMOS: Investigator-initiated grant and donation of study pills by Mars Edge; partial provision of study pills and packaging by Pfizer Consumer Healthcare (now GSK Consumer Healthcare); WHI: NIH/NHLBI HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. **Conflict of Interest:** Dr. Espeland receives research funding from the Alzheimer's Association and the NIH and is a paid member of a Steering Committee for a trial sponsored by Nestle.

P14- USE OF THE DIGIT SYMBOL SUBSTITUTION TEST (DSST) AS AN ENTRY CRITERION FOR A COGNITIVE STUDY OF A B2-AR AGONIST. G. Vargas[1], R. Martin[1], P. Butera[1], J. Reynolds[1], T. Anderson[2], A. Asher[3], E. Buntinx[4], A. Ford[1], J. Harrison[5] *(1. CuraSen - San Carlos (United States), 2. New Zealand Brain Research Institute - Christchurch (New Zealand), 3. MAC Clinical Research - Manchester (United Kingdom), 4. Anima Research Center - Alken (Belgium), 5. Metis Cognition - Kilmington Common (United Kingdom))*

Background: The locus coeruleus (LC) is a small nucleus located in the pons and is the primary source of noradrenaline in the forebrain. LC axons project to multiple cortical and subcortical regions that underlie memory including the hippocampus, frontoparietal cortex, and amygdala. Through its binding to both α and β adrenoceptors, noradrenaline plays a key role in a variety of essential central nervous system (CNS) functions such as learning and memory, arousal, attention, emotional processing and cognition. CuraSen is developing CNS-penetrant β2-AR agonists for the treatment of neurodegenerative disorders including Alzheimer's disease (AD). CuraSen's ongoing and completed early phase studies demonstrate that the β2-AR agonist CST-103 increases cerebral perfusion in healthy individuals and those living with Parkinson's disease (PD) and mild cognitive impairment (MCI). Data using a well-established cognitive assessment system suggests improved cognitive performance in healthy volunteers. The CLIN-011 study seeks to evaluate the safety and efficacy of CST-103 when dosed with nadolol in individuals with MCI, PD and Lewy body dementia. The key efficacy measures will evaluate the effects of treatment on cognition and mood. Early-stage disease can vary with respect to the presenting cognitive deficits. Individuals presenting with dementia commonly exhibit memory deficits. However, a significant proportion express deficits in other cognitive domains, such as attention, executive function and working memory. Selecting individuals with evidence of impairment based on Mini-Mental State Exam (MMSE) performance has been a common method of ensuring that study candidates show a rescuable memory deficit. However, the MMSE is deficient with respect to the assessment of other key cognitive domains. Thus, when enrollment of subjects with attention and/or executive function is required, the MMSE is an inadequate means of enriching the study population. We have therefore employed a different enrichment strategy. Study participation is contingent upon candidates exhibiting cognitive deficits on the Digit Symbol Substitution Test (DSST), a brief, reliable and well-validated cognitive test which is recognized by regulators as a measure of timed executive function. It is also an index of attention, working memory and other key cognitive domains known to be compromised early in AD. **Objectives:** The CLIN-011 study is a signal-seeking clinical trial to identify responsive patient populations as well as efficacy measures that are relevant for treatment with a β2-AR agonist. In order to maximize the prospects of detecting treatment effects we are enriching the MCI study population for the presence of objective measured cognitive deficits using the DSST. **Methods:** The study is a randomized, placebo-controlled, double-blind, crossover, study of the pharmacodynamic effects of CST-103 co-administered with nadolol on the CNS in subjects with neurodegenerative disorders. At enrollment, the eligibility of subjects with MCI are evaluated using the following inclusion criteria: Montreal Cognitive Assessment (MoCA) score $\geq$ 18 and $\leq$ 26. A score of greater than or equal to one standard deviation below age and educational norms in the DSST during screening. **Results:** In this abstract we report the baseline cognitive characteristics of the MCI population recruited into this study. In total 41 patients were recruited: 25 with PD, 13 with MCI and 3 with Lewy body dementia. In addition to the MoCA and DSST, all patients had cognitive testing using the Cambridge Neuropsychological Test Automated Battery at multiple scheduled time points throughout the study. The range of MoCA scores for enrolled subjects was between 18-27 with a mean of 22.7. The range of DSST scores was between 22-51 with a mean of 39.4. The ages of the subjects ranged between 52-69 and the average age was 61.2. The range of DSST scores for subjects who screen failed due to this criterion was between 42-80 with a mean of 58.4. As acknowledged above, attention and working memory deficits are unlikely to be observed in all subjects with early-stage disease and implicit in the use of this enrichment strategy is the possibility of significant rates of screen failure. Of the 44 individuals screened for inclusion in the MCI cohort there were 31 (70.5%) screen failures, 11 (35%) solely due to DSST performance exceeding the cut-off for inclusion. **Conclusion:** Selecting a patient population which has objectively identified cognitive deficits is essential in order to demonstrate positive drug effects on cognition. In the present study we have utilized an enrichment strategy based on use of the DSST, a well validated cognitive test which measures multiple cognitive domains. Use of the DSST as an entry requirement led to a number of screen failures but at a rate that is an acceptable trade-off to ensure that the population recruited into the study has cognitive deficits which can be remediated by treatment.

P16- ENHANCING RECRUITMENT OF UNDERREPRESENTED COMMUNITIES WITH THE DEPLOYMENT OF A MOBILE RESEARCH UNIT. J. Smith[1], J. Dwyer[1], D. Batchuluun[1], T. Magee Rodgers[1], L. Zisko[1] *(1. Global Alzheimer's Platform Foundation - Washington Dc (United States))*

Background: The prevalence of Alzheimer's disease is twice as high in the African American/Black population and 1.5 times higher in the Hispanic/Latino population when compared to the white/Caucasian counterparts. (2019 Alzheimer's disease facts and figures. Alzheimers Dement. 15, 321–387. doi: 10.1016/j.jalz.2019.01.010). In addition to increased rates, health care disparities continue to impact their access to health care and lack of awareness of clinical trial opportunities. Increasing awareness, education, and access to available clinical trial opportunities are essential to include a diverse candidate pool in Alzheimer's disease and Alzheimer's disease prevention studies, to ensure future treatments benefit patients of all races and ethnicities and growing expectations of regulators and payors are met. To do this, community-based engagement efforts embedded in local neighborhoods may be more successful than traditional recruitment methods, asking these same individuals to go to established clinical research sites. Additional efforts to bring clinical trial procedures directly to them in a community-setting may help engender trust and decrease reluctance to participate in research. **Objectives:** GAP's [STUDY] Mobile Unit will support prescreening efforts for an Alzheimer's prevention study. Additionally, to build trust and relationships within neighborhoods, it will provide education about Alzheimer's disease, Alzheimer's disease prevention, and memory loss in traditionally underrepresented communities, as well as access to free memory screenings. These efforts will occur at local settings such as libraries, senior centers, churches, and other neighborhood centers. The [STUDY] Mobile Unit will broaden

the reach and capacity of 10-12 southern Florida Alzheimer's research sites, beyond their general reach as established brick and mortar clinical research sites. Conducting low risk, low-cost genetic prescreening assessments within predominantly minority communities will also provide well characterized and a potentially more qualified diverse cohort of participants for screening, resulting in accelerated enrollment in the [STUDY] clinical trial. **Methods:** A customized 29' mobile research unit was designed with a reception area, a consultation/testing room, and phlebotomy suite. Some clinical research staff teams lack diversity, making it difficult to connect with local minority populations. Two permanently assigned staff members, who are Hispanic and Haitian Creole, will travel on the mobile research unit throughout Florida to partner with local research center staff at community outreach and engagement events. They will connect with local seniors to offer prescreening and educational activities in English and Spanish, further increasing local access to these resources. Along with site staff representatives from local research centers, staff on the mobile unit will: 1. Provide education, awareness and access to an Alzheimer's prevention study in communities in 7 distinct Florida regions where traditionally underrepresented senior populations reside. 2. Genetically prescreen people aged 60-80 for Alzheimer's disease at community outreach events, including health fairs, storefronts, churches, libraries, neighborhood senior centers and other local gathering locations. 3. Disseminate information about brain health, memory loss, and local resources via GAP's Acti-v8 Your Brain program and NIH materials. **Results:** The [STUDY] Mobile Unit will be deployed on July 1, 2022. Within a 60–90-day period of operations, GAP will be prepared to report on the number of: 1. Locations visited; 2. Events planned; 3. People reached with racial/ethnic breakdowns; 4. Prescreens conducted and referrals made. Additional comparisons may be made for these same metrics from within the sites' traditional efforts, not utilizing a mobile unit, further showing the effectiveness to consent with seniors in more local settings vs clinical settings. **Conclusions:** GAP's mobile unit is an innovative resource providing minority communities with increased education and access to an Alzheimer's prevention research study, resulting in materially significant numbers of referrals and enrollment of diverse populations. Successful strategies and tactics will inform best practices to be executed across other indications of AD trials. This significant investment will result in expedited enrollment overall and statistically significant increases in enrollment of traditionally underrepresented populations. * Note: [STUDY] name will be provided on study poster upon review of the final data by the partnering sponsor.

P17- GENOTYPIC EFFECTS OF THE TOMM40'523 VARIANT AND APOE ON LONGITUDINAL COGNITIVE CHANGE OVER 4 YEARS: THE TOMMORROW STUDY.

H. Zou[1], S. Luo[2], M.W. Lutz[2], D.A. Bennett[3], B.L. Plassman[2], K.A. Welsh-Bohmer[2] *(1. University of North Carolina- Chapel Hill - Chapel Hill (United States), 2. Duke University - Durham (United States), 3. Rush University - Chicago (United States))*

Background: Carriage of the APOE ε4 allele is a major risk factor for Alzheimer's disease (AD) symptom onset and accelerates the clinical progression of disease in the mild to moderate stages of AD dementia (Qian et al., 2021). Variations in a poly-T variant (rs10524523, '523) in TOMM40, a gene adjacent to the APOE gene on chromosome 19, have also been shown to influence AD expression within APOE ε3/3 carriers, who are typically considered as a group at a lower risk of AD relative to APOE ε4 carriers (data from the ROS-MAP cohorts: Yu et al., 2017). It is unclear whether variations in APOE and TOMM40 haplotypes contribute to the heterogeneity in disease expression occurring during the preclinical stages of AD. **Objectives:** To determine the impact of these genes in early preclinical expression, we used the clinical trial data from the recently concluded TOMMORROW study to examine the effects of APOE and TOMM40 genotypes on neuropsychological test performance, repeated every 6 months for up to four years, in clinically normal, older individuals enrolled in the trial. **Methods:** Participants from the TOMMORROW trial were stratified according to APOE genotype (APOE ε3/3, APOE ε3/4, APOE ε4/4). APOE ε3/3 carriers were further stratified based on TOMM40'523 genotype (i.e., we included individuals with "S/S", "S/VL", and "VL/VL" genotypes). The test battery of cognitive assessments contained a total of 12 tests, assessing 5 cognitive domains: episodic memory (short & long delay recall from California Verbal Learning Test-II [CVLT-II]; Brief Visuospatial Memory Test -Revised [BVMT-R] delayed recall), executive function (Trail Making Test Part B, WAIS-R Digit Span backwards span), expressive language (Multilingual Naming Test [MiNT], lexical fluency & "animal" verbal fluency test), attentional processing (Trail Making Test- Part A, WAIS-R Digit Span forward span), and visuospatial function (Clock drawing & figure copy BVMT-R). The final analysis dataset consisted of 1,330 patients and 7,001 visits, with a mean follow-up period of 2.21 (SD = 1.14) years. Linear mixed models were used to compare the rates of decline in cognition across APOE groups and the APOE ε3/3 carriers with different TOMM40'523 genotypes. **Results:** All genetic subgroups showed improving cognitive performance across all measures over the first two years of observation, regardless of APOE and TOMM40 genotypes. This finding is not unexpected given that individuals across all genotypic groups were cognitively healthy at enrollment into the study. In cognitively normal adults, test-retest improvement is anticipated with repeated cognitive measurement. However, there were performance differences across the different genotypes both in terms of initial level of performance and rates of cognitive decline. Within the APOE groups, APOE ε3/4 and APOE ε4/4 genotypes were associated with worse baseline performance on measures of global cognition, episodic memory, and expressive language, compared to those with the APOE ε3/3 genotype. Further, over the four years of observation, the APOE ε3/3 carriers with the TOMM40'523-S/S genotype showed better baseline global cognition and accelerated rates of cognitive decline on tests of global cognition, working memory, and attentional processing compared to APOE ε3/3 carriers with TOMM40'523-S/VL and VL/VL genotypes and compared to the APOE ε3/4 and APOE ε4/4 carriers. These genotypic findings are broadly consistent with prior reports in APOE ε3/3 carriers who are cognitively healthy and showed that the TOMM40'523-S/S genotype in APOE ε3/3 carriers was associated with accelerated rates of cognitive decline when compared to APOE ε3/3 carriers with TOMM40'523-S/VL and VL/VL genotypes (Yu et al., 2017), although the domains most impacted were episodic memory and expressive language/semantic memory in that report. Methodological differences across the studies in terms of the length of overall observation in the cohorts (4 years in TOMMORROW vs 20+ years in ROS-MAP dataset) and the frequency of measurement (every 6 months in TOMMORROW trial vs annual observations in ROS-MAP) as well as other sample differences (clinical trial cohort vs community cohorts) may explain the differences in the cognitive domains most affected across the genotypic groups. **Conclusions:** Variations

in the TOMM40 poly-T have an influence on cognitive function over time and can be observed in APOE ε3/3 carriers where a confounding influence of an APOE ε4 allele are not an issue. We suggest that both APOE and TOMM40 genotypes may contribute to cognitive heterogeneity in the pre-MCI stages of AD. Controlling for this genetic variability will be important in clinical trials designed to slow the rate of cognitive decline and/or prevent symptom onset in preclinical AD. **References:** Qian, J., Betensky, R.A., Hyman, B.T., & Serrano-Pozo, A. (2021). Association of APOE Genotype with heterogeneity of cognitive decline rate in Alzheimer disease. Neurology, 96 (19) e2414-e2428. Yu, L., Lutz, M. W., Wilson, R. S., Burns, D. K., Roses, A. D., Saunders, A. M., Gaiteri, C., De Jager, P. L., Barnes, L. L., & Bennett, D. A. (2017). TOMM40'523 variant and cognitive decline in older persons with APOE ε3/3 genotype. Neurology, 88(7), 661–668.

P18- RACIAL/ETHNIC GROUP DIFFERENCES IN RESPONSE RATE TO A MAIL INVITATION TO PARTICIPATE IN A LIFESTYLE INTERVENTION TRIAL TO PREVENT COGNITIVE DECLINE (U.S. POINTER TRIAL). V. Pavlik[1], M. Yu[1], A. Alexander[2], J. Valenta[2], R. Elbein[3], A. Mcdonald[3] *(1. Baylor College Of Medicine - Houston (United States), 2. Kelsey Research Foundation - Houston (United States), 3. Alzheimer's Association - Houston (United States))*

Background: There is an urgent need to identify efficient and effective methods to increase the diversity of participants in Alzheimer's disease treatment and prevention trials. **Objective:** To determine whether there are racial/ethnic group differences in response rate to a mailed recruitment letter inviting participation in a multi-modal lifestyle intervention trial to prevent cognitive impairment in older individuals with a high cardiovascular risk factor burden. **Methods:** Two clinic systems at one of five sites implementing the U.S. POINTER trial identified potential age and medical history eligible trial participants through an electronic medical record (EMR) query. Participants received a recruitment letter describing the trial and directing them to a web site to begin the eligibility screening process. A major goal of recruitment was to achieve a demographically diverse patient population. To assess the success of a mailed letter campaign as a recruitment tool, we analyzed the response rates to the letter in different race/ethnicity groups, adjusting for age, sex, and neighborhood. Five neighborhoods were defined based on broad geographic regions containing distinct urban and suburban communities within a large metropolitan area. **Results:** Of 81,302 patients who were sent recruitment letters, 76,163 (93.9%) had complete EMR data for analysis. The most common missing variable was race/ethnicity. The racial/ethnic distribution of letter recipients was 45.3% non-Hispanic white (NHW), 25.2% Black/African American (AA), 16.6% Hispanic, and 12.9% other. Overall, 1.6% of letter recipients responded by providing screening information on the study website. The highest response rate was in NHW recipients (2.3%) and the lowest in Hispanic recipients (0.9%). Within ethnic group, the response rate varied by neighborhood. For example, in NHW recipients the response rate ranged from 1.5%-3.1% and in Hispanic recipients it ranged from 0.6%-1.3%. Except for one neighborhood with a lower response rate, the response rate in AA recipients was 1.4% regardless of neighborhood. In logistic regression modeling, age, sex, race/ethnicity, neighborhood, and clinic system were independent predictors of response rate. Of the 1246 responders, 44.5% represented racial/ethnic groups other than NHW. **Conclusions:** Although response rates may vary by ethnic group, mailed invitations to participate in a dementia prevention trial can yield a diverse study population. Oversampling of some groups to achieve desired recruitment targets can compensate for response rate variability among specific racial/ethnic group. Special methods, such as community engagement or bilingual recruitment materials, which have not yet been deployed at our clinical site for the U.S. POINTER study, may be needed to increase recruitment yields in certain groups. All demographic variables included in this analysis were associated with differential response rates, indicating that complex factors in addition to race/ethnicity drive recruitment yields in a particular clinical trial context. Some potentially relevant variables, such as education and household income, were not available in the EMR for inclusion in the analysis. Covid-19 surges throughout the recruitment period may have contributed to the observed variability in response.

P19- DEVELOPMENT OF AN ABBREVIATED PRE-SCREENING COGNITIVE BATTERY TO ENHANCE REFERRAL TO CLINICAL TRIALS. A. O Connell[1], E. Fischer[1], L. Latham[1], L. Baker[1], S. Craft[1] *(1. Wake Forest Alzheimer's Disease Research Center - Winston-Salem (United States))*

Background: Timely enrollment of an eligible cohort into Alzheimer's disease (AD) clinical trials is critical in accelerating AD research, but as these trials increasingly target prodromal and preclinical AD, clinical trial sites face difficulty in determining whether prospective participants will meet cognitive eligibility criteria. This is especially problematic in prodromal trials, as these individuals often report subjective memory complaints but have not received any clinical evaluation of cognitive status and therefore lack any previous diagnosis or available neuropsychological testing to aid in evaluating study eligibility prior to conducting the clinical trial screening visit. As a result, screen fail rates based on screening cognitive assessments for these studies is high, study sponsors and clinical trial sites invest considerable time and resources in conducting screening visits, and the duration required to complete study enrollment is prolonged. **Objectives:** To develop and pilot a brief cognitive battery for use as a pre-screening tool in the evaluation of volunteers to the Wake Forest Alzheimer's Disease Research Center (ADRC) who lack prior cognitive testing. The aims of this pilot were: 1) to determine preliminary cognitive status of these participants and provide them feedback on this information, 2) screen out cognitively normal individuals with subjective complaints prior to referral to prodromal clinical trials, and 3) enhance referral to the Center's enrolling studies by using the results obtained to assess eligibility based on study-specific inclusion criteria. **Methods:** A working group comprised of the Wake Forest ADRC Directors, neuropsychologists, clinical study management team members, and Outreach Director collaborated to devise a cognitive battery that could be administered in under one hour, provide a preliminary assessment of a broad cross-section of cognitive domains, and obtain enough information to enable evaluation of cognitive eligibility for referral to Center-conducted studies enrolling cognitively normal, mild cognitive impairment (MCI), or mild AD participants. The resulting protocol included the administration of Montreal Cognitive Assessment (MoCA), WMS-III Logical Memory, Number Span Test Forward and Backward, Trail Making Tests A and B, Rey Auditory Verbal Learning Testing (RAVLT), and Benson Complex Figure Copy and Recall, and was implemented as a one-hour visit titled the Memory Screening Clinic (MSC). At

the point of initial intake to the ADRC, all potential participants completed a preliminary telephone screen that included the telephone interview for cognitive status (TICS), self-report of cognitive complaints, and collection of basic demographic and medical history information. Participants with TICS scores ≥ 34 who did not self-report as cognitively normal, or those with any TICS score who did not have a known diagnosis of MCI or AD with supporting neuropsychological testing, were then offered the one-hour MSC visit for preliminary cognitive screening and feedback. The visit included the informed consent presentation, completion of a brief medical history form, and the neuropsychological battery. A Center neuropsychologist then reviewed the cognitive assessments and medical history information to determine a preliminary cognitive impression, and these results were then reviewed by a referral coordinator to evaluate eligibility for currently enrolling studies. The preliminary cognitive impression and potential study options were then discussed with each participant, and a referral made to the appropriate study team as applicable. All individuals who completed the MSC received feedback that included whether they were eligible for further testing via a study-specific screening visit, materials with information about potential study opportunities, and their MoCA score. **Results:** Between October 2019 and June 2022, 459 individuals completed a phone screen intake with the Wake Forest ADRC and met eligibility for referral to the MSC. Of those participants, 268 (58%) completed a MSC visit (mean age= 68.1 (50-88), 181 Female/87 Male; 134 Normal Controls/134 Probable Impairment) while 191 (42%) did not continue following the phone screen (lost to follow-up, not interested in study participation, or ineligible based on global exclusion criteria). Of those who completed the MSC visit, 162 (60%) were not referred to a clinical trial (did not meet eligibility criteria, were not interested in available study options, or were interested in cognitive screening and feedback only) and 106 (40%) participants were interested in and eligible for referral to a clinical trial. Participants who completed the MSC visit and feedback only and were not referred to subsequent studies were generally cognitively normal and had self-referred to the ADRC with interest in cognitive screening and evaluation for MCI studies. Of the MSC participants referred to a clinical trial, 62 (58%) were eligible at screening and enrolled in a clinical trial, 37 screen-failed (35%), and 7 did not complete a screening visit (7%). **Conclusion:** The implementation of the MSC visit and abbreviated cognitive battery created a cost-effective, low-burden method of connecting with prospective research participants, providing preliminary cognitive feedback, and enhancing successful referral to and enrollment in Center clinical trials. **Disclosures:** The authors have no disclosures to share.

P20- LONG-TERM NICOTINE TREATMENT OF MILD COGNITIVE IMPAIRMENT (THE MIND STUDY): BASELINE CHARACTERISTICS AND STUDY PROGRESS. P. Newhouse[1], R. Raman[2], A. Saykin[3], J. Dumas[4], E. Levin[5], K. Kellar[6], P. Aisen[2] *(1. Vanderbilt University - Nashville (United States), 2. USC/ATRI - San Diego (United States), 3. Indiana University - Indianapolis (United States), 4. University of Vermont - Burlington (United States), 5. Duke University - Durham (United States), 6. Georgetown University - Washington, Dc (United States))*

Background: Cognitive decline in AD/MCI is related to loss of cholinergic neurons. However, inhibition of acetylcholine degradation has not sustained improvement nor slowed progression in patients with mild cognitive impairment (MCI). Treatment directly targeting nicotinic cholinergic receptors may be more helpful. We have shown proof of concept in a 6-month multicenter trial (Newhouse et al, Neurology, 2012; 78: 91–100) that transdermal nicotine provides significant improvement in attention, episodic memory, and global ratings of functioning with minimal side effects in MCI. The MIND trial (Memory Improvement with Nicotine Dosing) is a larger and longer (2-year) trial to determine whether long-term transdermal nicotine treatment results in persistence of cognitive improvement and attenuation of cognitive decline in patients with MCI. **Methods:** At 42 sites, MCI participants were randomized 1:1 to either transdermal nicotine, beginning at 3.5 mg/day, increasing to 21 mg/day or matching placebo by 5 weeks. Sample size was planned to be 300. Participants were assessed at 0, 3, 6, 12, 18, and 24 months, with a subset undergoing MRI scans at 0, 12, and 24 months, and CSF collection at 0 and 24 months. Primary cognitive outcomes included reaction time standard error change-from-baseline (Connors CPT) for attention and delayed word recall (Cogstate) for memory. Primary clinical outcome is the CGIC. Secondary clinical measures include behavioral/functional scales and the CDR-SOB. An MRI substudy is examining possible neural mechanisms. **Results:** To date, 684 participants were screened and 322 were randomized including 138 females (43%) and 184 males (57%). Mean age was 73.7±7.1, education 16±2.9 years. Mean MMSE was 27.4±1.8 and CDR Global was 0.5. Randomization of ethnoracial underrepresented populations (URPs) was 9.1% (Black/African-American 4%, Asian 2%, Hispanic/Latinx 3%). Treatment/Study discontinuations were higher than expected at 32% due in part to pandemic-related disruptions. The sample size has been increased to 380 to maintain statistical power. There are 115 completers thus far. Baseline MRI scans are 60 and LPs are 37. Safety results show that treatment has been generally well tolerated with no SAEs definitively or probably tied to study participation or investigational product thus far. **Conclusions:** If the hypotheses are validated, this will support a novel, broadly available, and inexpensive repurposed intervention for MCI and would encourage early treatment to improve symptoms, attenuate progression of cognitive impairment, and lead to combined trials with agents that interact with Aβ, tau or other mechanisms. Low URP recruitment and higher dropout rate remain challenging and are being specifically addressed in recruitment/enrollment/retention efforts moving forward to complete the trial. **Disclosures:** None relevant to this presentation.

P21- USING AN END-TO-END DEEP LEARNING MODEL IN OLDER ADULTS WITH MCI TO IDENTIFY AD RISK FACTORS ON CHROMOSOME 19 THAT EXACERBATE COGNITIVE DECLINE. J. Bae[1], L. Apostolova[1], V. Pentchev[1], D. Hammers[1], A. Polsinelli[1], K. Nudelman[1], A. Saykin[1], K. Nho[1] *(1. IUPUI - Indianapolis (United States))*

Background: Research into genetic mapping possesses strong potential to inform precision medicine and drug discovery in Alzheimer's disease (AD). The development of CRISPR – a technology, that allows the replacement of a given single nucleotide polymorphism (SNP) with another, opens the possibility for genome-level therapy. Due to the enormous size of the human genome and the countless genetic interactions, identifying the most relevant AD-risk SNPs remains challenging. Previous research has relied on feature selection methods to eliminate portions of the data based on presumed irrelevance to the model. However, this

approach limits discovery opportunity. Here we implemented a novel feature selection-free end-to-end deep learning model developed to reduce the dimensionality of omics data without losing key genetic information. We chose to focus on chromosome 19. First, our hypothesis-free model was trained on correctly predicting AD dementia vs cognitively unimpaired (CU) subjects. Next, the model was extended to further characterize all AD-relevant SNPs based on their interactive effects. Individual SNP impact was quantified by calculating a risk impact score (RIS). The identified SNPs were then tested for their ability to characterize participants with mild cognitive impairment (MCI) who were likely to convert to AD dementia (MCI-C) vs not (MCI-NC) over 3 years. **Objectives:** We hypothesized that AD-risk SNPs would have a higher RIS in MCI-C and would predict the rate of cognitive decline. Our second objective was to perform computational CRISPR-like experiment to determine the nucleotides with the greatest influence on the probability of progression from MCI to dementia. **Method:** A novel deep learning model utilizing Capsule Network was developed to analyze 266,161 SNPs from chromosome 19, from 313 AD and 457 CU participants enrolled in the Alzheimer's Disease Neuroimaging Initiative. The dataset was divided into train, validation, and test sets with a ratio of 60:20:20 (N=462, 154, and 154). The model examined the genetic interactions between all GWASed chromosome 19 SNPs and produced probability scores for AD and CU. Each SNP was sequentially deleted and the corresponding change in the prediction scores was measured. The SNP's RIS, corresponding to the averaged prediction decrease across participants when deleted, was computed. All 266,161 SNPs were rank-ordered based on their RIS. The highest RIS-ranked 35 SNPs were utilized to differentiate MCI-C (n=203) and MCI-NC (n=213) participants. Next, we predicted the rate of cognitive decline in MCI using multiple regression with 5 SNPs' RIS as predictors. All possible 5-SNP-combinations among the top 35 SNPs were tested for association with 4 cognitive composites (memory, language, executive, and visuospatial function) in participants with MCI. Lastly, we performed computational CRISPR to demonstrate the impact of SNP rs56131196 (APOC1), which represented the SNP with the greatest RIS value. **Results:** The model achieved 68.18% accuracy in classifying AD vs. CU. The SNPs with the highest 35 RIS included 11 SNPs from APOC1 gene, 10 SNPs from TOMM40, 5 SNPs from APOC2, and 1 SNP each from ERCC1, ZNF473, VRK3, and NECTIN2. The APOE haplotype SNPs, i.e., rs429358 and rs7412, which are well-known AD-risk SNPs, were not included in the highest RIS-ranked 35 SNPs. The same model was applied to predict MCI-C vs. MCI-NC, and RIS for the highest 35 SNPs were calculated. SNPs in APOC1, TOMM40, and NECTIN2 showed significantly stronger RIS for MCI-C than MCI-NC participants, $p < 0.001$. All regression models were significant using RIS for the 5 SNPs with the highest correlation coefficient as predictors of performance in each cognitive domain while controlling for age, sex, education, and APOE E4 genotype, $p < 0.001$. The r2-adjusted values were 0.279, 0.163, 0.098, and 0.178, for the memory, language, executive, and visuospatial models, respectively. The 5 top performing SNPs once again mapped to APOC1, TOMM40, ERCC1, and NECTIN2. The presence of adenine(A) at rs56131196 (APOC1) increases the risk of AD. Approximately 68.47% of MCI-C participants (N = 139) in our sample had either the AA or AG genotype at rs56131196 in APOC1. Using CRISPR simulations, we substituted the risk genotypes with GG in MCI-C participants. MCI-C participants with this substitution were predicted to have significantly lower likelihood of AD occurrence than those without substitution, $p < .001$. **Conclusions:** Our hypothesis-free deep learning model trained on AD and CU participants successfully determined SNPs that predict conversion from MCI to AD dementia. 5 SNPs accounted for a significant amount of the variance in cognitive decline across multiple cognitive domains. Genetic screening based on this information could be useful for patient selection in clinical trials with disease-modifying therapies. Furthermore, our computational CRISPR simulations in MCI-C confirm the significant promise of CRISPR for precision medicine. In vitro and in vivo animal and human studies exploring nucleotide-level substitutions are warranted to fully appreciate their role in translational neuroscience.

P22- PANDEMIC EFFECTS ON DUPLICATE SUBJECTS IN CLINICAL TRIALS OF ALZHEIMER'S DISEASE.

T. Shiovitz[1], C. Steinmetz[2], B. Steinmiller[2] *(1. California Neuroscience Research, CTSdatabase LLC - Sherman Oaks, Ca (United States minor outlying islands), 2. CTSdatabase LLC - Sherman Oaks, Ca (United States minor outlying islands))*

Background: Duplicate and professional subjects are a significant issue in clinical trials, particularly those in CNS and pain, where subjective endpoints allow potential subjects to magnify there symptoms in order to meet inclusion criteria. Even in Alzheimer's Disease trials, subjects may participate in concurrent trials to take advantage of different MOAs or to increase the chances of getting an effective treatment. Alternatively, they may be professional subjects, who, for instance, may participate in a Cognition in Schizophrenia study at one site and an Early AD study at another. The failure to address the problem of duplicate and professional subjects can lead to problems with both subject safety and data integrity. **Objectives:** To determine if there were pandemic-associated effects on the percentage of duplicate subjects found in clinical trials of Alzheimer's Disease by comparing those added to the CTSdatabase subject registry in the 2 years before the onset of the pandemic compared to the two years during the pandemic. **Methods:** We looked at pooled study data for all subjects that screened for an Alzheimer's Disease study in protocols that used CTSdatabase between February 2018 and March 2022. Actionable matches are defined as those that violated protocol I/E (including concurrent enrollment, participation in another study less than the number of days required or previously enrolled in a study for a prohibited indication). The number of actionable matches was divided by the number of subjects screened to determine the percentage of inappropriate subjects (duplicates or otherwise) for that study. The number of screened subjects was also divided into two equal parts for each study based on enrollment date, with March, 2020, as the dividing point for when the pandemic began in earnest. Actionable matches were tallied for each half of enrollment. **Results:** Of 1279 subjects entered into Phase 3 Alzheimer's Disease studies using CTSdatabase over the last 4 years, 4.7% (60) were excluded due to participating in another study concurrently, within an exclusionary timeframe or for an exclusionary diagnosis. While there was a trend toward more subjects being excluded during the pandemic, there was no significant difference in the percentage of those excluded before the onset of the pandemic and after the pandemic (3.9 vs 5.5%, p= 0.18). **Conclusion:** While there was a trend toward a higher percentage of potential Alzheimer's Disease subjects excluded during the pandemic, this was not significant. The percentage excluded (4.7%) overall was striking, given the indication. We hypothesize that while some of these subjects (and their cagregivers were professional subjects, many may have been

seeking an effective treatment, i.e they were duplicate, but not professional, subjects. A subject registry such as CTSdatabase is an important tool in identifying these subjects and either eliminating them or understanding how they may affect study results.

P23- THE TIME COMPONENT TEST IS INHERENTLY MEANINGFUL BECAUSE IT COMBINES EVIDENCE ACROSS OUTCOMES TO MEASURE THE IMPACT OF TREATMENT ON PROGRESSION RATE IN DEGENERATIVE DISEASES.

S. Dickson[1], S. Hendrix[1] *(1. Pentara Corporation - Salt Lake City (United States))*

Background: Degenerative diseases like Alzheimer's Disease and other progressive diseases present unique measurement challenges. Multiple components of disease occur over time like cognitive, functional, and global aspects which change at varying rates during different stages of disease partially due to ceiling and floor effects in the assessment tools. Additionally, the results of treatments that are intended to modify disease progression will be best measured when they account for all aspects of the disease, whereas symptomatic treatments may focus on only a single dimension of disease. These challenges make it difficult to create a single outcome to measure disease-modifying effects for all stages of disease. But requiring significance on multiple primary outcomes imposes an unusually high standard for approval of treatments for under-treated diseases that often have relatively small populations. We propose the Time Component Test (TCT), a global statistical test that combines outcomes to obtain an estimate of the impact of treatment on progression rate of the disease. **Objectives:** The objective of this presentation is to demonstrate that the TCT is inherently clinically meaningful because it is more effective method at marking disease progression than individual outcomes alone. **Methods:** Using historic data from ADCS, we demonstrate how the ADAS-cog, CDR-SB, and ADCS-ADL align with disease progression using principal component analysis individually and when combined into a TCT. We also use simulation to demonstrate how the TCT behaves asymptotically and in the presence of outcomes of varying discreteness. We simulate a treatment effect on top of historic data to compare power across outcomes. **Results:** The TCT more closely aligns with disease progression than any individual outcome. It achieves greater power without inflating type I error. Requiring co-primary outcomes can inflate sample size by as much as tenfold compared to the TCT. A TCT can be performed based on summary data and achieve similar performance as on the individual-level. Interpretation can be provided in terms of specific time savings of disease progression. **Conclusion:** The TCT can estimate time saved from disease progression, which is inherently meaningful to patients. Failure to appropriately account for disease progression by using all aspects of disease in a single outcome unnecessarily increases the sample size of clinical trials, creating a greater burden on those suffering from the disease, while also making it harder for effective treatment to make it to a broader market.

LP1- EFFECT OF TREATMENT WITH THE CHOLINERGIC PRECURSOR CHOLINE ALPHOSCERATE IN MILD COGNITIVE DYSFUNCTION (CARL): RESEARCH PROTOCOL

E. Traini[1], A. Carotenuto[1], V. Andreone[2], F. Amenta[1] *(1. University of Camerino - Camerino (Italy), 2. Neurology Complex Unit, Cardarelli Hospital - Naples (Italy))*

Background: Cognitive dysfunctions are characterized by a decrease in the weight and volume of the brain, due to cortical atrophy, with widening of the grooves and flattening of the convolutions. Brain atrophy involves mainly the hippocampus. It is related to the progression of cognitive impairment and the conversion from mild cognitive impairment (MCI) to over dementia. **Objectives:** A previous trial on Alzheimer's disease (AD) has shown that a marked cholinergic challenge obtained by associating the cholinergic precursor choline alphoscerate with the cholinesterase inhibitor donepezil counters the progression of brain atrophy in AD patients with vascular damage. Currently there is no treatment approved for MCI. We have decided to investigate if choline alphoscerate may have a therapeutic role on MCI. **Methods:** The study CARL (Choline Alphoscerate in mild cognitive dysfunction) is an explorative, no-profit, monocentric, randomized, double-blind and controlled vs placebo clinical trial, with a study duration of 12 (24) months. A total of 120 patients will be enrolled and randomized to choline alphoscerate arm or placebo arm, at a fixed dose of 1200 mg/day for 12 (24) months or until treatment is stopped prematurely. The trial: The CARL study intends to evaluate the efficacy of choline alphoscerate in patients with MCI and associated vascular damage, as the ability to induce: stability and / or slowing of hippocampal, entorhinal, cortical atrophy and ventricular dilation; Improvement of cognitive symptoms and / or slowing of their progression and Improvement of behavioral symptoms (mood and motivation disorders). The study will be carried out at the AORN Cardarelli of Naples, while for the organization and statistical analysis, will be under the responsibility of the Clinical Research Center of the University of Camerino. The data, collected at the site, will be entered in a dedicated Database. An electronic system, created and validated by the university Information Technology Group, will include the data entry pages prepared on the basis of the study flow-chart. **Conclusion:** The study will be conducted in compliance with either the Declaration of Helsinki or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice. The protocol was reviewed and approved by the competent Independent Ethics Committee (IEC) and by the competent Italian Regulatory Authority (AIFA). **Key words:** Mild cognitive impairment, hippocampus, choline alphoscerate, neuroimaging.

LP2- A TRICHOTOMY METHOD FOR DEFINING HOMOGENEOUS SUBGROUPS IN A DEMENTIA POPULATION.

G. Rosenberg[1] *(1. University of New Mexico - Albuquerque (United States))*

Background: Multiple pathological changes in the aging brain, including cerebrovascular disease, have confounded treatment trials with monotherapies. Use of multimodal biomarkers to create homogeneous patient groups could improve the success of clinical trials. In addition, biomarkers can aid in diagnosis of mixed dementia (MX), which is the most common type of dementia, and is difficult to diagnose during life. Earlier we showed that a 2-way clustering method with Alzheimer's disease (AD) and vascular disease (VD) improved diagnostic accuracy. Here we show that adding cognition further improves classification. **Objectives:** Smaller sample sizes with more homogeneous subgroups of participants improves efficiency of clinical trials. We hypothesized that a 3-way clustering method employing biological biomarkers for AD, VD, and cognition (COG) could be used to improve patient classification and to identify MX patients. **Methods:** Classification was based on three diagnostic axes: 1) AD

proteins in CSF (amyloidb1-42 and phosphoTau181), 2) vascular disease as shown by diffusion tensor imaging of mean free water and peak width of skeletonized mean diffusivity (PSMD) in white matter, and 3) executive and memory function as indicators of cognition. Previously, the double dichotomy concept was validated in the UNM cohort (N=80). The trichotomy method is applied to a larger group of Alzheimer's disease neuroimaging initiative (ADNI) (N=538) subjects. We defined continuous normalized composite scores for Alzheimer's disease (ADS), vascular disease (VDS), and cognition (CGS) with values from 0 to 1 and cut-offs of 0.5. **Results:** The trichotomy 3-way classification based on cut-off values divided the population into eight biologically defined subgroups. Cognition divided the cohorts into those with normal and poor cognition. These two groups were further divided into four groups each, based on the presence or the absence of AD and VD factors. The biological MX group had poor cognition with AD and VD factors. Four groups will need more study with long term follow-up: 1) leukoaraiosis (LA) group that had normal cognition with absence of AD factors and presence of VD factors; 2) poor cognition without AD or VD factors; 3) normal cognition with AD factors, and 4) normal cognition with both AD and VD factors. We found that using cognition, in addition to AD and VD factors to define subgroups, leads to homogenous clusters with well-defined characteristics. The classification results in the ADNI cohort were compared to those at UNM. In the UNM cohort there were 25% MX patients, but only 9.3% in the ADNI cohort, reflecting that the UNM group was enriched in vascular patients while AD was the focus of the ADNI study. In ADNI about 20% of the subjects had normal cognition with either AD or VD factors. VDS correlated with executive function and ADS with memory function. Finally, pTau181 contained information that was different from that of white matter damage, while Ab1-42 was correlated with white matter damage. Executive function was lowest in MX. **Conclusions:** We propose that expanding the ATN formula by adding vascular (V) and cognitive (C) factors to form ATNVC creates homogeneous patient groups and identifies MX patients during life. In addition, it justifies exclusion from clinical trials of asymptomatic leukoaraiosis subjects with white matter hyperintensities. Further studies will be needed to determine if a 3-way clustering method with multimodal biological biomarkers improves success of clinical trials. None of the authors have any conflicts of interest.

LP3- COMPLIANCE AND SATISFACTION IN THE ALZHEIMER'S PREVENTION INITIATIVE AUTOSOMAL-DOMINANT ALZHEIMER'S DISEASE COLOMBIA TRIAL. N. Acosta-Baena[1], C. Muñoz[1], P. Ospina[1], S. Del Rio[1], L. Lopez[1], M. Giraldo[1], S. Duque[1], A. Navarro[1], E.M. Reiman[2], N. Hu[3], K. Asik[3], P.N. Tariot[2], J.B. Langbaum[2], F. Lopera[1], S. Rios-Romenets[1] *(1. Grupo de Neurociencias de Antioquia (GNA), Universidad de Antioquia, Medellín, Colombia. - Medellín (Colombia), 2. Banner Alzheimer's Institute - Phoenix (United States), 3. Genentech Inc. - San Francisco (United States)*

Background: This double-blind, randomized, placebo-controlled Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease (API ADAD) Colombia Trial (NCT01998841) evaluated crenezumab in cognitively unimpaired adults (age 30-60). Study period A evaluated the efficacy and safety of crenezumab versus placebo in participants who carry the PSEN1 E280A autosomal-dominant mutation. A cohort of non-mutation carriers was enrolled in the placebo arm to maintain genetic status blinding. Crenezumab was administered for at least 5 years, given subcutaneously (SC) every 2 weeks or intravenously (IV) every 4 weeks. In study period B, mutation carriers had the opportunity to receive only crenezumab until post-trial access becomes available or development is discontinued. The retention strategies approved by the local research ethics committee included: monetary compensation for the inconvenience and time spent and travel assistance for trial visits and procedures; annual surveys of participants to assess satisfaction; strong and trusted relationships with participant and their families; comfortable environment; 24/7 availability of staff by phone; efforts to reduce visit duration; annual meetings for participants and study partners; a social plan developed with input from the trial's social and ethics advisory committee, with educational programs and other aid for family members; and a health plan where participants received earlier attention than would have been possible via their normal insurance, including access to contraception, care by specialists, including psychiatrist and psychologist (for early diagnosis, treatment and follow up of depressive symptoms) AD-related behavioral alteration, and adverse events. **Objectives:** To describe participant satisfaction and the retention rate of randomized participants who completed study period A. **Methods:** Annual "Adherence and Satisfaction surveys" were conducted by site staff by phone or in person during the corresponding visit to evaluate the participant's perception of protocol procedures and of quality of care provided by each staff member; to identify personal, family and job difficulties of each participant; and to detect those at risk of withdrawal. Here, we provide a descriptive summary of trial activities for participants who withdrew consent and of survey results. **Results:** Study period A ran from December 20, 2013 to April 01, 2022. 252 participants were included. At the main site in Medellin: 182 (72%). Participants in satellites sites: Yarumal 48 (19%), Armenia 15 (6%) and Bogotá 7 (3%). In June, 2019 the drug administration route was switched optionally from SC to IV. With the change to IV administration, the Yarumal satellite was closed and the participants had to attend Medellín every month. Participants from Bogota and Armenia were attended Medellin every 6 months. Approximately 84 participants (33%) attended the main site but lived in distant location, which required travel by bus more than four hours. At the end of period A, 228 active participants still received study medication [SC: 31(13.6%), IV:197 (86.4%)]. Neuropsychologists performed 3775 cognitive assessments, with an average of 15 visits per participant (3-19 evaluations). Four participants missed a cognitive assessment during the pandemic, and one was missed due to work-related reasons. The overall retention rate was 94% (237 subjects completed study period A). 90.5% completed treatment (228 participants). 24 discontinued investigational product and 9 were followed per protocol, without receiving study drug. Among the 24 who discontinued treatment, 5 (2.0%) participants discontinued due to an adverse event, 4 (1.6%) due to pregnancy, 2 (0.8%) due to non-compliance, 1 (0.4%) participant due to physician decision and 12 (4.8%) withdrew consent. The main reasons for withdrawal were change of residency to another country and work-related problems. Based on surveys conducted until 2021, 29 (12.7%) active participants had at some point considered withdrawing from the trial, due to depressive symptoms, health problems, or difficulties at work; 6% had jobs problems due to the trial visits; 4.2% lost employment due to participating in this trial. 86 % reported moderate or great satisfaction with the trial. 86% active participants rated their health as equal to or better than before they started the trial. **Conclusions:** Clinical trials in healthy adults, many of whom work, are challenging; here we had a

high retention rate. The study population has been followed up for 30 years by the Neurosciences Group of Antioquia (GNA). Participants are familiar with and trust GNA. The API ADAD Colombia trial is an example of a collaborative effort among the PSEN1 E280A kindred members, researchers, and sponsors in the search for an effective preventive treatment for AD. Preserving or improving quality of life of trial participants is the responsibility of sponsors and investigators. The social and health plans and the other adherence/retention strategies implemented strengthened this trial and may help with future ones, and demonstrates how ethical research is possible, contributing to the well-being of these people and their families.

LP4- THE GLOBAL ALZHEIMER'S PLATFORM FOUNDATION'S® (GAP'S) INCLUSIVE RESEARCH INITIATIVE: ENHANCING RECRUITMENT OF UNDERREPRESENTED COMMUNITIES THROUGH COMMUNITY CONNECTORS. D. Batchuluun[1], T. Rodgers[1], L. Zisko[1], M. Key[1], L. Thurman[1], J. Dwyer[1] *(1. Global Alzheimer's Platform Foundation - Washington (United States))*

Background: It is estimated that Alzheimer's disease (AD) clinical trials recruit between 1-5% of individuals from underrepresented populations. However, Blacks/African Americans are 2-3 times more likely and Hispanic/Latinos are 1.5 times more likely to develop Alzheimer's disease when compared to non-Hispanic whites (Alzheimer's Association, 2019). Diverse representation in AD clinical trials is not only critical in assessing safety and efficacy of treatment but helps to ensure equity and inclusion in the clinical research process. The benefits and risks of treatment cannot be fully investigated and understood without adequate representation of the entire population. The Global Alzheimer's Platform Foundation® (GAP) has created the Inclusive Research Initiative (IRI) for sites participating in its network (GAP-Net). GAP-IRI includes four Community Connectors who provide concierge level services throughout the East, West, Midwest and Southeast regions of the US to GAP-Net sites. Community Connectors plan customized community events, network within diverse communities, and conduct targeted outreach and recruitment strategies aimed at increasing diverse representation in AD clinical trials. **Objectives:** GAP's Community Connectors aim to improve recruitment of underrepresented and underserved communities into AD clinical trials through a) community mapping efforts, b) relationship building with community partners and c) Primary Care Provider (PCP)/Healthcare Provider (HCP) engagement. **Methods:** GAP-IRI was launched February 2022 as a direct response to positive outcomes from GAP's inclusive research support on GAP's investigator-initiated trial, Bio-Hermes. As of September 2022, the Bio-Hermes study has enrolled 22% from underrepresented communities. Six diverse Community Connectors were hired between February 2022 and September 2022 because of their experience in community outreach, advocacy, and engagement with underrepresented populations. Key responsibilities of Community Connectors include: a) Community mapping of each site/community to identify community partners, key influencers and leaders; b) Building relationships and creating partnerships with identified, trusted organizations that serve Black/AA, Hispanic/Latino and other underrepresented communities. - Leveraging those relationships to coordinate and speak at community health fairs, community senior centers, education / awareness events, memory screening events, etc. c) Engaging community healthcare providers (HCP) that serve in underrepresented communities to identify patients at heightened risk of Alzheimer's with potential to serve as referral pathways for clinical trials, memory care support, etc. d) Supporting sites with other recruitment and outreach strategies deemed appropriate and beneficial to recruit diverse participants in AD trials. **Results:** GAP's Inclusive Research Initiative (IRI) was launched February 2022 and Community Connector support with GAP-Net sites initiated in April 2022. The following outcomes will be measured: -The total number of GAP-Net sites that receive GAP-IRI/Community Connector support. -The total number of Community Connector visits to GAP-Net sites. -The total number of community partners identified in each region. -The total number of community outreach events held in each region. -The total number/percentage of underrepresented participants screened. -The total number/percentage of underrepresented participants randomized. Interim results and progress will be shared during CTAD's 2022 Annual Conference. **Conclusions:** Achieving representation in AD clinical trials involves grassroots initiatives and intentional efforts in relationship building and community engagement. GAP's Community Connectors aim to increase recruitment of underrepresented communities in AD clinical trials through these efforts to help ensure both equity and inclusivity. Key learnings and metrics from GAP's Inclusive Research Initiative and Community Connector role will help to inform the creation of future initiatives and roles in other therapeutic areas in addition to AD. **Acknowledgements:** We thank Joshua Travis, Mia Chester, Paula Atkinson, Philip Macias, Roldyne Dolce, and Janay Austin Todd for their contributions to the Inclusive Research Initiative. **References:** Alzheimer's Association (2019). 2019 Alzheimer's disease facts and figures. Alzheimers Dement. 15, 321–387. doi: 10.1016/j.jalz.2019.01.010

LP5- MITIGATING LOSS OF STATISTICAL POWER DUE TO OUTCOME IMBALANCE IN CLINICAL TRIALS. A. Tam[1], C. Laurent[1], C. Dansereau[1] *(1. Perceiv AI - Montreal (Canada))*

Background: Although cognitive changes are typical primary outcomes in Alzheimer's disease clinical trials, a significant proportion of participants will remain stable throughout a trial. Furthermore, randomization does not guarantee equal rates of decline between placebo and treatment arms. This outcome imbalance between the arms can reduce a trial's power and/or lead to erroneous conclusions on treatment efficacy. **Objectives:** We used machine learning models to identify individuals as likely decliners or likely non-decliners. We aimed to demonstrate that these prognostic labels can be used to increase a trial's power and mitigate the impact of outcome imbalance in two ways: post-randomization subgroup analysis of likely decliners and pre-randomization enrichment of likely decliners. **Methods:** We trained a machine learning model to classify decliners and non-decliners on 1329 individuals with mild cognitive impairment or Alzheimer's dementia from the ADNI (adni.loni.usc.edu) and NACC (naccdata.org) datasets. Decliners were defined as individuals who had increased CDR-SB scores at 24 months of follow-up compared to baseline, and the prevalence of decliners in this sample was 65%. Age, sex, APOE4 status, and gray matter volumes of brain regions extracted from MRI at baseline were used as input features. The model was trained and tested with nested 5-fold cross-validation. To assess the probability of outcome imbalance across placebo and treatment arms, we simulated 100,000 trials by randomly assigning individuals to placebo and treatment groups (n=250 per arm, based on a Phase 2 trial by Swanson

et al, 2021, Alzheimers Res Ther), while also stratifying for APOE4 and diagnosis, and we measured the differences in prevalence of decliners and non-decliners across the arms. We then assessed the impact of such imbalance on power to detect a 25% treatment effect across 1000 simulated trials at various levels of imbalance (ranging from 1% to 5% more decliners in the treatment arm). Furthermore, we studied whether covariate adjustment and enrichment with likely decliners predicted by the machine learning model can mitigate the loss in power associated with that imbalance. **Results:** The probability of observing at least a 5% outcome imbalance across arms (i.e. 5% more or fewer decliners in the treatment compared to placebo) was 22.4%. A perfectly balanced trial obtained a mean (± std) power of 89.2 ± 17.9% to detect a 25% treatment effect, while a trial that contained 5% more decliners in the treatment arm obtained only 73.8 ± 28.3% power, resulting in a drastic loss of 15% power. Covariate adjustment on common prognostic factors (e.g. APOE4 status, baseline diagnosis, baseline outcome score) increased power across levels of imbalance (97.2 ± 9.4% and 87.8 ± 21.5% in a perfectly balanced trial and a trial with 5% imbalance, respectively), but a 10% reduction in power still occurred at 5% imbalance. A subgroup analysis of the likely decliners (excluding the likely non-decliners) identified by the machine learning model increased power regardless of imbalance (balanced: 92.6 ± 14.1%; 5% imbalance: 85.2 ± 21.2%), despite the reduction in sample size (63% of the original size of 250 per arm), compared to using data from the full sample. A subgroup analysis of likely decliners with covariate adjustment achieved even greater power (balanced: 97.4 ± 8.2%; 5% imbalance: 92.2 ± 16.0%). Enriching a trial at the original sample size with 250 likely decliners per arm increased the power (balanced: 97.0 ± 9.4%; 5% imbalance: 92.1 ± 16.9%). We observed that the 5% imbalance resulted in only a 5% power reduction when using the enriched population, compared to the 15% reduction on the unenriched population. Finally, covariate adjustment on an enriched sample with 250 likely decliners per arm obtained the greatest statistical power (balanced: 99.1 ± 4.7%; 5% imbalance: 96.2 ± 11.8%). Compared to using the unenriched population where a 5% imbalance resulted in a 10% power reduction, using the enriched population led to a 3% power reduction, rendering the statistical analysis robust to imbalance. **Conclusion:** An outcome imbalance across trial arms as little as 5% significantly reduces a trial's power to detect a treatment effect. The likelihood of enrolling imbalanced samples is approximately 1 in 5 (for a 5% discrepancy between the placebo and treatment arms) for a typical Phase 2 trial with 250 individuals per arm, despite randomization and balancing for common prognostic factors. Therefore, trials need additional strategies to enroll balanced arms. Our prognostic model can prevent imbalance by identifying individuals as likely decliners and likely non-decliners prior to randomization. Enriching with likely decliners can mitigate the loss in power due to imbalance and boost power when there is perfect balance. Combining our enrichment strategy of selectively enrolling likely decliners with covariate adjustment enables even greater statistical power.

LP7- A SEAMLESS PHASE 2A-PHASE 2B MULTI-CENTER TRIAL TO TEST THE BENEFITS OF BENFOTIAMINE ON THE PROGRESSION OF ALZHEIMER'S DISEASE (BENFO-TEAM). H. Feldman[1,2], J. Luchsinger[3], K. Messer[2,4], D. Jacobs[1,2], D. Salmon[1], C. Revta[1,2], J.L. Lupo[1,2], G. Gibson[5,6] *(1. Department of Neurosciences, University of California San Diego - La Jolla (United States), 2. Alzhimer's Disease Cooperative Study, University of California San Diego - La Jolla (United States), 3. Departments of Medicine and Epidemiology, Columbia University Irving Medical Center - New York (United States), 4. Division of Biostatistics, University of California San Diego - La Jolla (United States), 5. Brain and Mind Research Institute, Weil Cornell Medicine - New York (United States), 6. Burke Neurological Institute - White Plains (United States))*

Introduction: There is an urgent need to accelerate and diversify therapeutic possibilities for patients with Alzheimer's disease (AD). Achieving clinical Proof of Concept (POC) represents a critical milestone for such candidate treatments. Benfotiamine provides an important novel therapeutic direction in AD with potential to achieve POC and with possible additive or synergistic effects to other current mainstream approaches. It has a unique mechanism of action, raising blood thiamine 50-100 times to pharmacological levels. In doing so, it addresses and treats a well-characterized tissue thiamine deficiency and related changes in glucose metabolism in AD, as well as post-translational modifications that are linked to thiamine-dependent processes including neuroinflammation, abnormalities of advanced glycation end products (AGEs), plaques and tangles, and downstream neurodegeneration. Results from a single-site pilot 12 month placebo controlled randomized clinical trial (RCT) of benfotiamine in persons with early AD demonstrated that this medication was safe and well tolerated, with encouraging pharmacokinetic (PK) and pharmacodynamic (PD) responses (Gibson et al., 2020). It also provided preliminary evidence of efficacy of benfotiamine on cognitive and functional outcomes. Taken together these results provide the Proof of Principle to justify benfotiamine advancing to a larger phase 2 RCT to further establish POC in early AD. **Objectives:** To conduct a seamless phase 2A-2B trial investigating tolerability, safety, and efficacy of benfotiamine, a prodrug of thiamine, as a first-in-class small molecule treatment for early AD. The primary objective of phase 2A is to initially determine the highest safe and well-tolerated dose of benfotiamine (600 mg or 1200 mg) to advance to long-term clinical endpoints. Phase 2B will assess the efficacy of benfotiamine on global function and cognition over 72 weeks. Secondary objectives include evaluating the effects of benfotiamine on other measures of cognitive function as well as its PK relationships with primary clinical outcome measures, imaging measures and PD biomarkers. **Methods:** This is a double-blind, placebo-controlled RCT of 18-months of benfotiamine in early AD with a randomized total sample of 406 participants. Participants will be amyloid positive (C2N Precivity AD plasma test) with MCI or mild AD dementia (NIA-AA Diagnostic Criteria) ages 50-89. During phase 2A, real-time monitoring of pre-defined safety stopping criteria in the first approximately 150 enrollees will help determine which dose (600 mg or 1200 mg) will be carried forward into phase 2B. The primary safety outcome in phase 2A is the rate of tolerability events (TE's) defined as any of the following: participant dropout; a post-randomization moderate or severe adverse event; failure to take at least 80% of prescribed doses of study medication. The phase 2A primary analysis will test whether the rate of TE's is unacceptably high in this high-dose

arm compared to placebo. The completion of phase 2A will seamlessly transition to phase 2B without pausing or stopping the trial. Following the identification of the optimal dose in phase 2A, all of its participants will switch to this optimal dose or remain on placebo while 256 new participants will be randomized 1:1 to this optimal dose or placebo. Phase 2B will allow the assessment of efficacy and longer-term safety of benfotiamine of all participants through 72 weeks of treatment. The co-primary efficacy endpoints in phase 2B are CDR-Sum of Boxes and ADAS-Cog-13. Secondary endpoints include safety and tolerability measures; PK measures of thiamine and its esters as PD blood markers of efficacy of drug delivery; FAQ and MoCA as additional measures of efficacy. Exploratory outcomes include the NPI, Neuropsychological Test Battery and cognitive composites (CFC2, ADAS-Cog Exec); neuroimaging (volumetric measures and regional cortical thickness); AGE levels in plasma and disease relevant plasma biomarkers (Ab42/ Ab40 ratio, total tau, p-tau 231, NfL and GFAP). **Results:** Results from the BENFO-TEAM trial are expected to identify the highest well-tolerated dose that has an acceptable safety profile. With the availability of measurable PK and PD biomarkers and a constellation of downstream plasma AD and neurodegenerative biomarkers, the trial will be able to test the sufficiency of target engagement and dose while evaluating longer term efficacy and safety of benfotiamine. The sample size is powered to determine if benfotiamine will benefit cognition and everyday function in individuals with early AD. **Conclusion:** The BENFO-TEAM trial is deploying an innovative seamless phase 2A-2B design to achieve POC. It includes an adaptive dose decision rule, thus optimizing the exposure to the highest and best-tolerated dose. Through its use of a plasma based amyloid biomarker test for inclusion, we add to the trial's important contributions by shifting away from invasive testing using lumbar puncture or expensive PET scanning with its significant radiation exposure. A positive phase 2 clinical POC trial of benfotiamine that is powered to provide evidence of clinically important benefit will further validate our approach of deploying seamless designs with adaptive dose finding and provide measures and effect sizes that can become new benchmarks. The BENFO-TEAM trial is funded by the National Institute on Aging (R01 AG076634).

LP8- SIMULATION-BASED POWER ANALYSIS COULD IMPROVE THE DESIGN OF CLINICAL TRIALS IN ALZHEIMER'S DISEASE. D. Andrews[1,2,3], D.L. Arnold[3,4,5], D. Bzdok[1,3,6], S. Ducharme[7,8,3], H. Chertkow[9,10,11,12], D.L. Collins[1,3,4] *(1. Department of Biomedical Engineering, McGill University - Montreal (Canada), 2. Department of Bioengineering, McGill University - Montreal (Canada), 3. McConnell Brain Imaging Centre, Montreal Neurological Institute and Hospital, McGill University - Montreal (Canada), 4. Department of Neurology and Neurosurgery, McGill University - Montreal (Canada), 5. NeuroRx Research - Montreal (Canada), 6. Mila – Quebec Artificial Intelligence Institute - Montreal (Canada), 7. Department of Psychiatry, McGill University - Montreal (Canada), 8. Douglas Mental Health University Institute, McGill University - Montreal (Canada), 9. Baycrest Centre for Geriatric Care - Toronto (Canada), 10. Kimel Centre for Brain Health and Wellness and Anne & Allan Bank Centre for Clinical Research Trials, Baycrest - Toronto (Canada), 11. Canadian Consortium on Neurodegeneration in Aging (Canada), 12. Division of Neurology, Department of Medicine, University of Toronto - Toronto (Canada))*

Background: A two-sample t-test is often used in power analysis to determine the sample size needed to obtain a statistically significant estimate for an anticipated treatment effect size. This approach was used in the Phase 3 trials of aducanumab, the first FDA-approved drug to potentially slow cognitive decline by attacking brain amyloid plaques in early-stage Alzheimer's disease (AD) patients. In AD, however, the t-test power analysis approach does not factor the uncertainty related to inter-individual variations in cognitive decline. In statistical terms, power analysis helps to avoid Type 1 (false positive) and Type 2 (false negative) errors by ensuring enough samples, given certain assumptions about the trial's future results. Two core assumptions of t-test power analysis are that the outcome metric will be normally distributed, and that the measured effect size will be greater than or equal to that anticipated. If these assumptions do not hold, the recommended sample size could be too small. An insufficient sample increases Type 2 error risk, potentially blinding the trial to an effect that is truly present. We propose a simulation-based power analysis approach that accounts for effect size uncertainty and does not require normally distributed outcome metrics. **Objectives:** 1) Use our method to analyse power in trials similar to the Phase 3 aducanumab trials EMERGE (NCT02484547) and ENGAGE (NCT02477800). 2) Compare our power results with those reported in the published EMERGE and ENGAGE Statistical Analysis Plans (SAPs). **Methods:** All our simulations use the observation sampling scheme specified in the above SAPs: 4 observations per subject spaced approximately 26 weeks apart, and 30% dropout by the Week 78 final observation [1]. We also use the same outcome metric: change from baseline in Clinical Dementia Rating Sum of Boxes (CDRSBΔbl). Instead of using categorical time in a mixed model with repeated measures to estimate the end point difference, we use a continuous time linear mixed effects model on the actual simulated visit dates to estimate group differences in slope for treated subjects vs. placebo. Simulated subjects fit the aducanumab trials' key inclusion criteria at baseline: subjects have mild AD or mild cognitive impairment due to AD, are between 50 and 85 years old, have a CDR score of 0.5 and an MMSE score between 24 and 30, are APOE genotyped, and are positive for abnormal amyloid levels [1]. We simulate many trials, each containing a different set of cognitive decline trajectories but the same overall treatment effect and sampling characteristics. "Power" is the proportion of simulations where a statistically significant treatment effect is detectable using the linear mixed effects model. We use this approach to analyze power with 10,000 simulated trials. **Results:** In Experiment 1 we asked: How many subjects per group are required to have 90% power at $\alpha = 0.05$ to detect a 25% reduction in the rate of CDRSBΔbl increase? Here our 10,000 simulations show that 750 subjects per group are required. This is 215 subjects more than the 535 subjects per group recommended by the two-sided t-test power analysis at this power and α level in the EMERGE and ENGAGE SAPs [1]. In Experiment 2 we asked: What is the power at $\alpha = 0.05$ to detect the 25% treatment effect described above if the trial has 535 subjects per group, as recommended by the SAPs? We obtained a statistically significant estimate for this treatment effect in 7,977 out of 10,000 simulations, signifying 79.77% power. This power is 10.23% lower than the 90% power at $\alpha = 0.05$ implied in the SAPs. In Experiment 3 we asked: How many subjects per group are required to have 90% power at $\alpha = 0.05$ to detect a 22% reduction in the rate of CDRSBΔbl increase, the amount measured as the statistically significant treatment effect in the EMERGE high dose group (2)? Our 10,000 simulations show that 950 subjects per group are required. This is 415 more subjects than were recommended by the SAPs' two-sided t-test power analysis. Also, our simulation-recommended number of subjects per group here is at least 402

more than were included in the real-world EMERGE high dose and placebo groups (547 and 548 subjects, respectively) (2). **Conclusion:** Our approach accounts for the cognitive decline variability that implicitly affects treatment effect size and trial power. Our simulations show that the number of subjects in the Phase 3 aducanumab trials' SAPs and the number included in the real trials may have been insufficient to give a high power to detect both the anticipated and measured treatment effect sizes. The SAPs may have overestimated the effect size without adequately considering uncertainty, potentially leading to underestimated sample size requirements. This could partly explain the detection of a statistically significant treatment effect in only one of the two Phase 3 aducanumab trials. 1) Biogen (2018). clinicaltrials.gov/ct2/show/NCT02484547; 2) Dhillon, S. (2021). Drugs, doi.org/10.1007/s40265-021-01569-z.

LP9- THE ALZMATCH STUDY: REMOTE PLASMA ACQUISITION TO PRE-SCREEN FOR PRECLINICAL ALZHEIMER'S DISEASE TRIALS. S. Walter[1], R. Raman[1], G. Jimenez-Maggiora[1], R. Rissman[1], J. Grill[2], J. Karlawish[2], O. Langford[1], S. Bruschi[1], M. Donohue[1], K. Yarasheski[3], M. Racke[4], R. Sperling[5], J. Cummings[6], P. Aisen[1] *(1. Alzheimer's Therapeutic Research Institute, USC - San Diego (United States), 2. University of California, Irvine - Irvine (United States), 3. C2N Diagnostics - St. Louis (United States), 4. Quest Diagnostics - Secaucus (United States), 5. Brigham And Women's Hospital, Massachusetts General Hospital, Harvard Medical - Boston (United States), 6. Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada - Las Vegas (United States))*

Background: Despite the tremendous public health need, enrollment in Alzheimer's disease (AD) clinical trials has encountered challenges that include lengthy enrollment periods, great expense, and failure to recruit cohorts that represent the diversity of the population at risk. These challenges have been notably acute in trials testing potential disease-modifying drugs in the pre-symptomatic or "preclinical" stage of disease. Enrollment was also thwarted during the COVID-19 pandemic. Advances in the ability to accurately assess AD pathology using plasma biomarkers have provided powerful new tools to address many of these challenges. These biomarkers reduce reliance on in-person, on-site assessments. Tools and mechanisms that reduce the need for in-person assessment are urgently needed to access broader socio-economic groups and minimize future pandemic-related disruptions. This project leverages two recent advances in the field of AD research. (1) The establishment of online registries to develop "trial ready cohorts", like the Alzheimer's Prevention Trials (APT) Webstudy, where participants are recruited and followed through remote assessments, allow for efficient identification of large numbers of individuals and the ability to collect risk information. (2) The ability to quantify plasma biomarkers, specifically concentration ratios of Aβ42/40 and phosphorylated tau species, as early screeners for eligibility in preclinical AD trials, allows researchers to rule out individuals who have low probability of brain amyloid pathology, thereby reducing burden to participants and reducing the number and cost of amyloid PET scans, which are typically required to determine trial eligibility. **Objectives:** The AlzMatch study examines the feasibility of blood testing at community-based laboratories that provide suitable plasma to qualified diagnostic laboratories. Validated biomarkers for AD pathology are quantified and used to assess eligibility for preclinical AD trial screening. **Methods:** The project will utilize the APT Webstudy, that has consented over 50,000 participants as of September 27, 2022. Participants enrolled in the registry must be over 50 years of age, with no diagnosis of dementia. After consent, the primary measures are engagement of eligible participants and collection of blood samples. Secondary measures include invitation responses, biomarker values obtained, completion of telephone communication of eligibility to screen for a study, and referral to either remote or in person research. Participants will be recruited in two stages; the first stage enrolls 500 participants, and the second stage will enroll up to 5,000. Participants are invited either from an online registry or from a community setting, sign electronic consent, and are given information to schedule their appointment a local Quest Diagnostics' phlebotomy lab. Plasma is aliquoted, frozen according to standardized procedures, and shared with multiple biofluid assay labs. AlzMatch eligibility status will be evaluated using a predictive algorithm that includes C2N Diagnostics' biomarker assay. All participants, irrespective of eligibility status, will be contacted by telephone and informed of their eligibility to be screened for a clinical study. Participants are told whether they are eligible or not eligible to be screened for a research study at a clinical trial site near where they live. Eligible participants that agree to referral will be connected to a local research site for in-person evaluation. **Results:** Initial findings from the first stage of the AlzMatch study will be presented. **Conclusion:** The AlzMatch study will improve our understanding of the feasibility of community-based plasma collection for in-person research. Referral of these pre-screened participants to clinical trial sites may offer a more efficient and decentralized screening approach that reaches a more representative group of participants for currently enrolling preclinical trials like AHEAD 3-45. Samples collected for this project may help refine the optimal cutpoints to identify participants with early AD pathology. The results of this study will also inform design of large-scale prevention trials.

LP10- DISEASE PROGRESSION MODELLING IDENTIFIED MRI-BASED SUBTYPES WITH COGNITIVE HETEROGENEITY IN A4 STUDY PRECLINICAL TRIAL COHORT. C. Shand[1], N.P. Oxtoby[1], M.C. Donohue[2], D.A. Alexander[1], F. Barkhof[1,3] *(1. University College London (United Kingdom), 2. Alzheimer's Therapeutic Research Institute, University Of Southern California (United States), 3. Amsterdam UMC (Netherlands))*

Background: Biological and clinical heterogeneity can confound clinical trials, where differences in subsequent disease progression independent of treatment effect are not detected/screened via typical inclusion criteria. This is particularly challenging in preclinical trials, where neuropsychological screening is augmented by biomarker measurements, usually with predefined cut-points for inclusion. Machine learning methods such as data-driven disease progression modelling can characterize subtle differences in high-dimensional data that traditional screening methods cannot. **Objectives:** First, to detect and characterize MRI-based heterogeneity (subtypes) in a large preclinical cohort from the A4 Study (1). Second, to look for subtype-cognition associations at baseline. Third, to generate hypothetical forecasts for A4 by analyzing cognitive decline in a matched ADNI subset. **Methods:** In brief, we fed MRI data into the Subtype and Stage Inference (SuStaIn) algorithm (2) to estimate neurodegeneration subtypes in the A4 Study pre-randomization data. We then compared demographic variables and cognitive scores across subtypes. Finally, we selected a subset of ADNI that matched the A4

Study inclusion criteria, and investigated longitudinal cognitive decline across the assigned subtypes. In detail, we used 3-Tesla T1-weighted MRI scans from the A4 Study, and processed them using FreeSurfer 7.1.1 to obtain cortical and subcortical volumes in bilateral averages of 13 regions of interest. 1240 Aβ+ individuals from the A4 Study were used as input into SuStaIn, following covariate adjustment and z-scoring relative to a control group of 407 Aβ− individuals. Cross-validation was performed to find the model that best fit the data, and to identify the most likely number of subtypes. This model was then used to assign a maximum-likelihood subtype and (disease) stage to the A4 cohort. The subtype groups were compared pairwise for differences (at baseline) in the trial's primary outcome (PACC — Preclinical Alzheimer Cognitive Composite) and a secondary outcome (CFI — Cognitive Function Index) using a two-tailed Mann-Whitney U-test, corrected for multiple comparisons. To understand the potential impact this could have on the trial, a simulation of the placebo arm was performed by selecting a subset of ADNI individuals that matched the A4 Study inclusion criteria (and had a 3T scan available, processed using the same FreeSurfer 7.1.1 pipeline). This subset was assigned a subtype and disease stage by the A4-trained SuStaIn model. A linear mixed effects model was used to assess cognitive decline, using the modified PACC (mPACC) and Clinical Dementia Rating Sum of Boxes (CDR-SB) as outcomes. The model included age at baseline, time since baseline (continuous), and subtype-by-time interactions as fixed effects, as well as allowing for participant-specific random intercepts. This analysis was restricted to data obtained over a length similar to the A4 trial (4 years from baseline). **Results:** Following cross-validation, SuStaIn identified three distinct subtypes: Typical, Cortical, and Subcortical. The Typical subtype showed early atrophy (z-score > 2 relative to Aβ− controls) in the hippocampus, amygdala, and temporal lobe, the Cortical subtype showed early atrophy in the cortical regions (including the cingulate gyrus), and the Subcortical subtype showed early atrophy in the putamen and thalamus. 523 (42.2%) of individuals belonged to these subtypes, with the remaining 717 (57.8%) assigned to Subtype Zero, having no abnormality (z-score < 1). There were no significant differences in demographic variables across the subtypes. There were statistically significant cognitive differences across subtypes in both the PACC and CFI. In particular, the Cortical subtype had the worst median cognitive scores, and worse PACC scores compared to Subtype Zero ($P < 0.0001$) and the Subcortical subtype ($P = 0.0006$), as well as worse CFI scores compared to Subtype Zero ($P = 0.0003$). In ADNI, the Cortical subtype displayed greater cognitive decline in the mPACC (-0.28/yr; 95% CI, -0.61 to 0.04; $P = 0.09$). Both the Cortical (+0.14/yr; 95% CI, 0.07 to 0.20; $P < 0.0001$) and Subcortical (+0.14/yr; 95% CI, 0.09 to 0.19; $P < 0.0001$) subtypes displayed greater cognitive decline on CDR-SB. **Conclusion:** We used an MRI-based data-driven disease progression model to identify clinically relevant baseline heterogeneity in the A4 Study cohort. The different neurodegeneration patterns, or subtypes, were associated with different cognitive profiles at baseline (in A4) and longitudinally (in ADNI). These findings have important ramifications for the design of secondary prevention trials in Alzheimer's disease, which could leverage disease progression modelling for screening, stratification, or covariate adjustment short of stratification. **References:** 1. Sperling RA, Rentz DM, Johnson KA, et al. The A4 Study: Stopping AD Before Symptoms Begin? Sci Transl Med. 2014;6(228). doi:10.1126/SCITRANSLMED.3007941; 2. Young AL, Marinescu R v., Oxtoby NP, et al. Uncovering the heterogeneity and temporal complexity of neurodegenerative diseases with Subtype and Stage Inference. Nature Communications 2018 9:1. 2018;9(1):1-16. doi:10.1038/s41467-018-05892-0.

LP11- LATAM-FINGERS STUDY DESIGN: A MULTICULTURAL HARMONIZATION WORK ACROSS LATIN AMERICA. L. Crivelli[1], C. Suemoto[2], I. Calandri[1], P. Caramelli[3], F. Lopera[4], R. Nitrini[5], A.L. Sosa[6], R.M. Salinas[6], L.M. Velilla[4], M. Yassuda[5], R.F. Allegri[1], H. Snyder[7], M. Kivipelto[8], M. Carrillo[7] *(1. Fleni - Buenos Aires (Argentina), 2. Division of Geriatrics, University of Sao Paulo Medical School - Sao Paulo (Brazil), 3. Behavioral and Cognitive Neurology Unit, Faculdade de Medicina, Universidade Federal de Minas Gerais - Belo Horizonte (Brazil), 4. Neuroscience Group of Antioquia Medical School, Antioquia University - Antioquia (Colombia), 5. Department of Neurology, University of São Paulo School of Medicine - Sao Paulo (Brazil), 6. Laboratorio de demencias del Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez - Mexico City (Mexico), 7. Alzheimer's Association - Chicago (United States), 8. Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet - Stockholm (Sweden))*

Background: At least 40% of dementia cases worldwide might be attributable to potentially modifiable risk factors. In Latin America (LA), 56% of dementia cases are attributable to these risk factors. Thus, interventions on these risk factors can significantly benefit dementia prevention in LA. LatAm-FINGERS is the first non-pharmacological multicenter randomized clinical trial (RCT) to prevent cognitive impairment in LA. It gathers 12 countries, including the Spanish- and Portuguese-speaking populations. The project is harmonized with both the original Finnish trial for the prevention of cognitive decline (FINGER) (Kivipelto et al., 2020) and the study to Protect Brain Health through a Lifestyle Intervention to Reduce Risk (U.S. POINTER). However, LA is a heterogeneous region with ethnic, linguistic, and cultural diversity. Thus, a harmonization process within LA, considering the cross-cultural variability of neuropsychological tests, was necessary to adapt eligibility criteria, outcomes, and interventions. **Objectives:** To investigate the feasibility of a multi-domain lifestyle intervention in LA and the efficacy of the intervention in improving cognitive function in 1200 participants (100 per country) within two years. We aim to present the study design and discuss strategies used for multicultural harmonization. **Methods:** The study design included an external harmonization process carried out to follow the original FINGER model and an internal harmonization to make this study feasible and comparable across the 12 countries. A workgroup of experts representing all the consortium countries was assembled. The aim of the inclusion criteria harmonization was to achieve a homogenous selection of participants in all countries. For that purpose, we compared normative values in neuropsychological tests across LA, considering different levels of education and age. Regarding outcomes, harmonization included using shared cognitive protocols for each variable. This task required comparing versions and arriving at a harmonized version in Spanish and Portuguese for each test and measure. Finally, regarding interventions, working groups (WG) of experts with at least one expert from each country were convened. WG included nutrition, physical activity, cognitive intervention, health monitoring, biobank, and neuroimaging subgroups. **Results:** Inclusion criteria harmonization was achieved using each country's normative z-scores. Educational level and age from each region were included to make the assessment fit regional standards. Barriers to these processes included

the absence of normative data for many countries regarding commonly used cognitive tests, such as the MMSE and CERAD. Outcome harmonization resulted in a Latin American Neuropsychological Test Battery (LatAm NTB). Finally, the intervention harmonization included local perspectives from participating countries, looking for feasibility and adherence. Interventions were adapted to have a common core but flexibility to allow local idiosyncrasies. LatAm-FINGERS recruitment started on December 2021, and up to date, 986 participants were screened, and 731 were randomized to the interventions. Regarding the sample's demographic characteristics, we must highlight the overrepresentation of women (from 60% in Peru to 89% in Colombia). The mean age is 67.8 (±4.8) years, the level of education is 12.4 years (±4.8), and the MMSE scores 27.3 (±1.7). The diversity of the population is reflected in self-reported ethnicity: 56% of the participants self-reported being Mestizo, and 35% as Caucasian. Other reported ethnicities included Mulatto (2.1%), African-American (1.9%), and Asian (0.7%). The preliminary recruitment results show a significant opportunity for improvement in cardiovascular and metabolic risk factors: 10% are current smokers, 42% have high systolic blood pressure (>130mmHg), 20% have blood diastolic pressure over (>85mmHg), 81% of participants were overweight (BMI ≥25 kg/m2), 42% had low HDL (<40 mg/dL in men or 50 mg/dL in women), 37% had hypertriglyceridemia(fasting triglyceride >150mg/dL), and 63% of had central obesity (waist circumference over 88 cm for women or 102 cm for men), 32% have abnormal fasting glucose (>100mg/dL), which indicate a metabolic syndrome prevalence of 38% in our sample. **Conclusion:** This is the first non-pharmacological lifestyle intervention trial to prevent cognitive decline, including participants from 12 LA countries. LatAm-FINGERS faces a significant challenge in combining the region's diversity into a single healthy lifestyle intervention feasible across LA. This report presents the results of the effort achieved by effective multicultural teamwork. Furthermore, LatAm-FINGERS is building the largest data set on people at risk of dementia in LA. With longitudinal follow-up, it has already grown to be the region's largest cognitive, imaging, biomarker, and genetic database of individuals at risk for dementia. LatAm-FINGERS aspires to be the foundation stone of dementia teamwork in LA, confirming the potential value of collaboration in the region.

LP12- RECRUITMENT ACCELERATOR FOR DIVERSITY.

M. Sano[1], J. Vasconcellos[2], M. Sewell[3], J. Neugroschl[3], M. Umpierre[3], S. Chin[3], S. Brangman[4], S. Mcnamara[4], N. Smith[4], K. Royal[4], M. Splaine[2] *(1. Icahn School of Medicine at Mount Sinai - New York City (United States), 2. Recruitment Partners LLC - Columbia (United States), 3. Icahn School of Medicine at Mount Sinai - New York (United States), 4. Upstate)*

Background: The RADAR-CLD R-24 grant leverages an Accelerator model to assist in improving recruitment of diverse participants in aging research on cognition at two study sites. The Accelerator model brings together a trans-disciplinary team of patients, advocates, clinicians, researchers, public health and industry leaders, to catalyze study operations by insuring communication between scientific and non-scientific stakeholders, improving the efficiency and effectiveness of research conduct. Over time, these collaborative teams become highly knowledgeable and effective in addressing needs of the community in cognition studies and understanding the unique skills and resources available in their communities to facilitate recruitment education and outreach. This report describes one of the Accelerator meetings at the Mount Sinai site. **Objectives:** The Sinai Accelerator group convened to engage in discussion regarding the role of registries in recruiting diverse older adults into research. The objectives of the meeting were to explore strategies to increase recruitment into research registries, identify the pros and cons of participating in a registry, and understand how to manage a research registry to maximize efficiency and recruitment success. **Methods:** Accelerator members of diverse backgrounds included (7) researchers, research staff and clinicians, (2) dementia caregivers, (2) community-based organization representatives, and (1) senior from the local community. The meeting was held over Zoom with a short question guide, designed to inspire open conversation. Meeting facilitators introduced a research registry as a database of research projects and personal information of potential research participants. The registry can be used by researchers to identify individuals that fit their eligibility criteria and can be used by potential participants to find study opportunities of interest for themselves and those they care for. **Results:** Major themes included building trust through relationship building and transparency. These themes are echoed in subsequent meetings that focus on actively enrolling studies at both sites. Additionally, stakeholders provided insight into the maintenance of registry data.Relationship building. Accelerator members suggested researchers provide community presentations and attend informal community gatherings. An example included a weekly coffee group at the local senior center. Accelerator members also stressed that outreach would ideally be in-person and would be enhanced by inclusion of community partners. A community partner could be someone well-known and trusted within the community, or someone who is generally familiar with the community and culture. Finally, dissemination of study findings back to community helps solidify the relationship and allows community members to see firsthand the impact of their contribution. The theme of relationship building has been echoed in subsequent Accelerator meetings at both Sinai and Upstate. Cultural Competency. Participants also noted that prior to soliciting research help, researchers need to have a level of 'cultural competency', a basic understanding of the community culture, and have had experiences and personal interactions with community members. At Upstate this concept is being successfully tested through community engagement by their Community Research Liaison and a team of Resident Health Advisors who are themselves residents of the target community. Transparency of Information Security. The group stressed the importance of researchers explaining their plan to keep personal information safe. As one caregiver expressed, a drawback to participating in research is forfeiture of some privacy. Greater data security transparency could quell some fears, and potentially make them more comfortable participating. Transparency of Registry Goals. Participants want to know why the research is important and how their participation will be beneficial. Additionally, researchers should convey to potential participants how entering a research registry will aid in efforts to increase diverse participation and why that is important. Information Collection. Maximizing the information provided upfront when joining a research registry is mutually beneficial for both researchers and participants. Participants would be contacted directly for studies that they are eligible for. This is in contrast to the traditional recruitment process, whereby the individual carries the burden of finding the studies they could be eligible for and then reaching out to the study themselves. Frequency of Registry Updates. Suggestions for how often to update registry data varied considerably. Those that suggested more frequent

updates explained that for older adults with ADRD, their health status and care situation is often rapidly evolving. Method of Registry Updates. Some suggested that there should be multiple methods of communication (phone, email and mail) available for participants due to varied technological abilities. Each individual's communication preference should be listed in the registry, so that the research team knows how to best contact them. Similarly, if the participant wants to offer updated information, they should be able use whichever communication method they so choose. **Conclusion:** The nature of the researcher-participant relationship can sometimes feel like a one-way transaction, in which the researcher's sole purpose is to collect information. By engaging in sustained community engagement efforts, trust can be built between researchers and the community, leading to successful and diverse registry recruitment and research recruitment.

LP13- PHYSICIAN-DRIVEN PATIENT RECRUITMENT ADDRESSES BARRIERS IN AD CLINICAL TRIAL ENROLLMENT. E. Beck[1], M. Eimerbrink[1], K. Tyler[1], D. Gautieri[1] *(1. SiteRx - New York (United States))*

Background: In April 2022, the Food and Drug Administration (FDA) released draft guidance for industry to develop, submit, and implement a plan to enroll participants representative of racial/ethnic diversity in the US. This is especially important in Alzheimer's disease (AD) clinical trials where enrollment of minority racial groups falls far behind US Census Bureau data. For example, 8.9% and 8.5% of US individuals 65 and older are Black/African American and Hispanic, respectively. However, a 2022 systematic review found only 1.2% of AD clinical trial participants were Black/African American and 5.6% were Hispanic. Establishing and acting on plans to achieve representative samples requires thought partnership and collaboration across sponsors, clinical trial sites, community-based treating physicians and patients. SiteRx, a physician-driven recruitment platform, uniquely bridges these stakeholders, democratizing access to clinical research for diverse communities and enabling patients to learn about relevant study opportunities from their trusted, treating physician. **Objectives:** This study seeks to investigate how the U.S. clinical research infrastructure is prepared to meet the current, growing and changing needs for diverse enrollment into AD clinical trials. We aim to evaluate the overlap between regional density of underrepresented minority persons with dementia (PWD), SiteRx Provider Network of community-based physicians and trial sites, with attention to how alignment impacts the ability to enroll study participants representative of the national population diagnosed with AD. **Methods:** Prevalence of AD by county and race was collected via the 2019 US Census Bureau. Trial site data was gathered using clinicaltrials.gov and a third-party service. Trial sites were mapped by ZIP code and limited to sites that were US-based and had open Phase 1-3 AD clinical trials as of June 2022. The SiteRx Provider Network and trial sites were mapped using ZIP codes from a proprietary database. Distance between SiteRx Provider Network and trial sites were analyzed using ZIP code, with attention to density of racially/ethnically diverse AD patients by county. Additionally, Orlando, FL, New York, NY and Los Angeles, CA, were used as case studies for evaluating referral and randomization of underrepresented minority participants through SiteRx community-based physicians. **Results:** The analysis revealed 78% of patients with AD live within 50 miles of a trial site and 92% live within 100 miles. Among underrepresented minority patients with AD, 84% live within 50 miles of a trial site and 92% live within 100 miles. This analysis suggests that density of non-white AD patients and clinical trial sites is reasonably aligned, buffering the travel barrier for many potential participants. SiteRx's physician-driven platform generated the following referral activity by race/ethnicity in the key geographies assessed: Orlando 26% Hispanic, 14% Black/African American, 3% Other, 2% Asian/Pacific Islander; NYC 27% Hispanic, 2% Other, 4% Asian/Pacific Islander; LA 60% White/Caucasian, 23% Hispanic, 13% Black/African American, 4% Asian/Pacific Islander. Importantly, the largest dropoff from referral to randomization is observed among the non-white participants indicating eligibility criteria and site dynamics may contribute to disparities in enrollment. **Conclusion:** As diversity goals become standard in AD clinical trials, new methods are needed to establish pathways for diverse communities to participate in research. The analysis demonstrated that sites are relatively well co-located with diverse AD patients across the U.S. and SiteRx HCP Network provides a unique bridge to community providers in these areas. SiteRx referral activity highlights the importance of leveraging longitudinal relationships with community providers for increasing diverse participation in research. However, exclusionary protocols and site limitations to support patients from diverse backgrounds results in disproportionately high screen fail rates among non-white participants. As key areas of trial design and planning continue to evolve, SiteRx offers a sustainable vehicle for industry sponsors and trial sites to increase diverse participation in AD research and further develop the science of recruitment.

LP14- A PHASE 3 CLINICAL TRIAL PROTOCOL TO EVALUATE THE EFFICACY AND SAFETY OF NA-831 IN SUBJECTS WITH EARLY ONSET OF ALZHEIMER'S DISEASE. L. Tran[1], M. Kurkinen[1], F. Vu[1] *(1. Biomed Industries, Inc. - San Jose (United States))*

Background: This phase 3 study consists of a Core and Open Label Extension (OLE) Phase in 465 participants with Early Alzheimer's Disease (EAD), and is being conducted to evaluate the efficacy and safety of NA- 831. The Core is a 52-week treatment, multicenter, double blind, placebo controlled parallel group study. **Methods:** Core Study: Participants will receive one capsule of 30 milligram (mg) NA-831 orally once a day in the morning. The core study will be double blinded. Placebo Comparator: The core study will be double blinded. Experimental: Open Label Extension Phase: Participants completing the core study will receive one 30 milligram (mg) NA-31 capsule orally once a day in the morning. Key Outcome Measures: 1. Core Study: Change from Baseline in the Clinical Dementia Rating; - Sum of Boxes (CDR-SB) Score at 48 Weeks [Time Frame: Baseline, Week 52]. 2. Open-Label Extension Phase: Number of Participants With Treatment-Emergent Adverse Events (AEs) [Time Frame: Up to Week 52 of Extension Phase] Secondary Outcome Measures: Cognition-13 (ADAS-Cog-13) at Weeks 24, 52 [Time Frame: Baseline, Week 24, Week 52 of Extension Phase] CORE STUDY: Mild cognitive impairment due to AD or mild AD dementia including 1. MMSE score equal to or greater than 24; 3. CDR global score of 0.5 3. CDR Memory Box score of 0.5 or greater. The Phase 3 clinical trial of NA-831 is being conducted in multicenters in the US and several countries. The details of the Phase 3 methodology and protocol will be presented and discussed.

LP14A- DEVELOPMENT OF AN ABBREVIATED PRE-SCREENING COGNITIVE BATTERY TO ENHANCE REFERRAL TO CLINICAL TRIALS. A. O'connell[1], E. Fischer[1], L. Latham[1], L. Baker[1], S. Craft[1] *(1. Wake Forest Alzheimer's Disease Research Center - Winston-Salem (United States))*

Background: Timely enrollment of an eligible cohort into Alzheimer's disease (AD) clinical trials is critical in accelerating AD research, but as these trials increasingly target prodromal and preclinical AD, clinical trial sites face difficulty in determining whether prospective participants will meet cognitive eligibility criteria. This is especially problematic in prodromal trials, as these individuals often report subjective memory complaints but have not received any clinical evaluation of cognitive status and therefore lack any previous diagnosis or available neuropsychological testing to aid in evaluating study eligibility prior to conducting the clinical trial screening visit. As a result, screen fail rates based on screening cognitive assessments for these studies is high, study sponsors and clinical trial sites invest considerable time and resources in conducting screening visits, and the duration required to complete study enrollment is prolonged. **Objectives:** To develop and pilot a brief cognitive battery for use as a pre-screening tool in the evaluation of volunteers to the Wake Forest Alzheimer's Disease Research Center (ADRC) who lack prior cognitive testing. The aims of this pilot were: 1) to determine preliminary cognitive status of these participants and provide them feedback on this information, 2) screen out cognitively normal individuals with subjective complaints prior to referral to prodromal clinical trials, and 3) enhance referral to the Center's enrolling studies by using the results obtained to assess eligibility based on study-specific inclusion criteria. **Methods:** A working group comprised of the Wake Forest ADRC Directors, neuropsychologists, clinical study management team members, and Outreach Director collaborated to devise a cognitive battery that could be administered in under one hour, provide a preliminary assessment of a broad cross-section of cognitive domains, and obtain enough information to enable evaluation of cognitive eligibility for referral to Center-conducted studies enrolling cognitively normal, mild cognitive impairment (MCI), or mild AD participants. The resulting protocol included the administration of Montreal Cognitive Assessment (MoCA), WMS-III Logical Memory, Number Span Test Forward and Backward, Trail Making Tests A and B, Rey Auditory Verbal Learning Testing (RAVLT), and Benson Complex Figure Copy and Recall, and was implemented as a one-hour visit titled the Memory Screening Clinic (MSC). At the point of initial intake to the ADRC, all potential participants completed a preliminary telephone screen that included the telephone interview for cognitive status (TICS), self-report of cognitive complaints, and collection of basic demographic and medical history information. Participants with TICS scores ≥ 34 who did not self-report as cognitively normal, or those with any TICS score who did not have a known diagnosis of MCI or AD with supporting neuropsychological testing, were then offered the one-hour MSC visit for preliminary cognitive screening and feedback. The visit included the informed consent presentation, completion of a brief medical history form, and the neuropsychological battery. A Center neuropsychologist then reviewed the cognitive assessments and medical history information to determine a preliminary cognitive impression, and these results were then reviewed by a referral coordinator to evaluate eligibility for currently enrolling studies. The preliminary cognitive impression and potential study options were then discussed with each participant, and a referral made to the appropriate study team as applicable. All individuals who completed the MSC received feedback that included whether they were eligible for further testing via a study-specific screening visit, materials with information about potential study opportunities, and their MoCA score. **Results:** Between October 2019 and June 2022, 459 individuals completed a phone screen intake with the Wake Forest ADRC and met eligibility for referral to the MSC. Of those participants, 268 (58%) completed a MSC visit (mean age= 68.1 (50-88), 181 Female/87 Male; 134 Normal Controls/134 Probable Impairment) while 191 (42%) did not continue following the phone screen (lost to follow-up, not interested in study participation, or ineligible based on global exclusion criteria). Of those who completed the MSC visit, 162 (60%) were not referred to a clinical trial (did not meet eligibility criteria, were not interested in available study options, or were interested in cognitive screening and feedback only) and 106 (40%) participants were interested in and eligible for referral to a clinical trial. Participants who completed the MSC visit and feedback only and were not referred to subsequent studies were generally cognitively normal and had self-referred to the ADRC with interest in cognitive screening and evaluation for MCI studies. Of the MSC participants referred to a clinical trial, 62 (58%) were eligible at screening and enrolled in a clinical trial, 37 screen-failed (35%), and 7 did not complete a screening visit (7%). **Conclusion:** The implementation of the MSC visit and abbreviated cognitive battery created a cost-effective, low-burden method of connecting with prospective research participants, providing preliminary cognitive feedback, and enhancing successful referral to and enrollment in Center clinical trials. **Disclosures:** The authors have no disclosures to share.

NEW THERAPIES AND CLINICAL TRIALS

P24- POTENTIAL REVERSAL OF ALZHEIMER'S DISEASE. S. Rasool[1], J. Johansson[1], L. Volobouéva[1], S. Lee[1], N. Lan[1], T. Ahmed[1], D. Sun[1] *(1. Truebinding Inc. - Foster City (United States))*

Background: Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder caused by multiple pathogenic factors including Amyloid-β (Aβ), phospho-Tau (pTau), a-synuclein, and ApoE4, etc. It is widely accepted that intermediate oligomeric forms, rather than monomers or mature fibrils, are more neurotoxic. Galectin-3 (Gal-3) was reported to be involved in Aβ oligomerization. Here, we show that Gal-3 promotes oligomerization of Aβ and other pathogenic factors, and TB006, a monoclonal antibody targeting Gal-3, acts as a possible treatment for AD by degrading neurotoxic oligomers and reducing inflammation. Pre-clinical studies show that TB006 is an efficacious therapeutic entity through preventing formation of toxic oligomers and blocking or even reversing AD progression. **Objectives:** Gal-3 expression is increased in brains from AD patients, particularly in microglia associated with amyloid plaques. Our objectives were to examine the role of Gal-3 in Aβ aggregation (conformational oligomer formation) and to investigate the therapeutic efficacy of our novel Gal-3 antibody for treatment of AD. **Methods:** We used two anti-Gal-3 antibodies, our clinical lead TB006 and a mouse cross-reactive surrogate, mTB001, to establish the benefits of Gal-3 neutralization in AD in vitro and in vivo. The effects of mTB001 were tested in three AD mouse models (two transgenic mouse models (APPSwe, 5xFAD) and an Aβ42-injected mouse model). After a two-week treatment, a spatial memory function test was

conducted, followed by biochemical and immunohistochemical characterizations. **Results:** Amyloid aggregation is a hallmark of several neurodegenerative diseases (including AD, Parkinson's disease and amyotrophic lateral sclerosis) affecting the brain or peripheral tissues, whose intermediates (oligomers, protofibrils) and final mature fibrils display different toxicity. In vitro, Gal-3 intrinsically and selectively promoted, while mTB001 and TB006 degraded, oligomerization of only pathogenic protein forms like Ab42/40, a-synuclein, pTau and ApoE4, but not of non-pathogenic normal Tau and ApoE2/3. Gal-3 enhanced, while mTB001 blocked, Ab42-induced lysosomal dysfunction and pro-inflammatory activation in BV2 microglial cells. Additionally, Ab42 and Gal-3 synergistically induced, while mTB001 reversed, neuronal death. In vivo, in three mouse models of AD, cognitive deficits were strongly attenuated after just two weeks of mTB001 treatment. Mechanistically, Gal-3 antibody blocked the initiating events in AD (Aβ aggregates), reduced inflammation and rescued neuronal damage. Furthermore, microhemorrhages, a potential safety liability seen in clinical stage drugs, were reduced. **Conclusion:** Pre-clinical studies show that TB006 is an efficacious therapeutic entity through preventing formation of toxic oligomers and blocking or even reversing AD progression. Clinically, TB006 has shown a superior safety profile without any drug-related adverse events in a nearly finished healthy volunteer trial. Promising efficacy data are expected in Q2/2022 from the ongoing phase I/II AD trial.

P25- WHOLE-BRAIN LOW-INTENSITY PULSED ULTRASOUND THERAPY FOR EARLY STAGE OF ALZHEIMER'S DISEASE (LIPUS-AD): A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL.

H. Shimokawa[1,2], T. Shindo[1], A. Ishiki[3], N. Tomita[3], K. Eguchi[1], T. Shiroto[1], J. Takahashi[1], K. Shiratsuchi[4], S. Yasuda[1], H. Arai[3]
(1. Tohoku University Graduate School Of Medicine - Sendai (Japan), 2. International University of Health and Welfare - Narita (Japan), 3. Institute Of Development, Aging And Cancer, Tohoku University - Sendai (Japan), 4. Sound Wave Innovation, Co. - Tokyo (Japan))

Background: Along with society aging, the prevalence of Alzheimer's disease (AD) has been rapidly increasing worldwide. However, effective and safe treatment of AD remains to be developed. For the last decades, amyloid β (Aβ) cascade hypothesis has been in the center of the pathogenesis of the disorder. Based on the hypothesis, a number of pharmacological agents that inhibit Aβ synthesis or promote its degradation have been developed without convincing success. It is widely known that AD and vascular dementia (VaD) share common risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus. Long-term exposure to these risk factors result in common outcome, i.e. impairment of vascular endothelial functions. Indeed, endothelial dysfunction with reduced nitric oxide (NO) availability has been suggested to play an important role in the pathogenesis of AD. Furthermore, the combination of amyloid pathology (e.g. Aβ deposition and neurofibrillary change) and cerebral ischemic pathology has been found as major triggering mechanisms of dementia. Thus, vascular dysfunction, especially cerebral microcirculatory dysfunction, should also be regarded as an important pathology of AD. We have developed a low-intensity pulsed ultrasound (LIPUS) therapy that upregulates endothelial NO synthase (eNOS) with resultant therapeutic angiogenesis and suppression of chronic inflammation. We demonstrated that the LIPUS therapy is effective and safe in animal models of chronic myocardial ischemia, myocardial infarction, and left ventricular diastolic dysfunction. We also demonstrated that the LIPUS therapy ameliorates cognitive dysfunctions in mouse models of AD, VaD and cerebral infarction. The effects of the LIPUS therapy is mainly mediated by upregulation of eNOS as its beneficial effects are absent in eNOS-deficient mice. **Objectives:** We thus performed a pilot study to address the efficacy and safety of our LIPUS therapy in patients with AD. **Methods:** We performed two trials of the LIPUS therapy for AD (mild cognitive impairment due to AD and mild AD); a roll-in open trial for safety and a randomized, double-blind, placebo-controlled (RCT) trial in a 1:1 fashion for efficacy and safety. The LIPUS therapy was performed for whole brain through the bilateral temporal bones alternatively for one hour 3 times per week as one session under the special conditions (1.3MPa, 32 cycles, 5% duty cycle) that we identified. The LIPUS therapy was performed for one session in the roll-in trial (N=5), and 6 sessions with a 3-month interval in the RCT trial (N=22). The primary efficacy endpoint was the changes in ADAS-J cog scores from baseline at 72 weeks. **Results:** Roll-in Trial. The 5 patients (M/F 4/1) were 70.8±9.5 year-old with MCI due to AD in 4 and mild AD in one and had MMSE-J score 24.8±3.4. Twelve weeks after the therapy, no adverse effects or abnormal MRI findings were noted. RCT Trial. In this trial, although the planned number of patients was 40, due to the COVID-19 pandemic in Japan, the trial was terminated prematurely, upon approval by the Pharmaceuticals and Medical Device Agency of Japan (PMDA) with a final number of 22 patients. Among them, 4 did not complete the planned protocol (withdrawal of consent in 1, operation for cholelithiasis in 1, worsening of cognitive functions in 2). Another patient was found to receive prohibited concomitant medications and was excluded from the analysis. Another 2 patients completed 4 sessions due to the early termination of the trial. Thus, a total of 19 patients were analyzed for efficacy and 18 for safety. Among them, 9 had MCI due to AD and 10 had AD. There were no significant differences in baseline clinical characteristics or cognitive functions between the 2 groups. For the safety issue, there was no adverse effects of the LIPUS therapy including brain MRI findings. For the efficacy issue, the changes in ADAS-J cog scores from baseline progressively worsened at 24, 48, and 72 weeks in the placebo group, whereas they remained unchanged in the LIPUS group. The difference in ADAS-J cog scores at 72 weeks between the 2 groups, which is the primary efficacy endpoint, did not reach a statistically significant level (P=0.257) due to a small number of patients. A number of 40~50 patients in each group would reach a statistically significant level. Importantly, the prevalence of responders with improvement or no worsening from baseline to 72 weeks was 50% (5/10) in the LIPUS group but 0% (0/5) in the placebo group. The prevalence of responders progressively increased only in the LIPUS group. There were no significant differences in other parameters between the 2 groups. **Conclusion:** These results suggest that the LIPUS therapy could suppress the progression of cognitive impairment in patients with AD. The present findings need to be confirmed in a next pivotal trial with a large number of patients. (Ref.) Eguchi K, et al. Whole-brain low-intensity pulsed ultrasound therapy markedly improves cognitive dysfunctions in mouse models of dementia -Crucial roles of endothelial nitric oxide synthase- Brain Stim 2018;11:959-973.

P26- CYP46A1 ACTIVATION BY LOW-DOSE EFAVIRENZ ENHANCES BRAIN CHOLESTEROL METABOLISM IN SUBJECTS WITH MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE. A. Lerner[1,2], S. Arnold[3], E. Maxfield[4], A. Koenig[3], M. Toth[1], B. Fortin[3], B. Trombetta[3], A. Pieper[5,6,7,8], C. Tatsuoka[9], I. Pikuleva[4] *(1. Brain Health And Memory Center, Neurological Institute, University Hospitals Cleveland Medical Center - Cleveland (United States), 2. Department of Neurology, Case Western Reserve University - Cleveland (United States), 3. Alzheimer's Clinical And Translational Research Unit, Massachusetts General Hospital - Boston (United States), 4. Department Of Ophthalmology And Visual Sciences, Case Western Reserve University - Cleveland (United States), 5. Harrington Discovery Institute, University Hospitals Cleveland Medical Center - Cleveland (United States), 6. Department Of Psychiatry, Case Western Reserve University - Cleveland (United States), 7. Geriatric Psychiatry, GRECC, Louis Stokes Cleveland VA Medical Center - Cleveland (United States), 8. Institute For Transformative Molecular Medicine, Case Western Reserve University - Cleveland (United States), 9. Department Of Population And Quantitative Health Sciences, Case Western Reserve University - Cleveland (United States))*

Background: Efavirenz is an anti-HIV drug, and cytochrome P450 46A1 (CYP46A1) is a CNS-specific enzyme that metabolizes cholesterol to 24-hydroxycholesterol (24HC). We have previously shown that allosteric CYP46A1 activation by low-dose efavirenz in a transgenic mouse model of Alzheimer's disease (AD) enhanced both cholesterol elimination and turnover in the brain and improved animal performance in memory tests. **Objectives:** We sought to determine whether CYP46A1 could be activated by a low-dose efavirenz in human subjects. **Methods:** This pilot study (ClinicalTrials.gov NCT03706885) enrolled 5 subjects with mild cognitive impairment due to AD. Participants were randomized to placebo (n=1) or two daily efavirenz doses (50 mg and 200 mg, n=2 for each) for 20 weeks and evaluated for safety and CYP46A1 target engagement (plasma 24HC levels). A longitudinal mixed model was used to ascertain statistical significance of CYP46A1 engagement. We also measured 24HC in CSF and conducted a unique stable isotope labeling kinetics (SILK) study with deuterated water to directly measure CYP46A1 activity changes in the brain. **Results:** In all subjects receiving efavirenz, there was a statistically significant increase ($P < 0.001$) in the levels of plasma 24HC. The levels of 24HC in the CSF of subjects on the 200 mg-dose of efavirenz were also increased. Target engagement was further supported by the labeling kinetics of 24HC by deuterated water in the SILK study. There were no serious adverse effects in any subjects. **Conclusions:** Our findings provide evidence of efavirenz target (CYP46A1) engagement in human subjects with AD. This supports pursuit of a larger trial for further determination and confirmation of the efavirenz dose that exerts maximal enzyme activation, as well as evaluation of this drug effects on AD biomarkers and clinical symptomatology.

P27- A PHASE 2 STUDY OF THE SIGMA-2 LIGAND CT1812 IN PARTICIPANTS WITH DEMENTIA WITH LEWY BODIES. J. Galvin[1], M. Tolea[1], M. Grundman[2], M. Hamby[3], A. Caggiano[4] *(1. Comprehensive Center for Brain Health, Department of Neurology, University of Miami Miller School of Medicine - Boca Raton, Fl (United States), 2. Grnd Partners - San Diego, Ca (United States), 3. Cognition Therapeutics - Pittsburgh, Pa (United States), 4Cognition Therapeutics - Purchase, Ny (United States))*

Background: CT1812 is an experimental orally delivered, brain penetrant, small molecule therapeutic in clinical development by Cognition Therapeutics for treatment of dementias related to both alpha-synuclein and beta-amyloid oligomers. CT1812 selectively binds the sigma-2 receptor, displaces toxic oligomers, and has been shown in non-clinical studies to normalize disrupted cellular processes, protect neurons, and restore cognitive function in transgenic animals. CT1812 is currently in clinical trials for Alzheimer's dementia (AD). In addition to the trial described here, the pharmacokinetics, safety and tolerability of CT1812 have been explored in multiple studies in healthy volunteers and individuals with AD. CT1812 has been generally well tolerated with headache and nausea as the most frequent adverse events (AEs). No serious AEs have been related to CT1812 use. CT1812 has been associated with transient and mild elevations in liver enzymes without concurrent changes in bilirubin or other signs of liver injury. **Objectives:** This will be the first study of CT1812 in patients with dementia with Lewy bodies (DLB) and is designed to explore safety and tolerability, cognitive function, and exploratory biomarkers of target engagement and disease modification. **Methods:** This is a parallel group, randomized, double-blind, placebo-controlled study (COG1201; NCT05225415) of up to 120 subjects with mild-to-moderate DLB as defined by the 4th report of the DLB Consortium. After consenting and meeting study criteria, subjects are randomized 1:1:1 to receive once-daily oral doses of 300 mg CT1812, 100 mg CT1812, or placebo for six months. Patients will be followed during the trial using the Montreal Cognitive Assessment, Cognitive Drug Research Battery, Alzheimer's Disease Cooperative Study - Activities of Daily Living scale, Neuropsychiatric Inventory, Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change, Unified Parkinson's Disease Rating Scale Part III, Clinician Assessment of Fluctuation, Epworth Sleepiness Scale and other standard measures. Cerebrospinal fluid and plasma will be acquired before and after the six-month treatment regimen to assess biomarkers via unbiased proteomics and standard ELISA. **Results:** This study is being conducted at academic and clinical research centers throughout the United States including many of the Lewy Body Dementia Association Research Centers of Excellence. This study recently opened for enrollment, remains blinded and top-line results are anticipated in 2024. **Conclusion:** CT1812 may provide a novel approach to the treatment of DLB. This phase 2 proof-of-concept study is being conducted by collaborating academic and industry organizations and is supported by the National Institute of Aging (R01AG071643). When completed, this study will provide key data on whether CT1812's blockade of alpha-synuclein and beta-amyloid oligomer toxicities via sigma-2 receptor modulation impacts clinical endpoints in people who have DLB. This study will also provide data on DLB-related proteins and disease pathways that may be affected by CT1812. CT1812 is an experimental therapeutic that is currently not approved for any indication. **Author conflicts of interest:** Anthony

Caggiano and Mary Hamby are employees and shareholders of Cognition Therapeutics which is the sole owner of CT1812. Michael Grundman is a consultant to Cognition Therapeutics. James Galvin is supported by grants from NIH: R01AG071514, R01AG071514S1, R01AG069765, R01NS101483, R01NS101483S1, R01AG057681, R01AG071643, P30AG059295, P01AG066584, and serves on Advisory Board for Alpha-Cognition, Biogen, Cognivue and Eisai. Magdalena Tolea has no conflicts to report.

P28- ALZLIGHT PILOT: PRELIMINARY REPORT ON SAFETY AND FEASIBILITY FROM A RANDOMIZED CONTROLLED TRIAL OF LIGHT-BASED BRAIN STIMULATION WITH 40 HZ INVISIBLE SPECTRAL FLICKERING LIGHT IN PATIENTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE. M. Agger[1,2], M. Carstensen[3], M. Horning[1,2], E. Danielsen[4], A. Baandrup[4], M. Nguyen[5], M. Henney[5], C.R.B. Jensen[5], K. Madsen[6,7], T.W. Kjær[1,2], K. Miskowiak[8,9], P.M. Petersen[3], P. Høgh[1,2] *(1. Department of Neurology, Zealand University Hospital - Roskilde (Denmark), 2. Department of Clinical Medicine, University of Copenhagen - Copenhagen (Denmark), 3. Dept. of Electrical and Photonics Engineering, Technical University of Denmark - Kgs. Lyngby (Denmark), 4. Department of Radiology, Zealand University Hospital - Roskilde (Denmark), 5. OptoCeutics ApS - Copenhagen (Denmark), 6. Dept. of Applied Mathematics and Computer Science, Technical University of Denmark - Copenhagen (Denmark), 7. Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital - Amager and Hvidovre - Copenhagen (Denmark), 8. Neurocognition and Emotion in Affective Disorders (NEAD) Group, Copenhagen Affective Disorder research Centre (CADIC), Psychiatric Centre Copenhagen - Copenhagen (Denmark), 9. Department of Psychology, University of Copenhagen - Copenhagen (Denmark))*

Background: There is no available disease modifying treatment for Alzheimer's disease (AD), except for limited US approval of Aducanumab which targets amyloid-β (1). The European Medical Agency (EMA) did not grant similar approval citing safety concerns and lack of evidence (2). Thus, novel treatment options are still needed. This study does this by a novel approach based on targeting neural networks through non-invasive light temporally modulated at 40 Hz using Invisible Spectral Flicker (ISF)(3,4). Induction of 40 Hz neural activity is shown to reduce the load of amyloid-β and tau as well as increase the visuo-spatial memory in transgenic mice (5). Although Human trials studying induction of 40 Hz neural activity are still limited and in a small scale, early indications points towards potential benefit (6). Both the studies in mice and humans have been conducted with the use of stroboscopic light, which may be associated with some amount of discomfort and therefore, may result in decreased adherence and compliance during clinical trials and real-world applications. As it has been suggested that the treatment should consist of 1-hour daily exposure there is a need for an easy-to-use and comfortable solution which may lead to increased adherence. **Objectives:** To investigate the feasibility and safety of a Light Therapy System (LTS) (EVY LIGHT, Optoceutics ApS, Copenhagen, Denmark) for induction of 40 Hz neural activity in future Phase 2/3 randomized controlled trials. The LTS used in this study is an easy-to-use device designed for use in the home of persons with AD. **Methods:** The ALZLIGHT S1 and S2 clinical trials are randomized, double-blinded, placebo-controlled, parallel-group, single-centre, pilot trials. They have been approved by the local scientific ethics committee of region Zealand (SJ-806) and the Danish Medicines Agency (CIV-19-12-031124). The trial was monitored by an external monitoring committee (The Good Clinical Practice Unit at Frederiksberg Hospitals). ClinicalTrials.gov Identifier: NCT04574921. ALZLIGHT S1 aimed for 4 healthy participants, age matched to patients with AD for 7 days of intervention. ALZLIGHT S2 aimed for recruitment of 10 patients with mild to moderate AD for 6 weeks of intervention followed by 6 weeks of no intervention. Both ALZLIGHT S1 and S2 used 1:1 allocation to active treatment of placebo. Both active treatment and placebo treatment was delivered by an identical LTS device set to either active setting or placebo setting. The active treatment consisted of 40 Hz ISF and the placebo setting consisted of color and intensity matched non-flickering white light, thus rendering the placebo mostly indistinguishable from the active providing good blinding of both subjects, caregivers, and study personnel. **Results:** ALZLIGHT S1 screened 10 potential participants before inclusion of 5 participants with 1 drop-out, due to events in their personal life. ALZLIGHT S2 screened 35 patients with mild to moderate AD of which 11 were included. No serious adverse events were observed, and all events were categorized as mild. Three events were evaluated to have a possible or probable relation to the intervention. The probable related event were troubles falling asleep related to improper use of device late in the evening. The two events with possible relation to the intervention were eyestrain and tiredness. Adherence to the intervention were measured by percentages of days with device turned on of the total number of days (i.e., 42 days ± 7 days depending on exact delivery of device and day of follow-up). In the healthy participants in ALZLIGHT S1 the adherence was 89.8 % (active treatment: 86.1 %, placebo treatment: 95.4 %). In the patients with mild to moderate AD the adherence was 94 % (Active treatment: 97.9 % placebo treatment: 90.1 %). **Conclusion:** These preliminary findings demonstrated that 40 Hz stimulation with ISF seems to be safe to use with a considerably high feasibility in terms of user adherence. Thus, the findings motivate the transition to comprehensive Phase 2/3 randomized controlled trials for evaluation of efficacy in mild-to-moderate Alzheimer's disease. **References:** 1) Dunn B et al 2021. 10.1001/jamainternmed.2021.4607 2) Mahase E et al 2021. 10.1136/bmj.n3127 3)Carstensen MS et al 2020. 10.1117/12.2544338 4) Agger MP et al 2022, 10.3233/JAD-220081 5) Adaikkan C et al 2020. 10.3233/JAD-220081 6) Chan D et al 2021 10.1101/2021.03.01.21252717. **Conflict of Interest:** MPA and MH have received direct, or indirect funding from Optoceutics ApS through management of collaborative grants. MSC, MN, MAH, and CRBJ are employees at Optoceutics ApS. MSC, MN, ERD, and PMP has partial ownership of Optoceutics ApS. AO, KHM, TWK, KM and PH have no conflicts of interest.

P29- CHARACTERIZATION OF AMYLOID-BETA PROTOFIBRILS IN ALZHEIMER'S DISEASE BRAIN AND THE UNIQUE BINDING PROPERTIES OF LECANEMAB. L. Lannfelt[1], L. Söderberg[1], M. Johannesson[1], N. Fritz[1], E. Gkanatsiou[1], A. Rachalski[1], H. Kylefjord[1], G. Osswald[1], C. Möller[1] *(1. BioArctic AB - Stockholm (Sweden))*

Background: Immunotherapy against amyloid-beta (Aβ) has emerged as a promising treatment option for Alzheimer's disease (AD). Although many challenges remain, Aβ immunotherapy from late-phase clinical trials have shown promising results. Soluble Aβ aggregates, oligomers and protofibrils, are believed to be the most toxic species of Aβ. Lecanemab is a humanized IgG1 monoclonal antibody, selectively targeting Aβ protofibrils. In a Phase 2b clinical trial in early AD subjects, lecanemab demonstrated potential disease-

modifying effects on both clinical endpoints and clearance of Aβ plaques in the brain, with an incidence of the side-effect ARIA-E (amyloid related imaging abnormalities-edema) of approximately 10% at the highest dose. **Objectives:** We have characterized the main target for lecanemab, i.e. Aβ protofibrils, in AD brain, describing the content of Aβ, as well as levels and size of Aβ protofibrils, in relation to the APOE genotype. The binding of lecanemab to Aβ protofibrils and the mechanism of action in clearance of Aβ was studied. **Methods:** Soluble species of Aβ were extracted from post-mortem human AD brain tissue (n=24) and non-demented controls (NDE, n=12), and characterized regarding AD pathologies and APOE status using tissue from the Netherlands brain bank. Aβ protofibril levels were measured by immunoprecipitation (IP) using the protofibril selective antibody mAb158, the murine precursor to lecanemab. Size exclusion chromatography (SEC) and density gradient ultra-centrifugation were used to characterize protofibrils and to evaluate lecanemab's binding profile. The specificity of lecanemab in binding to synthetic Aβ protofibrils was evaluated by IP in the presence of a 1000-fold excess of Aβ monomers. The lecanemab-mediated uptake of synthetic Aβ protofibrils was also studied in a human monocytic THP-1 cell model. The clearance of Aβ plaques in human AD brain section, mediated by lecanemab, was investigated. **Results:** Aβ protofibril levels in AD brain (mean 168 ng/g tissue) were shown to be statistically significantly elevated compared to levels in non-demented control brain (mean 1.5 ng/g tissue). AD subjects, especially APOE E4 carriers, had the highest protofibril levels. Protofibrils were shown to be predominantly composed of Aβ42, with approximately 40 times higher levels of Aβ42 compared to Aβ40. SEC and density gradient ultracentrifugation showed that protofibrils extracted from AD brain were heterogenous in size, between 80 to >500 kDa, and lecanemab was shown to bind similarly to protofibrils of all sizes. Dose-dependent lecanemab-mediated phagocytosis of protofibrils in THP-1 cells (EC50 3 nM) was demonstrated as well as dose-dependent clearance of Aβ plaques in human brain sections. Lecanemab's binding to protofibrils remained strong and was not affected by a 1000-fold excess of Aβ monomers, further supporting the unique selectivity of the antibody. **Conclusion:** Soluble aggregated Aβ species, i.e. toxic protofibrils, are significantly elevated in AD brains, especially in ApoE4 carriers when compared to non-demented controls. Lecanemab has a unique binding profile with a high selectivity for protofibrils and has been shown to effectively clear Aβ protofibrils and amyloid plaqu

P30- AD101 - THE CLINICAL PROFILE OF A NEW, FIRST-IN-CLASS TREATMENT FOR ALZHEIMER'S DISEASE.

J. Burmeister[1], S. Gauthier[2], S. Rogers[1] *(1. AmyriAD Pharma, Inc. - Los Angeles (United States), 2. McGill University - Montréal (Canada))*

Background: AD101 is a new small molecule agent ready for Phase 3 clinical trials as a treatment to improve the core symptoms of Alzheimer's Disease (AD). AD101 is a modulator of low-voltage-gated T-type calcium channels. In animal studies it produced improvement in a variety of learning and memory models, including models both dependent and independent of beta amyloid and tau for the creation of learning and memory deficits. These effects were concurrent with increases in basal release of acetylcholine. The data suggested AD101 would be a promising agent for improving the core symptoms of AD, particularly in those already receiving stable cholinesterase inhibitor therapy where basal ACh is protected from degradation. **Objectives:** To characterize the pharmacokinetics, tolerability, and potential for efficacy of AD101. **Methods:** AD101 was investigated in a series of randomized, double-blind and placebo-controlled Phase 1 clinical pharmacology and Phase 2 preliminary efficacy studies, along with one open-label extended safety study. Primary outcomes across all studies were safety and tolerability. Pharmacokinetics and QTc interval duration were characterized in Phase 1 and effects of AD101 on global function and cognition were examined in Phase 2, using the ADCS-CGIC and the ADAS-cog 11 as efficacy variables. **Results:** A total of 446 subjects have received AD101 in clinical studies. Of them, 365 subjects with AD have been exposed to AD101 at doses up to 180 mg once daily (QD) for a total duration of up to 6 months. AD101 generally has been well tolerated without identification of clinical risks or safety signals of potential clinical concern that were considered related to its administration to healthy adult volunteers and to patients with AD. In single- and multiple- dose Phase 1 studies of 10 through 180 mg, pharmacokinetic parameters were proportional across the dose range. Time to tmax averaged 1 hour and mean half-life was 13 hours. At all dose levels, AD101 exhibited linearity in its PK over time and steady-state conditions were obtained by Study Day 5. There were no dose-limiting adverse events and detailed QTc analysis demonstrated no impact of AD101 on QT, QTcF, or QTcB intervals across treatment groups, plasma drug concentrations or in association with the duration of exposure to AD101. The primary Phase 2 study examined safety and the potential for efficacy of 10, 60 or 120 mg of AD101 vs. placebo as an add-on therapy for AD patients who were on a stable 10 mg dose of donepezil for at least 90 days prior to screening (n=~50/group, 210 total). In this 12-week proof-of-concept study, pooled analysis of scores 1-3 on the ADCS-CGIC demonstrated twice as many patients were considered to be clinically improved 12 weeks after the addition of AD101 to their treatment regimen ($p = 0.0294$ Per Protocol population). This occurred in conjunction with improvement on ADAS-cog that was statistically significant at 12 weeks after treatment initiation ($p = 0.0434$, Per Protocol analysis). Across both Phase 2 studies and the open-label extended safety study, the most commonly reported adverse events were urinary tract infections (8.4% AD101 vs 6.5% placebo), falls (6.2% AD101 vs 4.3% placebo) and dizziness (5.9% AD101 vs 8.6% placebo) There were no abnormalities in clinical laboratory values or shifts in values related to any dose of AD101. There were no clinically significant treatment-emergent arrhythmias and interval duration analyses demonstrated no changes in QTcB or QTcF related to any study treatment. The double-blind Phase 2 studies reported a total of 26 serious adverse events (SAEs) within the approximately 378 patients (n=284 AD101 and n= 94 placebo) enrolled. The number of subjects with SAEs per treatment group were: 6 - Placebo, 4 – 10 mg, 1 – 30 mg, 7 – 60 mg, 3 – 90 mg, 1 – 120 mg and 3 – 180 mg. Only 1 of the events was assessed as possibly related to study drug. This was a woman with aphasia/seizure in the 90 mg dose group. **Conclusion:** AD101 represents a new first-in-class treatment for improvement of global function and cognition when added on to donepezil, the current standard of care for AD. Deficiencies in function drive the cost of care in AD and these data from controlled clinical trials suggest AD101 could be an important addition to patient management. The overall safety profile is favorable for dosages up to 180 mg daily.

P31- IMPACT OF PIMAVANSERIN ON COGNITIVE MEASURES IN PATIENTS WITH NEUROPSYCHIATRIC MANIFESTATIONS OF ALZHEIMER'S DISEASE: RESULTS FROM 3 PLACEBO-CONTROLLED CLINICAL STUDIES.

C. Ballard[1], V. Abler[2], S. Pathak[1], P. Tariot[1], B. Coate[2], A. Berrio[2], J.M. Youakim[2], S. Stankovic[2] *(1. Departments of Psychiatry and Neurology, Perelman School of Medicine at the University of Pennsylvania - Philadelphia (United States), 2. ACADIA Pharmaceuticals Inc. - Princeton (United States))*

Background: Neuropsychiatric symptoms associated with Alzheimer's disease (AD), including psychosis, are common among patients with dementia and are associated with poorer clinical outcomes. There are no therapies approved by the Food and Drug Administration to treat dementia-related psychosis. Off-label use of atypical antipsychotics is common but is associated with significant adverse outcomes, including acceleration of cognitive decline. Pimavanserin is a selective 5-HT2A receptor inverse agonist/antagonist approved to treat hallucinations and delusions associated with Parkinson's disease psychosis and is being studied in AD psychosis. In earlier studies, unlike atypical antipsychotics, pimavanserin did not have a negative impact on cognitive function and the incidence and types of adverse events were comparable with pimavanserin versus placebo. **Objectives:** Evaluate the impact of pimavanserin treatment on cognitive measures in patients with neuropsychiatric manifestations of Alzheimer's disease pooled from 3 clinical studies. **Methods:** Cognitive function (as measured by Mini-Mental State Examination [MMSE]) was a pre-specified safety outcome evaluated in 3 double-blind (DB), placebo-controlled, parallel design studies with pimavanserin (34 mg) treatment to assess the effects on cognition in a pool of elderly subjects with Alzheimer's disease. A meta-analysis of the treatment difference comparing pimavanserin to placebo in the change from Baseline in MMSE from mixed-effect model repeated measures (MMRM) analysis for Studies 019, 032, and 046 were performed using the DerSimonian and Laird random effects model. Treatment-emergent adverse events (TEAEs) associated with cognition were examined across studies using a Standardized Medical Dictionary for Regulatory Activities Query based on the High-Level Group Term "Cognitive and attention disorders and disturbances," plus one other relevant Preferred Term ("confusional state"), for a total of 14 terms. Whole-population mean changes in MMSE observed cases over time and outlier analyses of individual patient-level data were also evaluated. Study 019 (NCT02035553) was a phase 2 study in patients with Alzheimer's disease (AD) psychosis living in care homes randomized to receive pimavanserin 34 mg or placebo for 12 weeks. Patients with MMSE scores ≥1 and ≤22 were eligible. Results on Day 85 from a MMRM (observed cases) fit to the Safety Analysis Set were used for meta-analysis. Study 032 (NCT02992132) was a DB, placebo-controlled phase 2 study evaluating the safety and efficacy of pimavanserin (20 mg and 34 mg) for the treatment of agitation and aggression in AD. Patients with MMSE scores ≥5 and ≤26 were eligible. Results at Week 12 from a MMRM (observed cases) fit to the Full Analysis Set (MMSE was an exploratory efficacy endpoint in Study 032) were used for meta-analysis. Study 046 (NCT03575052) is an ongoing DB phase 3b study of the safety of pimavanserin (34 mg) for up to 8 weeks in patients with NPS related to neurodegenerative disease. Patients with MMSE scores ≥6 were eligible. Results at Week 8 from an MMRM (observed cases) fit to the Safety Analysis Set were used for meta-analysis. **Results:** Data from an integrated analysis of these studies showed no decline in cognitive function, as measured by MMSE score with pimavanserin treatment compared with placebo. Mean baseline (standard error [SE]) MMSE scores were similar for pimavanserin (14.7 [0.35]; n=292 and placebo (14.8 [0.37]; n=276). The pooled difference in MMRM least-squares (LS) mean (SE) was not significantly different for pimavanserin versus placebo (difference in LS means [SE]: 0.29 [0.325]; 95% CI of Difference [-0.34, 0.93]). Of the terms queried, only confusional state (reported in 6 [2.1%] pimavanserin and 2 [0.7%] placebo patients) was reported as a TEAE. **Conclusions:** Evidence from 3 randomized, placebo-controlled clinical studies of patients with Alzheimer's disease treated with pimavanserin show that mean changes in MMSE scores were small and similar to placebo. Cognition-related TEAEs were reported infrequently. These results demonstrate that treatment with pimavanserin did not have a negative impact on cognitive function with up to 12 weeks of treatment. **Disclosures:** CB: received grants and personal fees from ACADIA and Lundbeck, and personal fees from Heptares, Roche, Lilly, Otsuka, Orion, GlaxoSmithKline, and Pfizer. VA, SP, PT, BC, AB, JY, SS: employees of ACADIA Pharmaceuticals Inc (San Diego, CA, USA).

P32- IMPACT OF PIMAVANSERIN TREATMENT ON MOTOR FUNCTION IN PATIENTS WITH NEUROPSYCHIATRIC MANIFESTATIONS OF ALZHEIMER'S DISEASE: RESULTS FROM 3 CLINICAL STUDIES.

D. Weintraub[1], V. Abler[2], C. Ballard[1], B. Coate[2], A. Berrio[2], S. Pathak[2], J.M. Youakim[2], S. Stankovic[2] *(1. Departments of Psychiatry and Neurology, Perelman School of Medicine at the University of Pennsylvania - Philadelphia (United States), 2. ACADIA Pharmaceuticals Inc. - Princeton (United States))*

Background: Patients with dementia, including Alzheimer's disease (AD), commonly experience hallucinations and delusions, called dementia-related psychosis (DRP). There are no therapies approved by the Food and Drug Administration to treat DRP. Commonly used off-label antipsychotics have substantial safety concerns, including worsening motor function, and extrapyramidal symptoms (EPS) specifically, perhaps primarily due to brain dopamine receptor antagonism. Pimavanserin is a 5-HT2A receptor inverse agonist/antagonist without appreciable affinity for dopamine receptors in vitro and is currently approved to treat hallucinations and delusions associated with Parkinson's disease psychosis (PDP). In clinical studies of patients with PDP, pimavanserin did not show an impact on motor function, suggesting it might be well-tolerated and is being studied in AD psychosis. **Objectives:** Evaluate changes in motor function during pimavanserin treatment in patients with neuropsychiatric manifestations of AD pooled from 3 double-blind, placebo-controlled, randomized controlled trials (RCT). **Methods:** Motor function was evaluated in a subset of patients with neuropsychiatric manifestations of Alzheimer's disease (AD) from 3 independent studies. Logistic regression analysis was performed to obtain the odds ratios comparing pimavanserin to placebo in the incidence of extrapyramidal symptoms (EPS) performed on the 3 pooled studies. The logistic regression model included the binary outcome of EPS event (Yes, No) with treatment group as a factor. Treatment-emergent adverse events (TEAEs) related to motor function were examined across studies using a Standardized Medical Dictionary for Regulatory Activities Query for Extrapyramidal syndrome. Motor function was directly measured using validated scales. Study 019 (NCT02035553) was a phase 2 RCT study in patients with AD psychosis living in care homes randomized to receive pimavanserin 34 mg or placebo for 12 weeks. Study 032 (NCT02992132) was a phase 2 RCT study

evaluating the safety and efficacy of pimavanserin (20 mg and 34 mg) for the treatment of agitation and aggression in AD. Study 046 (NCT03575052) is a phase 3b study of the safety of pimavanserin (34 mg) for up to 8 weeks in a subgroup of AD patients with neuropsychiatric symptoms related to neurodegenerative disease. **Results:** Data from the integrated clinical development program in a subset of subjects with AD showed no evidence of a worsening of motor function, as measured by EPS events with 34 mg pimavanserin treatment compared with placebo in these 3 short-term studies. Incidence rates of EPS were similar for pimavanserin (3.4%; 10/292) and placebo (4.3%; 12/282). Moreover, the odds of an EPS event demonstrated no difference in the pimavanserin arm when compared to placebo with an odds ratio (OR, 95% Confidence Interval [CI]) of 0.80 (0.34, 1.88). TEAEs related to motor function included tremor (PBO=3 [1.1%], PIM=3 [1.0%]), mobility decreased (PBO=3 [1.1%], PIM=2 [0.7%]), restlessness (PBO=3 [1.1%], PIM=1 [0.3%]), dyskinesia (PBO=1 [0.4%], PIM=1 [0.3%]), gait disturbance (PBO=0, PIM=2 [0.7%]), muscle rigidity (PBO=0, PIM=2 [0.7%]), parkinsonism (PBO=1 [0.4%], PIM=1 [0.3%]), akathisia (PBO=0, PIM=1 [0.3%]) and musculoskeletal stiffness (PBO=1 [0.4%], PIM=0), none of which were different between pimavanserin and placebo. **Conclusions:** Decrease in motor function was minimal in pimavanserin-treated patients and similar to placebo across 3 randomized placebo-controlled studies in patients with Alzheimer's disease. In pimavanserin-treated patients, TEAEs related to motor dysfunction were reported infrequently and at similar rates to placebo. Pimavanserin did not have a negative impact on motor function in this aggregated subset of data in patients with Alzheimer's disease. **Disclosures:** DW: received research funding or support from the Michael J. Fox Foundation for Parkinson's Research, Alzheimer's Therapeutic Research Initiative (ATRI), Alzheimer's Disease Cooperative Study (ADCS), the International Parkinson and Movement Disorder Society (IPMDS), and National Institute on Aging (NIA); honoraria for consultancy from ACADIA, CHDI Foundation, Clintrex LLC (Aptinyx, Avanir, Otsuka), Eisai, Janssen, Sage, Signant Health, and Sunovion; and license fee payments from the University of Pennsylvania for the QUIP and QUIP-RS. VA, BC, AB, SP, JMY, and SS: employees of ACADIA Pharmaceuticals Inc. (San Diego, CA, USA). CB: received grants and personal fees from ACADIA and Lundbeck, and personal fees from Heptares, Roche, Lilly, Otsuka, Orion, GlaxoSmithKline, and Pfizer.

P33- INTRAVENOUS TREATMENT WITH BRICHOS MOLECULAR CHAPERONE DESIGNED AGAINST AMYLOID-B TOXICITY IMPROVES FEATURES OF ALZHEIMER DISEASE PATHOLOGY IN MICE. J. Johansson[1] *(1. Karolinska Institutet - Huddinge (Sweden))*

Background: Attempts to treat Alzheimer's disease with immunotherapy against the amyloid-β peptide (Aβ) or with enzyme inhibitors to reduce Aβ production have not yet resulted in an effective treatment, suggesting that alternative strategies may be useful. Recombinant human (rh) BRICHOS can inhibit Aβ42 fibril formation, and it also prevents neurotoxicity of Aβ42, both in hippocampal slice preparations and in a Drosophila melanogaster fly model. The neurotoxicity of Aβ42 is prevented by a unique mechanism: rh BRICHOS efficiently blocks the kinetic step that generates a major part of neurotoxic Aβ42 oligomers and BRICHOS can also rescue already established Aβ42 induced deterioration of hippocampal neural network activity in vitro. **Objectives:** We aimed to explore the possibility to target the toxicity associated with Aβ aggregation by using a blood brain barrier permeable rh Bri2 BRICHOS chaperone domain, mutated to act selectively against Aβ42 oligomer generation and neurotoxicity in vitro. **Methods:** We treated Aβ precursor protein (App) knock-in mice with repeated intravenous injections of rh Bri2 BRICHOS R221E, from an age close to the start of development of Alzheimer-like pathology or about four months after Alzheimer-like pathology was already established. **Results:** Rh Bri2 BRICHOS R221E treatment improved recognition and working memory assessed during novel object recognition and Y-maze tests, and reduced Aβ plaque deposition and activation of astrocytes and microglia. When treatment was started after pathology was established Aβ plaque deposition and gliosis were reduced, and substantially reduced astrocyte accumulation in the vicinity of Aβ plaques was observed. The degrees of treatment effects observed in the App knock-in mouse models correlate with the amounts of Bri2 BRICHOS detected in brain sections after the end of the treatment period. **Conclusions:** This is the first study showing the effects of intravenous treatment with rh Bri2 BRICHOS R221E in Alzheimer mouse models and the results motivate further work to enable evaluation of BRICHOS treatment in clinical trials of Alzheimer disease.

LP15- COMPUTERIZED COGNITIVE TRAINING RESTORES NEURAL ACTIVITY WITHIN THE COGNITION AND APATHY-RELATED NETWORK IN MILD COGNITIVE IMPAIRMENT. J.M. Kang[1], N. Kim[2], S.K. Yun[3], H.E. Seo[4], S. Kim[5], S.J. Cho[6] *(1. Department of Psychiatry, Gil Medical Center, Gachon University College of Medicine - Incheon (Korea, Republic of) - Incheon (Korea, Republic of), 2. Department of Biomedical Engineering Research Center, Gachon University, Incheon, Republic of Korea. - Incheon (Korea, Republic of), 3. Department of Nursing, Saekyung University College of Nursing, Yeongwol, Republic of Korea - Yeongwol (Korea, Republic of), 4. Neuroscience Research Institute, Gachon University - Incheon (Korea, Republic of), 5. Department of Psychiatry, Gachon University Gil Medical Center - Incheon (Korea, Republic of), 6. Department of Psychiatry, Gil Medical Center, Gachon University College of Medicine - Incheon (Korea, Republic of))*

Background: Computerized cognitive training (CCT) is accepted as a potential therapy for cognitive decline. However, the neural basis of multidomain CCT is unclear. **Objective:** The aim of this study is to find neural basis of CCT in patients with mild cognitive impairment (MCI) in a randomized controlled trial. **Methods:** Twenty-seven patients with MCI were recruited and randomized into either CCT group (n=14) or control group (n=13). CCT group were trained by five-domain CCT and control group conducted an educational book reading twice a week for two months. All participants underwent comprehensive neuropsychological function and psychiatric symptom tests and resting-state functional MRI (rsfMRI) at baseline and after training. Group comparisons, pre-post time comparisons, and generalized linear model were used in descriptive data and seed-to-voxel analyses in relative networks were used in MRI data. In all analyses, confounders such as age, sex, years of education, vision state, family history of dementia, alcohol consumption, and mild behavioral impairment scores were adjusted. **Results:** CCT group showed improvements in memory ($p = 0.020$), executive function ($p = 0.024$), positive affect ($p = 0.037$), and apathy ($p = 0.047$) after CCT compared to control group. In rsfMRI, functional connectivity was increased in memory-related hippocampal network, executive function-related frontal pole network, and apathy-related insula network.

Conclusion: Two months of CCT improved the typical two domains of cognition, memory and executive function, and apathy in MCI patients. CCT also restored the functional connectivity in memory, executive function, and apathy-related networks. These results can add an evidence in neural basis for CCT compared to classical training as well as general cognitive interventions in the prodromal stage of dementia. Future trials with larger sample size, various intervention method, and sophisticated design would find the effect of the CCT. The authors have no conflicts of interest to declare.

LP16- ALZHEIMER'S COGNITIVE DECLINE STOPPED FOR AT LEAST 2½ YEARS BY IN-HOME TRANSCRANIAL ELECTROMAGNETIC TREATMENT. G. Arendash[1], H. Abulaban[2,3], S. Steen[2], R. Andel[4], Y. Wang[5,6], Y. Bai[5], R. Baranowski[7], X. Lin[5,8], N. Shen[9], A. Aljassabi[5,6], Y. Li[5], C. Cao[5,6] *(1. NeuroEM Therapeutics, Inc. - Phoenix (United States), 2. Axiom Clinical Research of Florida - Tampa (United States), 3. University of South Florida/Byrd Alzheimer's Institute - Tampa (United States), 4. Edson College of Nursing and Health Innovation, Arizona State University - Phoenix (United States), 5. MegaNano Biotech - Tampa (United States), 6. Taneja College of Pharmacy, University of South Florida - Tampa (United States), 7. Left Coast Engineering - Escondido (United States), 8. Taneja College of Pharmacy, University of South Florida - Tampa (United States), 9. School of Arts and Sciences, University of South Florida - Tampa (United States))*

Background: Up until recently, there were no published papers showing that any therapeutic intervention can stop/stabilize or reverse the progressive cognitive decline of Alzheimer's Disease (AD) - especially over an extended period of time. However, publication of our 2019 (1) and 2022 (2) clinical papers involving a new bioengineering-based technology against AD called Transcranial Electromagnetic Treatment (TEMT) may be changing that. Our pre-clinical studies consistently showed that TEMT protects against or reverses cognitive impairment in AD transgenic mice and affect AD markers. To translate these AD mouse findings to human AD subjects, NeuroEM developed a self-contained device called the "MemorEM", which allows near-complete mobility while providing in-home 1-hour sessions once or twice daily, as administered by their caregivers. Through eight highly-specialized emitters embedded between an inner and outer head cap connected to a small EMF generator and battery worn on the arm, the MemorEM device provides TEMT that easily penetrates the human bony cranium to provide electromagnetic waves in the RF range to all neurons in the entire human forebrain. Our initial clinical study (1) showed that 2 months of daily TEMT to eight mild/moderate AD subjects reversed their cognitive impairment in several tasks, including ADAS-cog13 and Rey AVLT. Moreover, fMRI after these 2 months of daily treatment revealed enhanced functional connectivity in the cingulate cortex of all subjects, FDG-PET scans showed enhanced energy utilization in some subjects, and CSF/blood AD markers in all subjects collectively were affected. OBJECTIVES: The present study extends this initial study by providing TEMT through 31 months from the initial study's baseline in five of the original mild/moderate AD subjects. Results from our just-published paper (2) and new up-dated analyses from that study will be presented. METHODS: Mild/moderate AD subjects were all given daily TEMT over a total of 31 months, with breaks between 2-10 months and between 14–19 months during this period (18 months of daily TEMT total). At multiple time points during the 2½-year treatment period, cognitive/functional assessments were performed, blood/CSF collected, and MRI scans performed. Safety was continually monitored. RESULTS: TEMT administration was completely safe over the 2½-year period, with no deleterious side effects. Six cognitive/functional tasks (including ADAS-cog13, Rey AVLT, MMSE, and ADL) were analyzed separately or collectively using a multivariate mixed-effects model. For all tasks, separately or collectively, no significant decline in any cognitive measure occurred over the 2½-year treatment period. As well, caregiver assessment of the GDS stage of cognitive decline indicated no decline of treated AD subjects to a worse stage of cognitive functioning throughout the entire 2½ years of TEMT. Qualitative assessment of anatomic MRI imaging at 19 and/or 31 months from baseline commonly indicated no progression of cerebral atrophy, particularly in the hippocampus/temporal lobe. Long-term TEMT induced substantial reductions in both CSF and plasma levels of C-reactive protein, which is consistent with the "rebalancing" of both brain and peripheral (blood) cytokines by TEMT that we have recently reported in AD subjects (3). Long-term reductions in CSF levels of p-tau217, Aβ1-40, and Aβ1-42 were also observed, while a modulation of CSF oligomeric Aβ levels was present. In plasma, long-term TEMT modulated/rebalanced levels of both p-tau217 and total tau. CONCLUSION: Although only a limited number of AD patients were involved in this long-term study and no placebo group was included, the results suggest that TEMT can stop the cognitive decline of AD over a period of at least 2½ years, and do so with no safety issues. This stoppage of AD cognitive decline appears to be due to the multi-mechanistic actions of TEMT that include: 1) disaggregation of both Aβ and p-tau oligomers, 2) enhancement of intraneuronal mitochondrial function, and 3) a "rebalancing" of the immune system in both brain and peripherally. A placebo-controlled, double-blinded Phase IIb/III clinical trial is currently being initiated. **References:** 1. Arendash G, Cao C, Abulaban H, Baranowski R, Wisniewski G, Becerra L, Andel R, Lin X, Zhang X, Wittwer D, Moulton J, Arrington J, Smith A. A Clinical Trial of Transcranial Electromagnetic Treatment in Alzheimer's Disease: Cognitive Enhancement and Associated Changes in Cerebrospinal Fluid, Blood, and Brain Imaging. 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LP17- FIRST-IN-HUMAN CLINICAL TRIAL OF IBC-AB002, A PROPRIETARY HUMAN ANTI-PD-L1 ANTIBODY, IN PERSONS WITH EARLY ALZHEIMER'S DISEASE: TRIAL DESIGN AND OBJECTIVES. J. Cedarbaum[1], P. Scheltens[2], C. Mummery[3], C. David[4], D. Bracha[4], E. Yoles[4], K. Baruch[4], M. Schwartz[5] *(1. Immunobrain Checkpoint - Woodbridge, Ct (United States), 2. Amsterdam UMC, Alzheimer Center - Amsterdam (Netherlands), 3. Dementia Research Centre, Institute of Neurology, University College London - London (United Kingdom), 4. Immunobrain Checkpoint - Nes Ziona (Israel), 5. Weizmann Institute - Rehovot (Israel))*

Background: The difficulty in finding an effective disease-modifying therapy for Alzheimer's disease (AD) highlights

the need for a renewed look at the mechanisms that drive pathophysiology. Aging is the greatest risk factor for AD, and it is associated with senescence/exhaustion of the adaptive immune system as well as chronic brain inflammation. The roles of the immune system in brain maintenance and repair have been increasingly recognized over the last two decades. Activity of the peripheral immune system outside the brain can impact progression of these processes and mitigate brain pathology. Inhibitory immune checkpoints maintain the immune system under tight control, preventing overreaction that may lead to autoimmune diseases. Immune checkpoint activity also contributes to immune exhaustion, which may restrict ability to cope with disease pathology. Well-controlled, intermittent blockade of the PD-1/PD-L1 immune checkpoint pathway is a potential means of releasing "brakes" from the peripheral immune system, thereby augmenting the body's natural defenses against neurodegeneration. Anti-PD-L1 antibody treatment reduced brain levels of aggregated proteins, modulated neuroinflammation and improved cognitive performance in five transgenic Ab and tau models. IBC-Ab002 is a proprietary anti-PD-L1 antibody engineered to treat AD, with a reduced potential to generate autoimmune adverse effects (Baruch et al., 2020). **Objectives:** Here we describe the design of the First-in-Human (FIH) clinical trial of IBC-Ab002 in persons with Early AD (EAD) and the rationale and preclinical data underlying this novel therapeutic approach. **Methods:** This combined Single and Multiple-Ascending Dose study will enroll approximately 40 participants with AD-like CSF profiles in Clinical Stages 3 and 4, at 12 sites in Israel, Netherlands and the UK. The primary objective will be to assess safety and tolerability of IBC-Ab002 in this population. Secondary objectives include description of pharmacokinetics and detection of anti-drug antibodies. Exploratory Objectives are demonstration of target engagement and pharmacodynamics in blood assessed by measuring Receptor Occupancy on peripheral T cells, levels of soluble PD-L1 and changes in immune cell populations. Effects on disease biology will be assessed using plasma and CSF fluid biomarkers and resting-state EEG. Clinical outcomes include the Amsterdam Cognitive-Functional Composite (CFC), CDR-SB, and NPI. **Results:** The study is planned to start in Q4 of 2022. **Conclusion:** Immune checkpoint blockade via inhibition of the PD-1/PD-L1 pathway is a novel and promising potential approach for modulating the adaptive immune system to treat AD, and perhaps other neurodegenerative conditions as well.

LP19- PEPINEMAB, A SEMA4D BLOCKING ANTIBODY, IS A NOVEL POTENTIAL TREATMENT FOR NEURODEGENERATIVE DISEASE: CLINICAL PROOF OF CONCEPT IN PHASE 2 HD STUDY SUPPORTS CLINICAL DEVELOPMENT IN AN ONGOING PHASE 1/2 AD STUDY.

T. Fisher[1], E. Evans[1], M. Boise[1], V. Mishra[1], C. Mallow[1], E. Smith[1], J. Leonard[1], A. Feigin[2], E. Siemers[3], E. Sheldon[4], R. Turner[5], M. Farlow[6], A. Porteinsson[7], W. Bond[8], M. Zauderer[1]
(1. Vaccinex, Inc. - Rochester (United States), 2. NY Langone Health, and for HSG and SIGNAL-HD PIs and coordinators - New York (United States), 3. Siemers Integration LLC - Zionsville (United States), 4. JEM Research Institute - Atlantis (United States), 5. Re-cognition Health - Fairfax (United States), 6. Indiana University - Indianapolis (United States), 7. University of Rochester - Rochester (United States), 8. Neuropsychiatric Research Center of Southwest Florida - Fort Myers (United States))

Background: Pepinemab (VX15/2503) is a humanized IgG4 monoclonal antibody that blocks the binding of semaphorin 4D (SEMA4D) to its plexin receptors. SEMA4D is upregulated in neurons during Huntington's Disease (HD) and Alzheimer's Disease (AD) progression and triggers astrocytes that express plexin-B1/B2 receptor to undergo reactive gliosis with concomitant loss of normal astrocyte functions1. Drivers of glial cell activation represent novel targets to modify progression of neurodegenerative pathology. Blocking antibody to SEMA4D has been shown to reduce neurodegenerative processes in the SIGNAL-HD (NCT02481674) Phase 2 trial2 as well as in preclinical models of HD and AD. These studies provided clinical rationale for the ongoing Phase 1/2 SIGNAL-AD study (NCT04381468). **Objectives:** Present the updated safety, efficacy, and biomarker data from the completed SIGNAL-HD trial2. In addition, describe how neuroimaging and subgroup analysis of the clinical HD results provide further rationale for investigation in AD, and present the trial design, enrollment status, and updated blinded safety data for the Phase 1b/2a double-blind, randomized, placebo-controlled SIGNAL-AD trial. **Methods:** The SIGNAL-HD phase 2 study included 301 subjects with late prodromal (LP) and early manifest (EM) HD. Subjects were treated with monthly infusions of pepinemab for at least 18 months and evaluated for safety and a variety of clinical parameters including cognition (HD-CAB). Imaging endpoints included structural MRI to assess brain atrophy and FDG-PET to assess brain metabolism. The SIGNAL-AD study is in progress and is planned to enroll up to 40 subjects with early AD treated for approximately 1 year. Objectives include safety, change in brain metabolism via FDG-PET, and clinical endpoints including the Alzheimer's Disease Assessment Scale – cognition (ADAS-cog) and Clinical Dementia Rating Scale – sum of boxes (CDR-SB). **Results:** In SIGNAL-HD, pepinemab was well-tolerated and was shown to cross the BBB at a concentration sufficient to engage its target. While co-primary efficacy outcome measures did not achieve statistical significance in this study, multiple exploratory and post-hoc measures indicated significant cognitive benefit and were supported by pre-specified FDG-PET imaging that indicated significant reversal of decline in metabolic activity ($p \leq 0.05$) in 15/26 brain regions of interest. Treatment effects were observed in EM but not LP subjects. In 179 EM subjects, a treatment benefit was observed in 6/6 components of the HD-CAB cognitive assessment battery, with a significant treatment effect on the HD-CAB composite index ($p=0.007$). Post-hoc analysis of the HD-CAB results showed pepinemab treatment preserved the ability of EM subjects to learn from experience during sequential administration of HD-CAB and that the cognitive treatment benefit was greater in subjects that were more cognitively impaired at baseline, as judged by Montreal Cognitive Assessment (MoCA) score <26 vs. ≥26. The largest metabolic decline in HD is observed in caudate and putamen. It is, therefore, striking that a treatment effect on FDG-PET SUVR was not observed in caudate and putamen of either EM or LP subjects. Since degeneration of medium spiny neurons in striatum is an early event in prodromal HD that continues following motor diagnosis, this could account for reduced glucose utilization that is not SEMA4D-dependent and, therefore, not affected by pepinemab treatment. Our data support an important glial contribution to glucose utilization in other brain regions that is reduced by reactive gliosis and restored by pepinemab treatment. This suggests distinct early and late stages of pathology during disease progression. The ongoing blinded SIGNAL-AD trial has enrolled approximately half of the 40 planned subjects, and top line data for a full year of randomized, double-blind treatment is anticipated in Q1 2024. It will be of particular interest to determine

whether metabolic changes in the entorhinal cortex, a region of early degeneration in AD, are less SEMA4D-dependent than for other cortical regions that degenerate somewhat later in disease progression. **Conclusions:** SIGNAL-HD showed a favorable safety profile and positive trends in cognition and imaging endpoints that encourage continued development in both HD and AD. The Phase 1b/2a study in AD (SIGNAL-AD), is currently enrolling and initial blinded safety review has suggested pepinemab is well tolerated in AD as well. **References:** 1. Evans et al, Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity. J Neuroinflammation, 2022. https://doi.org/10.1186/s12974-022-02509-8; 2. Feigin et al, Pepinemab antibody blockade of SEMA4D in early Huntington's disease: a randomized, placebo-controlled, phase 2 trial. Nature Medicine, 2022. https://doi.org/10.1038/s41591-022-01919-8.

LP20- DOES BRAIN-GUT PHOTOBIOMODULATION HAVE THERAPEUTIC POTENTIAL IN ALZHEIMER'S DISEASE? DESIGN OF A PIVOTAL SHAM-CONTROLLED, RANDOMIZED, DOUBLE-BLIND, MULTICENTRIC CLINICAL INVESTIGATION.

J. Delrieu[1], A. Relano-Gines[2], P. Cristofini[2], J. Bisiaux[3], S. Guillemin[3], G. Blivet[2], J. Touchon[4] *(1. Toulouse University Hospital Gerontopole - Toulouse (France), 2. REGEnLIFE - Paris (France), 3. RCTs - Lyon (France), 4. University of Montpellier - Montpellier (France)*

Background: Alzheimer's disease (AD) represents a serious public health problem, for which no clearly efficient treatment is currently available. REGEnLIFE RGn600 is a brain-gut photobiomodulation (PBM) medical device. Results from a first pilot clinical trial demonstrated safety, patient compliance and revealed efficacy trends in 53 mild-to-moderate AD patients treated with PBM therapy (Blivet et al., A randomized, double-blind, and sham-controlled trial of an innovative brain-gut photobiomodulation therapy: safety and patient compliance. J Alzheimer's Dis. 2022, 90: 2, in press). This study provides valuable insights for the design of the next phase, a pivotal investigation, which will evaluate the cognitive benefits of PBM therapy, in a larger sample of AD patients. **Objectives:** The primary endpoint of this pivotal clinical trial is the evolution of patient's cognition after 26 weeks of PBM therapy as measured with the ADAS-cog score. Neuropsychological functions, autonomy, overall clinical response, quality of life, blood and fecal markers as well as medico-economic interest will be investigated as secondary endpoints. The safety of RGn600 treatment will also be evaluated. **Methods:** The RGn600 is a non-invasive medical device, manufactured by REGEnLIFE, which takes the form of a helmet and an abdominal belt combining PBM technology from red to near-infrared wavelengths and static magnetic stimulation. A multicentric, double-blind, randomized, sham-controlled, pivotal clinical trial will be initiated at S1 2023 at the Toulouse University Hospital Gerontopole. In total, 96 patients with NIA-AA diagnosis criteria of AD will be included and randomized into a treated group (n=48) and sham group (n=48). They will receive 84 PBM therapy sessions of 20 min over 26 weeks. **Results:** The First Patient First Visit is expected for February 2023. The analysis will be performed in the Full Analysis Set, Per Protocol populations and Treated Set. **Conclusion:** REGEnLIFE RGn600 brain-gut PBM therapy, as a disease-modifying treatment, could potentially offer a safe, well-tolerated method, with medical and economic benefits, to treat mild-to-moderate AD patients. The design of this study, named LIGHT4LIFE, evaluating such an innovative medical device for the treatment of AD will be detailed. The advantages and limitations of such a clinical trial will be discussed. **Conflict of Interest/Disclosure Statement**: Guillaume Blivet: employee, stock ownership, REGEnLIFE. Aroa Relano-Gines: employee, REGEnLIFE. Patrice Cristofini: CEO, stock ownership, REGEnLIFE. Julie Bisiaux, employee, RCTs. Sara Guillemin, employee, RCTs.

LP21- AC-0027875, A NOVEL GAMMA-SECRETASE MODULATOR FOR THE TREATMENT OF ALZHEIMER'S DISEASE.

J. Sandin[1], M. Dahlström[1], V. Lidell[1], A. Rasti[1], P. Forsell[1], S. Juric[1], M. Halldin[1], M. Backlund[1], G. Nordvall[1] *(1. AlzeCure Pharma AB - Huddinge (Sweden))*

Background: The process of amyloid beta (Aβ) amyloidosis plays a pivotal role in the onset of Alzheimer's Disease (AD) and starts decades prior to symptoms onset. It is conceivable that an Aβ-targeting drug would be most beneficial as a chronic therapy initiated during the pre-symptomatic or preclinical phase, i.e. at the earlier stages of Aβ amyloidosis. As such, the therapy needs to be safe and well tolerated while still effective. Aβ is a family of postproteolytical peptides (Aβ31 to 43) and is generated as the result of gamma-secretase mediated processing of the amyloid precursor protein (APP). Aβ42 is particularly prone to aggregate and is also the primary Aβ component of amyloid plaques, whereas shorter Aβ peptides appear less amyloidogenic. Recent studies in humans have also shown that the shorter Aβ38 peptide may have some protective properties. Gamma-secretase modulators (GSMs) are a class of anti-amyloidogenic agents that exhibit several key features that make them suitable for the treatment of preclinical AD: 1) they target and reduce amyloidogenic Aβ42 production, while stimulating the formation of the shorter peptides Aβ37 and 38, 2) they modulate but do not affect all gamma-secretase activity, i.e. for other substrates such as Notch, a property that is of central importance from a safety perspective, and 3) they do not affect the total amount of Aβ, so if Aβ does have a physiological function it only alters the ratio between longer vs. shorter fragments. A GSM is suitable as a stand-alone preventive therapy but may also be an attractive option as a conjunctive treatment together with Aβ-antibody therapies. **Objectives:** The promising profile of a new class GSMs led us to develop a novel GSM for the treatment of early Alzheimer´s disease. Herein we present preclinical data of AC-0027875. **Methods:** The effect of AC-0027875 on Aβ42 production was explored both in HEK/APPswe cells and mouse primary cortical neurons (mPCN) and analyzed with an Aβ42 specific ELISA. After oral administration of AC-0027875 to C57BL/6J mice as well as Wistar rats, plasma and brain were collected and compound exposure in plasma and brain tissue was determined by LC-MS/MS. The reduction of soluble Aβ42 in the brain was determined by ELISA. The pharmacokinetic profile of AC-0027875 was determined in both rat and mouse. **Results:** The GSM AC-0027875 displays high potency in HEK/APPswe cells as well as in primary cortical neurons with an IC50 of 10 nM. In vivo studies shows that it is highly efficacious in lowering Aβ42 levels in both mice and rats. Dose-response studies as well as time-response studies in mice indicate a potent reduction of Aβ42 over time. The PK properties indicate a rapid uptake of the drug and good exposure as well as an excellent brain-to-plasma ratio indicating a suitable profile for further progression. **Conclusion:** The newly developed GSM AC-0027875 is a promising candidate for further development for the treatment of Alzheimer´s disease.

LP22- IMPACT OF ICOSAPENT ETHYL ON ALZHEIMERS DISEASE BIOMARKERS IN PRECLINICAL ADULTS: BRAIN AMYLOID AND VASCULAR EFFECTS OF EIOSCAPENTAEOIC ACID (BRAVE-EPA) STUDY DESIGN AND BASELINE CHARACTERISTICS.

C. Van Hulle[1,2], H. Zylstra[3], C. Aleshia[4], E. Allison[5], E. Beckman[6], K. Lazar[7], B. Madeleine[8], C. Kate[1], C. Gleason[2], S. Johnson[1,2,9], S. Asthana[1,2,10], C. Cynthia[1,2,10,11] *(1. Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison - Madison (United States), 2. Wisconsin Alzheimer's Disease Research Center, University of Wisconsin-Madison - Madison (United States), 3. School of Medicine and Public Health, University of Wisconsin-Madison - Madison (United States), 4. Wisconsin Alzheimer's Institute Center, University of Wisconsin-Madison - Madison (United States), 5. Medical College of Wisconsin-Green Bay - Madison (United States), 6. Bold Insight - Downer's Grove (United States), 7. Exact Sciences - Madison (United States), 8. Cleveland Clinic Lerner College of Medicine - Cleveland (United States), 9. Wisconsin Alzeimer's Institute, University of Wisconsin-Madison - Madison (United States), 10. Geriatric Research Education and Clinical Center, William S. Middleton Memorial Veterans Hospital - Madison (United States), 11. Wisconsin Alzheimer's Institute, University of Wisconsin-Madisonn (United States))*

Background: Veterans are at higher risk for dementia due to Alzheimer's disease (AD) than the general population, possibly due to increased exposure to factors that accelerate AD pathology, including vascular risk factors, traumatic brain injury (TBI), and post-traumatic stress disorder (PTSD). AD pathology occurs decades before cognitive symptoms occur and is characterized by amyloid plaques, neurofibrillary tangles, and reduced regional cerebral blood flow (rCBF) in areas of the brain related to memory and learning. **Objectives:** Here we describe baseline characteristics for a proof-of-concept randomized, placebo-controlled, double-blind, parallel-group clinical trial assessing the efficacy of icosapent ethyl (IPE) (Vascepa, Amarin Corp.), a purified prescription form of the omega-3 fatty acid eicosapentaenoic acid (EPA). Outcomes include the effect of IPE on magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), and cognitive biomarkers for AD in cognitively-unimpaired Veterans ages 50–75 years. The primary aim of the trial is to assess whether IPE increases 18-month rCBF in a statistically-defined region of interest compared to placebo. Secondary aims assess whether IPE modifies CSF β-amyloid (Aβ) and improves cognitive performance on the ADCS-PACC battery compared to placebo. **Methods:** VA-eligible Veterans living in WI and parts of IL, IA, and MN were invited to enroll; 788 interested Veterans were prescreened, 179 consented and 131 randomly assigned in a 1:1 ratio to either placebo or 4g/day IPE. Prior to enrollment, participants were screened for suspected memory impairment. Other exclusion criteria included inability to safely take study medication or participate in study procedures. The Montreal Cognitive Assessment (MoCA), body mass index (BMI), waist-hip ratio (WHR), blood pressure, and cholesterol levels were obtained prior to randomization. After randomization, MRI, lumbar puncture, and cognitive testing occurs at baseline, 9 months, and 18 months. Participants' self-reported medication use, health conditions, physical and mental activities are also recorded at baseline, 9-month and 18-month visits. At baseline, participants reported on their military experience, TBI exposure, and PTSD symptoms. CSF samples are collected in the morning after a 12-hour fast with a Sprotte 25- or 24-gauge needle using gentle extraction into polypropylene collection syringes. Twenty mL of CSF are collected into sterile polypropylene syringes, then combined, gently mixed, and centrifuged prior to freezing in 0.5 mL aliquots. rCBF is measured using arterial spin labeling (ASL). Additional scans include pcVIPR to measure cerebral velocity and pulsatility, T1*weighted MRI to provide anatomic information, T2 fluid-sensitive inversion recovery (FLAIR) to quantify white matter hyperintensities, and diffusion tensor imaging to measure white matter structural integrity. **Results:** Participants were primarily non-Hispanic white (125/131; 95%) and male (112/131; 85%) and had a parental history of dementia (69/131; 57%). Mean age at baseline was 65.8 (7.0) years. Most participants served in the Army (40%) followed by the Navy (24%), Air Force (15%) and Marines (11%); 80/131 (61%) went on one or more deployments. The proportion of participants with a four-year degree, 48/131 (36%), was higher than the state average of 30%. Although 51% of participants reported witnessing a traumatic event, none reported having PTSD symptoms. One in five participants reporting losing consciousness for more than 1 minute after a blast or crash and 37/131 (28%) reported having a concussion or head injury. The average total cholesterol was 175.4 mg/dL (43.2 mg/dL) which is lower than the state average for ages 40-65 (200.2 mg/dL) and ages >65 (187.1 mg/dL). Self-reported chronic conditions included high cholesterol (48.5%), high blood pressure (48.5%), and diabetes (18.9%). The sample was mildly obese, with a mean BMI and WHR of 30.1 (4.82) and 0.978 (0.07) respectively. Likewise average blood pressure was slightly elevated (mean systolic = 136 [16.5], mean diastolic = 82.5 [7.8]). The frequency of chronic conditions, BMI and blood pressure are broadly in line with the WI state population. The average MOCA score at baseline was 25.6 (2.6); 46/131 (35%) of participants fell below the suggested cut-off of 25 for cognitively unimpaired participants. Participants with a college degree scored slightly higher on ADCS-PACC constituent measures: Logical Memory delayed recall (p=.08), Logical memory immediate recall (p=.02), digit symbol substitution (p=.02), and Mini Mental State Exam (p=.02). However, baseline cognitive scores were unrelated to age, having one or more chronic conditions, number of deployments, or possible TBI. 116/131 (89%) participants had a successful LP and 115/131 (89%) participants had useable MRI scans. Mean total hippocampal volume was 7,941.9 mm3 (844.14). After adjusting for white and gray matter volume, total hippocampal volume at baseline was unrelated to age, education level, number of deployments, having one or more chronic conditions, or possible TBI. **Conclusions:** US military Veterans are an important cohort to study in identifying mechanisms to reduce AD risk. These data support the feasibility of recruiting cognitively unimpaired Veterans into a randomized, placebo-controlled clinical trial assessing the impact of IPE on MRI, CSF, and cognitive AD biomarkers. Trial data collection is ongoing and will be completed in September 2023.

LP23- A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED ASCENDING DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS (PK) AND PHARMACODYNAMIC (PD) EFFECTS OF POSIPHEN® IN SUBJECTS WITH MILD ALZHEIMER'S DISEASE/ MCI. D. Galasko[1], M. Farlow[2], B. Lucey[3], L. Honig[4], A. Moghekar[5], D. Elbert[6], R. Bateman[3], J. Momper[1], R. Thomas[1], R. Rissman[1], A. Balasubramaniam[1], M. Maccecchini[7], H. Feldman[1] *(1. UC San Diego - San Diego (United States), 2. Indiana University - Indianapolis (United States), 3. Washington University - St. Louis (United States), 4. Columbia Unversity - New York (United States), 5. Johns Hopkins University - Baltimore (United States), 6. University of Washington - Seattle (United States), 7. Annovis Pharmaceuticals - Berwyn (United States))*

Background: Preclinical studies show that posiphen acts as a post-transcriptional repressor at iron-responsive elements and can decrease the production of APP and Aβ. Prior clinical studies have explored different dose regimens, but data on pharmacokinetics and pharmacodynamics are still limited to inform dosing for phase 2 or 3 clinical trials. **Objectives:** To conduct a Phase 1b multicenter, double-blind, placebo-controlled RCT evaluating safety, tolerability, PK and PD of Posiphen, with sequential ascending dose cohorts (NCT02925650). To determine PK and PD at a steady state of drug dosing, serial CSF sampling with an indwelling lumbar CSF catheter to allow analysis of Stable Isotope Labeling and Kinetics (SILK™). To study feasibility of SILK at multiple centers and acceptability by patients. **Methods:** Subjects with MCI or mild AD dementia (age 55-89, MMSE 17-30, CDR = 0.5-1.0), in good general health, with CSF Aβ42/40 < 0.131, measured by mass spectrometry, were enrolled at 5 centers. Subjects were randomized to posiphen or placebo (5:3) in 3 sequential dose cohorts: 60 mg once/day, 60 mg twice/day and 60 mg 3 times/day for 21 days. On day 22, participants were admitted for confinement, placement of a CSF catheter and venous lines and intravenous loading with 14C-leucine. They received dosing with Posiphen/placebo and had serial plasma and CSF collection over 36 hours to allow SILK analysis. As outcome measures, safety and tolerability were assessed with clinical and laboratory tests. PK of Posiphen, N1 and N8 metabolites in plasma and CSF were measured during confinement. For PD, the fractional synthesis rate (FSR) of Aβ40 in CSF was calculated. Feasibility was assessed by accuracy of collection of CSF catheter and blood samples and acceptability by patient satisfaction surveys. Secondary analyses included changes in CSF Aβ38, Aβ40, Aβ42, sAPPα, sAPPβ and t-Tau from screening to confinement, FSR of Aβ38 and Aβ 42 and changes in cognitive tests and behavioral assessments including ADAS cog 12, MMSE and NPI. **Results:** Dose cohorts 1 (n=9) and 2 (n=8) were completed from 2018 – 2021. Cohort 3 (n=2) closed in December 2021, when the study was closed due to end of funding. There were substantial delays and challenges due to Covid-19 related restrictions and the 14C-leucine supply chain. Among the 19 subjects who were randomized, one did not have any post-randomization visits, therefore the mITT population included 7 placebo and 11 posiphen subjects. They were well-matched for demographic and clinical measures. 3 subjects had early termination: 1 had unsuccessful CSF catheter placement; for 2 others, catheterization was not done because 14C-leucine had expired. Posiphen was safe and well-tolerated, with no significant differences in vital signs, laboratory tests, AEs or SAEs between active drug and placebo subjects. 8/19 participants reported headache either during CSF sampling (4), after the procedure (3), or both (1). 5 had blood patches with rapid resolution of headache. 15/16 CSF catheterizations were successfully completed. We obtained > 89% of all scheduled plasma and CSF samples from these 15 subjects and could model SILK data adequately. Measures of research satisfaction of participants using the modified Research Satisfaction Questionnaire were favorable. PK parameters for posiphen and its N1 and N8 metabolites were correlated with one another in plasma and CSF. The mean posiphen elimination half-life in plasma was 3.8 hours. Posiphen Cmax was 56.4 ng/mL in plasma and 2.9 ng/mL in CSF following 60 mg once daily dosing. Exposures of posiphen and metabolites in CSF and plasma increased less than proportionally when dosed two and three times per day, raising the possibility of a potential food effect on bioavailability. SILK data were modeled using two approaches. A model using nonlinear fitting yielded the most accurate slopes. Mean FSRs (SD) for Aβ40 did not differ in the placebo, 60 mg once/day or 60 mg BID groups. Concentrations of Aβ38, 40, 42, sAPPα, sAPPβ and total tau in CSF were not significantly changed from baseline to confinement in treatment vs placebo groups, regardless of dose. There were no differences in changes from screening to 21 days for cognitive tests or for NPI scores. **Conclusions:** A multi-Center CSF catheter and SILK study was feasible, with high success of obtaining the necessary CSF and plasma samples. Patients were generally positive about participation. The study was impacted by COVID 19 and did not achieve full recruitment. Data on 60 mg three times daily are limited. Posiphen was safe and well-tolerated at 60 mg once or twice per day. PK data showed a short T ½ in plasma. The longer T ½ in CSF, minimal differences in PK and lack of differences in FSR and other SILK data for the 60 mg once/day and BID groups suggest that once per day dosing may be adequate. Posiphen treatment did not show an effect on FSR for Aβ40. Further analyses of slopes and other parameters derived from the SILK data are in progress.

LP24- PRECLINICAL CHARACTERIZATION OF ACD856, A COGNITIVE ENHANCER IN CLINICAL DEVELOPMENT FOR THE TREATMENT OF COGNITIVE DYSFUNCTION IN ALZHEIMER'S DISEASE, DEMONSTRATES INCREASED PLASTICITY, NEUROPROTECTION AND A POSSIBLE DISEASE MODIFYING EFFECT. C. Parrado-Fernández[1], G. Nordvall[1], S. Juric[1], N. Madjid[1], M. Backlund[1], M. Dahlström[1], J. Sandin[1], P. Forsell[1] *(1. Alzecure Pharma AB - Huddinge (Sweden))*

Background: Neurotrophins are a class of growth factors that regulate neuronal function, survival, differentiation and plasticity. The neurotrophins, including nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and neurotrophin (NT) 3 and NT-4/5, bind and mediate their effects through the tropomyosin-receptor kinase (Trk) family of receptors (TrkA, TrkB and TrkC). A large body of pathological and mechanistic evidence suggests that loss of NGF contributes significantly to the dysfunction of basal forebrain cholinergic neurons observed in Alzheimer's disease (AD). Indeed, the characteristic impairments in formation and retrieval of episodic memory observed in the disease have been reported to be partly due to this cholinergic dysfunction. Another area that is affected early in AD is the hippocampus, which plays a critical role in learning and memory processes. Interestingly, neurotrophic signalling, and in particular BDNF signalling, plays a pivotal role in hippocampal neurogenesis, synaptogenesis and synaptic plasticity. Several studies have also shown a decrease in BDNF levels in the hippocampus

and in CSF in disorders with cognitive decline, including AD. Interestingly, the BDNF-Val66Met polymorphism has been demonstrated to affect the anatomy of hippocampus and prefrontal cortex in normal individuals and to moderate effects on episodic memory, hippocampal function and hippocampal volume in patients with either sporadic or familial AD. Thus, existing data strongly support and validate the development of enhancers of neurotrophin signaling as novel and promising therapeutic strategies for AD. AlzeCure Pharma has developed novel positive modulators of Trk-receptors and has with ACD856 demonstrated clear effects in various in vitro and in vivo models. Considering the neuroprotective and neuro-regenerative effects of neurotrophins, there is also a potential for ACD856 to demonstrate disease-modifying effects in neurodegenerative disorders like AD. **Objective:** Based on the extensive amount of supporting data for the role of neurotrophins in neuronal support and protection, the objective of these studies was to assess whether ACD856 exert any effect on neuronal plasticity and possible disease-modification effects in vitro and in vivo. **Methods:** Positive allosteric modulators of BDNF and NGF were identified and characterized using the TrkA- or TrkB cell-based assays in U2OS cells overexpressing human TrkA or TrkB receptors, respectively. In vitro functional modulation of the TrkB receptor was evaluated in SHSY5Y-TrkB cells treated with BDNF and increasing concentrations of ACD856. A phospho-TrkB ELISA was used to determine the levels of phosphorylated TrkB. Regulation of endogenous BDNF release was quantified in mouse embryonal primary cortical neurons (PCN). Effects of ACD856 were evaluated in NGF-induced neurite outgrowth in PC12 cells by immunostaining for SNAP-25 and tubulin III. Furthermore, effects on ATP levels and cellular permeability were investigated in mice PCN using energy-deprivation neurotoxicity assay, being glutamine the main source of energy. In vivo effects were studied in models assessing cognitive function using scopolamine-induced memory impairment using the passive avoidance model and antidepressant-like effects using the forced swim-test in mice. **Results:** We identified ACD856 as a potent positive modulator of human TrkA and TrkB receptors with EC50 of 314 nM and 226 nM, respectively. In the in vitro functional studies, ACD856 enhances the phosphorylation of TrkB in SHSY5Y-TrkB cells and upregulate the release of endogenous BDNF in mouse PCN. Studies in NGF-differentiated PC12 cells demonstrate that ACD856 increases both NGF-induced neurite outgrowth and SNAP-25 levels in neurites, suggesting neurorestorative effects. Furthermore, mouse PCN treated with ACD856 in media deprived of glucose and pyruvate, exhibits neuroprotective effects that correlate with an improved mitochondrial function in terms of increased ATP levels. In the in vivo behavioral studies, ACD856 demonstrated sustained antidepressant-like effects in FST, even up to three days after the last administration. This long-term effect was comparable to the long-term effects of ketamine in the same model. ACD856 could also reverse scopolamine-induced memory impairment, an effect that was significantly more pronounced after repeated dosing using 0.1 mg/kg as compared to a single administration using 0.1 mg/kg, which was ineffective. Minimal effective dose for a single administration was determined to 0.3 mg/kg. Furthermore, repeated administration was without any effects on motor function or anxiety. **Conclusion:** We identified ACD856 as a positive allosteric modulator of Trk-receptors acting as a cognitive enhancer in vivo and demonstrate herein promising results supporting increased plasticity, neurorestorative and neuroprotective properties. The results of repeated administration of ACD856 indicate that the compound improves neuronal plasticity or in other ways increase network connectivity in regions of importance for depression and cognition. In summary, repeated administration induces long-term effects, thus supporting a role of ACD856 in long-term modification and increased plasticity. This notion is in line with the positive findings of ACD856 on neurite outgrowth, SNAP25 expression and increased BDNF levels in cortical neurons. The fact that ACD856 shows potential disease-modifying effects is of high importance for the future treatment of cognitive dysfunction in Alzheimer's disease.

LP25- OVERVIEW OF THE PRECLINICAL PROGRAM FOR OLX-07010 - A NOVEL INHIBITOR OF TAU SELF-ASSOCIATION. J. Moe[1], B. Levine[2], E. Cheesman[1], P. Lopez[1], W. Erhardt[1], E. Davidowitz[1] *(1. Oligomerix, Inc. - White Plains (United States), 2. Levine Tox Consulting, LLC - Chicago (United States))*

Background: Tau has been implicated in the pathogenesis of multiple neurodegenerative diseases associated with the accumulation of abnormal species of tau, collectively called tauopathies. Mutations in MAPT can cause a range of rare inherited tauopathies to develop due to overproduction of specific tau isoforms or changes in the structure of tau, both of which can cause tau to aggregate. In AD, tau pathology is driven by numerous posttranslational modifications that lead to loss of normal function and/or gain of toxic function. Neurofibrillary tangles, composed primarily of tau, accumulate in a highly reproducible spatiotemporal order starting in the transentorhinal/entorhinal regions and spreading through the hippocampal structure to the neocortex demonstrating a close association between tau aggregation and AD progression. Tau prion-like propagation through neuronal communication pathways uses a seeding mechanism of templated misfolding and is accelerated by the presence of brain Aβ. Multiple studies have shown that tau oligomers, not fibrils or tangles, are closely correlated with neuronal loss and memory impairment. We have shown that tau oligomers cause disruption of neuronal signaling and inhibit the formation of memory in mice (Fá M et al., 2016). Memory formation was impaired following administration of oligomeric tau to hippocampi, areas of the brain involved in short-term memory formation. But similar treatment with tau monomer (tau that did not self-associate) did not have an effect. This impairment of memory was also found using oligomers formed from hyperphosphorylated tau purified from human AD brain specimens. Memory-specific mechanisms involved in gene regulation were shown to be disrupted by these extracellular tau oligomers. We have found that certain forms of tau oligomers are toxic when applied to cultured neurons, whereas tau monomer was not toxic at the same concentrations (Tian H et al., 2013). Our in vivo efficacy studies were carried out in two different transgenic mouse models, the htau model that expresses all 6 human isoforms with no mutations, and the JNPL3 model that has 4R0N tau with a P301L mutation. Treatment with the lead caused significant reduction in tau aggregates in blinded preventive studies (Davidowitz EJ et. al., 2020) in the htau model and also showed efficacy in both preventive and therapeutic studies in JNPL3 mice modeling 4R tau aggregation in tauopathies. Taken together these studies support the development of OLX-07010. **Objectives:** The overall goal of this program is to develop a small molecule therapeutic targeting tau self-association for Alzheimer's disease and related tauopathies. The aim of this preclinical development program was to perform the studies needed for an IND application for a first-in-human

clinical study for the safety and pharmacokinetics of OLX-07010. To achieve this aim, studies were required to evaluate the pharmacodynamics, pharmacokinetics, metabolism and toxicity of the candidate. Process development and manufacture of the drug substance (DS) for the non-clinical studies (non-GMP) and for the GMP manufacture of drug product (DP) were needed to perform the safety studies and to evaluate the stability of the DS and DP. **Methods:** All toxicology, metabolism, and transporter studies, as well as DS and DP manufacture and testing were performed at CROs. The 14-day toxicity studies (non-GLP) had once daily oral gavage to rats at dose levels of 100, 300, and 1,000 mg/kg/day, and once daily oral gavage to Beagle dogs at dose levels of 50 and 150 mg/kg/day. The dose levels in the 28-day toxicity studies (GLP) were 30, 100 and 300 mg/kg/day in rats and 15, 50 and 150 mg/kg/day in dogs. The Functional Observational Battery was performed as part of the 28-day rat study to evaluate CNS effects. **Results:** OLX-07010 demonstrated: pharmacologic activity in two mouse models of tauopathy; reasonable pharmacokinetic characteristics; minimal DDI potential; lack of genotoxicity; minimal off-target activity in safety pharmacology profiling with tier 1 and 3 safety panels; lack of/minimal effects on cardiovascular, pulmonary and CNS systems; relatively modest findings which were not considered adverse were observed in 28-day rat and dog GLP toxicity studies; the drug substance showed high purity and stability, and the drug product showed good stability. **Conclusion:** The preclinical development program demonstrated that OLX-07010 is an excellent candidate for clinical development. Long-term treatment for chronic diseases such as AD requires safe, effective, and economically feasible approaches. This small molecule, CNS drug-like lead substantially fulfills these requirements based on our preliminary results and the fact that it would not need cold-storage nor expensive infusion centers for administration for ease of treatment to address the unmet global health crisis. **References:** Fá M et al., Sci Rep. 2016 Jan 20;6:19393. PMC4726138; Tian H, et. al., Int J Cell Biol. 2013, 260787. PMC3789488; Davidowitz EJ et al., J Alzheimers Dis. 2020; 73(1):147-161. PMC6957711.

CLINICAL TRIALS: RESULTS

P34- CLINICAL OUTCOMES FROM A PHASE 2, OPEN-LABEL STUDY OF NE3107 IN PATIENTS WITH COGNITIVE DECLINE DUE TO DEGENERATIVE DEMENTIAS.

E. Rindner[1], K. Mahdavi[1,2], J. Haroon[1], K. Jordan[1], M. Zielinski[1], V. Venkatraman[1,3], D. Goodenowe[4], C. Ahlem[5], C. Reading[5], J. Palumbo[5], B. Pourat[6], S. Jordan[1,3] *(1. The Regenesis Project - Santa Monica (United States), 2. Synaptec Network, - Santa Monica (United States), 3. Synaptec Network - Santa Monica (United States), 4. Prodrome Sciences USA LLC - Temecula (United States), 5. Biovie Inc. - Carson City (United States), 6. Pourat MD - Beverly Hills (United States))*

Background: Therapies targeting amyloid beta (Aβ) and phosphorylated tau (P-tau), two of the most well-characterized biomarkers of Alzheimer's disease (AD), have been associated with unclear clinical benefit. During the past decade, brain glucose hypometabolism, insulin resistance (IR), and neuroinflammation have emerged as important contributors to the pathophysiology of AD. Chronic inflammation is thought to induce IR and promote Aβ and P-tau accumulation, oxidative stress, and apoptosis, eventually leading to neuronal death and reduced cognitive performance. Studies suggest that increasing insulin sensitivity might reduce AD incidence and improve cognitive performance and brain glucose metabolism in AD patients. NE3107 is an oral, small, blood-brain–permeable molecule that binds and selectively inhibits inflammatory mediators and, as a consequence, improves insulin signaling. Across several clinical studies, NE3107 increased insulin sensitivity and restored metabolic homeostasis in patients with type 2 diabetes and inflammation, altered inflammatory biomarkers that have been associated with cognitive decline, and was well tolerated. **Objectives:** The present Phase 2, open-label study was designed to evaluate the potential efficacy of NE3107 in patients with mild cognitive impairment (MCI) or mild dementia through neuroimaging, cognitive performance testing, assessments of glucose and insulin homeostasis, and changes in AD and inflammatory biomarkers. Clinical outcomes of this study included changes in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 12) evaluations in addition to a battery of neuropsychological testing. **Methods:** Twenty-three participants were enrolled and received 20-mg oral NE3107 twice daily for 3 months. Participants were between 50-89 years old with MCI or mild dementia (Quick Dementia Rating Scale [QDRS] cutoff range: 1.5-12.5; Clinical Dementia Rating [CDR] score range: 0.5-1). AD markers (Aβ and P-tau) were evaluated at baseline and treatment termination. Primary endpoints evaluated neurophysiological health using multi-modal brain MRIs at baseline and treatment termination, including changes in glutathione levels, arterial perfusion, and functional connectivity of the nucleus basalis of Meynert (NBM) with both hippocampi. Secondary endpoints evaluated changes in serological inflammatory markers, glucose and insulin homeostasis, and cognitive functioning (clinical outcomes) using the QDRS, CDR score (estimated by the QDRS), ADAS-Cog 12 (scored from 0-70), the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment (MoCA). Upon completion of the protocol, participants and their families were asked to report a Global Rating of Change (GRC) and complete a Patient Health Questionnaire-9 (PHQ-9). **Results:** Participants had a mean age of 71.6 (SD = 9.63) years and 15 (65%) were females. At baseline, the mean QDRS score was 5.07, 18 (78%) participants had a CDR score of 0.5, and 5 (22%) participants had a CDR score of 1. Results from clinical outcomes will be presented at the conference. **Conclusion:** Using an array of well-established neuropsychological assessments to ascertain participants' cognitive abilities before and after treatment with NE3107, this study aimed to demonstrate the potential therapeutic efficacy and cognitive improvements associated with NE3107 treatment in patients with MCI. **Funded by:** BioVie Inc. **Disclosures:** ER, KM, KJ, JH, MZ, VV, and SJ have received grant support from BioVie Inc. DG has nothing to disclose. BP has nothing to disclose. CA, CR, and JP are employees of BioVie Inc.

P35- META-ANALYSIS OF HIGH-CLEARANCE ANTI-AMYLOID IMMUNOTHERAPIES TRIALS IN EARLY ALZHEIMER'S DISEASE: A SIGNIFICANT CLINICAL EFFECT BUT A LOW BENEFIT/RISK RATIO.

N. Villain[1], V. Planche[2] *(1. Ap-Hp Sorbonne Université, Hôpital Pitié-Salpêtrière, Department Of Neurology, Institute Of Memory And Alzheimer's Disease - Paris (France), 2. Univ. Bordeaux, Cnrs, Imn, Umr 5293 - Bordeaux (France))*

Background: In the last three years, three over four phase II or III clinical trials using high-dose anti-amyloid immunotherapies in early Alzheimer's disease (AD) have turned out to be positive on clinical outcomes: aducanumab (one of two), donanemab, and lecanemab. These results contrast with the previous failures of anti-amyloid immunotherapies.

Despite different pharmacodynamic properties, these drugs share a new characteristic: the high clearance of amyloid load as measured with amyloid positron emission tomography. In the meantime, the Food and Drug Administration's conditional approval of aducanumab has led to unprecedented scientific controversies. **Method:** We used the data from the highest dose group (i.e., the groups used for approval application or ongoing phase III trials) versus placebo after 18 months of the lecanemab and donanemab phase II trials and of the two aducanumab phase III trials to perform a meta-analysis. Regarding clinical efficacy, we analyzed the CDR-SB, ADASCog, and MMSE data. Regarding safety, we analyzed the occurrence of any Amyloid-Related Imaging Abnormalities (ARIA), of ARIA-edema (ARIA-E), of ARIA-hemorrhage (ARIA-H), and of symptomatic and serious ARIA. The analyses were performed using RevMan 5.4.1 and a random effect model. **Results:** High-clearance anti-amyloid immunotherapies were shown to significantly slow down cognitive decline after 18 months as measured with CDR-SB (weighted mean=-0.24 points; p=0.04), and ADAS-Cog (weighted mean=-1.25 points; p=0.0003), but not with MMSE (weighted mean=+0.31 points; p=0.23) when compared to placebo. In parallel, the drugs significantly increased the occurrence of any ARIA (risk ratio=3.68; p<0.0001), of ARIA-E (risk ratio=13.39; p<0.0001), of ARIA-H (risk ratio=2.78; p=0.0002), and of symptomatic and serious ARIA (7/1321=0.53% in the high dose groups versus 0/1446 in the placebo groups; risk ratio=6.44; p=0.04). **Conclusion:** When pooled together, the data from high-clearance anti-amyloid immunotherapies trials confirm a significant clinical effect after 18 months. However, this effect remains below the established minimal clinically relevant values. Safety remains an issue with 0.5% of symptomatic and serious ARIA, significantly beyond chance, despite thorough in-trial monitoring and management. The benefit/risk ratio of this class of drugs in early AD is thus questionable after 18-months. Identifying subgroups of better responders and the perspective of combination therapies may help improve their clinical relevance.

P36- LILYPADD TRIAL: TARGETING HIPPOCAMPAL HYPERCONNECTIVITY IN COGNITIVELY NORMAL OLDER ADULTS AT RISK FOR ALZHEIMER'S DISEASE WITH AGB101. S.J. Li[1], A. Bakker[2], B.D. Ward[3], Y. Wang[4], S. Schold[5], P. Antuono[5], E.D. Granadillo[5], M. Franczak[5], J. Goveas[6] *(1. Department of Biophysics, Department of Radiology, Department of Psychiatry and Behavioral Medecine, Medical College of Wisconsin - Milwaukee (United States), 2. Department of Psychiatry and Behavioral Sciences, Johns Hopkins University - Baltimore (United States), 3. Department of Biophysics, Medical College of Wisconsin - Milwaukee (United States), 4. Department of Biophysics, Department of Radiology, Department of Psychiatry and Behavioral Medecine, Department of Neurology, Medical College of Wisconsin - Milwaukee (United States), 5. Department of Neurology, Medical College of Wisconsin - Milwaukee (United States), 6. Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin - Milwaukee (United States))*

Background: The burden of Alzheimer's disease (AD), with a predicted prevalence rising to over 100 million patients worldwide by 2050, could be dramatically reduced by effective interventions. Aging represents the greatest risk for AD although the boundary between healthy aging and the earliest emergence of AD remains poorly understood. Amnestic mild cognitive impairment (aMCI) due to AD is recognized as a prodromal phase between normal aging and a clinical diagnosis of AD dementia. aMCI is characterized by greater memory impairment than expected for a person's age and by augmented hippocampal hyperactivity. Strong evidence from both studies of animal models and humans have observed that hyperactivity in neuronal circuits contributes to the accumulation and spread of AD pathology and forecasts subsequent cognitive decline. Evidence also shows that hippocampal hyperactivity as well as altered functional connectivity between neuronal networks occurs in cognitively normal (CN) older adults. In elderly CN individuals elevated hippocampal connectivity at rest is associated with lower age-related episodic memory performance and greater subsequent decline in memory function (Salami et al., 2014), conferring increased risk for progression to dementia. In patients with aMCI low dose levetiracetam was previously demonstrated to normalize hippocampal hyperactivity and improved memory function on an episodic memory task designed to tax hippocampal functioning (Bakker et al., 2012). The current study was aimed to examine whether low dose levetiracetam can be used to reduce functional connectivity of the hippocampus in cognitively normal older adults as a primary endpoint, with secondary endpoints examined by neuropsychological assessments. **Objectives:** To assess the efficacy of AGB101, a once daily extended-release formulation containing 220 mg of levetiracetam, on bilateral hippocampus functional connectivity measured by resting-state functional MRI when compared to placebo. Secondary outcomes determined the efficacy of AGB101 versus placebo on performance on neuropsychological assessment of episodic memory using the Rey Auditory Verbal Learning Test. **Methods:** Participants were cognitively normal older adults between the ages of 55-75 who were free of major neurological, psychiatric conditions or medically unstable conditions. Participants completed a randomized, double-blind, placebo-controlled crossover trial conducted at the Medical College of Wisconsin in Milwaukee, Wisconsin, between May 2018 and March 2021. Group A subjects received an oral placebo tablet daily for two weeks followed by a four-week wash-out period. Those participants subsequently received an oral AGB101 tablet daily for two weeks (two weeks placebo treatment – four weeks washout – two weeks AGB101 treatment). Group B participants received the treatment protocol using the reverse sequence (two weeks AGB101 treatment – four weeks washout – two weeks placebo treatment). At each study visit, participants completed a neurological exam, neuropsychological assessment, MRI session and a blood draw. **Results:** Thirty-five cognitively normal older adults were evaluated for eligibility and enrollment. Nine participants did not meet criteria and were not enrolled. One subject did not have detectable levetiracetam in their blood sample after treatment and was excluded from analysis. A total of 25 participants, including 15 women (mean [SD] age of 65.9 [3.8]) and 10 men (mean [SD] age of 66.7 [5.5]) were randomized (12 participants to group A and 13 participants to group B) were included in the analysis. Blood plasma values (mean [SD] of 4.34 [1.32] mg/ml) were consistent with previous reports (Bakker et al., 2012). No effect of treatment order was observed in the study. Treatment with AGB101 significantly decreased bilateral functional connectivity of the bilateral hippocampus network ($p < 0.0098$). No effect of treatment was observed on episodic memory performance on the Rey Auditory Verbal Learning Test. **Conclusions:** In this clinical study two weeks of daily treatment with AGB101 was well tolerated and although no treatment effect on episodic memory performance was observed, treatment with AGB101 significantly decreased functional connectivity of the hippocampus network when compared to placebo. These proof-of-concept results warrant

further assessment of AGB101 in cognitively normal older adults in the earliest phases of the AD continuum before symptomatic cognitive impairment and a diagnosis of aMCI. A more extended treatment protocol could be used to determine whether progression of impairment can be attenuated by such intervention. **ClinicalTrials.gov Identifier:** NCT03461861. **Supported by National Institute on Aging:** R21MH126479. **References:** A. Salami, S. Pudas, L. Nyberg. (2014). Elevated hippocampal resting-state connectivity underlies deficient neurocognitive function in aging. Proceedings of the National Academy of Sciences, 111, 49: 17654-17659. A. Bakker, G. Krauss, M.S. Albert, C.L. Speck, L.R. Jones, C.E. Stark, M.A. Yassa, S.S. Bassett, A.L. Shelton, M. Gallagher. (2012). Reduction of hippocampal hyperactivity improves cognition in amnestic mild cognitive impairment. Neuron, 74: 467-474.

P37- PLANNING THE NEXT GENERATION OF ALZHEIMER'S DISEASE CLINICAL TRIALS USING DIVERSE PATIENT-LEVEL DATABASE FROM THE CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) CONSORTIUM.

S. Sivakumaran[1], N. Cullen[1], Z. Cui[1], E. Priest[1], C. Lau[1], H. White[1], M. Irizarry[2], K. Romero[1], Y. Karten[1] *(1. Critical Path Institute - Tucson (United States), 2. Eisai Inc. - Nutley (United States))*

Background: Critical Path Institute (C-Path) coordinates the Critical Path for Alzheimer's Disease (CPAD) Consortium. To accelerate drug development for Alzheimer's Disease (AD), CPAD has previously developed two regulatory-endorsed clinical trial simulators (CTS) that sponsors can use to help optimize clinical trial design in 1) the pre-dementia stages of AD, using CDR-SB as the primary endpoint, and 2) mild-to-moderate AD, using ADAS-cog as the primary cognitive endpoint. These models incorporate demographic covariates, like sex and age, as well as baseline severity (MMSE), and APOE4 genotype. The pre-dementia model incorporates baseline hippocampal volume, as an enrichment biomarker. The natural next step in the evolution of these quantitative tools requires the consideration of additional baseline and longitudinal biomarkers. Recently, CPAD members have begun to share data from several contemporary Phase III clinical trials, offering an opportunity to enrich and expand these model-based tools with additional fluid and imaging biomarker information, data from predementia subjects and treatment arms. **Method:** By integrating patient-level data from high quality Alzheimer's disease (AD) clinical trials, models will be developed to model natural AD progression for multiple cognitive and functional endpoints, as well as biomarkers, adjusted for demographics, baseline severity, time from and to diagnosis, and genetic status (APOE4). Such progression models will be fit using non-linear mixed effects methods and Monte Carlo simulations will be performed to evaluate model fit across a variety of covariates. Moreover, the rich collection of biomarker data will be leveraged to build statistical models which will address unmet needs at multiple points in the clinical trial design process: reducing unnecessary PET scans by screening with accessible blood-based biomarkers, optimized patient selection by contributing to PET analysis pipelines, and reduced trial size (and/or increased statistical power) with the help of enrichment models that predict cognitive decline using combinations of AD biomarkers. Finally, longitudinal biomarker data will be modelled against longitudinal cognitive trajectories to better understand the selection of biomarker-based endpoints to measure reduction in AD pathology in response to treatment. **Results:** As of January 2022, CPAD's clinical trial repository contains 61 studies with 40,122 individual anonymized patient records. Analysis subsets generated from 6 key datasets, rich in fluid and imaging biomarkers, were used to develop of a preliminary set of disease progression models that characterize the time course of clinically relevant measures (ADAS-Cog, CDR-SB, other clinical assessment scales and biomarkers). A two-level regression model was applied to predict baseline CDR-SB using baseline covariates (demography, ApoE4 status, fluid and imaging biomarkers) and identify significant variables. Base models using parametric mixed-effects approaches were developed with selection based on goodness-of-fit plots. In terms of addressing clinical trial design needs, a screening model has been developed to predict amyloid PET status from a combination of demographics, cognition, and blood-based biomarkers, an enrichment model has been developed to predict longitudinal cognitive decline from a combination of screening biomarkers plus amyloid PET, and the association between longitudinal CSF and plasma biomarkers versus longitudinal cognitive has been evaluated. **Conclusion:** The disease progression models will serve as the basis for clinical trial simulation tools to facilitate informed decision making in the drug development process and optimize patient and endpoint selection, as well as design of efficacy studies. The trial design models will serve to influence core clinical trial design decisions and thereby usher in the next generation of biomarker-driven clinical trials characterized by greatly improved efficiency and reduced costs. CPAD will advance the tools through the formal FDA Fit for Purpose pathway, to achieve regulatory endorsement and provide confidence to sponsors for the adoption of the tools.

P38- CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) CONSORTIUM: ACCELERATING AND DE-RISKING THERAPEUTIC DEVELOPMENT IN AD BY BUILDING REGULATORY DECISION-MAKING TOOLS.

S. Sivakumaran[1], N. Cullen[1], C. Lau[1], E. Priest[1], H. White[1], M. Irizarry[2], K. Romero[1], Y. Karten[1] *(1. Critical Path Institute - Tucson (United States), 2. Eisai - Nutley (United States))*

Background: The Critical Path Institute (C-Path) coordinates the Critical Path for Alzheimer's Disease (CPAD) Consortium, a global, neutral convener, bringing together diverse stakeholders across industry, regulatory agencies, patient advocacy organizations and academia within a pre-competitive forum under a data-driven, regulatory framework to accelerate therapeutic innovation in Alzheimer's disease (AD). In partnership with C-Path's Quantitative Medicine Program, CPAD members, and regulatory agencies (FDA, EMA), CPAD's Quantitative Modeling Working (QMWG) and Focus Groups identify key questions and unmet needs in AD drug development. To address the unmet needs, we use our core competencies in data management and standards, advanced quantitative analytics, biomarkers, clinical outcome assessment tools and regulatory science to develop actionable solutions that help de-risk decision making in the AD drug development process. **Method:** Patient-level data and neuroimages from contemporary Phase II and Phase III AD clinical trials and observational studies re acquired through formal data contribution agreements with CPAD. Clinical data is curated in collaboration with data contributors, standardized to common structure and terminology, and assembled into analysis subsets. From the integrated data, analysis ready subsets are created for development of a comprehensive set of disease progression models across the

continuum of the disease. Models characterize the time course of clinically relevant measures (ADAS-Cog, CDR-SB, other clinical assessment scales and biomarkers). The models will serve as the basis for clinical trial simulation tools to facilitate informed decision making in the drug development process and optimize patient and endpoint selection and design of efficacy studies. To incorporate imaging biomarkers as key covariates in the disease progression modeling, there is a need for post-acquisition data 'harmonization' tools and analysis methods that reduce variance across studies, sites, and scanners, while retaining the power to study complex disease related effects. To that end, we will develop a harmonized image analysis methodology for the purpose of deriving imaging biomarkers. **Results:** As of May 2022, CPAD's clinical trial repository contains 61 studies with 40,122 individual anonymized patient records. Analysis subsets generated from 6 key datasets, rich in fluid and imaging biomarkers, were used to develop a preliminary set of disease progression models that characterize the time course of clinically relevant measures (ADAS-Cog, CDR-SB, other clinical assessment scales and biomarkers). In addition, we initiated a collaboration with the USC Laboratory of Neuro Imaging (LONI) and Global Alzheimer's Association Interactive Network (GAAIN) on an image analysis pipeline developed by LONI, to develop a multimodal harmonized neuroimage analysis tool, based on the LONI Pipeline and GAAIN research interface. The tool will be leveraged for automated quantification of image-derived biomarkers, which will be used in disease progression modeling. Examples of such neuroimaging biomarkers include amyloid (amyloid PET), tau (tau PET), and neurodegeneration (hippocampal volume). CPAD will also leverage this pipeline to advance our understanding of ARIA, in partnership with members and collaborators. Finally, we will integrate various modeling and analytical approaches being pursued by all stakeholders within CPAD into a comprehensive disease progression model as the basis to develop a clinical trial simulation tool. **Conclusion:** C-Path provides the legal, scientific, and regulatory infrastructure to generate a unique neutral environment for relevant stakeholders in the AD drug development field to collaborate. The precompetitive space is imperative to stakeholders sharing information and data and transforming those into actionable tools and solutions that address specific unmet needs in the drug development process. Through formal submissions for regulatory review and potential endorsement of solutions, CPAD can build consensus among experts and stakeholders and provide confidence to sponsors for the adoption of the tools.

P39- EFFECTIVENESS OF A DIGITALLY SUPPORTED CARE MANAGEMENT PROGRAM FOR FAMILY AND OTHER INFORMAL DEMENTIA CAREGIVERS: BASELINE DATA AND FIRST RESULTS FROM THE GAIN RANDOMIZED CONTROLLED TRIAL.

I. Kilimann[1], O. Klein[2], J.R. Thyrian[3], M. Boekholt[3], S. Teipel[1], W. Hoffmann[4] *(1. Deutsches Zentrum Für Neurodegenerative Erkrankungen Dzne Rostock/greifswald And University Medical Center Rostock, Department Psychosomatics And Psychotherapy - Rostock (Germany), 2. Deutsches Zentrum Für Neurodegenerative Erkrankungen Dzne Rostock/greifswald - Rostock (Germany), 3. Deutsches Zentrum Für Neurodegenerative Erkrankungen Dzne Rostock/greifswald - Greifswald (Germany), 4. Deutsches Zentrum Für Neurodegenerative Erkrankungen Dzne Rostock/greifswald And University Hospital Greifswald, Institute For Community Medicine - Greifswald (Germany))*

Background: Almost two-thirds of people with dementia (PwD) living at home receive care from a family or other informal caregiver. For the caregiver this can result in a work load comparable or above a full-time employment position. Evidence shows that family caregivers have a higher risk for psychiatric and non-psychiatric diseases like depression, anxiety, and arterial hypertension compared to non-caregivers. A dyadic approach on disease management and the assessment of unmet needs can help to reduce the burden of care and increase the quality of life of caregivers and PwD. The cluster randomized trial "Gesund Angehörige Pflegen" (GAIN) conducted in general practitioner (GP) practices and memory clinics in Northern Germany aimed to evaluate the effectiveness of a 6-months digitally supported care management program to reduce unmet needs of informal caregivers of PwD. **Methods:** Primary outcomes are the number of identified and addressed caregivers' self-reported unmet needs (related to the caregiver and related to the PwD, Camberwell Assessment of Need for the Elderly, CANE) and the health-related quality of life (EQ-5D-5L). The recruitment for the GAIN trial began in October 2020 and ended in January 2022 with a total number of n=192 participants (mean age: 65 years, women 75%). The intervention and all follow-up visits will be completed by August 2022. In addition to the primary outcomes, caregivers' burden (Zarit Burden Interview, ZBI), social support (Lubben Social Network Scale, LSNS), use of medical and non-medical services (FIMA), and resource utilization (RUD) were assessed. **Results:** Results from the effectiveness analysis will be available and presented at the conference. Baseline data showed that the GAIN questionnaire has a high potential to identify unmet needs. On average 8.66 unmet needs were identified in a dyad: 3.99 unmet needs related to the caregiver and 4.67 unmet needs were in relation to the PwD. The number of identified unmet needs was higher compared to previous studies e.g. from the European Actifcare Study. The intervention targeting caregiver burden was triggered the most (n=141), followed by interventions addressing a missing disability certificate) (n=116) and reduced physical activity (n=90). **Conclusion:** The use of a tablet-based expert assessment system GP practices and in memory clinics to identify unmet needs is well feasible and identifies a higher number of unmet needs compared to previous studies. The high average number of unmet needs among family caregivers indicates the importance of a structured and in-depth assessment to allow a personalized and dyadic treatment of family caregivers and the PwD. Further results from the primary outcome analysis will be presented at the conference.

P40- REPEAT IV AND SC DOSING OF THE ANTI-SORTILIN ANTIBODY AL101. M. Ward[1], F. Yeh[1], L. Park[1], D. Maslyar[1], Y. Liao[1], H. Long[1], H. Picard[1], M. Kurnellas[1], M. Vadhavkar[1], A. Silva[1] *(1. Alector, Inc. - South San Francisco (United States))*

Background: Variants in GRN, the coding gene for progranulin (PGRN), have been implicated in a number of neurodegenerative disorders, including Frontotemporal dementia (FTD), Alzheimer's disease (AD) and Parkinson's disease (PD). Sortilin, expressed on neurons and microglia, is a key regulator of PGRN levels through sortilin-mediated degradation. Increasing PGRN levels, may be an effective therapeutic approach, potentially reducing the rate of neuronal loss and clinical decline in individuals with neurodegenerative diseases. AL101 is a human IgG1 monoclonal antibody that downregulates sortilin and increases PGRN levels in preclinical models. AL101 is being developed by Alector for the treatment of neurodegenerative disorders, including AD and PD. **Objectives:** The extension of this first-in-human Phase 1 study is designed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) following repeated administration of AL101, administered intravenously (IV) and subcutaneously (SC). **Methods:** Healthy volunteers received repeat doses of AL101 in two cohorts: 300 mg SC q2w for a total of 7 doses and 30 mg/kg IV q4w for a total of 4 doses. Assessments included standard clinical safety measures, pharmacokinetic (PK) and pharmacodynamic (PD) markers in plasma and CSF. Plasma profiles of AL101 and PGRN were measured up through day 113 for the SC cohort and day 141 for the IV cohort. CSF was sampled at baseline and at timepoints after the last administered dose. Safety follow-up was conducted for up to 20 weeks in the IV cohort and up to 16 weeks in the SC cohort. **Results:** Reported AEs were generally mild to moderate in severity and self-limiting, in line with preliminary AL101, single dose safety data. There were no severe or serious adverse events related to repeat dose administration. Subjects in the SC repeat-dose cohort reported a higher number of overall injection site reactions although these were all mild in severity. Repeat-dose AL101 increased the levels of PGRN in the CSF of healthy volunteers up to approximately 80% above baseline levels. PK/PD modeling, based on PK and PD data from these repeat-dose cohorts, supports dosing intervals of q8w. **Conclusion:** Multiple IV or SC administration of AL101 is generally safe and well tolerated in healthy volunteers. AL101 is a potent modulator of PGRN levels in the CSF, with a PK/PD profile that supports its further development in chronic neurological conditions such as Alzheimer's and Parkinson's disease.

P41- SAL-AD: A PHASE 1B, 12-MONTH, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY EFFICACY OF SALSALATE IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE. P. Ljubenkov[1], L. Vandevrede[1], J. Rojas[1], M. Honey[2], A. Lario Lago[1], R. Tsai[3], M. Koestler[1], R. La Joie[1], K.A. Johnson[4], L. Gan[5], S. Lessig[6], J. Brewer[6], H. Feldman[6], C. Teunissen[7], A. Boxer[1] *(1. UCSF Memory and Aging Center - San Francisco (United States), 2. Amsterdam UMC - Amsterdam (Netherlands), 3. Denali Therapeutics - San Francisco (United States), 4. Harvard Medical School - Boston (United States), 5. Weill Cornell Medical College - New York (United States), 6. UC San Diego - San Diego (United States), 7. Amsterdam UMC - Amsterdam (United States))*

Background: Tau acetylation at Lys174 may impair tau clearance and is an early pathological change present in patients with Alzheimer's disease (AD) and murine models of tauopathy. Salsalate is a nonsteroidal anti-inflammatory (NSAID) which inhibits p300 acetyltransferase and thereby reduces tau acetylation. In a PS19 transgenic mouse model of tauopathy, salsalate treatment lowered p300 activity, decreased acetylation at Lys174, decreased total tau levels, increase tau turnover, reduced memory deficits, and prevented hippocampal atrophy. Given salsalate's potential utility in a preclinical model, we sought to conduct a phase 1b randomized, double-blind, placebo-controlled of salsalate in patients with mild to moderate Alzheimer's disease. **Objectives:** The primary objective was to assess the safety and tolerability of salsalate in patients with mild to moderate AD. Secondary objectives were to assess blood and CSF pharmacokinetic (PK) measures of salsalate. Exploratory objectives included assessment of salsalate's pharmacodynamic (PD) impact on cerebrospinal fluid (CSF) biomarkers of AD severity (total tau [t-tau], phosphorylated tau [p-tau181], and amyloid beta [Aβ1-42] measured on the Elecsys platform), CSF neurofilament light chain [NfL], CSF acetylated tau, CSF acetylated histones, measures of AD clinical severity, volumetric brain MRI measures, and brain uptake of 18F-MK6240 positron emission tomography (PET) tracer. **Methods:** N=40 patients with biomarker confirmed (via amyloid PET or CSF amyloid and tau) AD and mild to moderate dementia (Mini Mental Status Exam [MMSE] Scores≥14) were enrolled from August 2017 to February 2020 at University of California, San Francisco, and University of California, San Diego. Patients were randomized 1:1 to one year of blinded treatment with either placebo or salsalate 3000 mg daily. CSF, plasma, volumetric imaging, and exploratory clinical measures were collected at baseline, 6 months, and 12 months. The final 21 participants were enrolled in a secondary cohort that included assessment with brain 18F-MK6240 PET imaging at baselined and at 12 months of treatment. Linear mixed effect models determined interactions between treatment assignment (salsalate vs placebo) and time in determining change in exploratory measures. **Results:** Patients randomized to salsalate and placebo were comparable in terms of baseline mean age (66.7 [SD 8.5] years vs 65.8years [10.5] respectively), gender distribution (12 women/8 men, 13 women/7 men), Clinical Dementia Rating Scale (CDR) global score (0.9 [0.4]) vs 0.8 [0.4]), MMSE score (20.8 [5] vs 21.1 [4.5]), CSF total tau (353.9pg/ml [154.6] vs 349.4pg/ml [225.3]), CSF p-tau181 (34.7pg/ml [15.7] vs 34.2pg/ml [24.3]), and CSF NfL (1571.2pg/ml [746.7] vs 1362.5pg/ml [504.8]). However, patients randomized to salsalate tended to have a greater baseline cognitive impairment on the eleven item Alzheimer's Disease

Assessment Scale–Cognitive Subscale (ADAS Cog 11) (45.4 [16.1] vs 38.4 [12.3], p=0.016), and lower baseline CSF Aβ1-42 values (447.7pg/ml [142.0] vs 536.4pg/ml [151.4], p=0.01). The trial experienced a high rate of early discontinuations (45%) in the context of the COVID-19 pandemic; the number of early terminations was higher in patients randomized to salsalate (n=11) compared to the placebo group (n=7; Fisher's exact test p=0.043). The number of patients who experienced adverse events was otherwise similar between cohorts (salsalate n=16, placebo n=15). In intention-to-treat and on treatment analyses, no beneficial effects of salsalate treatment were observed on 52-week changes in CSF biomarkers of AD biology (t-tau, p-tau181, Aβ1-42), NfL, or acetylated tau; or on clinical endpoints. Further analyses of primary, secondary, and exploratory endpoints including tau PET are ongoing and will be presented. **Conclusion:** Salsalate was safe and well tolerated, without evidence of beneficial treatment effects on CSF biomarkers or clinical measures. Further analysis of PK and PD results (including tau PET to evaluate target engagement) are pending. The trial's high dropout rate and baseline differences in cohorts may have impacted the interpretability of the results.

P42- EARLY EXPERIENCE WITH HOME ADMINISTRATION OF SUBCUTANEOUS GANTENERUMAB BY STUDY PARTNER (NON-PROFESSIONAL CARE PARTNER) IN THE GRADUATION STUDY.

R. Perry[1], F. Boess[2], M. Scelsi[3], T. Grimmer[4], R. Arroyo[5], C. Lane[3], C.J. Lansdall[2], J. Smith[3] *(1. Imperial College London - London (United Kingdom), 2. F. Hoffmann-La Roche Ltd - Basel (Switzerland), 3. Roche Products Ltd - Welwyn Garden City (United Kingdom), 4. Klinikum rechts der Isar, Technical University of Munich - Munich (Germany), 5. Quirónsalud Madrid University Hospital - Madrid (Spain))*

Background: Gantenerumab is an investigational, fully human anti-amyloid-beta (Aβ) immunoglobulin G1 monoclonal antibody in development as a subcutaneous (SC) treatment for early (prodromal-to-mild) and preclinical Alzheimer's disease (AD). Gantenerumab has high affinity for aggregated Aβ and promotes its removal via Fcγ receptor-mediated microglial phagocytosis.1,2 Open-label extensions of the Phase III SCarlet RoAD (NCT01224106) and Marguerite RoAD (NCT02051608) trials showed robust Aβ removal after treatment with SC gantenerumab.3 Two multicenter, randomized, double-blind, placebo-controlled, Phase III studies, GRADUATE I (NCT03444870) and GRADUATE II (NCT03443973) are ongoing to assess the efficacy and safety of SC gantenerumab in early AD, using a titration over 9 months and a target dose of 510 mg every 2 weeks (Q2W) with change from baseline to Week 116 in Clinical Dementia Rating scale – Sum of Boxes as the primary endpoint. The GRADUATION trial (NCT04592341) will evaluate the safety, pharmacodynamics (PD), and pharmacokinetics (PK) of once-weekly (Q1W) SC administration of gantenerumab (255 mg) in participants with early AD. AD has a substantial, all-encompassing impact on the daily life of both patients and their care partners.4 SC Q1W administration of gantenerumab in the home setting by a care partner may allow for additional flexibility and convenience and reduce the burden of frequent clinic visits. The GRADUATION trial allows for home dosing by a willing study partner (non-professional care partner), deemed able to administer SC gantenerumab by the treating physician after a standardized training. SC administration has potential benefits over intravenous administration, as it enhances access to diverse populations, reduces costs for payers, and allows flexibility for people living with Alzheimer's and care partners. Care partners will respond to a questionnaire to assess their confidence, ease of use, convenience, and overall satisfaction of SC gantenerumab administration in the home setting. **Objectives:** The primary objective of the GRADUATION study is to evaluate the PD effect of a Q1W dosing regimen of gantenerumab on brain amyloid load, measured by positron emission tomography (PET). Secondary objectives include the assessment of gantenerumab administration by the care partner in the home setting, safety, and PK/PD relationships. Exploratory objectives include additional imaging and plasma biomarkers, and cognitive and functional assessments. The focus of this interim analysis is to evaluate care partner confidence and overall satisfaction with home administration. The corresponding endpoint consists of the responses to the care partner questions of the home administration questionnaire. **Methods:** In this open-label, single-arm, Phase II study, participants will receive gantenerumab by SC injection over a 2-year period, starting with 120 mg every 4 weeks (Q4W), followed by 255 mg Q4W and Q2W for 12 weeks each, and a target dose of 255 mg Q1W. This target dose is hypothesized to be equivalent to the 510 mg Q2W studied in the GRADUATE trials. Eligibility criteria include: age 50–90 years at screening; clinical diagnosis of early AD, operationalized as prodromal AD (mild cognitive impairment due to AD) or probable AD dementia according to the National Institute on Aging – Alzheimer's Association diagnostic criteria; and evidence of AD pathology confirmed by amyloid PET scan. The home administration questionnaire will be completed at site visits, and includes items addressing the confidence with administration, convenience, ease of use, and overall satisfaction. Each item is rated on a 4-point verbal Likert scale and respondents will be asked to consider their most recent at home administration. Week 52 analyses of the subset of participants with care partners willing and capable to administer SC injections in the home setting will be analyzed and presented using descriptive statistics. **Results:** Recruitment for GRADUATION is complete. One hundred and ninety-two participants were enrolled from 8 countries (Belgium, France, Germany, Italy, Poland, Spain, United Kingdom, and United States). Baseline characteristics for home administration participants and their care partners and results from a pre-specified Week 52 interim analysis of home administration questionnaire responses with database lock in Q3/2022 will be presented. **Conclusions:** The GRADUATION study will determine the effect of Q1W administration of SC gantenerumab on pharmacodynamics (including brain amyloid load), pharmacokinetics and safety in participants with early AD, and assess the feasibility of administration by care partners at home. The option of home administration with gantenerumab may provide additional convenience and reduced burden for people living with Alzheimer's and their care partners. **References:** 1. Ostrowitzki S, Deptula D, Thurfjell L, et al. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol. 2012;69:198–207; 2. Bohrmann B, Baumann K, Benz J, et al. Gantenerumab: A novel human anti-Aβ antibody demonstrates sustained cerebral amyloid-β binding and elicits cell-mediated removal of human amyloid-β. J Alzheimers Dis. 2012;28:49–69; 3. Klein G, Delmar P, Kerchner G, et al. Thirty-six-month amyloid positron emission tomography results show continued reduction in amyloid burden with subcutaneous gantenerumab. J Prev Alzheimers Dis. 2021;8:3–6; 4. WHO. Dementia. www.who.int/news-room/fact-sheets/detail/dementia Accessed 1 June 2022. **Conflict of interest:** Frank Boess is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd.

P43- A PHASE 1B STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACODYNAMICS OF PRI-002 IN MCI AND MILD AD. O. Peters[1], N.C. Cosma[1], J. Kutzsche[1], D. Willbold[1] *(1. Charité hospital - Berlin (Germany))*

Background: PRI-002 is an orally available anti-amyloid beta (Aβ) prionic compound developed to disassemble toxic Aβ oligomers. PRI-002 has shown to improve cognition in animal models and has demonstrated its safety profile in healthy volunteers (Kutzsche et al. 2020). **Objectives:** To evaluate the safety, tolerability and pharmacodynamics of PRI-002 in early stages of AD. **Methods:** 20 patients in early AD disease stages were recruited to participate in a single center, randomized, placebo –controlled, double-blind study. All participants had to fulfill the ATN-criteria for AD. Patients received once daily oral doses of 300 mg PRI-002 or placebo for 28 days. Safety and efficacy assessments were executed at baseline, day 14, day 28 and day 56 (follow up). Blood sampling was carried out at each time point, EEG and CSF measurements before and at the end of treatment. Imaging (MRI) and functional tests (CERAD, CDR) were performed in parallel to EEG/CSF and additionally at follow up. **Results:** 10 patients (age 76.9±3.4, MMSE 28±1.6) received placebo and 9 patients PRI-002 (72.4±6.9, 27.2±2.9). One patient withdraw informed consent before treatment was initiated. 13 patients reported in total 27 adverse events while no serious adverse event was noted. There was no statistical difference regarding adverse events between treatment and placebo. EEG and MRI revealed no changes after treatment. Especially no ARIA-E or ARIA-H were noted. No significant changes were detected in p-TAU, Abeta1-42 and Aβ oligomers in CSF before and after treatment. Patients that had received PRI-002 for four weeks significantly performed better than those receiving placebo in the CERAD word list 28 days after treatment had ended ($p \leq 0.05$). **Conclusions:** PRI-002 showed an excellent safety profile in AD patients. No biomarker changes were detected after short treatment period of 4 weeks, while a slight improvement of memory function was noted at follow up. A multicenter phase 2 study will be initiated in the near future. Kutzsche J, Jürgens D, Willuweit A, Adermann K, Fuchs C, Simons S, Windisch M, Hümpel M, Rossberg W, Wolzt M, Willbold D. Safety and pharmacokinetics of the orally available antiprionic compound PRI-002: A single and multiple ascending dose phase I study. Alzheimers Dement (N Y). 2020 Mar 20;6(1):e12001. doi: 10.1002/trc2.12001.

P44- ENABLING SUBCUTANEOUS DOSING OF GANTENERUMAB IN ALZHEIMER'S DISEASE. B. Bittner[1], D. Schwab[1], A. Portron[1], D. Lott[1], F. Boess[1], R. Kohler[1], J. Wojtowicz[1], C. Hofmann[1] *(1. F. Hoffmann-La Roche Ltd - Basel (Switzerland))*

Background: Subcutaneous (SC) dosing of biotherapeutics such as monoclonal antibodies (mAb) represents a convenient and resource-efficient dosing alternative to more invasive intravenous (IV) infusions across different therapeutic areas. In light of increasingly cost-constrained global healthcare markets and the coronavirus pandemic, SC administration of mAbs is a key enabler for a flexible care setting in which people living with Alzheimer's disease (pwAD) and care partners can choose the place of drug administration according to their preferences and capabilities. Today, technical challenges associated with high-dose SC mAb administration are increasingly overcome with the development of high-concentration dosing solutions, co-administration of the dispersion enhancer hyaluronidase, as well as ready-to-use and automated injection devices. **Objectives:** Gantenerumab is a fully human anti-amyloid-beta (Aβ) immunoglobulin G1 mAb with highest affinity for aggregated Aβ that removes Aβ via microglia-mediated phagocytosis. It is in development for the treatment of AD with a SC administration regimen. The development of SC dosing has to consider factors of local tolerability and associated pain at the injection site. Respecting the needs of individual patients, the feasibility of care partner-assisted at-home dosing is currently being assessed (NCT04592341). **Methods:** To generate initial safety and efficacy data, early clinical trials with gantenerumab were conducted with the IV formulation, such that SC formulation development and SC tolerability assessments could be conducted in parallel. Assessment of local tolerability following SC administration is part of the standard safety assessments in clinical trials. A dedicated randomized placebo-controlled crossover study was conducted in healthy participants investigating injection pain following SC administration of gantenerumab versus placebo. Plasma concentrations of gantenerumab were collected throughout the clinical studies and the pharmacokinetic characteristics of gantenerumab with SC dosing were characterized by integrating the data from different clinical trials in a population pharmacokinetic model analysis. Possible home-administration is supported with human factors (HF) studies and a care partner questionnaire. **Results:** Gantenerumab entered the clinic with an IV formulation, but solely utilized SC administration in Phase II and III trials after bridging to SC dosing in a healthy volunteer study. Thus, a large clinical database is available for gantenerumab following SC administration. Gantenerumab was locally well tolerated with predominantly mild, reversible, and self-limited injection- site reactions observed as main adverse effects associated with the SC route of administration (Ostrowitzki 2017). The evolving development program included a dedicated randomized, placebo-controlled, crossover study in healthy participants investigating injection pain following SC administration by means of a disposable handheld syringe equipped with a flange to assist with injection force and a spacer to help setting the needle depth and angle. This study demonstrated minimal to slight pain after needle insertion with minor differences in pain recorded for gantenerumab or placebo administered. Visual analogue scales (VAS scale from 0 (no pain) to 100 (worst pain possible)) least square means were at 15.006 vs. 9.526, respectively (mean difference 5.48; 95% CI (-1.971 to 12.931)). Pain was reported only directly after injection and did subside within 5 minutes (VAS < 5 mm); this data was complemented by a verbal rating scale resulting in minimal to slight pain reporting after needle insertion and immediately after injection only. The pharmacokinetics of gantenerumab administered SC provided comparable results across studies and were well characterized by population pharmacokinetic analysis (Retout 2022). To guide adequate dosing in a decentralized setting, the overall clinical data package is complemented with HF data collected in usability studies with pwAD, lay care partners, and healthcare professionals (HCPs). Additionally, a home-administration questionnaire is included in an ongoing Phase II study in participants with early AD (NCT04592341) to assess confidence of non-professional care partners as drug administrators, ease of use, and convenience of SC gantenerumab administration in the home setting. **Conclusion:** Gantenerumab SC administration is locally well tolerated and provides reliable drug exposure with minimal pain experience in the range of what was observed previously for other SC administered mAbs. The SC dosing regimen is expected to support convenient and cost-efficient dosing in a flexible care setting. To further support compliance with

the drug administration procedure in a non-HCP supervised setting, the value of connected devices and corresponding health apps will be assessed for their potential to complement conventional patient support programs. 1. Ostrowitzki S, et al. SCarlet RoAD Investigators. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimers Res Ther. 2017 Dec 8;9(1):95. DOI: 10.1186/s13195-017-0318-y. Erratum in: Alzheimers Res Ther. 2018 Sep 27;10(1):99. 2. Retout S, et al. Disease modeling and model-based meta-analyses to define a new direction for a phase III program of gantenerumab in Alzheimer's disease. Clin Pharmacol Ther. 2022 Apr;111(4):857-866. DOI: 10.1002/cpt.2535. Epub 2022 Feb 28. Lead author disclosure: Beate Bittner is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd.

P45- THE INTERNET-BASED CONVERSATIONAL ENGAGEMENT CLINICAL TRIAL (I-CONECT) IN SOCIALLY ISOLATED ADULTS 75+ YEARS OLD: PRIMARY ANALYSES RESULTS. H. Dodge[1], P. Pruitt[1], K. Yu[1], C.Y. Wu[1], J. Kaye[1], L. Silbert[1], I. Conect-Team[1] *(1. Oregon Health & Science University - Portland (United States))*

Background: Social isolation is a risk factor for dementia. Increasing social interactions using webcam/internet could offer a cost-effective prevention approach that provides cognitive stimulation and slows cognitive decline. This paper describes the results of the primary and secondary outcomes and an exploratory outcome of the recently completed project named "Internet-Based Conversational Engagement Clinical Trial (I-CONECT)" (ClinicalTrial.gov: NCT02871921) where socially isolated subjects with normal cognition (NOC) or mild cognitive impairment (MCI) aged 75 and older were recruited through mass-mailing and community outreach. **Methods:** I-CONECT is a multi-site, assessor-blind, randomized controlled behavioral intervention trial (RCT) aimed to enhance cognitive reserve by providing frequent video chats to socially isolated older old subjects. The detailed protocol was published previously (Yu, et al., 2021). The intervention group had video chats with trained study staff for 30 minutes per day, 4 times per week for 6 months (high dose), and then twice per week for additional 6 months (maintenance dose). Both video chat intervention and control groups had a brief (10 minute) telephone check-in with study staff once per week. We used linear regression and repeated measure mixed-effects models (MMRM) to assess the efficacy of global and domain-specific cognitive test scores at month 6 and month 12. As a part of exploratory analyses, among a subgroup of participants with MCI or NOC who completed both baseline and month 6 MRI assessments, we examined the difference between the two arms in resting-state functional MRI-derived (rsfMRI) connectivity for the following 4 large networks at month 6, controlling for potential confounders: Default Mode Network (DMN), Salience Network (SN), Front-Parietal Network (FPN) and Dorsal Attention Network (DAN). **Results:** We aimed to randomize 160 subjects each of non-white and white socially isolated subjects aged 75 and older. Despite the COVID-19 pandemic and resultant research hiatus, we achieved 96% of the targeted sample size for white participants. However, we achieved only 23% of non-white participants. Overall, we randomized 186 non-demented socially isolated adults 75+ years old either with MCI or NOC (mean age: 81.1 (sd = 4.6), women: 69.9 %, MCI: 53.8%, African Americans: 19.9%) into either the video chat intervention Group (N=94) or the control group (N=92). Compared with the control group, the experimental group had 1.75 (p=0.03) higher Montreal Cognitive Assessment (MoCA) scores (primary outcome, tapping global cognition) at month 6 with cohen's d=0.73, and 2.19 higher Craft Story Immediate Recall scores at month 12 (p=0.03) (secondary outcome, immediate memory/encoding ability) with cohen's d of 0.66 among the participants with MCI. Aa for rsfMRI results, the experimental group was associated with higher connectivity within the DAN at month 6, compared with the control group (p=0.03), based on linear regression models controlling for age, sex, scanner motion, site, and connectivity at baseline. **Conclusions:** Despite the challenges induced by the COVID-19 pandemic and the resultant reduced sample size and other protocol modifications, we found significant efficacy in the primary and secondary outcomes along with potential biological modification in specific brain connectivity. The intervention that provides social interactions through user-friendly subject-centered video chats has the potential to impact the overall dementia prevalence by delaying the cognitive decline associated with MCI. Phase III study will confirm the efficacy in delaying the onset of dementia. **Conflict of Interest:** No author has a conflict of interest in presenting this work. **Funding sources:** National Institute on Aging (NIA) Grant Nos. R01AG051628, R01AG056102. **References:** Yu K, Wild K, Potempa K, Hampstead BM, Lichtenberg PA, Struble LM, Pruitt P, Alfaro EL, Lindsley J, MacDonald M, Kaye JA, Silbert LC and Dodge HH (2021) The Internet-Based Conversational Engagement Clinical Trial (I-CONECT) in Socially Isolated Adults 75+ Years Old: Randomized Controlled Trial Protocol and COVID-19 Related Study Modifications. Front. Digit. Health 3:714813. doi: 10.3389/fdgth.2021.714813. (PMC8521795) **Key words:** ADRD; Behavioral intervention; RCT; Trial protocol; Cognitive health; Cognitive reserve, Social interaction; Technology-ICT; Social isolation and loneliness.

P46- COMPUTERIZED GAMES VERSUS CROSSWORDS TRAINING IN MILD COGNITIVE IMPAIRMENT. D. Devanand[1], T. Goldberg[1], M. Qian[1], M. Doraiswamy[2] *(1. Columbia University Medical Center - New York (United States), 2. Duke University - Durham (United States))*

Background: Mild cognitive impairment (MCI) increases the risk of progression to dementia. The efficacy of cognitive training in MCI is unclear. **Methods:** In a two-site, blinded, 78-week trial, patients with MCI, stratified by age, severity (early/late MCI) and site, were randomized to 12 weeks of intensive, home-based, computerized training with web-based cognitive games or crossword puzzles, followed by 6 booster sessions. In mixed model analyses, the primary outcome was change in Alzheimer's Disease Assessment Scale (ADAS-Cog). Secondary outcomes were neuropsychological composite, UCSD Performance-Based Skills Assessment (UPSA, functional outcome) and the Functional Activities Questionnaire (FAQ, functional outcome). Changes in MRI hippocampal volume and cortical thickness were assessed. **Results:** In 107 patients (51 games, 56 crosswords), mean (+/-SD) age was 71.2 years (8.8) and 42% were male. ADAS-Cog showed a small decline for games compared to improvement for crosswords at week 12 (LS means difference -1.35, 95% CI -2.71, 0.00) and week 78 (LS means difference -1.44, 95% CI -2.83, -0.06; p=0.04). From baseline to week 78, mean ADAS-Cog worsened for games (9.53 to 9.93) and improved for crosswords (9.59 to 8.61). Late MCI, but not early MCI, showed this difference. Change in UPSA and neuropsychological composite showed no group differences. FAQ showed greater worsening with games than crosswords at week 78. Adjusted for stratification variables, decreases in hippocampal volume and cortical thickness were

smaller for crosswords than games. **Conclusions:** Home-based computerized training with crosswords demonstrated superior efficacy to games on cognitive and functional measures with reduced brain atrophy over 78 weeks. **Trial Registration: ClinicalTrials.gov Identifier:** NCT03205709.

P47- PIMAVANSERIN AND CARDIOVASCULAR/ELECTROCARDIOGRAM SAFETY IN PATIENTS WITH ALZHEIMER'S DISEASE. P. Tariot[1], V. Abler[2], S. Pathak[2], B. Coate[2], M.E. Turner[2] *(1. Banner Alzheimer's Institute and University of Arizona College of Medicine - Phoenix, AZ (United States), 2. Acadia Pharmaceuticals Inc. - San Diego, CA (United States))*

Background: Cardiovascular adverse events (AEs) contribute to increased mortality associated with antipsychotic use in elderly patients with dementia-related psychosis and prolonged QT intervals in such patients increase risk of serious/fatal arrhythmias. Thus, cardiovascular safety is an important consideration when treating patients with neurodegenerative disorders, including Alzheimer's disease (AD). This is particularly relevant when considering that patients with AD are often older adults with multiple comorbid conditions. Pimavanserin is a selective 5-HT2A receptor inverse agonist/antagonist approved to treat hallucinations and delusions associated with Parkinson's disease psychosis and is being studied for AD psychosis. **Objectives:** To evaluate the cardiovascular safety of pimavanserin in a large population of patients with AD. **Methods:** Safety data were pooled from three studies (NCT02035553, NCT02992132, and NCT03575052) of patients with AD treated with ≥1 dose of pimavanserin (34 mg) or placebo once daily. Electrocardiograms were reviewed centrally, and electrocardiogram parameters from this evaluation were summarized with descriptive statistics as changes from baseline to last-postbaseline assessment and proportion of patients with potentially clinically important electrocardiogram changes. The QT interval was corrected using the Fridericia's formula (QTcF). **Results:** Among the 292 and 282 patients treated with pimavanserin and placebo, respectively, median ages were 76.0 and 78.0 years, 91.8% and 93.5% were white. The majority of the patients in both groups had vascular disorders (61.3% of pimavanserin and 63.1% of placebo) and 45.5% and 48.2%, had hypertension, respectively. Mean (SE) change in QTcF from baseline to last-postbaseline assessment was 6.2 ms (1.03) in the pimavanserin group and −1.1 ms (1.01) in the placebo group. Change from baseline to last post-baseline assessment in QTcF >500 ms and QTcF >60 ms was reported in 0.4% of the pimavanserin group and none of the patients in the placebo group. Overall, the number of patients with cardiovascular AEs were numerically higher for pimavanserin (6.2%) than placebo (4.3%). Electrocardiogram-associated treatment-emergent AEs reported in ≥1% were prolonged QT (1.4% pimavanserin, 1.4% placebo). Other cardiovascular AEs reported in ≥1% were peripheral edema (3.1% pimavanserin, 1.1% placebo). There were no reports of torsade de pointes or ventricular tachycardia. There was one fatal case of cardiopulmonary failure reported in the placebo group. **Conclusions:** Baseline characteristics demonstrated that many of these patients with AD were older and comorbidities were common, including vascular disorders and hypertension. These higher-risk characteristics underscore the importance of a thorough understanding of the safety of medications used in these patients. Data from this large group of patients with AD shows that pimavanserin prolonged the QTcF interval by an average of 6.2 ms and resulted in a change from baseline in elevated QTcF intervals (ie, >60 or >500 ms) in less than 0.5% of patients, each. Results were consistent with previous findings in AD and prescribing information for pimavanserin. **Disclosures:** This study was sponsored by Acadia Pharmaceuticals Inc. PT: received research support from and Novartis. Dr. Tariot has received consulting fees from Acadia Pharmaceuticals, AC Immune, Axsome, Bioexcel, Otsuka, Syneos Health, and T3D. Dr. Tariot has received consulting fees and research support from Abbvie, Biogen, Cortexyme, Eisai, Lilly, Lundbeck, Merck & Co., and Roche. Dr. Tariot also owns stock in Adamas Pharmaceuticals and is supported by the National Institute on Aging (RF1 AG041705, 1UF1AG046150, R01 AG031581, R01 AG055444, P30 AG19610), the Arizona Department of Health Services, Alzheimer's Association, Banner Alzheimer's Foundation, FBRI, GHR, Nomis Foundation, Flinn Foundation, and the Geoffrey Beene Foundation. VA, SP, BC, MET are employees of Acadia Pharmaceuticals Inc.

P48- THE EFFECTS OF THE NOVEL PHOSPHODIESTERASE 9 (PDE9) INHIBITOR E2027 (IRSENONTRINE) ON CSF CGMP, ADDITIONAL CSF AND PLASMA BIOMARKERS, AND CLINICAL OUTCOMES IN AMYLOID POSITIVE AND AMYLOID NEGATIVE PATIENTS WITH DEMENTIA WITH LEWY BODIES (DLB) AND PARKINSON'S DISEASE DEMENTIA (PDD). P. Sachdev[1], K. Pinner[2], T. Devins[1], L. Reyderman[1], D. Li[1], S. Dhadda[1], L. Kramer[1], A. Koyama[1], M. Irizarry[1], S. Hersch[1] *(1. Eisai Inc. - Nutley (United States), 2. Eisai Ltd. - Hattfield (United Kingdom))*

Background: Irsenontrine is a potent and selective PDE9 inhibitor that increases cellular cGMP and enhances glutamatergic synaptic function currently under investigation to improve cognition in Lewy Body Dementia (LBD; DLB and PDD). Data from Eisai's recent phase II study in DLB patients suggested that irsenontrine could be more effective for cognition in DLB patients without amyloid copathology. The suggestion of efficacy in the "pure" DLB subgroup, lacking AD co-pathology, led to the hypothesis that irsenontrine preferentially increases CSF cGMP in pure DLB relative to mixed AD/DLB due to relative preservation of synapses (the site of action of PDE9 inhibition) in patients lacking amyloid co-pathology. **Objectives:** The primary objective of the current study was to assess whether the presence or absence of amyloid co-pathology could differentially affect pharmacodynamic response based on CSF levels of cGMP in patients with either DLB or PDD treated with irsenontrine. Exploratory outcomes included other biomarkers and clinical scales. **Methods:** 83 subjects were screened to enroll 34 subjects meeting diagnostic and eligibility requirements for DLB or PDD who were assigned to four different subgroups - DLB amyloid positive (n=11), DLB amyloid negative (n=10), PDD amyloid positive (n=3), and PDD amyloid negative (n=10) using the plasma PrecivityAD™ Aβ42/40 ratio (cut-point of 0.092). All subjects were treated with 50 mg irsenontrine daily (QD) for 12 weeks. Lumbar puncture was performed at baseline and 9 weeks with change from baseline of CSF cGMP being the primary outcome. Clinical assessments included the electronic Montreal Cognitive Assessment (eMOCA), Wechsler Adult Intelligence Scale IV - Digit Symbol Coding subtest (WAIS-IV DSC), Clinicians Interview Based Impression of Change (CIBIC-Plus), Mini-mental State Examination (MMSE), Cognitive Function Inventory (CFI), Scale for the Assessment of Positive Symptoms (SAPS-PD), Functional Activities Questionnaire (FAQ), and Clinicians Global Impression of Change (CGI-C).

Biomarkers included ApoE4; plasma Aβ42/40, p-tau181, NfL, GFAP, and CSF Aβ42/40, p-tau181, total tau, neurogranin, and NfL at baseline and nine weeks. Exploratory analyses were also performed using CSF Aβ42/40 ratio (cut-point of 0.0571) to assign subgroups. The study was designed to identify a >50% increase in CSF cGMP in amyloid negative subjects compared to amyloid positive subjects, considered to be pharmacologically relevant. Analyses were not controlled for multiplicity or powered for the detection of statistically significant differences; the small number of PDD amyloid negative subjects limits interpretation of comparisons between the PDD groups. **Results:** Amyloid positive and negative DLB patients and amyloid negative PDD patients were readily enrolled, however amyloid positive PDD patients were uncommon and enrollment was closed before reaching the targeted numbers. The treatment was well tolerated with the majority of treatment-emergent adverse events being mild/moderate. There was a robust increase in CSF levels of cGMP for all groups averaging 239% of baseline, which was consistent across each diagnostic cohort. For amyloid status defined by plasma Aβ42/40, the comparison of percent change from baseline of the cGMP in the DLB amyloid negative (n=7) vs positive (n=10) groups showed Least Square Mean (LSM)s at Week 9 of 230% vs 250%, respectively (LSM diff. (95% CI) -20% (-78%, 38%)), for PDD amyloid negative (n=8) vs positive (n=3) 187% vs 363%, respectively (LSM diff. (95% CI) -176% (-287%, -64%)). The effects of treatment on the MoCA at Week 12, using plasma amyloid definitions, were inconsistent (change from baseline mean, SD) DLB- (-0.4, 2.7), DLB+ (-1.9, 4.0), PDD- (1.8, 3.3) and PDD+ (-4.7, 3.5). When amyloid status was defined by CSF Aβ42/40, subgroup assignment and CSF cGMP results were still consistent across diagnostic cohorts:, DLB amyloid negative (n=6) vs positive (n=11) groups showed LSMs at Week 9 of 274% vs 225%, respectively (LSM diff. (95% CI) 50% (-6%, 105%)), for PDD amyloid negative (n=10) vs positive (n=1) 212% vs 466%, respectively (LSM diff. (95% CI) -254% (--429%, -79%)). CNS biomarkers were unchanged over 9 weeks of treatment. **Conclusion:** Irsenontrine was safe and well-tolerated in LBD and achieved robust pharmacodynamic responses in all subgroups regardless of amyloid status. The results did not support a differential pharmacodynamic effect of irsenontrine with regards to presence or absence of amyloid copathology within DLB or PDD patients. **Acknowledgements:** We thank Robert Lai and June Kaplow for contributing to protocol and translational medicine strategy development and Takuya Yagi for serving as medical monitor.

P49- CLINICAL ACTIVITY OF THE P38A KINASE INHIBITOR NEFLAMAPIMOD ON VERBAL LIST LEARNING MAY BE TAU PATHOLOGY DEPENDENT IN DEMENTIA WITH LEWY BODIES (DLB).

J. Alam[1], J. Conway[1], H.M. Chu[2], K. Blackburn[1] *(1. EIP Pharma, Inc - Boston (United States), 2. Anoixis Corporation - Natick (United States))*

Background: Neflamapimod (NFMD) targets pathogenic mechanisms that underlie basal forebrain cholinergic (BFC) neurodegeneration (Pensalfini et al, 2020; Alam & Nixon, 2021), considered to be a major driver of dementia in DLB; and in preclinical studies neflamapimod rescues neurodegeneration in the basal forebrain (Jiang, 2019). The final results from an exploratory 91-patient, 16-week placebo-controlled phase 2a study ("AscenD-LB Study") in mild-to-moderate DLB were reported at last year's CTAD meeting. In that study, NFMD demonstrated clinically meaningful, statistically significant improvement, relative to placebo, on cognition (evaluated by Neuropsychological Test Battery designed to assess attention and executive function), motor function (evaluated by Timed Up and Go (TUG) Test, and on the Clinical Dementia Rating Scale Sum-of-Boxes (CDR-SB). The results were dose-dependent, with the most prominent effects being seen at 40mg TID (for the cognitive effect the results were only significant for NFMD 40mg TID vs placebo; while for TUG and CDR-SB both all NFMD, which included both 40mg BID and 40mg TID recipients, vs. placebo and the comparison of NFMD 40mg TID vs placebo were significant). Also presented at last year's meeting, were the results of AscenD-LB stratified by baseline plasma p-tau181 levels, a biomarker for the absence or presence of AD co-pathology (most specifically absence or presence of medial temporal lobe tau pathology by PET scan; van der Lee et al, 2021). Compared to the results in the overall population, the magnitude of the neflamapimod treatment effect relative to placebo for the individual clinical endpoints was 1.5 to 2.0-fold greater in the population without elevated plasma ptau181 (i.e., less than the prospectively defined cut-off of 2.2 pg/mL at baseline), with effect sizes ranging from 0.56 (NTB) to 0.74 (TUG, CDR-SB) for the comparison of 40mg TID vs. placebo. As the endpoints that were positively impacted may be connected in DLB to cholinergic function, the reported clinical results from the AscenD-LB study are consistent with the preclinical results, i.e., neflamapimod positively impacts the function of the basal forebrain cholinergic system. Herein we report on the effects of neflamapimod, stratified by baseline plasma ptau181 on the International Shopping List Test (ISLT), a verbal list learning test that is considered to be primarily a measure of hippocampal function (though modulated by cholinergic input). **Objectives:** To evaluate the effects of neflamapimod on the International Shopping List Test (ISLT), stratified by baseline plasma ptau181. **Methods & Patients:** Mild-to-moderate (MMSE 15-28) probable DLB by consensus criteria (McKeith et al, Neurology, 2017; 89:88–100), including a positive DaTscan™, and currently receiving cholinesterase inhibitor therapy. Treatment: 40 mg NFMD capsules or matching placebo capsules administered with food for 16 weeks; dosing regimen was based on weight: subjects weighing <80 kg received capsules twice-daily (BID) and those weighing ≥80 kg received capsules TID. Plasma ptau181 levels were determined by Simoa® pTau181 Assay (Quanterix) at the VU Medical Center, where the in-house defined cut-off for AD pathology was set at 2.2 pg/mL. To evaluate treatment effects, linear mixed effects model for repeated measures with baseline as a covariate was utilized. **Results:** At baseline, 22 of 41 (53%) of placebo and 22 of 42 (54%) of neflamapimod participants in the efficacy analysis population (baseline and on-treatment data on at least one efficacy endpoint) had ptau181 below the cut-off (2.2 pg/mL). Baseline CDR-SB at 5.6 (SD=2.8) in subjects with ptau181≥2.2 pg/mL was higher than in subjects below the cut-off [4.5(2.3), p=0.053 for the difference). Similarly, baseline ISLT Immediate recall [13.0(5.0) vs. 14.7(5.0)] and Delayed Recall [4.3(2.5) vs. 3.8(2.4)] were numerically lower in participants above the cut-off. As reported previously, in the overall population there were no differences between placebo and NFMD treated patients in the ISLT measures. However, in participants with baseline plasma ptau181<2.2 pg/mL (i.e., those without medial temporal lobe tau pathology by PET) at 40mg TID vs. placebo there was a positive trend for ISLT Immediate Recall [p=0.053, difference=+2.1 words (95% CI: -0.03, 4.17), Cohen's d effect size=0.28] and a significant positive difference for ISLT recognition [p=0.024, difference=+1.4 words, 95%CI=0.2, 2.5, d=1.0)}. No differences were seen for ISLT delayed recall,

nor on any of the ISLT measures in participants with plasma ptau181≥2.2. **Conclusion:** Neflamapimod may improve verbal learning, as assessed by the ISLT, particularly with respect to recognition. This potential effect is consistent with an effect of neflamapimod on the cholinergic system and a conceptual model in which a treatment that acts on the cholinergic input to the hippocampus is able to improve verbal learning, but only in the context of an intact hippocampus, and is not able to do so in the presence of significant neurodegeneration in the hippocampus. Longer duration studies would be required to assess the impact of such a therapy on the progression of hippocampal neurodegeneration. **Conflict of Interest:** JJA, JC and KB are employees of EIP Pharma Inc, the sponsor of the AscenD-LB clinical trial.

LP26- FINAL 4 YEARS RESULTS OF THE CLINICAL TRIAL ASCOMALVA. A. Carotenuto[1], A. Fasanaro[1], E. Traini[1], F. Amenta[1] *(1. University of Camerino - Camerino (Italy))*

Background: Cholinesterase inhibitors (ChE-Is) are used for symptomatic treatment of mild-to-moderate Alzheimer's disease (AD), but long-term effects of these compounds are mild and not always obvious. Preclinical studies have shown that combination of ChE-Is and the cholinergic precursor choline alphoscerate is more effective than single compounds alone in rising brain acetylcholine levels. **Objective:** The study Effect of association between a ChE-I and choline alphoscerate on cognitive deficits in AD associated with cerebrovascular injury (ASCOMALVA) is a double-blind trial that has investigated the efficacy of the combined treatment donepezil + choline alphoscerate versus donepezil alone. **Methods:** This 4 years trial has recruited 210 AD patients with associated ischemic brain damage documented by neuroimaging. Patients were randomly assigned to an active treatment group [donepezil (10 mg/day) + choline alphoscerate (1,200 mg/day), D+CA] or to a reference group [donepezil (10 mg/day) + placebo, D+P]. The 48.6 % of patients recruited have completed 4 years of observation. Cognitive functions were assessed by the Mini-Mental State Evaluation and Alzheimer's Disease Assessment Scale Cognitive subscale. Daily activity was evaluated by the basic and instrumental activities of daily living tests. Behavioral symptoms were assessed by the Neuropsychiatric Inventory. Among patients who underwent annual Magnetic Resonance Imaging (MRI), 56 patients were selected (27 treated with D+P; 29 treated with D+CA). The selection was made to allow the comparability of the data, electing resonances obtained with similar and new generation equipment. Data from magnetic resonance were used for the voxel morphometric cerebral volume analysis. **Results:** After 4 years of observation, patients of the reference group (D+P) showed a time-dependent worsening in all parameters investigated. Treatment with D+CA significantly slowed changes of the different items analyzed. The volume analysis of hippocampus and amygdala grey matter has shown a progressive reduction in the volume of these two areas noticeable along the course of the study. These reductions were more pronounced in the D+P group than in the D+CA group. The reduction of the volumes of grey and white matter was compensated by a significant increase in cerebrospinal fluid volume. **Conclusions:** These findings suggest that the combination of choline alphoscerate and donepezil counters to some extent the loss in volume occurring in some brain areas of AD patients. Cognitive, functional and behavioral parameters tested suggests that morphological changes observed may have clinical relevance and that the combination of the cholinergic precursor choline alphoscerate with a ChE-I may prolong/increase the effectiveness of cholinergic therapies in AD associated with cerebrovascular injury. **Key words:** Alzheimer's disease, cerebrovascular injury, choline alphoscerate, donepezil, association

LP27- AGE-DEPENDENT EFFECTS OF THE P75 MODULATOR LM11A-31 ON ALZHEIMER'S DISEASE BIOMARKERS IN A 26-WEEK SAFETY AND EXPLORATORY ENDPOINT TRIAL. H. Shanks[1], S. Massa[2,3], M. Windisch[4], A. Borjesson-Hanson[5], F. Longo[6], T. Schmitz[1] *(1. Western University - London (Canada), 2. University of California San Francisco - San Francisco (United States), 3. SFVAHCS - San Francisco (United States), 4. Neuroscios - Graz (Austria), 5. Karolinska University Hospital - Stockholm (Sweden), 6. PharmatrophiX - Menlo Park (United States))*

Background: The p75 neurotrophin receptor (p75NTR) modulates degenerative signaling networks active in Alzheimer's disease and mitigates amyloid- and pathological tau-induced synaptic degeneration in preclinical models. LM11A-31 is a first-in-class, small molecule modulator of p75NTR that downregulates degenerative signaling. Because p75NTR is highly expressed on neuronal populations vulnerable to both 'pure' AD pathology and other heterogeneous age-related risk factors, we hypothesized that the potential disease-modifying effects of LM11A-31 on a cohort of AD patients would be additionally moderated by their age. Indeed, we noted that age range of our cohort at baseline spanned multiple decades (50-84 years). We therefore examined the potential age effects of LM11A-31 on our predefined endpoint biomarkers of disease progression. **Methods:** A safety and exploratory endpoint phase 2a trial was conducted by PharmatrophiX in five countries in Europe with each site led by a site principal investigator. The study included three arms: placebo, 200mg bid and 400mg bid LM11A-31 administered by oral capsules for a duration of 26-weeks. Enrollment criteria included a diagnosis of mild to moderate AD according to McKhann (2011) criteria and assessment of CSF amyloid-beta. Given the short treatment interval of this trial (26-weeks) and thus limited degree of progression of cognitive decline, we prioritized age-effect analysis of potential disease-modifying effects of drug on biomarkers of pathological progression. Biomarkers included CSF assays of amyloid, tau and synaptic degeneration; and structural magnetic resonance imaging (sMRI) assays of gray matter volume which serve as a surrogate marker for neuronal/synaptic integrity. For the study population, age groups were defined using a median-split: younger (<72 years) and older (>=72 years). **Results:** Significant attenuating effects of drug on multiple longitudinal biomarkers of disease progression were detected. Age moderated many of the drug's attenuating effects. Results outlining age-group specific effects of LM11A-31 on longitudinal CSF and sMRI biomarkers will be presented. **Conclusions:** This investigation points to the possibility that certain biomarkers can demonstrate age-dependency in response to therapeutic interventions in the context of mild-moderate AD. Because increasing age tends to increase the heterogeneity of brain pathophysiology, the disease modifying effects of LM11A-31 on biomarkers of neuronal and synaptic degeneration may be impacted by the age of the patient sample, in line with prior theoretical modeling work (Bernick et al., 2012). Our results thus inform biomarker selection and age stratification of future studies of LM11A-31 in human AD. **Acknowledgments:** We thank the participating subjects and families as well as the site teams. Funding: NIA Pilot AD Trial Program. **Conflict of Interest:** FL has equity

interest, is a board member and has a consulting relationship with PharmatrophiX. FL and SM are listed as inventors of LM11A-31 and hence entitled to royalties and related payments. **References:** Yang et al. Small molecule modulation of the p75 receptor inhibits multiple amyloid beta-induced tau pathologies. Sci Reports 2020a; Yang et al. Small-molecule modulation of the p75 receptor inhibits a wide range of tau molecular pathologies and their sequelae in P301S tauopathy mice. Acta Neuropath Comm 2020b.

LP28- CLINICAL PHASE IB DATA OF THE ORALLY AVAILABLE ANTI-PRIONIC COMPOUND RD2 THAT DISASSEMBLES AB OLIGOMERS INTO AB MONOMERS.

D. Willbold[1,2,3], N.C. Cosma[4], J. Kutzsche[1], O. Peters[4] *(1. Institute of Biological Information Processing (IBI-7), Forschungszentrum Jülich - Jülich (Germany), 2. Institut für Physikalische Biologie, Heinrich-Heine-Universität Düsseldorf - Düsseldorf (Germany), 3. Priavoid GmbH - Düsseldorf (Germany), 4. Department of Psychiatry and Psychotherapy, CampusBenjamin Franklin, Charité Berlin - Berlin (Germany))*

Background: We have developed the anti-prionic mode of action to disassemble toxic protein assemblies, like oligomers and amyloids, into functional monomeric building blocks. This mode of action is realized by all-D-enantiomeric peptide ligands that stabilize the respective monomers in their native conformations, mostly intrinsically disordered proteins (IDP). This is a purely thermodynamic mode of action, which does not require inhibition of enzymes or ion channels, and is therefore not prone to show side effects. RD2 is an all-D-enantiomeric peptide developed to stabilize Aβ monomers in their IDP conformation. RD2 has been demonstrated to disassemble Aβ oligomers into Aβ monomers in vitro, in vivo and ex vivo, only recently. There, RD2 disassembled Aβ oligomers from brain tissue of former AD patients into Aβ monomers by ex vivo treatment. RD2 has been previously shown to reverse cognition deficits and decelerate neurodegeneration in four different transgenic and non-transgenic animal models. RD2 has also demonstrated safety and tolerability in healthy young volunteers. **Objectives:** To investigate safety and tolerability in the target age group, we carried out a randomized, placebo-controlled, double-blind, Phase 1b study to evaluate the safety, tolerability and pharmacodynamics of RD2 in patients suffering from MCI due to AD and mild AD. **Methods:** 20 AD patients in early disease stages fulfilling all three ATN-criteria were recruited to participate in a single center, randomized, placebo –controlled, double-blind study. Patients received once daily oral doses of 300 mg RD2 or placebo for 28 days. Safety and efficacy assessments were executed at baseline, day 28 and day 56 (follow up). Blood sampling was carried out at each time point, EEG and CSF measurements before and at the end of treatment (day 1 and day 28). Imaging (MRI) and functional tests (CERAD, CDR) were performed in parallel to EEG/CSF and additionally at follow up. **Results:** 10 patients (age 76.9±3.4, MMSE 28±1.6) received placebo and 9 patients RD2 (72.4±6.9, 27.2±2.9). One patient withdraw informed consent before treatment was started. 13 patients reported in total 27 adverse events while no serious adverse event was noted. There was no statistical difference regarding adverse events between treatment and placebo. In contrast to reported anti-Aβ-antibody-treatments, no ARIA events have been observed. EEG and MRI revealed no changes after treatment. While no significant changes were detected in p-TAU, Aβ1-42 and Aβ oligomers in CSF before and after treatment, patients receiving RD2 significantly performed better than those receiving placebo in the CERAD word list at follow up ($p \leq 0.05$). Each single dosed patient increased his/her word list score, whereas the patients of the placebo group behaved heterogeneously and did not change significantly as a group. Oral uptake of RD2 was inter-individually very heterogeneous. This allowed pseudo-dose-response correlation analysis. Although changes in Aβ oligomer concentrations in CSF between day 28 and day 1 were not significant between the groups or between time points, there was a significant inverse correlation between changes in Aβ oligomers in CSF (between day 28 and day 1) and the blood plasma concentrations of RD2 in the dosed patients. **Conclusions:** RD2 showed an excellent safety profile in MCI and mild AD patients. While no significant biomarker changes were detected after 4 weeks of treatment interestingly, a significant improvement of memory function was noted at follow up. To be very conservative and cautious, due to the low number of patients, we do not claim this as a target engagement, nor do we claim the results of the CERAD word list result as a proof of concept. Anyway, despite the small number of patients, we feel that this phase Ib study results deserve reporting to the scientific community. A phase 2 study is scheduled.

LP29- LATE-LIFE DEPRESSION, SUBJECTIVE COGNITIVE DECLINE, AND THEIR ADDITIVE RISK IN INCIDENCE OF DEMENTIA: A NATIONWIDE LONGITUDINAL STUDY.

S.Y. Park[1], W.M. Bahk[2], S.M. Wang[2], H.K. Lim[2], Y.J. Kwon[3], B.H. Yoon[4], K.H. Lee[5], S.Y. Lee[6], M.D. Kim[7], B.W. Nam[8], E.S. Lim[9] *(1. Keyo hospital - Uiwang-Si (Korea, Republic of), 2. Yeouido St. Mary's Hospital - Seoul (Korea, Republic of), 3. Soonchunhyang University Cheonan Hospital - Cheonan (Korea, Republic of), 4. Naju National Hospital - Naju (Korea, Republic of), 5. College of Medicine, Dongguk University - Gyeongju (Korea, Republic of), 6. Wonkwang University Hospital - Iksan (Korea, Republic of), 7. Jeju National University School of Medicine - Jeju (Korea, Republic of), 8. Dr. Nam's Psychiatric Clinic - Chungju (Korea, Republic of), 9. Shinsegae Hyo Hospital - Kimje (Korea, Republic of))*

Background: Late-life depression, subjective cognitive decline, and their additive risk in incidence of dementia: A nationwide longitudinal study. **Objective:** Late-life depression and subjective cognitive decline (SCD) are significant risk factors for dementia. However, studies with a large sample size are needed to clarify their independent and combined risks for subsequent dementia. **Methods:** This nationwide population-based cohort study included all individuals aged 66 years who participated in the National Screening Program between 2009 and 2013 (N = 939,099). Subjects were followed from the day they underwent screening to the diagnosis of dementia, death, or the last follow-up day (December 31, 2017). **Results:** Depressive symptom presentation, recent depressive disorder, and SCD independently increased dementia incidence with adjusted hazard ratio (aHR) of 1.286 (95% CI:1.255–1.318), 1.697 (95% CI:1.621–1.776), and 1.748 (95% CI: 689–1.808) respectively. Subjects having both SCD and depression had a higher risk (aHR = 2.466, 95% CI:2.383–2.551) of dementia than having depression (aHR = 1.402, 95% CI:1.364–1.441) or SCD (aHR =1.748, 95% CI:1.689–1.808) alone. **Conclusions:** Depressive symptoms, depressive disorder, and SCD are independent risk factors for dementia. Co-occurring depression and SCD have an additive effect on the risk of dementia; thus, early intervention and close follow up are necessary for patients with co-occurring SCD and depression.

LP31- EFFICACY AND SAFETY OF BENFOTIAMINE PLUS DONEPEZIL FOR THE TREATMENT OF PATIENTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE IN A PHASE 2 CLINICAL TRIAL. X. Pan[1], Q. Zhao[2], S. Sang[1], C. Zhong[1] *(1. Zhongshan Hospital, Fudan University - Shanghai (China), 2. Huashan Hospital, Fudan University - Shanghai (China))*

Background: Pyruvate dehydrogenase (PDH), α-ketoglutarate dehydrogenase (KGDH), and transketolase are three important enzymes involved in intracellular glucose metabolism. The reduction in the activities of these enzymes has been well demonstrated in patients with Alzheimer's disease (AD) (1, 2). Thiamine diphosphate (TDP) is the common coenzyme of these enzymes. Our previous studies have demonstrated that TDP reduction is AD-specific (3) and contributes to cerebral glucose hypometabolism of the disease (4). Benfotiamine, a thiamine derivative able to elevate in vivo TDP level (5-7), has showed the beneficial effect on delaying cognitive decline of patients with mild cognitive impairment and dementia due to AD defined by positive amyloid PET scan and the Mini Mental Status Examination (MMSE) scores > 21 in a phase IIa trial (8). The results suggest that benfotiamine is an effective drug candidate and TDP reduction is a potential target for AD treatment. **Objective:** To assess the efficacy and safety of benfotiamine treating mild-to-moderate AD delimited by the MMSE scores of 11 to 24 (inclusive). **Methods:** A randomized, double-blind, placebo-controlled, multicenter trial was conducted in China from Mar 10, 2018 to Apr 28, 2020. Individuals aged between 50 to 80 years (inclusive) who took donepezil (5 mg daily) over six months (inclusive) were screened, enrolled, and randomly assigned (1:1:1 allocation) to high-dose benfotiamine(600 mg daily), low-dose benfotiamine (300 mg daily) or placebo groups. All participants continued to take donepezil (Eisai, Suzhou, China) after the enrollment. The blinded study and treatment period was 52 weeks. The cognitive abilities were measured at weeks 0 (baseline), 12, 24, 36, and 52. The safety evaluation, including adverse events and vital signs, were performed every 4 weeks. The primary endpoint outcome was the change of Assessment Scale-Cognitive Subscale 11(ADAS-cog) score at week 52 from baseline. The secondary endpoint outcomes included the changes of MMSE, Alzheimer's Disease Cooperative Study-activities of daily living (ADCS-ADL), Neuropsychiatric Inventory–Nursing Home version (NPI–NH), NPI caregiver distress scale (NPI-D), and Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) scores at week 52 from baseline. The missing data of the ADAS-cog, MMSE, and ADCS-ADL scores were imputed using the last observation carried forward (LOCF). The other indicators, NPI-NH, NPI-D, and CIBIC-plus scores, were analyzed using the data without imputation. The ADAS-cog scores at baseline were adjusted using mixed methods for repeated measures (MMRM) model and the gate-keeping strategy was utilized for inter-group comparison. The differences between high-dose and placebo groups were first compared. If p value is less than 0.05 (inclusive) between high-dose benfotiamine and placebo groups ($\alpha = 0.05$), then the differences between benfotiamine treatment group (combining high-dose with low-dose groups) and placebo group were compared. If that p value is also less than 0.05 (inclusive), the differences between low-dose and placebo groups were compared ($\alpha = 0.05$). **Results:** Three hundred two subjects were enrolled and divided into high-dose benfotiasmine (99), low-dose benfotiamine (104), and placebo (99) groups. In the overall population, the mean changes of ADAS-cog scores at week 52 from baseline did not reach significant difference between high-dose benfotiamine or benfotiamine treatment and placebo groups. This result drove us to perform a further ad-hoc analysis to examine the changes of ADAS-cog scores at week 52 from baseline in the placebo group based on the severity of the disease assayed by MMSE scoring at baseline. The results showed that the changes of ADAS-cog scores were not significant in patients with the MMSE scores of 20 to 24 but exhibited obvious increases in patients with the MMSE scores of 11 to 19 in placebo group. Therefore, we divided the participants into two subgroups: mild subgroup delimited by the MMSE scores of 20 to 24 and moderate subgroup with the MMSE scores of 11 to 19 at baseline. Post hoc analyses indicated that the increases of ADAS-cog scores at week 52 from baseline were the least in high-dose subgroup of moderate cases (-3.07, $p = 0.027$) and the second least in low-dose subgroup (-1.49, $p > 0.05$) as compared with that in placebo subgroup in the full analysis set. The significant differences in ADAS-cog scores of patients with moderate AD between high-dose benfotiamine and placebo groups were further verified using the imputation methods of the copy-reference multiple-imputation and the worst observation carried forward (the worst values from individual self during the treatment). Changes in all secondary outcomes at week 52 from baseline did not exhibit statistical differences. The incidences of adverse events had no significant differences among three groups. **Conclusions:** Benfotiamine is effective in delaying cognitive decline of AD patients with excellent safety, preliminarily demonstrating the concept of TDP reduction as a therapeutic target for AD. Further large-sample clinical trials should be performed. Donepezil treatment seriously interferes with the efficacy observation of new drugs in the treatment of mild AD, which should be paid attention to in the future studies. **Disclosure:** Chunjiu Zhong holds shares of Shanghai Rixin Bitech Co., Ltd., which is dedicated to developing drugs for the prevention and treatment of AD. The other authors declare that they have no competing interests. **References:** 1. Gibson GE, Sheu KF, Blass JP, et al. Reduced activities of thiamine-dependent enzymes in the brains and peripheral tissues of patients with Alzheimer's disease. Arch Neurol 1988; 45(8):836-840. 2. Butterworth RF, Besnard AM. Thiamine-dependent enzyme changes in temporal cortex of patients with Alzheimer's disease. Metab Brain Dis 1990; 5(4):179-184. 3. Pan X, Fei G, Lu J, et al. Measurement of blood thiamine metabolites for Alzheimer's disease diagnosis. EBioMedicine 2016; 3:155-162. 4. Sang S, Pan X, Chen Z, et al. 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LP32- VIVIAD, A PHASE 2B STUDY INVESTIGATING VAROGLUTAMSTAT IN PATIENTS WITH MCI AND MILD AD: UPDATE ON DOSE SELECTION AND INTERIM BLINDED SAFETY RESULTS. F. Weber[1], M. Schaeffer[2] *(1. CMO Vivoryon Therapeutics N.V. - München (Germany), 2. CBO Vivoryon Therapeutics N.V. - München (Germany))*

Background: Varoglutamstat (PQ912), a small molecule glutaminyl cyclase (QPCT) inhibitor, reduces the brain levels of pyroglutamate-3-Abeta (N3pE-Abeta), a toxic Abeta variant shown to play a pivotal role in the development and progression of Alzheimer's disease (AD). A prior Phase 2a study (NCT02389413) reported encouraging first evidence of the disease-modifying activity of varoglutamstat, most importantly with statistically significant change from baseline in working memory after only 12 weeks of treatment. Thus, showing a positive effect on a hallmark feature of AD. While varoglutamstat was generally well tolerated, a maximum tolerated dose (MTD) was reached at 800 mg twice daily (BID). These results led to the initiation of a state-of-the-art Phase 2b trial investigating multiple cognitive, safety and biomarker endpoints. Safety data reported to date show no on-target toxicity and no clinical signs of amyloid-related imaging abnormalities (ARIA), a severe side effect reported for antibody-based AD therapies. **Objectives:** To evaluate the safety and efficacy of Varoglutamstat in patients with early AD and mild cognitive impairment (MCI). To convey and update on the status of the Phase 2b study. **Methods:** VIVIAD (NCT04498650) is a multicenter randomized, placebo-controlled, double-blind, parallel group dose finding Phase 2b study in patients with early Alzheimer's disease (MCI due to AD and mild AD). The treatment duration varies between 48 and 96 weeks depending on the time of inclusion. Efficacy is assessed by the Cogstate NTB and the Amsterdam Quality of Life Questionnaire. Secondary endpoints include functional read-outs by EEG and assessment of functional and inflammatory biomarkers. In June 2022, an independent Data Safety Monitoring Board (DSMB) decided that the highest dose tested, 600 mg BID, a dose known to result in a target occupancy of close to 90%, was well tolerated and safe to be carried forward for the second part of the study. Patients previously randomized to 300 mg BID have been blindly up-titrated to 600 mg BID. All data remain blinded outside the DSMB. **Interim Results:** As of September 6, 2022, the study has enrolled 224 patients with a planned total of 250 participants. Per September 6th, 376 patients were screen failures. Of the 224 patients randomized, 114 were female and 110 male, with a mean age of 68 years. As recommended by the DSMB, all patients are dosed with either 600 mg BID varoglutamstat or placebo. As of September 6, 175 patients had reached week 12, 66 patients had reached week 48 and 17 patients had reached week 84 of treatment. The occurrence of adverse events normalized per 100 visits continues to be stable around 31, indicating that up-titration from 300 to 600 mg twice daily did not result in an increased frequency of adverse events. Overall, 4 treatment emergent adverse events have led to discontinuation. Further updates on the safety data and the baseline characteristics of the patients enrolled into the trial so far will be reported at CTAD 2022. **Conclusion:** The state-of-the-art Phase 2b study VIVIAD aims to yield important results in early AD for Varoglutamstat, the first small molecule and only project in clinical development selectively targeting the de novoproduction of neurotoxic N3pE-Abeta. Through a carefully crafted study design, the study was able to achieve improved tolerability for Varoglutamstat compared to a prior Phase 2a study (NCT02389413), without significantly sacrificing target engagement. The study continues as planned, with participants receiving 600 mg active treatment BID or placebo for at least 48 weeks.

LP33- QUANTITATIVE EEG RESULTS FROM A MULTIPLE ASCENDING DOSE STUDY IN HEALTHY VOLUNTEERS WITH NEURORESTORE ACD856, A POSITIVE MODULATOR OF NEUROTROPHIN TRK-RECEPTORS. K. Önnestam[1], B. Nilsson[1], M. Rother[1], E. Rein-Hedin[2], P. Anderer[3], M. Kemethofer[3], M. Halldin[1], P. Forsell[1], G. Nordvall[1], J. Sandin[1], M. Segerdahl[1] *(1. AlzeCure Pharma AB - Huddinge (Sweden), 2. CTC Clinical Trial Consultants AB - Uppsala (Sweden), 3. The Siesta Group Schlafanalyse GmbH - Vienna (Austria))*

Background: Quantitative EEG results from a multiple ascending dose study in healthy volunteers with NeuroRestoreÒ ACD856 is a novel positive allosteric modulator of Trk-receptors in clinical development for the treatment of Alzheimer's disease (AD) and other disorders where cognition is impaired. Neurotrophin signalling pathways, such as those mediated by NGF (nerve growth factor) and BDNF (brain derived neurotrophic factor), have in numerous studies been shown to be important for neuronal cell function, communication, and cell survival in brain areas vital for cognitive function, such as the hippocampus and basal forebrain. BDNF and NGF mediate their effects by binding to their Trk- receptors; TrkA or TrkB, respectively. A large body of pathological and mechanistic evidence suggests that loss of NGF signaling contributes significantly to the dysfunction of basal forebrain cholinergic neurons during the course of AD. Several studies have also shown a decrease of BDNF in the hippocampus and in cerebrospinal fluid (CSF) in disease states with cognitive decline, including AD. This suggests that decreased BDNF signalling may contribute to the progression of hippocampal dysfunction. Increased NGF and BDNF signalling could potentially enhance cholinergic function, synaptic plasticity and improve cognition. This supports the development of stimulators of NGF and BDNF signalling, such as ACD856, as cognitive enhancers for the treatment of Alzheimer's disease. **Objectives:** The aim of the multiple ascending dose (MAD) study was to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of multiple ascending doses of ACD856. As part of this study, quantitative electroencephalography (qEEG) was included to allow for an exploratory analysis of pharmacodynamic effects of ACD856 on CNS activity and target engagement. **Methods:** ACD856 was administered once daily over a treatment period of 7 days in 3 ascending dose cohorts. Subjects in each cohort were randomised to receive either ACD856 (n=6) or placebo (n=2). qEEG was recorded for the two last study cohorts. This resulted in 6 subjects treated with 30 mg ACD856, 6 subjects with 90 mg ACD856, and 4 placebo subjects. EEG recordings were performed at baseline, 1.5, 6 and 24 hours following the first dose, and at 1.5 hours following the last dose of ACD856. **Results:** The qEEG results show that treatment with ACD856 significantly increases the relative theta power and decreases fast alpha and beta power which leads to an acceleration of the delta+theta centroid and an increase in the theta/beta ratio (TBR). These effects are seen both in comparison to placebo (TBR: $p<0.05$) and when analysing intraindividual treatment induced EEG changes (TBR: $p<0.01$). These effects are most evident in the vigilance-controlled EEG recordings with eyes closed as opposed to resting EEG recordings with eyes closed or open and are

most pronounced at 24 hours post 1st dose and 1.5 hours after dose on day 7. **Conclusion:** NeuroRestore ACD856 has a pharmacodynamic effect on EEG activity in healthy volunteers suggestive of target engagement. The qEEG results are in line with previously reported exposure of ACD856 in the cerebrospinal fluid, with relevant concentrations reaching CNS. The new data shows that ACD856 not only passes the blood brain barrier but also has an effect on neuronal pathways in the CNS. In the next step, ACD856 will be evaluated in a patient population to better understand the clinical relevance of these results.

LP34- A RANDOMIZED DOUBLE-BLIND STUDY TO ASSESS THE SKIN IRRITATION AND SENSITIZATION POTENTIAL OF ONCE-WEEKLY DONEPEZIL TRANSDERMAL DELIVERY SYSTEM. M. Sabbagh[1], P. Mathew[2], A. Blau[3] *(1. Barrow Neurological Institute - Phoenix (United States), 2. Novum Pharmaceutical Research Services - Toronto (Canada), 3. Corium Inc - Grand Rapids (United States))*

Background: Oral donepezil, a reversible acetylcholinesterase inhibitor, is the most used treatment for dementia of the Alzheimer's type. Once-weekly donepezil TDS (Adlarity®) was approved in 2022 by the US Food and Drug Administration for the treatment of mild, moderate, and severe dementia of the Alzheimer's type. Previous study results showed that 10-mg/d and dose-normalized 5-mg/d donepezil TDSs are bioequivalent to 10 mg/d of oral donepezil, with an acceptable skin adhesion and safety profile (Tariot PN, et al. J Alzheimers Dis. 2022;9:doi:10.3233/JAD-220530). **Objective:** This study's aim was to assess the skin irritation and sensitization potential of once-weekly 5-mg/d donepezil TDS. **Methods:** In this placebo (vehicle) TDS-controlled, randomized, double-blind phase 1 trial (NCT03397862), healthy volunteers aged ≥40 years with Fitzpatrick skin type of I, II, or III and without a history of severe allergies to medical adhesive tapes and dressings were evaluated for the primary end points of skin irritation and sensitization potential. There was a 30-day screening phase before TDS application. During a 21-day induction phase, participants received weekly both the 5-mg/d donepezil TDS and a placebo TDS, without donepezil, to opposite sides of their back. Participants were randomized to receive applications of donepezil TDS on one side of the back and placebo TDS on the opposite side, or vice-versa, with 3 consecutive weekly TDS applications to the same skin site. After completion of the induction phase, participants entered a ~14-day rest period, followed by a challenge phase for skin sensitization assessments. During this challenge phase, donepezil TDS and placebo TDS were applied to naïve skin sites on opposite sides of the back in a randomized manner for 48 hours followed by a 3-day observation period. After a 4–8-week rest phase some participants also underwent a 48-hour rechallenge phase if the participant was designated as potentially sensitized to one or both TDSs. The combined skin irritation score was based on the sum of the dermal response scale score (range, 0 [no evidence of irritation] to 7 [strong reaction spreading beyond application site]) and other effects scale score (range, 0 [none observed or slight glazed appearance] to 3 [glazing with fissures, dried serous exudate film covering all or part of the patch site, or small petechial erosions and/or scabs]). Skin irritation scoring was performed 30 minutes after TDS removal on days 8, 15, and 22 in the induction phase. **Results:** Among the 256 participants who were randomized and received ≥1 dose of any treatment, the mean (SD) age was 54.3 years (9.4 years); 48% were aged 50-64 years, 16% were aged ≥65 years, and 59.4% were women. After the first weekly TDS application (day 8) in the induction phase, the incidence of combined irritation scores of 0 (no evidence of skin irritation) and 1 (minimal irritation) were similar between donepezil (189/195 TDSs [96.9%]) and placebo (186/194 TDSs [95.9%]). Two donepezil TDSs (1%) had a score of 4 (definite edema), and there were no scores ≥5 (erythema, edema, and papules). There were no scores >2 for the placebo TDSs. At the third weekly TDS application (day 22) in the induction phase, irritation scores were higher for donepezil TDS versus the placebo TDS. For donepezil (n = 195 TDSs), 76 TDSs (39.0%) had a skin irritation score of 0 and 72 TDSs (36.9%) had a score of 1; 39 TDSs (20.0%) had a score of 2, 3 TDSs (1.5%) had a score of 3, and 2 TDSs (1.0%) had a score of 4. For placebo (n = 193 TDSs), most scores were 0 (164 TDSs [85.0%]) and 1 (25 TDS [13.0%]); 4 TDSs (2.1%) had a score of 2, and there were no placebo TDSs with scores ≥3. The average of the mean combined irritation score was 0.55 out of a possible maximum 7, indicating none to minimal skin irritation for donepezil TDS, and 0.19, indicating no skin irritation for placebo TDS (treatment difference, −34 [95% CI, −0.43 to −0.25]). TDS skin irritation scores during the induction phase appeared to be independent of age, ethnicity, or sex, although there was a slight numerical trend of better skin tolerability in the ≥65-year-old versus the <65-year-old age group. In total, 4 of 198 participants (2.0%) were considered potentially sensitized to donepezil TDS treatment, and no participants were potentially sensitized to placebo TDS. **Conclusion:** Once-weekly 5-mg donepezil TDS demonstrated acceptable skin tolerability, with minimal skin irritation under conditions of use of 3 consecutive weekly patch applications to the same skin site and minimal sensitization potential, supporting its use as treatment for dementia of the Alzheimer's type.

LP36- ABVAC40 ELICITS A PREDOMINANTLY TH2 IMMUNE RESPONSE THAT SUPPORTS ITS EXCELLENT SAFETY PROFILE. M. Montañés[1], C. Martín-Fortún[1], S. Castillo[1], E. Molina[1], J. Terencio[1], M. Sarasa[1] *(1. Araclon Biotech-Grifols - Zaragoza (Spain))*

Background: The balance between Th1 (cell-mediated) and Th2 (humoral) immune pathways is a key factor in determining the safety of a vaccine. AN1792, the first Alzheimer´s disease (AD) vaccine entered clinical trials, was terminated due to meningoencephalitis attributed to a cell-mediated immflamatory response (1, 2). Subsequent to the experience gained from AN1792 vaccine, immunotherapies for AD that predominantly activate Th2 cells would be strongly recommended. ABvac40, was designed as the first active immunotherapy against the C-terminal end of amyloid β 1-40 (Aβ40) in order to avoid antibody binding to the unprocessed amyloid precursor protein (APP) inserted in the cell membrane. This vaccine has shown a great safety and tolerability profile in a phase I clinical trial as well as in the preliminary data from a currently ongoing phase II clinical trial. Confirmation of a Th2 biased immune response would suggest that ABvac40 does not induce a proinflammatory response, in agreement with the safety results reported. **Objective:** The aim of this study is to determine whether the drug substance, i.e., the hapten Aβ33–40 coupled to the carrier protein, induces a Th1 or Th2 polarized immune response in patients from phase II clinical trial AB1601, since aluminum hydroxide used as an adjuvant in ABvac40 is known to have a Th2-polarizing activity. **Methods:** Peripheral blood mononuclear cells (PBMCs) obtained from verum (n=37) and placebo (n=12) treated patients recruited to ABvac40

phase II study were stimulated in vitro by the drug substance of the vaccine. The frequency of IFN-γ or IL-4-secreting T cells as prototypic Th1 and Th2 cytokines, respectively, were determined, at both the preimmune visit and after-five vaccine inoculations employing a commercially available IFN-γ/IL-4 dual FluoroSpot kit. Number of spot forming units (SFUs) in negative controls (non-stimulated PBMCs) were subtracted from stimulated samples to account for background responses. All differences in SFUs between groups were examined using Mann Whitney test, except for preimmune versus after-five inoculations time points that were analyzed using Wilcoxon´s test. **Results:** A significantly higher frequency of IL-4 SFUs was found in ABvac40 treated samples compared to IFN-γ ($p < 0.0001$) while no placebo response was observed with any cytokine. To be noted that, among patients samples receiving ABvac40, 35 out of 37 developed a polarized Th2 response. The frequency of IFN-γ and IL-4 secreting cells increased significantly after five immunizations ($p < 0.0001$ in both cases) compared to the basal time point in the verum group. In the placebo samples, no significant changes were found in any case. As expected, since the patients at the preimmune timepoint were not in contact with the vaccine, no significant changes between the stimulated and non-stimulated samples in the preimmune group were detected. **Observed:** SFUs were specific to the cells stimulated by the ABvac40 drug substance, since in the verum group a significant increase of both cytokines was observed in response to ABvac40 stimulation ($p<0.0001$). **Conclusion:** ABvac40 drug substance induces a Th2 polarized T-helper immune response that promotes a humoral response and minimizes a proinflammatory effect, which is consistent with the excellent safety profile shown by ABvac40 in phase I and phase II studies. **References:** Pride M et al., Neurodegener Dis. 2008; 5(3-4):194-6. Mantile F and Prisco A. Biology (Basel). 2020 Nov 27;9(12):425. M .Montañés, C .Martín-Fortún, S .Castillo, E. Molina, J. Terencio and M. Sarasa are full-time employees at Araclon Biotech-Grifols.

LP37- CY6463 ADMINISTRATION IN HEALTHY PARTICIPANTS WAS ASSOCIATED WITH IMPROVEMENTS IN ALZHEIMER'S DISEASE-RELEVANT BIOMARKERS BASED ON A SYSTEMATIC ANALYSIS OF MULTIPLE PHASE 1 CLINICAL TRIALS USING KEM® EXPLAINABLE AI.

M. Kindermans[1], H. Chakroun[1], J. Chickering[2], C. Glasser[2], P. Iriso[1], F. Parmentier[1], T. Milne[2], P. Wilson[2], M. Afshar[1] *(1. Ariana Pharma - Paris (France), 2. Cyclerion - Cambridge (United States))*

Background: CY6463 is a first-in-class, CNS-penetrant, soluble guanylate cyclase (sGC) stimulator that modulates a key node in a fundamental signaling pathway. CY6463 has been evaluated in two Phase 1 studies (NCT03856827, NCT04240158) and is in clinical development for the treatment of CNS diseases including Alzheimer's disease (AD). A total of 134 healthy participants were enrolled across 2 randomized, placebo-controlled, Phase 1 studies in which single ascending doses, multiple ascending doses, food effect (crossover design), and the pharmacology of CY6463 (crossover design) were evaluated. In each study, safety, pharmacokinetic, and pharmacodynamic assessments were collected at baseline and at the end of dosing. Safety assessments included adverse event collection, clinical laboratory values, vital signs, and electrocardiography. Pharmacodynamic assessments included electroencephalography (EEG) measures, cognitive performance tests, saccadic eye movement (SEM) evaluations, and cerebrospinal fluid (CSF) biomarkers. KEM (Knowledge Extraction and Management) explainable Artificial Intelligence (xAI) is a tool that systematically extracts and evaluates all associations between all variables in a database. An objective of such an analysis is the identification of potential subgroups with higher chances of treatment response, paving the way to the development of a precision-medicine approach and potentially increasing chances of clinical success. **Objectives:** The goal of this post hoc analysis was to use KEM xAI to characterize CY6463 impact on a range of endpoints and to identify characteristics of subgroups that had a greater pharmacodynamic response. **Methods:** All data were integrated into a single, consolidated meta-database totaling 134 subjects and 48,300 variables. Data across the 4 different study designs were integrated into a common data-driven framework with doses and plasma concentrations binned into three different levels – low, medium, and high. The analysis was divided into two steps: first, the impact of CY6463 on all pharmacodynamic outcomes was assessed to identify changes associated with CY6463 treatment; second, subgroups of subjects with a further improved response were characterized. In the first step, KEM explored the associations between pharmacokinetic and pharmacodynamic variables in the meta-database. Filtering the associations using metrics such as Support (number of examples), Confidence (conditional probability), Lift (relative probability) and Fisher's p-value (unadjusted for multiplicity), identified the associations with the greatest support for future hypothesis testing. In total, 1015 theoretical associations between all variables were explored by KEM, extracting a subset of 20,860,826 associations that were further reduced to a subset of 67 using the filtering metrics. In a second step, KEM was used to identify biomarkers that stratified the patients within the identified associations. **Results:** On safety, our analysis showed that headache was the only adverse event associated with CY6463 treatment, with transient headache occurring more often in subjects with high total dose of CY6463. Headaches were generally mild and did not lead to discontinuation. No other associations among safety variables were identified. On pharmacodynamics, our analysis showed that faster speed and better accuracy in the Milner Maze Test (MMT) was associated with a high total dose of CY6463 (nominal $p=0.004$ for speed and nominal $p=0.045$ for accuracy). Increase in alpha power (Pz-O1) as measured by EEG during eyes closed resting state was also associated with high total CY6463 dose (nominal $p=0.003$). Additionally, decrease in CSF levels of matrix metalloproteinase 3 (MMP3; nominal $p=0.008$) and increase in CSF levels of cyclic guanosine monophosphate (cGMP; nominal $p=0.013$) were associated with CY6463 treatment. In the second step of the analysis, baseline age, blood pressure, and certain neurophysiological measures were found to be associated with greater pharmacodynamic response on some endpoints. For example, greater CY6463 treatment-associated improvement in MMT (Cohen's d increase by respectively 39% and 157% for respectively the speed and the accuracy) was seen in participants with high baseline systolic blood pressure (≥121mmHg). Similarly, greater CY6463 treatment-associated improvements in MMT were seen in those with higher age (≥49y): Cohen's increase by respectively 40% and 120%. Focusing on subjects with higher age also enables the identification of additional signals such as the decrease in EEG theta power Pz-O2 eyes closed (nominal $p = 0.005$). **Conclusion:** Results for safety endpoint associations were consistent with the favorable safety profile of CY6463 previously reported. On pharmacodynamics, this analysis identified CY6463 treatment-associated, positive effects on endpoints that have been linked with AD. For example, AD patients have been described in

previous studies as showing increased theta and decreased alpha power by EEG as well as increased MMP3 and decreased cGMP levels. Demonstration of improvement on these AD-associated endpoints as well as identification of candidate patient-selection criteria lay a promising foundation for the design of hypothesis-testing, next-phase studies. This analysis of Phase 1 data in healthy participants demonstrates the ability of explainable AI tools, such as KEM, to integrate and analyze broad and heterogeneous sources of data from different trials, to provide insight into a drug's mechanism of action, to generate testable hypotheses, and to guide optimal design of clinical development next steps.

LP38- A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO ASSESS TOLERABILITY, SAFETY, PHARMACOKINETICS AND EFFECT OF AZP2006 ON CEREBROSPINAL FLUID BIOMARKERS IN 36 PATIENTS WITH PROGRESSIVE SUPRANUCLEAR PALSY. P. Verwaerde[1], N. Callizot[1], S. Del Signore[1], A. Blondel[1], C. Estrella[1] *(1. Alzprotect - Loos (France))*

Background: Progressive Supranuclear Palsy (PSP) is a rare, rapidly progressing, neurodegenerative 4-repeat tauopathy. Currently, no medications are approved for treatment of PSP. AZP2006 (EZEPROGIND) is a first-in-class disease-modifying small molecule that modulates the release of progranulin (PGRN). In vitro, AZP2006 promotes neuron survival, enhances synaptic function, decreases Tau hyperphosphorylation and reduces neuroinflammation via PGRN. The chronic oral administration (3mg/kg/day) to rodent models of Tauopathy, AD and PD, showed to prevent and reverse both cognitive and motor deficits. Phase-1 studies (SAD and MAD) demonstrated that oral administration of AZP2006 (liquid formulation) to healthy adults was well tolerated, had a good safety profile and no side effects were observed. Orphan drug designation has been granted to AZP2006 by the EMA and the FDA. **Objectives:** Primary objectives are to determine safety and tolerability of AZP2006 12-week oral administration in patients suffering from PSP, and the pharmacokinetic profile in plasma, blood, and CSF. Secondary objectives are to determine the effect of AZP2006 on up to 21 CSF biomarkers including PGRN, Tau, P-Tau, NfL, and amyloid peptides at baseline and after 12-week treatment with 2 different doses of AZP2006 or placebo, and to evaluate the exposure-response relationship (PK/PD) of AZP2006 on CSF and plasma putative pharmacodynamic biomarkers. Exploratory objectives are to evaluate the effects on clinical endpoints including SPS-RC rating scale. **Methods:** AZP2006C04 (NCT04008355) is a phase-2a study conducted in 3 French clinical centers. It is a randomized, double-blind, placebo-controlled, parallel group study, comparing 2 doses of AZP2006 (60 mg once daily during the 12-week treatment period and 80 mg once daily for 10 days followed by 50 mg once daily), versus placebo in 36 patients with PSP (men and women aged ≥40 years and ≤80 years). Lumbar punctures were performed on D1 and D84. PK blood sampling was performed 36 times throughout the treatment and a further 12-week follow-up period. Randomized patients underwent a comprehensive clinical evaluation at Day-1, Day 84 (end of treatment) and Day 180. **Results:** AZP2006C04 successfully completed the enrollment of 36 patients in January 2022. Last patient visit occurred in July 2022. Database lock and unblinding was performed in September 2022 followed by data analysis. Both AZP2006 60 mg/day and 80mg/50mg/day 12-week administration were well tolerated, no product related SAEs was reported. Baseline clinical characteristics of the enrollees, baseline and changes of CSF and plasma biomarkers upon 12-week treatment will be presented. In addition, selected disease characteristics evolution (including PSP-RS and MDS-UPDRS Part II) will be revealed. **Conclusion:** AZP2006C04 represents an original approach based on Progranulin modulation to treat PSP. AZP2006 12-week administration was well tolerated by patients and safety was overall satisfactory. Final validated unblinded results will be discussed. AZP2006 will be followed by AZP2006C05 which is designed as a pivotal Phase 2/3 study for the treatment of PSP and should take place in Europe and the USA. **Reference:** Callizot, N., Estrella, C., Burlet, S. et al. AZP2006, a new promising treatment for Alzheimer's and related diseases. Sci Rep 11, 16806 (2021). https://doi.org/10.1038/s41598-021-94708-1

LP39- THREE-YEAR OMEGA-3 PUFA TRIAL TARGETING CEREBRAL WHITE MATTER LESIONS AND INTEGRITY BREAKDOWN IN OLDER ADULTS: APOE STRATIFIED AND EXPLORATORY RESULTS. G. Bowman[1], C. Murchison[2], L. Silbert[3], H. Dodge[4], K. Hagen[4], D. Lahna[4], H. William[5], J. Kaye[3], J. Quinn[3], L. Shinto[4] *(1. McCance Center for Brain Health, Department of Neurology, Massachusetts General Brigham and Harvard Medical School - Boston (United States), 2. Department of Biostatistics, University of Alabama at Birmingham - Birmingham (United States), 3. Department of Neurology, Oregon Health & Science University and Veterans Affairs Portland Health Care System - Portland (United States), 4. Department of Neurology, Oregon Health & Science University - Portland (United States), 5. Department of Internal Medicine, University of South Dakota School of Medicine and Fatty Acid Research Institute - Sioux Falls (United States))*

Background: Intake and blood n-3 PUFA [20:5 and 22:6] are lower in people with MRI derived white matter lesions (WML) suggesting that these fatty acids with known anti-inflammatory and neuroprotective properties have a role in the prevention of a major vascular contribution to cognitive impairment and dementia. **Objective:** This trial was designed to examine whether n-3 slows total WML progression and sustains white matter integrity in older adults with baseline enrollment evidence of WML and suboptimum blood n-3. **Methods:** Double-blind, placebo-controlled trial in non-demented adults with plasma n-3 < 110 ug/mL and total WML ≥ 5 cm3. Participants randomized to 1.65 g of n-3 or placebo. Primary outcome was annual WML change. Diffusion tensor imaging fractional anisotropy (DTI-FA) was a secondary outcome. Treatment stratification by apoE genotype was pre-specified. Linear mixed-effects models used for hypothesis testing. **Results:** 102 participants were randomized (51 per group; 75-96 years old; 60% female, 28% apoE4 positive). 78 completed the 3-year visit (39 per group). ITT showed annual WML increase of 1.34 cm3 (95%CI: 0.80-1.88) vs 1.19 (0.64-1.74)(p=0.303) and annual DTI-FA change was -0.002718 vs -0.001352 (p=0.069) in the placebo and active, respectively. ApoE4 carriers on placebo had annual DTI-FA decline of -0.005 vs -0.002 in n-3 treatment group (p=0.037). An exploratory comparison of participants with study exit plasma n-3 ≤ 110 ug/mL vs >110 ug/mL exhibited annual WML increases of 1.71 vs. 0.99 cm3 (p=0.026). **Conclusion:** N-3 PUFA failed to slow total WML progression in all randomized participants; however, those that superseded plasma n-3 >110 ug/mL by study exit had a 50% reduction in annual total WML increase. ApoE4 carriers with accelerated white matter integrity breakdown may benefit from n-3 PUFA. A more extensive, well-powered trial to confirm or refute these results are necessary.

LP40- ACCOUNTING FOR DISEASE MODIFICATION IN MODELS OF COST EFFECTIVENESS OF MABS SUCH AS LECANEMAB AND DONANEMAB. S. Hendrix[1], C. Mallincrodt[1], S. Dickson[1] *(1. Pentara Corporation - Millcreek (United States))*

Objectives: The first treatment for Alzheimer's disease was approved nearly 30 years ago and most treatments on the market today are considered primarily symptomatic. In the past 20 years, dozens of companies have tested treatments thought to be disease modifying with minimal or no success. Only recently have disease modifying therapies achieved success in clinical trials. The distinction between disease modification and symptomatic therapies is critical and can be based on clinical patterns of treatment response as well as biomarker outcomes. The distinction between symptomatic and disease modifying effects results in striking differences in the cost effectiveness modeling associated with each type of treatment. **Methods:** We define disease modification as a treatment benefit that is maintained if treatment is discontinued, but continues to accrue over the time during treatment, and can be modeled as a slowing of progression time. A symptomatic benefit is one that achieves benefit only when the treatment is in the body and is lost with clearance of treatment. Disease modifying effects are expected to be larger in early stages of disease (pre-dementia AD) and smaller in later stages of disease, when measured in terms of time savings, although point benefits may be larger in later stages due to ceiling effects in early disease. Symptomatic treatments work best in later disease stages when symptoms are prominent. **Results:** Combining these definitions and expected patterns of treatment response results in implicit models of economic cost savings. Both lecanemab and donanemab have shown slowing in the range of 30% during 1-1.5 years of treatment. A 30% slowing of progression results in a 5 month time savings with 1 year of treatment, calculated as (0.3*12)/(1-.3). With this rate of slowing, 2 years and 4 months of treatment would postpone all AD costs for 1 year over the course of disease. If direct annual costs associated with dementia are in the range of $27,000 (USD), and additional indirect costs are also considered, such as lost work for caregivers, then a cost per year in the range of $20-30K could be justified. If treatment is started earlier, and the treatment effect is larger in early disease as expected, then these cost savings could be much larger and maintaining patients in a very mild stage of disease could allow this larger effect to be self-aggregating. **Conclusion:** Disease modifying treatments require a different approach for analysis than symptomatic treatments. Focusing on point benefits at a single time point is appropriate for symptomatic treatments, but not for disease modification. The permanent benefit achieved with disease modifying treatments translates into a benefit across the remaining lifespan of a treated patient and should be taken into consideration when evaluating cost effectiveness of new therapies.

LP41- EFFECTIVENESS OF DIGITAL-BASED MULTIDOMAIN INTERVENTION FOR MILD COGNITIVE IMPAIRMENT. M.D. Patterson[1], J. Leonardo[1], S.B. Jabar[1], Y.G. Rykov[1], B.A. Gangwar[1], J. Yee[1], N. Kandiah[2], K.P. Ng[3] *(1. Neuroglee Therapeutics - Singapore (Singapore), 2. Lee Kong Chian School of Medicine - Singapore (Singapore), 3. National Neuroscience Institute - Singapore (Singapore))*

Background: Pharmacological treatments for Alzheimer's Disease (AD) have had little success at slowing its progressive development. This may be because treatments began too late, after brain damage was already irreversible. However, more recent research has targeted a prodromal stage of AD, Mild Cognitive Impairment (MCI) (Petersen, 2016). Targeting modifiable lifestyle risk factors is a non-pharmacological approach to treating MCI since up to 40% of AD cases may be preventable by modifying lifestyle factors if treatment occurs at an early enough stage (Livingston et al., 2020). The most successful previous attempt at modifying lifestyle factors was a multidomain intervention, the FINGER study which demonstrated that diet, exercise, and cognitive training could significantly improve cognitive scores and reduce the risk of cognitive decline (Ngandu et al., 2015). Thus, multidomain lifestyle interventions hold much promise in preserving cognition. However, this approach does not scale well, is expensive, and is difficult to monitor individuals' progress and to tailor the interventions for greatest individual benefit. Digital therapeutics offers an approach to overcome these issues, making treatment more accessible, allows monitoring of each individual, and allows improved health outcomes on a larger scale. **Objectives:** The objective of this study was to evaluate the effectiveness and safety of a 12-week multidomain intervention delivered using a digital platform, NG-001, on cognitive function, mental health, and quality of life of older adults (50-70 years old) diagnosed with MCI. Participants were tested at week 1 and week 12 of the study. The primary outcome measures were changes in processing speed and executive function, as measured by the Neuropsychological Test Battery (NTB), and changes in depression, anxiety, and stress as measured by the Depression Anxiety Stress Scale (DASS-21). The secondary outcome measures were changes for overall cognition from the NTB, and Quality of Life (QOL), as measured by a subset of the QOL-AD questionnaire. The exploratory outcome measures were changes in memory measures from the NTB in MCI patients, and changes on the Zarit Burden Interview for care partners. **Methods:** A 12-week open-label clinical trial was conducted in older adults diagnosed with amnestic MCI (n=27). Participants undertook 10 roughly 1-hour long sessions delivered weekly via a digital tablet at their own convenience consisting of: 1) health literacy education; 2) physical and mindfulness exercises; 3) reminiscence therapy; 4) cognitive games. Participants completed the Neuropsychological Test Battery (NTB), Depression Anxiety Stress Scale (DASS), and Quality of Life in Alzheimer's Disease (QoL-AD) surveys at baseline and at the end of the trial. The NTB was similar to that used in the FINGER Study. Results were adjusted for the participants' age and education levels using normative data, before being converted to composite scores representing overall cognition, processing speed, executive function, overall memory, immediate memory, and delayed memory. Fifteen of the MCI patients were enrolled with care partners who installed a care partner app on their own mobile phones where they were able to monitor their partner's progress on completing the therapy. The care partner app included articles that provided information about MCI and compensatory strategies for their partner's cognitive decline. Care partners completed the Zarit Burden Interview before and after the trial. Changes in NTB, DASS, QoL-AD, and Zarit Burden Interview scores were assessed using paired Wilcoxon signed ranked tests (two-tailed) to determine if differences between baseline and post-intervention scores were significant at a statistical significance of $p<.05$. Hedge's g was calculated for effect size. **Results:** Significant cognitive improvements were seen across MCI participants, whose compliance with the therapies was over 96%. For our primary outcome measures, there were no

significant changes in Executive Functioning (mean z-score of -0.491 vs -0.424) or Processing Speed (0.153 vs. 0.178), (both p>.05). MCI participants showed improvements in mood as measured by DASS. Depression (4.643 vs. 3.214, g = 0.228), Anxiety (6.357 vs. 3.786, g = 0.440) and Stress (7.786 vs. 5.429, g = 0.356) scores all decreased significantly (all p<.05). Secondary outcome measures of NTB Overall Cognition (-0.440 to -0.213) were significantly (p<.001, g = 0.352) improved, but QoL-AD scores were not significantly affected by the intervention (p>.05). Other exploratory outcome measures, Overall Memory (-0.587 to -0.132, g = 0.407), as well Immediate (-0.549 to -0.030, g = 0.512) and Delayed memory (-0.626 to -0.233, g = 0.305) were significantly improved from baseline to post-intervention (all p<.001). Zarit Burden scores given by caregivers were not significantly changed (p>.05). **Conclusions:** This study demonstrated that older adults with MCI who underwent the NG-001 digital multidomain intervention experienced statistically significant improvements in overall cognition, memory (overall, immediate, and delayed), depression, anxiety, and stress levels, improved cognition and mental health. Further research should be conducted to investigate larger populations and with a matched control group of MCI patients.

LP42- THE SENSE-COG TRIAL: A EUROPE-WIDE RANDOMISED CONTROLLED TRIAL OF HEARING AND VISION AUGMENTATION IN DEMENTIA. I. Leroi[1], E. Camacho[2], N. Chaghil-Boissier[3], A.P. Charalambous[4], J.P. Connelly[1], F. Constantinidou[5], R. David[6], R.A. Elliott[2], E. Frison[3], M. Hann[2], A. Holden[2], S.P. Kennelly[1], B.A. Lawlor[1], J. Longobardi[3], A.M. Politis[7] *(1. Trinity College Dublin - Dublin (Ireland), 2. University of Manchester - Manchester (United Kingdom), 3. University of Bordeaux - Bordeaux (France), 4. European University of Cyprus - Nicosia (Cyprus), 5. University of Cyprus - Nicosia (Cyprus), 6. University of Nice Sophia Antipolis - Nice (France), 7. National and Kapodistrian University - Athens (Greece))*

Background: Hearing and vision impairments are highly prevalent in people with dementia (PwD) and may have a negative impact on quality of life and other dementia-related outcomes. Intervening to optimise sensory impairment and support sensory function may be a means of improving dementia-related outcomes. The SENSE-cog Trial evaluated whether a home-based multi-part 'sensory support' intervention (SSI) is effective in improving quality of life and other key outcomes in PwD (including hearing and/or vision problems), and their companions. **Methods:** This was a pan-European, multi-centre, observer blind, randomised controlled trial (RCT), of PwD with hearing and/or vision impairment and their companions. We evaluated a multi-part complex intervention of hearing and vision rehabilitation tailored to each participant dyad, compared to care as usual (CAU). The intervention included at a minimum: assessment and correction of hearing and/or vision impairments; home-based, therapist-delivered sensory support (i.e., adherence with devices; improving the sensory environment (i.e., lighting), communication training, and signposting to other support agencies. **Results:** Across 7 centres in the UK, Ireland, Greece, France and Cyprus, 291 participants with dementia were randomised from May 2018 to May 2021 to receive either 'care as usual', or a multi-component sensory intervention (10 visits over 18 weeks). Mitigating strategies to adapt study procedure to the COVID-19 pandemic were implemented. No significant difference in Quality of Life at 36 weeks was found. Average DEMQoL scores at week 36, adjusted for model covariates, were lower (poorer quality-of-life) in the CAU group but, at most, by 0.3 units/ points. A significant difference was observed in Quality of Life at 18 weeks. The average DEMQoL scores at week 18, adjusted for model covariates, were lower in the CAU group by between 2.6 and 2.7 units/ points. There were no Significant differences in care burden, activities of daily living or hearing impairment at 36 weeks, as assessed by the care companion were also not observed. No serious adverse effects were related to the intervention; low grade adverse effects related to the intervention were reported by five participants only. **Conclusions:** Hearing and vision support and rehabilitation in PwD living at home is a potentially important means of improving the lived experience of dementia and may represent a critical step in the diagnostic and post-diagnostic care pathway. However, effects may not be sustained over the longer term. **Trial registration:** ISRCTN (Trial ID: ISRCTN17056211)

LP43- MRI CHANGES FOLLOWING TREATMENT OF GLP-1 ANALOGUE, LIRAGLUTIDE, IN PATIENTS WITH ALZHEIMER'S DISEASE (ELAD STUDY). P. Edison[1], G.D. Femminella[1], C. Craig[2], J. Joseph[2], N. Nicholas[1], Z. Walker[3], B. Basil[4], H. Hilary[5], S. Salman[6], G. George[7], K. Paul[7], C. Christian[8], R. Rainer[9], P. Peter[10], B. Clive[11] *(1. Imperial College London - London (United Kingdom), 2. The university of Edinburgh - Edinburgh (United Kingdom), 3. University College London - London (United Kingdom), 4. Brighton and Sussex University Hospitals NHS Trust - Brighton (United Kingdom), 5. University of Bristol - University Of Bristol (United Kingdom), 6. Lancashire NHS Trust - Lancashire (United Kingdom), 7. Birmingham University Hospital - Birmingham (United Kingdom), 8. Henan University of Chinese Medicine - Henan (China), 9. University of Manchester - Manchester (United Kingdom), 10. Queens University - Belfast (United Kingdom), 11. University of Exeter - Exeter (United Kingdom))*

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue licensed for the treatment of type 2 diabetes mellitus (T2DM). Preclinical evidence in transgenic models of Alzheimer's disease suggests that liraglutide exerts neuroprotective effects by reducing amyloid oligomers, normalising synaptic plasticity and cerebral glucose uptake, and increasing the proliferation of neuronal progenitor cells. ELAD is a 12-month, multi-centre, randomised, double-blind, placebo-controlled, phase IIb trial of liraglutide in participants with mild to moderate Alzheimer's dementia), conducted at several centres in the UK. As a part of this study, MRI brain scans of all patients were performed at baseline and after 12 months treatment with liraglutide or matching placebo, along with neuropsychometric evaluation and [18F]FDG PET. A total of 204 Alzheimer's participants were randomised to receive either liraglutide or placebo as a daily subcutaneous injection for 12 months. All subjects underwent volumetric MRI scans at baseline, and repeat scans were performed in all subjects who completed 52 weeks of treatment. Volumetric changes from baseline to follow-up MRI scans were evaluated using both regional volume analysis and voxel-based morphometric analysis. MRI analysis demonstrated that temporal lobe volume (p<0.001), total grey matter volume (p<0.002) and frontoparietal volume were higher in liraglutide treated patients compared to the placebo group. Voxel-based morphometry (VBM) analysis demonstrated that liraglutide-treated participants showed that whole cortical grey matter, frontal, temporal and parietal lobe volume was higher in participants treated with liraglutide compared to placebo. This was associated with better cognitive function (ADAS-EXEC) (p=0.01) in patients treated with liraglutide compared to the placebo. However, there was no difference in

glucose metabolism between the two groups. These findings highlight the potential of GLP-1 analogues in the treatment of Alzheimer's disease.

LP44- THE EFFECTS OF POMEGRANATE SEED OIL ON MILD COGNITIVE IMPAIRMENT. T. Chatzikostopoulos[1], M. Tsolaki[1] *(1. Greek Association of Alzheimer's Disease and Related Disorders - Thessaloniki (Greece))*

Background: In recent years, there has been a growing interest, supported by a large number of experimental, epidemiological and clinical studies, about the beneficial effects of pomegranate in preventing various pathologic conditions, including brain neurodegeneration. The Pomegranate Seed Oil (PSO) contains high level phytosterols and vitamin C. Its antioxidant and antiapoptotic properties are helpful in the treatment of neuroinflammation. Specifically, it increases the the levels of Interleukin-17 and Interferon-γ, modulates mucosal immune responses and reduces the expression of TNf-α and Interleukin-6. **Methods:** The Greek Association of Alzheimer's Disease and Related Disorders is conducting randomized clinical trial on the effects of PSO on cognition and mental health of patients with Mild Cognitive Impairment (MCI). The rigor methodological plan of the present randomized clinical trial will cover every aspect of the disease and eliminate possible limitations with careful selection of inclusion and exclusion criteria, with randomization of the sample and with the use of all the contemporary means and measures, such as neuropsychological assessment, MRI and analysis of blood biomarkers. The effects of PSO (experimental group) will be compared with the effects of Mediterranean Diet (control group) and the participants will be divided further into Apolipoprotein ε3 carriers and Apolipoprotein ε4 carriers in order to clarify the role of this specific allele in the treatment. **Objectives:** So, the present study is going to be the first in vivo clinical trial internationally which will examine thoroughly the effects of PSO on MCI patients. However, this study is ongoing and almost completes one year of treatment. For this reason, the results after six months and one year of treatment will be presented with evidence from the neuropsychological assessment. **Results:** The statistical analysis using Wilcoxon Signed-Ranks test and indempendent samples T-Test have shown statistically significant improvement of the experimental group in processing speed and working memory meausured by Trail Making Test B ($p<.01$) and verbal episodic memory measured by Rey Auditory Verbal Learning Test ($p<.05$). **Discussion:** The results of the present study confirmed the findings of previous studies on laboratory animals supporting that PSO has positive effects on memory. Besides that, due to the use of an extensive neuropychological assessment exact types of memory were identified that they can benefit from PSO. **Conclusions:** The PSO can be beneficial for MCI patients leading to prevention of dementia. As far as it is a natural product that does not burden the human body, it can be used by MCI patients and be a significant and promising part of holistic treatments for dementia.

BEYOND AMYLOID AND TAU: EMERGING SOLUTIONS

P50- MITOCHONDRIAL METHYLCYTOSINES AS NOVEL BLOOD-BASED BIOMARKERS FOR PREDICTING PROGRESSION TO ALZHEIMER'S DISEASE DEMENTIA AT THE MILD COGNITIVE IMPAIRMENT STAGE: A MACHINE LEARNING APPROACH. J.L. Mosquera[1], M. Blanch[1], N. Rojo[2], I. Rico[2], J. Campdelacreu[2], B. Fontal[1], P. Ferrer[1], C. Fowler[3], S. Laws[4], A. Tort-Merino[5], R. Sanchez-Valle[5], R. Rene-Ramirez[2], J. Gascon[2], M. Barrachina[1] *(1. ADmit Therapeutics SL - Barcelona (Spain), 2. Functional Unit of Dementia, Service of Neurology, Bellvitge University Hospital, Bellvitge Biomedical Research Institute, IDIBELL - Barcelona (Spain), 3. The Florey Institute, The University of Melbourne - Melbourne (Australia), 4. Collaborative Genomics and Translation Group, Centre for Precision Health, School of Medical and Health Sciences, Edith Cowan University - Joondalup (Australia), 5. Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona - Barcelona (Spain))*

Background: The prediction of progression to Alzheimer's disease dementia (ADD) at the Mild Cognitive Impairment (MCI) stage is an unmet medical need. The current inclusion criteria for clinical trials destinated to AD drug development is MCI patients with CDR=0.5, and a positive bA-PET scan. However, the Sensitivity and Specificity of bA-PET scan for the progression of MCI stage to AD show variability depending on the clinical study. In addition, the inclusion of false positives is impairing the success rate of clinical trials. Several studies have reported mitochondrial dysfunction in AD at cerebral and systemic level. Our proof of concept was obtained from human post-mortem brains, showing and altered mtDNA methylation pattern along AD disease progression (Blanch et al. 2016). Interestingly, similar results have recently been described in blood samples from MCI patients (Stoccoro et al. 2022). ADmit has developed a cutting-edge epigenetic technology based on next-generation sequencing. It identifies differential mtDNA methylation patterns in blood samples from MCI patients providing a percentage of progression to ADD using a machine learning approach. **Objectives:** Our main objective is to develop a model to classify patients diagnosed with MCI susceptible of progressing to ADD. **Methods:** A total of 211 subjects recruited from three logitudinal prospective clinical studies were studied: Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL, 129 subjects), ADmit (74 subjects recruited in Bellvitge University Hospital), and Hospital Clínic de Barcelona (8 subjects). In our prototype, two clinical variables were examined: (1) Group (response variable) consists of three levels which are Controls, MCI Non-progressed to ADD, and MCI Progressed to ADD; (2) bA-PET scan measurement to detect positive or negative levels of cerebral b-amyloid. In addition, more than 200 mitochondrial cytosines were analyzed using MiSeq platform (Illumina). Each of these variables indicates the percentage of methylation for a single specific cytosine in CpG and non-CpG sites for D-Loop region and ND1 gene. Only blood samples from the baseline visit for control (CDR=0) and MCI subjects (CDR=0.5) were epigenetically analyzed. An MCI patient was considered to have progressed to ADD when one of the following criteria was met: CDR change from 0.5 to 1, or ≥2-point deterioration in CDR-SOB from baseline, or ≥1-point deterioration in at least four instrumental activities of daily living measured by the FAQ adaptation questionnaire. The Random Forest, a supervised learning method, was applied

to build our prototype, which was run using a 3 repeated 10-fold Cross-Validation, and the total number of parameter combinations evaluated was 5. To measure the performance of the classification predictions a confusion matrix was built to show a cross-tabulation of the observed and predicted classes. **Results:** Three groups of individuals were considered: Control subjects (n=68, CDR=0, MMSE=29.21 ± 1.10, 68.85 ± 5.34 years old; 16% E4 carriers; 0% positive bA-PET scan) with clinical follow-up greater than 10 years; MCI patients Non-progressed to ADD (n=58, CDR=0.5, MMSE=27.19 ± 2.02, 70.76 ± 7.80 years old; 29% E4 carriers; 19% positive bA-PET scan) and a clinical follow-up greater than 36 months without showing progression symptoms; and MCI patients progressed to ADD (n=85; CDR=0.5, MMSE=25.69 ± 2.53, 74.69 ± 6.62 years old; 56% E4 carriers; 79% positive bA-PET scan). Control subjects were only available on the AIBL cohort, however MCI patients were recruited from all three cohorts. Sex showed a balanced number, 52.4% were females and 47.6% were males. The time frame of ADD progression was between 1 and 5 years. Data splitting generated a first subset of 170 subjects for the training model process and a second subset of 41 individuals for testing the classification model. Results of the model training indicated that the best performance was the Random Forest, with an average Accuracy of 0.760 and an average Kappa value of 0.636. The model predictions on the testing data results in an overall Accuracy score of 0.756 with a 95% Confidence Interval of 0.597 to 0.876, and a Kappa value of 0.63. Sensitivity and Specificity of the model to classify a subject as an MCI progressed to ADD is 0.76 and 0.92, respectively. The precision of the model is 0.87, and the F1-score is 0.81. The Positive Predictive Value is 0.87, and the Negative Predictive Value is 0.85. The ROC curve showing the performance of the classification model for the MCI progressed versus MCI non-progressed patients has an AUC=0.791. **Conclusion:** Our classification model performs a good classification of ADD at MCI stage CDR=0.5 up to 5 years before the appearance of dementia. These novel blood-based biomarkers could support bA-PET scan-based patients' stratification in clinical trials. This protoype is currently under review with a higher sample size in order to improve the tuning process during the model training. This fact, might cause that estimates provided in this study as well as its associated metrics to evaluate the performance of the classification could be slightly modified.

P51- IMPROVEMENT OF COGNITIVE DYSFUNCTION FOLLOWING REPEATED INFUSION OF ADIPOSE TISSUE-DERIVED STEM CELLS. K. Shigematu[1], M. Ideno[2], N. Komori[3], H. Yamagishi[4] *(1. Minami Kyoto Hospital - Joyo (Japan), 2. Takara Bio Inc. - Kyoto (Japan), 3. Nagitsuji Hospital - Kyoto (Japan), 4. Kyoto Prefectural University Of Medicine - Kyoto (Japan))*

Background: Adipose tissue-derived stem cells (ADSCs) secrete neprilysin, an enzyme that degrades amyloid associated with Alzheimer's disease, and secrete nerve cell growth factors and cytokines, which may be effective in cognitive dysfunction. **Objectives:** To investigate whether repeated infusion of ADSCs improves cognitive function. ADSCs has been suggested to be useful in several neurological disorders. Cognitive function is supported by neurons in the broad cerebral cortex, so administration of ADSCs may have a positive effect on those neurons, resulting in improved cognitive function. **Methods:** First, we confirmed the presence of neprilysin activity in ADSCs. We examined 15 ADSCs-treated patients who had some cognitive dysfunction to see if there were any changes in cognitive function. Approximately 100 million ADSCs were administered intravenously six times at approximately one-month intervals. Cognitive function was assessed with the Montreal Cognitive Assessment (MoCA). The patient and caregiver were asked monthly about the effects or any adverse events from before administration to about 1 month after the 6 doses. As part of the questionnaire, the respondents were asked to select «improved,» «unchanged,» or «worsened» as their final overall evaluation. If the neurologist judged that the patient had difficulty answering a question on the MoCA test because he or she did not understand it, the score was zero with no educational history correction.The patient was accompanied by his/her physician during the administration of ADSCs infusion to ensure safety. After the observation period, i.e., one month after the end of the administration, the safety and efficacy of the ADSCs are being monitored for as long as possible. **Results:** Underlying diseases of the patients in this study who had cognitive changes were Alzheimer's disease (9 patients), Parkinson's disease (4 patients), amyotrophic lateral sclerosis (1 patient), and chronic obstructive pulmonary disease (1 patient), for a total of 15 patients. MoCA scores before ADSCs administration were 17, 15, 13, 10, 9, 9, 3, 3, 0, 24, 19, 17, 9, 13, 12 (mean 11.5, standard deviation 6.5), respectively, and those after 6 doses were 22, 23, 19, 19, 19, 17, 14, 10, 8, 0, 29, 28, 28, 28, 28, 23, 28 (mean 19.7, standard deviation 8.7). The change in MoCA scores before and after the last dose was an improvement of 7.6 (95% confidence interval 5.2-10.1, $p < 0.01$; t-test). In the post-treatment assessment by patient caregivers (family members), all selected «no deterioration» or «improved» for patient cognitive function after treatment, and none selected «worsened. No changes in vital signs, abnormal bloodchemistry tests, or any suspected side effects, including subjective or objective symptoms, were observed. **Discussion:** The results suggest that administration of ADSCs may improve cognitive dysfunction. Since neprilysin activity was identified in the administered ADSCs, amyloid removal was a possible mechanism of action for the effect. It is noteworthy that the improvement was not limited to Alzheimer's disease. It is possible that neprilysin activity worked other than in Alzheimer's disease, since amyloid is deposited with aging. ADSCs secrete several nerve growth factors as well as other factors that may be useful for neuronal repair and activation, which may have contributed to the improvement in cognitive function. In neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and ALS, inflammatory responses are known to occur at lesion sites, which may have two implications for the actions of ADSCs: ADSCs secrete several cytokines to control inflammation, and inflammation may facilitate ADSC accumulation in the brain parenchyma, especially at lesion sites. Although ADSCs have the ability to differentiate into neurons, the actual strength of their regenerative potential in the brain is unknown; however, it is possible that they work to regenerate nerves at the site of brain damage, and it will be a challenge to determine how long this takes and how long the effect lasts. This ADSCs treatment study has limitations, first of all, it is not a double-blind controlled trial. The placebo effect cannot be completely ruled out. However, the improvement in generally progressive cognitive impairment, along with the lack of side effects associated with this treatment, supports further study as a promising treatment modality for dementia in the future. **Conclusion:** The results suggest that intravenous administration of ADSCs may improve cognitive dysfunction independent of the underlying disease, i.e., cognitive dysfunction associated with lung disease in addition to several neurodegenerative diseases. This also suggests that ADSCs administered into the bloodstream can

reach and act on the cerebral cortex. The possible mechanisms of action include neuroregeneration, neuroprotection/repair, anti-inflammation, improvement of blood flow, and removal of abnormal proteins.

P52- NOVEL APPLICATION OF DEEP CANONICAL CORRELATION ANALYSIS IDENTIFIES REGIONAL BRAIN ATROPHY LINKED TO PROINFLAMMATORY GUT MICROBIAL GENERA BEFORE COGNITIVE DECLINE. M.B. Heston[1,2], Z. Meng[3], A. Kohli[1,2], A. González[4], S.C. Johnson[1,2,5], R. Knight[4,6,7,8], R.F. Kaddurah-Daouk[9,10,11,12], F.E. Rey[13], V. Singh[3,14,15], B.B. Bendlin[1,2,5] *(1. Wisconsin Alzheimer's Disease Research Center - Madison (United States), 2. Division of Geriatrics, Department of Medicine, University of Wisconsin School of Medicine and Public Health - Madison (United States), 3. Department of Biostatistics and Medical Informatics, University of Wisconsin-Madison - Madison (United States), 4. Department of Pediatrics, University of California, San Diego - La Jolla (United States), 5. Wisconsin Alzheimer's Institute - Madison (United States), 6. Department of Bioengineering, University of California, San Diego - La Jolla (United States), 7. Department of Computer Science & Engineering, University of California, San Diego - La Jolla (United States), 8. Center for Microbiome Innovation, University of California, San Diego - La Jolla (United States), 9. Department of Psychiatry and Behavioral Sciences, Duke University - Durham (United States), 10. Department of Medicine, Duke University - Durham (United States), 11. Duke Institute of Brain Sciences, Duke University - Durham (United States), 12. Duke University Medical Center - Durham (United States), 13. Department of Bacteriology, University of Wisconsin- - Madison (United States), 14. Department of Computer Sciences, University of Wisconsin-Madison - Madison (United States), 15. Department of Statistics, University of Wisconsin-Madison - Madison (United States))*

Background: The gut microbiome modulates neurodegeneration through proposed pathways including inflammation and epigenetic modifications. We published the first human study linking the gut microbiome to Alzheimer's disease (AD) pathology; this and subsequent studies identified trends between proinflammatory taxa and greater amyloid and tau burden. A recent study also linked gut microbiome composition and cognition in midlife, suggesting the microbiome plays a role in preclinical AD development. However, it remains unknown whether the associations with cognition and AD pathology are reflected in preclinical brain atrophy. **Objectives:** This study tested the hypothesis that a proinflammatory microbial profile is linked to greater cortical atrophy before AD dementia onset. To accomplish this, we used deep canonical correlation analysis (DCCA), which employs neural networks to develop a sparse representation of high-dimensional data, then performs CCA to correlate bacterial taxa and regional volumes. DCCA enables estimation of unknown nonlinear relationships, which frequently occur among microbiome data. This is the first recorded use of DCCA to link gut microbiome composition and neuroimaging data. **Methods:** 157 cognitively unimpaired participants provided fecal samples and T1-weighted neuroimaging through the Microbiome in Alzheimer's Risk Study (NIA R01AG070973), Wisconsin Alzheimer's Disease Research Center (WADRC), and Wisconsin Registry for Alzheimer's Prevention (WRAP). These mid- to late-life cohorts are enriched for participants at risk for developing AD. T1-weighted images were collected using published methods; CAT12 was used to preprocess images and quantify regional gray matter volumes with the Automatic Anatomically Labeled Atlas 3. Fecal samples were collected at home, returned chilled, and subsequently weighed, scored using the Bristol scale, and frozen at -80°C. Using published methods, 16S rRNA V4 sequencing was performed on previously frozen samples. Taxa were denoised and classified (Qiita and QIIME2), filtered to 5% prevalence, and agglomerated at the genus taxonomic rank (phyloseq). DCCA was used to identify a maximally correlated set of genera and brain regions. Multinomial regression (songbird) was used to calculate differentials, or log fold change in genus abundance, associated with increases in regional volume. Differentials were ranked (qurro), and genera ranked first and last (indicating positive and negative correlations, respectively) were used to evaluate relationships with gray matter volume. Regression covariates included age at fecal sample and sex. **Results:** Participants were demographically representative of the WADRC and WRAP cohorts. Age at fecal sample was 66.25±6.73 years (mean±SD), and imaging was obtained within 0.66±0.48 years of fecal samples. 104 (66%) participants were female, and 52 (33%) were APOE e4 allele carriers. Average body mass index was 28.71±5.64 kg/m2, and average fecal sample Bristol score was 3.89±1.23. Microbiome processing resulted in 86 genera present in 5% of samples. DCCA identified 7 genera (Akkermansia, Anaerostipes, Bacteroides, Clostridium, Coprococcus, Ruminococcus, unidentified Lachnospiraceae genus) correlated with 18 regions (bilateral (b): cerebellar crus I (CERCRU1), cerebellar lobule 8 (CER8), postcentral gyrus (PoCG), superior frontal gyrus (SFG); left (l): calcarine cortex (CAL), cerebellar crus II (CERCRU2), middle occipital gyrus (MOG), middle temporal gyrus (MTG), precentral gyrus (PreCG), temporal pole: superior temporal gyrus (TPOsup); right (r): cerebellar lobule 6 (CER6), supracallosal anterior cingulate cortex (ACCsup), opercular inferior frontal gyrus (IFGoperc), middle frontal gyrus (MFG)). The rACCsup, lTPOsup, rCER6, and lCERCRU1 had strongest genus associations; magnitudes of their differentials ranged from 0.53 (rACCsup) to 0.22 (lCERCRU1). Anaerostipes negatively correlated with volumes of bCERCRU1, bSFG, lTPOsup, lMTG, lPreCG, rPoCG, lCERCRU2, rCER6, lCER8, and lCAL. Bacteroides positively correlated with lTPOsup, rACCsup, rCERCRU1, bSFG, lMOG, and rIFGoperc. Clostridium correlated negatively with lPoCG, rMFG, and rIFGoperc, and positively with lCERCRU2. Ruminococcus positively correlated with lCERCRU1, bCER8, and lMTG. The Lachnospiraceae genus positively correlated with rPoCG, lPreCG, and rMFG. Coprococcus positively correlated with lCAL and rCER8, while Akkermansia negatively correlated with rACCsup and lMOG. **Conclusions:** This study further implicates the microbiome in preclinical AD, and demonstrates the potential clinical utility of fecal samples as a low-cost, noninvasive source of biomarkers early in AD development. Selected brain regions included temporal and frontal regions susceptible to AD pathology, as well as several cerebellar regions that exhibit reduced connectivity with cerebral regions early in AD. Higher gray matter volume was linked to more abundant genera with short chain fatty acid-producing species, and less abundant Clostridium, a genus with several opportunistic pathogens. Interestingly, Akkermansia and Anaerostipes, two genera with known anti-inflammatory species, were less abundant with higher volumes. Akkermansia has been identified as elevated in untreated multiple sclerosis, and Anaerostipes supplementation aggravated intestinal lesions in a colitis mice model, suggesting variable roles in modulating inflammation. To determine whether the microbiome-brain correlations vary with AD severity, future analyses will evaluate the moderating effect of amyloid burden on the present relationships. Further,

to identify effects on the earliest AD-related changes in neuroarchitecture, microbiome composition will be evaluated against gray matter microstructure captured via multishell diffusion-weighted imaging.

P53- BEYOND TARGETING AB AND TAU: NOVEL FORMULATIONS OF ALPHA-CYCLODEXTRINS FOR THE SAFE (NOT OTOTOXIC) AND CONVENIENT (ORAL) PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE. K. Wittkowski[1] *(1. Asdera Llc - New York (United States))*

Introduction: More than 6M US people are living with Alzheimer's disease (AD). This number is projected to double by 2050, when dementias will cost the nation >$1T/yr. Still, few, if any, early interventions or disease-modifying drugs (DMTs) are available to prevent or treat AD and other dementias. Most AD drugs are cholinesterase inhibitor (donepezil), glutamate regulator (memantine), or directly targeting beta-amyloid (aducanumab) or tau-protein. HP-beta-cyclodextrin (HPβCD), which was shown to be active across the blood-brain barrier (BBB), has also shown effectiveness against the inherited childhood disease Niemann-Pick type C, which shows parallels with AD in cellular pathology. However, HPβCD has consistently caused cholesterol-related hearing loss, often permanent, both in animal models (Davidson CD, 2016, Ann Clin Transl Neurol 3: 366) and in clinical trials. **Methods:** Since Ohdner's 1900 mechanical calculator, each advance in computer technology has made more statistical methods available. After 2001, a computational biostatistics approach to the analysis of GWAS data, developed over 20 years at The Rockefeller University (Wittkowski KM, 2018, PLoS One 13: e0199012), yielded insights about high levels of endocytosis during accelerated age-related (AR) decline of lysosomal function as a key component in the etiology of AD. A review of AD-related publications investigated the role of (1) Ab and tau as causative vs reflective of the etiology of AD and (2) cholesterol vs phospholipids as the lipids involved in the etiology of AD. ASDERA developed interventions to improve AR health by addressing two common components in the etiology of AR conditions at a fraction of the cost for society: garb-aging and inflamm-aging. ASD-IFM (as a nutraceutical) and ASD-005 (as a drug for treatment) lowered serum phospholipids (PLs) to mimic the benefits of intermittent fasting: less activity of PLA2s reduces inflammation and also reduced endocytosis, which prevents aging lysosomes from becoming overloaded and, in turn, disrupts autophagy (causing accumulation of substrates, incl. Ab and tau). **Results:** Studies of HPbCD have often assumed that it acted by "depleting cholesterol" (Simons M, 1998, PNAS 95: 6460), rather than other lipids, including phospholipids, even though this was not fullly supported by evidence. For instance, an official name of "ABCA1, a membrane cholesterol transporter" (Yao J, 2012, J Exp Med 209: 2501) is "Phospholipid-Transporting ATPase" (genecards). Unfortunately, HPβCD also causes cholesterol-related permanent hearing loss. Animal studies have shown HPαCD (6 sugars, too small to fit cholesterol) to be more effective than HPβCD (7 sugars) in breast cancer (reducing endocytosis and inflammation) and also effective in movement disorders, incl. HD and ALS, by improving weight gain, as a DMT, the opposite effect of reducing body weight in wild type animals and human trials (Wittkowski KM (2019) WO 2019/067269 A2). αCD was more effective than HPβCD in vitro against various lysosomal storage diseases (McKew 2014 US 201715620753 A). In the absence of dietary milkfat (eg, with animal chow), αCD is not excreted into urine, but βCD was absorbed in pre-weaned rats (De Schaepdrijver L, 2015, Reprod Toxicol 56: 87). In human trials (Wittkowski KM (2019) l.c.), no αCD was excreted into urine in the absence of dietary milkfat, some αCD and small increases in PLs were seen in urine when milk or capric acid (C10) added, and much more when αCDs and C10 were formulated as a non-covalently bound clathrate. The nutraceutical ASD-IFM and the drug ASD-005 are formulated with GRAS αCD or the drug HPαCD, respectively. Oral ASD-IFM and -005 (related US claims accepted, PCT pat. pend.) are absorbed from the intestine. Hence, CDs can now be administered orally, avoiding the need of overnight iv infusion. **Discussion:** Intermittent fasting (IF) and the IF mimetics HPαCD (too small to fit cholesterol) were previously shown to be more effective than HPβCD in LSDs, NDDs and cancer, diseases characterized by different manifestations of dysfunctions along the endocytosis/lysosome/autophagy (ELA) axis. With the new results showing that: • the MoA of HPbCD is via PLs, not cholesterol, • the clathrates ASD-005/IFM of aCDs and C10 are intestinally absorbed and safe, • αCDs have systemic effects in various cardiometabolic conditions and diseases involving ELA axis dysregulation, • the FDA has accepted HP-CDs as drugs with activity across the BBB, several barriers against a more convenient, safer, and potentially more effective prevention and DMT for ND diseases have been overcome. Most of the benefits of aCD have been demonstrated in clinical trials and health claims are already approved (US) or authorized (EU) for use with nutraceuticals and supplements. HP-CDs were recently accepted by the FDA as drugs, so the more water-soluble HPaCD can undergo clinical trials as a DMT (mono- or adjuvant therapy) against AD and other ND diseases.

P55- ESTABLISHING FLUID BIOMARKERS ASSOCIATED WITH CELLULAR SENESCENCE IN ALZHEIMER'S DISEASE. B. Ng[1], A. Heslegrave[1,2], N. Fox[1,3], H. Zetterberg[1,2] *(1. Dementia Research Institute, University College London - London (United Kingdom), 2. Department of Neurodegenerative Disease, University College London - London (United Kingdom), 3. Dementia Research Centre, Queen Square Institute of Neurology, University College London - London (United Kingdom), 4. Department of Psychiatry and Neurochemistry, University of Gothenburg - Molndal (Sweden))*

Background: Chronological age is the biggest non-genetic risk factor of Alzheimer's disease (AD). However, there is a wide range in age at onset (AAO) such that chronological age itself is a poor predictor of risk or AAO. Biological age may offer a more precise molecular measure of ageing, but it is currently unclear how biological ageing is associated with AD. Recently, pathological hallmarks of AD have been reported to be alleviated by removing senescent glial cells in the brains of AD mouse models. We therefore hypothesise that biomarkers of biological ageing measured in cerebrospinal fluid (CSF), specifically linked to the process of cellular senescence, can serve as biomarkers of AD. **Objectives:** We set out to measure fluid biomarkers of biological ageing specifically linked to cellular senescence and selected based on their implication in AD, and compare their associations with CSF biomarkers of AD. **Methods:** Using CSF samples from a biomarker discovery cohort in Sweden, we quantified the levels of multiple candidate biomarkers associated with ageing and cellular senescence with various immunoassays. The levels of biological ageing markers were then analysed with clinical and pathological data from the sample donors. **Results:** The levels of Growth differentiation factor-15 (GDF-15), Interleukin-6 (IL-6), Osteopontin and Klotho

in human CSF were measured (n = 67) to assess their relevance in the context of existing CSF biomarkers of AD. The levels of all four candidate biomarkers change with chronological age (increase, except decrease for Klotho), and both GDF-15 and Osteopontin levels can differentiate individuals with high level of CSF amyloid-β1-42 (Aβ1-42) from those with low levels of Aβ1-42. In addition, the levels of Osteopontin correlate positively with those of phosphorylated tau-181 while the levels of IL-6 correlate positively with both GDF-15 and Osteopontin. **Conclusion:** Our data support the relevance of biological ageing in the context of AD and the need for further investigation. The abovementioned candidate biomarkers, among others in consideration, will be quantified in clinically characterised AD cohorts to result in a consolidated molecular signature for biological ageing.

P56- THE GUT-PRO STUDY: A PILOT PROBIOTIC INTERVENTION STUDY IN ALZHEIMER'S DISEASE. J.W. Kang[1], S.J. Harding[1], M. Heston[1], A.E. Braceros[1], N. Davenport-Sis[1], N. Chin[1], H. Zetterberg[2], F. Rey[1], B. Bendlin[1] *(1. University of Wisconsin-Madison - Madison (United States), 2. University of Gothenburg, Sahlgrenska University Hospital - Mölndal (Sweden))*

Background: Recently, gut microbiome has emerged as a potentially modifiable factor that may contribute to exacerbate development of Alzheimer's disease (AD) pathology. Our research group previously found altered gut microbiome composition among individuals with AD and abundance of specific microbiota was associated with AD pathology; however, no studies have tested whether restoring the relative abundance of gut bacteria that are depleted in AD, i.e., Bifidobacterium and Lactobacillus impacts AD or related pathology. **Objectives:** The primary objective of this study is to assess the safety and feasibility of an oral probiotic intervention in humans with or at risk for dementia due to AD. The secondary objective is to test the effects of a probiotic intervention on the composition and function of the gut microbiota in humans with or at risk for dementia due to AD as well as collect preliminary biomarker and cognitive data to estimate sample size and other critical parameters for a larger study. **Methods:** A randomized, double blind, and placebo-controlled clinical study will be conducted in 40 participants, including 20 participants with mild cognitive impairment (MCI) or early AD dementia and 20 cognitively unimpaired enriched for elevated amyloid (CU-EA). An equal number (ten) of MCI/AD dementia and CU-EA participants will be randomly assigned to intervention (probiotic) and ten participants in each group will be assigned to placebo control. The probiotic group will receive probiotic capsules comprising a custom formulation of probiotics for 6 months, and the placebo group will receive placebo capsules for 6 months. Study participants will be followed for 1 year, and will participate in stool collection, cognitive and functional assessments, actigraphy, and blood draw for plasma biomarkers of AD. **Discussion:** Probiotics, including those that impact abundance of Bifidobacterium and Lactobacillus, have previously been shown to impact digestive and immune function, as well as lower symptoms associated with digestive disorders, reduce inflammatory markers, and improve cognitive function. Gut microbiota and their secondary metabolites, including short chain fatty acids, indoles, and bile acid profiles, have the potential to modulate the central nervous system via the gut-brain axis. Ongoing human and animal studies in our lab are testing the pathways by which gut microbiome may impact AD, including via gut permeability, gut microbial metabolites, and immune-related mechanisms. Given few effective treatment options to support maintained cognition and function in the context of AD, modulating the composition of the gut microbiota deserves further testing. **Conflict of interests:** Authors declare that they have no competing interests.

P57- THE POTENTIAL OF FLAVONOIDS TO ENHANCE MITOCHONDRIAL FUNCTION AND PROTECT NEURONS FROM DEGENERATION IN ALZHEIMER'S DISEASE. M. Ankarcrona[1], L. Naia[1], G. Dentoni[1], M. Shimozawa[1], E. Bereczki[1], X. Li[2], J. Liu[3], N. Santos Leal[3], B. Portal[4], M. Lindskog[4], P. Nilsson[1], M. Gaetani[1] *(1. Karolinska Institutet (KI) - Solna (Sweden), 2. Tsinghua University - Tsinghua (China), 3. Karolinska Institutet (KI) - Huddinge (Sweden), 4. Uppsala University - Uppsala (Sweden))*

Background: Mitochondrial dysfunction and decreased energy production occur early in the Alzheimer's disease (AD) process. Hence, mitotherapeutics may be valuable disease modifiers for AD. We have previously identified the flavonoid luteolin as a mitochondrial enhancer in primary neurons (Naia et al 2021). We revealed a novel mechanism showing that luteolin increase mitochondria-endoplasmic reticulum (ER) contact, ER to mitochondria Ca2+-transfer and ATP production. We believe that flavonoids have the potential to enhance mitochondrial function, support synaptic activity and halt the progression of AD. To validate our findings with luteolin and other flavonoids and to understand the molecular mechanism in depth we have here identified appropriate disease models and performed target identification. **Objectives:** -to characterize AD-mouse models in terms of mitochondrial function; -to perform target analysis for flavonoids using the Proteome Integral Solubility Alteration (PISA) Assay. **Methods:** RNA sequencing was performed on hippocampal tissue isolated from knock-in AppNL-F (6, 12, 18 months old animals) and AppNL-G-F (2, 6, 12 months old animals) AD-mouse models and wild-type (WT) mice where APP is expressed at physiological levels under its endogenous promoter with a humanized amyloid β-peptide (Aβ) sequence and familial AD mutations. AppNL-F and AppNL-G-F mice display an increased Aβ42/40 ratio and accumulate amyloid plaques (Saito et al 2014). Data were analyzed by gene ontology enrichment analysis, pathway analysis and unsupervised genome-wide clustering. Primary cortical neurons were derived from mouse embryos at embryonic day 16–17, WT embryos were generated from inbred C57B6/J parent and AppNL-F embryos from homozygous C57B6/J AppNL-F parents. Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) evaluation was performed using a XFe96 SeaHorse Analyzer. Calcium (Ca2+) uptake by mitochondria (AppNL-G-F and WT) was measured using the Ca2+-sensitive probe Calcium Green-5N and Ca2+-retention capacity calculated. Patch-clamp recording spontaneous activity of neurons was recorded and miniature EPSCs were recorded in the presence of 0,5μM of tetrodotoxin (TTX) in the extracellular solution to block action potentials. Mitochondrial movement MitoDsRed-transfected neurons were washed and imaged at 37 °C in Na+ medium using a 63x objective with NA=1.4 in the LSM710 confocal microscope (Zeiss). Mitochondrial movement analysis was done using the Kymograph Macro in Fiji. Mitochondria-ER contacts (MERCS) were analyzed by electron microscopy and confocal microscopy using split-GFP-based contact site sensor (SPLICS) analysis. Proteome Integral Solubility Alteration (PISA) Assay a high throughput method based

on protein solubility/stability upon thermal treatment was used for target analysis of flavonoids in cortical primary WT neurons. **Results:** Energy metabolism emerged as one of the most significantly altered pathways in young AppNL-F and AppNL-G-F knock-in (KI) mice. Functional experiments in brain mitochondria isolated from two months old AppNL-G-F mice subsequently identified upregulation of oxidative phosphorylation driven by the activity of mitochondrial complexes I, IV and V, combined with higher susceptibility to Ca2+-overload. Consequently, mitochondrial function was impaired in 12 months old AppNL-G-F mice as reflected in the transcriptome analysis. In AppNL-F primary neurons derived from mouse embryos, also displaying an increased Aβ42/40 ratio, we detected an upregulation in mitochondrial oxygen consumption with concomitant downregulation in glycolytic reserve. Furthermore, AppNL-F neurons were more susceptible to cell death triggered by mitochondrial electron transport chain inhibition. Juxtaposition between ER and mitochondria was found to be substantially upregulated, which account for increased transfer of Ca2+ from ER to mitochondria and upregulated mitochondrial-derived ATP production. However, anterograde mitochondrial movement was severely impaired in this model along with loss in synaptic vesicle protein and impairment in pre- and post-synaptic function. PISA analysis with several flavonoids revealed cytosolic and mitochondrial targets which are now further analyzed in silico, in vitro and in vivo. **Conclusion:** We report for the first time an upregulation of brain mitochondrial function in young AppNL-G-F mice which was subsequently impaired in old animals. Interestingly, mitochondria from young AppNL-G-F mice had impaired Ca2+-buffering capacity. AppNL-F primary cortical neurons show a similar phenotype with upregulated mitochondrial function, increased ECAR (reflecting a lower glycolytic reserve) and impaired mitochondrial Ca2+-buffering capacity. We have previously shown that WT cortical neurons exposed to Aβ42 display increased oxygen consumption rate (OCR) and increased juxtaposition between ER and mitochondria (Leal et al 2020). Even though Aβ accumulates in AppNL-F and AppNL-G-F mice, we cannot exclude other triggers of mitochondrial alterations. However, we show here that these App KI animal models are appropriate for studies with molecules boosting mitochondrial function. Therefore, we are now performing target validation and proof-of-concept studies of the potential protective effect of flavonoids in these AD-models. We report no conflicts of interest.

P58- AN ONLINE DEMENTIA PREVENTION USING THE COGSTIM MODEL: A PILOT STUDY. R. Ownby[1,2] *(1. Nova Southeastern University - Fort Lauderdale Fl (United States), 2. Enalan Communications, Inc. - Fort Lauderdale Fl (United States))*

Background: Given limited progress in creating treatments for dementia, interest has increased in the possibility of dementia prevention through lifestyle interventions. A large number of factors that have been related to risk and protection from dementia, however, and patients may not be able to choose among confusing claims to develop their own brain health plans, and may have difficulty initiating and maintaining behavior change. We developed the Cogstim shared decision-making model to help patients and clinicians to address these issues. The model organizes brain health activities according to the putative mechanisms through which they affect brain health, lays out evidence-based criteria for activity choices, and integrates both with behavior change techniques. Further, during the COVID-19 pandemic it was difficult to do in-person education or support patients' behavior change efforts, making the development of an online intervention desirable. **Objectives:** The purpose of this study was to carry out a test of the Cogstim model for dementia prevention delivered completely online. Persons receiving the model-based intervention were compared to a group receiving an educational intervention without structured goal setting and behavior change techniques. **Methods:** Individuals 50 years of age and older were recruited from local organizations for older adults and by word of mouth from other participants. They completed baseline cognitive assessments and a series of self-report inventories evaluating mood, stress, and knowledge of dementia risk and protective factors. The primary outcome measure was score on the Alzheimer's Disease Risk Inventory (ADRI) with secondary outcomes designated as self-reports on the Memory Self-Efficacy scale (MSE) and the Dementia Knowledge Scale, Risk subscale (DKAS). Acceptability of the intervention was assessed with a questionnaire based on the Technology Acceptance Model. Participants also completed exit and three-month follow-up interviews. Participants were randomly assigned to 12 weekly videoconference sessions of either (1) the Cogstim (CS) intervention, comprising structured goal setting, weekly review of goals, and problem-solving of behavior change strategies or (2) treatment as usual (TAU), comprising the same educational sessions without structured goal setting and support for behavior change. As part of the study, we tested a brain health tracking tool that asked participants to report daily brain health activities. Participants completed these logs for 7 consecutive days during weeks 1, 6, and 12 of the study. Change over time for outcome measures was assessed with mixed effects models in R, and group differences in report of brain health activities were evaluated using interrupted time series analyses (ITSA) completed in Stata. This study was registered on ClinicalTrials.gov (NCT04822129). **Results:** Eighteen individuals (6 men 12 women, 2 blacks and 16 whites, average age 72.7 years, average years of education 17.9) were enrolled; 16 completed the study. Twelve completed all follow-up self-report questionnaires (5 in the TAU and 7 in the CS groups). For the primary outcome measure (ADRI), persons in the CS group showed larger increases than those in the TAU group, and although the difference did not reach statistical significance ($t = 1.72$, $p = 0.11$) it represented a large effect size ($d > 1.00$). Analyses for the two secondary measures (MSE, DKAS) showed no between-group differences (all $ps > 0.20$). The ITSA models for the composite Cogstim index of brain health activities showed a positive effect over time in both groups, suggesting that persons in both groups increased their brain health activities over time, but no between-group difference existed (linear trend for TAU: $t = 2.73$, $p = 0.01$, for CS: $t = 3.12$, $p = 0.004$; between group difference: $t = 0.25$, $p = 0.81$. On the Technology Acceptance Model (TAM) questionnaire, participants rated the intervention positively for both its usefulness (mean rating 5.38, SD 0.68, on a scale from 0 to 6, with 6 indicating a positive rating) and ease of use (mean 5.33, SD 0.91). Test of group differences in TAM ratings did not suggest that group membership affected ratings (all $ps > 0.10$). All 16 completers provided interview data at immediate and three-month follow-up. Interviews showed that the intervention was viewed positively by participants. All 16 participants felt the program was helpful to them in developing better brain health, while 15 indicated they enjoyed the program. All stated they would to the program again. **Conclusions:** This pilot study shows that an online dementia prevention intervention based in the Cogstim model is feasible and acceptable to older

persons. The Cogstim daily index may be useful to support self-monitoring persons developing a brain health plan. The Cogstim model provided a useful framework that supported participants' efforts at change, and this pilot study provides preliminary evidence of the intervention's a positive effect on participants' behavior. **Conflicts:** Dr. Ownby is a major stockholder in Enalan Communications, Inc., a company that develops digital health interventions.

P59- EFFECTS OF NON-INVASIVE BRAIN STIMULATION ON INDIVIDUAL ALPHA POWER. O.A. Onur[1], R. Fassbender[1] *(1. Department of Neurology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany - Cologne (Germany))*

Background: In Germany, more than one million people suffer from dementia. Due to the steadily increasing life expectancy in our society, the number of dementia patients with all the resulting social and economic consequences will continue to increase in the future. However, the pharmacological therapies established in the treatment of Alzheimer's disease (AD) show only a limited effect on mnestic deficits, which are the leading symptom of Alzheimer's dementia. In recent years, non-invasive brain stimulation has revealed promising findings for modulating cognitive functioning in AD patients, although some of these effects have not been replicated. One reason for these contradictory findings could be a variable reactivity of each individual to stimulation, so that personalized stimulation protocols hold great potential in the therapy of cognitive and mnestic deficits in these patients. **Objectives:** The aim of this study was to evaluate non-invasive brain stimulation as a therapeutic tool in Alzheimer's disease by individually adapting stimulation protocols. **Methods:** 17 MCI patients based on Alzheimer's disease with a typical cerebrospinal fluid profile (amyloid- and pTau-positivity) were recruited via the memory clinic of the University Hospital Cologne and 19 age-matched healthy control via public announcement. All subjects were examined with regard to the effectiveness of non-invasive brain stimulation. Data collection was successfully completed in September 2020 after a pandemic-related break in data collection. Study participants first underwent a detailed neuropsychological assessment to evaluate cognitive status. Subsequently, two sessions took place in which non-invasive brain stimulation was performed simultaneously with EEG measurements (rTMS-EEG). For rTMS four circular coils for low-intensity (<10 mT) and high-frequency stimulation were placed in a cushion (CERTIS, ABNeurotech). Subjects were asked to lay their head in the cushion sitting in an upright position. The head was positioned in a way that the coils targeted parietal and occipital areas on both hemispheres. In one of the two sessions, sham stimulation was performed in randomized order as a control condition. At the beginning of the rTMS-EEG sessions, a baseline EEG resting state measurement was performed. This was followed by real time quantitative electroencephalography (qEEG) in parallel to the application of four different stimulation protocols to determine the optimal stimulation pattern for each subject. The stimulation protocols differed in the design of the stimulation trains. For the rest of the experiment the stimulation protocol resulting the highest power spectral density (PSD) of the alpha frequency band (alpha power) in parietal and occipital areas was chosen. Stimulation or sham stimulation occurred throughout the duration of the item-memory object-location paradigm performed, consisting of encoding, immediate recall, consolidation (10 minutes), and delayed recall. The memory task under stimulation or sham stimulation was followed by another resting state EEG measurement. Behavioral measures, relative PSD and individual alpha peak level (iAPL) were analyzed using SPSS and EEGlab. **Results:** The stimulation was well tolerated, subjects could not determine whether stimulation took place or not (stimulation vs sham). PSD analysis in the resting state before the stimulation revealed a decrease of alpha power and an increase in theta power in the group of AD patients as described before. Relative PSD yielded no stimulation effect. However, during stimulation, in contrast to sham stimulation, increased iAPL was detected at the occipital electrodes in the group of AD patients. In contrast, no effect of stimulation on memory performance during the paradigm was found. **Conclusion:** In this study, we were able to demonstrate that a single session of low-intensity and high-frequency rTMS is capable to increase iAPL in AD patients. It remains to be determined in which stage of the learning process stimulation could have the most beneficial behavioral effect. In addition, it is yet unclear if repetitive stimulation over a certain period of time reveals stronger effects. However, this rTMS-system is a promising approach as it could be easily applied also in out-of-hospital settings due to the small coils and the low-intensity of the magnetic field.

P60- A PRAGMATIC ASSESSMENT OF ULTRA-FAST MRI IN REAL-LIFE CLINICAL AND RESEARCH COGNITIVE PRACTICE. M. Rosa-Grilo[1], E. Mulroy[1], M. Beament[1], H. Chughtai[2], D. Thomas[1], G. Parker[2], N. Fox[1], C. Mummery[1] *(1. UK Dementia Research Centre at University College London (UCL) - London (United Kingdom), 2. Centre for Medical Image Computing, Department of Medical Physics & Biomedical Engineering and Department of Neuroinflammation at University College London (UCL) - London (United Kingdom))*

Background: Structural brain imaging is an essential component of the diagnostic workup for cognitive disorders, enabling the exclusion of reversible causes and assisting dementia subtype diagnosis. Further, with the emergence of disease-modifying therapies for neurodegenerative disease, demand for MRI imaging is likely to increase, both to facilitate early diagnosis, and safety monitoring, particularly for amyloid-related imaging abnormalities (ARIA). MRI has several advantages over other imaging techniques, including its lack of ionizing radiation and excellent soft-tissue contrast. However, MRI scans are time-consuming, costly, and less widely available than their closest alternative, CT scans. Together, these factors contribute to variability in availability and quality of MRI access leading to inequality in diagnosis. Reducing MRI scan time is a critical step in increasing efficiency, reducing cost, and enabling more widespread adoption of MRI as the first-line imaging modality for neurodegenerative diseases. **Objectives:** Current conventional MRI protocols typically require patients to stay in the MRI scanner for 20-30 minutes. Recent developments in accelerated MRI acquisition techniques have enabled us to design a protocol greatly reducing this time to below 10 minutes whilst retaining good image quality. The performance of this novel protocol will be compared against a conventional 3T MRI protocol in a pilot cohort of patients with varied diagnoses recruited from cognitive disorders outpatient clinics and research studies. Our primary aim is to demonstrate that, by using a new ultra-fast MRI protocol, we will be able to reduce barriers to the widespread use of MRI. To do so, we aim to evaluate the non-inferiority of this rapid scanning protocol, providing equivalent diagnostic utility to current conventional scanning protocols.

Secondary objectives include the assessment of qualitative and quantitative scan metrics (image resolution, motion artefacts, signal-to-noise ratio, tissue volumes). **Methods:** For the pilot study, 40 individuals will be consecutively recruited from a single UK centre (National Hospital for Neurology and Neurosurgery, London). Eligible participants are individuals who are having a conventional 3T MRI scan as a part of their diagnostic workup. Recruiting in this way ensures that individuals are representative of the population of interest in a real-life environment. We aim to compare the conventional MRI protocol to the pilot rapid protocol, which uses wave-controlled aliasing in parallel imaging (Wave-CAIPI) work-in-progress sequences implemented on a Siemens 3T Prisma system. The rapid Wave-CAIPI protocol includes sequences widely used clinically and in clinical trials (3D MPRAGE, 3D FLAIR, 3D T2, and 3DT2*) and has been optimized to achieve a balance between acquisition speed and image resolution/quality. We will perform a head-to-head comparison of the images using a predefined 5-point Likert-scale from -2 to +2, with 0 being equivalent. Each sequence will be rated for utility in making a radiological diagnosis and assessed for qualitative and quantitative scan metrics. Quantitative analysis will involve calculation, and comparison of key structural measurements (e.g. cortical grey matter, deep grey matter, white matter, and hippocampal volumes) for the two protocols using tools such as FreeSurfer. **Results:** Recruitment began in March 2022 and is projected to take five months. We will test for noninferiority of the accelerated sequences compared to standard sequences in the head-to-head analysis and agreement of quantitative measures will be assessed through Bland-Altman analysis to evaluate any differences between the two protocols. **Conclusion:** Worldwide population ageing brings with it an ever-increasing incidence of dementia and augments demands on our healthcare systems. Rapid and accurate structural brain imaging is key to meeting such demands. This ultra-fast MRI protocol, investigated in real-life clinical and research cognitive practice, holds the potential to significantly increase efficiency, reduce costs and enhance diagnostic yield, all while affording patients greater convenience and comfort. In addition to the enhanced diagnostic capabilities, rapid imaging holds many other uses in neurodegenerative diseases. With the advent of disease-modifying therapies for Alzheimer's disease, rapid brain imaging will also be invaluable for the management of clinical trials by enabling earlier diagnosis, optimizing the efficacy of therapeutics, improving drug safety, and reducing patient burden. The results of this study will provide crucial insights into the utility of rapidly acquired MRI sequences in a real-world cohort of people with suspected cognitive decline, informing the set-up of larger research studies on the topic. **Acknowledgments:** This study has been funded by Biogen Idec UK. No conflicts of interest.

P61- OPTIMAL CONDITIONS FOR ENTRAINING GAMMA WAVES USING SENSORY STIMULATION IN OLDER ADULTS. Y. Park[1], E. Yoon[1], K.W. Kim[1] *(1. Seoul National University - Seoul (Korea, Republic of))*

Objective: Although light flickering at 40 Hz reduced Alzheimer's disease (AD) pathologies in mice by entraining gamma waves, it failed to reduce cerebral amyloid burden in patients with AD or mild cognitive impairment. We investigated the optimal parameters of the flickering light stimulus for entraining gamma waves in older adults with aging in eyes and brain. **Methods:** We measured electroencephalography (EEG) during the FLS presented. We compared the event-related synchronization (ERS) and spectral Granger causality (sGC) of entrained gamma rhythm in 26 cognitively normal older adults between different colors, luminance intensities and flickering frequencies of lights. We investigated the relationship between white matter integrity and entrainment and propagation using fractional anisotropy (FA).**Results:** Entrained gamma activity started after the FLS onset, lasted during the FLS, and diminished after the FLS offset which was observed most highly at parietal area and steadily decreased from the parietal to the frontal area. In human, FLS entrained significantly higher event related synchronization (ERS) at the lower frequencies than 40 Hz. In addition, the stronger FLS entrained higher ERS with stronger parietooccipital to frontotemporal connectivities. Adverse effects were tolerable and comparable between FLS conditions in older adults. Lower WM microstructural integrity was related to weaker gamma entrainment and propagation. **Conclusion:** Optimal FLS did work, but lower white matter integrity was related to less gamma entrainment and propagation.

P62- SERUM LEVELS OF GLYCAN EPITOPE CORRELATE WITH TAU AND PREDICT PROGRESSION TO DEMENTIA IN COMBINATION WITH APOE4 ALLELE STATUS. R.Z. Zhou[1], D.L. Vetrano[2], G. Grande[2], B. Winblad[1], L. Tjernberg[1], S. Schedin-Weiss[1] *(1. Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Karolinska Institutet - Solna (Sweden), 2. Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University - Stockholm (Sweden))*

Background: Identifying early biomarkers for Alzheimer's disease (AD) is crucial for starting potential treatments at the right time. Recent investigations with high-performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (MS/MS) have shown alternations in N-glycosylation patterns in cerebrospinal fluid of AD patients (1). Therefore, glycan biomarkers may prove to be useful, novel alternatives or complements to existing AD biomarkers. As serum samples are more available and easier to obtain than CSF samples, a glycan biomarker in blood would be preferrable. One type of N-glycosylation pattern of interest is the "Bisecting GlcNAc" epitope, which is highly expressed in brain and thus more likely to be altered in cerebral disease (2). Bisecting GlcNAc is synthesized by the enzyme N-acetylglucosaminyltransferase-III (GnT-III) and has been shown to be linked to AD by regulating β-site APP-cleaving enzyme-1 (BACE1) (2). Using an assay based on Phaseolus vulgaris erythroagglutinin (PHA-E), which binds specifically to the "Bisecting GlcNAc" epitope, we found elevated levels of this epitope in CSF of AD patients compared to control subjects (3). Thus, we were interested in evaluating this potential biomarker in blood. **Objectives:** To evaluate Bisecting GlcNAc levels in serum as a glycan biomarker for early detection of dementia. **Methods:** We developed a plate-based enzyme-linked lectin assay (ELLA) with PHA-E coupled to biotin functioning as an epitope-binding lectin (3). We optimized sample dilutions for serum analysis and used a final dilution of 1:100000. In a pilot study, we analyzed baseline and 6-year follow-up serum samples from 233 individuals enrolled in the Swedish National study on Aging and Care in Kungsholmen (SNAC-K). The average age at baseline was 77.6 years (SD = 10.1, range 60.2 – 96.6), with 62 % females. Cognitive status of patients was followed for up to 15 years, during which 52 of 233 individuals developed dementia. The serum samples were

also analyzed for several proteins, including total tau, with a R&D Luminex© biomarker assay. **Results:** At baseline, serum PHA-E fluorescence correlated with tau levels in individuals who later developed dementia (r2 = 0.30). The correlation was much weaker in individuals who did not develop dementia (r2 = 0.07). At 6-year follow-up, the individuals who already developed dementia exhibited an even stronger PHA-E to tau correlation (r2 = 0.63). Individuals were then stratified into three groups according to their relative baseline tau/PHA-E ratio: high, intermediate, or low. Intermediate tau/PHA-E ratio was identified as a predictor for future dementia diagnosis (AUC = 0.61, 95 % CI: 0.52 – 0.70, $p < 0.05$). Thus, in our cohort, intermediate tau/PHA-E levels in an individual more accurately predicted future dementia diagnosis than having at least one APOE4 allele (AUC = 0.58, 95 % CI: 0.49 – 0.67, $p > 0.05$). Progression to dementia diagnosis was significantly more common in individuals with intermediate tau/PHA-E ratio compared to individuals with low/high tau/PHA-E ratio ($p < 0.05$). In subjects with one or two APOE4 alleles, the risk of progression to dementia compared with subjects with no E4 alleles was even higher if they also had intermediate tau/PHA-E levels ($p < 0.05$). **Conclusion:** Serum PHA-E correlates with total plasma tau in individuals who later develop dementia. An intermediate PHA-E/tau ratio was a risk factor in dementia development and added predictive value to other known risk predictors such as heterozygous or homozygous APOE4 status. Interestingly, the PHA-E to total tau correlation has been previously shown in cerebrospinal fluid of patients with Subjective Cognitive Impairment (SCI) (3). Our results support the usefulness of glycan biomarkers in blood for prediction of dementia. **References:** 1. Gaunitz S, Tjernberg LO, Schedin-Weiss S. What Can N-glycomics and N-glycoproteomics of Cerebrospinal Fluid Tell Us about Alzheimer Disease? Biomolecules. 2021 Jun 9;11(6):858. 2. Kizuka Y, Taniguchi N. Neural functions of bisecting GlcNAc. Glycoconjugate Journal. 2018 Aug 16;35(4):345–51. 3. Schedin-Weiss S, Gaunitz S, Sui P, Chen Q, Haslam SM, Blennow K, et al. Glycan biomarkers for Alzheimer disease correlate with T-tau and P-tau in cerebrospinal fluid in subjective cognitive impairment. The FEBS Journal. 2020 Aug 14;287(15):3221–34.

P63- SERUM PROBDNF PREDICTS MEMORY GAINS AFTER LIFESTYLE CHANGES IN ELDERLY PERSONS - A SUBGROUP ANALYSIS AMONG ADHERENT PARTICIPANTS IN THE FINGER STUDY.

A. Matton[1], K. Håkansson[1], J. Goicolea[1], M. Daniilidou[1], T. Ngandu[2], G. Gerenu[1], A. Solomon[3], H. Soininen[3], T. Laatikainen[2], M. Kivipelto[1] *(1. Karolinska Institutet - Solna (Sweden), 2. Finnish Institute on Health and Welfare - Helsinki (Finland), 3. University of Eastern Finland - Kuopio (Finland))*

Background: Brain-derived neurotrophic factor (BDNF), including the mature form (mBDNF) and its precursor (proBDNF), has an important role in brain plasticity, and is possibly also involved in neuroprotective mechanisms against development of dementia. **Objective:** In this study we relate, for the first time, serum levels of both mBDNF and proBDNF with cognitive changes in elderly persons at risk of dementia during a comprehensive life-style intervention. **Methods:** A sub-sample of 151 participants from the Finnish Geriatric Intervention Study to prevent cognitive impairment and disability (FINGER), aged between 60 and 79 years, and with high adherence to the intervention protocol were included in the analysis. The multidomain intervention combined several lifestyle changes in parallel (diet, exercise, cognitive training, social stimulation, and vascular risk management) over 24 months. Serum mBDNF and proBDNF levels were measured at baseline and after after 24 months, and were related to changes in cognitive performance using multiple linear regression models. **Results:** We found a positive association between proBDNF levels at baseline and improved memory performance over the 24-month intervention period. This association was especially strong for changes in complex memory performance. In addition, participants with larger increases in their proBDNF levels over the intervention period also had larger gains in memory performance. We found no associations between levels of mBDNF, or changes in mBDNF levels, and performance changes in any cognitive domain. **Conclusion:** These results suggest that proBDNF may have a key role in molecular processes underlying memory improvement, and that proBDNF availability can serve as a predictor of memory benefits from comprehensive lifestyle changes in elderly persons.

P64- EVALUATION OF LONG-TERM SAFETY AND COMPLIANCE TO A MULTINUTRIENT INTERVENTION FOR UP TO 8 YEARS IN MILD COGNITIVE IMPAIRMENT / PRODROMAL ALZHEIMER'S DISEASE: DATA FROM THE RANDOMISED CONTROLLED LIPIDIDIET TRIAL.

T. Hartmann[1,2], A. Solomon[3,4,5], P. Visser[6,7], K. Blennow[8,9], M. Kivipelto[5,10,11], H. Soininen[10,12] *(1. Deutsches Institut fur Demenzpravention, Saarland University - Homburg (Germany), 2. Experimental Neurology - Homburg (Germany), 3. Neurology, Institute of Clinical Medicine, University of Eastern Finland - Kuopio (Finland), 4. Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institute - Stockholm (Sweden), 5. Clinical Trials Unit, Theme Aging, Karolinska University Hospital - Huddinge (Sweden), 6. Department of Neurology, Alzheimer Center, VU University Medical Center - Amsterdam (Netherlands), 7. Department of Psychiatry and Neuropsychology, Alzheimer Center Limburg, University of Maastricht - Maastricht (Netherlands), 8. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg - Mölndal (Sweden), 9. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, - Mölndal (Sweden), 10. Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland - Kuopio (Finland), 11. Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institute - Stockholm (Sweden), 12. Neurocenter, Department of Neurology, Kuopio University Hospital - Kuopio (Finland))*

Background: Lifestyle factors such as nutrition and diet are increasingly recognized as modifiable risk factors for the progression of mild cognitive impairment (MCI) to Alzheimer's disease (AD). Previous studies with the multinutrient combination Fortasyn Connect (Souvenaid) have shown benefits on memory and functional connectivity in mild AD dementia (1, 2). The LipiDiDiet (3, 4) study was designed to investigate the effects of Fortasyn Connect in individuals with prodromal AD. With up to 6 years of randomised, double-blind, placebo-controlled (RCT) intervention and an additional 2 years of open-label intervention, LipiDiDiet is a unique long-running RCT with a nutritional intervention in prodromal AD/MCIAD. Results over the first 2 and 3 years of intervention showed that Fortasyn Connect slowed cognitive decline and reduced brain atrophy (5, 6). **Objectives:** Here we report on compliance and long-term safety of the use of Fortasyn Connect compared to control over a maximum of 8 years of intervention. **Methods:** LipiDiDiet was a double-blind, parallel-group, multi-center randomized controlled clinical trial conducted between 2009 and 2013 in 11 sites across Finland, Germany, the Netherlands,

and Sweden. A total of 311 participants with prodromal AD, defined according to the International Working Group (IWG)-1 criteria, were enrolled and randomized (1:1) to the active product (125ml once-a-day drink; Fortasyn Connect) or a calorie-matched placebo control. Following the first 2 years of intervention, participants could opt in for annual extensions up to a maximum of 6-year double-blind and 2-year open-label intervention. When participants started the trial, they were not taking any pharmaceutical AD drugs. Once individual participants progressed to mild dementia during the double-blind intervention period, they were provided with AD drugs and/or open-label Souvenaid (together referred to as open-label medication) and could continue in the trial. Main efficacy outcomes included measures of cognition, function, brain atrophy, and disease progression. Safety assessments included (serious) adverse events, concomitant medication use, vital signs, and clinical safety laboratory tests, analysed in all participants who received at least one dose of study product. To allow for separate evaluation of safety data collected before and after a switch to open-label Souvenaid, analyses were done in two safety phases: the double-blind treatment phase and the open-label treatment phase. Product compliance was assessed by participants' recording of product use in a daily dairy and calculated as the percentage of study product used throughout the study period compared with the prescribed dosage, both over the entire intervention period and separately for each year of double-blind or open-label intervention. **Results:** From the 311 participants randomized at baseline, n=245, 162, 84, 49, 29, 17, 8 participants completed respectively the 24-, 36-, 48-, 60-, 72-, 84-, and 96-month intervention periods. The frequency, severity and types of recorded adverse events were consistent with the studied population and none of the serious adverse events was related to the study product as assessed by the investigators. The overall incidences of (serious) adverse events were comparable between groups, both while on double-blind treatment over the first 6 years and while on open-label treatment from dementia diagnosis or start open-label intervention onwards. Self-reported compliance to the study product was high throughout the entire intervention period, ranging from 85% to 98% across the different intervention years. **Conclusion:** Inherent to long-term follow-up studies like LipiDiDiet, interpretability of the safety and compliance data is complicated by several factors like decreasing sample size, treatment switching, potential non-compliance, differential attrition, and gradual underreporting of events. Despite that, the current results showed that participants' compliance to the study product remains high over a long-term intervention period and there was no indication for a health concern related to the use of Fortasyn Connect for up to 8 years in a prodromal AD/MCIAD population. **References:** 1. Scheltens P, et al. Alzheimers Dement. 2010;6:1-10 e1. 2. Scheltens P, et al. J Alzheimers Dis. 2012;31:225-236. 3. Dutch Trial Register: NL1620 (NTR1705). 4. Funding by EU-FP7 211696, EU JPND EURO-FINGERS. 5. Soininen H, et al. Lancet Neurol. 2017;16:965-975. 6. Soininen H, et al. Alz Dementia. 2021;17:29-40.

P66- CLINICAL UTILITY OF NON-INVASIVE WHOLE TRANSCRIPTOMIC PROFILING OF ALZHEIMER'S DISEASE. S. Toden[1], J. Zhuang[1], S. Quake[2], R. Rissman[3], J. Brewer[3], J. Sninsky[1] *(1. Molecular Stethoscope - South San Francsico (United States), 2. Stanford University - Stanford (United States), 3. University of California, San Diego - San Diego (United States))*

Background: Histological analysis and gene expression profiling studies using post-mortem human brain tissues have provided insight into the disrupted pathological networks of Alzheimer's disease (AD). The resulting insights, however, are qualified because only end stage disease is surveyed, patient selection bias occurs due to informed consent, tissue sampling bias needs to be considered and pathology review introduces subjectivity. Recently, blood-based liquid biopsies assessing circulating nucleic acids have emerged as an alternative for non-invasive examination of molecular alterations in multiple diseases. Although quantification of cell-free messenger RNA (cf-mRNA) was considered challenging due to low abundance in the circulation, we have developed a next generation sequencing (NGS) based platform that enables hypothesis-independent transcriptome characterization of the cf-mRNA secretome from low volume plasma/sera. Noninvasive testing provides the opportunity to collect information along the disease continuum, may provide differential diagnosis for dementias and identify potential additional therapeutic targets that trigger later stages of disease pathology. **Objectives:** Using a cf-mRNA RNA-Sequencing AI/Machine learning platform, we evaluated plasma cf-mRNA profiles of AD subjects with a range of severity and non-cognitively impaired (NCI) individuals. We examined genes and associated pathways that are dysregulated in cf-mRNA transcriptome of AD subjects. Furthermore, we evaluated whether these dysregulated genes in AD subjects could be used to build an AD diagnostic classifier. Finally, we assessed the contribution of brain cell type-specific transcripts in cf-mRNA transcriptome of AD and NCI subjects. **Methods:** Plasma samples were collected from 126 AD and 116 NCI subjects with a similar age distribution from five independent institutions. Subsequently, cell free RNA was isolated from plasma samples and sequencing libraries were generated. Sequencing was performed using Illumina NextSeq500 platform. Differential expression analysis was conducted with DESeq2 using read counts for each gene as input. Pathway analysis was conducted using Ingenuity Pathway Analysis software. Samples were split into "training" and "testing" cohorts and an AD diagnostic classifier was built using training cohort with logistic regression with L2 regularization. Classifier performance was evaluated using the independent "testing' cohort. The Tabula Sapiens single cell datasets were used to estimate the abundance of brain cell type-specific transcripts. **Results:** We identified 2,591 dysregulated genes in the cf-mRNA of AD patients. These identified genes recapitulated biological processes associated with AD, such as synaptic dysfunction, mitochondrial dysfunction and inflammation. Unsupervised decomposition analysis using differentially expressed genes resulted in identification of 6 gene clusters and a subset of these clusters were associated with the processes known to be involved in AD onset and progression. The AD diagnostic classifier derived from the training cohort was able to discriminate AD from NCI subjects in the testing cohort. Quantification of the brain cell type-specific genes indicated that a subset of brain cell types such as Bergmann glia cells were less abundant in cf-mRNA of AD subjects compared to those of NCI. **Conclusion:** Collectively,

our study highlights cf-mRNA profiling as a potential tool to non-invasively characterize neurological diseases such as AD. Pathway and cell type analyses revealed potential diagnostic and therapeutic targets of AD beyond the ATN framework.

P67- DEVELOPMENT OF A SELECTIVE ESTROGEN B-RECEPTOR PHYTOESTROGEN FORMULATION – PHYTOSERM – FOR IMPROVING COGNITIVE HEALTH TO REDUCE ALZHEIMER'S RISK AND MENOPAUSAL SYMPTOMS: A PHASE 2 RANDOMIZED CLINICAL TRIAL.
C. Lopez[1], M. Drew[1], G. Hernandez[1], R. Brinton[1] *(1. University of Arizona - Tucson (United States))*

Background: Accumulating evidence points to life-time estrogen exposure as a protective factor against cognitive decline and Alzheimer's disease (AD) in women, and to the menopause transition as a trigger for an existing AD predisposition. If estrogen therapy is effective for sustaining neurological health and preventing AD, why are women reluctant to use this therapy? Fear of breast cancer is the principal reason menopausal women report for rejecting estrogen replacement therapy. While women forego pharmaceutical hormone therapy, they extensively, utilize over the counter products labeled natural and considered to be safer. Thus, to attain brain protection, we also had to address breast protection. To achieve this goal, we developed a rationally designed combination of select ERβ-selective phytoestrogens that promote brain health to reduce AD risk while also reducing breast cell proliferation. The greatest risk factors for AD are age, APO ε4 allele and female sex. Close to two thirds of the Alzheimer population are women and women bear the greatest burden of the disease. The estimated lifetime risk for AD is 19.5% for women compared to 10.3% in men. Multiple conditions that emerge during menopause, such as cognitive decline, dysregulated glucose metabolism, insomnia, depression, are associated with increased AD risk. Adverse outcomes of ovarian hormone loss, especially estrogen, in midlife (average age 51) can initiate a 15–20-year prodromal phase between menopause and AD onset. While the clinical definition of menopause focuses on reproductive function, the symptoms of this midlife aging transition are largely neurological1. Although about 20% of women transition through menopause without symptoms, 80% of women experience symptoms and over 70% of these experience multiple symptoms associated with risk of Alzheimer's disease. Previous phase 1b/2a trial outcomes demonstrated that the PhytoSERM formulation was safe, well-tolerated, and had an adequate pharmacokinetic profile. An optimal dose of 50mg was established. Based on such outcomes, we designed a phase 2 efficacy trial to further assess PhytoSERM as a safe and effective alternative to hormone therapy for menopause-associated hot flashes and cognitive decline. **Objectives:** To conduct a phase 2 clinical trial to determine the effect of oral PhytoSERM (50mg) for 24 weeks in regional brain glucose metabolism standardized uptake value ratio (SUVR) by FDG PET. To assess change in cognitive function, vasomotor symptoms, and sleep. To measure single-dose pharmacokinetics of PhytoSERM in a subset of 12 participants. To evaluate the effect of PhytoSERM on exploratory MRI imaging outcomes and blood-based biomarkers. **Methods:** This is a single-center, double-blind, parallel-group, randomized-controlled phase 2 clinical trial. A total of 100 participants, 50 per treatment arm, will be enrolled. Eligible participants are female, age 45 to 60 years old, peri or post-menopausal (last menstrual period completed ≥ 60 days and ≤ 4 years), cognitively normal (MMSE ≥27) and experiencing ≥7 hot flashes per day. Participants will be randomized to 50 mg of PhytoSERM (administered orally, once per day) or matching placebo, 1:1 allocation, for a 24-week period. FDG-PET scans to evaluate the primary endpoint will be conducted at baseline and 24 weeks. Cognitive endpoints and clinical ratings will be assessed at baseline, 12 and 24 weeks. Hot flashes will be measured both subjectively with a diary and objectively with a digital wristband measuring electrodermal activity. **Results:** Primary Endpoints: Change from baseline to 24 weeks in regional brain glucose metabolism standardized uptake value ratio (SUVR) by FDG PET. Secondary Endpoints: Mean rate of change in cognitive outcomes: Verbal Paired Associates score, List Sorting Working Memory Test score, WAIS digit symbol test score, and Selective Reminding Task score. Mean rate of change in frequency of hot flashes and menopause rating scale score. Mean rate of change in affect score and sleep quality index score. Pharmacokinetic parameters (Cmax, tmax, t1/2, AUC). Exploratory Endpoints: Mean change from baseline in regional brain volumes (mm3). Mean change from baseline in fractional anisotropy (FA). Mean change from baseline in quantitative anisotropy (QA). Mean change from baseline in functional connectivity (Hedges' g). Mean change from baseline in cerebral blood perfusion (perfusion clusters) on arterial spin labeling (ASL). **Conclusion:** Herein we present a phase 2 proof-of-concept framework to assess the efficacy of PhytoSERM as a non-pharmacologic therapeutic to improve cognitive health and reduce menopausal symptoms. Results from this study will validate previous findings that indicate that PhytoSERM is safe alternative to hormone therapy and has the potential to sustain neurological health and preventing AD during the menopausal transition.

LP45- PHYLUM FIRMICUTES ABUNDANCE IS ASSOCIATED WITH BRAIN VOLUMES IN A COGNITIVELY UNIMPAIRED COHORT ENRICHED FOR ALZHEIMER'S DISEASE RISK.
M. Ibrahim[1], H. Margo[1], J.W. Kang[1], G. Ennis[1], S. Harding[1], S. Johnson[1], S. Asthana[1], B. Bendlin[1], A. González[2], F. Rey[1], R. Knight[2], R. Kaddurah-Daouk[3] *(1. University of Wisconsin school of Medicine and Public Health - Madison (United States), 2. department of pediatrics, university of california, san diego – la jolla - La Jolla (United States), 3. Department of Psychiatry and Behavioral Sciences, Duke - Durham (United States))*

Background: The gut microbiome has recently received attention as a potential modifiable risk factor for Alzheimer's disease (AD). To understand how the gut microbiome may affect AD pathology, our research group previously compared the gut microbiome compositions of people with AD dementia to those of healthy controls, finding that gut microbiome composition is altered in AD. We also found associations between microbial abundance and amyloid and tau pathology, even among cognitively unimpaired individuals. However, the microbiome's preclinical relationships with measures of neurodegeneration, such as gray and white brain matter volume require further examination. **Objectives:** The primary objective of this study was to evaluate the extent to which abundances of gut microbial phyla were associated with brain tissue volumes. We hypothesized that lower relative abundances of Bacteroidetes and Actinobacteria phyla would be associated with lower white and gray matter volumes. **Methods:** 157 cognitively unimpaired participants from the Wisconsin Alzheimer's Disease Research Center (WADRC) and Wisconsin Registry for Alzheimer's Prevention (WRAP) study provided fecal samples and underwent T1-weighted neuroimaging

through the Microbiome in Alzheimer's Risk Study (NIA R01AG070973). The sample was enriched for participants in the preclinical stage of AD and presence of the APOE ε4 genotype. Fecal samples were typically collected at home, returned chilled, and subsequently weighed, scored using the Bristol scale, and frozen at -80°C. CAT12 software implemented in SPM12 was used to process and quantify brain images with the Automatic Anatomically Labeled Atlas 3. 16S ribosomal RNA V4 bacterial genome sequencing was performed on the frozen fecal samples using published methods. Taxa were denoised, classified (Qiita and QIIME2), and agglomerated at the phylum taxonomic rank. Multiple regressions were run to ascertain associations of each bacterial phylum with gray and white matter individually, as well as combined brain volume (calculated as the sum of gray and white matter). Covariates included age, sex, APOE ε4, and total intracranial volume. **Results:** Participants demographically represented the WADRC and WRAP cohorts. Age at fecal sample was 66.25±6.73 years (mean±SD), and imaging was obtained within 0.66±0.48 years of fecal samples. 104 (66%) participants were female, and 52 (33%) were APOE ε4 allele carriers. Average body mass index was 28.71±5.64 kg/m2, and average fecal sample Bristol Stool Scale score was 3.89±1.23. Seven different phyla were observed in the samples, namely: Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, Proteobacteria, Tenericutes, and Verrucomicrobia. All seven phyla showed no significant relationships with gray and white matter volumes individually, and six of the seven showed no significant relationships with combined brain volume ($p>0.1$). Firmicutes, however, showed a significant positive correlation with total brain volume ($p=0.04$) and a positive correlation with white matter, although the latter relationship did not meet the threshold for significance ($p=0.07$). **Conclusions:** These results further validate the association of the gut microbiome and brain in the context of AD risk by showing that lower Firmicutes relative abundance is associated with smaller total brain volume. The results are also consistent with a previously published finding from our lab that showed reduced Firmicutes in AD in a smaller sample. Firmicutes has been implicated in Parkinson's disease pursuant to its association with several microbiota-associated epitopes that play significant roles in inflammatory responses. Further analysis of Firmicutes may help elucidate how chronic inflammation and gut microbiome alterations are associated with cognitive decline in Alzheimer's disease. Determining a role for gut microbiome in the etiopathogenesis of AD or related dementias may provide a potentially modifiable target, as well as contributing to the development of therapeutics that may mitigate the development and progression of the disease. Future analyses will extrapolate the genera or species of bacteria from phylum Firmicutesthat are absent in people with AD. With that, probiotic options could be explored to ameliorate AD pathology or neurodegeneration in AD.

LP46- OPTIMIZING DETECTION OF PRODROMAL ALZHEIMER DISEASE IN MILD COGNITIVE IMPAIRMENT – A 4-YEAR CEREBROSPINAL FLUID STUDY OF MILD BEHAVIORAL IMPAIRMENT IN ADNI AND MEMENTO. *Z.* Ismail[1], R. Leon[2], B. Creese[3], C. Ballard[3], P. Robert[4], E.E. Smith[1] *(1. University of Calgary - Calgary (Canada), 2. Hotchkiss Brain Institute - Calgary (Canada), 3. University of Exeter - Exeter (United Kingdom), 4. Université Côte d'Azur - Nice (France))*

Background: Recruitment inefficiencies and even failures in the Alzheimer's disease (AD) modifying drug clinical trial program can be attributed to suboptimal detection of early phase illness. Imprecise case ascertainment of prodromal AD based on standard clinical assessment necessitates further investigations such as detailed neuropsychological testing and biomarker confirmation with cerebrospinal fluid (CSF) or positron emission tomography (PET), which are time consuming and expensive. Further, high screen-failure rates contribute to cost inflation, prohibitive for some drug developers, rendering some trials infeasible. Simple, inexpensive, and scalable proxy markers that improve AD detection in participants with MCI are required, to recruit into trials more efficiently and reduce screen failures. Neuropsychiatric symptoms (NPS) can emerge early in the disease course; 30% of AD cases present with NPS in advance of a cognitive diagnosis. Mild Behavioral Impairment (MBI) is a syndrome that exploits this early manifestation of NPS to identify a high-risk group for incident cognitive decline and dementia. The ISTAART-AA criteria for MBI stipulate that NPS must emerge de novo in later life and persist for at least 6 months to qualify, echoed in descriptions of pre-dementia NPS in the NIA-AA research framework for AD. Using these criteria, epidemiological studies have demonstrated a significantly higher incidence rate of cognitive decline and dementia in participants with MBI compared to participants with no NPS or with NPS not meeting MBI criteria (NPSnotMBI). Specific to MCI, a recent study found that when participants were stratified by NPS status (i.e., noNPS, NPSnotMBI, or MBI), MBI was associated with a higher progression rate to dementia, and a lower reversion rate to normal cognition. These findings demonstrate the utility of behavioral-risk stratification (represented by MBI) in conjunction with cognitive-risk stratification (represented by MCI) to improve specificity, and highlight the advantage of the MBI framework over conventional models of NPS for dementia prognostication. However, biomarker confirmation of AD status in the MCI progressors is required to move this approach forward into clinical trial recruitment. Preliminary evidence using plasma, CSF, and PET data has demonstrated mostly cross-sectional associations between MBI and amyloid and p-tau. Definitive studies are still required. Here, in MCI participants in two independent studies (ADNI and MEMENTO), we explore cross-sectional and longitudinal associations between MBI and CSF biomarkers (Aβ42, Aβ40, t-tau, p-tau, Aβ42/40, t-tau/Aβ42, and p-tau/Aβ42), and conduct survival analyses for incident AD over 4 years. **Objectives:** In MCI participants, to assess cross-sectional associations between MBI, NPSnotMBI, and no NPS and AD biomarkers measured in CSF. To assess 4-year longitudinal changes in AD biomarkers comparing persistent (MBI) and transient (NPSnotMBI) NPS. To determine relative rates of incident dementia in MBI and NPSnotMBI compared to no NPS. **Methods:** The primary dataset comprised 352 ADNI participants and the validation dataset 158 MEMENTO participants. MCI was defined by standard criteria. MBI was defined in accordance with the ISTAART-AA MBI criteria, in comparison to NPSnotMBI and noNPS. In the ADNI analyses, the Roche Elecsys assay was used for Aβ42, p-tau, and t-tau levels, and mass spectrometry method was used for Aβ42/40 levels. In MEMENTO, Innotest was used for all biomarkers. Linear regressions were fitted to determine cross-sectional associations between NPS status as independent variable, and CSF biomarkers (Aβ42, Aβ40, t-tau, p-tau, Aβ42/40, t-tau/Aβ42, and p-tau/Aβ42) as continuous dependent variables. Hierarchical linear mixed-effects models were implemented to assess the longitudinal relationship between NPS profile (MBI vs NPSnotMBI) and repeated measures of CSF biomarkers over

4-years. Kaplan-Meier and Cox proportional hazards models determined NPS group differences in dementia-free survival time and rates of incident AD. **Results:** ADNI participants had a mean age of 72 (43.5% female, median MMSE=28); MEMENTO participants had a mean age of 69 (46.2% female, MMSE=28). In ADNI, cross-sectional linear regressions showed that compared to noNPS, MBI was associated with lower CSF Aβ42 level and Aβ42/40 ratio, higher CSF p-tau and t-tau levels, and higher t-tau/Aβ42 and p-tau/Aβ42 ratios. NPS-not-MBI was associated only with lower Aβ42/40 ratio. Linear mixed effects models revealed this same AD-specific biomarker profile over 4 years in association with MBI, whereas NPS-not-MBI was associated with higher tau levels. Survival analyses revealed lower AD-free survival and greater rate of incident dementia in MBI (Hazard Ratio (HR) 3.5) relative to comparator groups. ADNI and MEMENTO findings were consistent. MEMENTO, a memory clinic study, demonstrated a similar magnitude and direction of effect for all biomarkers, but with a greater MBI-associated reduction in Aβ40; HR for incident dementia was 3.93 in MBI and 1.83 in NPS-not-MBI. **Conclusion:** We have demonstrated the utility of applying the MBI criteria to MCI to improve the specificity for detection of prevalent AD, and prediction of incident AD dementia. These results are congruent with the a priori goals in development of the MBI criteria, and have implications for research methodology, clinical trial recruitment, drug development, clinical care, and public health efforts. **Disclosures:** All authors report no relevant disclosures.

LP47- COMPARISON OF CYTOKINE PROFILE IN OLDER ADULTS WITH POSITIVE AND NEGATIVE PROTEIN BIOMARKERS AB42, P-TAU, T-TAU AND P-TAU /AB42 RATIO. I.C. Bolaños Burgos[1,2,3,4], G.T. Oliveira Engelmann[4,5,6], E. Oliveira Hansen[7], N. Silva Dias[2,8], A. Teixeira Carvalho[9], D. Valadão[4,10], D. Miranda[2,10,11], M.A. Romano-Silva[2,4,10], B. Mattos Viana[2,8,12], M.A. Camargos Bicalho[1,2,4,5] *(1. Adult Health Sciences Applied Program - Belo Horizonte (Brazil), 2. Hospital das Clínicas - Belo Horizonte (Brazil), 3. National Institute of Science and Technology of Molecular Medicine (INCT-MM), Faculdade de Medicina, Universidade Federal de Minas Gerais - Belo Horizonte (Brazil), 4. Universidade Federal de Minas Gerias - Belo Horizonte (Brazil), 5. Molecular Medicine Program - Belo Horizonte (Brazil), 6. Jenny de Andrade Faria Institute– Reference Center for the ElderlyHospital das Clínicas - Belo Horizonte (Brazil), 7. Jenny de Andrade Faria Institute– Reference Center for the Elderly, Hospital das Clínicas - Belo Horizonte (Brazil), 8. Older Adult Psychiatry and Psychology Extension Program (PROEPSI) - Belo Horizonte (Brazil), 9. René Rachou Institute, Oswaldo Cruz Foundation (Fiocruz) - Belo Horizonte (Brazil), 10. National Institute of Science and Technology of Molecular Medicine (INCT-MM)Faculdade de Medicina, Universidade Federal de Minas Gerais - Belo Horizonte (Brazil), 11. Universidade Federal de Minas Gerias - Belo Horizonte (Bouvet Island), 12. Department of Mental HealthFaculdade de Medicina, Universidade Federal de Minas Gerais - Belo Horizonte (Brazil))*

Background/Objectives: Cytokines are small proteins that indicate inflammatory activity and may impair cognitive function. Moreover, in Alzheimer's disease (AD) the inflammation has been considered one of its neuropathological processes. Deposition of beta-amyloid in the brain may trigger inflammatory processes, as well as the inflammation may accelerate beta-amyloid (Aβ) deposition. Exaggerated release of pro-inflammatory cytokines and chemokines, may result in synaptic dysfunction, neurodegeneration and progression of the disease. Therefore, it's relevant to know the inflammatory profiles of the Cerebrospinal Fluid (CSF) of patients in the AD biomarker continuum. This study aims to compare CSF cytokines levels in older adults with positive and negative biomarkers of proteins Aβ42, p-Tau, t-Tau, and p-Tau/Aβ42 ratio. **Methods:** We collected 80 older adults' CSF by lumbar puncture and stored it at -80ºC. Aβ42, p-Tau, t-Tau, and 27 cytokines were assessed by Luminex xMAP technique. The levels of Aβ42, p-Tau, and t-Tau were determined using the cut-off points for each protein, and made a categorical classification in groups: Aβ42+, Aβ42-, p-Tau+, p-Tau-, t-Tau+, t-Tau- and p-Tau/Aβ42+ e p-Tau/Aβ42-. Comparations of CSF's cytokine levels between these groups were assessed with Mann-Whitney U Test. **Results:** Significantly lower IL-8 levels were found in Aβ42+ compared to Aβ42- groups [U=473,0, p=.029]. The granulocyte colony-stimulating factor (G-CSF) was significantly higher in p-Tau+ [U=625,0, p=.014] and p-Tau/Aβ42+ [U=752,0, p=.033] groups. No significant differences were found between the groups in t-Tau+, and t-Tau-. **Conclusion:** Elevated levels of IL-8 in patients with negative Aβ42 may be related to cell recruitment in response to damage caused by the accumulation of β-amyloid plaques. Increases in G-CSF levels in the p-Tau/Aβ42+ group could be associated with decreased Aβ plaques and greater disease severity. The authors declare that they have no competing interests.

LP48- EARLY DETECTION OF ALZHEIMER'S DISEASE USING MICRORNAS. B. Steinkraus[1], M. Heuvelman[1], J.L. Cummings[2], J. Manson[3], C. Ritchie[3] *(1. Hummingbird Diagnostics - Heidelberg (Germany), 2. Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas - Las Vegas (United States), 3. Centre for Clinical Brain Sciences, The University of Edinburgh - Edinburgh (United Kingdom))*

Background: MicroRNAs (miRNAs) represent a class of ~22nt short non-coding RNAs that have been identified as a sophisticated layer of post-transcriptional regulation, governing many cellular, inflammatory and vascular processes. This characteristic, together with the observation that miRNAs are frequently secreted into the extracellular space and stable in blood and other body fluids, make them specific, robust and above all non-invasive biomarkers that could qualify to augment the amyloid and tau framework. miRNAs have been used for the detection of Alzheimer's disease (AD) in its early forms (e.g., mild cognitive impairment (MCI) due to AD) and to distinguish AD from other dementias. However, to date no miRNA panel has been translated into a clinical test. **Objectives:** With funding from the Alzheimer's Drug Discovery Foundation (ADDF) Hummingbird Diagnostics (HBDx) is developing a blood-based microRNA (miRNA) biomarker intended to inform the diagnosis and prognosis of Alzheimer's disease (AD). The project objective is two-fold: a) to evaluate the diagnostic performance of a miRNA panel in the following deeply phenotyped cohorts: i) amyloid-positive MCI due to AD subjects (prodromal AD), ii) amyloid-negative cognitively unimpaired control subjects, iii) amyloid-positive cognitively unimpaired subjects (preclinical AD), iv) amyloid-negative MCI (due to non-AD conditions) subjects. And, b) to compare baseline small RNA profiles with longitudinal profiles (≥2 years) and clinical outcome data. HBDx seeks to explore biomarkers that can be utilized to characterize clinicopathologic heterogeneity and could lead to the discovery of identifiers of disease prognosis (e.g. rapidly progressive AD). **Methods:** Through collaboration with the European Prevention of Alzheimer's Dementia (EPAD) consortium, we have analyzed 3,302 blood samples of 1,895 patients from over 20 European sites. To ensure a simple, robust, and reproducible platform,

the IVD-certified PAXgene Blood RNA System (PAXgene) was used for the collection, lysis, and subsequent RNA stabilization of whole blood samples to enable "pipetting- and cell sorting-free" sample collection in the clinic. Analytical processes, including RNA extraction, library preparation, and next-generation sequencing (NGS) were optimized to measure a whole blood, immune enriched, small RNA expression profile. We analyzed 1,895 prospectively enrolled individuals ≥50 years of age, 1540 were amyloid negative (81%) and 355 were amyloid positive (19%). Abeta_1_42/P-tau-181 > 0.024 was used as the threshold. We deployed 100-fold cross validation of a linear regression classifier to construct and validate small RNA feature models to evaluate their utility as biomarkers for amyloid positivity as well as for MCI with or without amyloid positivity. **Results:** We generated small RNA feature models and report a median diagnostic receiver operating area under the curve (AUC) of 0.64 for amyloid positivity (Abeta_1_42/P-tau-181 > 0.024). Amyloid positive MCI (CDR 0.5) individuals could be discerned from cognitively unimpaired (CDR 0) amyloid negative individuals with an AUC of 0.75. In a cross-sectional analysis of amyloid positive individuals, we could predict MCI (CDR 0.5) with an AUC of 0.76. Deconvolving the signature into its blood cell and plasma origin, revealed that ~38% of features used for the analysis were found in plasma whilst ~62% originated from circulating immune cells. **Conclusion:** These data suggest the potential of a small RNA-based blood test as a viable complement to the AT(N) framework for the management of individuals at risk for AD.

CLINICAL TRIALS IMAGING

P69- DO THE RADIOMICS OR STRUCTURAL AND FUNCTIONAL MAGNETIC RESONANCE IMAGING GIVE ADDITIONAL INFORMATION TO PREDICT BRAIN AMYLOID POSITIVITY?

Y. Lee[1], S. Jo[1], J. Lee[1] *(1. Asan Medical Center - Seoul (Korea, Republic of))*

Background: Cerebral beta amyloid deposition is a characteristic pathological change in Alzheimer's disease (AD) and precedes the emergence of dementia symptoms by a couple of decades. Current methods to measure amyloid deposition include cerebrospinal fluid study or positron emission tomography (PET). However, these methods are difficult to be used in a large number of population because they are invasive or expensive in nature. **Objectives:** We aimed to predict amyloid positivity using conventional T1 image, radiomics and functional magnetic resonance image (MRI). **Methods:** We included 186 patients with mild cognitive impairment (MCI) who underwent florbetaben positron emission tomography (PET), MRI (3D T1 and diffusion tensor image), neuropsychological tests, and APOE genotyping at Asan Medical Center. We developed separate machine learning algorithm using each MRI feature (T1 volume, cortical thickness, and radiomics, and fractional anisotropy (FA) from diffusion tensor image) in addition to demographics, neuropsychological tests, and APOE genotype to predict amyloid positivity on florbetaben PET. We used 5-fold cross-validation scheme and the procedure were repeated 20 times. We compared the performance of each algorithm based on the MRI features used. **Results:** Study population included 72 patients with MCI in Aβ- group, and 114 patients with MCI in Aβ+ group. The median (IQR) age was 74.0 (65.0-77.5) in Aβ- group and 72.0 (64.0-77.0) in Aβ+ group. The machine learning algorithm using T1 volume performed better than that using only clinical information (0.770 vs. 0.757, p=0.01). The machine learning algorithm using T1 volume showed better performance than that using cortical thickness (mean AUC 0.770 vs. 0.738, p<0.001) or texture (mean AUC 0.770 vs. 0.754, p<0.001). The performance of machine learning algorithm using FA in addition to T1 volume was worse than that using T1 volume only (0.76 vs. 0.77, p<0.01). **Conclusion:** Among MRI features, T1 volume could be used for the prediction of amyloid PET positivity, but radiomics or diffusion tensor image might not have additional benefit.

P70- DIFFERENTIAL EFFECTS OF CARDIOMETABOLIC SYNDROME ON BRAIN AGE IN RELATION TO SEX AND ETHNICITY.

S.H. Kang[1], M. Liu[2], S.W. Seo[3], H. Kim[2] *(1. Department Of Neurology, Korea University Guro Hospital, Korea University College Of Medicine - Seoul (Korea, Republic of), 2. Usc Steven Neuroimaging And Informatics Institute, Keck School Of Medicine Of University Of Southern California - Los Angeles (United States), 3. Departments Of Neurology, Samsung Medical Center, Sungkyunkwan University School Of Medicine - Seoul (Korea, Republic of))*

Background: The incidence of cardiometabolic syndrome (CMS) and the effect of CMS on dementia were different among sex and ethnicity. Although there were growing evidence that CMS exerts on cortical atrophy, the differential effect of CMS on brain age remains unclear. Deep learning approach enable to compute the exact difference between the predicted brain age by the algorithm and the chronological age, called the brain age index (BAI). **Objectives:** To investigate the possible differential effects of CMS on aging based on different ethnicity/race and sex, we firstly estimated the BAIs of both populations without CMS components and analyzed them in relation to sex and ethnicity. Then, we tested whether the association of each CMS component and BAI is modified by either sex or ethnicity. **Methods:** We retrospectively recruited 5,541 cognitively unimpaired participants at Samsung medical center in Korea, and 9,903 participants from UK biobank. We developed BAI prediction model using graph-convolutional networks. We analyzed the associations of CMS and BAI using generalized linear models and three-way interactions with sex and ethnicity. **Results:** The BAI of healthy populations was lower in women than in men regardless of ethnicity (UK, $p = 0.006$, Cohen's $d = 0.12$; Korean, $p < 0.001$, Cohen's $d = 0.39$). Particularly, the difference in BAI between men and women was more prominent in the Korean compared to the UK metabolically healthy population (p for interaction = 0.002). Diabetes was associated with a higher BAI regardless of sex or ethnicity ($p < 0.001$ in all groups), and hypertension significantly increased BAI for all participants except the Korean men ($p < 0.001$ in UK men, UK women and Korean women; $p = 0.390$ in Korean men). Furthermore, the effects of diabetes and hypertension on BAI showed significantly interactive effects between sex and ethnicity (diabetes, p for interaction < 0.001; hypertension, p for interaction = 0.005). Specifically, diabetes and hypertension had more deleterious effects on brain aging in Korean women compared to that in Korean men, whereas they had more deleterious effects on brain aging in UK men than that in UK women. **Conclusions:** Our findings suggest that metabolically healthy women may have a lower brain age than men regardless of ethnicity. However, cardiometabolic risk factors may exert differential effects on brain age in relation to sex and ethnicity. Consequently, ethnic- and sex-specific prevention strategies are recommended to protect against accelerated brain aging.

P71- GENOME-WIDE ASSOCIATION STUDY OF THE FUNCTIONAL BRAIN NETWORK FOR ALZHEIMER'S DISEASE. M. Kim[1], J.M. Lee[2] *(1. Department Of Electronic Engineering, Hanyang University - Seoul (Korea, Republic of), 2. Department Of Biomedical Engineering, Hanyang University - Seoul (Korea, Republic of))*

Background: Genome-Wide Association Study (GWAS) with neuroimaging-derived endophenotypes can serve as a screening tool to analyze the association between genetic variants and disease-associated brain traits to elucidate the genetic basis of the disease. **Objectives:** The goal of this study was to identify genetic risk loci significantly associated with functional brain network properties in AD. **Methods:** Data were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The subjects who had both resting-state functional MRI (rs-fMRI) and single nucleotide polymorphism (SNP) genotype data were selected from the ADNI2. The sample consisted of 137 individuals with 5 groups including CN (n = 31), SMC (n = 21), EMCI (n = 28), LMCI (n = 29) and AD (n = 28). For genetic data, un-genotyped SNPs were imputed and quality-control procedures for samples and SNPs were performed using PLINK v1.9 software. Finally, 7,618,009 bi-allelic SNPs in autosomal chromosomes remained. The rs-fMRI preprocessing was conducted using Statistical Parametric Mapping (SPM12) software and Data Processing Assistant for Resting-State fMRI Advanced edition (DPARSFA). After removing the first 5 time points, the images were slice timing corrected, realigned, spatially normalized into the MNI space and resampled. Time-series data were smoothed and filtered with 0.01 ~ 0.1 Hz. The cerebrospinal fluid and the white matter signals were removed as nuisance covariates. In the process of preparing endophenotypes for GWAS, the static functional brain network was constructed using Graph thEoreTical Network Analysis (GRETNA) toolbox. After mean time series were computed in each of the functional ROIs based on the Dosenbach-160 atlas, a connectivity matrix per subject was constructed. Binary networks were obtained by thresholding with a wide range of sparsity (5% to 50%) with intervals of 0.05. Finally, the following 7 global network metrics were calculated as AUC values: clustering coefficient, characteristic path length, normalized clustering coefficient, normalized characteristic path length, small-worldness, global efficiency and local efficiency. To measure the allelic effects of all SNPs on the 7 global network properties as phenotypes, we performed GWAS using PLINK software. As our phenotypes showed skewed distributions, the values were quantile normalized. Linear additive models considering age, sex, education level and ApoE4 genotype as covariates were used. SNPs that passed the genome-wide significance threshold of $p < 5e-08$ were considered statistically significant. The less stringent threshold was set at $p < 1e-07$. Subsequently, we calculated gene-based p-values from SNP p-values using KGG4 software and conducted a gene-based association analysis. The ideal statistical threshold was $p < 2.5e-06$ considering 20,000 genes. The suggestive threshold was set at $p < 2.5e-05$. As a post-GWAS, we conducted an expression quantitative trait locus (eQTL) analysis to figure out the functional effect of identified candidate genetic variants. Data were downloaded from the Brain eQTL Almanac (Braineac) database and gene expression levels were investigated in 10 brain regions. The significance threshold was $p < 0.05$. **Results:** From GWAS, no SNP passed the genome-wide significance threshold ($p < 5e-08$). As a result, all genetic variants that exceeded the less stringent threshold ($p < 1e-07$) were regarded as candidate genetic variants and two SNPs were identified. The rs7140236 on chromosome 14 showed a negative correlation with global efficiency ($p = 5.328e-08$) and the rs59143542 on chromosome 7 showed a positive correlation with local efficiency ($p = 9.269e-08$). In the gene-based association analysis, genes that satisfied the suggestive significance ($p < 2.5e-05$) were chosen for further analysis. LOC101928575 on chromosome 14 was detected for the global efficiency metric ($p = 6.03e-06$). Characteristic path length property was affected by the TTC9 gene on chromosome 14 ($p = 2.48e-05$). The peak SNP in the previous analysis with the same metric was rs7140236. In the eQTL procedure, the LOC101928575 was not found in the database. Expression levels of the gene TTC9 were stratified by rs7140236 in the hippocampus ($p = 0.0041$), substantia nigra ($p = 0.044$), temporal cortex ($p = 0.0047$), frontal cortex ($p = 0.035$) and putamen ($p = 0.046$). **Conclusion:** In this study, we performed GWAS, gene-based association study, and eQTL analysis of the whole-brain functional network properties to identify genetic risk loci for AD. We found that rs7140236 in TTC9 on chromosome 14 and rs59143542 on chromosome 7 are associated with global efficiency and local efficiency, respectively. Especially, the rs7140236 was repeatedly detected as a candidate genetic locus in further analyses. This result suggests that rs7140236 can be a candidate genetic risk locus for AD in that it negatively affects the global efficiency of the brain and regulates the expression level of the protein-coding gene in AD-related brain regions.

P72- CLINICAL AND RADIOMIC FEATURES FOR PREDICTING THE TREATMENT RESPONSE OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN MAJOR NEUROCOGNITIVE DISORDER. H. Lu[1], S.S.M. Chan[1], S.L. Ma[1], V.C.T. Mok[1], L. Shi[1], A.D.P. Mak[1], L.C.W. Lam[1] *(1. The Chinese University of Hong Kong - Hong Kong (Hong Kong))*

Background: Image-guided repetitive transcranial magnetic stimulation (rTMS) has shown clinical effectiveness in senior adults with co-occurring depression and cognitive impairment, yet the imaging markers for predicting the treatment response are less investigated. In this clinical trial, we examined the efficacy and sustainability of 10 Hz rTMS for the treatment of depression and cognitive impairment in major neurocognitive disorder (NCD) patients and tested the predictive values of imaging-informed radiomic features in response to rTMS treatment. **Methods:** Fifty-five major NCD patients with depression were randomly assigned to receive a 3-week rTMS treatment of either active 10 Hz rTMS (n=27) or sham rTMS (n=28). Left dorsolateral prefrontal cortex (DLPFC) was the predefined treatment target. Based on individual structural magnetic resonance imaging scans, surface-based analysis was conducted to quantitatively measure the baseline radiomic features of left DLPFC. Severity of depression, global cognition and the serum brain-derived neurotrophic factor (BDNF) level were evaluated at baseline, 3-week, 6-week and 12-week follow-ups. **Results:** Logistic regression analysis revealed that advanced age, higher baseline cognition and randomized group were associated with the remission of depression. Increased cortical thickness and gyrification in left DLPFC were the significant predictors of clinical remission and cognitive enhancement. **Conclusions:** A 3-week course of 10 Hz rTMS is an effective adjuvant treatment for rapid ameliorating depressive symptoms and enhancing cognitive function. Pre-treatment radiomic features of the stimulation target can predict the response to rTMS treatment in major NCD. Cortical thickness and folding of treatment target may serve as imaging

markers to detect the responders. **Trial registration:** ChiCTR-IOR-16008191, registered on March 30, 2016. The authors have no conflicts of interest.

P73- ASSOCIATION OF REGIONAL AMYLOID BURDEN AND BRAIN VOLUME WITH COGNITIVE PERFORMANCES AMONG INDIVIDUALS WITH SUBJECTIVE COGNITIVE DECLINE. C. Lee[1], D.W. Yang[1], Y.J. Hong[2], S. Ho[3], J.H. Jeong[4], K.H. Park[5], S. Kim[6], M.J. Wang[7], S.H. Choi[8], S. Lee[9] *(1. Neurology, Catholic University Of Korea, Seoul St. Mary's Hospital - Seoul (Korea, Republic of), 2. Neurology, Catholic University Of Korea, Seoul St. Mary's Hospital - Uijeongbu (Korea, Republic of), 3. Neurology, Changwon Hanmaeum Hospital - Changwon (Korea, Republic of), 4. Neurology, Womans University School Of Medicine, Ewha Womans University Seoul Hospital - Seoul (Korea, Republic of), 5. Neurology, Gachon University Gil Hospital - Incheon (Korea, Republic of), 6. Neurology, Seoul National University College Of Medicine, Seoul National University Bundang Hospital - Seongnam (Korea, Republic of), 7. Neurology, Roa Clinic - Seongnam (Korea, Republic of), 8. Neurology, Inha University School Of Medicine, Inha University Hospital - Incheon (Korea, Republic of), 9. Neolab Convergence Inc. - Seoul (Korea, Republic of))*

Background: Subjective cognitive decline (SCD) is now regarded as the first preclinical stage of Alzheimer's disease (AD) spectrum disorders. Previous studies showed neurodegeneration and amyloid deposition in SCD are similar to those in AD, suggesting the possible relationship between SCD and AD pathology. **Objectives:** In this study, we aimed to evaluate associations between regional amyloid burden and volume changes with cognitive performances among individuals with SCD. **Methods:** This cross-sectional study examined baseline automatic regional brain magnetic resonance imaging (MRI) volumetric data, visual and SUVR analysis of 18F-Florbetaben brain amyloid Positron Emission Tomography (PET), demographics and cognitive data from the cohort of the CoSCo study in republic of Korea from July 2018 to December 2020. A subset of this sample, 87 amyloid-negative and 20 amyloid-positive individuals included in this study. Considering Alzheimer's disease pathology, we mainly analyzed volume of hippocampus and entorhinal cortex (z-scores adjusted for age, sex and intracranial volume) and SUVR of precuneus, inferior temporal, superior orbitofrontal, middle orbitofrontal and post cingulate cortex in amyloid PET. All patients underwent the standardized neuropsychological test battery of the Seoul Neuropsychological Screening Battery (SNSB) that assesses five cognitive domains (attention, language, visuospatial function, memory and frontal/executive function). Correlations between both regional brain volume, SUVR and neuropsychological test percentile scores were determined using Pearson's or Spearman's correlation tests according to the variable distribution in each amyloid group. **Results:** Of the 107 patients (mean (SD) age, 70.7 (6.2) years); 59 were women (55.1%). Amyloid PET results were positive for 20 patients (18.7%). Amyloid-positive patients were older and more educated than amyloid-negative patients ($p \leq 0.05$). Seoul Verbal Learning Test: 20 minutes delayed recall scores in amyloid positive group were significantly lower than amyloid negative group (p=0.005). In amyloid positive group, partial correlation analysis controlled for education showed significant positive correlation between Korean-Color Word Stroop Test : color reading and both left entorhinal cortex (r=0.534, p=0.019) and left hippocampal (r=0.593, p=0.009) volume. In amyloid negative group, left hippocampal volume was significantly and negatively correlated with Digit Span Forwards test (r=-0.226, p=0.036). Right hippocampal volume was positively correlated with Rey Complex Figure Test : 20 minutes delayed recall (r=0.250, p=0.020). Korean-Boston Naming Test showed negative correlation with regional SUVR values of 4 areas (precuneus, inferior temporal cortex, middle orbitofrontal cortex and post cingulate cortex) in amyloid positive group. In amyloid negative group, both precuneus and post cingulate cortex SUVR were positively correlated with Korean Trail Making Test B. Inferior temporal cortex SUVR was positively correlated with both Digit Span Forwards and Korean-Color Word Stroop Test : color reading. **Conclusions:** Our study showed distinctive correlation pattern between both structural changes, amyloid burden and cognitive tests scores in each SCD group with or without amyloid. Amyloid positive SCD showed higher correlation between regional brain volume and cognitive subtest scores. These findings may be helpful for the screening of SCD population at risk of conversion to MCI or dementia. CoSCo study was supported by a grant from the Ministry of Health and Welfare, HI18C0530

P74- THE ROLE OF SUBTHRESHOLD LEVELS OF AMYLOID DEPOSITION ON DEMENTIA CONVERSION-VALIDATED WITH ADNI. H.J. Kim[1], J.H. Lee[2] *(1. Uijeongbu Eulji Medical Center - Uijeongbu-Si (Korea, Republic of), 2. Asan Medical Center - Seoul (Korea, Republic of))*

Background: About 40–50% of patients with amnestic mild cognitive impairment (MCI) are found to have no significant Alzheimer's pathology based on amyloid PET positivity. Notably, conversion to dementia in this population is known to occur much less often than in amyloid-positive MCI. However, the relationship between MCI and brain amyloid deposition remains largely unknown. **Object:** We investigated the influence of subthreshold levels of amyloid deposition on conversion to dementia in amnestic MCI patients with negative amyloid PET scans. **Methods:** This study was a retrospective cohort study of patients with amyloid-negative amnestic MCI who visited the memory clinic of Asan Medical Center. All participants underwent detailed neuropsychological testing, brain magnetic resonance imaging, and [18F]-florbetaben (FBB) positron emission tomography scan (PET). Conversion to dementia was determined by a neurologist based on a clinical interview with detailed neuropsychological test or a decline in the Korean version of Mini-Mental State Examination score of more than 4 points per year combined with impaired activities of daily living. Regional cortical amyloid levels were calculated and a receiver operating characteristic (ROC) curve for conversion to dementia was obtained. To increase the reliability of the results of the study, we analyzed Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset together. **Results:** During the follow-up period, 36% (39/107) of patients converted to dementia from amnestic MCI. The dementia converter group displayed increased standardized uptake value ratio (SUVR) values of FBB on PET in the bilateral temporal, parietal, posterior cingulate, occipital, and left precuneus cortices as well as increased global SUVR. Among volume-of-interests, the left parietal SUVR predicted conversion to dementia with the highest accuracy in the ROC analysis (area under the curve [AUC] = 0.762, $P < 0.001$). The combination of precuneus, parietal cortex, and FBB composite SUVRs also showed a higher accuracy in predicting conversion to dementia than other models (AUC = 0.763). Of the results of ADNI data, the SUVR of the left precuneus SUVR showed the highest AUC (AUC = 0.596, P = 0.006). **Conclusion:** Our findings suggest that subthreshold amyloid levels may contribute to conversion to

dementia in patients with amyloid-negative amnestic MCI. The authors declare no competing interests.

P75- EVALUATION OF A CLINICALLY VALIDATED DIGITAL PLATFORM TO PROVIDE DIFFUSION MRI BIOMARKERS IN ALZHEIMER'S DISEASE. E. Bories[1], A. Bezie[1], D. Cassereau[1], J. Rachline[1], I. Trimeche[1], J.B. Martini[1], V. Perlbarg[1] *(1. BRAINTALE SAS - Strasbourg (France))*

Background: White matter alterations are observed at a very early stage of Alzheimer's disease (1), including demyelination, axonal loss and abnormalities of oligodendrocyte lineage cells (2). Research studies in Alzheimer's disease showed that diffusion tensor imaging (DTI) allows to detect white matter alterations (3). The translation into the clinic of meaningful biomarkers developed or used in research framework remains a major challenge, especially to monitor the efficacy of new therapeutics in real life conditions and ultimately to monitor disease and enable efficient follow up of patients. brainTale-care, a recently CE-marked platform, overcomes this issue by providing standardized DTI parameters and designing fit-for-purpose digital biomarkers. These biomarkers are relevant for several purposes, such as predicting the outcome of comatose patients in ICU settings with extensive clinical validation (4) or monitoring the efficacy of drug candidates in clinical development settings notably in adrenoleukodystrophy (5). **Objectives:** The main objective of this study was to test whether standardized DTI biomarkers, activable in clinical routine through a clinically validated CE-marked platform, can discriminate between patients with Alzheimer's disease from age-matched normal controls and subjects with mild cognitive impairments (MCI). **Methods:** MRI data, including diffusion weighted imaging sequences, were obtained from 113 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) : 66 healthy controls (HC), 34 patients with MCI and 13 diagnosed with dementia (DEM). These subjects have been selected from 5 different centers for which the same MRI diffusion weighted sequence have been acquired in HC than in patients to ensure proper calibration of DTI parameters required for multicentric data comparisons. The brainQuant module of brainTale-care v2.2 was used to extract standardized DTI parameters (Fractional Anisotropy: FA, Mean Diffusivity: MD, Axial Diffusivity: AD, Radial Diffusivity: RD) from deep white matter consisting in 20 regions of interest covering the main cerebral white-matter tracts (6). Kruskal-Wallis H-tests were used for group comparisons following post-hoc Mann-Whitney tests in case of significant ($p<0.05$) group effects. **Results:** Significative group effects were found for all DTI parameters. Post-hoc test for group comparison showed significant differences between DEM and HC groups as well as between MCI and HC groups. Decrease FA and increase MD, AD and RD were observed in pathological conditions. In more details, MD, AD and RD significantly increase for DEM and MCI in comparison to controls as well as FA decrease in MCI compared to controls. **Conclusions:** This study shows that global alterations within the main cerebral white-matter tracts from brainQuant module of Braintale care- platform enabling analysis are relevant biomarkers of disease severity. The access to these biomarkers in a CE-marked medical device opens the potential of this approach to be transferred in the clinic for diagnosis, disease monitoring decision-making and also potentially clinical trials recruitment and management. **References:** 1. Lee et al. White matter hyperintensities are a core feature of Alzheimer's disease: Evidence from the dominantly inherited Alzheimer network. Ann Neurol. 2016; 2. Nasrabady et al. White matter changes in Alzheimer's disease: a focus on myelin and oligodendrocytes. Acta Neuropath Comm. 2018; 3. Mayo et al., Alzheimer's Disease Neuroimaging Initiative. Longitudinal changes in microstructural white matter metrics in Alzheimer's disease. Neuroim Clin. 2016; 4. Velly L et al. Use of brain diffusion tensor imaging for the prediction of long-term neurological outcomes in patients after cardiac arrest: a multicentre, international, prospective, observational, cohort study. Lancet Neurol. 2018; 5. Vincent Perlbarg et al. Myelin content monitoring by diffusion biomarkers in a therapeutic trial with leriglitazone in men with adrenomyeloneuropathy (P1-1.Virtual). Neurology May 2022, 98 (18 Supplement); 6. Van der Eerden et al. White matter changes in comatose survivors of anoxic ischemic encephalopathy and traumatic brain injury: comparative diffusion-tensor imaging study. Radiology. 2014. **Disclosures:** EB, AB, IT, JB and VP are employees of BrainTale, inc. in Paris, France; VP is co-founder of BrainTale, inc. in Paris, France; DC and JR are consultants of BrainTale, inc. in Paris, France.

P76- INCREASE IN WHITE MATTER VOLUME AND MYELINATION AFTER 6 MONTHS. X. Da[1], E. Hempel[1], H. Mrozak[1], Z. Malchano[1], B. Vaughan[1], J.T. Megerian[1], M. Hajos[1,2], A. Cimenser[1] *(1. Cognito Therapeutics - Cambridge, Ma (United States), 2. Yale University School of Medicine - New Haven, Ct (United States))*

Background: Alzheimer's Disease (AD) is characterized by the pathological changes in the brain gray matter, however recent studies have also demonstrated pathologies in white matter, including significant volume loss. Since white matter comprises axons, microglia, oligodendrocyte precursor cells and myelin-producing oligodendrocytes, degeneration in this region ultimately affects the neuronal network connectivity and function. Advanced imaging techniques have further revealed micro- and macro- structural abnormalities of the white matter in AD, and significant differences between AD patients and age-matched healthy controls. Furthermore, enhancing myelination has been suggested as a therapeutic strategy for improving cognition in AD (Chen et al., 2021). Gamma sensory stimulation has been proposed as a potential treatment of AD, and multiple studies have showed positive effects of 40Hz gamma sensory stimulation in AD transgenic mouse models (for review, see Adaikkan & Tsai, 2020), and more recently, in AD patients (He et al., 2021, Cimenser et al., 2021). However, potential impact of this therapy on white matter and myelination has not been studied. **Objectives:** The present study evaluated whether gamma sensory stimulation could impact white matter atrophy and myelination in patients on AD spectrum who received gamma stimulation therapy for a 6-month period. Changes in entorhinal region was measured since this region is a key structure providing connections for transferring bidirectional information between cortical and hippocampal networks. Furthermore, both histological and neuroimaging studies have shown that the entorhinal region is one of the brain regions impacted in early stage of the AD. **Methods:** Neuroimaging data collected in Cognito Therapeutics' Overture clinical trial is used in this study. Overture is a randomized, placebo-controlled feasibility study (NCT03556280) in patients (MMSE 14-26) on AD spectrum. In this trial, subjects in the active treatment arm received daily, at-home, 40Hz gamma sensory stimulation for a 6-month period while the placebo arm subjects received sham stimulation. Structural magnetic resonance imaging (MRI) data was obtained at baseline, month 3 and month 6 visits using 1.5 Tesla MRI scanner. FreeSurfer and

SPM12 plugin toolbox, MRTool, were used to study multiple white matter structures for 38 participants (66% Treatment, 34% Placebo). Volume assessments were done using T1 MRI. Myelination assessments were done using T1w/T2w ratio. Due to T2w image quality, 2 patients were excluded from the myelination analysis. Bayesian linear mixed effects modeling was used to assess the changes from baseline. Changes in white matter volume and myelination were compared between treatment group and placebo group participants after 6 months of treatment. **Results:** With respect to baseline levels, we observed that the treatment group demonstrated 1.06±5.35 cm3 increase and the placebo group demonstrated –12.37± 6.81 cm3 decrease in total cerebral white matter volume. The difference between the treatment and the placebo groups was statistically different ($p<0.036$). Entorhinal white matter showed profound changes: The treatment group demonstrated 0.08±0.06 cm3 increase, while the placebo group demonstrated -0.13±0.07 cm3 decrease in volume. The difference between these two groups was statistically significant ($p<0.004$). Within the same region, the treatment group demonstrated 2.78±4.97 % increase and the placebo group demonstrated -10.59±5.63 % decrease in myelination. This difference was also statistically significant ($p<0.003$) between groups. **Conclusion:** We conclude that 40Hz gamma sensory stimulation led to beneficial effects on both white matter volume and myelination after 6 months of treatment. Specifically, the treatment may significantly reduce white matter atrophy and substantially prevent white matter myelin damage in the entorhinal region. Damage of this brain region is particularly relevant to AD pathology due to its afferent connections to the hippocampus and the entorhinal cortex. Further larger studies are warranted to confirm effects of gamma sensory stimulation on white matter atrophy and myelination and provide an insight to potential mechanism. **References:** Adaikkan C, Tsai LH. Gamma Entrainment: Impact on Neurocircuits, Glia, and Therapeutic Opportunities. Trends Neurosci. 2020 Jan;43(1):24-41. Cimenser A, Hempel E, Travers T, Strozewski N, Martin K, Malchano Z, Hajós M. Sensory-Evoked 40-Hz Gamma Oscillation Improves Sleep and Daily Living Activities in Alzheimer's Disease Patients. Front Syst Neurosci. 2021 Sep 24;15:746859. Chen JF, Liu K, Hu B, Li RR, Xin W, Chen H, Wang F, Chen L, Li RX, Ren SY, Xiao L, Chan JR, Mei F. Enhancing myelin renewal reverses cognitive dysfunction in a murine model of Alzheimer's disease. Neuron. 2021 Jul 21;109(14):2292-2307.e5. He Q, Colon-Motas KM, Pybus AF, Piendel L, Seppa JK, Walker ML, Manzanares CM, Qiu D, Miocinovic S, Wood LB, Levey AI, Lah JJ, Singer AC. A feasibility trial of gamma sensory flicker for patients with prodromal Alzheimer's disease. Alzheimer's Dement (N Y). 2021 May 13;7(1):e12178.

P77- SUMMARY OF ACR PHANTOM MRI SITE QUALIFICATION FINDINGS OVER 7 YEARS AND RECOMMENDATIONS MOVING FORWARD.

L. Bracoud[1], J. Oh[2], Q. Cao[2], C. Conklin[3], M. Ingalhalikar[3], H. Pham[2], D. Scott[2], J. Suhy[2] *(1. Clario (formerly Bioclinica) - Lyon (France), 2. Clario (formerly Bioclinica) - San Mateo (United States), 3. Clario (formerly Bioclinica) - Princeton (United States))*

Background: As part of qualification activities for MRI sites participating in Alzheimer's disease and related dementia type trials, where quantitative volumetric analyses are involved, it has become the norm that phantom scans be performed to verify scanner performance and MRI protocol set-up ahead of the first subject scan. Such phantom scans are also typically performed periodically as a longitudinal follow-up to monitor scanner performance. For that purpose, the American College of Radiology (ACR) phantom has been employed. It consists of a short, hollow cylinder of acrylic plastic closed on both ends. While resulting images will by no means visually compare to in-vivo data, inside the phantom are structures designed for performing several quantitative tests. Further, the phantom is filled with a solution of nickel chloride and sodium chloride to simulate a typical electric load of a human head, therefore justifying that data be reflective of future image quality. **Objectives:** Having accumulated multiple thousands of such scans over the past years, the objective of this retrospective analysis was to identify the types of issues commonly found in the ACR phantom scans and their frequency. After years of collecting these scans across sites globally, the impression was that actual scanner performance issues are becoming extremely uncommon, and that it may not be necessary to impose this process to all imaging sites, as this is a time-consuming procedure that adds burden to the sites, together with the cost associated with acquiring and assessing the scans. **Methods:** We included analysis results of ACR phantom scan submissions (N=9080) collected from 2015 to 2021 from 11 global trials in 38 countries worldwide on 1.5T and 3T scanners manufactured by GE, Philips and Siemens. MRI data consisted of the T1-weighted MRI sequences recommended in the ACR scanning guidelines, that is a single-slice Sagittal T1 Spin Echo (in-plane resolution = 0.98×0.98 mm2, slice thickness = 10 mm), and an 11-slice Axial T1 Spin Echo (same resolution, slice thickness = 5 mm, slice gap = 5 mm). Besides, all mandatory brain MRI sequences expected from study participants were also required, so that the MRI protocol settings could be automatically verified based on DICOM header information. Most of the tests recommended in the ACR guidelines were conducted per these instructions, namely a qualitative evaluation, together with tests for geometrical accuracy, high contrast spatial resolution, image intensity uniformity, low contrast object detectability and percent signal ghosting. The outcome of this Quality Control (QC) was either to pass the scan (and therefore qualify the scanner) or ask for servicing of the MRI scanner and/or adjustments of the settings used, with or without requiring a new scan to take place. Only after successful resolution of all pending issues would the scanner be qualified. **Results:** Of the 9080 QC results reviewed, outcome was pass in 86.5% of cases. Among the 13.5% that failed, the most common issue reported was the use of incorrect (or suboptimal) imaging parameters (85.7%), followed by poor positioning of the ACR phantom (6.6%), use of an incorrect scanner, coil or phantom (3.7%) or data format issues (1.5%). Only in 0.1% of cases was there an actual technical issue related to scanner malfunction. Such low failure rate can be explained by the fact that all MRI scanners are subjected to regular (daily or weekly) maintenance and monitoring procedures at local site level, as well as by the continuous improvement in the stability of MRI scanners. **Conclusions:** The first goal sought during site qualification, which is to verify proper implementation of the study MRI protocol, can be achieved without a dedicated ACR phantom scan. A regular MRI-compatible phantom or test object could be used, but this would still require time spent running the MRI protocol on the scanner. A more efficient and equally thorough method could consist of collecting a protocol export generated from the scanner and submitted electronically, for a similarly automated and effective verification of parameters used. This could lower the site burden by not having the site perform a dedicated phantom scan and shorten the start-up timeline with no impact on the quality of the site qualification process. The use of protocol exports may not catch the use of the improper

coil, or the over-masking of DICOM tags. But it was found that these issues may still occur on the first subject scans irrespective of what was observed on preceding phantom scans. Therefore, the benefit-risk ratio is still highly in favor of phasing out ACR phantom scans as the means by which to qualify sites and monitor scanner performance.

P79- EFFECTS OF ALZHEIMER AND LEWY BODY DISEASE PATHOLOGIES ON BRAIN METABOLISM.

B.S. Ye[1], S.W. Kang[2] *(1. MD. PhD - Seoul (Korea, Republic of), 2. MD - Seoul (Korea, Republic of))*

Background: In vivo detection of mixed pathologies in patients with neurodegenerative dementia would have clinical importance for treatment and predicting prognosis. **Objective:** This study aimed to determine the pattern of18F-fluorodeoxyglucose positron emission tomography (FDG-PET) related to postmortem Lewy body disease (LBD) pathology in clinical Alzheimer disease (AD). **Methods:** FDG-PET scans were analyzed in 62 autopsy-confirmed patients and 110 controls in the Alzheimer's DiseaseNeuroimaging Initiative. Based on neuropathologic evaluations on Braak stage for neurofibrillary tangle, Consortium toEstablish a Registry for AD score for neuritic plaque, and Lewy-related pathology, subjects were classified into AD()/LBD(), AD()/LBD(+), AD(+)/LBD(), and AD(+)/LBD(+) groups. The association between postmortem LBD and ADpathologies and antemortem brain metabolism was evaluated. **Results:** AD and LBD pathologies had significant interaction effects to decrease metabolism in the cerebellarvermis, bilateral caudate, putamen, basal frontal cortex, and anterior cingulate cortex in addition to the left sideof the entorhinal cortex and amygdala, and significant interaction effects to increase metabolism in the bilateralparietal and occipital cortices. LBD pathology was associated with hypermetabolismin the cerebellar vermis, bilateral putamen, anterior cingulate cortex, and basal frontal cortex, corresponding to the Lewy body-relatedhypermetabolic patterns. AD pathology was associated with hypometabolism in the bilateral hippocampus,entorhinal cortex, and posterior cingulate cortex regardless of LBD pathology,whereas LBD pathology wasassociated with hypermetabolism in the bilateral putamen and anterior cingulate cortex regardless of ADpathology. **Conclusion:** Postmortem LBD and AD pathologies had significant interaction effects on the antemortem brainmetabolism in clinical AD patients. Specific metabolic patterns related to AD and LBD pathologies could be elucidatedwhen simultaneously considering the two pathologies.

P80- REDUCING SLEEP APNOEA FOR THE PREVENTION OF DEMENTIA (RESHAPED): THE PROTOCOL OF A MULTI-SITE FEASIBILITY RANDOMISED CONTROLLED TRIAL.

S. Naismith[1], C. Hoyos[1], C. Phillips[1], Y. Kristine[2], R. Martins[3], N. Marshall[1], J. Lagopoulos[4], M. Jackson[5], L. Mowszowski[1], R. Grunstein[1] *(1. University of Sydney - Sydney (Australia), 2. University of California - San Francisco (United States), 3. University of Macquarie - Sydney (Australia), 4. University of Sunshine Coast - Sunshine Coast (Australia), 5. Monash University - Melbourne (Australia))*

Background: Obstructive sleep apnoea (OSA) is a sleep disorder characterised by complete or partial cessation of breathing during sleep. The rates of OSA increases up to 70% in older adults. There is accumulating evidence that has linked OSA with increased risk of cognitive decline, increase in beta-amyloid, and dementia (Leng et al. 2017). Preliminary evidence suggests that continuous positive airway pressure (CPAP) may be beneficial for cognition. In mild cognitive impairment, a pilot study of 3-months (n=26) showed that CPAP was associated with improvements in verbal learning and memory in older adults with mild cognitive impairment (Hoyos et al., 2022). In a 1-year quasi-experimental pilot trial with older adults with MCI and were CPAP adherent (use of 4 hours or more; n=29) showed improvements in memory, attention, and daytime sleepiness compared to those who were not adherent (Richards et al., 2020). These preliminary findings suggest that CPAP for older adults with concomitant OSA and cognitive impairment may show improvement in cognitive function or slow cognitive decline. However, larger randomised controlled trials (RCT) are necessary to confirm these findings. **Objectives:** As defined in the UK MRC framework of complex interventions, it is critical to firstly establish feasibility of the recruitment strategy, methods, measures, and intervention before proceeding to a full-scale RCT. Here we present a national multi-site randomised controlled, parallel open-label trial which aims to evaluate the feasibility for a full-scale trial investigating the effects of treating OSA on cognitive decline in older adults at risk of dementia with OSA within memory clinic settings. The primary outcome of the study are 1) demonstrating acceptability by ≥50% of eligible participants randomised; 2) alleviating hypoxic burden by reducing OSA severity by ≥30%; 3) Determining tolerability of the outcome assessment of the planned primary outcome. Secondary outcomes include safety (the rate of participants who drop in or out of treatment, as well as rate and types of adverse events) and cognitive function (assessed using traditional and online measures) after 2-years of treatment. **Methods:** Participants will be randomized to either the treatment intervention group or control group for 2-years. This feasibility study aims to randomise 180 older adults aged between 50-75 years with mild-severe OSA (defined as an average ODI ≥ 10 with 3% oxygen desaturation determined by wrist oximetry over two nights) and subjective cognitive complaints or MCI. Participants will be recruited through hospital, university and private memory clinics. OSA will be diagnosed with at-home oximetry screening using a wrist-worn device with a finger sensor (WristOx, Nonin). The treatment intervention arm intends to achieve an optimal treatment response based on reducing hypoxic burden with either CPAP, mandibular advancement splint, positional therapy, or oxygen therapy. Furthermore, participants in this arm will receive up to 8 treatment sessions which involve motivational interviewing, collaborative goal setting, and behavioural sleep management. The control arm will not receive OSA treatment as part of this trial, however there will be no OSA treatment restrictions and any treatment will be documented. Data collection and assessments will occur at baseline, 6-month, and 24-month timepoints. These assessments will involve medical assessment, full cognitive battery (processing speed, executive function, learning and memory), blood collection (ApoE4, hsCRP, p-tau181, p-tau 217, Gfap, and Nfl) and brain magnetic resonance imaging scan (optional). This clinical trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621001190897). The study is funded by the National Health and Medical Research Council (NO:1171479). The sponsor is The University of Sydney. Recruitment has commenced in 2022 with an expected recruitment end date of 2026. **References:** Hoyos, C. M., Cross, N. E., Terpening, Z., D'Rozario, A. L., Yee, B. J., LaMonica, H., Marshall, N. S., Grunstein, R. R., & Naismith, S. L. (2022). CPAP for Cognition in Sleep Apnea and Mild Cognitive Impairment:

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P81- ARTERIAL STIFFNESS IS ASSOCIATED WITH CORTICAL TAU BURDEN. Y. Noh[1] *(1. Gachon University Gil Medical Center - Incheon (Korea, Republic of))*

Objectives: Previous studies have shown that vascular risk factors are also risk factors of Alzheimer's disease frequently. However, the relationship between cerebrovascular disease and Alzheimer's pathology remains unclear. In this study, we evaluated the relationship between arterial stiffness and cortical tau burden with consideration of β-amyloid burden. **Methods:** Total number of 153 participants was included (cognitively normal, 57; Alzheimer's disease, 53; non-AD dementia and MCI, 43). They took detailed neuropsychological tests, magnetic resonance imaging (MRI), 18F-Flutemetamol [FLUTE] PET as amyloid PET, 18F-MK-6240 PET as tau PET and transcranial Doppler (TCD). We evaluated arterial stiffness with penetrating arterial pulsation using the sonographic resistance index (RI) along the M1 segment of middle cerebral artery (MCA). MRIR was defined as distal RI divided by proximal RI. We used generalized additive model (GAM) to check if there is a non-linear relationship between arterial stiffness (MRIR) and tau burden adjusted for age, gender, educational years, Framingham Heart Study cardiovascular disease (FHS-CVD) score, total metabolic equivalents (METS), and diagnosis. Multivariable linear regression was used to check if there is a linear relationship between MRIR and tau burden or amyloid burden, where MRIR >=1. Lastly, we used causal mediation analysis to check if amyloid burden mediates the association between MRIR and tau burden where MRIR >=1. **Results:** Between MRIR and tau burden, U-shaped relationship was statistically significant (p=0.026). Linear relationship was only shown where MRIR was 1 or greater. In the participants with 1 or greater of MRIR, as MRIR increased by 0.1, cortical SUVR of 18F-MK-6240 PET increased by 1.23 (β-coefficient, SE=0.48, p=0.014, adjusted R2=0.39). Cortical SUVR of FLUTE increased 0.21, as MRIR increased by 0.1 (β-coefficient, SE=0.10, p=0.049, adjusted R2=0.37). In the causal mediation analysis, average causal mediation effect and proportional medicated (indirect effect/total effect) were statistically significant. **Conclusion:** In the elderly participants with substantial arterial stiffness (MRIR >=1), arterial stiffness was associated with tau burden, where amyloid burden mediated the relationship.

P82- APPLICATION OF FULLY AUTOMATIC HIPPOCAMPAL SUB-FIELD SEGMENTATION VOLUMES TO STANDARD RESOLUTION T1 MR IMAGING IN ALZHEIMER'S DISEASE. R. Joules[1], R. Wolz[1] *(1. IXICO - London (United Kingdom))*

Background: Volumetric analysis of the hippocampus is an established biomarker in the study of Alzheimer's disease as well as other neurodegenerative diseases. The assessment of hippocampal sub-field volumes is of great interest as it may provide increased sensitivity to earlier pathological changes as well as effects of clinical interventions when compared to whole hippocampus volume. The segmentation of hippocampal sub-fields is complex, resource intensive and susceptible to variability if undertaken manually and additionally requires specialised scans. Several fully automatic methods have been proposed allowing utilisation of subfield volumes without the need for specialised manual segmentation. Hippocampal subfield segmentation is preferably performed using a combination of T1 and high-resolution (HR) T2 images. Such multi-spectral analysis permits segmentation of small hippocampal regions, not distinguishable from T1 contrast alone. However, HR T2 imaging can increase scan time and patient burden and is commonly absent from legacy datasets limiting applicability of such analysis in retrospective analysis of existing datasets or a routine clinical setting. Existing methods may be applied to standard resolution (~1mm3) T1 MRI for segmentation of larger robustly defined sub-regions (e.g. CA1). These existing methods commonly employ multi-atlas based methodology and can be significantly influenced by the atlas prior in the absence of clear bounds and often require the generation of specific templates for the given population/therapeutic area to optimally perform. Deep learning approaches have been applied to the problem of both full hippocampal and hippocampal sub-field segmentation; while limited by availability of sufficient high quality training data, recent work has demonstrated state of the performance for multi-modal hippocampal segmentation of HR T2 and T1 data using methods based on convolutional neural networks (CNN). Here we extend such work to investigate the application of CNN approaches to segment hippocampal subfields from 1mm3 T1 MRI using publicly available data with high quality manual segmentation labels. **Objectives:** This work aims to develop methods for hippocampal subfield segmentation of standard resolution, 1mm3, T1 MRI using publicly available few-shot training data with T1 images and manually refined hippocampal labels. Segmentation models will be assessed in terms of segmentation accuracy and association with disease state and clinical scores for utility in clinical trials and clinical assessments. **Methods:** In this work we utilise a publicly available dataset of 25 subjects with manually segmented labels for a 3-part parcellation of the hippocampus (CA1-3, CA4/DG, and Subiculum) and a 3D-MPRAGE-T1 at 1mm3 aligned to MNI152 space (https://www.nitrc.org/projects/mni-hisub25). Images were pre-processed with N4 bias field correction, skull stripping and affine (12-dof) registration to MNI space. A template in label image was generated for each region of interest (ROI) in MNI space to allow approximate placement of bounding boxes centres by registration. Images are z-normalised within the brain masked area and augmentation is employed to apply random bias effects, noise, motion, sharpening, and spatial deformation. Images are cropped to bounding box cantered around the approximate position of the target ROI as estimated from non-linear registration of a ROI template to the input image. To maximise the limited dataset available, we reflect the right laterality ROIs and associated anatomical images to generate a left oriented dataset of 50 samples from 25 subjects. For the whole hippocampus and each of the 3 ROIs, we train a binary segmentation model using the popular UNET architecture. A multi-label segmentation may be generated through combination of the outputs from each model in a subsequent refinement process, permitting future flexibility for combining models from different training data

and parcellation schema. Models were trained with a 5-fold cross validation where 10 samples (5 subjects) were withheld for testing and a 0.8 training (16 subjects) validation (4 subjects) split. Due to the randomness of the augmentation and shuffled train/validation split, multiple models were trained in each fold where the mean softmax can be computed across all models for each segmentation. **Results:** Total hippocampal and subfield segmentations were generated for all test subjects standard resolution T1 images in each cross validated loop and the DICE overlap with the ground truth label computed. Preliminary results indicate near state-of-the-art segmentation quality, comparable to using both T1 and HR T2 in combination, for the test data with mean DICE in whole Hippocampus = 0.943(std: 0.017), CA1-3 = 0.902(std:0.032), CA4/DG = 0.895(std: 0.052), and Subiculum = 0.891(std:0.041). Optimisation and testing are ongoing with final results for the optimised framework, its comparison to other methods for disease state discrimination, and segmentation agreement is expected for presentation at the CTAD conference. **Conclusion:** We have presented a framework and preliminary results for a CNN based segmentation of hippocampal subfields based on a deep learning approach trained with limited publicly available data. Preliminary results indicate competitive performance in terms of DICE overlap with training labels. Further optimisation and refinement are required with testing on independent data to assess sensitivity to disease state and clinical measures.

P83- AMYLOID PET CENTILOID: IMPACT OF CALIBRATION AND PROCESSING STEPS. L. Presotto[1], M. Shekari[2], L.E. Collij[3], R. Manber[1], D. Vállez García[3], J.D. Gispert López[2], R. Wolz[1] *(1. IXICO - London (United Kingdom), 2. Barcelonaβeta Brain Research Centre, Pasqual Maragall Foundation - Barcelona (Spain), 3. Amsterdam UMC - Amsterdam (Netherlands))*

Background: Centiloids (CL) were introduced to consistently quantify amyloid load across tracers and analysis pipelines. CL linearly scale activity ratios so that in two reference groups (young healthy subjects, converted AD subjects) an average load 0 and 100 CL, respectively, is measured. Such linear scalings are unique for each combination of tracer, analysis algorithm, and reference region (1). **Objectives:** As part of centiloid calibration in the AMYPAD project, the impact of applying different processing steps on centiloid analysis results were compared. Here, we summarize key options considered and present the impact on centiloid analysis in two AMYPAD cohorts. **Methods:** As a first step, CL equations were computed using the GAAIN Flutemetamol datasets. Two linear regression strategies were compared: 1. calibrated pipeline Flutemetamol vs GAAIN PiB values, then apply GAAIN provided anchor points; 2. both PiB SUVr and anchor points estimated with the calibrated pipeline. Three approaches were compared to obtain a segmentation of the global cortical average (GCA) target region: I. registering a GCA template (1) from MNI space using NiftyReg for registration; II. like I) but using SPM for registration; III. using a subject-specific segmentation from a multi-atlas segmentation approach (LEAP) to define the GCA. Four reference regions obtained from LEAP were compared: a) whole cerebellum; b) cerebellar grey matter; c) Pons; d) white matter. The effect of the different options was evaluated on datasets independent from the calibration dataset from two cohorts in non-demented participants of at least 50 years of age: 83 datasets from the EPAD cohort and 163 datasets from the PreclinAD Twin60++ cohort. Data in the PreclinAD study was acquired on a single PET/MR scanner and data in the EPAD cohort was acquired from a range of PET/CT scanners with a separate MRI scan. Approaches were considered to be comparable if the mean CL difference were below 2 CL (within the error), and r2>0.9. **Results:** On both validation datasets the different linear regression options (1. / 2.) impacted average CL values by less than 1.5 CL. This is less than the statistical error on the anchor points used for CL definition. Registering the GCA region using NiftyReg (I.) or SPM (II.) resulted in no notable differences (r2>0.94, TWINS: no difference, EPAD: -2.6±0.6, whole cerebellum reference). Comparing GCA vs subject specific segmentation (III.) also shows that CL scaling is robust (r2=0.96, TWINS: no bias, EPAD: -1.5±0.5, whole cerebellum reference). Comparing alternative reference regions to the whole cerebellum has a significant impact. EPAD (TWINS) cohort mean difference: gray cerebellum: -5.5 (-5.3), pons: +17.1 (+22.1) and white matter: +7.9 (+10.3). **Conclusion:** The CL approach appears to be robust to different technical implementations, including definition of the target region and spatial registration algorithm. Different reference regions, however, are not comparable over multiple cohorts. Su et al previously reported that comparing different reference regions in a cohort independent from the calibration dataset can result in bias (2). Longitudinal studies (e.g. Chen et al) also showed that using different reference regions can impact data comparison (3). Additional work is required to understand the impact of the technique used to segment reference regions. **References:** 1. Klunk, William E., et al. «The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET.» Alzheimer's & dementia 11.1 (2015): 1-15. 2. Su, Yi, et al. «Utilizing the Centiloid scale in cross-sectional and longitudinal PiB PET studies.» NeuroImage: Clinical 19 (2018): 406-416. 3. Chen, Kewei, et al. «Improved power for characterizing longitudinal amyloid-β PET changes and evaluating amyloid-modifying treatments with a cerebral white matter reference region.» Journal of Nuclear Medicine 56.4 (2015): 560-566.

P84- INDEPENDENT EFFECTS OF HIPPOCAMPAL SUBFIELD VOLUMES AND P-TAU ON MEMORY PERFORMANCE IN CLINICALLY UNIMPAIRED OLDER ADULTS. T. Tran[1], A. Trelle[1], W. Edward[1], G. Deutsch[1], S. Sha[1], K. Andreasson[1], V. Carr[1], G. Kerchner[1], E. Mormino[1], A. Wagner[1] *(1. Stanford University - Stanford (United States))*

Background: Prior work has demonstrated that abnormal cerebral spinal fluid (CSF) biomarkers, including p-tau181, are associated with diminished performance across several hippocampally-dependent memory tasks in clinically unimpaired (CU) older adults. It is unknown whether structural differences in medial temporal lobe (MTL) subfields are associated with (1) elevated p-tau181 and (2) poorer memory performance in CU older adults. Furthermore, it is unclear whether any relationship between structural volume and memory performance may be mediated by p-tau181. **Objective:** To understand how structural volumetric measures of the hippocampal subfields relate to p-tau181 and memory performance in CU older adults. **Methods:** The current study draws on a cohort of cognitively unimpaired older adults from the Stanford Aging and Memory Study that completed CSF, genetic, and neuropsychological testing, along with 3T fMRI and MRI and 7T MRI. In the current analysis, 147 participants completed both 3T MRI and lumbar puncture. Participants ranged from 66 – 88 years of age. To examine memory performance, participants completed two hippocampally-dependent tasks: a paired associate cued recall task and a mnemonic similarity task (MST) that examined discrimination

between previously studied "old" objects, novel "foil" objects and perceptually similar "lure" objects. Lure trials were binned in five difficulty levels, ranging from low to high similarity compared to previously studied stimuli. Hippocampal subregions (CA1, CA3/DG, subiculum) and MTL cortical subregions were manually delineated following Carr et al., 2017. CSF was processed with Lumipulse to measure Ab42:Ab40 ratio and p-tau181. Linear multiple regression models were used to assess the relationship between p-tau181 and structural volume, as well as between volume and associative memory d' from the paired associate task. Given the repeated measures design of the MST task across five similarity bins, linear mixed models were conducted to examine the association between hippocampal subfields and p-tau181 on performance as a function of similarity level (Trelle et al., 2021). Age, sex, and education level were controlled in all models. **Results:** P-tau181 significantly negatively correlated with reduced left CA1 volume (partial r = -0.20, p = 0.02), but not with volume in other hippocampal subfields (partial r = -0.04 to -0.13, p > 0.05), nor with the left (partial r = -0.07, p = 0.40) or right total hippocampal volume (partial r = -0.04, p = 0.61). When examining the relationship between volume and memory, increased CA1 volume positively associated with better memory performance, including higher associative memory and old-lure discrimination. However, after controlling for p-tau181, CA1 volume was no longer significantly associated with performance on the associative memory task but remained significantly correlated with old/lure discrimination. Similarly, although DG/CA3 volume was not associated with p-tau181, DG/CA3 volume significantly correlated with old/lure discrimination on the mnemonic similarity task. Notably, increased CA1 and DG/CA3 volume associated with overall discrimination for old/lure trials, independent of the difficulty level, whereas the association between p-tau181 and performance was strongest at the lower similarity level. **Conclusions:** Although there is a relationship between p-tau181 and CA1 volume, these biofluid biomarker and structural measures explain unique variance in predicting memory performance in CU older adults. Critically, the memory tasks utilized included an associative memory task that assayed the retrieval of episodic memory details. This task has been hypothesized to depend, in part, on hippocampal CA1, due to the role of CA1 in linking pattern completion processes in DG/CA3 with the reinstatement of event features in neocortex. In contrast, the MST task has been hypothesized to be sensitive to DG and CA3 function by taxing both pattern separation and pattern completion processes. DG is theorized to orthogonalize sensory inputs into nonoverlapping memory representations, while CA3 is hypothesized to reactivate memories (pattern completion). Memory representations are passed from CA3 to CA1, where CA1 also acts as a comparator of the match between remembered and presently-perceived representations. Consistent with these theories of hippocampal subregion function, we find that CA1 volume is related to overall performance on both the associative memory task and the MST, while DG/CA3 volume is also associated with performance on the MST task. Furthermore, the independent effects of hippocampal subfield volume and p-tau181 on memory performance suggest they capture distinct age-related changes. Hippocampal subfield volume may be impacted by multiple drivers of individual differences in MTL integrity, while p-tau181 may reflect pathological Alzheimer's disease processes occurring in this preclinical population. Collectively, the combination of biofluid biomarkers and high-resolution MRI has the potential to further delineate mechanisms underlying age-related memory decline and preclinical Alzheimer's disease processes in clinically unimpaired older adults.

P85- SUPPORTING THE COMMUNICATION OF MODERN ALZHEIMER'S DATA THROUGH AUGMENTED REALITY AND WEB TECHNOLOGIES. T. Ard[1], B. Michael[1], A. Toga[1] *(1. USC Stevens Neuroimaging and Informatics Institute - Los Angeles (United States))*

Background: Alzheimer's disease research is based on many forms of data, from MRI scans to microscopic image stacks. Unfortunately, while throughout the course of research these types of data can be effectively digitally viewed, for publication all data is typically reduced to 2D static images. Ultimately, this leads to incomplete and suboptimal reporting, dramatically hindering our ability to effectively communicate modern data. Digital supplementary materials held some promise to address this situation, however recent metrics indicate these materials are accessed by as few as .04% of readers (1). Over the last several decades many additional attempts have also been made to modernize scientific articles and communications, however none have yet reached the adoption level necessary to displace the standard of static text and images as the major mode of communication (2, 3). However, recent technological advances such as augmented reality (AR) and web graphical integration now make it possible to merge data directly with scientific publications in a manner not previously feasible. **Objectives:** We aim to provide a framework that supports the inclusion of the scientific digital data directly with articles and other means of communication. We particularly aim for this platform to fluidly integrate data with articles in a manner where the data travels with the paper independent of publishers, submission status, or which technologies are supported through various submission systems. Further, we aim for the system to be highly accessible to readers, avoiding shortcomings that have contributed to low adoption rates of previous efforts to integrate data with communications. **Method:** We introduce a data layering approach for directly including modern digital information on top of scientific figures, enabling entire datasets to be included with scientific articles, posters, and other communications. Through this approach standard PDFs and other printable documents can incorporate modern data by layering digital augmentations 'on top' of figures. These augmentations can provide dynamic viewing of scientific information in an interactive manner, while requiring no changes to the format of scientific articles or to the publishing system that distributes them. This approach is supported through web and mobile applications as well as cloud infrastructure, all of which is accessible by readers and authors through our framework, termed 'Schol-AR'. **Result:** Data layering facilitates communication and comprehension of data that underlies clinical trials and Alzheimer's research by enabling accessible viewing of complex information directly with scientific articles, posters, and other formats. Authors can augment their own communications by uploading their datasets and the figures data should be 'attached' to. The framework then automatically renders the data readily accessible to any reader viewing those figures, regardless of where the document is hosted or published. **Conclusion:** Using augmented reality and web technologies we can modernize communication of Alzheimer's research, bridging the gap between the digital basis of modern science and the natural limitations of journal articles. Incorporating augmentation into scientific publishing can support the inclusion of full datasets with publication in a manner that can be highly accessible by the general readership

of the articles and communication. As such this technique can not only enhance the comprehension of scientific materials, but also the thoroughness in which data is reported, ultimately improving the state of scientific communication. 1. Flanagin, A. et al. Editorial Evaluation, Peer Review, and Publication of Research Reports With and Without Supplementary Online Content. JAMA 319, 410 (2018). 2. Sopinka, N. et al. Envisioning the scientific paper of the future. FACETS 5, 1–16 (2020). 3. Shotton, D. Semantic publishing: the coming revolution in scientific journal publishing. Learned Publishing 22, 85–94 (2009). **Competing Interests:** T.A. has a financial interest in Ardist Inc. No other authors have any competing interests. This report does not analyze or interpret any scientific data.

P86- LONGITUDINAL ASSESSMENT OF NOVEL IMAGING MARKERS OF NEUROINFLAMMATION, AXONAL DENSITY AND DEMYELINATION AS BIOMARKERS IN ALZHEIMER'S DISEASE.

M. Roy[1], M. Dumont[1], J.C. Houde[1], M. Descoteaux[1], J.R. Bélanger[1] *(1. Imeka - Sherbrooke (Canada))*

Aims: Three recent quantitative white matter (WM) measures from diffusion MRI (dMRI) were analyzed: i- free-water, a marker of neuroinflammation ii- apparent fiber density, a marker of axonal integrity iii-tissue radial diffusivity, a marker of myelin content. Our objective was to establish the dynamics of these three markers over 2 years in ADNI. **Methods:** All ADNI cohorts with dMRI at 3-, 6-, 12- and 24-months were included, which resulted in 51 NC, 78 MCI and 37 AD. In the MCI group, 15 subjects converted to AD over the 24 months (MCI converters). From dMRI, free-water, apparent fiber density and tissue radial diffusivity maps were computed. Then, a composite quantitative track-specific score (AD-bundles) was calculated combining the WM bundles altered in AD (the fornix, cingulum, arcuate, uncinate, inferior fronto-occipital and inferior longitudinal fasciculi, genu and splenium of the corpus callosum). Diffusion measures were analyzed with a general linear model using age, sex, apolipoprotein E4 status, intracranial volume and total WM hyperintensities volume as covariates. **Results:** In AD patients, free-water in AD-bundles was increased by 5.7, 7.6, 9.6 and 14.4% at 3, 6, 12 and 24 months respectively. In AD patients, fiber density in the fornix was decreased by 1.6, 2.7, 4.5 and 8.4% at 3, 6, 12 and 24 months respectively. Fornix reductions in fiber density at 24 months were larger in AD vs NC ($P< 0.001$), and trending toward statistically significant in MCI vs NC ($P= 0.062$). At 24 months, tissue radial diffusivity increase in the arcuate fasciculus was 89% higher in AD vs NC. At baseline, MCI converters had 14% higher free-water ($P< 0.001$), 15% lower fiber density ($P= 0.002$) and 10% higher tissue radial diffusivity ($P= 0.009$) in the fornix compared to MCI stable. **Conclusions:** In MCI, the three markers in the fornix may be considered a prognostic biomarker of conversion to AD. In clinical trials, stabilizing (or reversing decline) fiber density and tissue radial diffusivity measures would suggest tissue repair, strengthened axons and potential remyelination, making the case that they may be used as a monitoring biomarker. **Disclosures:** MD, JCH are shareholders of Imeka Solutions Inc. MR and MD are employees of Imeka Solutions Inc.

P87- PREDICTING PET-DETERMINED ATN BIOMARKER STATUS IN ALZHEIMER'S DISEASE WITH MRI USING DEEP CONVOLUTIONAL NEURAL NETWORKS.

C. Lew[1], L. Zhou[1], M. Mazurowski[1], P.M. Doraiswamy[1], S. Landau[2], J. Petrella[3] *(1. Duke Unversity Medical Center - Durham (United States), 2. University of California, Berkeley - Berkeley (United States), 3. Duke University Medical Center - Durham (United States))*

Background: Pathological hallmarks of Alzheimer's disease (AD), including amyloid, tau, and neurodegenerative pathology constitute a subject's "ATN" status, a unique endophenotype which has been proposed as a research framework aimed at a biological, rather than clinical, definition of AD. These hallmark pathologies can be detected as ATN biomarkers on positron emission tomography (PET). However, multiple PET scans are expensive and involve ionizing radiation. On the other hand, magnetic resonance imaging (MRI) is routinely obtained in patients undergoing workup of Alzheimer's and related dementias, though its use in characterizing AD biomarkers is limited. Deep learning techniques such as convolutional neural networks (CNN) show great potential is uncovering hidden patterns in MRI data to aid in AD diagnosis and prognosis. Although there are previous applications of deep learning techniques that utilize MRI data to determine other aspects of AD, such disease progression and diagnosis, there are no prior studies, to our knowledge, that predict ATN biomarker status. **Objective:** The purpose of this study was to determine the predictive efficacy of deep learning applied to MRI data and other readily available patient diagnostic data for PET-determined ATN biomarker status. **Methods:** MRI data from the Alzheimer's Disease Imaging Initiative (ADNI) was paired with PET biomarker data within 30 days of MRI acquisition date, resulting in 2372 amyloid-, 557 tau-, and 2769 FDG-MRI scan pairs. MRI data was preprocessed with bias field correction, skull stripping, and intensity normalization. For each biomarker, data was split into training, validation, and testing sets with a 70%/10%/20% split. Biomarker values were thresholded into positive vs. negative labels using bimodal gaussian mixture models based on training set values. The MRI data was input into a CNN to generate 100 imaging features. These features were combined with normalized patient diagnostic data, including sex, age, APOE status, hippocampal volumes, cognitive scores, and clinical diagnosis, in a logistic regression classifier model to output a binary prediction for each of the three PET biomarkers. Model performance was evaluated for each biomarker using accuracy and area under the receiver operator characteristic curve (AUROC). In addition to the above model that combined MRI data with patient diagnostic data, we evaluated models that utilized MRI data alone and patient diagnostic data alone. **Results:** The deep learning method that combined MRI data and diagnostic data outperformed methods that utilized each individually. For the deep learning method that utilized patient diagnostic data alone, we found the following AUROC values for the validation/training set; amyloid: 0.67/0.71, tau: 0.70/0.54, neurodegeneration: 0.70/0.76. For the deep learning method that utilized MRI data alone, we found the following AUROC values for the validation/training set; amyloid: 0.63/0.73, tau: 0.76/0.80, neurodegeneration: 0.81/0.85. For the deep learning method that combined both MRI data and patient diagnostic data, we found the following AUROC values for the validation/training set; amyloid: 0.74/0.79, tau: 0.83/0.69, neurodegeneration: 0.84/0.86. **Conclusion:** Our deep learning method was able to predict amyloid and neurodegeneration

biomarker status with high diagnostic efficacy and tau with moderate efficacy by utilizing MRI and other readily available patient diagnostic data. This method may reduce the need for costly PET procedures in select groups of patients needing AD biomarker evaluation. **Conflicts of Interest:** Dr. Doraiswamy has received grants, advisory or board fees and/or stock from several biotech companies and is a coinventor on several patents. All other authors declare that they have no conflicts of interest to disclose.

P88- EARLY [18F]-PI-2620 TAU PET SIGNAL IN THE STAGES PRECEDING AD DEMENTIA. C. Young[1], H. Vossler[1], E. Wilson[1], A. Trelle[2], K. Poston[1], M. Zeineh[1], M. Greicius[1], G. Zaharchuk[1], V. Henderson[1], A. Wagner[2], K. Andreasson[1], G. Davidzon[1], E. Mormino[1] *(1. Stanford ADRC - Stanford (United States), 2. Stanford Department of Psychology - Stanford (United States))*

Background: Although [18F]-PI-2620 has shown promise in visualizing tau aggregates in Alzheimer's disease (AD), no studies have examined how signal of this novel second generation tracer is impacted by methodological considerations or how it relates to amyloid burden and CSF pTau early in the AD pathological cascade. **Objectives:** To determine whether methodological considerations including timing acquisition and reference region selection impact PI2620 signal, and to evaluate this tracer in stages preceding AD dementia. **Methods:** We scanned a total of 61 participants with PI2620 Tau PET who were either clinically unimpaired (CU, N=52) or had Mild Cognitive Impairment (MCI, N=9), recruited from either the Stanford Aging and Memory Study (SAMS) or the Stanford Alzheimer's Disease Research Center (ADRC). Of the 61 total participants, 39 CU had CSF AB42:40 and pTau-181 available measured by Lumipulse immunoassay. The remaining 22 had amyloid PET with Florbetaben. Using z-scored tau PET SUVRs that were standardized in reference to amyloid negative CU participants, we examined the impact of acquisition time (45 – 75 min vs. 60 – 90 min) and reference region (inferior cerebellum vs. white matter) on regional tau PET in the medial temporal lobe (entorhinal, hippocampus, amygdala), inferior temporal (IT) cortex, and striatum. We then examined associations of regional tau with age, amyloid status, continuous amyloid burden, and pTau-181. **Results:** Across all 61 participants, a 45-75 min or 60-90 min acquisition time did not significantly affect regional tau PET signal (all ps > 0.05) except in IT when a white matter reference region was used [B (SE) = 1.319 (0.295), p < 0.001]. As expected, age was not associated with regional tau PET (all ps > 0.300) except in striatum where off-target binding is expected [inferior cerebellum reference region: B (SE) = 0.074 (0.019), p < 0.001; white matter reference region: B(SE) = 0.077 (0.018), p < 0.001] and in IT with a white matter reference region [B (SE) = -0.045 (0.019), p = 0.020]. Amyloid positive individuals had significantly higher SUVRs than amyloid negative individuals in entorhinal, amygdala, and IT using either reference region (all ps < 0.05), as well as in hippocampus using an inferior cerebellum reference region [B (SE) = 0.923 (0.430), p = 0.036] when controlling for diagnostic status; there were no significant differences based on amyloid status in striatum (all ps > 0.100). Within the 39 CU participants with tau PET and CSF, regional tau PET was related to CSF AB42:40 in entorhinal, amygdala, and IT using either reference region (all ps < 0.05), but not in hippocampus (all ps > 0.05). Regional tau PET was also related to CSF pTau181 in entorhinal, hippocampus, amygdala, and IT using either reference region (all ps < 0.01) except for IT when a white matter reference region was used (p>0.05). Within the subset of 22 CU and MCI participants with amyloid PET, global amyloid SUVRs were associated with regional tau PET in amygdala [B (SE) = 5.003 (2.083), p = 0.027] and IT [B (SE) = 5.362 (1.474), p = 0.002] when using an inferior cerebellum reference region, but these associations were not present when using a white matter reference region (all ps > 0.140); global amyloid SUVR was also not significantly related to entorhinal or hippocampal tau using either reference region (all ps>0.130). **Conclusion:** Methodological considerations of acquisition time and reference region selection had minimal impact on tau associations with amyloid status, continuous amyloid, and pTau181 in medial temporal lobe regions, whereas reference region did impact some associations in IT. How reference region influences PI2620 signal in cortical regions warrants further investigation. Additionally, our results show that amyloid-related regional PI2620 tau elevations are present in individuals without dementia. Future studies with larger samples and longitudinal follow up are needed to evaluate the regionally specificity of early PI2620 tau PET signatures in preclinical and prodromal AD.

P89- AMYLOID AND TAU BURDEN IN AN AT-RISK, COGNITIVELY UNIMPAIRED CLINICAL TRIAL COHORT: NEUROIMAGING DATA FROM THE U.S. POINTER TRIAL. A.E. Murphy[1], T.M. Harrison[1], T.J. Ward[1], P. Vemuri[2], R. Koeppe[3], S.N. Lockhart[4], M.A. Espeland[4], D.J. Harvey[5], J. Masdeu[6], H. Oh[7], D. Gitelman[8], N.T. Aggarwal[9], L.D. Baker[4], C. Decarli[5], S.M. Landau[1] *(1. U.C. Berkeley (United States), 2. Mayo Clinic (United States), 3. University of Michigan (United States), 4. Wake Forest School of Medicine (United States), 5. U.C. Davis (United States), 6. Houston Methodist (United States), 7. Brown University (United States), 8. Advocate Lutheran General Hospital (United States), 9. Rush University Medical Center (United States))*

Background: Measurement of beta-amyloid (Aß) and tau in a clinical trial setting makes it possible to identify individuals on the Alzheimer's disease (AD) pathway and determine whether a therapeutic intervention targets these pathologies. The neuroimaging substudy of the U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER) trial is examining Aß and tau PET and cerebrovascular biomarkers measured with MRI in older individuals (60-79 years), in order to determine whether lifestyle-based interventions are associated with changes in these biomarkers. AD and cerebrovascular biomarkers assessed prior to intervention could also help determine which biomarker characteristics predict a beneficial cognitive response to lifestyle changes. All POINTER imaging substudy participants are enrolled in the U.S. POINTER parent trial, which will test whether random assignment to either of two multidomain lifestyle interventions (nutrition, exercise, cognitive stimulation, health coaching) that differ in intensity and format affects cognitive outcomes. POINTER participants lack significant memory impairment, but are sedentary, have a suboptimal diet, and are at risk for future cognitive decline based on family history of memory impairment, race/ethnicity, and/or other risk factors. Enrollment into the U.S. POINTER Trial and the POINTER imaging substudy is ongoing. **Objectives:** The primary aim of this work is to examine the demographic characteristics, hippocampal volume (HCV), white matter hyperintensities (WMH) and prevalence of elevated Aß and tau in currently enrolled POINTER imaging participants (N=481, approximately 50% of the anticipated total sample with 18F florbetaben and 18F

MK-6240 scans; 60-79 years) in relation to a comparable subset of ADNI participants (N=524, cognitively normal and early MCI individuals with a Clinical Dementia Rating (CDR)<2, 18F florbetaben or 18F florbetapir, and 18F flortaucipir (FTP) scans; 55-90 years). This comparison was used to examine the influence of the at-risk characteristics of the POINTER sample on AD and cerebrovascular biomarkers. All individuals have contemporaneous Aß PET, tau PET, and structural MRI scans, measured at the baseline visit for POINTER imaging participants. A secondary aim is to examine MK-6240 tau PET (POINTER) and FTP tau PET (ADNI) in relation to Aß PET (florbetaben or florbetapir) in order to determine if the tau PET tracers differ in terms of sensitivity to early tau (entorhinal cortex) deposition. **Methods:** To quantify PET SUVrs and MRI structural data, we segmented MRIs with Freesurfer, coregistered PET to MRI, and sampled PET means within AD-related regions of interest (Aß: cortical summary; tau: entorhinal cortex, temporal composite) relative to established tracer-specific reference regions. WMH were calculated from T1 and FLAIR images using a Bayesian estimation approach that integrates likelihood estimates, spatial priors, and tissue class information, and subsequently log-transformed and adjusted for head size. We categorized subjects into Aß+/- and tau +/- groups using previously-validated positivity thresholds for cortical Aß burden (florbetapir: 1.11, florbetaben: 1.08) and, for tau, the upper 90th percentile of Aß-negative normals in ADNI (FTP: 1.25) and POINTER (MK-6240: 1.20). We compared cohort data with two-sample t-tests and chi-square tests. Effect sizes of Aß +/- group differences in tau SUVrs were evaluated using Cohen's d. Linear regression was used to measure the relationships between PET and age, WMH, and HCV. Results were considered statistically significant at α=0.05. **Results:** POINTER imaging participants were younger (POINTER: 70.0±5.0 vs. ADNI: 73.0±7.5 years) and had fewer years of education (11.3±2.0 vs. 16.7±2.4 years), higher BMIs (29.8±5.1 vs. 28.0±5.8), a higher proportion of females (66% vs. 57%), more individuals with smoking history (45% vs. 16%), a higher proportion from underrepresented racial/ethnic groups (27% vs. 15%), and more participants with a global CDR greater than zero (22% vs. 10%). The samples did not differ on Aß status (POINTER: 32% vs ADNI: 36%), WMH, or HCV; but POINTER had fewer individuals with elevated temporal tau (9% vs. 19%). In addition, POINTER entorhinal (1.12±0.29) MK-6240 SUVrs had a broader dynamic range compared to ADNI entorhinal (1.15±0.14) FTP SUVrs, but the temporal dynamic ranges were similar. However, effect sizes reflecting Aß status group differences were larger for entorhinal and temporal FTP/ADNI than MK-6240/POINTER. Entorhinal tau was correlated with older age in both samples, but age explained a greater amount (5%) of entorhinal tau variance in POINTER than in ADNI (3%), suggesting that MK-6240 variability may reflect sensitivity to early tau accumulation. **Conclusions:** Despite worse cognition and other at-risk characteristics of the POINTER imaging sample, ADNI and POINTER individuals had similar Aß, WMH burden, and HCV. The ADNI subsample had a greater proportion of individuals with elevated tau, perhaps due to older age and/or differences in the tau tracers used in these studies. Longitudinal data and head-to-head comparisons of the two tau tracers will be critical for determining whether the broader dynamic range of entorhinal tau observed with MK-6240 reflects greater sensitivity to early tau accumulation compared with FTP.

LP50- FIRST MICROTUBULE-BASED PET IMAGING STUDIES IN COGNITIVELY NORMAL AND IMPAIRED OLDER ADULT SUBJECTS--A PILOT STUDY. N. Damuka[1], B. Bhoopal[1], M. Miller[1], I. Krizan[1], S. Lockhart[1], M. Rundle[1], A. Mintz[2], S. Craft[1], K.K. Solingapuram[1] *(1. Wake Forest School of Medicine - Winston Salem (United States), 2. Columbia University Medical Center - New York (United States))*

Introduction: Disruption of the structural integrity of microtubule (MT) network and impairment of MT function are critical for pathophysiology of Alzheimer's disease (AD) and related disorders (ADRDs). Additionally, MT-based pathophysiology is commonly associated with tauopathies. Our lab reported the first brain-penetrant PET radiotracer [11C]MPC-6827 to image MTs in vivo in both rodent and non-human primate models of AD. Our mechanistic studies demonstrated that [11C]MPC-6827 uptake is elevated with destabilized tubulins. We reported the dosimetry of [11C]MPC-6827 in healthy adults (WMIC 2021). Here we report the first clinical [11C]MPC-6827 PET imaging study in age-matched cognitively normal and impaired male older adult subjects from Wake Forest ADRC clinical cohort (Craft, PI). **Methods:** Two cognitively normal (both [11C]PiB Aβ and [18F]flortaucipir [FTP] tau-PET negative) and two cognitively impaired (both Aβ-PET and FTP positive) male subjects (79-85 y) with brain MRI brain scans were recruited from Wake Forest Alzheimer's Disease Research Center (ADRC) Clinical Cohort. [11C]MPC-6827 was produced from the corresponding phenol precursor following our reported methods. Dynamic 0-60 min brain PET imaging was obtained with an intravenous injection of [11C]MPC-6822 (9±0.5 mCi, <10 μg) using the GE Discovery PET/CT scanner. ROIs were drawn on whole brain, cortex, thalamus, putamen, cerebellum, hypothalamus, and hippocampus from the fused PET/MR DICOM images using the PMOD software. Time activity curves (TACs), standard uptake values (SUV) were determined and correlated closely with FTP tau, PiB Aβ PET, and age. As FTP primarily measures phosphor-tau expression in AD brains, we closely correlated its uptake with our destabilized MT tracking radiotracer, [11C]MPC-6827. **Results:** [11C]MPC-6827 was produced with high radiochemical purity (>99.8%) and specific activity (3960 ± 100 mCi/μmol). Based on the SUV analysis, uptake of radiotracer was higher in the cognitively impaired subjects compared to the controls in all the studied brain regions. Radiotracer uptake was positively correlated with their age, Aβ, and tau uptake—validating its relevance with existing AD biomarkers. When examined with the Braak-based analyses (tau staging scheme) with SUVRs from both FTP (80-100 min post injection) and [11C]MPC-6827 (28-60 min post injection) with inferior cerebellar reference for both radiotracers, [11C]MPC-6827 and FTP SUVR values were positively correlated (*p=0.077) and the scatterplot exhibited an L-shaped association, such that elevated FTP (phosphor-tau) uptake was present only when [11C]MPC-6827 (MT destabilization) uptake was already present. **Conclusion:** Our preliminary results here suggest that MT destabilization precedes paired helical filaments of tau in neurofibrillary tangles. We are currently collecting data on more subjects to exploit the clinical significance of the MT-based PET in AD imaging.

LP51- COMPARATIVE STUDY ON THE PREDICTIVE VALUE OF DIFFERENT RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING PARAMETERS IN PRECLINICAL ALZHEIMER'S DISEASESE. W.M. Bahk[1], Y.J. Kwon[2], B.H. Yoon[3], K. Lee[4], S.Y. Lee[5], M.D. Kim[6], B. Nam[7], S.Y. Park[8], E. Lim[9], S.M. Wang[1], H.Y. Lim[1] *(1. The Catholic University of Korea - Seoul (Korea, Republic of), 2. Soonchunhyang University - Cheonan (Korea, Republic of), 3. Naju National Hospital - Naju (Korea, Republic of), 4. Dongguk University - Gyeongju (Korea, Republic of), 5. Wonkwang University - Iksan (Korea, Republic of), 6. Jeju National University - Jeju (Korea, Republic of), 7. Dr. Nam's Psychiatric Clinic - Chungju (Korea, Republic of), 8. Keyo Hospital - Uiwang (Korea, Republic of), 9. Shinsegae Hyo Hospital - Kimje (Korea, Republic of))*

Objective: Diverse resting-state functional magnetic resonance imaging (rs-fMRI) studies showed that rs-fMRI might be able to reflect the earliest detrimental effect of cerebral beta-amyloid (Ab) pathology. However, no previous studies specifically compared the predictive value of different rs-fMRI parameters in preclinical AD. **Methods:** A total of 106 cognitively normal adults (Ab+group=66 and Ab− group=40) were included. Three different rs-fMRI parameter maps including functional connectivity (FC), fractional amplitude of low-frequency fluctuations (fALFF), and regional homogeneity(ReHo) were calculated. Receiver operating characteristic (ROC) curve analyses were utilized to compare classification performance of the three rs-fMRI parameters. **Results:** FC maps showed the best classifying performance in ROC curve analysis(AUC, 0.915, $p < 0.001$). Good but weaker performance was achieved by using ReHo maps (AUC, 0.836, $p < 0.001$) and fALFF maps (AUC, 0.804, $p < 0.001$). The brain regions showing the greatest discriminative power included the left angular gyrus for FC, left anterior cingulate for ReHo, and left middle frontal gyrus for fALFF. However, among the three measurements, ROI-based FC was the only measure showing group difference in voxel-wise analysis. **Conclusion:** Our results strengthen the idea that rs-fMRI might be sensitive to earlier changes in spontaneous brain activity and FC in response to cerebral Ab retention. However, further longitudinal studies with larger sample sizes are needed to confirm their utility in predicting the risk of AD. **Key words:** magnetic resonance imaging, Alzheimer's disease, amyloid.

LP52- DEVELOPMENT OF RANDOM FOREST ALGORITHM BASED PREDICTION MODEL OF ALZHEIMER'S DISEASE USING NEURODEGENERATION PATTERN. K.H. Lee[1], W.M. Bahk[2], Y.J. Kwon[3], B.H. Yoon[4], S.Y. Lee[5], M.D. Kim[6], B.W. Nam[7], S.Y. Park[8], E.S. Lim[9], S.M. Wang[2], H.K. Lim[2] *(1. Department of Psychiatry Dongguk University Hospital - Gyeongju (Korea, Republic of), 2. Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of), 3. Department of Psychiatry, Soonchunhyang University Cheonan Hospital, Soonchunhyang University, - Cheonan (Korea, Republic of), 4. Department of Psychiatry, Naju National Hospital, - Naju (Korea, Republic of), 5. Department of Psychiatry, Wonkwang University Hospital, Wonkwang University School of Medicine, - Iksan (Korea, Republic of), 6. Department of Psychiatry, Jeju National University School of Medicine, - Jeju (Korea, Republic of), 7. Dr. Nam's Psychiatric Clinic - Chungju (Korea, Republic of), 8. Department of Psychiatry, Keyo Hospital, - Uiwang (Korea, Republic of), 9. Department of Psychiatry, Shinsegae Hyo Hospital - Kimje (Korea, Republic of))*

Objective: Alzheimer's disease (AD) is the most common type of dementia and the prevalence rapidly increased as the elderly population increased worldwide. In the contemporary model of AD, it is regarded as a disease continuum involving preclinical stage to severe dementia. For accurate diagnosis and disease monitoring, objective index reflecting structural change of brain is needed to correctly assess a patient's severity of neurodegeneration independent from the patient's clinical symptoms. The main aim of this paper is to develop a random forest (RF) algorithm-based prediction model of AD using structural magnetic resonance imaging (MRI). **Methods:** We evaluated diagnostic accuracy and performance of our RF based prediction model using newly developed brain segmentation method compared with the Freesurfer's which is a commonly used segmentation software. **Results:** Our RF model showed high diagnostic accuracy for differentiating healthy controls from AD and mild cognitive impairment (MCI) using structural MRI, patient characteristics, and cognitive function (HC vs. AD 93.5%, AUC 0.99; HC vs. MCI 80.8%, AUC 0.88). Moreover, segmentation processing time of our algorithm (<5 minutes) was much shorter than of Freesurfer's (6–8 hours). **Conclusion:** Our RF model might be an effective automatic brain segmentation tool which can be easily applied in real clinical practice.

LP53- ASSOCIATION BETWEEN WHITE MATTER HYPERINTENSITIES (WMH) VOLUME AND COGNITIVE FUNCTION IN ALZHEIMER`S DISEASE.

Y. Bo-Hyun[1], B. Won-Myong[2], K. Young-Joon[3], L. Kwanghun[4], L. Sang-Yeol[5], K. Moon-Doo[6], N. Beomwoo[7], P. Sung-Yong[8], L. Eunsung[9]
(1. Department of Psychiatry, Naju National Hospital - Naju (Korea, Republic of), 2. Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of), 3. Department of Psychiatry, Soonchunhyang University Cheonan Hospital, Soonchunhyang University - Cheonan (Korea, Republic of), 4. Department of Psychiatry, College of Medicine, Dongguk University - Gyeongju (Korea, Republic of), 5. Department of Psychiatry, Wonkwang University Hospital, Wonkwang University School of Medicine - Iksan (Korea, Republic of), 6. Department of Psychiatry, Jeju National University School of Medicine - Jeju (Korea, Republic of), 7. Dr. Nam's Psychiatric Clinic - Chugnju (Korea, Republic of), 8. Department of Psychiatry, Keyo Hospital - Uiwang (Korea, Republic of), 9. Department of Psychiatry, Shinsegae Hyo Hospital - Kimju (Korea, Republic of))

Background: WMH in MRI are common among the elderly. WMH are associated with increased cognitive impairment and risk of Alzheimer`s disease (AD). Although WMH contribute to AD pathology, their clinical implications are not fully understood. This study aimed to assess whether WMH predict AD and investigate the association between WMH (including subclassified WMH volume) and cognitive function in AD. **Method:** This study enrolled 171 patients with AD. All participants underwent clinical evaluations including brain MRI study and neuropsychological tests using the CERAD-K neuropsychological assessment battery. In addition, Charlson comorbidity index, the Korean version of the Geriatric Depression Scale short from were administered. WMH volume was calculated using automated quantification method with SPM and MATLAB image processing software. WMH were classified according to the distance from the ventricular surface. WMH located in juxtaventricular areas, within 3 mm from the ventricular surface, were classified as juxtaventricular with matter hyperintensities (JVWMH). WMH located within 3-13 mm or farther than 13 mm from the ventricular surface were classified as periventricular white matter hyperintensities (PVWMH) or deep white matter hyperintensities (DWMH), respectively. WMH volume data were right-skewed. Consequently, WMH volume data were logarithmic transformed. **Result:** The AD group had a higher mean WMH volume(20.7 ± 18.2 ml). Multivariate linear regression analysis showed that total WMH volume in AD was associated with poor performance in categorical verbal fluency test ($p = 0.008$) and word list memory test ($p = 0.023$). JVWMH volume in AD was associated with poor performance on categorical verbal fluency test ($p = 0.013$) and digit span test forward ($p = 0.037$). PVWMH volume in AD was associated with poor performance on categorical verbal fluency test ($p = 0.011$) and word list memory test ($p = 0.021$), whereas DWMH volume showed no association with cognitive dysfunction in AD. **Conclusion:** Total WMH, JVWMH and PVWMH were associated specifically with executive function, immediate memory, and working memory, independently of hippocampal atrophy in AD. WMH were associated with AD risk and cognitive dysfunction differentially according to the distance from the ventricular surface. **Key words:** Alzheimer's disease, cognition and white matter disease

LP53A. CROSS SECTIONAL ASSOCIATION BETWEEN FRAILTY AND WHITE MATTER HYPERINTENSITY AMONG ALZHEIMER`S DISEASE.

K. Moon-Doo[1], B. Won-Myong Bahk[2], K. Young-Joon[3], Y. Bo-Hyun[4], L. Kwanghun[5], L. Sang-Yeol[6], N. Beomwoo[7], P. Sung-Yong[8], L. Eunsung[9]
(1. Department of Psychiatry, Jeju National University School of Medicine - Jeju (Korea, Republic of), 2. Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of), 3. Department of Psychiatry, Soonchunhyang University Cheonan Hospital, Soonchunhyang University - Cheonan (Korea, Republic of), 4. Department of Psychiatry, Naju National Hospital - Naju (Korea, Republic of), 5. Department of Psychiatry, College of Medicine, Dongguk University - Gyeongju (Korea, Republic of), 6. Department of Psychiatry, Wonkwang University Hospital, Wonkwang University School of Medicine - Iksan (Korea, Republic of), 7. Dr. Nam's Psychiatric Clinic - Chugnju (Korea, Republic of), 8. Department of Psychiatry, Keyo Hospital - Uiwang (Korea, Republic of), 9. Department of Psychiatry, Shinsegae Hyo Hospital - Kimje (Korea, Republic of))

Purpose: With an aging global population, recent years have seen rapid expansion in the attention of the frailty. Thus, understanding, and determinant the potentially modifiable risk factor for frailty is a major concern for health care policy and provision. **Material and method:** Subjects were recruited for the study from the dementia clinic of Jeju National University Hospital between January 2018 and January 2020. All of the subjects were evaluated by using CERAD-K and diagnosed probable AD and possible AD by a panel of two experienced dementia research neuropsychiatrists. WMH volume was calculated using automated segmentation analysis and further partitioned into three categories (Kim, BIOL PSYCHIATRY 2008). Frailty evaluated by Korean Frailty Index (KFI) and classified into three categories according to the cutpoints. Other physical performances such as BMI, muscle mass index, grip strength, and gait speed measures were performed by experienced researchers specialized in geriatric assessment. comorbidity status using the Charlson comorbidity index, and depressive symptoms using GDS was examined. **Results:** In total, 34 subjects (23.6 %) were classified as frail 47 subjects (32.6 %) were classified as prefrail, and 63 subjects (43.8 %) were classified as a non-frail group. The frail group had higher WMH volume compared to the non-frail group ($p=0.002$), and these trends remained significant after linear regression analyses. According to the new subclassification of WMH, using the non-frail group as a reference, total WMH volume (OR=6.297, $p=0.013$), JVWMH volume (OR=12.955, $p=0.014$), and PVWMH (OR=3.382, $p=0.025$) were associated with frail. Furthermore, according to the path model, only the gait speed mediated the association between WMH and frailty. **Conclusion:** In our study provides evidence of a cross-sectional relationship between WMH and frailty, and there is a difference in the association between the subclassification of WMH volume and frailty. Furthermore, we suggest that gait speed could be a useful biomarker for assessment of the frailty.

LP54- CLINICAL AND BIOMARKER CHARACTERISTICS OF SUBJECTIVE COGNITIVE DECLINE WHO PROGRESSED TO MCI WITHIN 24-MONTHS FOLLOW-UP.

D.W. Yang[1], C.H. Lee[1], Y.J. Hong[2], S. Ho[3], J.H. Jeong[4], K.H. Park[5], S.Y. Kim[6], M.J. Wang[7], S.H. Choi[8], S.G. Lee[9] *(1. Department Of Neurology, College Of Medicine, The Catholic University Of Korea - Seoul (Korea, Republic of), 2. Department of Neurology, The Catholic University of Korea Uijeongbu St. Mary's Hospital, Uijeongbu, Republic of Korea - Uijeongbu (Korea, Republic of), 3. Department of Neurology, Changwon Hanmaeum Hospitaljeongbu, Republic of Korea - Changwon (Korea, Republic of), 4. Department of Neurology, Womans University School of Medicine, Ewha Womans University Seoul HospitalChangwon Hanmaeum Hospitaljeongbu, Republic of Korea - Seoul (Korea, Republic of), 5. Department of Neurology, Gachon University Gil Hospital - Inchon (Korea, Republic of), 6. Department of Neurology, Seoul National University College of Medicine, Seoul National University Bundang Hospital - Bundang (Korea, Republic of), 7. Neurology, ROA Clinic - Bundang (Korea, Republic of), 8. Department of Neurology, Inha University School of Medicine, Inha University Hospital - Inchon (Korea, Republic of), 9. NeoLAB convergence Inc - Seoul (Korea, Republic of))*

Background: Subjective cognitive decline (SCD) refers to the status concerning the self-experienced memory decline but preserving cognitive function on the standardized neuropsychological tests. Finding risk factors associated with progression from SCD to mild cognitive impairment (MCI) became important for disease modifying treatment. **Objectives:** We investigated the characteristics of SCD patients who progressed to MCI or dementia during 24-months follow-up. **Methods:** 120 patients with SCD were enrolled in this prospective study. All participants were recruited as part of the multicenter cohort study to identify predictors for the clinical progression to MCI or dementia from subjective cognitive decline (CoSCo study). Demographics and clinical information were collected at baseline. Participants were assessed by using neuropsychological tests annually. At baseline, all subjects underwent 18F-florbetaben PET and 3T MRI. At the 24-months follow-up we compared the clinical, neuroanatomical, and biomarker characteristics of the SCD who progressed to MCI. **Results:** From the 120 subjects 107 participants were followed-up and nine progressed to MCI during 24 months. The conversion rate to MCI was 8.41% (9/107). The SCD patients who progressed to MCI showed significantly lower frequency of alcohol consumption (0/9 (0.0%) vs. 41/98 (41.8%), p=0.012) compared to the stable SCD patients. There were no significant differences in the frequency of APOE e4 carriers, various leisure and physical activities, and accompanying psychiatric symptoms between the two groups. The neuropsychological tests at baseline showed significantly poorer performance in the digit span forward test (-0.4111 ± 1.1135 vs. 0.6521 ± 1.1077 in percentile, p=0.004) and global cognition, the Mini-Mental State Examination (MMSE) score (25.22 ± 2.539 vs. 27.39 ± 1.826, p=0.009) in the SCD patients with conversion to MCI. The frequency of amyloid PET positivity was significantly higher in the SCD subjects with progression (5/9 (55.6%) vs. 20/98 (20.4%), p=0.031). In volumetric analysis the converters to MCI showed significantly lower regional volume in the left inferior parietal, left inferior temporal, right paracentral cortical areas, left pallidum, and putamen. **Conclusion:** At the 24-month follow-up, the subjects who progressed to MCI showed significantly decreased function in attention and global cognition at baseline. Considering the significantly higher frequency of positive amyloid PET scans and lower regional brain volume in the progression group, the most critical condition associated with progression to MCI might be having the Alzheimer's pathology and atrophic changes of brain thereafter. We need additional follow-up period for detailed investigation of the biomarker profiles, underlying risk factors, and cognitive status that could tell us the prognosis of SCD. This study was supported by the Ministry of Health and Welfare, HI18C0530

LP55- IN VIVO HEAD-TO-HEAD COMPARISON OF [18F] GTP1 AND [18F]MK6240 IN ALZHEIMER'S DISEASE.

M. Tonietto[1], C. Constantinescu[2], S. Sanabria Bohorquez[3], R. Gunn[4], D. Russell[5], E. Teng[3], D. Abramzon[3], K. Pickthorn[3], G. Klein[1] *(1. Hoffmann-La Roche, Ltd. - Basel (Switzerland), 2. Invicro, LLC - Needham (United States), 3. Genentech, Inc. - South San Francisco (United States), 4. Invicro, LLC - London (United Kingdom), 5. Invicro, LLC - Needham (United Kingdom))*

Background: In participants with Alzheimer's disease (AD), tau Positron Emission Tomography (PET) signal is closely related to cognitive status and subsequent rates of disease progression. Tau PET is increasingly being used in clinical trials as a downstream pharmacodynamic biomarker and to select participants at higher risk for clinical decline. Several radiotracers targeting tau tangles have been examined in human studies. Although abundant data exist for individual tracers, there is only limited in-vivo data from head-to-head tracer comparisons. Head-to-head comparisons are important for the contextualization of tau PET data from clinical trials using different tracers and will enable the simultaneous use of multiple tau tracers in future observational and therapeutic studies. While a harmonized scale like the amyloid centiloid has not yet been developed for tau PET, the slope of regional linear regressions from head-to-head tau PET studies as reported here will help to better understand treatment effects observed using different tau PET tracers. **Objectives:** This study compared in vivo the characteristics of two second generation tau PET tracers, [18F]GTP1 and [18F]MK6240, in a cohort of participants ranging from cognitively unimpaired to moderate AD. **Methods:** To date, 9 participants (age 69±4 years; 5F) have completed imaging with both [18F]GTP1 and [18F]MK6240: 5 cognitively unimpaired (MMSE=[29,30], CDR=0), 1 prodromal AD (MMSE=29; CDR=0.5), 2 mild AD (MMSE=[21,22]; CDR=0.5), and 1 moderate (MMSE=17; CDR=0.5) AD. All cognitively unimpaired participants were beta-amyloid negative while all AD participants were beta-amyloid positive, as assessed by amyloid PET. [18F]GTP1 images were acquired from 60 to 90 min post injection of 259±9 MBq of [18F]GTP1. [18F]MK6240 images were acquired from 90 to 110 min post injection of 190±6 MBq of [18F]MK6240. Tracer scan order was balanced, with a mean interval between the two exams of 10±12 days. All PET images were acquired on a Siemens Biograph 6 PET-CT and reconstructed with an iterative reconstruction algorithm (OSEM four iterations, 16 subsets) and a post hoc 5-mm Gaussian filter. A structural three-dimensional sagittal T1-weighted MR image was also acquired for all participants. Image processing was performed using the PNEURO module within PMOD and included the following steps: motion correction of PET images, alignment of time-averaged PET to the corresponding T1-weighted image, normalization of the T1-weighted image to MNI space and the associated transformation of PET data into MNI space, application of the Hammers Atlas to calculate regional Standardized Uptake Value (SUV) and SUV Ratio (SUVR) values from the PET data. The inferior cerebellar cortex was used as reference region, and two sets of regions of interest (ROIs) were defined: one

based on the six Braak stages, the other on the brain lobes: medial temporal, lateral temporal, frontal, parietal, and occipital cortex. Pearson correlation coefficient and linear regression analyses were used to compare SUVR values in different ROIs between tracers. Linear regression coefficients (slope and intercept) were computed using a total least square approach and expressed with [18F]GTP1 as the independent variable (i.e., SUVR_MK6240 = slope * SUVR_GTP1 + intercept). **Results:** [18F]MK6240 had significantly higher SUV values in the inferior cerebellar cortex compared to [18F]GTP1 (mean difference =-0.23±0.16 SUV; p=0.0025). SUVRs values were highly correlated in all Braak ROIs except for Braak II (i.e., hippocampus). Excluding Braak II, correlation coefficients ranged from r=0.96 in Braak III to r=0.996 in Braak IV. In Braak II, SUVRs between tracers were not significantly correlated (r=0.21, p=0.59). In the lobar ROIs, correlation coefficients ranged between r=0.88 in the medial temporal lobe to r=0.998 in the occipital lobe. After removing the hippocampus from the medial temporal lobe, the correlation coefficient in this ROI increased to r=0.94. The average regression slope across the Braak ROIs (Braak II excluded) was 2.9±0.4 and the average intercept was -2.3±0.5. Similar results were found using the lobe ROIs, with an average slope of 2.9±0.7, and an average intercept of -2.2±0.8. **Conclusion:** [18F]GTP1 and [18F]MK6240 SUVR values were highly correlated in all the ROIs considered with exception of Braak II/hippocampus. The reasons behind the divergent results in this latter region are currently being investigated. The linear regression analysis showed that [18F]MK6240 had a wider SUVR range compared to [18F] GTP1 in all regions considered (slope greater than 1). This study is currently ongoing and additional data analyses are pending. These preliminary results support the development of categorical and standardized quantification scales for bridging existing data sets and enabling the use of both tracers in future studies.

LP56- EVALUATING THE IMPACT OF CAROTID ENDARTERECTOMY ON COGNITION AND HIPPOCAMPAL FRACTIONAL ANISOTROPY.

A. Bernstein[1], J. Arias[1], C. Weinkauf[1], T. Trouar[1] *(1. University of Arizona - Tucson (United States))*

Background: Vascular contributions to cognitive impairment and dementia (VCID) have growing relevance in understanding Alzheimer's disease (AD). However, in the absence of acute ischemic events such as stroke and/or TIA, whether large vessel disease of the carotid artery, asymptomatic extracranial carotid atherosclerotic disease (aECAD), and its treatment with carotid endarterectomy (CEA) affect AD risk is poorly understood. **Objectives:** This work seeks to investigate the changes in brain structure and function that occur in presence of untreated aECAD and following carotid endarterectomy using a battery of neurocognitive tests and diffusion MRI. **Methods:** This prospective, non-randomized study enrolled a total of twenty-six patients with aECAD and various ethnic backgrounds recruited from Vascular Surgery clinics in Tucson, Arizona. Thirteen subjects had high grade ≥ 70% stenosis in at least one carotid artery and received CEA). Thirteen had <70% stenosis, therefore not qualifying for revascularization. Participants underwent cognitive evaluation using the Montreal Cognitive Assessment (MoCA) test and multi-shell, high angular resolution diffusion magnetic imaging (dMRI) of the brain at two different timepoint visits, baseline and six months follow-up. MoCA scores and fractional anisotropy (FA) along the hippocampal tracks were used for analysis. **Results:** Baseline results showed that FA was statistically lower along the ipsilateral hippocampus in subjects with severe aECAD compared to subjects without severe aECAD. MoCA scores were lower in these individuals, but this did not reach statistical significance. At follow-up, MoCA scores increased significantly in subjects who received CEA and remained equal in control subjects that did not have CEA. FA remained unchanged in the CEA group and decreased in the control group. **Conclusions:** These results indicate that there may be detrimental changes in the microscopic structure of hippocampal white matter in the presence of aECAD and that surgical treatment with CEA may prevent further deterioration of brain structure. These findings have important clinical implications because they question the diagnosis of "asymptomatic" ECAD, suggesting that aECAD may contribute to cognitive dysfunction.

LP57- NEW INSIGHTS INTO THE CONTRIBUTION OF TAU PET IMAGING IN AD THERAPEUTIC TRIALS.

J. Lagarde[1,2,3], P. Olivieri[1], M. Tonietto[3,4], P. Gervais[3], F. Caillé[3], M. Moussion[5], M. Bottlaender[3,6], M. Sarazin[1,7,8] *(1. Department of Neurology of Memory and Language, GHU Paris Psychiatrie & Neurosciences, Hôpital Sainte Anne, F-75014, Paris, France - Paris (France), 2. Université Paris Cité, F-75006 Paris, France - Paris (France), 3. Université Paris-Saclay, BioMaps, Service Hospitalier Frédéric Joliot CEA, CNRS, Inserm, F-91401, Orsay, France - Orsay (France), 4. Research and Early Development (pRED), Hoffmann-La Roche, Basel, CH - Basel (Switzerland), 5. Centre d'Evaluation Troubles Psychiques et Vieillissement, GHU Paris Psychiatrie & Neurosciences, Hôpital Sainte Anne, F-75014, Paris, France - Paris (France), 6. Université Paris-Saclay, UNIACT, Neurospin, Joliot Institute, CEA, F-91140, Gif sur Yvette, France - Gif Sur Yvette (France), 7. Université Paris Cité, F-75006 Paris, France - Paris, 8. Université Paris-Saclay, BioMaps, Service Hospitalier Frédéric Joliot CEA, CNRS, Inserm, F-91401, Orsay, France - Orsay)*

Background: Alzheimer's disease (AD) is a complex and heterogeneous disease, both in terms of clinical presentation and rapidity of cognitive impairment. Molecular imaging by positron emission tomography (PET) enables the in vivo detection of amyloid and tau pathologies, the latter being closely associated with clinical symptoms. To optimize the design of therapeutic trials, it is necessary to predict cognitive and functional decline by developing surrogate markers that accurately reflect the clinical course of the disease. Tau-PET imaging is a sensitive tool to measure the extent of tau pathology (that precedes neurodegeneration), which should be considered as a potential predictor of neurodegeneration and of subsequent cognitive decline as well as a longitudinal biomarker of disease progression. **Objectives:** We aimed at exploring whether regional tau binding measured at baseline was associated with the rapidity of AD progression after 2 years of follow-up assessed in terms of both (a) cognitive decline in specified cognitive domains, and (b) the progression of regional brain atrophy. We also explored the longitudinal progression of the tau radiotracer binding by performing a second tau-PET at 2 years, and the progression of cortical atrophy in a cohort of well-characterized prodromal and mild AD patients compared with controls, and their relationships with (a) baseline regional tau load, and (b) clinical decline in the same cognitive domains. **Methods:** Thirty-six AD patients (positive CSF biomarkers and amyloid-PET) and fifteen controls underwent a complete neuropsychological assessment, 3T brain MRI, [11C]-PiB and [18F]-flortaucipir PET imaging (Tau1), and were monitored annually over 2 years, with a second brain MRI after 2 years. We used mixed effects models to explore the relations between tau-PET, amyloid-PET, CSF

biomarkers and MRI at baseline and cognitive decline and the progression of brain atrophy over 2 years in AD patients. Among these subjects, twenty-seven AD patients and twelve amyloid-negative controls also underwent a second tau PET imaging (Tau2) performed after 2 years. We studied the longitudinal progression of tau radiotracer binding (Tau2-Tau1) in AD patients compared with controls and its association with baseline tau load. We used mixed effects models to explore the relations between the progression of tau radiotracer binding or cortical atrophy and cognitive decline over 2 years. **Results:** Tau tracer binding at baseline was associated with the subsequent cognitive decline in various brain areas depending on each cognitive component. In contrast, no significant relationship was observed between cognitive decline and initial amyloid load, regional cortical atrophy or CSF biomarker levels. We also found associations between tau tracer binding and subsequent cortical atrophy in the superior temporal, parietal and frontal association cortices. In the tau-PET longitudinal study, we found an average longitudinal increase in tau radiotracer binding, especially in frontal regions, in contrast with an average decrease in the lateral temporoparietal cortex. In this region, individual analyses revealed two distinct evolutions of tau radiotracer binding according to Tau1 uptake. Specifically, low Tau1 patients (SUVr < 1.6) demonstrated an increase in tau radiotracer uptake over time and a slow clinical progression, whereas high Tau1 patients demonstrated a paradoxical plateauing or decrease of tau tracer uptake over time and a faster clinical progression. This decreased tau binding may be explained by a lower affinity of the tracer during the transition to ghost tangles, which leads to a predominance of 3R tau. Cognitive decline was weakly associated with Tau2-Tau1. A strong association was noted between regional cortical atrophy progression and cognitive decline predominating in regions based on the cognitive component considered. **Conclusion:** Beyond the utility of tau-PET for determining AD diagnosis, especially when CSF biomarkers are equivocal, our results suggest that tau tracer binding is predictive of cognitive decline in AD in domain-specific brain areas, particularly in the temporo-parietal and frontal cortices. This may be used to refine the selection of patients for inclusion in clinical trials in order to include patients in the prodromal stage of the disease who are at high risk of rapid cognitive decline. On the other hand, selecting AD patients with higher tau load, may lead to a misinterpretation of the progression of tracer binding over time due to the possible transition to ghost tangles. To avoid such difficulties, the choice of PET as well as MRI neuroimaging outcomes deserves to be discussed on the basis of studies with larger numbers of patients in the early stages of the disease and by using different methods for the analysis of the longitudinal data, which raises important methodological issues. **Conflicts of interest:** none declared.

LP58- METHODS TO DECREASE SAMPLE SIZE NEEDED FOR LONGITUDINAL FLORTAUCIPIR TAU PET. S. Baker[1], P. Aguilar Dominguez[1], S. Landau[2], T. Harrison[2], R. Lajoie[3], T. Ward[2], K. Zhuang[2], G. Rabinovici[3], W. Jagust[2] *(1. Lawrence Berkeley National Lab - Berkeley (United States), 2. University of California, Berkeley - Berkeley (United States), 3. University of California, San Francisco - San Francisco (United States))*

Background: Tau PET is highly correlated with cognition (1), making tau an attractive target for intervention. Flortaucipir (FTP) is the most widely used radiotracer for tau PET imaging. Although this tracer can differentiate between healthy controls and subjects with Alzheimer's disease, it is well known that FTP images have focal areas of off-target signal (ie basal ganglia) (2). However, less well known is that the cortex also suffers from off-target signal (3), and cortical FTP in the absence of tau correlates with thalamus and putamen off-target signal explaining 64% of the variability in the cortical signal in a cross-sectional cohort of amyloid negative (Aβ-) cognitively unimpaired (CU) subjects (4). **Objectives:** In this study, we explored the impact of partial volume correction (PVC), reference region, and regressing out the thalamic signal (as defined in an Aβ-CU cross-sectional cohort) on longitudinal meta temporal FTP PET effect size and sample size in Aβ- and Aβ+CU and Aβ- cognitively impaired (CI) subjects. **Methods:** Data from the Alzheimer's Disease Neuroimaging Initiative and Lawrence Berkeley National Lab were combined to create a cross-sectional cohort of Aβ-CU (n=245), and a longitudinal cohort of Aβ-CU (n=103), Aβ+CU (n=119), and Aβ+CI (n=137). The FTP tau PET scans were averaged, coregistered to an MPRAGE which was segmented using Freesurfer7. Two possible reference regions were explored, inferior cerebellar gray (ICG) and eroded white matter (WM), and quantification was done with and without a FTP-tailored geometric transfer matrix PVC (5, 6). The equation for regressing out the thalamus was defined in the cross-sectional Aβ-CU cohort and then applied to the individual scans in the longitudinal cohorts. The annual change was calculated in the longitudinal cohorts in the meta temporal region (7) with and without thalamic regression, with and without PVC, and with the two reference regions. The impact was quantified by calculating Hedges' Effect Size (ES) and sample size (power = 0.80 and significance level = 0.05) needed to differentiate between Aβ+CI > Aβ-CU, Aβ+CI > Aβ+CU, and Aβ+CU > Aβ-CU. **Results:** There was no statistically significant difference between cross-sectional Aβ-CU thalamus and baseline thalamus in the longitudinal groups or change in thalamus between the longitudinal groups for all quantification methods. We then compared annual change between groups across different analyses and calculated the ES and sample size. Alone, regressing out the thalamus or performing PVC both resulted in modest increases in effect size. However, when comparing ES between no thalamic regression+no PVC to thalamic regression+PVC, the effect size increased from 0.60 to 0.71 (Aβ+CI > Aβ-CU), 0.40 to 0.53 (Aβ+CI > Aβ+CU), and 0.46 to 0.58 (Aβ+CU > Aβ-CU), translating to a decrease in sample size to 72% (Aβ+CI > Aβ-CU), 55% (Aβ+CI > Aβ+CU) and 63% (Aβ+CU > Aβ-CU) of the sample size needed in the no thalamic regression+no PVC analysis. For WM reference region, when comparing ES between no thalamic regression+no PVC to thalamic regression+PVC, the effect size increased from 0.69 to 1.13 (Aβ+CI>Aβ-CU), 0.44 to 0.84 (Aβ+CI > Aβ+CU), and from 0.38 to 0.42 (Aβ+CU>Aβ-CU), translating to a decrease in sample size to 37% (Aβ+CI > Aβ-CU), 28% (Aβ+CI > Aβ+CU) and 82% (Aβ+CU > Aβ-CU) of the sample size needed in the no thalamic regression+no PVC analysis. **Conclusion:** There are many difficulties when measuring annual change in tau PET such as low amounts of change expected especially at earlier stages in the disease when treatment is most likely to be effective. Any improvement that can be made in increasing the signal and decreasing the noise can result in lower sample sizes. We have shown that PVC+thalamic regression results in an average of 63% decrease from the original sample size for ICG reference region and 49% for WM reference region. **References:** 1. Pontecorvo, M.J., et al., A multicentre longitudinal study of flortaucipir (18F) in normal ageing, mild cognitive impairment and Alzheimer's disease dementia. Brain, 2019. 142(6): p. 1723-1735. 2. Marquie, M., et al., Lessons learned about

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LP59- PREVALENCE OF MICROHEMORRHAGES, SUPERFICIAL SIDEROSIS AND OTHER MRI ABNORMALITIES IN A POPULATION OF COGNITIVELY UNIMPAIRED OLDER ADULTS FROM THE CHARIOT-PRO STUDY.

L. Bracoud[1], C. Udeh-Momoh[2], Z. Saad[3], D. Kafetsouli[4], E. Daly[4], O. Okoye[4], P. Giannakopoulou[4], D. Scott[5], J. Suhy[5], S. Baker[6], G. Novak[6], C. Ritchie[7], L. Middleton[2], L. Middleton[8] *(1. Clario - Lyon (France), 2. AGE Research, School of Public Health, Imperial College of London - London (United Kingdom) - London (United Kingdom), 3. Janssen Research and Development - La Jolla (United States), 4. AGE Research, School of Public Health, Imperial College of London - London (United Kingdom), 5. Clario - San Mateo (United States), 6. Janssen Research and Development - Titusville (United States), 7. University of Edinburgh - Edinburgh (United Kingdom), 8. Imperial College Healthcare NHS Trust - London (United Kingdom))*

Background: Hemosiderin deposits, including microhemorrhages (MH) and superficial siderosis (SS), have been termed as Alzheimer's Related Imaging Abnormalities - Hemosiderin (ARIA-H) in anti-amyloid drug trials. MH and SS have also been observed in asymptomatic older adults, in contrast to ARIA-E (edema/effusion) abnormalities that have never been reported outside the context of such trials. **Objectives:** With the expected increased availability of disease-modifying therapies targeting Alzheimer's disease in its preclinical and early clinical stages, we aimed at evaluating the prevalence of MH and SS in asymptomatic older adults, from the CHARIOT PRO prospective, biomarker enriched study at Imperial College London and Edinburgh University, and also assess the presence of white matter hyperintense lesions (WML) and other brain pathologies, based on structural MRI, at screening. **Methods:** We included 1414 cognitively unimpaired men and women, aged 60 to 85 years, through population-based regional registries, in years 2015-2018. Each participant was scanned on Siemens 3T scanners, using a standardized MRI protocol, including 2D axial FLAIR and T2* Gradient Echo sequences (5 mm slices, 0.5 mm interslice gap, 0.94×0.94 mm2 in-plane resolution). FLAIR and T2* data were reviewed by blinded neuroradiologist as part of central eligibility reading activities, in order to report the number, shape and size of hemosiderin deposits. MH were defined as punctate T2* hypointensities of <10 mm in diameter. SS were defined as linear/curvilinear T2* hypointensities, irrespective of size. WML extent was reported using the Wahlund Age Related White Matter Changes (ARWMC) scale. WML volume was, also, automatically estimated using FreeSurfer WM hypointensities category, to benefit from a rough quantitative estimate. Among these subjects, 1076 subjects also underwent Amyloid PET imaging, using one of three approved 18F tracers (Florbetapir n=170, Florbetaben n=602 or Flutemetamol n=304). PET positivity was determined using a hybrid approach taking visual and quantitative (SUVR) results into account. APOE E4 carrier status was available in 613 of the cohort participants. Relationship between age, sex, APOE4 carrier status, quantitative PET values and positivity status, hypercholesterolemia/hyperlipidemia , hypertension, Type 2 diabetes, and each of the variables of interest (MH, SS and WML) was studied by fitting linear models. **Results:** The presence of MH ranged from 5.8% in the younger group (60-65 years old) to 16.3% in the older group (80-85). Overall, only 1.3% had ≥4 MH. Similarly, the presence of SS ranged from 0.6% in the younger group to 2.2% in the older group. Overall, 0.9% had one area of SS and 0.4% had more than one. 4.2% of subjects with MH had SS. The presence of WMH increased from 47.1% in the 60-65 age group to 79.3% in the oldest (80-85) age group. Average ARWMC severity ranged from 1.0 (SD=1.3) in younger participants to 3.0 (2.8) in the older group and lesion volume (in mL) from 1.9 (1.3) to 6.7 (6.3). Linear models confirmed that older age was significantly associated ($p<0.001$) with the presence of MH, irrespective of sex, PET status (either dichotomized as positive or negative, or using SUVR value) and APOE4 carrier status. In the entire cohort, the number of MH was significantly associated with male sex and older age ($p<0.05$). Only age remained significantly associated ($p<0.05$) in the sample where PET was available (n=1076). In the sample where APOE4 status was available (n=613), age and hypercholesterolemia/hyperlipidemia were significantly associated ($p<0.05$) with the number of MH, and hypercholesterolemia/hyperlipidemia was significantly associated ($p=0.04$) with the presence of ≥4 MH. In the entire cohort, the presence of SS was positively associated with male sex and older age and the presence of Type 2 diabetes ($p<0.05$). This association was no longer seen in the smaller cohorts where PET or APOE4 status were available. Severity of WML was associated with age ($p<0.001$), sex ($p<0.01$) and hypertension ($p<0.001$). There was no evidence of ARIA-E in this study. Other MRI abnormalities, including infarcts, vascular malformations/aneurysms, meningiomas and other space occupying lesions and encephalomalacia, were found in 4% of participants, with no category exceeding 1%. **Conclusions:** The CHARIOT-PRO data provide valuable insights into the prevalence of microhemorrhages, superficial siderosis and white matter lesions in a large sample of cognitively asymptomatic older adults. Microhemorrhages may be present in up to 16.3% and superficial siderosis up to 2.2%, in the older old adults, with age being the main predictor. Further research should elucidate their potential role in subsequent cognitive trajectories and on risk for ARIA-H and ARIA-E, as adverse occurrences of therapeutic trials.

LP60- PREDICTION OF LONGITUDINAL CHANGE IN CDR SUM OF BOXES USING A CORTICAL MICROSTRUCTURAL AD SIGNATURE FROM BASELINE DIFFUSION MRI.

G. Ridgway[1], M. Torso[1], D. Tzaferou[1], M. Valotti[1], I. Hardingham[1], S. Chance[1], & Alzheimer's Disease Neuroimaging Initiative[2] *(1. Oxford Brain Diagnostics Ltd - Oxford (United Kingdom), 2. Alzheimer's Disease Neuroimaging Initiative (United States))*

Background: The Clinical Dementia Rating (CDR; PMID:9447441) is widely used in the staging of Alzheimer's disease; it comprises 6 domains, each rated on a 5-point scale

(0, 0.5, 1, 2, 3), combined to give the global CDR on the same scale. CDR Sum of Boxes (CDR-SB) adds the scores on the 6 domains to give a more granular score from 0 to 18, and is a very common endpoint in clinical trials, for example being the primary endpoint in the recently reported phase 3 Clarity AD trial of Lecanemab. There can be substantial inter-individual variation in annualised change in CDR-SB, and the ability to predict CDR-SB change from screening or baseline data could inform patient selection or stratification, and might have clinical utility. Diffusion MRI can be used to assess the microstructure of the cerebral cortex, and has been shown to relate to microstructural measures from histology (PMID:31355989). In past work, we have shown the utility of novel cortical diffusivity measures to detect neurodegeneration in AD (PMID:33174658) and to predict subsequent macrostructural atrophy (DOI:10.14283/jpad.2022.59). **Objectives:** Prior work has investigated the prediction of CDR-SB change using MRI measures including AD signature regional summaries of cortical thickness (Hibar et al., 2021, CTAD). Here, we develop a novel cortical microstructural AD signature using diffusion MRI, and evaluate its ability to predict subsequent longitudinal progression in CDR-SB. **Methods:** Data were obtained from the Alzheimer's Disease Neuroimaging Initiative, including T1-weighted and diffusion MRI, CDR, and Elecsys CSF biomarkers of amyloid beta 42 and p-tau 181. Subjects were selected to have CSF samples within 180 days of MRI. Diffusion MRI and T1-weighted MRI were processed using FSL, FreeSurfer, and proprietary algorithms, to produce three novel cortical diffusivity measures (AngleR – the angle between the principal diffusion direction and the radial minicolumnar direction within the cortex; ParlPD – the principal diffusion component parallel to the minicolumnar direction; and PerpPD+ – the components of diffusion perpendicular to the minicolumnar direction; PMID:31355989). Imaging metrics were summarised by region using the Desikan-Killiany parcellation (PMID:16530430). To derive regional AD signatures, a conservatively low threshold (0.0198) for the ptau181/Abeta42 ratio was applied to define a restricted group of biomarker-negative cognitively normal (CN-) participants (n=158), and a conservatively high threshold (0.028) was applied to define a confidently biomarker-positive AD+ group (n=66). These groups were contrasted, adjusting for age, gender, total intracranial volume (TIV), diffusion MRI head movement, scanner model, number of diffusion volumes, and diffusion TE/TR ratio. Effect-sizes from left and right hemispheres were averaged, and the top 8 regions for each metric (AngleR, ParlPD, PerpPD+ and cortical thickness) were used to define AD signatures. Average values of the metrics within their signature regions were calculated at baseline, together with hippocampal volume as a fraction of TIV as a comparator. Annualised change in CDR-SB was calculated for a subset of 201 participants with longitudinal CDR-SB available over a nominal 12m or 24m interval. Delta CDR-SB was related to the five baseline metrics, adjusting for age, gender, scanner model, number of diffusion directions and the diffusion voxel volume. The 201 participants were categorised using an intermediate ptau181/Abeta42 threshold of 0.021 into 80 CN-, 32 CN+, 31 MCI-, 36 MCI+, 4 AD- and 18 AD+. **Results:** The cortical thickness signature comprised entorhinal, superior temporal, parahippocampal, middle temporal, inferior parietal, inferior temporal, fusiform, and precuneus. Compared to a previously published six-region AD signature from the Mayo Clinic (PMID:28050342), five regions overlap, the present signature adds superior temporal and precuneus, and replaces the angular gyrus with the broader inferior parietal region. The original AD signature for cortical thickness (PMID:18632739) differs more substantially, but still contains multiple temporal lobe regions, precuneus and angular gyrus. Considering the four sets of eight regions across the different signatures, 19 unique regions are featured, with the following regions present in three of the four signatures: entorhinal, fusiform, inferior temporal. Across the 201 participants with longitudinal CDR-SB, partial correlations of CDR-SB changes with all considered metrics were significant; in ascending order of magnitude: ParlPD ($r = 0.145$, $p = 0.042$), AngleR ($r = 0.299$, $p < 0.001$), cortical thickness ($r = -0.457$, $p < 0.001$), hippocampal volume fraction ($r = -0.461$, $p < 0.001$), and PerpPD+ ($r = 0.475$, $p < 0.001$). In the 67 MCI participants, PerpPD+ was again the most strongly correlated ($r = 0.39$, $p = 0.002$) followed by cortical thickness ($r = -0.365$, $p = 0.004$) and hippocampal volume fraction ($r = -0.312$, $p = 0.014$), with the other metrics non-significant. In the 36 MCI+ individuals, only PerpPD+ was able to predict CDR-SB change with statistical significance ($r = 0.438$, $p = 0.014$). **Conclusion:** A cortical microstructural measure – PerpPD+ – calculated from baseline diffusion MRI and summarised over bespoke microstructural AD signature regions, predicts subsequent progression in the widely used outcome measure CDR-SB, more strongly than an equivalently-derived cortical thickness signature or hippocampal volume fraction.

LP61- CORTICAL MICROSTRUCTURAL MEASURES FROM DIFFUSION MRI CORRELATE WITH COGNITIVE COMPOSITE SCORES AND PREDICT THEIR LONGITUDINAL CHANGES. M. Torso[1], G. Ridgway[1], M. Valotti[1], I. Hardingham[1], S. Chance[1], & Alzheimer's Disease Neuroimaging Initiative[2] *(1. Oxford Brain Diagnostics Ltd - Oxford (United Kingdom), 2. Alzheimer's Disease Neuroimaging Initiative (United States))*

Background: Neuropsychological assessment contributes greatly to characterizing dementia forms associated with neurodegenerative processes, identifying the most salient and earliest cognitive deficits, and suggesting the underlying neuropathology. In individuals with suspected Alzheimer's Disease, the neuropsychological assessment is crucial to assessing the presence and severity of memory deficits associated with a memory complaint, assessing the presence of cognitive deficits that involve other cognitive domains (e.g. executive functions, language, visual-spatial), and contributing to staging and monitoring the progression using standardized tests. As shown by previous lines of evidence, neuropsychological batteries can differ across studies and cohorts, and for valid and reliable diagnostic procedures, harmonized composite scores are necessary to allow the comparison of participants' performances acquired in different centres. Some MRI measures focused on cortical changes at macrostructural level (e.g. cortical volume, cortical thickness) have been proposed to investigate the cortical alterations underlying memory deficits in Alzheimer's patients, while the measures of cortical microstructural changes are still largely unexplored. **Objectives:** The main goal of the present study was to explore the ability of a novel set of cortical diffusivity metrics to detect the cortical microstructural changes underlying memory deficits and to predict longitudinal changes in Memory scores. **Methods:** Data of 113 participants (46 cognitively normal, 44 Mild Cognitive Impairment and 23 AD) with T1-weighted, diffusion MRI and memory composite scores, were obtained from the Alzheimer's Disease Neuroimaging Initiative. For each participant, the memory composite score (1) was used as a measure of memory deficit. Structural

T1-weighted and diffusion MRI (dMRI) were used to calculate three novel cortical diffusivity measures: the angle between the radial minicolumnar direction and the principal diffusion direction (AngleR); the principal diffusion component parallel with the minicolumns (ParlPD), and the diffusion components perpendicular to the minicolumns (PerpPD+) (2). Cortical mean diffusivity (MD) was also assessed. Whole-brain and regional cortical values were calculated using the Desikan-Killiany parcellation (3). The memory composite scores and diffusivity measures (whole brain and regional) at baseline were used to investigate the association between cortical macrostructural changes and memory deficits. To test the hypothesis that baseline cortical diffusivity values can predict change in memory composite scores over approximately 24 months, the annual change in composite memory score was computed as Δ = (follow up value – baseline value) / (time-interval). Associations between the memory composite scores and the cortical diffusivity measures were evaluated with partial correlation analysis, adjusting for age, sex, scanner model, number of diffusion directions and dMRI voxel volume. Only results surviving False Discovery Rate (FDR) correction were reported. **Results:** At baseline, across all participants, statistical analysis showed significant associations between all whole-brain cortical diffusivity measures and memory composite scores (AngleR: pFDR= 0.036, η2= 0.045; ParlPD: pFDR= 0.027, η2= 0.053; MD: pFDR= 0.005, η2= 0.085) with PerpPD+ showing the strongest association (pFDR <0.001, η2= 0.138). Regional analysis showed a significant bilateral pattern of association between PerpPD+ values and baseline composite score values that include the main cortical regions involved in memory processes, such as entorhinal (left: pFDR <0.001, η2= 0.401; right: pFDR= 0.003, η2= 0.313), fusiform (left: pFDR <0.001, η2= 0.477; right: pFDR <0.001, η2= 0.424), inferior temporal (left: pFDR <0.001, η2= 0.401; right: pFDR <0.001, η2= 0.387), middle temporal (left: pFDR <0.001, η2= 0.405; right: pFDR= 0.005, η2= 0.303), parahippocampal (left: pFDR <0.001, η2= 0.479; right: pFDR= 0.014, η2= 0.248), precuneus (left: pFDR <0.001, η2= 0.481; right: pFDR= 0.004, η2= 0.301) and superior temporal (left: pFDR= 0.002, η2= 0.326; right: pFDR= 0.027, η2= 0.220). Investigating the prediction of longitudinal changes in memory composite using baseline regional cortical diffusivity measures revealed a significant PerpPD+ bilateral temporal pattern. The most significant regions associated with longitudinal memory changes were: bilateral banks of the superior temporal sulcus (left: pFDR <0.001, η2= 0.403; right: pFDR= 0.005, η2= 0.312), entorhinal (left: pFDR= 0.001, η2= 0.352; right: pFDR= 0.005, η2= 0.319), fusiform (left: pFDR <0.001, η2= 0.385; right: pFDR <0.001, η2= 0.383), inferior temporal (left: pFDR <0.001, η2= 0.428; right: pFDR <0.001, η2= 0.485), insula (left: pFDR <0.001, η2= 0.357; right: pFDR= 0.019, η2= 0.263) and parahippocampal (left: pFDR <0.001, η2= 0.344; right: pFDR= 0.032, η2= 0.229). **Conclusion:** Novel cortical diffusivity measures can detect microstructural alterations underlying memory deficits across the Alzheimer's continuum. Baseline cortical diffusivity predicts subsequent decline in memory, with potential utility for clinical trial stratification or subgrouping, as well as potential utility in clinical practice. **References:** 1; Crane, P., Carle, A., Gibbons, ... & Mungas, D. (2012). Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Brain Imaging and Behavior, 6:502-516. 2. McKavanagh, R., Torso, M., Jenkinson, M., ... & Chance, S. (2019). Relating diffusion tensor imaging measurements to microstructural quantities in the cerebral cortex in multiple sclerosis. Human Brain Mapping, 40:4417-4431. 3. Desikan, R., Ségonne, F., Fischl, B., ... & Killiany, R. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage, 31:968-980.

LP62- APOEE4 CARRIERSHIP AND AB POSITIVITY FOR THE POPULATIONAL ENRICHMENT OF CLINICAL TRIALS TESTING DRUG EFFECTS ON TAU TANGLES.

J.P. Ferrari-Souza[1], P. Ferreira[1], B. Bellaver[1], G. Povala[1], F. Lussier[1], D. Leffa[1], C. Tissot[2], J. Therriault[2], T. Karikari[3], J.P. Soucy[2], S. Gauthier[2], E. Zimmer[4], P. Rosa-Neto[2], T. Pascoal[1]
(1. University of Pittsburgh - Pittsburgh (United States), 2. McGill University - Montreal (Canada), 3. University of Gothenburg - Mölndal (Sweden), 4. Universidade Federal do Rio Grande do Sul - Porto Alegre (Brazil))

Background: Tau tangles deposition is a potential secondary outcome for clinical trials in Alzheimer's disease (AD). The use of enrichment strategies is of paramount importance in selecting the individuals with the highest probability of AD-related progression in typical clinical trial time frames. Although both amyloid-β (Aβ) pathology and the apolipoprotein E ε4 (APOEε4) genotype have been shown to accelerate tau accumulation, it is still not clear whether assessing both APOEε4 carriership and Aβ positivity statuses is a useful strategy to enrich AD clinical trials using tau positron emission tomography (PET) as an outcome. **Objective:** Here, we investigated whether APOEε4 carriership is associated with higher longitudinal rates of tau tangles accumulation in a group of Aβ positive cognitively impaired (CI) individuals. **Methods:** We studied 63 CI (Clinical Dementia Rating ≥ 0.5) individuals across the AD continuum from the McGill Translational Biomarkers in Aging and Dementia (TRIAD) cohort. Study participants underwent clinical assessments, APOE genotyping, magnetic resonance imaging, PET for Aβ ([18F]AZD4694) and tau ([18F]MK6240) at baseline, as well as an additional follow-up tau-PET scan. All included participants were Aβ positive, which was determined as global [18F]AZD4694 SUVR ≥ 1.55 (24 Centiloid units). We assessed [18F]MK6240 SUVR in the temporal meta-ROI, a common summary measure of tau-PET. We calculated the annual rate of change in tau-PET SUVR between baseline and follow-up as follows: (follow-upSUVR – baselineSUVR) / Δtime. We compared biomarker changes between APOEε4 carriers and noncarriers using regression models adjusted for age, sex, and clinical status. Additionally, we estimated the sample sizes needed for trials testing a 25% drug effect with 80% power at alpha level 0.05 on reducing tau-PET accumulation by using Aβ-PET alone or Aβ-PET in combination with APOEε4 genotype for participant selection. **Results:** The mean (standard deviation [SD]) age of participants was 68.9 (8.1) years, and the mean (SD) follow-up time was 2.0 (0.6) years. We found that APOEε4 carriers had significantly higher rates of tau-PET SUVR increase in the temporal meta-ROI compared to APOEε4 carriers (fold change = 6.4, P = 0.005). The use of Aβ positivity alone for population enrichment of a clinical trial focusing on CI individuals would require a sample size of 1,175 individuals per study arm to test a 25% drug effect on tau-PET accumulation. Notably, a similar clinical trial with a population enrichment strategy using Aβ positivity plus APOEε4 carriership would require a sample size of as few as 367 individuals per study arm (reduction of 69% in relation to using only Aβ positivity) to test the same drug effect. **Conclusion:** Our results reveal that APOEε4 carriership is associated with higher rates of tau tangles accumulation in CI individuals who are Aβ positive. Clinical trials testing drug effects on tau tangles deposition may benefit from

assessing both APOEε4 carriership and Aβ positivity statuses as enrollment criteria to select individuals at higher risk of fast tau accumulation, resulting in a more cost-effective clinical trial.

CLINICAL TRIALS: BIOMARKERS INCLUDING PLASMA

P90- IMPACTS OF AMYLOID BURDEN ON LONGITUDINAL COGNITIVE DECLINES IN SUBJECTIVE COGNITIVE DECLINE: A PROSPECTIVE COHORT STUDY. Y.J. Hong[1], D.W. Yang[2], S. Ho[2], K. Park[3], J.H. Jeong[4], K.H. Park[5], S. Kim[6], M.J. Wang[6], S.H. Choi[7], S. Lee[8] *(1. Uijeongbu St. Mary's Hospital - Uijeongbu (Korea, Republic of), 2. Seoul St. Mary's Hospital - Seoul (Korea, Republic of), 3. Pusan National University Yangsan Hospital - Yangsan (Korea, Republic of), 4. Ewha Womans University Seoul Hospital - Seoul (Korea, Republic of), 5. Gachon University Gil Hospital - Incheon (Korea, Republic of), 6. Seoul National University College Of Medicine, Seoul National University Bundang Hospital - Seongnam (Korea, Republic of), 7. Inha University School Of Medicine - Incheon (Korea, Republic of), 8. Neolab Convergence Inc. - Seoul (Korea, Republic of))*

Background: Subjective cognitive decline (SCD) is known to be a risk group of Alzheimer's disease (AD), however, the rates of cognitive declines are variable according to underlying pathologies. We planned a longitudinal observational study to assess baseline characteristics and biomarkers related with clinical progressions in elderly participants with SCD during 24 months. **Objectives:** Our study aimed to assess whether SCD participants show different cognitive and biomarker trajectories according to baseline amyloid depositions. **Methods:** This study is a part of a prospective longitudinal cohort study named 'CoSCo'. CoSCo study is being conducted in 6 centers in South Korea and enrolled SCD participants between May 2018 and December 2021. A total of 120 elderly participants with SCD were enrolled at baseline. Individuals who were diagnosed as SCD were eligible for the study. Inclusion criteria are as follows: 1) aged 60 years old or older, 2) complaint of persistent cognitive decline, 3) normal performance in detailed neuropsychological tests named Seoul neuropsychological screening battery (SNSB) version II, 4) performance range between 7 to 50 percentile (adjusted by age, gender, and education) of the verbal memory delayed recall test (Seoul Verbal Learning Test, SVLT). Regional volumetry, quantitative amyloid burden represented by standardized uptake value ratio (SUVR) were measured. We divided participants into 2 groups: group 1) SCD with amyloidosis (global SUVR ≥1.391) and group 2) SCD without amyloidosis (global SUVR<1.391). We compared cognitive and atrophic changes during 24 months between the two groups. **Results:** Finally 107 participants completed the study. Follow-up completed participants (n= 107) were not different from dropped out subjects (n= 13) in regards of baseline characteristics except the education. Baseline cognitive scores were not different between the groups except the SVLT delayed recall scores. After 24 months, SVLT delayed recall scores, a part of frontal executive tests showed more cognitive declines in Aβ-positive SCD participants. Baseline left entorhinal volumes and global SUVR values were relevant factors related with the cognitive declines. In regards of neurodegenerative changes, hippocampal and left entorhinal atrophic changes were more prominent in Aβ-positive SCD participants. **Conclusion:** Aβ-positive SCD participants showed more cognitive declines and medial temporal atrophic changes after 24 months. Baseline entorhinal volumes and amyloid burden were relevant factors related with cognitive declines in SCD during the study period.

P91- PREDICTIVE VALUE OF PLASMA P-TAU181 VERSUS BASELINE AMYLOID-PET FOR LONGITUDINAL AMYLOID ACCUMULATION IN ASYMPTOMATIC ALZHEIMER'S DISEASE. R. Vandenberghe[1], S. De Meyer[1], E. Luckett[1], J.E.R.O.E. Vanbrabant[2], J. Schaeverbeke[1], M. Reinartz[1], I. Cleyne[3], E. Stoops[2], E. Vanmechelen[2], K. Van Laere[4] *(1. Alzheimer Research Centre Ku Leuven, Leuven Brain Institute - Leuven (Belgium), 2. Adx Neurosciences - Zwijnaarde (Belgium), 3. Laboratory For Complex Genetics - Leuven (Belgium), 4. Nuclear Medicine Service, University Hospitals Leuven - Leuven (Belgium))*

Background: The dynamic phase of asymptomatic Alzheimer's Disease (AD), characterized by the phase of rising cortical amyloid load, is a key target for early intervention. This phase of amyloid accumulation opens perspectives for more efficacious amyloid lowering intervention. **Objectives:** In this study we compared the ability of baseline plasma p-tau181 and baseline amyloid-β (Aβ)-PET to predict longitudinal amyloid accumulation in community-recruited cognitively unimpaired (CU) elderly, along with age, an AD polygenic risk score and baseline cognition. **Methods:** Plasma p-tau181 was quantified with a novel phospho-specific Simoa assay (ADx NeuroSciences, Ghent) in a cohort of 77 CU elderly (baseline age[mean] = 70 years, 48% female, 45% APOE-ε4 carriers, 13% Aβ-PET positive at baseline) participating in the Flemish Prevent AD Cohort KU Leuven, a prospective community-recruited longitudinal observational cohort study. Plasma sampling, amyloid-β (Aβ)-PET ([18F]flutemetamol or [11C] PiB) and an episodic memory test (average Buschke Selective Reminding total retention /12) were performed at baseline and Aβ-PET was repeated on average 4.97 years later (SD: 2.01, range 0.94 - 10.46 years). The Aβ-PET rate of change was calculated by dividing the difference between baseline and follow-up tracer uptake in Centiloids (CLs) by the time interval between scans (in years). A polygenic risk score (PRS) for AD was calculated with exclusion of the APOE region (chromosome 19 45-48.8 Mb) and SNP inclusion threshold of 5x10-8 with the addition of the weighted sum of directly genotyped APOE-ε2 and -ε4 alleles. Individuals with an Aβ-PET rate of change that exceeded the median Aβ-PET rate of change of the subset (N = 41) that remained Aβ-PET negative (CL < 23.5) at both time points by at least 1.5 standard deviations, were considered to be amyloid accumulators. The ability of plasma p-tau181, baseline Aβ-PET as well as a demographic model of age and PRS to predict longitudinal amyloid accumulation was determined through ROC analyses and compared using DeLong tests. Spearman correlations between longitudinal amyloid accumulation, baseline plasma p-tau181, baseline amyloid load, baseline episodic memory, age, and PRS were calculated. Standard scores of all variables were entered into a hierarchical regression analysis in a stepwise manner based on correlation strength. **Results:** Fourteen (18%) subjects fulfilled the criterion of amyloid accumulators. Baseline plasma p-tau181 (AUC = 0.76) predicted longitudinal amyloid accumulation equally well as baseline Aβ-PET load (AUC = 0.74, P = 0.84). Both baseline plasma p-tau181 and baseline Aβ-PET load were better predictors of longitudinal amyloid accumulation than the combination of age and PRS (P = 0.01 for p-tau181 and P = 0.03 for Aβ-PET). However, only baseline plasma p-tau181 (Spearman's rho = 0.27, P = 0.02) and not baseline Aβ-PET load (Spearman's rho = 0.18, P = 0.12) correlated significantly with longitudinal amyloid accumulation. Since plasma p-tau181 demonstrated the strongest correlation with longitudinal amyloid accumulation out of all tested variables, it was used as

a sole predictor of amyloid accumulation in the base regression model. This base model ($F(1,75) = 7.5$, $P = 0.008$) explained 27% of the variance (R2) in longitudinal amyloid accumulation. Stepwise addition of baseline amyloid load, baseline episodic memory score, PRS score or age did not further improve the model. **Conclusion:** Plasma p-tau181 measured with the novel phospho-specific Simoa assay is able to discriminate amyloid accumulators in the asymptomatic phase of AD equally well as a baseline Aβ-PET scan and superior to the combination of age and PRS. **Conflicts of interest:** The plasma p-tau181 assay was performed without cost by ADx Neurosciences. RV's institution has an MTA (RV as PI) with ADx Neurosciences. The 18F flutemetamol tracer delivery for the baseline scan was delivered free of cost by GEHC. RV was PI of the 18F flutemetamol phase 1 and 2 clinical trials. RV's institution has Clinical Trial Agreements (RV as PI) with Biogen, J&J, Novartis, NovoNordisk,Roche, and UCB.

P92- BLOOD BIOMARKERS FOR ALZHEIMER'S DISEASE TO PREDICT DEMENTIA RISK IN A LARGE CLINIC-BASED COHORT: IMPLICATIONS FOR CLINICAL TRIALS. V. Planche[1], V. Bouteloup[1], G. Chêne[1], C. Dufouil[1] *(1. Bordeaux University - Bordeaux (France))*

Background: Blood biomarkers for Alzheimer's disease (AD) have consistently proven to be associated with CSF or PET biomarkers and effectively discriminate AD from other neurodegenerative diseases. It is now proposed to use them to select patients for clinical trials in early AD. To achieve this goal, blood biomarkers still need to be tested in large multicentric unselected prospective clinic-based cohorts where patients present with a large spectrum of complaints or mild cognitive deficits. **Methods:** The MEMENTO cohort enrolled 2323 outpatients with subjective cognitive complaint (SCC) or mild cognitive impairment (MCI) consulting in 26 French memory clinics. Participants had neuropsychological assessments, brain MRI and blood sampling at baseline. CSF sampling and amyloid PET were optional. Baseline blood Aβ42/40 ratio, total-tau, p181-tau, and neurofilament light chain (NfL) were measured using a Simoa HD-X analyzer. An expert committee validated incident dementia cases during a 5-year follow-up period. **Results:** Overall, 2277 individuals had at least one baseline blood biomarker available (n=357 for CSF subsample, n=649 for PET subsample), among whom 257 were diagnosed with clinical AD/mixed dementia during follow-up. All blood biomarkers but total-tau were mildly correlated with their equivalence in the CSF ($r=0.33$ to 0.46, $p<0.0001$) and were associated with amyloid-PET status ($p<0.0001$). Blood p181-tau was the best blood biomarker to identify amyloid-PET positivity (AUC=0.74 [95%CI=0.69-0.79]). Higher blood and CSF p181-tau and NfL concentrations were associated with accelerated time to AD dementia onset with similar incidence rates, whereas blood Aβ42/40 was less efficient than CSF Aβ42/40. Blood p181-tau alone was the best blood predictor of 5-year AD/mixed dementia risk (c-index=0.73 [95%CI=0.69-0.77]); its accuracy was higher in patients with CDR=0 (c-index=0.83 [95% CI=0.70;0.97]) than in patients with CDR=0.5 (c-index=0.70 [95% CI=0.66;0.74]). A "clinical" reference model (combining demographics and neuropsychological assessment) predicted AD/mixed dementia risk with a c-index=0.88 [95%CI=0.86-0.91] and performance increased to 0.90 [95%CI=0.88;0.92] when adding blood p181-tau+Aβ42/40. A "research" reference model (clinical model+ApoE genotype and AD-signature on MRI) had a c-index=0.91 [95%CI=0.89-0.93] increasing to 0.92 [95%CI=0.90;0.93] when adding blood p181-tau+Aβ42/40. **Conclusion:** In a clinic-based cohort of patients with SCC or MCI, blood biomarkers may be good hallmarks of underlying pathology but add little to 5-year dementia risk prediction models including traditional predictors. In the context of a clinical trial, they thus seem useful for easily selecting patients in the AD continuum, but do not seem suitable for selecting progressors. The authors declare that they have no competing interests related to the present work.

P93- INDEPENDENT EFFECT OF BODY MASS INDEX VARIATION ON AMYLOID-B POSITIVITY. S.H. Kang[1], J.H. Kim[2], K. Kim[2], S.W. Seo[3] *(1. Department Of Neurology, Korea University Guro Hospital, Korea University College Of Medicine - Seoul (Korea, Republic of), 2. Department Of Digital Health, Saihst, Sungkyunkwan University - Seoul (Korea, Republic of), 3. Department Of Neurology, Samsung Medical Center, Sungkyunkwan University School Of Medicine - Seoul (Korea, Republic of))*

Background: The relationship of body mass index (BMI) changes and variability with amyloid-β (Aβ) deposition remained unclear, although there were growing evidence that BMI is associated with the risk of developing cognitive impairment or AD dementia. **Objectives:** To determine whether BMI changes and BMI variability affected Aβ positivity, we investigated the association of BMI changes and BMI variability with Aβ positivity, as assessed by PET in a non-demented population. **Methods:** We retrospectively recruited 1,035 non-demented participants ≥50 years of age who underwent Aβ PET and had at least three BMI measurements in the memory clinic at Samsung Medical Center between August 2015 and August 2020. To investigate the association between BMI change and variability with Aβ deposition, we performed multivariable logistic regression. Further distinctive underlying features of BMI subgroups were examined by employing a cluster analysis model. **Results:** Decreased (odds ratio [OR] = 1.68, 95% confidence interval [CI] 1.16 to 2.42) or increased BMI (OR = 1.60, 95% CI 1.11 to 2.32) was associated with a greater risk of Aβ positivity after controlling for age, sex, APOE e4 genotype, years of education, hypertension, diabetes, baseline BMI, and BMI variability. A greater BMI variability (OR = 1.73, 95% CI 1.07 to 2.80) was associated with a greater risk of Aβ positivity after controlling for age, sex, APOE e4 genotype, years of education, hypertension, diabetes, baseline BMI, and BMI change. We also identified BMI subgroups showing a greater risk of Aβ positivity. **Conclusions:** Our findings suggest that participants with BMI change, especially those with greater BMI variability, are more vulnerable to Aβ deposition regardless of baseline BMI. Furthermore, our results may contribute to the design of strategies to prevent Aβ deposition with respect to weight control.

P94- PHASE 2 STUDY REVEALS AN ADEQUATE PK/PD RELATIONSHIP OF BOSUTINIB IN DEMENTIA WITH LEWY BODIES AND CLEARS THE PATH FOR LARGER PHASE 2/3 INVESTIGATIONS. C. Moussa[1], F. Pagan[2], T.Y. Yasar[2], H. Michaleine[1], T. Raymond[1], A. Jaeil[1] *(1. Georgetown University Medical Center - Washington (United States), 2. Medstar Georgetown Hospital - Washington (United States))*

Background: Bosutinib (Bosulif, Pfizer) is a potent tyrosine kinase (Abl/SRC) inhibitor that is FDA-approved at 500mg oral daily dose for leukemia. The effects of bosutinib were investigated in Dementia with Lewy Bodies (DLB). We investigated bosutinib, 100mg, which is equivalent to the lowest effective intraperitoneal daily dose (5mg/kg) in

pre-clinical studies. Bosutinib was investigated in several models of neurodegeneration and it was shown to facilitate clearance of alpha-synuclein and other neurotoxic proteins via autophagy, protect dopaminergic neurons and improve motor and cognitive behavior in animals. **Objectives:** To investigate safety, pharmacokinetics (PK), pharmacodynamics (PD) and biomarkers effects of the lowest effective dose of Bosutinib in Dementia with Lewy Bodies (DLB). **Methods:** A single center, Phase 2, randomized, double-blind, placebo-controlled study primarily investigated safety and PK/PD relationship of 12-week oral treatment of bosutinib,100mg. Biomarkers and clinical outcomes were exploratory. **Results:** Approximately 120 subjects were approached, 39 were screened, 13 did not meet inclusion criteria and 26 were randomized and included male and female (12:1) in bosutinib and male (13) in placebo with average age 72.94±8.8 (year±SD). There was no serious adverse events (SAEs) and no difference in AEs and no dropouts. Bosutinib, 100mg, was detected in the cerebrospinal fluid (CSF) and inhibited both Abl and Src. Bosutinib significantly reduced CSF alpha-synuclein ($p=0.023$) and the ratio of oligomeric/total alpha-synuclein ($p=0.045$) compared to placebo. There was also significant decrease in plasma oligomeric alpha-synuclein ($p=0.04$) and ptau181/Aβ42 ($p=0.03$). Bosutinib significantly ($p=0.034$) improved activities of daily living (ADCS-ADL-MCI) compared to placebo. **Conclusion:** This study showed that bosutinib is safe and enters the brain. Bosutinib, 100mg, inhibited Abl/Src indicting dual target engagement, reduced brain alpha-synuclein and improved activities of daily living, suggesting that this is lowest effective dose (100mg) in DLB. This study is underpowered (by design) but the data will guide adequately powered future studies of a higher dose range of bosutinib (100-400mg) over longer time (6 months) in DLB. **Funding:** This work was supported by the Alzheimer's Association Part the Cloud grant PTC-19-604235 to Charbel Moussa. **Disclosures:** Charbel Moussa is an inventor on a Georgetown University (GU) US and International Patent to use Bosutinib in neurodegenerative diseases, including alpha-synucleinopathies. GU exclusively licensed Bosutinib use patent to KeiffeRx. Charbel Moussa and Fernando Pagan are co-founders and shareholders of KeiferX, and Charbel Moussa and Jaeil Ahn are paid consultants to KeifeRX.

P95- BIOMARKER ASSESSMENTS FROM A PHASE 2, OPEN-LABEL STUDY OF NE3107 IN PATIENTS WITH COGNITIVE DECLINE DUE TO DEGENERATIVE DEMENTIAS. J. Haroon[1], K. Mahdavi[1,2], K. Jordan[1], E. Rindner[1], M. Zielinski[1], V. Venkatraman[1,2], D. Goodenowe[3], K. Hofmeister[3], C. Ahlem[4], C. Readin[4], J. Palumbo[4], B. Poura[5], S. Jordan[1,2] *(1. The Regenesis Project - Santa Monica (United States), 2. Synaptec Network - Santa Monica (United States), 3. Prodrome Sciences USA LLC - Temecula (United States), 4. Biovie Inc. - Carson City (United States), 5. Pourat MD - Beverly Hills (United States))*

Background: Chronic neuroinflammation and insulin resistance (IR) contribute to the pathophysiological development of Alzheimer's disease (AD), including the accumulation of amyloid-β (Aβ) plaques and phosphorylated tau protein (P-tau). Aβ and P-tau subsequently activate pro-inflammatory pathways, including mitogen-activated protein kinase (MAPK/ERK) signaling and tumor necrosis factor-α (TNFα) release, to perpetuate inflammation and accelerate neurodegeneration. Several other cytokines, including interleukin (IL)-1β, IL-6, IL-12, and tumor growth factor β (TGFβ), have been implicated in AD pathophysiology. Additionally, brain IR lowers glucose metabolism in neurons, leading to neuronal dysfunction and death. Insulin-sensitizing and anti-inflammatory agents may be beneficial in improving brain glucose metabolism and cognitive function, but their use may be limited due to poor blood-brain permeability or safety concerns. NE3107 is an oral, blood-brain–permeable agent that is well tolerated, selectively inhibits several inflammatory mediators (via MAPK/ERK regulation), and improves insulin signaling. Across several clinical studies, NE3107 increased insulin sensitivity and restored metabolic homeostasis in patients with type 2 diabetes and inflammation, and it was also shown to alter inflammatory biomarkers that have been associated with cognitive decline. **Objectives:** The present Phase 2, open-label study was designed to evaluate the potential efficacy of NE3107 in patients with mild cognitive impairment (MCI) or mild dementia using AD and inflammatory biomarkers, changes in glucose metabolism, cognitive performance testing, and neuroimaging endpoints. **Methods:** Twenty-three participants were enrolled and received 20-mg oral NE3107 twice daily for 3 months. Participants were between 50-89 years old with MCI or mild dementia (Quick Dementia Rating Scale [QDRS] score cutoff range: 1.5-12.5; Clinical Dementia Rating [CDR] score range: 0.5-1). Primary endpoints evaluated neurophysiological health using multi-modal brain MRIs at baseline and treatment termination. Secondary endpoints evaluated changes in glucose metabolism using markers, such as hemoglobin A1c (HbA1c) and urinary glucose levels; changes in inflammatory markers, including high-sensitivity C-reactive protein, erythrocyte sedimentation rate, TGFβ, and several other cytokines, such as TNFα, IL-1β, IL-6, and IL-12; and changes in cognitive performance between baseline and treatment termination. Additionally, AD biomarkers were evaluated at baseline and treatment termination using lumbar puncture to measure Aβ42 and tau protein levels. **Results:** Participants had a mean age of 71.6 (SD = 9.63) years and 15 (65%) were females. At baseline, the mean QDRS score was 5.07, 18 (78%) participants had a CDR score of 0.5, and 5 (22%) participants had a CDR score of 1. Study findings related to changes in glucose metabolism and AD and inflammatory biomarkers will be presented at the conference. **Conclusion:** Chronic neuroinflammation and IR are thought to fuel AD progression and contribute to physiological impairment and decreased cognitive performance. Elements of AD neuropathology may then exacerbate IR and promote a perpetual state of low-grade inflammation. This study assessed key biomarkers associated with AD to provide an exclusive set of mechanistic insights into dementia and the potential therapeutic efficacy and anti-inflammatory effects associated with NE3107 treatment in patients with MCI. **Funded by:** BioVie Inc. **Disclosures:** JH, KM, KJ, ER, MZ, VV, and SJ have received grant support from BioVie Inc. DG has nothing to disclose. KH has nothing to disclose. BP has nothing to disclose. CA, CR, and JP are employees of BioVie Inc.

P96- ROBUSTNESS OF CEREBROSPINAL FLUID (CSF) AMYLOID-B 1–42/AMYLOID-B 1–40 (AB42/AB40) AND PHOSPHORYLATED TAU/AMYLOID-B 1–42 (PTAU/AB42) BIOMARKER RATIOS IN CLASSIFICATION OF AMYLOID POSITRON EMISSION TOMOGRAPHY (PET) POSITIVITY IN ROUTINE CLINICAL USE. C. Logan[1], H. Schinke[1], C. Rabe[2], M. Simon[3], O. Hansson[4,5], K. Blennow[6,7], E. Stomrud[4,5] *(1. Roche Diagnostics Gmbh - Penzberg (Germany), 2. Genentech, Inc., - South San Francisco (United States), 3. Roche Diagnostics International Ltd - Rotkreuz (Switzerland), 4. Clinical Memory Research Unit, Department Of Clinical Sciences Malmö, Lund University - Malmö (Sweden), 5. Memory Clinic, Skåne University Hospital - Malmö (Sweden), 6. Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At The University Of Gothenburg - Mölndal (Sweden), 7. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden))*

Background: Cerebrospinal fluid (CSF) amyloid-β 1–42/amyloid-β 1–40 (Aβ42/Aβ40) and phosphorylated tau (pTau)/Aβ42 biomarker ratios have been shown to be highly concordant with amyloid positron emission tomography (PET) in people presenting with cognitive impairment (CI). The robustness of a biomarker assesses how variability impacts clinical decision-making; such variability is expected in a prospective routine clinical setting. In practice, there is documented inter-center variability in the measurement of CSF Aβ42 and Aβ401 that may limit utility of the Aβ42/Aβ40 ratio in routine clinical use. Previous studies suggested that the CSF pTau/Aβ42 ratio may have greater robustness than Aβ42/Aβ402, but this has not yet been investigated in the intended use population for the diagnostic test. **Objective:** To evaluate and compare the robustness of CSF Aβ42/Aβ40 and pTau/Aβ42 ratios in the diagnostic evaluation of Alzheimer's disease in people with mild CI (MCI) or subjective cognitive decline (SCD), with respect to the theoretical bias that may be observed in routine clinical use (±10%). **Methods:** This retrospective analysis utilized biomarker measurements from the Elecsys® β-Amyloid(1–42) CSF and Phospho-Tau (181P) CSF immunoassays and the research use only β-Amyloid(1–40) CSF immunoassay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) in previously frozen samples from subjects with MCI/SCD enrolled in the BioFINDER1 cohort who had a visual amyloid PET result. Summary statistics were calculated for CSF Aβ42/Aβ40 and pTau/Aβ42 ratios across all subjects and by amyloid PET status. For each biomarker ratio, biomarker status (i.e., below or above the respective cut-off value) was compared with amyloid PET status to determine positive and negative percent agreement (PPA and NPA, respectively) for the respective optimal cut-off values (Aβ42/Aβ40: 0.050 [Youden Index]; pTau/Aβ42: 0.022 [predetermined from a prior clinical study]). To estimate robustness in routine clinical use, reclassification rates and changes in PPA and NPA were calculated with respect to the maximum theoretical bias expected in routine clinical use (based on the addition of ±10% bias to each individual biomarker). **Results:** The mean CSF Aβ42/Aβ40 ratio in amyloid PET-positive subjects was 0.0360 (standard deviation [SD]: 0.0084) and 0.0750 (SD: 0.0187) in amyloid PET-negative subjects. For CSF pTau/Aβ42, the mean ratio in amyloid PET-positive subjects was 0.0460 (SD: 0.0196) and 0.0145 (SD: 0.0152) in amyloid PET-negative subjects. The median ratio of CSF Aβ42/Aβ40 and pTau/Aβ42 in amyloid PET-positive subjects was 0.0350 and 0.0804, respectively and in PET-negative subjects was 0.0423 and 0.0100, respectively. When comparing the performance of the biomarker ratios with amyloid PET status, for CSF Aβ42/Aβ40 (area under the curve [AUC]: 0.94), the PPA was 0.96 and NPA was 0.88; for pTau/Aβ42 (AUC: 0.95) the PPA was 0.92 and NPA was 0.89. Following adjustment for theoretical bias, up to 10.5% of people tested using CSF Aβ42 (+10%)/Aβ40 (-10%) would be reclassified (ΔPPA: -20% and ΔNPA: +4.2%) vs. 1.4% tested using pTau (-10%)/Aβ42 (+10%; ΔPPA: +3.7% and ΔNPA: -3.6%). **Conclusion:** Compared with CSF Aβ42/Aβ40, pTau/Aβ42 shows greater robustness to bias (±10%); therefore, in routine clinical use, pTau/Aβ42 is likely to have greater diagnostic performance and a lower risk of misclassification for people with borderline results. 1. Hansson, O et al. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther 2019;11:34. 2. Rabe, C et al. Utility of plasma Aβ1-42/Aβ1-40 as a screening tool is limited due to lack of robustness. Poster presentation at CTAD 2021; Nov 9–12. **Conflict(s) of interest:** CL and HS are employees of Roche Diagnostics GmbH and hold shares in F. Hoffmann-La Roche. CR is an employee of Genentech, Inc. OH has received Institutional research support from AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, GE Healthcare, Pfizer, and Roche and consultancy/speaker fees from Alzpath, Biogen, Cerveau, Genentech, Roche, and Siemens. KB has acted as a consultant at advisory boards and data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program and has received support from the ALF-agreement (#ALFGBG-715986), the Alzheimer's Association 2021 Zenith Award (ZEN-21-848495), the Alzheimer Drug Discovery Foundation (ADDF; USA; #RDAPB-201809-2016615), the European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236), Hjärnfonden (Sweden; #FO2017-0243), the National Institute of Health (NIH; USA; grant #1R01AG068398-01), the Swedish Alzheimer Foundation (#AF-742881), the Swedish Research Council (#2017-00915), and the Swedish state under the agreement between the Swedish government and the county councils. ES has no conflict of interest.

P97- THE BIOMARKER-BASED ETIOLOGICAL DIAGNOSIS OF NEUROCOGNITIVE DISORDERS: THE EUROPEAN INTER-SOCIETAL DELPHI CONSENSUS.

S. Orini[1,2], C. Festari[3], F. Massa[4], M. Cotta Ramosino[5,6], F. Nobili[7,8], G.B. Frisoni[9,10], E. The European Inter-Societal Consensus On The Biomarker-Based Diagnosis Of Dement[11] *(1. Alzheimer's Unit-Memory Clinic, Irccs Istituto Centro San Giovanni Di Dio Fatebenefratelli - Brescia, (Italy), 2. Dipartimento di Scienze Cliniche e Sperimentali, Università degli Studi di Brescia, - Brescia (Italy), 3. Laboratory Of Alzheimer's Neuroimaging And Epidemiology, Irccs Istituto Centro San Giovanni Di Dio Fatebenefratelli, - Brescia, (Italy), 4. Department Of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal And Child Health (dinogmi), University Of Genoa - Genoa (Italy), 5. Unit Of Behavioral Neurology, Irccs Mondino Foundation, - Pavia (Italy), 6. Department of Brain and Behavioral Sciences, University of Pavia, - Pavia, (Italy), 7. Department Of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal And Child Health (dinogmi), University Of Genoa, - Genoa (Italy), 8. IRCCS Ospedale Policlinico San Martino, - Genoa (Italy), 9. Laboratory Of Neuroimaging Of Aging (lanvie), University Of Geneva, - Geneva (Switzerland), 10. Geneva Memory Center, Department of Rehabilitation and Geriatrics, Geneva University Hospitals, G - Geneva (Switzerland), 11. The European Inter-Societal Consensus On The Biomarker-Based Diagnosis Of Dementia))*

Background: In the field of neurocognitive disorders, the perspective offered by new disease-modifying therapy increases the importance of etiological diagnosis. The prescription of cerebrospinal fluid analysis (CSF) and imaging biomarkers is a common practice in the clinic but is often driven more by personal expertise and local availability of diagnostic tools than by evidence of efficacy and cost-effectiveness analysis. This leads to a widely heterogeneous dementia care across Europe. **Objectives:** A European initiative is currently being conducted to establish a consensus for biomarker-based diagnosis of patients with mild cognitive impairment (MCI) and mild dementia. Preliminary results will be reported here, pending final consensus, which is expected to be available in late October 2022. **Methods:** Since November 2020, an European multidisciplinary task force of 22 experts from eleven scientific societies have been defining a diagnostic workflow for the efficient use of biomarkers. To achieve the goal, the Delphi consensus procedure was used to bridge the gaps of incomplete scientific evidence on biomarker prioritization with expert opinion and experience. The project has been in two phases. During the preparatory phase (Phase 1), we conducted a literature review on the accuracy of imaging, CSF, neurophysiological and blood biomarkers in predicting the clinical progression or in defining the underpinning aetiology of main neurocognitive disorders. Evidence was provided to support the panelists' decisions. In phase 2, a modified Delphi procedure was implemented, based on virtual rounds. Consensus was reached at a threshold of 70% agreement, or 50%+1 when a question required rediscussion. **Results:** In phase 1, 2200 papers were screened. Among them, only 167 provided validated measures of biomarker diagnostic accuracy compared with a gold/reference standard or in predicting progression or conversion of MCI to the dementia stage. Fifty studies provided accuracy values for MRI, 41 for CSF, 37 for FDG-PET, 15 for DaT-imaging, 10 for amyloid-PET, 2 for tau-PET and 6 for myocardial MIBG-scintigraphy and EEG. During phase 2, six rounds have been completed. Panelists agreed on the clinical workspace of the workflow (specialist outpatient service), the stage of application (prodromal and mild dementia), and the patient age window (biomarker use strongly encouraged below 70 years and of limited usefulness over age 85). The workflow is patient-centered and features three levels of assessment (W): W1 defines eleven clinical profiles based on integrated results of neuropsychology, MRI atrophy patterns, and blood tests; W2 describes the first-line biomarkers according to W1 versus clinical suspicion; and W3 suggests the second-line biomarkers when the results of first-line biomarkers are inconsistent with the diagnostic hypothesis, uninformative or inconclusive. More specifically, CSF biomarkers are first-line in the suspect of Alzheimer's disease (AD) and when inconsistent neuropsychological and MRI findings hinder a clear diagnostic hypothesis; dopamine SPECT/PET for those leading to suspect Lewy body spectrum. FDG-PET is first-line for the clinical profiles leading to suspect frontotemporal lobar degeneration and motor tauopathies and is followed by CSF biomarkers in the case of atypical metabolic patterns, when an underlying AD etiology is conceivable. None of these biomarkers is indicated when clinical profiles suggest vascular cognitive impairment or other neurological disorders. **Conclusions:** The workflow will promote consistency in diagnosing neurocognitive disorders across countries and rational use of resources. The initiative has some limitations, mainly linked to the Delphi procedure (e.g., kick-off questions were driven by the moderators, answers are driven by the Delphi panel composition, a subtle phrasing of the questions may drive answers, and 70% threshold for convergence is conventional). However, the diagnostic workflow will be able to help clinicians achieve an early and sustainable etiological diagnosis and enable the use of disease-modifying drugs as soon as they become available. **Conflict of Interest:** The presenting author has no relevant disclosures regarding this abstract. **Funding sources.** This project received an unrestricted grant from F. Hoffmann-La Roche Ltd., Biogen International GmbH, Eisai Europe Limited, and Life Molecular Imaging GmbH. Funders had no role in the conception, design, and implementation of the project nor on data collection, data analysis, and interpretation and discussion of the results.

P98- PREDICTING AMYLOID POSITIVITY WITH BLOOD-BASED BIOMARKERS INCLUDING P-TAU181.

H.S. Hyuk Sung[1], E.H. Eun-Hye[1], H.H. Hyun-Hee[1], K. Seong-Ho[1] *(1. Department of Neurology, Hanyang University Guri Hospital, Hanyang University College of Medicine - Guri (Korea, Republic of))*

Background: Detecting amyloid pathologies has become increasingly important for selecting patients for clinical trials and diagnosing Alzheimer's disease (AD) in clinical practice. Although amyloid beta (Aβ) positron emission tomography (PET) imaging and cerebrospinal fluid concentration of Aβ42 and/or Aβ40 reflect the presence of amyloid pathologies, these methods are expensive and/or invasive. To overcome these limitations, studies have focused on the use of blood-based biomarkers. **Objectives:** We aimed to determine the efficacy of combining plasma phosphorylated tau (p-tau)181, Aβ42/Aβ40, neurofilament light (NfL) and apolipoprotein E (APOE) genotypes in detecting positive amyloid positron emission tomography (PET) in a prospective cohort of individuals with and without AD. **Methods:** Biomarkers were measured using single-molecule array (Simoa) methods in participants who were cognitively unimpaired (CU, n=8), had mild cognitive impairment (MCI, n=53), and had dementia (n=49). All participants underwent 18F-florbetaben amyloid PET. Statistical analyses were performed to determine the best model. The significant change of area under the curve (AUC)

and Akaike information criterion value were considered to find the best model. **Results:** In total participants, univariate analysis revealed a significant association of Aβ positivity with plasma p-tau181 (AUC=0.848, P< .001) and with APOE ε4 status (AUC=0.704, P< .001). The model that included p-tau181 alone distinguished Aβ status with high accuracy. Adding APOE ε4 or NfL improved model fitness; however, it did not significantly improve the AUCs. In each MCI or dementia group, the addition of other biomarkers to p-tau181 did not improve the performance of p-tau181 alone. **Discussion:** Plasma p-tau181 showed a high performance in determining Aβ-PET positivity. Adding plasma NFL and APOE ε4 status improved the model fit without significant improvement of AUC. In MCI or dementia patients, adding other biomarkers did not improve the model performance. **Conflict of interest:** The authors declare no competing interests.

P99- DATA-DRIVEN 18F-FLORTAUCIPIRT CUT-OFFS FOR PRECLINICAL AND EARLY AD. G. Quattrini[1,2], C. Ferrari[3], M. Pievani[1], F. Ribaldi[4], S. Tomczyk[4], G.B. Frisoni[4], V. Garibotto[4], M. Marizzoni[1] *(1. Laboratory Of Alzheimer's Neuroimaging And Epidemiology (lane), Irccs Istituto Centro San Giovanni Di Dio Fatebenefratelli, Brescia, Italy - Brescia (Italy), 2. Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy - Brescia (Italy), 3. Unit Of Statistics, Irccs Istituto Centro San Giovanni Di Dio Fatebenefratelli, Brescia, Italy - Brescia (Italy), 4. Memory Clinic And Lanvie-Laboratory Of Neuroimaging Of Aging, University Hospitals And University Of Geneva, Geneva, Switzerland - Geneva (Switzerland))*

Background: Clinical trials for Alzheimer's disease (AD) are starting to use tau PET positivity (T+) as eligibility criterion (e.g., the TRAILBLAZER-ALZ donanemab trial, Mintun et al., 2021). Furthermore, topographic PET staging schemes have potential for early diagnosis, predicting disease progression, and studying disease mechanism (Chen et al., 2021). Several thresholding methods have been proposed to dichotomize the tau PET uptake values and define the tau PET negativity (T-)/T+, but with considerable methodological variability (Weigand et al., 2022). Importantly, none of these previous approaches was data-driven. Here, we determined PET cut-offs for in-vivo tau PET positivity and staging in AD using a data-driven approach. The effects of potential confounders (APOE4 carriage, age, and sex) on cut-offs estimation were also explored. **Methods:** Amyloid negative (Aβ-) cognitively normal (CN) and amyloid positive (Aβ+) CN (preclinical AD), Aβ+ mild cognitive impairment ([MCI]; prodromal AD), and Aβ+ AD (AD dementia) subjects were included from the ADNI (n=475) and the Geneva Memory Center (GMC, n=99) cohorts. Weighted means of 18F-Flortaucipir standardized uptake value ratio (SUVr, with the inferior cerebellar gray matter as reference region) were calculated for the most commonly used regions of interest (ROI): temporal meta-ROI (as a general measure of tau positivity; Jack et al, 2017) and Braak-based stages I-VI (as a measure of disease progression; Cho et al., 2016). For each subject, the highest regional SUVr value between the left and the right hemisphere was selected. Data-driven SUVr cut-offs were estimated from the ADNI cohort applying the Gaussian mixture model (GMM) on the Aβ- CN and AD dementia subgroup (n=269), using an online application we recently developed (admodelling.org/). Cut-offs were also estimated including confounders in GMMs. Sensitivity and classification analyses were conducted by applying the GMM-based cut-offs both internally (ADNI) and externally (GMC). Previously published 18F-Flortaucipir cut-offs (Jack et al, 2017, and Maass et al., 2017, for the temporal meta-ROI; Mattsson et al., 2017, for Braak-based stages) were also applied to both cohort, to compare with GMM-based threshold. Finally, in the GMC cohort tau PET images underwent to visual rating, and the intraclass correlation coefficient (ICC2,k) was computed with the classification according to GMM-based cut-offs. **Results:** GMM-based SUVr cut-offs were 1.36 for temporal meta-ROI and ranged from 1.20 (stage V) to 1.39 (stage VI) for Braak-based scheme. Similar values were found when confounders were included in the GMMs. In the ADNI cohort, the sensitivity increased from Aβ- CN to preclinical, prodromal, and AD dementia for the temporal meta-ROI (2%, 13%, 49 %, 85%) and, similarly, for Braak-based stages I-VI. CNs were mainly tau negative (Aβ- : 96%, Aβ+: 76%), while the highest percentages of prodromal AD (35%) and AD dementia (38%) were classified as tau negative and stage VI, respectively. These results were confirmed in the GMC cohort. Compared to previously published values, GMMs-based cut-offs values were generally higher, denoting a more conservative threshold, and generally detected lower percentages of tau positive subjects in all subgroups. Finally, GMM-based cut-offs showed excellent (ICC=0.91, for the temporal meta-ROI) to good (ICC=0.85, for Braak-based staging) reliability with visual rating, while previously published cut-offs showed fair reliability (ICC=0.58 for the temporal meta-ROI, and ICC=0.62 for the Jack and Maass cut-offs respectively, ICC=0.56 for Mattsson's Braak-based cut-offs). **Conclusion:** We provided reliable data-driven 18F-Flortaucipir SUVr cut-offs, which could be useful for study population selection in preclinical and early AD clinical trials. Lower percentages of Aβ- T+ subjects in CNs suggests less impact of type 1 error (false positive rates) than previously published cut-offs.

P100- BIOLOGICAL BRAIN AGE PREDICTION USING MACHINE LEARNING ON STRUCTURAL NEUROIMAGING DATA: MULTI-COHORT VALIDATION AGAINST BIOMARKERS OF ALZHEIMER'S DISEASE AND NEURODEGENERATION STRATIFIED BY SEX.

I. Cumplido Mayoral[1,2], M. Milà-Alomà[1,2,3,4], L. Lorenzini[5], A.M. Wink[5], H.J.M.M. Mutsaerts[5], S. Haller[6], G. Chetelat[7], F. Barkhof[5,8], M. Carboni[9], G. Kollmorgen[10], H. Zetterberg[11,12,13,14], K. Blennow[11,12], M. Suárez-Calvet[1,3,4,15], V. Vilaplana[16], J.D. Gispert[1,3,17] *(1. Barcelonaβeta Brain Research Center (bbrc), Pasqual Maragall Foundation - Barcelona (Spain), 2. Universitat Pompeu Fabra - Barcelona (Spain), 3. IMIM (Hospital del Mar Medical Research Institute) - Barcelona (Spain), 4. CIBER Fragilidad y Envejecimiento Saludable (CIBERFES) - Madrid (Spain), 5. Department of Radiology and Nuclear Medicine, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC - Amsterdam (Netherlands), 6. CIRD Centre d'Imagerie Rive Droite - Geneva (Switzerland), 7. Imaging of Neurological Disorders», Institut Blood and Brain @ Caen-Normandie, Cyceron - Caen (France), 8. Institutes of Neurology and Healthcare Engineering, University College London - London (United Kingdom), 9. Roche Diagnostics International Ltd - Rotkreuz Zg (Switzerland), 10. Roche Diagnostics GmbH - Penzberg (Germany), 11. Institute of Neuroscience and Physiology, University of Gothenburg - Mölndal (Sweden), 12. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 13. Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology - London (United Kingdom), 14. UK Dementia Research Institute at UCL - London (United Kingdom), 15. Servei de Neurologia, Hospital del Mar - Barcelona (Spain), 16. Department of Signal Theory and Communications, Universitat Politècnica de Catalunya - Barcelona (Spain), 17. Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN) - Madrid (Spain))*

Background: Age is the strongest risk factor for Alzheimer's disease (AD) and other neurodegenerative diseases. Still, the biological mechanistic links between age and AD are fundamentally unknown. A better understanding of these links is an urgent priority to develop effective strategies to deal with their rising burden amid an ageing population. Therefore, a growing amount of research is focusing on using neuroimaging techniques to develop a biomarker of biological brain aging. In this framework, the concept of brain-age has emerged as a marker that enables determining on an individual basis, the risk for age-associated brain diseases. Brain-age can be inferred from structural neuroimaging, by which individuals with a predicted brain-age higher than their chronological age may have an "older" brain than expected. Subtracting chronological age from estimated brain-age hence provides an estimate of accelerated/decelerated brain aging, namely the brain-age delta. Recent literature has shown the adequacy of using a brain-age predicted measurement in the assessment of the clinical severity of AD, but there remains a need to study the associations between brain-age delta and biomarkers of AD and neurodegeneration in preclinical stages and in independent cohorts. Moreover, given that female individuals have a higher AD prevalence compared to males and display different lifetime trajectories in the brain morphological features, it is of interest to determine the effect of sex on brain-age delta and its interaction with AD and neurodegeneration biomarkers. **Objectives:** We aimed to validate brain-age delta as a relevant biomarker related to AD, neurodegeneration, and cerebrovascular disease in non-demented individuals. Furthermore, we also aimed to study between-sex differences in the brain areas that better predict age, as well as to study the sex effects with these biomarkers on brain-age delta. **Methods:** We trained XGBoost regressor models to predict brain-age separately for cognitively unimpaired (CU) females and males using volumes and cortical thickness in regions of the Desikan-Kiliany atlas (obtained with Freesurfer 6.0) from the UKBioBank cohort (N=22,661). Using this trained model, we estimated brain-age delta (predicted brain-age – chronological age) in CU and mild cognitive impaired (MCI) individuals from four independent cohorts: ALFA+ (NCU=380), ADNI (NCU=253, NMCI=498), EPAD (NCU=653, NMCI=155) and OASIS (NCU=407). Chronological age, sex, MMSE and APOE categories were available for all subjects. ALFA+, ADNI and EPAD cohorts included data for amyloid-β (Ab) status determined by CSF Aβ42 levels according to established cut-offs (<1098pg/mL for ALFA+ and EPAD and <880pg/mL for ADNI), for AT stages determined by CSF Aβ42 and CSF p-tau (<24pg/mL) and for White Matter Hyperintensities (WMH). OASIS had data for amyloid-β status determined by amyloid-β PET (Centiloid<17). CSF and plasma neurofilament light (NfL) was available as a biomarker of neurodegeneration in ALFA+ and ADNI. Linear regression models, including chronological age and sex as covariates were used to identify associations between brain-age delta and biomarkers and, additionally, we conducted these analyses stratifying by sex. We next tested for interactions between sex and the validation variables on brain-age delta using linear regression models and including chronological age as covariate. Lastly, we studied the differences in volumes and cortical thickness between females and males in the UK BioBank for the brain regions that contributed the most to the prediction. To do so, we performed regression models for each brain region with sex as predictor variable, in which linear and quadratic expansions of age, site and total intracranial volume (only included for volumetric measurements), were included as covariates. **Results:** Brain-age delta was associated with abnormal amyloid-β (P<0.001), more advanced AT stages (P<0.001), APOE-β4 status (P<0.001) and increased WMH (P<0.001). Brain-age delta was positively associated with plasma neurofilament light (P=0.002), and sex differences in the brain effects of this marker were found, in which both plasma and CSF NfL were positively associated with brain-age delta in females (CSF: P=0.042, plasma: P=0.001), but not in males (CSF: P=0.959, plasma: P=0.254). Furthermore, we found between-sex differences in the most predictive brain regions: we found reduction in the superior-frontal, isthmus-cingulate and pars orbitalis regions within males and regions such as inferior-parietal, pars triangularis and paracentral within females. We also found regions that had a high impact on the prediction for both females and males, which, in addition, overlapped with regions included in the aging signature, such as the precentral sulcus, insula, superior frontal and rostral middle frontal regions. **Conclusion:** These results validate brain-age delta as a non-invasive marker of biological brain aging related to markers of AD, neurodegeneration, and cerebrovascular disease. Our results also indicate that there are sex differences in the development of brain aging trajectories and suggest the prevalence of different neuropathological pathways involved in brain aging within females and males. Therefore, these results show the necessity to consider different approaches for assessing aging and neurodegeneration differently for each sex.

P101- CEREBROSPINAL FLUID PLACENTAL GROWTH FACTOR IN RELATION TO CEREBROVASCULAR DISEASE AND DIABETES IN NON-DEMENTED ELDERLY. E.C. Gertje[1,2], S. Janelidze[1], D. Van Westen[3,4], E. Stomrud[1,5], S. Palmqvist[1,5], O. Hansson[1,5], N. Mattsson-Carlgren[1,6,7] *(1. Clinical Memory Research Unit, Department Of Clinical Sciences Malmö, Lund University - Malmö (Sweden), 2. Department of Internal Medicine, Skåne University Hospital - Lund (Sweden), 3. Diagnostic Radiology, Department Of Clinical Sciences Lund, Lund University - Lund (Sweden), 4. Imaging and Function, Skåne University Hospital - Lund (Sweden), 5. Memory Clinic, Skåne University Hospital - Malmö (Sweden), 6. Department of Clinical Sciences Lund, Neurology, Lund University, Skåne University Hospita - Lund (Sweden), 7. Wallenberg Center for Molecular Medicine, Lund University - Lund (Sweden))*

Background: Placental growth factor (PlGF) is a pro-inflammatory marker of angiogenesis, which is upregulated by hyperglycemia and involved in diabetic retinopathy. We previously found that cerebrospinal fluid (CSF) PlGF is strongly associated with white matter lesions (WML) in non-demented elderly. WML are commonly used to quantify cerebrovascular disease and correlate with cognitive decline. It is unclear to what degree CSF PlGF, and the relationship between CSF PlGF and WML, are influenced by diabetes. **Objectives:** To investigate associations between CSF PlGF (and the related protein vascular endothelial growth factor A, VEGF-A), WML and diabetes. **Methods:** 247 patients with mild cognitive impairment (MCI) and 495 cognitively unimpaired (CU) elderly from the Swedish BioFINDER study were included. CSF samples were analyzed for PlGF, VEGF-A, and β-Amyloid 40 (Aβ40) and Aβ42. 9.8% MCI and 9.1% CU subjects had diabetes. Associations between WML and CSF PlGF or CSF VEGF-A as well as their associations with diabetes were tested with linear regression models. Analyses were adjusted for age, gender, Aβ status, and intracranial volume. **Results:** CSF PlGF and VEGF-A correlated in both CU (β=0.36, CI 0.29 to 0.44) and MCI (β=0.56, CI 0.42 to 0.71). CSF PlGF was associated with WML in MCI (β=0.17, CI 0.11 to 0.24) and CU (β=0.16, CI 0.10 to 0.21). CSF VEGF-A was associated with WML in MCI (β=0.39, CI 0.09 to 0.69), but not in CU (β=0.06, CI -0.05 to 0.22). Participants with diabetes had significantly higher CSF PlGF, both in MCI (mean difference [MD] =-0.03, 95% confidence interval [CI] -0.07 to -0.001), and CU (MD=-0.03, CI -0.05 to -0.01), whereas CSF VEGF-A did not correlate with diabetes in any of the groups. In addition, participants with diabetes had slightly more WML compared to non-diabetes participants in MCI (MD=-0.27, CI -0.52 to -0.02), but no difference in WML was seen in CU (MD=-0.07, CI -0.03 to 0.12). The associations between CSF PlGF and WML were robust in non-diabetic subjects (MCI: β=0.19, CI 0.12-0.26; CU: β=0.18, CI 0.12-0.24), but absent in subjects with diabetes (MCI: β=-0.05, CI -0.21-0.11; CU: β=-0.03, CI -0.18-0.13). **Conclusion:** CSF PlGF was strongly associated with diabetes, which could indicate alterations in endothelial function, frequently seen in diabetes complications. However, the association between CSF PlGF and WML in non-demented individuals was absent in subjects with diabetes. This points out that diabetes may cause dysregulation of PlGF which attenuates associations with hallmarks of brain disease. This is relevant both for further studies of CSF PlGF as a marker of cerebrovascular disease, and for studies of CSF biomarkers in general, since biomarkers may be susceptible to confounding factors such as diabetes. The presenting author has no disclosures.

P102- PLASMA AD BIOMARKERS CAN PREDICT HIPPOCAMPAL ATROPHY. H.J. Kim[1], J.H. Lee[2] *(1. Uijeongbu Eulji Medical Center - Uijeongbu-Si (Korea, Republic of), 2. Asan Medical Center - Seoul (Korea, Republic of))*

Background: Biomarkers have now become an essential component of Alzheimer's research. Extracellular amyloid plaque and intraneuronal hyperphosphorylated tau accumulation are considered hallmarks of Alzheimer's disease (AD). Neuroinflammation has been deemed a secondary phenomenon, but is now emerging as a central player in the development in AD. The soluble fraction of triggering receptor expressed on myeloid cells 2 (sTREM2) is regarded as a marker for microglial activation. However, the relationship of AD biomarkers, particularly plasma biomarkers with anatomical patterns of cortical atrophy has not been extensively studied. **Objective:** We investigated the relationship between fluid AD biomarkers including sTREM2 and anatomical patterns of cortical atrophy. **Methods:** This study was a single-institutional, prospective cohort study of who visited the memory clinic of Asan Medical Center aged over 40 years and under 90 years, from June 2018 to July 2020. All subjects underwent brain magnetic resonance image (MRI), detailed neuropsychological testing, [F18]-florbetaben amyloid PET, cerebrospinal fluid (CSF) and blood analysis. Subjects were stratified by their amyloid positivity and clinical status. sTREM2, amyloid-β42 (Aβ42), amyloid-β40 (Aβ40), phosphorylated tau-181 (pTau181), total tau, and neurofilament light chain (NfL) levels were measured in the plasma as well as CSF. Among 104 subjects, 42 subjects without 3-dimentional T1 image were excluded and 62 subjects were finally included in the dataset. **Results:** Of 62 subjects, 33 subjects were classified AD-continuum based on amyloid PET. The cortical thickness did not show a significant statistical association with fluid AD biomarkers. There was no significant association in terms of neuroinflammatory biomarkers between CSF and plasma sTREM2. However, CSF pTau181 showed significant association between bilateral CA4 (left, $r = -0.39$, $P = 0.003$; right, $r = -0.30$, $P = 0.022$) and whole hippocampal volume ($r = -0.31$, $P = 0.02$). Furthermore, plasma pTau181 was significantly correlated with bilateral molecular layer (left, $r = -0.33$, $P = 0.011$; right, $r = -0.37$, $P = 0.0017$) and the whole hippocampal volume ($r = -0.3$, $P = 0.023$). CSF Aβ42/Aβ40 ratio showed correlation with bilateral molecular layer (left, $r = 0.37$, $P = 0.005$; right, $r = 0.27$, $P = 0.041$). **Conclusion:** Higher levels of CSF and plasma pTau181 correlated well with decreased hippocampal volume. Plasma pTau181 might be a useful, promising biomarker in predicting neurodegeneration. Further research on the relationship between plasma AD biomarkers and volumetric change of the brain is warranted for each stage of AD-continuum. The authors declare no competing interests.

P103- ASSESSMENT OF PLASMA P-TAU181 IN TANGO, A PHASE 2 STUDY OF GOSURAMEMAB IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE. J. Czerkowicz[1], J. Kong[1], A. Racine[1], C. Rubel[1], J. Collins[1], M. Shulman[1], D. Graham[1], J. Beaver[1], S. Budd Haeberlein[1] *(1. Biogen - Cambridge (United States))*

Background: Gosuranemab is a humanized monoclonal antibody that binds to the N-terminus of tau with high affinity. TANGO was a Phase 2 clinical study designed to assess the safety and efficacy of gosuranemab in participants with mild cognitive impairment due to Alzheimer's disease (AD) or with mild AD dementia with confirmed amyloid positivity (via either positron emission tomography (PET) or cerebrospinal

fluid (CSF)). No treatment difference was observed between gosuranemab and placebo on the primary efficacy or exploratory efficacy endpoints. Exploratory biomarker sub-studies of TANGO included examining the effects of gosuranemab on tau protein concentrations in CSF and blood, and the effects of gosuranemab on cerebral tau changes by tau PET. Emerging data on blood-based biomarkers in AD, including phosphorylated tau (p-tau) suggest multiple potential applications to clinical trials, including patient selection and treatment response. Multiple p-tau epitopes demonstrate potential ability to discriminate AD from non-AD, and correlate to amyloid pathology, tau pathology and cognitive decline. **Objectives:** Our objective is to examine p-tau181 levels in plasma samples collected during the TANGO study to assess the potential use of this biomarker as a tool to identify patients with baseline pathology and predict disease progression in AD clinical trials. **Methods:** Plasma was collected from randomized TANGO subjects at baseline, and weeks 16, 48, 60 and 76 post-baseline. Plasma p-tau181 was measured using the Quanterix Simoa p-tau181 V2 Advantage assay. Baseline plasma p-tau181 was measured in all subjects. Due to drug interference in the assay, longitudinal (post-baseline) plasma p-tau181 was analyzed only in placebo subjects. Additional exploratory biomarker analyses included CSF and PET. CSF was collected in a sub-study of n=327 subjects, and CSF tau and p-tau181 were measured using the Lumipulse assay up to Week 76 post-baseline. Tau PET was measured in a sub-study of n=357 subjects at baseline and Weeks 52 and 78 post-baseline, using the 18F-MK-6240 tau PET tracer. Amyloid PET was only measured at screening, using 18F-florbetapir in n=322 subjects. Statistical analysis was performed using Spearman correlation coefficient. **Results:** CSF and plasma p-tau181 were correlated at baseline (Spearman = 0.35, p-value <0.0001). Baseline plasma p-tau181 levels were correlated with both baseline amyloid PET using SUVR in composite regions of interest (Spearman = 0.31, p-value <0.0001) and baseline Tau PET using SUVR in composite regions of interest corresponding to Braak stages I-II, III-IV, and V-VI (Spearman range = 0.38-0.50, p=value <0.0001). Despite this evidence of correlation between baseline plasma p-tau181 levels and baseline Tau PET, some subjects with similar plasma p-tau181 levels were observed to have considerable variability in Tau PET binding patterns. TANGO subjects with higher concentrations of plasma p-tau181 at baseline showed a statistically significant correlation with a greater rate of clinical decline at week 78, using multiple cognition assessment scales, including ADAS-Cog13 (p=0.0001), CDR-Sum of Boxes (p=0.0023), and MMSE (p=0.0001). The ADCS-ADL scale was not significantly correlated with baseline plasma p-tau181 at week 78 (p=0.2053). **Conclusions:** Plasma p-tau181 data from the TANGO study will help inform our understanding of plasma biomarkers in AD, and the utility of this marker as a tool for patient selection and as a biomarker of disease progression. The correlations of plasma p-tau181 with amyloid and tau PET at baseline suggests a relationship with the underlying pathological hallmarks of AD. Furthermore, the correlation of baseline plasma p-tau181 and clinical decline observed over the course of the TANGO trial supports the utility of plasma p-tau181 as a potential prognostic biomarker of disease. However, there are limitations associated with this study that prevent us from drawing conclusions on the utility of plasma p-tau181 as a standalone biomarker for patient selection and disease progression. The patient population for the TANGO study was 100% amyloid PET positive at enrollment, with approximately 85% of these subjects also tau PET positive (Racine, et al, AAIC poster, 2022), making it difficult to establish a threshold for patient selection without a well-powered negative population. Due to the interference of gosuranemab binding to tau, there is limited longitudinal plasma p-tau181 data to assess the relationship with cognitive decline over the course of the study. Assay standardization to support consistency of data and continued advancement of the p-tau methods to further optimize assay characteristics such as robustness and dynamic range will be important to increase utility of this emerging biomarker. Generation of additional datasets from AD clinical trials that include PET-imaging and CSF collections will be critical to advancing towards this goal.

P104- CORNEAL CONFOCAL MICROSCOPY AND MRI BRAIN VOLUMETRY: PROGNOSTIC BIOMARKERS FOR PROGRESSION FROM MILD COGNITIVE IMPAIRMENT TO DEMENTIA. G. Ponirakis[1], R. Malik[1] *(1. Weill Cornell Medicine in Qatar - Doha (Qatar))*

Background: There is an urgent need for biomarkers that identify subjects with mild cognitive impairment (MCI) at increased risk of progression to dementia. We have previously used corneal confocal microscopy (CCM) to identify corneal nerve degeneration in subjects with MCI and dementia. **Objectives:** This study compared the utility of corneal nerve measures with brain volumetry for predicting progression to dementia in people with MCI. **Methods:** Participants with MCI underwent assessment of cognitive function, brain MRI and CCM and followed-up to identify progression to dementia. Corneal nerve fiber density (CNFD), length (CNFL) and branch density (CNBD) and the volume of different brain structures were quantified. **Results:** Of 107 subjects with MCI aged 68.4±7.7 years, 33 (30.8%) progressed to dementia over a mean follow-up of 2.6 years. Subjects with MCI who progressed to dementia had a significantly lower CNFD (20.6±9.3 fibers/mm2 vs 28.8±8.2 fibers/mm2, P<0.0001), CNBD (43.3±28.9 branches/mm2 vs 70.8±37.2 branches/mm2, P<0.0001), and CNFL (14.3±6.3 mm/mm2 vs 19.9±5.7 mm/mm2, P<0.0001) compared to those who did not progress. Corneal nerve measures had a higher prognostic accuracy (72-75% vs 68-69%) and specificity (78-84% vs 60-62%) and very high negative predictive value (80-84%) compared to hippocampus and whole brain volume for identifying subjects who progressed to dementia. The adjusted odds ratio for progression to dementia was 6.1 (95%CI:1.6-23.8) and 4.1 (95%CI:1.2-14.2) higher with abnormal CCM measures but was not significant for abnormal brain volume. **Conclusions:** Abnormal CCM measures had a higher prognostic accuracy than brain volumetry for predicting progression to dementia in people with MCI. CCM could be used to identify subjects with MCI at greater risk of progression to dementia for inclusion in clinical trials of neuroprotective or disease modifying therapies.

P105- OLIGOMER BIOMARKERS FOR PRECLINICAL AND CLINICAL DRUG DEVELOPMENT IN NEURODEGENERATIVE DISORDERS. O. Bannach[1,2], L. Blömeke[1,2], B. Kass[1], A. Chen-Plotkin[3], O. Peters[4], D. Willbold[1,5] *(1. Forschungszentrum Jülich - Jülich (Germany), 2. attyloid GmbH - Düsseldorf (Germany), 3. University of Pennsylvania - Philadelphia (United States), 4. Charité Universitätsmedizin Berlin - Berlin (Germany), 5. Heinrich-Heine-Universität Düsseldorf - Düsseldorf (Germany))*

Background: The major pathological hallmark among neurodegenerative diseases is formation of toxic oligomers, comprising proteins such as amyloid-beta (Aβ) alpha-synuclein (aSyn) and Tau protein (Tau). Consequently, such oligomers

are promising biomarker candidates for diagnostics and drug development. However, measuring oligomers in body liquids such as cerebrospinal fluid (CSF) or even blood is technically challenging as extreme sensitivity and selectivity is required. We have previously developed surface-based fluorescence intensity distribution analysis (sFIDA), a method featuring single particle sensitivity and absolute specificity for oligomers. **Objectives:** Our objective was to deliver proof-of-concept that sFIDA can be applied to quantify oligomers in preclinical and clinical samples. **Methods:** In brief, sFIDA combines the selectivity of an immunoassay with the digital sensitivity of fluorescence microscopy. sFIDA employs capture and probe antibodies directed against the same epitope rendering the assay selective for oligomers and insensitive for monomers. Subsequent sFIDA readout is imaging-based, capturing the number of pixels with intensity exceeding background threshold. **Results:** We applied sFIDA to determine aSyn and Tau oligomer titers in the CSF of different disease groups and determined elevated Tau oligomers in Progressive Supranuclear Palsy and elevated aSyn oligomers in Parkinson's Disease and Lewy Body Dementia patients (Blömeke et al 2022). We further demonstrate that the oligomer disassembling (anti-prionic) compound RD2 indeed disassembles Aβ oligomers in AD patient-derived brain tissue homogenates (Kass et al. 2022). Finally, we will report yet unpublished data on elevated Aβ oligomers in the CSF of mild cognitively impaired (MCI) due to AD patients. **Conclusion:** In drug development, sFIDA is useful to validate any oligomer disassembling mechanism of action of a given drug in vitro, in animal models, and in ex vivo tissue homogenates. Further, sFIDA is a valuable biomarker assay for patient inclusion/exclusion, patient stratification, target engagement and drug effect monitoring in AD, and other protein misfolding diseases. **References:** Blömeke et al. (2022), Quantitative Detection of α-Synuclein and Tau Oligomers and other Aggregates by Digital Single Particle Counting", NPJ Parkinsons Dis., 8, 68. https://doi.org/10.1038/s41531-022-00330-x. Kass et al. (2022), Aβ oligomer concentration in mouse and human brain and its drug induced reduction ex vivo. Cell Reports Medicine, 3, 100630 https://doi.org/10.1016/j.xcrm.2022.100630. **Competing Interests:** D.W. is a founder and shareholder of the company Priavoid and member of its supervisory board. D.W. and O.B. are founders and shareholders of attyloid. D.W. is member of attyloid's supervisory board. This had no influence on the interpretation of the presented data.

P106- EXPLORATORY STUDY ON THE PROTEOMIC AND TRANSCRIPTOMIC CONTENT OF PLASMA EXTRACELLULAR VESICLES IN AD PATIENTS.

M. Solaguren-Beascoa[1], A. Gámez-Valero[1,2], A.M. Ortiz[3], C. Minguet[3], R. Gonzalo[3], G. Escaramís[1,2], M. Costa[3], E. Martí[1,2]
(1. Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Institut of Neurociencies, Universitat de Barcelona - Barcelona (Spain), 2. Centro de Investigación Biomédica en Red sobre Epidemiología y Salud Pública (CIBERESP) - Barcelona (Spain), 3. Grifols Bioscience Research Group - Barcelona (Spain))

Background: Biomarkers for Alzheimer's disease (AD) are important for diagnosis, patients' stratification for inclusion in clinical trials and for treatment eligibility. Advances in the development of sensitive analytical tools have boosted biomarker discovery. Detection of beta-amyloid (Aβ42), Tau protein (Tau), neurofilament light (NfL), and/or glial fibrillar acidic protein (GFAP) proteins in plasma and other biofluids, has been successfully achieved in AD and other neurodegenerative diseases. Nevertheless, changes are very heterogeneous, and conflicting results have been reported. Most biomarkers only reflect clinical stages of the disease once the pathology has widely spread in the brain. To date, it remains unknown if other molecular changes, more sensitive and specific for AD, may be observed in blood. Specifically, early transcriptomic deregulation occurs in AD long before clinical onset, and several studies have explored the utility of plasma microRNAs and cell-free mRNA as biomarkers for AD. However, other highly abundant RNA species in plasma have been largely overlooked. In plasma, proteins and RNAs can be found as freely circulating and/or enclosed inside extracellular vesicles (EVs). EVs, which are naturally released by almost all types of cells, are known to mediate cell-to-cell communication. Proteins, nucleic acids, metabolites and lipids found inside EVs may reflect the physiological and/or pathological state of the cell/tissue of origin. In AD, EVs have been reported as important players in spreading AD pathology between brain cells. Diverse studies have found specific proteins or miRNAs deregulated in AD plasma EVs; however, the overall content of plasma EVs (proteins and small RNAs) has been scarcely explored. A detailed study of the whole vesicular content may provide new promising and more sensitive biomarkers reflecting changes occurring at different stages of AD. **Objectives:** The overall aim of the present proposal is to characterize the molecular content (small RNA transcriptome and proteome) of plasma EVs in AD patients in comparison to healthy individuals. We expected to identify new molecules with high biomarker potential that could be further profiled in the course of the disease and facilitate the establishment of earlier diagnosis and prognosis tools. **Methods:** Plasma samples from mild-to-moderate AD patients (n=10) and age matched healthy non-cognitive affected individuals (n=10) were processed by size exclusion chromatography to obtain EVs. The obtained EVs were characterized following MISEV (International Society for Extracellular Vesicles) guidelines and were further processed for transcriptomic and proteomic analyses. Vesicular RNA was extracted from half of the EV preparation and treated with T4 polynucleotide kinase; small RNA (sRNA) libraries were prepared and sequenced in an Illumina HiSeq2500. Adapters were removed with cutadapt and reads were mapped with the STAR aligner. We used the SeqCluster tool to organize sRNAs in clusters of co-expressed sRNA consistently and non-redundantly mapping onto the same precursor. Differential expression (DE) analysis was performed via negative-binomial general linear models implemented in the R package DESeq2. The other half of the EV preparation was used for proteomic analyses by LC-MS/MS. MaxQuant computational platform and Perseus software were used for protein identification and quantification, and DE was analyzed using a Student's t-test. To select DE sRNAs or proteins we used a 1.3-fold change cut-off, with ratios below the low range of 0.77 considered as downregulated and those above 1.33 as upregulated. **Results:** Plasma EVs were successfully isolated from 1mL of plasma samples, both in AD and healthy samples (CTRL). No significant differences in EV markers CD9, CD81 and CD63 intensity were found by flow cytometry, neither in EV-size or concentration as shown by cryoTEM and nanoparticle tracking analysis between both cohorts. The proteomic profiling of EVs rendered a similar number of detected proteins, both in AD (358.3 ± 43) and CTRL (315.3 ± 69) samples, with several described as EV-enriched or exosome-related. DE analyses identified differentially deregulated proteins in AD versus CTRL; with 16 proteins downregulated and 15 proteins overexpressed (p-value<0.05).

The AD upregulated proteins showed significant enrichment in proteins of the endoplasmic reticulum chaperone complex, involved in protein folding. Regarding small RNA vesicular content, similar diversity and relative abundance of the different types of sRNAs were found in both group of samples. Tissue enrichment analysis suggests that most AD-EVs enriched sRNAs mapped onto genes highly represented in the brain. DE analysis identified 56 sRNAs over-represented in AD-EVs compared to CTRL (adj p-value < 0,05), with 45 % of them mapping onto gene fragments. Specific AD-EVs overexpressed sRNAs map onto genes already described as altered in AD, and some deregulated miRNAs validated previous findings in plasma of AD patients. **Conclusion:** Plasma extracellular vesicles can be used for parallel analysis of the proteome and transcriptome. Current study suggests that proteomic and transcriptomic content of plasma extracellular vesicles from AD patients differ from healthy controls and deserve further investigation. Observations of the present study highlight the potential of plasma EVs molecular content (proteomic and transcriptomic) to contribute to a diagnostic blood biomarker panel. This study was supported by Grifols.

P107- TOWARDS THE DEVELOPMENT AND VALIDATION OF A GENERAL-PURPOSE REGULATORY-GRADE NEUROIMAGE ANALYSIS TOOL. N. Henscheid[1], I. Pappas[2], R. Cabeen[2], J. Podichetty[1], S. Hobel[2], C. Weber[3], Y. Karten[1], K. Romero[1], S. Sivakumaran[1], A. Toga[2] *(1. Critical Path Institute - Tucson (United States), 2. University of Southern California - Los Angeles (United States), 3. Alzheimer's Association - Chicago (United States))*

Background: The Global Alzheimer's Association Interactive Network (GAAIN) and the Critical Path for Alzheimer's Disease (CPAD) Consortium have undertaken a collaborative effort to develop a multimodality regulatory-grade neuroimage analysis tool, leveraging a comprehensive dataset of individual patient-level records, rich in fluid and imaging biomarkers from global clinical trials and observational studies. This effort is based on the LONI Pipeline, a tool that allows a variety of brain processing pipelines to be executed on any brain data modality, and GAAIN's federated architecture, a system for sharing Alzheimer's-related data stored in independently operated repositories owned by the data partners. This software tool will package previously validated image analysis pipelines with a user-friendly graphical interface allowing for rapid, automated quantification of image-derived biomarkers. It is envisioned that pipelines can be constructed and validated for any modality and analysis target, including both MRI-based and PET-based imaging. This tool will help advance the understanding of Alzheimer's disease progression and treatment effects, in addition to answer drug development and regulatory needs, by harmonizing the quantitation of neuroimaging biomarkers and subsequent correlations with fluid markers, cognitive assessments and patient characteristics, across different cohorts, tracers and demographics. **Methods:** The existing LONI Pipeline software was containerized to facilitate both its incorporation into the GAAIN system, as well as its proper validation. Specifically, the GAAIN system was expanded to allow users to submit requests to initialize LONI Pipeline processes in remote brain data repositories as part of its federated architecture. A set of procedures was developed to validate both the general-purpose aspects of the Pipeline software as well as task-specific analysis pipelines. To demonstrate analytical validity for a specific task, a cohort of interest in the CPAD database was created using GAAIN's interrogator. A brain volumetry processing request was initiated remotely, and hippocampal volumes were obtained from the brain images of that CPAD cohort. For validation, these results were tested against values calculated semi-automatically by a software-assisted human observer. The results were made available both within GAAIN as additional variables and in the CPAD database. To demonstrate clinical utility, we explored correlations of these values against blood-based biomarkers available from the CPAD database and other archives using the GAAIN system. **Results:** The containerized software provides a solid platform for future development of a user-friendly interface through GAAIN. Adequate correlation was found between volumetric measurements computed using the automated structural pipeline and the semi-automatic results computed by human readers. These results demonstrate the ability to provide validated regulatory-grade analyses through an existing data analytics platform. **Conclusion:** As novel anatomical and molecular neuroimaging techniques emerge it is essential that rigorously validated analysis software is made readily available for researchers to quickly calculate consistent results. The proposed framework will expand the existing GAAIN framework to include a regulatory-grade image analysis tool, allowing researchers to execute analysis on the GAAIN server and perform further analysis there. Expansion of the tool to include validated quantification of PET images (beta-amyloid and tau), as well as further demonstration of the scientific impact of the tool, is ongoing. **Note:** Nicholas Henscheid and Ioannis Pappas contributed equally to this work.

P108- COMPARATIVE PERFORMANCE OF PLASMA AB42/AB40 AND P-TAU181 FOR THE DETECTION OF EARLY BRAIN AMYLOID DEPOSITION IN INDIVIDUALS WITH SUBJECTIVE COGNITIVE DECLINE. M. Pascual-Lucas[1], J.A. Allué[1], L. Sarasa[1], N. Fandos[1], S. Castillo[1], J. Terencio[1], M. Sarasa[1], J.P. Tartar[2], Á. Sanabria[2,3], L. Tárraga[2,3], A. Ruiz[2,3], M. Marquié[2,3], M. Boada[2,3] *(1. Araclon Biotech-Grifols - Zaragoza (Spain), 2. Ace Alzheimer Center Barcelona - Universitat Internacional de Catalunya - Barcelona (Spain), 3. CIBERNED, Network Center for Biomedical Research in Neurodegenerative Diseases, National Institute of Health Carlos III - Madrid (Spain))*

Background: In the last years, blood-based biomarkers have shown high accuracy for the identification of early alterations of Alzheimer's disease (AD). Among them, plasma amyloid-beta (Aβ)42/Aβ40 and phosphorylated tau 181 (p-tau181) have been proved to be reliable biomarkers of brain amyloid deposition. However, the quantification of these molecules in plasma, mainly Aβ42, presents analytical difficulties and, therefore, high reliability analytical assays are needed in order to avoid biased conclusions about the comparative performance of both biomarkers. In this study, we aim to avoid these uncertainties by the introduction of a high sensitivity assay based on HPLC-MS for the quantification of Aβ peptides in plasma. **Objectives:** To compare the ability of plasma Aβ42/Aβ40 ratio measured with a mass spectrometry-based assay and plasma p-tau181 measured with a high-sensitivity technology to detect early brain amyloid deposition in individuals at risk of AD. **Methods:** 152 subjects with subjective cognitive decline from the Fundació ACE Healthy Brain Initiative (FACEHBI) cohort(1) were included in the present study. Participants underwent comprehensive neurological evaluation and cognitive testing, APOE genotyping and 18F-florbetaben (FBB)-PET brain imaging. 16% of the participants were classified as Aβ-PET positive according to the cutoff for early amyloid deposition established at >13.5 centiloids (CL)(2). Plasma Aβ40

and Aβ42 were quantified with a high-sensitivity antibody-free mass spectrometry-based assay (ABtest-MS, Araclon Biotech) (3). Plasma p-tau181 was measured with Simoa® pTau-181 V2 Advantage Kit (Quanterix). The ability of plasma biomarkers alone, combined or after the addition of demographic covariates, to detect Aβ-PET positivity was assessed by logistic regression and ROC curve analysis. The fitting of the regression models was assessed using the Akaike's Information Criterion (AIC) value. Area under the ROC curves (AUCs) were compared using DeLong test. **Results:** The regression model of plasma Aβ42/Aβ40 presented lower AIC (101.3) than the model composed of plasma p-tau181 (AIC=115.7), and discriminated Aβ-PET status with an AUC=0.86 (95% CI 0.78-0.94), compared to an AUC=0.83 (95% CI 0.76-0.90) for plasma p-tau181. At the maximum Youden index, both plasma biomarkers showed a sensitivity of 81.5%, but Aβ42/Aβ40 presented slightly superior specificity (84.0%) and overall accuracy (83.6%) than p-tau181 (80.8% and 80.9%, respectively). The combination of both plasma biomarkers yielded an AIC=94.7 and AUC=0.88 (95% CI 0.82-0.95). The inclusion of demographic covariates (age and APOE ε4 number of alleles) in the model increased the AUC up to 0.90 (95% CI 0.85-0.96), whereas the AIC was not further improved (AIC=94.4). Both Aβ42/Aβ40 and p-tau181 contributed significantly to this model (P<0.0001 and P=0.04, respectively). Moreover, the full model significantly outperformed plasma p-tau181 alone (ΔAUC=0.07, P=0.04), but did not differ from plasma Aβ42/Aβ40 (ΔAUC=0.04, P=0.09). **Conclusion:** The use of a high reliability method for the quantification of plasma Aβ based on HPLC-MS (ABtest-MS) suggests that plasma Aβ42/Aβ40 ratio could be a more accurate biomarker of early brain amyloid deposition than p-tau181 in the first stages of AD. 1. Rodriguez-Gomez O et al., J Prev Alzheimers Dis. 2017;4(2):100. 2. Bullich S et al., Alzheimers Res Ther. 2021;13(1):67. 3. Jang H et al., Alzheimers Res Ther. 2021; 13:179. **Disclosures:** M. Pascual-Lucas, J.A. Allué, L. Sarasa, N. Fandos, S. Castillo and J. Terencio are full-time employees at Araclon Biotech-Grifols. J.P. Tartari, A. Sanabria, L. Tárraga and M. Marquié report no disclosures. A. Ruiz has consulted for Grifols, Prevail Therapeuthics and Landsteiner Genenmed. He reports grants/research funding from Abbvie, Janssen, Grifols and Fundación Bancaria LaCaixa. A. Ruiz has stocks in Landsteiner Genmed. M. Boada has consulted for Araclon, Avid, Grifols, Lilly, Nutricia, Roche, Eisai and Servier. She received fees from lectures and funds for research from Araclon, Biogen, Grifols, Nutricia, Roche and Servier. She reports grants/research funding from Abbvie, Araclon, Biogen Research Limited, Bioiberica, Grifols, Lilly, S.A, Merck Sharp & Dohme, Kyowa Hakko Kirin, Laboratorios Servier, Nutricia SRL, Oryzon Genomics, Piramal Imaging Limited, Roche Pharma SA, and Schwabe Farma Iberica SLU, all outside the submitted work. She has not received personal compensations from these organizations.

P109. EVALUATION OF BLOOD-BASED PLASMA BIOMARKERS AS POTENTIAL MARKERS OF AMYLOID BURDEN IN PRECLINICAL ALZHEIMER'S DISEASE.

C.N. Winston[1], O. Lanford[2], N. Levin[1], R. Raman[2], K. Yarasheski[3], T. West[3], S. Abdel-Latif[2], M. Donohue[2], A. Nakamura[4], K. Toba[5], C.L. Masters[6], J. Doecke[7], R.A. Sperling[8], P.S. Aisen[9], R.A. Rissman[10] *(1. Department of Neurosciences, University of California San Diego - La Jolla (United States), 2. Alzheimer's Therapeutic Research Institute, Keck School of Medicine, University of Southern California - San Diego (United States), 3. C2N Diagnostics - St. Louis (United States), 4. Department of Biomarker Research, National Center for Geriatrics and Gerontology - Obu (Japan), 5. National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, and Tokyo Metropolitan Institute of Gerontology - Obu (Japan), 6. The Florey Institute, The University of Melbourne - Parkville (Australia), 7. he Commonwealth Scientific and Industrial Research Organization - Herston Qld (Australia), 8. Harvard Medical School - Boston (United States), 9. Alzheimer's Therapeutic Research Institute, Keck School of Medicine, University of Southern California - Los Angeles (United States), 10. Department of Neurosciences, University of California San Diego and VA San Diego Healthcare System - La Jolla (United States))*

Background: Participant eligibility for the A4 Study was determined by amyloid PET imaging. Given its disadvantages in accessibility and cost, blood-based biomarkers may serve as a reliable and more cost-effective screening tool for patient enrollment into preclinical AD trials. **Objective:** To determine if a blood-based screening test can adequately identify amyloid burden in participants screened into a preclinical AD trial. **Methods:** In this cross-sectional study, 224 A4 Study participants received an amyloid PET scan (18Florbetapir) within 90 days of blood sample collection. Approximately 38% of all participants contained at least one APOE ε4 allele while 93% of all participants identified as non-Hispanic white. Blood samples were processed within 24 hrs (Protocol 1) or 2 hrs after phlebotomy (Protocol 2). Plasma amyloid measures were quantified by Shimazdu and C2N Diagnostics using mass spectrometry-based analytical platforms under Protocol 2. A corresponding subset of blood samples (n=100) were processed under Protocol 1 and analyzed by C2N. Plasma biomarker values from Shimadzu and C2N were transferred to ATRI statisticians for analysis. Primary outcomes included plasma amyloid measures Aβ40, Aβ42 and Aβ42/Aβ40. Shimadzu provided a Composite score, generated by averaging the normalized scores of APP669711/Aβ42 and Aβ40/Aβ42. Both labs were blinded to participant demographics and meta-data. **Results:** Plasma Aβ42/Aβ40 demonstrated the highest association for Aβ accumulation in the brain with an AUC 0.76 (95% CI = 0.69, 0.82) at C2N and 0.80 (95% CI = 0.75, 0.86) at Shimadzu. Plasma Aβ42/Aβ40 diagnostic performance for a subset of 100 samples (Protocol 2) was significantly better than that for the same participants' samples processed using Protocol 1 (AUC 0.80 vs. 0.64; p <0.001). Age, sex, and APOE ε4 carrier status did not improve the diagnostic performance of plasma Aβ42/Aβ40 to predict amyloid PET status. **Conclusions:** Plasma Aβ42/Aβ40 shows great promise as a reliable biomarker for predicting elevated amyloid in the brain. Utilizing blood testing over PET imaging can improve screening efficiency into clinical trials. Future studies are required to understand how sample pre-and post-processing, patient characterization variables, and amyloid tracer sensitivity impacts the biomarker performance of plasma Aβ42/Aβ40.

P110. MYOCARDIAL SYMPATHETIC DENERVATION BIOMARKERS FOR EARLY DETECTION OF PRODROMAL DLB. M.Y. Park[1], D.S. Shin[1] *(1. Neurology Yeungnam University Medical Center - Daegu (Korea, Republic of))*

Background: Because of the time course of detecting DLB symptoms and signs, DLB is poorly diagnosed and hardly differentiate from AD, especially in early stage of dementia without the core clinical features of DLB. We investigated patients with a clinical diagnosis of amnestic mild cognitive impairment (MCI) and early AD whether they had cardiac sympathetic denervation, detected by cardiac 123I-MIBG scintigraphy. And we also assessed presynaptic nigrostriatal dopaminergic system by 18F FP-CIT-PET imaging to distinguish between DLB and AD. **Methods:** Thirty patients (72±9.0 yrs old: M:F 17:13) with a clinical diagnosis of amnestic MCI and early AD (CDR 0.5/SOB 3) who have been had visual hallucination and/or suspicious fluctuating cognition history without parkinsonism (n=20, prodromal DLB group) and who have not been had visual hallucination and/or suspicious fluctuating cognition history (n=10, eAD group) enrolled in this study. 123I-Metaiodobenzylguanidine (MIBG) uptake was assessed using the ratio of the heart to the upper mediastinum (H/M ratio), and we also assessed presynaptic nigrostriatal dopaminergic system by 18F FP-CIT-PET imaging to distinguish between prodromal DLB and eAD. Autonomic function tests and orthostatic vital signs were recorded. **Results:** The H/M ratio were decreased in pDLB group, and the mean H/M ratio was significantly lower (early/delayed uptake:1.72±0.61/1.65±0.63) compared with eAD group (early/delayed uptake:2.36±0.50/2.15±0.29) in 123I-MIBG scintigraphy ($p<0.05$). Presynaptic nigrostriatal dopaminergic deficits were founded in 18F FP CIT PET and orthostatic hypotension was evident only in pDLB group regardless of spontaneous Parkinsonism (n=17, 85%). **Conclusion:** Myocardial postganglionic sympathetic denervation and autonomic dysfunctions especially orthostatic hypotension can be good biomarkers to predict DLB before core clinical symptoms appear, and may useful to distinguish from AD even in early stage. This study is under long term follow up. **Key words:** DLB, 123I-MIBG scintigraphy, orthostatic hypotension.

P111- PTAU181 PLASMA BIOMARKER PERFORMANCE AS AN INCLUSION CRITERION IN THE RETHINK-ALZ AND REFOCUS-ALZ TRIALS IN MILD-TO-MODERATE ALZHEIMER'S DISEASE. A. Mammel[1], P. Kumar[2], L. Burns[3], D. Biehl[1], M. Encarnacion[2], A. Cruz[2], G.Y.R. Hsiung[4], I. Mackenzie[4], V. Hirsch-Reinshagen[4], A. Mousavi[2], R. Fortna[1,5], J. Kupiec[3], H. Frykman[2] *(1. Neurocode - Bellingham, Washington (United States), 2. BC Neuroimmunology - Vancouver (Canada), 3. Cassava Sciences - Austin, Texas (United States), 4. University of British Columbia - Vancouver (Canada), 5. Northwest Pathology - Bellingham, Washington (United States))*

Background: Alzheimer's disease (AD) biomarkers have enabled more accurate, timely diagnoses and improved staging of disease, supporting clinical trials as inclusion criteria and secondary endpoints. While cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers are commonly used to demonstrate AD neuropathology, these biomarkers are invasive and have limited availability and scalability. By contrast, blood-based biomarkers are non-invasive, scalable, and are increasingly used both for diagnosis and entry into clinical trials. Advances in ultrasensitive detection techniques for blood biomarkers have facilitated the development of assays to detect and quantify AD-specific phosphorylated Tau proteins, including Tau phosphorylated at threonine 181 (pTau181) (1, 2). We have established superior analytical and clinical performance of a new research use only (RUO) plasma pTau181 single molecule array (SIMOA) assay on a well-characterized clinically diagnosed AD cohort (3, 4). We evaluated the clinical performance of this RUO pTau181 assay to qualify mild-to-moderate AD patients in the RETHINK-ALZ and REFOCUS-ALZ clinical trials. **Objective:** To evaluate the clinical performance of a new plasma pTau181 assay to confirm AD pathology as an entry criterion for two large Phase 3 clinical trials. **Methods:** The University of British Columbia (UBC) biobank plasma samples from clinically diagnosed AD patients were used to establish clinical and analytical validity of the pTau181 plasma assay per CLSI guidelines (3, 4). We assessed the analytical measurement interval, clinical reportable range, linearity, intra-laboratory precision, specimen stability, interference, and clinical performance. RETHINK-ALZ and REFOCUS-ALZ subject plasma samples, along with clinical diagnosis, MMSE and PET data were also used to evaluate performance of the assay and the pTau181 biomarker. RETHINK-ALZ will randomize 750 subjects (1:1) to placebo or simufilam 100 mg and REFOCUS-ALZ will randomize 1083 subjects (1:1:1) to placebo or simufilam 50 or 100 mg. Subjects are MMSE ≥ 16 and ≤ 27, age 50-87 in both studies. **Results:** The clinical cut-point for this plasma pTau181 assay for clinical trial inclusion was set as ≥ 30 ng/L using the ROC curve (AUC - 0.92) and the Youden Index (34.3 ng/mL), which maximizes sensitivity and specificity, generated from a clinical validation study of clinically diagnosed AD and cognitively unimpaired control specimens (3, 4). The cut-point (≥ 30 ng/L) had 100% sensitivity and 88% specificity for AD diagnosis in 22 autopsy-confirmed samples (3). The clinical reportable range for the assay is 6.17 to 300 ng/L, with a limit of quantification ≤ 22.2 ng/L. The analytical performance of the assay meets method validation guidelines of ≤ 20% intra-laboratory variation, no detectable interference, linearity to 300 ng/L, and sample stability up to three freeze-thaw cycles. We determined the percentage of subjects screened for RETHINK-ALZ and REFOCUS-ALZ that met the ≥ 30 ng/L pTau181 plasma concentration. Current data show 83.2% (n = 321) and 89.8% (n = 333) of subjects screened for RETHINK-ALZ and REFOCUS-ALZ, respectively, meeting this criterion. Clinical sites screen subjects with an established clinical diagnosis of AD or who are suspected to have AD. 86% of the sites participating in the REFOCUS-ALZ study and 78% of sites participating in the RETHINK-ALZ had at least 70% of screened subjects meet this criterion. We also compared plasma pTau181 concentrations in RETHINK-ALZ and REFOCUS-ALZ subjects with MMSE and PET findings. The concentration of pTau181 does not correlate with MMSE score, possibly because the dynamic range of the pTau181 assay and its variability within this mild-to-moderate population is much greater than the relatively narrow range of their MMSE scores. Alternatively, the level of cognitive impairment may not correlate well with this biomarker. However, pTau181 concentrations were elevated (> 50 ng/L) in all subjects with prior Tau or amyloid-beta PET confirmation of pathology (8 of 8) enrolled in these studies, suggesting an excellent correlation of plasma pTau181 with AD neuropathology. **Conclusion:** This pTau181 plasma assay provides a robust and accurate biomarker approach for independent determination of AD, with an AUC of 0.92 in a validation study. This pTau181 assay appears to be performing well as a screening method for inclusion of mild-to-moderate AD subjects in two large Phase 3 clinical trials. This robust plasma biomarker measured by our

RUO assay has great potential both as a diagnostic tool and to streamline clinical trials in AD. **References:** 1. Karikari TK, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol. 2020 May;19(5):422-433. 2. Bayoumy S, et al. Clinical and analytical comparison of six Simoa assays for plasma P-tau isoforms P-tau181, P-tau217, and P-tau231. Alzheimers Res Ther. 2021 Dec 4;13(1):198. 3. H. Frykman et al. Plasma ptau-181 concentrations accurately predict pathologically confirmed Alzheimer's Disease cases, poster presented at Tau 2022 global conference. 4. H. Frykman et al. Analytical and clinical performance of plasma p-tau181 assay on the high-sensitivity Simoa HD-X platform, poster accepted in AAIC 2022.

P112- CRITICAL EVALUATION AND COMPARISON OF BIOMARKER VALUES IN COMMERCIAL CSF WITH LUMIPULSE® TO SUPPORT ASSAY DEVELOPMENT FOR CLINICAL TRIALS. H. Vanderstichele[1], M. Rafizadeh[2], E. Cline[2], J. Derrick[3], E. Simmons[3], R. Dean[2], J. Jerecic[2] *(1. Biomarkable - Gent (Belgium), 2. Acumen Pharmaceuticals - Charlottesville (United States), 3. B2S Life sciences - Indianapolis (United States))*

Background: Cerebrospinal fluid (CSF) has many applications in the study of central nervous system drug delivery and biomarker analysis. The qualification of this difficult to obtain and costly biofluid is highly dependent on the techniques and methods used to analyze, handle, and store the material. When obtained from commercial suppliers, only limited information typically is available on sample quality and collection procedures. The lack of such information can impede development timelines for assay development, validation, and ongoing quality control. Proper interpretation of CSF composition is highly dependent on test procedures used for protein analysis and directly impacts biomarker assay development. **Objectives:** Here we describe selection criteria for CSF research samples purchased from PrecisionMed LLC. followed by comparative quantitation of CSF biomarker profiles with the recently FDA-cleared Lumipulse®G 1200 (β-Amyloid 1-40, ß-Amyloid 1-42, total tau, pTau181) immunoassays (Fujirebio Diagnostics, Malvern, PA, US) and the qualification of the specimen collection and storage tubes that are now being used in an ongoing clinical trial, INTERCEPT-AD. **Methods:** The CSF research sample inventory at PrecisionMed LLC. provides a comprehensive list of clinical criteria for diagnosis, such as donor ID, age baseline, age at visit, gender, ethnicity, baseline diagnosis, visit number, Mini Mental State Examination (MMSE), sample volume, Clinical Dementia Rating (CDR), Hachinski score and a Case Report Form (CRF). Biomarker data available from PrecisionMed LLC. (e.g., AßN-42, AßN-40, AßN-38, total tau) are generated on the Mesoscale Discovery platform (MSD), using the Aß Peptide Panel Kit K15200G and Human Total Tau Kit K15AGPS. No CSF phospho Tau or plasma biomarker data were available at the time. We have applied the following selection criteria to identify samples from subjects with dementia due to Alzheimer's disease (AD), subjects without dementia, or healthy controls. For all subjects the age group was more than 65 years and preferably first visit. For subjects with dementia due to AD, low MMSE scores, the ratio Aß42/Aß40 less than 0.06, total tau more than 600 pg/mL but not extremely high, and no extremely low values for Aß40 and Aß42, normally not detected in samples from AD or healthy control. Five control CSF samples and eight AD CSF samples were selected for further analysis. To evaluate antigen retrieval and potential loss via passive absorption when using selected tube types, we aliquoted each CSF sample in two different reagent tubes: Fujirebio (low protein binding, part of the kits), Sarstaedt tubes (Low protein-binding, Sarstedt Inc, cat 72.694.600), One series of Sarstaedt tubes was left at room temperature for 30 minutes prior to freezing to verify potential adsorption problems. Another series was pre-washed before further processing. All samples were frozen and subsequently processed for biomarker concentration batch-mode analysis in the facilities of Fujirebio Diagnostics, USA. **Results:** CSF analytes were measured in all selected samples (n=13) using the low-protein binding tubes from Sarstaedt. Results were compared to values obtained in low protein binding tubes from Fujirebio. First, our selection criteria applied to the Precisionmed CSF biomarker list allowed us to differentiate CSF samples with or without an AD biomarker profile and subsequently compare CSF biomarker levels quantified with the Lumipulse® immunoassays for total tau, pTau181, Aß1-42, and Aß1-40. The best separation of AD and non-AD samples was obtained using the MSD ratio of Aß42/Aß40 as described in the research databank. Secondly, samples were tested after aliquotation, after one extra serial transfer, and after pre-wetting tubes before addition of CSF. These experiments were done to simulate sample handling in the lab. Results revealed no adsorption problems for the Sarstaedt tubes for individual analytes or for a ratio of analytes. **Conclusions:** The applied selection criteria for identification of biomarker levels in CSF samples provided by PrecisionMed LLC. via the MSD multiplex assay identified AD and healthy control samples suitable for further analysis. Comparison of the MSD assay platform with the FDA-cleared Lumipulse® immunoassays showed a good correlation in values for all samples for AßN-42, AßN-40, and total tau. In addition, the evaluation of selected Sarsteadt tubes for levels of absorption and loss of biomarker signal further confirmed reagent suitability for use in clinical trials.

P113- DETECTION OF CSF ALPHA-SYNUCLEIN IN PATIENTS WITH PRODROMAL LEWY BODY DISEASE. M. Plastini[1], C. Abdelnour[1], M. Shahid[1], M. Medina[2], N. Kha[2], H. Hovren[2], J. Lamoureux[2], V. Henderson[1], K. Poston[1] *(1. Stanford University - Palo Alto (United States), 2. Amprion Clinical Laboratory - San Diego (United States))*

Background: Lewy body disease (LBD) is characterized by the deposit of intracytoplasmic inclusions of misfolded alpha-synuclein (αSyn) and ubiquitine named Lewy bodies and Lewy neurites. LBD is clinically classified as Parkinson's disease (PD) and dementia with Lewy bodies (DLB), and is considered the second most common cause of neurodegenerative dementia. Before the dementia stage, patients can present several prodromal presentations: mild cognitive impairment (MCI), isolated REM sleep behavior disorder (iRBD), delirium onset, among others. In addition, misfolded αSyn can co-occur with other pathologies in mixed etiology dementias, such as patients with clinical Alzheimer's dementia (AD). Identifying underlying pathologies at the prodromal stage or in mixed etiology dementias is of particular interest when developing proteinopathy-specific therapies. Although some biomarkers like FP-CIT SPECT or PET imaging and 123iodine-MIGB myocardial scintigraphy have shown good sensitivity for LBD diagnosis, they can lack specificity and are not proteinopathy specific. A novel approach utilizing Seed Amplification Assay (SAA) technology could overcome this challenge. This new technique has been clinically validated to detect aggregates of misfolded αSyn in cerebrospinal fluid (CSF) of patients

with PD and DLB demonstrating high sensitivity and specificity. However, little is known about the performance of SAA testing in patients with MCI. **Objectives:** Our objective was to determine whether the SAA test detects aggregates of misfolded αSyn in the CSF from patients with MCI, AD, and LBD. Our hypothesis is that the αSyn-SAA will correctly identify patients with MCI due to LBD and distinguish these from patients with MCI due to AD neuropathologic change. **Methods:** We studied 154 cross-sectional CSF samples from the Stanford ADRC and Pacific Udall Center. Clinical evaluation included history, physical examination, neuropsychological assessments, and general neurological examination, including detailed motor testing. Final motor and cognitive diagnosis were determined during a consensus meeting after each annual visit. CSF was collected via lumbar puncture using a 20-22 G spinal needle that was inserted in the L4-L5 or L5-S1 interspace and CSF was collected in polypropylene tubes. The tubes were immediately frozen at -80°C in a centralized freezer. Samples blinded to all clinical and demographic data were tested in Amprion's CLIA Laboratory for the presence of misfolded αSyn aggregates using a SAA test (SYNTap® Biomarker Test). The SAA platform is based on amplification of minute levels of misfolded aggregates of αSyn present in CSF to levels that can be detected by Thioflavin T fluorescence. Chi squared test was conducted for analysis between categorical variables. The Wilson-Brown method was used to calculate the sensitivity and specificity of the αSyn-SAA test for the detection of αSyn aggregates in the CSF. **Results:** The final diagnostic groups included 69 LBD spectrum [34 PD-normal cognition, 21 PD-MCI, 14 PD-Dementia/DLB), 22 AD, 29 MCI and 34 sex and age-matched healthy controls. First, we compared healthy controls and PD normal cognition to determine the concordance between LBD diagnosis and αSyn-SAA testing in a cognitively normal population. CSF αSyn was detected in 88.24% of PD patients compared to 11.76% of controls ($p < 0.0001$). We next studied participants with MCI, with and without an LBD diagnosis. Similarly, CSF αSyn was detected in 85.71% of PD-MCI patients compared to 17.24% of MCI patients ($p < 0.0001$). Finally, we compared participants with dementia, with and without an LBD diagnosis. CSF αSyn was detected in 85.71% of PDD/DLB compared to 13.64% of AD cases ($p < 0.0001$). Interestingly, of the 82.76% of MCI cases that had no αSyn detected, 42.31% have at least one APOE4 allele. Future studies will determine whether combining genetic and protein misfolding assay data can best predict clinical subgroups in MCI cases and give insight into possible future co-pathologies. **Conclusion:** Early detection of αSyn aggregates by SAA testing can help identify LBD patients prior to dementia onset and identify clinical AD patients with likely underlying mixed etiology dementia. Together, these data suggest αSyn-SAA testing can widen the therapeutic window to provide earlier interventions and personalized therapeutic options. Future studies determining whether αSyn-SAA can be used to track disease progression and determining its relationship with other CSF protein biomarkers, like amyloid and tau, is warranted. **COI Disclosure:** Manuel J Medina, Nelson Kha, Hanna L. Hovren, Jennifer Lamoureux are employees of Amprion and Dr. Kathleen Poston is an advisor to Amprion.

P114- EFFECT OF BUTYRYLCHOLINESTERASE GENOTYPE ON PATIENTS WITH ALZHEIMER'S DISEASE TREATED WITH RIVASTIGMINE. H. Kim[1,2], S.Y. Cho[3], G. Nam[2], K. Kim[2,4], E. Kim[3], J.Y. Lee[2] *(1. Emocog Inc. - Seoul (Korea, Republic of), 2. Department of Psychiatry, Seoul Metropolitan Government-Seoul National University Boramae Medical Center - Seoul (Korea, Republic of), 3. Department of Psychiatry, Institute of Behavioral Science in Medicine, Brain Korea 21 Plus Project for Medical Science, Yonsei University College of Medicine - Seoul (Korea, Republic of), 4. Epi Biotech Co., Ltd. - Incheon (Korea, Republic of))*

Background: Acetylcholine (Ach), a cholinergic neurotransmitter, regulates many brain processes such as memory, learning, and behavior. Acetylcholinesterase and Butyrylcholinesterase (BChE) hydrolyze Ach for normal cholinergic function. BChE gene (BCHE) is known to influence the onset and progression of Alzheimer's disease (AD). Studies have been published on the effects of the BCHE K variant (BCHE-K), the most common BCHE polymorphism, on AD, but the results are conflicting. **Objectives:** In this study, we investigated how the genotype of BCHE affects the changes in cognitive function, gray matter volume, and cortical thickness in AD patients treated with rivastigmine. **Methods:** Blood samples were genotyped for the BCHE-K. The Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) scores and brain magnetic resonance images (MRI) of AD patients were collected before and after the rivastigmine treatment. The degree of change over time was analyzed according to BCHE genotype. **Results/Conclusion:** BCHE genotype significantly affected the changes in cognitive function and brain anatomy of AD patients treated with rivastigmine for 1 year. The protective effect of wild-type BCHE (BCHE-WT) on the cognitive function of AD patients was identified by measuring total score of ADAS-cog 12-item. Among 12 items, word finding, constructive praxis, and orientation were significantly correlated with BCHE genotype. However, in patients with BCHE-WT, the brain atrophy rate, particularly in frontal lobe, was higher than the patients with BCHE-K. These results suggest that BCHE-WT does not affect the spontaneous progression of brain atrophy in AD, but is sufficient to maintain the cognitive function in response to the rivastigmine treatment.

P115- IMPACT OF ALZHEIMER'S DISEASE BIOMARKER DISCLOSURE TO COGNITIVELY UNIMPAIRED INDIVIDUALS: EXPERIENCES FROM A TRUNCATED RANDOMIZED PHASE 2B/3 CLINICAL TRIAL. J. Grill[1], R. Raman[2], G. Miller[2], K. Ernstrom[2], M. Donohue[2], P. Aisen[2], R. Sperling[3], D. Henley[4], H.R. Brashear[4], G. Romano[4], G. Novak[4] *(1. University of California Irvine - Irvine (United States), 2. Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA - San Diego (United States), 3. Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA - Boston (United States), 4. Janssen Research & Development LLC - Titusville (United States))*

Background: Numerous ongoing and planned clinical trials are testing putative disease modifying therapies for Alzheimer's disease (AD) at preclinical stages, prior to the onset of demonstrable symptoms. These studies simultaneously test candidate treatments and the implications of disclosing biomarker information to cognitively unimpaired individuals. **Objectives:** To report psychological safety and impact of biomarker disclosure on participants with preclinical AD in the EARLY trial (ClinicalTrials.gov Identifier: NCT02569398). **Methods:** We used data from a randomized, double-blind,

placebo-controlled, phase 2b/3 study conducted from November 2015 to December 2018. Participants aged 60-85 years and deemed cognitively unimpaired (Clinical Dementia Rating Scale score of 0) were disclosed a binary AD biomarker result as having elevated or not elevated brain amyloid levels, based on amyloid PET imaging or cerebrospinal fluid (CSF) amyloid protein analyses. The study was conducted at 143 centers across 14 countries. We compared elevated and not elevated amyloid groups prior to testing and disclosure on the 15-item Geriatric Depression Scale (GDS), the six "state" items of the State-Trait Anxiety Scale (STAI), and the Columbia Suicide Severity Rating Scale (CSSRS). Additional scales assessed specific disclosure outcomes, including the Concerns for AD (higher scores associated with greater concern), Future Time Perspective (FTP, higher scores associated with greater perceived future time), and Views and Perceptions of Amyloid Imaging (higher scores associated with greater endorsement of reasons for undergoing amyloid PET). After disclosure, we assessed for differences in the Impact of Events Scale (IES) measure of intrusive thoughts and distress related to a specific event, as well as the disclosure-related measures. Comparisons between groups (elevated vs. not elevated amyloid) were performed using t-tests for continuous variables and Pearson's Chi-Squared test for categorical variables. We used ANCOVA models to assess associations with change in scores for outcomes available pre- and post-disclosure (as the dependent variable), including amyloid group as the main independent variable and adjusting for covariates including age, sex, family history of AD, and Cognitive Function Instrument (used as a continuous measure). **Results:** Among 3686 screened participants, 2066 underwent amyloid PET imaging,1394 underwent CSF biomarker assessments, and 226 underwent both. Among biomarker tested participants with at least one change score on an outcome of interest (Views and Perceptions, Concerns about AD, or Future Time Perspective), 680 had an elevated brain amyloid result and 2698 had a not elevated result and were included in this analysis. We observed no differences in measures of depression (mean [SD] GDS: elevated 3.2 [3.3] vs. not elevated 3.1 [3.5]; p=0.72), anxiety (mean [SD] STAI: elevated 8.9 [2.9] vs. not elevated 8.7 [2.9]; p=0.31), or suicidality (mean [SD] CSSRS: elevated 0.25 [1.1] vs. not elevated 0.27 [1.2]; p=0.63) between the groups prior to biomarker testing. We observed slightly higher scores prior to biomarker testing among participants with elevated amyloid compared to participants with not elevated amyloid for the Concerns about AD (mean [SD]: elevated 21.1 [4.8] vs. not elevated 20.0 [4.8]; p<0.0001), Views and Perceptions of Amyloid Imaging (mean [SD]: elevated 32.4 [6.7] vs. not elevated 31.5 [6.7]; p=0.046), and Future Time Perspective (mean [SD]: elevated 44.9 [11.6] vs. not elevated 44.7 [11.1]; p=0.04). These patterns were consistent, regardless of whether participants underwent amyloid PET or CSF biomarker testing. Compared to participants learning a not elevated amyloid result (5.1 [8.4]), those disclosed an elevated amyloid result demonstrated higher scores on the IES (9.6 [10.8]) after disclosure. In an ANCOVA model that adjusted for covariates, amyloid group (elevated vs. not elevated) remained statistically significant. Younger age and female sex were also significantly associated with higher IES scores. Participants disclosed an elevated amyloid result demonstrated increased Concerns about AD scale scores overall, while those with not elevated amyloid showed decreased scores (mean change [SD], 0.61 [4.48] for elevated vs. -1.63 [4.71] for not elevated). The elevated and not elevated amyloid groups demonstrated slight increases in FTP; no difference between the amyloid groups was observed in the degree of change (mean change [SD], 1.1 [8.53] for elevated vs. 1.47 [8.14] for not elevated). Views and Perceptions of Amyloid Imaging scores increased in both the elevated (mean change [SD], 1.15 [9.75]) and not elevated amyloid groups (1.58 [9.82]), such that the difference between groups was no longer apparent after disclosure. **Conclusion:** AD biomarker disclosure caused greater intrusive thoughts and avoidance for participants learning an elevated compared to a not elevated result and resulted in adjustment of perceived risk for AD for all screened participants in this study.

P116- PHARMACODYNAMIC EFFECTS OF SEMORINEMAB ON PLASMA AND CSF TAU BIOMARKERS IN A PHASE 2 TRIAL IN MILD-TO-MODERATE ALZHEIMER'S DISEASE (LAURIET)

S. Schauer[1], J. Lee[1], V. Anania[1], B. Toth[1], L. Honigberg[1], K. Wildsmith[1], V. Ramakrishnan[1], M. Dolton[1], S. Sanabria Bohorquez[1], E. Teng[1], C. Monteiro[1] *(1. Genentech, Inc. - South San Francisco (United States))*

Background: Semorinemab is a humanized anti-tau IgG4 monoclonal antibody that targets the N-terminal domain of tau and is under investigation as a treatment for Alzheimer's disease (AD). Mild-to-moderate AD patients treated with semorinemab demonstrated a significant reduction in decline in cognition (ADAS-Cog11) relative to those treated with placebo (Lauriet study, NCT03828747). However, no treatment effects were observed on the co-primary functional endpoint (ADCS-ADL), the secondary endpoints (CDR-SB, MMSE), or on exploratory Tau PET endpoints. Longitudinal plasma and CSF samples were available from a subset of participants for fluid biomarker assessments. **Objectives:** To determine the effects of chronic treatment with semorinemab on plasma total Tau, plasma phospho-Tau217, CSF total Tau, CSF phospho-Tau181, phospho-Tau217, and CSF N-terminal Tau in participants with mild-to-moderate AD. **Methods:** Lauriet was a multicenter, double blind, placebo controlled study that enrolled 272 participants aged 50-85 years who fulfilled National Institute on Aging-Alzheimer's Association criteria for probable AD dementia and had MMSE scores of 16-21 (inclusive) and global CDR scores of 1 or 2. Participants were initially randomized to receive monthly IV doses of either placebo or semorinemab (4500 mg) over 48 weeks, but the blinded dosing period was extended to 60 weeks for a subset of participants who experienced study disruptions attributable to the COVID-19 pandemic. CSF collection was optional; samples were obtained from 48% of participants at baseline and 20% of participants at Weeks 49 or 61. Total Tau, phospho-Tau181, and phospho-Tau217 were measured using qualified ELISAs. N-terminal Tau was measured using a targeted mass spectrometry method. **Results:** In participants treated with semorinemab, plasma total tau and plasma phospho-Tau217 levels increased substantially (>20-fold) compared to baseline, consistent with strong peripheral target engagement. Plasma total Tau plateaued by approximately Week 5, and plasma phospho-Tau217 peaked by Week 24. Levels for both Tau species remained elevated over the course of treatment. CSF samples were available from a subset of participants at baseline and either Week 49 or 61 (n=52) post treatment. These samples were analyzed for semorinemab exposure and four Tau indices: total Tau, pTau181, pTau217, and N-terminal Tau (amino acids 2-24; includes target epitope for semorinemab). Semorinemab pharmacokinetics in CSF and plasma were consistent with previously reported data from healthy volunteers and participants with prodromal-to-mild AD, including a mean CSF/serum ratio of 0.29% (SD 0.13). A reduction in CSF

total Tau was observed with semorinemab but not placebo (change from baseline: placebo 1%, semorinemab -12%; p=0.01). Similarly, reductions in CSF pTau181 and pTau217 were observed with semorinemab but not in placebo at both Weeks 49 and 61 (pTau181 change from baseline: placebo -1%, semorinemab -14% p=0.01; pTau217 change from baseline: placebo +19%, semorinemab -27% p=0.01). No significant changes from baseline were observed for N-terminal Tau in either treatment group (change from baseline: placebo +3%, semorinemab +2%). **Conclusion:** In participants with mild-to-moderate AD, treatment with semorinemab resulted in increases in plasma tau levels and reductions in the levels of CSF tau species associated with AD pathology. These data provide further evidence that semorinemab engages and modulates Tau both peripherally and in the central nervous system in a manner consistent with what was previously reported from participants with prodromal-to-mild AD patients (Tauriel study, NCT03289143). The mechanistic interpretation of the observed reductions in CSF tau indices in both the Lauriet and Tauriel studies remains uncertain given that relative reductions in cognitive decline were seen with semorinemab treatment in mild-to-moderate AD (Lauriet) but not prodromal-to-mild AD (Tauriel). SS: Employee of Genentech, Inc., shareholder F. Hoffmann-La Roche, Ltd.

P117- NOVEL TECHNOLOGY PLATFORM FOR THE DIRECT AND SENSITIVE DETECTION OF CIRCULATING AD-RELATED MOLECULES IN BLOOD. C. Lim[1] *(1. Sunbird Bio - Singapore (Singapore))*

Background: Current molecular diagnostic tools of Alzheimer's disease (AD), such as Positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) tests, are challenging to access and implement widely, impeding early detection as well as development of potential therapeutics. With the development of disease-modifying therapeutics for an exponentially growing global AD population, major efforts have been made to develop blood tests for AD as they are safe, affordable and easy to administer. However, current blood-based detection technologies under investigation are confounded by low sensitivity for the detection of brain-related molecules and poor accuracy to disease pathology. Extracellular vesicles (EVs) have recently emerged as a promising circulating biomarker for neurodegenerative diseases. Actively released by diverse cells, EVs are nanoscale membrane vesicles. They abound in blood, readily cross the blood-brain barrier, and carry diverse molecular cargoes in different organizational states. While the inherited constituents could serve as cell surrogate biomarkers, we have recently discovered that extravesicular association could reflect structural states of the bound molecules, revealing distinct subpopulations with different biophysical and/or biochemical properties. **Objectives:** To develop a scalable and versatile molecular detection platform for the investigation of diverse circulating EV-associated biomarkers to facilitate AD detection for disease diagnosis and monitoring. **Methods:** Leveraging on our discovery that prefibrillar Aβ preferentially associates with EVs, we developed a dedicated detection platform that is size-matched for the enhanced detection of exosomes directly from blood. Termed amplified plasmonic exosome (APEX) platform, it is designed to overcome numerous challenges of blood-based measurement of EV-associated biomarkers. Unlike conventional sensing technologies with limited compatibility to reveal nanoscale EV features, the highly sensitive APEX platform technology uses Transmission Surface Plasmon Resonance to enable the detection of EVs directly from biofluids, such as blood, without any pre-enrichment. The direct detection of intact EVs preserves the extra-vesicular association of EVs with molecules, thus enabling the in-depth study of different EV-associated molecules that were previously challenging to detect due to limitations in conventional technologies. Using the APEX technology, we conducted blood-based measurements of the total, unbound and EV-associated Aβ populations in a clinical cohort with subjects across the AD spectrum, as well as clinical controls with vascular dementia. Through recent developments, we have advanced the APEX platform by implementing design improvements on the platform for scalability. Not only is the newly developed platform capable of multiplexing with increased throughput, it is also highly adaptable for the detection of diverse EV-associated biomarkers in circulation. **Result:** We have found that the extravesicular association of Aβ proteins could reflect the aggregation states of the bound proteins, thereby enabling biophysical and biochemical subtyping of the associated biomarkers, to achieve more accurate blood-based characterization of neurodegenerative diseases. Blood-based APEX measurements of EV-associated Aβ showed a very good correlation to PET imaging measurements of amyloid deposition in the brain, unlike measurements of circulating total and unbound Aβ populations. With the recent improvements in the design and fabrication process of the sensor chips, the sensors are fabricated with standard manufacturing processes. Through partnerships with commercial foundries, the current sensor chips can robustly fabricated and scaled up to demand. The improved APEX platform is highly versatile for the detection of different disease-related and cell-origin related markers, making it highly compatible for exploring novel biomarkers as well as investigating different types of EV subpopulations in circulation. To demonstrate its capabilities, we have developed a panel of assays for the detection of a variety of EV-associated biomarkers. **Conclusion:** We have developed a scalable and versatile platform technology, specifically designed for the investigation of EV-associated biomarkers directly from biofluids. We have demonstrated its capability in the development of an accurate blood test for AD. Specifically, we conducted direct blood-based measurement of EV-associated Aβ in an AD clinical cohort, and showed that the APEX measurements reflect amyloid deposition in brain measured by PET imaging. With the ability to detect EVs directly from a small volume of blood, the platform has the potential to reveal new insights through the evaluation of novel subpopulations previously masked by bulk measurements. Moreover, it can be easily adapted for the detection of diverse markers of interest to investigate other features of the AD pathology, facilitating the further development of accurate and comprehensive tests that are reflective of disease pathology in AD.

P118- RECRUITMENT OF AMYLOID POSITIVE INDIVIDUALS AND EARLY ALZHEIMER'S PATIENTS IN A PRIMARY CARE SETTING – RESULTS FROM THE BIOFINDER PRIMARY CARE STUDY. S. Palmqvist[1], P. Tideman[1], E. Stomrud[1], R. Smith[1], A. Leuzy[1], S.J. Jasem[1], N. Mattsson-Carlgren[1], A. Orduña Dolado[1], S. Janelidze[1], O. Hansson[1] *(1. Lund University - Malmö (Sweden))*

Background: Primary care units serve as the first point of contact for patients with cognitive impairment. From there, only a minority are referred to memory clinics and other specialist settings where tools with high diagnostic accuracy for Alzheimer's disease (AD) are available. To improve the

diagnostic accuracy of AD, facilitate correct referrals to memory clinics, and enable a broader enrolment of participants to clinical AD trials, it is of great importance to implement new tools in the diagnostic work-up of cognitive impairment in primary care. **Objectives:** To examine the diagnostic accuracy of plasma phosphorylated-tau217 (P-tau217) implemented in primary care as a test of β-amyloid (Aβ) positivity and AD, alone and in combination with other accessible measures. **Methods:** Data used in the analyses were collected from the BioFINDER Primary Care study which consecutively enrolls patients seeking care due to cognitive symptoms at 20 primary care units in Sweden. P-tau217 was measured using a Meso Scale Discovery (MSD) assay in monthly batches from plasma collected at the primary care units. Patients with subjective cognitive decline (SCD), mild cognitive impairment (MCI) or mild dementia were included. Aβ status was determined using CSF Aβ42/Aβ40 or Aβ PET. All patients underwent a full investigation at the BioFINDER Memory Clinic, including lumbar puncture or Aβ PET, neuropsychological testing and assessment by senior specialists in dementia disorders (blinded to plasma and cognitive test results from primary care). **Results:** 193 patients had complete Aβ and plasma P-tau217 data. The mean (range) age was 75.8 (60-90). 27% had SCD, 17% were diagnosed with MCI due to AD, 18% with dementia due to AD, 33% with MCI due to other causes, and 5% with dementia due to other causes. 56% were Aβ positive. Plasma P-tau217 discriminated Aβ positives versus negatives with an AUC of 0.88 (95% CI 0.83-0.93). Adding APOE genotype increased the AUC to 0.90 (0.86-0.94). For AD versus non-AD, plasma P-tau217 had an AUC of 0.86 (95% CI 0.80-0.91). Combined with APOE, the AUC increased to 0.88 (0.83-0.93). A predefined diagnostic AD algorithm consisting of plasma P-tau217, APOE genotype, and 10-word delayed recall (Palmqvist et al., Nature Medicine, 2021) was examined. When applied to a subset of the BioFINDER Primary Care dataset (n=132), it had an AUC of 0.92 (95% CI 0.87-0.97). Based on the individual probability for AD, it correctly identified 93% of non-AD patients as having a low risk of AD and 84% of AD patients as having a high risk. Only 6% were classified as borderline cases (of which 40% had AD). **Conclusion:** In this pilot analysis, we show that P-tau217 analyzed in monthly batches using plasma collected and handled in primary care has a high accuracy for Aβ status and AD in an unselected primary population. Plasma P-tau217 combined in an algorithm with cognitive testing and APOE show potential as a diagnostic decision support tool for primary care physicians. Updated results with patients recruited during the summer and fall of 2022 will be presented at the conference, including the effect of adjusting plasma analyses for body mass index, kidney function and co-morbidities.

P119. DEEP PLASMA AND CSF PROTEOMICS PROFILING OF THE AMBAR STUDY. C. Feng[1], R. Gonzalo[2], C. Minguet[2], P. Lafuente[2], A.M. Ortiz[2], S. Lohr[1], M. Boada[3], O. López[4], A. Paez[2], S. Braithwaite[1], M. Costa[2], B. Lehallier[1] *(1. Alkahest, a Grifols company - San Carlos (United States), 2. Grifols - Barcelona (Spain), 3. Universitat Internacional de Catalunya - Barcelona (Spain), 4. University of Pittsburgh - Pittsburgh (United States))*

Background: AMBAR (Alzheimer's Management By Albumin Replacement) is a multicenter, randomized, double-blinded, placebo-controlled, phase 2b/3 clinical trial to evaluate the efficacy of plasma exchange (PE) with albumin replacement (PE-Alb) in participants with mild-to-moderate Alzheimer's disease (AD). Previous analyses detected significant improvement in cognitive functions in PE-treated participants compared to participants in the placebo group (Boada et al. 2020; Boada, Martinez-Lage, et al. 2021; Boada, Lopez, et al. 2021). Since PE-Alb strongly modulates proteins abundance and function, monitoring proteomics changes in plasma and CSF offer a unique opportunity to better understand molecular mechanisms of therapeutic treatment and to identify potential biomarkers for new drug target and patient selection. Here we report the results of the plasma and CSF proteomics profiling of more than 7000 unique proteins in subjects enrolled in the AMBAR trial. **Objective:** To identify proteomics responses and to understand molecular mechanisms of PE-Alb treatment. **Methods:** The AMBAR treatment consists in an intensive period comprising 6 weeks of conventional therapeutic PE (TPE: processing 1 plasma volume [≈2500- 3000 mL]) with albumin 5% replacement (1 TPE/week) followed by a maintenance period of 12 months of low volume PE (LVPE: removing approximately 1/3 plasma volume [≈690- 880 mL]) with albumin 20% replacement (1 LVPE/month) for all active arms. A total of 671 plasma samples (from 148 subjects in 5 visits) and 422 CSF samples (from 144 subjects in 3 visits) were analyzed using the aptamer-based proteomic technology SomaScan (SomaLogic, Boulder, Colorado, US). The 5 visits for plasma proteomics included baseline, immediately after the first TPE, intermediate (1-2 weeks after the intensive period), immediately after the first LVPE and end of study (EOS) (1-2 weeks after the maintenance period). The 3 visits for CSF samples covered the baseline, intermediate and EOS. Adjusted linear mixed models were used to identify proteins significantly changed after PE treatment at different times, and pathway enrichment analysis was performed using Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome databases. **Results:** Our analyses detected profound acute proteomic changes in the plasma proteome after PE treatment in mild-to-moderate AD. Immediately after the first TPE, 88% of plasma proteins were significantly changed and majority of them were downregulated (98%, based on BH corrected pvalue, $q<0.05$). On the other hand, dozens of proteins were up-regulated, part of them might be due to albumin injection and the rest reflecting acute response to PE. TPE treatment significantly down-regulated 461 proteins ($log2FC < -1$ and $q<0.05$) that were enriched for biological pathways increased in AD including humoral immune response, inflammatory response, and ion transport (Calabro et al. 2021; Seto et al. 2021; Ramachandran et al. 2021; Rayaprolu et al. 2021). TPE treatments also significantly up-regulated 39 proteins ($log2FC>1$ and $q<0.05$) that were involved in pathways decreased in AD such as Wnt signaling pathway (Ramachandran et al. 2021; Rayaprolu et al. 2021). The LVPE procedure acutely affected 27% of the plasma proteins with both down-regulation and up-regulation but with a smaller magnitude than acute TPE procedure. LVPE treatment significantly down-regulated regulatory RNA binding (based on 107 proteins with $log2FC< -0.5$ and $q<0.05$), which was found to be increased in AD patients (Rayaprolu et al. 2021) and up-regulated chromatin remodeling pathways, such as DNA methylation (based on 25 proteins increased $log2FC>0.5$ and $q<0.05$), which was decreased during AD progression and caused overexpression of AD-related genes (Yi-Ping Zhu 2015). Proteomics analysis also detected lasting effect of TPE in both plasma and CSF proteomes. There were 29 plasma proteins remaining significantly changed 1-2 weeks after the intensive period, mainly down-regulated and significantly enriched in immune response pathway. One of them was also significantly down-regulated in CSF samples after 6-week TPE period. Neither plasma proteins nor CSF proteins remained significantly changed at EOS after correction for multiple

comparisons but 5 plasma proteins were strongly modulated weeks after the last PE (p.value<0.0005). Down-regulated proteins were involved in complement activation, calcium signaling, CREB, and Reelin pathways, while up-regulated were in Wnt signaling and immune response. **Conclusion:** Our deep proteomics profiling detected complex changes after PE-Alb treatment and demonstrated that PE-Alb-related response could last for weeks in plasma and CSF. Multiple pathways were modulated after PE-Alb, including a downregulation of the immune and inflammatory responses, supporting the multimechanistic basis of AMBAR therapeutic approach that may contribute to slowing AD progression. These results deserve further investigation and validation. **Conflict of interest:** CF, SL, SB, BL are employees of Alkahest, a Grifols company, RG, CM, PL, AO, AP, MS are employees of Grifols.

P120. ASSOCIATION OF NEIGHBORHOOD-LEVEL SOCIOECONOMIC. G. Ennis[1], M. Zuelsdorff[1], R. Powell[1], T. Betthauser[1], W. Buckingham[1], Y. Ma[1], C. Van Hulle[1], M. Carboni[2], G. Kollmorgen[3], C. Gleason[1], S. Johnson[1], K. Blennow[4], H. Zetterberg[4], A. Kind[1], B. Bendlin[1] *(1. University of Wisconsin - Madison - Madison (United States), 2. Roche Diagnostics International Ltd - Rotkreuz (Switzerland), 3. Roche Diagnostics GmbH - Penzberg (Germany), 4. University of Gothenburg - Gothenburg (Sweden))*

Background: Social determinants of health are the conditions within the environments in which people are born, live, and age that affect a wide range of health outcomes and risks. Socioeconomic disadvantage measured at the neighborhood level has been linked to cardiovascular disease and diabetes, well-known risk factors for Alzheimer's disease (AD) and related dementias. However, there are few studies that have examined the association between neighborhood-level socioeconomic disadvantage and the development of AD pathology and subsequent neurodegeneration. A cross-sectional study of cognitively unimpaired middle-aged and older adults found that living in the most disadvantaged neighborhoods was related to lower total cerebral and hippocampal volume. A post-mortem study reported that living in the most disadvantaged neighborhood at year of death was associated with increased odds of AD neuropathology. The present study sought to build upon these findings by examining the relationship between neighborhood-level disadvantage and cerebrospinal fluid (CSF) biomarkers of AD pathology (β-amyloid 42/40 and phosphorylated-tau [P-tau]), total-tau (T-tau), neurodegeneration (neurofilament light chain [NfL]), and synaptic degeneration/dysfunction (neurogranin) in a sample of predominantly nondemented middle-aged and older adults. **Objective:** We tested whether middle-aged and older adults living in the most (vs. least) disadvantaged neighborhoods had on average lower concentrations of CSF β-amyloid 42/40 and higher concentrations of CSF P-tau, T-tau, neurogranin, and NfL. **Methods:** Participants (N=622) were enrolled in the Wisconsin Registry for Alzheimer's Prevention (WRAP) or the Wisconsin Alzheimer's Disease Research Center (WI-ADRC) Clinical Core and had 1-7 CSF samples collected as part of study participation. 33.1% had >1 CSF samples collected over an average of 4.8 years. At baseline, mean age was 63.3 years (standard deviation = 8.7), 62.2% identified as female, 8.0% had MCI, and 7.7% had dementia (n=1 converted to dementia during follow-up). 40.4% were APOE4 allele carriers and 95.5% were non-Hispanic White Americans. Neighborhood-level disadvantage was assessed using the Area Deprivation Index (ADI), a measure based on American Community Survey 5-year averages of socioeconomic disadvantage collected at the Census Block Group (i.e., neighborhood-level). ADI scores were ranked into relative deciles based on Wisconsin statewide distributions. A dichotomous ADI variable constructed from these rankings allowed comparison between the most disadvantaged (deciles 9-10) and the least disadvantaged (deciles 1-8) neighborhoods. Twenty-seven participants were in the most disadvantaged group. CSF biomarkers of AD pathology (β-amyloid 42/40 and P-tau), total-tau (T-tau), and neurodegeneration (NfL and neurogranin) were measured with the Roche NeuroToolKit panel using either the Elecsys® β-Amyloid (1-42), Total-Tau and Phospho-Tau (181P) CSF immunoassays, or robust prototype assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). Linear mixed-effects models tested the relationship between dichotomous ADI and average concentration of CSF biomarkers of AD pathology, total-tau, and neurodegeneration. Age, sex, APOE4 carriership and cognitive status were controlled. Follow-up linear regression sensitivity analyses were performed to test the relationship between ADI and baseline CSF biomarkers in cognitively unimpaired participants (n=518), controlling for age, sex, and APOE4 carriership. CSF P-tau, T-tau, neurogranin, and NfL were natural log-transformed to meet model assumptions. **Results:** The most disadvantaged group (n=27) did not significantly differ from the least disadvantaged group (n=595) in age, sex, APOE4 carriership or cognitive status. A greater proportion of participants who identified as Black Americans were in the most disadvantaged group (5/27 vs. 15/595). In linear-mixed effects models controlling for age, sex, and APOE4 carriership, ADI (0=least and 1=most disadvantaged) was not significantly associated with CSF β-amyloid 42/40 and ln(NfL) but was significantly related to higher concentrations of CSF ln(P-tau) [β= .41, p= .02], ln(T-tau) [β= .39, p = .04], and ln(neurogranin) [β= .47, p = .02]. The addition of the social construct self-identified race (Black vs non-Black) as a covariate did not change results. The pattern of relationships between ADI and CSF biomarkers was similar when testing the baseline data of cognitively unimpaired participants (n=22 in most disadvantaged group). Associations between ADI and CSF ln(P-tau), ln(T-tau), and ln(neurogranin) were not statistically significant (ps = .06 to .07) when controlling for age, sex, and APOE4 carriership but were significant when self-identified race was added as a covariate: ln(P-tau) [β= .42, p= .04], ln(T-tau) [β= .42, p = .04], and ln(neurogranin) [β= .48, p = .03]. **Conclusions:** In a sample of predominantly nondemented middle-aged and older adults, living in the most disadvantaged neighborhoods was related to higher concentration of CSF biomarkers of AD pathology (P-tau), total-tau (T-tau), and synaptic degeneration/dysfunction (neurogranin). These findings support previous research indicating that neighborhood-level socioeconomic disadvantage may contribute to AD pathology and neurodegeneration. Because the size of the most disadvantaged group was small and few participants in that group had >1 CSF samples, we were unable to test the relationship between ADI and longitudinal change in biomarkers. Longitudinal studies with greater sociocontextual representation are needed to investigate mechanisms accounting for associations found here and to examine whether neighborhood-level disadvantage accelerates tau and neurogranin trajectories prior to dementia onset. **Conflict of interest:** AK, BB: NIA (R01-AG070883); AK, BB, TB: NIA (RF1-AG057784); SJ, TB: NIA (RF1-AG027161); SJ, TB: NIA (R01-AG027161); AK, BB, SJ, TB: NIA (P30AG062715); CG: NIA (R01-AG054059); GE: Alzheimer's Association 2019-AARF-643973; KB: Swedish Research Council (#2017-00915), the Alzheimer

Drug Discovery Foundation (ADDF), USA (#RDAPB-201809-2016615), the Swedish Alzheimer Foundation (#AF-742881), Hjärnfonden, Sweden (#FO2017-0243), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (#ALFGBG-715986), and European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236); HZ: Swedish Research Council (2018-02532); European Research Council (#681712); Alzheimer Drug Discovery Foundation (ADDF) (#201809-2016862); AD Strategic Fund and the Alzheimer's Association (ADSF-21-831376-C, ADSF-21-831381-C, ADSF-21-831377-C); Olav Thon Foundation; Erling-Persson Family Foundation; Stiftelsen för Gamla Tjänarinnor; Hjärnfonden (#FO2019-0228); European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement (#860197); UK Dementia Research Institute at UCL; MZ: Alzheimer's Association (AARF-18-562958); NIA (R03AG063303).

P121- USE OF THE PRECIVITYAD BLOOD TEST IN REGULAR CLINICAL PRACTICE: PRELIMINARY OBSERVATIONS FROM A DEMENTIA CLINIC. J. Drake[1,2], L. Daiello[1,2], C.K. Wu[1,2] *(1. Rhode Island Hospital - Providence (United States), 2. Warren Alpert Medical School of Brown University - Providence (United States))*

Background: Plasma biomarker assays represent a promising approach to addressing practical limitations to widespread availability of biomarker diagnosis of Alzheimer's disease (AD); however, information on the use of these assays outside research settings is limited. We participated in a quality improvement (QI) program with C2N Diagnostics, LLC in order to assess the utility of the PrecivityAD blood test in the outpatient clinical setting. **Objective:** To describe clinicians' perspective of the feasibility, patient acceptability, and diagnostic utility of PrecivityAD blood test use in routine dementia clinic practice in comparison with other available AD-specific biomarker modalities. **Methods:** A limited number of PrecivityAD blood test kits were provided to our neurology subspecialty dementia clinic as part of the QI program at a discounted out-of-pocket cost to patients. Diagnostically challenging patients in whom AD was etiologically possible and biomarker diagnosis had the potential to change prognosis and/or management as part of routine clinical care were offered the PrecivityAD blood test in addition to lumbar puncture (LP) and amyloid PET imaging. Potential for physician bias was minimized by equitably discussing strengths and limitations of each assay with patients as part of good clinical practice. **Results:** The PrecivityAD blood test was more feasible to implement and universally more acceptable to patients within the workflow of routine clinical practice, given the convenient nature of blood-based diagnostics. It should be noted that patients found the non-invasiveness of the blood test and amyloid PET similarly appealing; however, the steeply discounted cost of the blood test as part of the QI program was a clear influence versus amyloid PET, in addition to the convenience of a simple blood-based test that could be obtained the same day. Patients were able to understand the Amyloid Probability Score (APS), the main result of the PrecivityAD blood test, in the context of routine diagnosis and management in a similar manner to CSF biomarker or amyloid PET results in our hands. Analogous to routine clinical use of CSF biomarkers, strongly positive or negative APS results of the PrecivityAD blood test were the most diagnostically useful. APS results that were intermediate and/or incongruent with Aβ42/40 ratio were of limited utility in informing management. **Conclusion:** In our experience, the convenience and non-invasiveness of a plasma-based AD biomarker assay such as the PrecivityAD blood test offered clear advantages to LP and amyloid PET imaging in routine clinical practice. Lack of insurance coverage for plasma- and PET-based diagnostics still remains a significant barrier to more widespread biomarker diagnosis, based upon our informal observations in clinical discussions. Practically speaking, the APS value was easy to interpret, disclose to patients, and integrate into routine clinical care, analogous to use of CSF- and PET-based biomarkers. However, one general limitation in the confident use of plasma-based biomarkers for informing diagnostic and management decisions was the novelty of an indirect measure of cerebral amyloid, in contrast with CSF- or PET-based biomarkers. Another limitation specific to APS use arose in some cases where the APS and Aβ42/40 ratio were incongruent. Further validation of plasma biomarkers and use of a probability-oriented scoring system will be important for guiding evidence-based use of this modality in routine clinical practice.

P122- GENOME-WIDE ASSOCIATION STUDIES OF ARIA FROM THE ADUCANUMAB PHASE 3 ENGAGE AND EMERGE STUDIES. S. Loomis[1], R. Miller[1], C. Castrillo-Viguera[1], K. Umans[1], W. Cheng[1], J. O'gorma[1], R. Hughe[1], S. Budd Haeberlein[1], C. Whelan[1] *(1. Biogen - Cambridge (United States))*

Background: Amyloid-related imaging abnormalities (ARIA) refer to a range of findings detected on brain magnetic resonance imaging (MRI) that are associated with the use of monoclonal antibodies (mAbs) targeting amyloid beta (Aβ) in patients with Alzheimer's disease. ARIA can manifest as brain edema or sulcal effusion (ARIA-E) or as hemosiderin deposits presenting as microhemorrhages (hemorrhages >1 cm) in the brain parenchyma and/or localized superficial siderosis (ARIA-H). ARIA was the primary adverse event in the phase 3 clinical trials of aducanumab, a human mAb that selectively targets aggregated forms of Aβ, including soluble oligomers and insoluble fibrils, which has been approved by the US Food and Drug Administration (FDA) for the treatment of Alzheimer's disease. Analyses of clinical studies of Aβ-targeting therapies, including aducanumab, have indicated increased risk of ARIA in apolipoprotein E (APOE) ε4 carriers. However, the rest of the human genome has yet to be interrogated for additional genetic risk factors associated with ARIA. The systematic identification of genetic variants associated with ARIA among aducanumab treated patients may help predict individuals at greater risk of these adverse events, facilitating risk-benefit treatment decisions for patients, caregivers and prescribing physicians. **Objectives:** We sought to determine, in a hypothesis-free manner, whether genetic variation influences risk of ARIA in aducanumab-treated patients in the phase 3 clinical trials ENGAGE and EMERGE in genome- and exome-wide association studies (GWAS, EWAS). **Methods:** EMERGE (NCT02484547) and ENGAGE (NCT02477800) included participants aged 50 to 85 years with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia and confirmed amyloid pathology. Study participants were randomized (1:1:1) based on APOE e4 carrier status to receive low-dose aducanumab, high-dose aducanumab, or placebo every 4 weeks over 76 weeks. Of the full study cohort, 2412 participants provided consent for genetic analysis, and had sufficient DNA samples available. These samples were genotyped on the Illumina Infinium Global Screening Array and exome sequenced using paired-end reads at the Broad Institute

(Cambridge, MA). Genotyping and exome sequencing data underwent standard quality control, and genotyping data were imputed to the 1,000 Genomes reference panel, resulting in 9.5 million variants in the genotyping data and >560,000 variants in the exome data. For this genetic analysis of ARIA among aducanumab treated patients, we included all trial participants who were randomized and received at least one dose of study treatment (intent-to-treat [ITT] population) during the placebo-controlled or the long-term extension period, underwent at least one post-baseline MRI scan, and had quality controlled genetic data available (N=1691). GWAS and EWAS were performed separately for ARIA-E, ARIA-H microhemorrhage and ARIA-H superficial siderosis. Additionally, we ran secondary analyses stratified by symptomatic status and radiographic severity. **Results:** In the GWAS, we identified a genome-wide significant (p<5x10-8) association at the chromosome 19 locus encompassing APOE; no additional signals were observed beyond this region. The APOE association with ARIA was stronger in ε4/ε4 homozygotes than in ε3/ε4 heterozygotes across ARIA-E (ε4/ε4: OR=4.3, p< 2x10-16; ε3/ε4: OR=1.7, p=1.6x10-4), ARIA-H microhemorrhage (ε4/ε4: OR=4.6, p=2.9x10-14; ε3/ε4: OR=1.5, p=0.03) and ARIA-H superficial siderosis (ε4/ε4: OR=7.8, p=7.8x10-15; ε3/ε4: OR=3.1, p=3.2x10-6). A similar pattern of larger effect sizes with increasing number of ε4 alleles for association with ARIA was observed at all levels of radiographic severity, with a trend towards increased odds of ARIA-E and ARIA-H for severe (ε4/ε4 OR=7.0-24.6, p 2.7x10-5) vs mild (ε4/ε4 OR=3.2-5.0, p 1.4x10-5) cases. APOE ε4 was also significantly associated with both symptomatic ARIA-E and ARIA-H (ε4/ε4 OR=3.6-9.5; p 4.2x10-3) and asymptomatic ARIA-E and ARIA-H (ε4/ε4 OR=4.2-7.9, p 1.7x10-11) cases; however, APOE genotype did not modulate symptomatic status among those with ARIA (p>0.05). The EWAS showed similar results to the GWAS, with no additional robust associations beyond the APOE region. **Conclusions:** We found a strong, genome-wide significant association between APOE and risk of ARIA; no other genetic risk factors associated with ARIA were identified. Participants with two copies of the APOE ε4 allele showed the highest odds of ARIA-E and ARIA-H, consistent with prior studies of anti-amyloid therapies. Future, larger-scale studies may be better powered to detect genetic associations beyond APOE. These findings indicate that APOE is the strongest genetic risk factor and the most salient genetic candidate to use for prospective ARIA risk stratification.**Conflict of interest:** All authors are current or former employees of Biogen and hold stock in the company.

P123- LOW PLASMA AB42/AB40 RATIO IN OLDER ADULTS WITH ENLARGED PERIVASCULAR SPACES. A. Kapoor[1], A. Gaubert[1], A. Nguyen[1], B. Yew[2], J.Y. Jang[1], S. Dutt[2], Y. Li[1], J.P. Alitin[3], J.K. Ho[1], A.E. Blanken[2], I.J. Sible[2], A. Marshall[2], A. Martini[1], E. Head[1], D.A. Nation[1] *(1. University of California, Irvine - Irvine (United States), 2. University of Southern California - Los Angeles (United States), 3. University of California, Irvine - Irvine (United States) - Irvine (United States))*

Background: Perivascular spaces (PVS) are fluid-filled spaces surrounding arterioles, capillaries and venules in the brain, which facilitate flow of various substances and enable clearance of waste. Dilation of PVS may indicate poor fluid drainage due to accumulation of perivascular cell debris, waste, and proteins, including amyloid-beta (Aβ). Aβ deposition is currently considered a hallmark and key pathophysiological marker of Alzheimer's disease (AD). Novel assays now allow Aβ to be measured in plasma, and low plasma Aβ42/Aβ40 ratio has been associated with higher cortical amyloid deposition and risk of developing AD. However, to the best of our knowledge, no prior study has assessed whether lower plasma amyloid levels are related to enlargement of PVS. **Objective:** To examine whether plasma Aβ levels are elevated in individuals with higher number of enlarged PVS visible on MRI. We hypothesized that lower Aβ levels will be associated with higher number of enlarged PVS. **Methods:** Independently living older adults (N = 56, mean age = 68.2 years; SD = 6.5; age range 55-84 years; 30.4% male) free of dementia or clinical stroke were recruited from the community and underwent brain MRI, and blood draw. PVS were qualitatively scored using an existing 5-point scale in the basal ganglia, and centrum semiovale. Overall PVS score was the highest score of all anatomical regions. Scores were dichotomized to low enlarged PVS burden (scores of 0-1, none or mild) or high enlarged PVS burden (score >1, moderate-severe). Plasma was assayed using the Quanterix Simoa® Neurology 3-Plex A Advantage Kit to quantify Aβ42 and Aβ40 levels and ratio was then determined. One-way ANCOVA was conducted to compare Aβ42, Aβ40, Aβ42/Aβ40 ratio between low and high enlarged PVS burden controlling for age. **Results:** Thirty-seven (66.1%) participants had high burden of enlarged PVS in the centrum semiovale, 17 (30.4%) had high burden in the basal ganglia and 39 (69.6%) had high overall burden. There was a significant difference in plasma Aβ42/Aβ40 ratio between low and high overall PVS burden, controlling for age ($F(1,53) = 5.59$ $p = 0.022$, $\eta 2 = .10$), with lower Aβ42/Aβ40 ratio in high PVS burden group (estimated marginal mean = .050) compared to low (estimated marginal mean = .062). This difference was driven primarily by enlarged PVS in the centrum semiovale ($F(1,53) = 6.07$ $p = 0.017$, $\eta 2 = .10$). No difference in plasma Aβ42/Aβ40 ratio was observed between low versus high PVS burden in the basal ganglia. No difference was observed in Aβ42 or Aβ40 levels between groups, although the difference in Aβ42 levels between low and high overall burden of PVS was approaching significance ($F(1,53) = 3.65$ $p = 0.064$, $\eta 2 = .06$). **Conclusion:** Prior studies have demonstrated that elimination of Aβ from the brain occurs via perivascular spaces and hypothesized that failure to eliminate Aβ may contribute to the pathogenesis of AD. Our findings suggest that lower plasma Aβ42/Aβ40 ratio, which may indicate higher cortical amyloid deposition, is associated with greater dilation of PVS. Future studies are needed to elucidate the relationship between vascular damage and the pathogenesis of AD.

P124- NADALS: AN OPEN-LABEL BASKET TRIAL EVALUATING THE JAK INHIBITOR BARICITINIB IN ALZHEIMER'S DISEASE AND AMYOTROPHIC LATERAL SCLEROSIS. S. Daneshvari[1], P. Webb[1], A.M. Willsv, J. Berry[1], S. Arnold[1], M. Albers[1] *(1. MGH - Boston (United States))*

Background: Chronic neuroinflammation has been implicated in Alzheimer's disease (AD) pathology. JAK kinases play a central role in innate immune signaling, often triggering an interferon response. These finding converged with our independent, laboratory study that discovered a strong interferon response in autopsied AD and ALS brains with cytoplasmic TAR DNA-binding protein 43 (TDP-43) inclusions. We found that cytoplasmic inclusions of TDP-43 were associated with cytoplasmic double stranded RNA (cdsRNA), a root cause of interferon signaling and JAK kinase activation. Baricitinib, an FDA approved JAK inhibitor FDA-approved for rheumatoid arthritis, COVID-19, and alopecia, is a top hit in an orthogonal machine learning approach to repurpose

drugs in Alzheimer's disease. Baricitinib rescued differentiated human neural cell death and neuroinflammation evoked by cdsRNA in a dose dependent manner. In animal models, activation of type I interferon signaling by cdsRNA leads to propagated neurodegeneration within a neural circuit. The interferon response gene, PKR, is a biosensor for dsRNA in neurons. Elevated levels of activated PKR are associated with cognitive decline and progression of disease. Baricitinib lowered PKR levels in human neural cells and baricitinib structural analog lowers levels of PKR in an AD patient. Moreover, we further validated that baricitinib rescues neuroinflammation and neuronal death in a mouse model of cdsRNA-evoked neurodegeneration. We seek to further validate this mechanism of action in patients with AD, mild cognitive decline (MCI), or subjective cognitive decline (SCD) who have elevated markers of interferon signaling in their cerebrospinal fluid (CSF). **Objectives:** The primary objectives of the study are: 1. to assess whether an oral dose of baricitinib 2 mg and 4 mg per day achieves measurable levels of baricitinib in the CSF of patients with AD. 2. To determine whether an oral dose of baricitinib 2 mg or 4 mg per day decreases levels of the inflammatory biomarker chemokine ligand 2 (CCL2) in the CSF of patients with AD, MCI, or SCD. The secondary objectives of the study are: 1. to determine whether an oral doses of baricitinib 2 mg and 4 mg per day decrease levels of the inflammatory biomarkers, phospho-protein kinase R (pPKR), PKR, the pPKR / PKR ratio, C-X-C motif chemokine ligand 10 (CXCL10), and Interferon Gamma (IFNG) in the CSF of patients with AD, MCI, or SCD; 2. to determine whether the oral doses of baricitinib 2 mg and 4 mg per day decrease levels of neuronal death biomarkers of neurofilament light chain (NfL), tau, and phospho-tau in CSF and TDP-43 levels in the plasma in patients with AD, MCI, or SCD. 3. to determine whether the measured concentration of baricitinib in the CSF or blood (pharmacokinetics) correlates with the changes in CSF biomarkers (pharmacodynamics); 4. to demonstrate that baricitinib 2 mg and 4 mg by mouth daily is safe and tolerable in patients with AD, MCI, and SCD. **Methods:** This is a lead-in, open-label, biomarker-driven trial of baricitinib in patients with AD, MCI, and SCD (NCT05189106). All participants will have a lumbar puncture (LP) at screening, and if their CSF level of CCL2 is ≥ 250 pg/mL, participants will be enrolled. After 8 weeks, a baseline LP will be performed, and each participant will treated with open-label baricitinib 2 mg by mouth daily for 8 weeks. A third LP will be performed after 8 weeks on the drug. CSF examination will be conducted to measure levels of study drug in the plasma and CSF two to four hours after dosing and levels of CCL2 (MCP1), pPKR, PKR, pPKR/PKR, CXCL10, IFNG, nNfL, Abeta, tau, and phospho-tau as well as exploratory biomarkers. Blood will be collected for safety labs, and to measure levels of TDP-43 and exploratory biomarkers in the plasma. The baricitinib dose will be increased to 4 mg by mouth daily with a fourth LP and CSF examination will be conducted at the Week 16 Visit. Clinical endpoints such as the ADAS-COG, a cognitive battery will be collected at final clinic visit at 24 weeks. **Results:** CCL2 levels are elevated in about 50% of patients diagnosed with AD, MCI, and SCD from the Massachusetts Alzheimer's Disease Research Center BioBank, which is consistent with the prevalence of TDP-43 inclusions in AD brains. **Conclusion:** We are conducting a pilot clinical trial to determine whether baricitinib 1. significantly reduces inflammatory and/or neuronal death biomarkers in the CSF, 2. is safe and tolerable in AD, MCI, and SCD patients. Unbiased analysis of proteomics of CSF samples may refine the biomarker profile of patients that responded to baricitinib. Regardless if the clinical trial achieves its endpoints, this biomarker discovery work can be incorporated into future AD clinical trials to offer more precise eligibility criteria and deep phenotyping.

P125- EXAMINING THE TRAJECTORY OF NEURODEGENERATION BIOMARKERS AND ITS ASSOCIATION WITH COGNITIVE PROFILES AND AMYLOID IN LATE MIDDLE-AGED ADULTS: RESULTS FROM THE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION (WRAP). L. Du[1,2], T. Betthauser[1,3,4], K. Cody[1,3,4], E. Jonaitis[1,3,4], C. Burghy[1], B. Hermann[1,5], B. Larget[6], R. Chappell[2,3], S. Johnson[1,3,4,7], R. Koscik[1,3,4] *(1. Wisconsin Alzheimer's Institute, University of Wisconsin-Madison School of Medicine and Public Health - Madison, Wi (United States), 2. Department of Biostatistics and Medical Informatics, School of Medicine and Public Health, University of Wisconsin-Madison - Madison, Wi (United States), 3. Wisconsin Alzheimer's Disease Research Center - Madison, Wi (United States), 4. Department of Medicine, University of Wisconsin-Madison School of Medicine and Public Health - Madison, Wi (United States), 5. Department of Neurology, University of Wisconsin-Madison School of Medicine and Public Health - Madison, Wi (United States), 6. Department of Statistics, University of Wisconsin-Madison - Madison, Wi (United States), 7. Madison VA GRECC, William S. Middleton Memorial Hospital - Madison, Wi (United States))*

Background: Several computerized methodologies for the analysis of structural magnetic resonance imaging (MRI) have been used to assess Alzheimer's disease (AD)-related neurodegeneration. Accumulating evidence indicates that the underlying neuropathological mechanisms associated with AD begin a decade or more before the emergence of cognitive impairment. This has led to an increasing interest in understanding the order and magnitude of biomarker changes during preclinical AD, beginning with amyloid onset. **Objectives:** Our objectives included: 1) characterize neurodegeneration biomarker change points (CPs, age in years) and related slope parameters in a longitudinal cohort study; 2) examine how these parameters varied across cognitive trajectory clusters derived from longitudinal WRAP cognitive data; and 3) examine whether the random effects or the within-person differences between the cognitive and neurodegeneration biomarkers' CPs differ between those with and without amyloid as measured by PET amyloid scans. **Methods:** WRAP participants were included in analyses for the first two objectives (n = 581), if they had at least one structural MRI scan, were dementia-free at baseline, and had longitudinal cognitive data. Neurodegeneration measures included MRI hippocampal volume z-scores (HV, adjusted for total intracranial volume [TICV]) and global brain atrophy (GBA, CSF volume / GM + WM volume). Objective 1: Person-level posterior median-estimate CPs, slopes pre- and post-CP, and intercepts at CP for the two neurodegeneration biomarkers were extracted using Bayesian random CP mixed models (BRCPMM; age = time scale). Objective 2: In a previous analysis of a larger WRAP sample using BRCPMM, we extracted posterior median person-level CPs, slopes pre- and post-CP, and intercepts at CP using longitudinal cognitive performance on a 3-test Preclinical Alzheimer's Cognitive Composite (PACC3; n=1068). We then used these random effects and K-means clustering to identify cognitive trajectory profiles and we identified when PACC3 CPs occurred ("CP-Timing group"; before, during or after the follow-up time period: 5 (0.9%), 63 (10.8%)) and 513 (88.3%), respectively). We then compared last observed HV and GBA across cognitive trajectory profiles and CP-Timing groups; and compared the BRCPMM HV and GBA random

effects using non-parametric statistics by cognitive trajectory clusters and PACC3 CP-Timing groups. Significant omnibus tests ($p < .05$) were followed with pairwise comparisons. For the third objective, in the subset people with ≥1 positron emission tomography (PET) [C-11] Pittsburgh Compound B scan (PiB; n = 361), we compared the PACC3, HV, GBA CPs, slopes post-CP, intercepts at CP, and within-person differences between the cognitive and neurodegeneration biomarkers' CPs using non-parametric statistics by amyloid status (A+/-, using a previously validated global DVR threshold of > 1.19). **Results:** Mean(sd) last MRI scan age was 67.1(6.9) years. Posterior median random CPs estimates (corresponding 95 credible intervals from 20000 BRCPMM runs) were at 67.35 [61.05, 72.74] for HV and 69.13 [61.03, 74.65] for GBA. The three cognitive trajectory profiles identified included groups at Highest Risk of cognitive decline (relatively average PACC3 performance at CP with faster decline than the other clusters both before and after CP), Intermediate Risk (generally low-average performance at CP, later age of CP and weakly negative trajectories after CP), and Lowest Risk (high-average performance at CP and positive slopes after change point). In these analyses, 40(6.9%), 223 (38.4%) and 318 (54.7%) were in the High, Intermediate, and Low Risk groups, respectively. The Highest Risk group had lower HV and higher GBA. The "after" CP-Timing group had higher HV and lower GBA than the other CP-Timing groups ($p < 0.001$). The highest risk group has earlier CPs, lower HV at CPs, higher GBA at CPs and decline faster after CPs in Hippocampal volume. The "after" CP-Timing group has later CPs, lower GBA at CPs and less negative slope after CPs in HV than during group. In the subset with PiB, the A+ group had earlier CP's and worse PACC3 and HV slopes post-CP than the A- group. Relative to PACC3 CP, the median CPs and 95% credible interval of GBA was 6.4 [4.7, 8.5] years earlier, HV was 8.1 [6.5, 9.7] years earlier. The within-person paired differences between GBA and HV CP's was 1.7 [-0.5, 3.3] between GBA and HV CP's. Patterns differed significantly between A+ and A- as follows: PACC3 to GBA CP median differences were 6.6 for A- and 5.7 for A+ ($p = 0.006$); PACC3 to HV CP median differences were 8.1 for A- and 7.5 for A+ ($p = 0.04$). A+ and A- groups did not differ on HV to GBA CP differences. **Conclusion:** The timing and rates of change in neurodegeneration biomarkers differed by cognitive trajectory profiles. In this initially non-demented sample, the overall cognitive change point occurred ~6 years later than global atrophy and ~8 years after hippocampal volume, and HV change points occurred 1 year later in the amyloid negative group. These findings highlight the long period of time prior to symptom onset during which AD pathology is accumulating in the brain. Identifying person-level neurodegeneration biomarker trajectories and their differences in CP within cognition may provide an opportunity to find sensitive biomarkers for early intervention in a clinical trial.

LP63 RACIAL DIFFERENCES IN PREDICTING CONCURRENT AND LONGITUDINAL COGNITIVE OUTCOMES BY CSF BIOMARKERS OF ALZHEIMER DISEASE AMONG COGNITIVELY NORMAL INDIVIDUALS. C. Xiong[1], J. Lah[2], C. Manzanares[2], A. Levey[2], D. Wolk[3], L. Shaw[3], S. Schindler[1], R. Henson[1], A. Fagan[1], J. Hassenstab[1], T. Benzinger[1], Q. Bui[1], F. Agboola[1], J. Gray[1], J. Morris[1] *(1. Washington University - St. Louis (United States), 2. Emory University - Atlanta (United States), 3. University of Pennsylvania - Philadelphia (United States))*

Background: Molecular biomarkers of Alzheimer disease (AD) are correlated with concurrent cognitive outcomes and also predict longitudinal cognitive changes in biomarker studies of predominantly White participants. Secondary prevention trials of AD enroll cognitively normal individuals with a positive profile of biomarkers of AD at baseline in hope of establishing preventive efficacy in slowing cognitive decline. Multiple recent studies have demonstrated cross-sectional differences in concentrations of the cerebrospinal fluid (CSF) proteins Aβ42, Aβ40, total tau (t-tau), and tau phosphorylated at position 181 (p-tau181) between self-reported Blacks and Whites. The consequences of these differences in designing and analyzing secondary prevention trials of AD remain, however, poorly understood. **Objectives:** We first aim to examine possible racial differences in predicting concurrent and longitudinal cognition by CSF biomarkers from a multi-center observational study. Based on these data, we then aim to estimate the sample size of both Blacks and Whites necessary for a future prevention trial of AD to adequately power the test of efficacy hypothesis on a cognitive endpoint. **Methods:** We analyzed cross-sectional CSF biomarker data and longitudinal cognitive data from cognitively normal participants from the Washington University (WU) Knight Alzheimer Disease Research Center (ADRC), UPenn ADRC, and Emory University Goizueta ADRC. The cohort included 110 self-reported Black/African Americans and 801 self-reported White individuals. Participants underwent a lumbar puncture (LP) and received cognitive assessment at baseline, and then longitudinally after the LP. CSF samples were centrally processed via an automated immunoassay by WU and UPenn ADRC Fluid Biomarker Cores (led by Drs. Suzanne Schindler and Les Shaw, respectively) with appropriate bridging between the labs. A cognitive composite was formed by averaging the z-scores from 12 tests in the NACC UDS. We analyzed the association of each CSF biomarker with concurrent cognitive performance and its ability to predict future cognitive decline by implementing random intercept and slope models that allowed both fixed intercept (concurrent cognition) and slope (i.e., rate of change) as functions of biomarker status and self-reported race. Racial differences in the intercept and slope were estimated and tested. Assuming a future secondary prevention trial of AD enrolls Black and White participants similar to the biomarker positive groups into the placebo arm, we further estimated the sample size of both Blacks and Whites necessary to adequately power the test of efficacy hypothesis on cognition. **Results:** Cognitively normal Black participants had a higher level of CSF Aβ42/40 ($p=0.0022$), lower level of CSF t-tau, p-tau181, and NfL ($p's<=0.0070$), but similar level of CSF Aβ42 ($p=0.1902$). CSF Aβ42/40 was correlated with concurrent cognition in Whites ($r=0.18$, $p<0.0001$) but not Blacks ($r=-0.07$, $p=0.4505$). CSF t-tau, p-tau181, and NfL correlated with concurrent cognition in Whites ($r=-0.22$, $p<0.0001$; $r=-0.24$, $p<0.0001$; $r=-0.30$, $p<0.0001$, respectively) but not Blacks ($r=-0.1$, $p=0.3045$; $r=-0.05$, $p=0.5940$; $r=-0.19$, $p=0.0637$, respectively). However, the racial difference in these correlations was statistically significant only for CSF Aβ42/40 ($p=0.0137$). At baseline, lower cognitive performance was observed for Blacks, in comparison to Whites ($p<0.0001$), both in biomarker positive and negative groups. Regardless of self-reported race, biomarker positive participants had a faster rate of cognitive decline than those who were negative ($p's<=0.0089$ for all CSF biomarkers). Further, the annual rate of cognitive decline since baseline did not differ by race among biomarker positive individuals ($p's>=0.5345$ for all CSF biomarkers). Using the average annual rate of cognitive decline and the associated variance components between Aβ42/40 positive Black and White participants, and assuming a race-stratified randomization in a future 1:1 (active treatment vs.

placebo) secondary prevention trial with semi-annual cognitive assessments over 2 years, a total of 2886 participants (289 Black and 2597 White participants for a ratio of 1:9, i.e., 10% Blacks) are needed to power (80%) the detection of a 50% reduction on the annual rate of cognitive decline between the active treatment and placebo arm. The sample size is reduced to 1386 (347 Black and 1039 White participants) to detect the same effect size with the same power if Black enrollment is increased to 25%. When CSF p-tau181 was used to define biomarker positivity, the sample sizes were 3550 (355 Black vs. 3195 White participants=1:9) and 1704 (426 Black vs. 1278 White participants=1:3), respectively. **Conclusion:** Cross-sectional racial differences in CSF biomarkers of AD and their association with concurrent and future cognition among cognitively normal Black and White individuals have consequences to the design and analysis of future secondary prevention trials of AD. The similar longitudinal rate of cognitive decline among cognitively normal and biomarker positive Black and White older adults, if confirmed, however, allows these trials to target a shared endpoint. Increased representation of Black participants in these trials improves the statistical power to detect the cognitive efficacy of interventions.

LP64- BLOOD-BASED DEMENTIA PATHOLOGY STRATIFICATION UTILIZING NEURON-DERIVED EXOSOMES. E. Eitan[1], O. Volpert[1], K. Elgart[1] *(1. NeuroDex - Natick (United States))*

Background: Over 50M people worldwide suffer from dementia, and the numbers are rising with the aging population. While therapeutics and diagnostics in development focused predominantly on Alzheimer's disease (AD), most (over 80%) dementia patients display a combination of pathological features (mixed brain pathology), which include amyloidosis, tauopathy, Lewy bodies, TDP43, and vascular pathology. Recently, a few targeted therapies emerged after a long period with no available disease-modifying treatments. However, these therapies are directed against amyloidosis, and patient selection based on amyloid PET scans lacks consideration of non-amyloid pathologies that could alter treatment response. **Objectives:** This study aims to develop a blood test to detect divergent brain pathologies associated with or leading to dementia, including Lewy bodies (alpha-synuclein), TDP43, and tauopathy. This blood test may serve as a stand-alone assay for a detailed diagnosis of dementia pathologies to enable a precision medicine approach to neurodegeneration. Alternatively, the same test can be used as a preliminary screen to determine the need for more invasive CSF and PET tests. **Methods:** NeuroDex's blood assay is based on ExoSORT™, a proprietary immunoaffinity platform for isolating and characterizing neuronal extracellular vesicles (NDEs) from blood plasma. ExoSORT technology relies on antibodies against two particular neuronal markers, GAP43 and NLGN3. The downstream measurements of alpha-synuclein, alpha-synuclein phosphorylated on serine-129 residue, TDP43, and P181-Tau. Our second approach, based on Luminex technology, allows us to characterize proteins on intact extracellular vesicles (EVs) surface. This assay, dubbed Lumin-EX, measures alpha-synuclein on the outer leaflet of plasma EVs released by neurons and oligodendrocytes, multiplex measurements. **Results:** ExoSORT was optimized for NDEs isolation. Its specificity for NDEs was determined by the enrichment of neuron-specific proteins Tau, SYP, proBDNF, ENO2, NFL, etc., and of neuron-specific mRNA encoding NEFL, PSD95, NRGN, etc. Unbiased proteomic and RNAseq analyses also demonstrated the enrichment of neuronal markers. Moreover, we recently published a correlation between changes observed in mice NDEs and brains. The recovery of spiked neuron-specific material was used to determine about 55% recovery, which is consistent between samples and experiments. The robust nature of the method was assessed by evaluating the day-to-day precision and reproducibility of the data between multiple operators and by independent laboratories. Next, the assays were tested on a cohort encompassing patients diagnosed with AD (N=30), PD (N=40), Multiple Systems Atrophy (N=20), Dementia with Lewy Bodies (N=20), and Amyotrophic Lateral Sclerosis (N=30), as well 40 disease-free controls. In NDEs isolated using ExoSORT, alpha-synuclein measurements showed significantly higher levels in the samples from PD and LBDs than in control (2.8-fold, AUC=0.87) or ALS samples. At the same time, AD patients were segregated into two groups, wherein 40% of AD patients presented with over 2.5-fold increase, and the other 60% were all within the range of the non-disease control samples. In contrast, synuclein levels in the NDEs from MSA and ALS patients showed no significant differences from controls; However, preliminary analysis showed significantly elevated synuclein levels in oligodendrocyte-derived EVs from MSA patients (2.2-fold, AUC=0.83). Alpha-synuclein measurements on EVs surface showed similar patterns with elevated levels in PD (3.5-fold, AUC=0.83) and DLB (2.2-fold, AUC=0.81) and separated the AD samples into two groups. Surface alpha-synuclein was also significantly higher in MSA (2.4-fold). TDP43 levels were significantly higher in NDEs isolated from plasma samples of ALS patients (1.8-fold, AUC=0.91) and correlated ($R=0.32$, $P<0.01$) with the functional/behavioral scores (ALSFRS-R slope). TDP43 was also significantly higher in approximately 70% of AD samples, generating an overall significant effect (a 2.2-fold increase of the average). Furthermore, we used the Lumin-EX assay to measure synaptic proteins on the surface of plasma EVs including NRGN, PSD95, Syntaxin-1, and GLUR2. In plasma samples from AD patients, EV-associated NRGN levels were higher, PSD95 and GLUR2 were lower compared to controls, and these changes correlated ($R=0.46$, $P<0.002$) with cognition scores (MMSE and CDR). In PD, Syntaxin-1 was elevated, and GluR2 was decreased compared to the control group. We are working on expanding the clinical cohort and validating the results with plasma samples from postmortem confirmed patients, expected results before the conference. **Conclusion:** The methodology we developed to isolate and characterize plasma EVs opens a new avenue for neurodegenerative diagnosis. The ability to detect different dementia-associated pathologies by a single blood test can be a game-changer for clinical trials and diagnosis. When fully developed, our blood test could provide a tool to screen the elderly population for better prognosis and treatment selection. The next test generation will include other aspects like autophagy, mitochondria, neuroinflammation, and metabolism. **Conflict of interest:** Dr. Eitan, Dr. Volpert, and Dr. Elgart work and receive salaries from NeuroDex. Dr. Eitan is also a shareholder in NeuroDex.

LP65. SEX-SPECIFIC DIAGNOSTIC PROPERTIES OF AD PLASMA BIOMARKERS IN COGNITIVELY UNIMPAIRED AT-RISK INDIVIDUALS. M. Mila Aloma[1], N. Ashton[2], T. Karikari[2], A. Brugulat Serrat[1], E. Vanmechelen[3], J. Vanbrabant[3], E. Stoops[3], T.A. Day[4], M.T. Ferretti[5], J.L. Molinuevo[1], J.L. Dage[6], H. Zetterberg[2], J.D. Gispert[1], K. Blennow[2], M. Suárez-Calvet[1] *(1. Barcelonabeta Brain Research Center - Barcelona (Spain), 2. University of Gothenburg - Mölndal (Sweden), 3. ADx Neurosciences - Ghent (Belgium), 4. Lilly Research Laboratories, Eli Lilly and Company - Indianapolis (United States), 5. Women's Brain Project - Guntershausen (Switzerland), 6. Stark Neurosciences Research Institute, Indiana University School of Medicine - Indianapolis (United States))*

Background: Increasing evidence shows promise of plasma biomarkers indicative of Alzheimer's disease (AD) pathology to be used in clinical trials. This can be for screening purposes and/or monitor treatment response. As AD clinical trials move towards targeting the preclinical stage of the disease, it is paramount to identify those cognitively unimpaired individuals that are at a higher risk of developing AD symptomatology. There is still very limited evidence on the factors, like sex, that may influence the levels of plasma biomarkers and their performance to detect Aβ pathology. Sex is one of the main risk factors for AD and sex differences are known in disease manifestation, biomarkers trajectories and susceptibility to risk factors. However, it remains to be elucidated whether plasma biomarkers perform differently in men than in women, particularly in the preclinical stage of AD. Answering this question will have relevant implications for the accurate use of plasma biomarkers in preventive clinical trials. **Objectives:** To test sex differences in AD plasma biomarker diagnostic properties in cognitively unimpaired individuals at risk for AD. **Methods:** We studied 397 cognitively unimpaired individuals from the ALFA+ cohort (mean age 61.1 years old, 34% CSF Aβ42/40-positive) with CSF and plasma biomarkers measurements. A subset of 337 participants also had available Aβ PET visual read (VR) assessments. We measured plasma Aβ42/40, p-tau181, p-tau231, GFAP and NfL using the Simoa HD-X (Quanterix Corp) and plasma p-tau217 and t-tau using MSD-based assay measures (Eli Lilly and Company). Sex differences in the levels of plasma biomarkers were analysed with an ANCOVA adjusted by age. We performed Receiver Operating Curve (ROC) analyses and calculated the specificity, sensitivity, negative predictive value (NPV), positive predictive value (PPV) and Youden's index to study the performance of plasma biomarkers to discriminate Amyloid-positivity (defined by CSF Aβ42/40 or Aβ PET VR) separately in men and in women. The AUC of each biomarker alone, and when combined with risk factors (age and APOE status) were compared to the risk factors alone using DeLong tests. We also performed logistic regressions adjusted by age and APOE status to study sex differences in the capacity of each plasma biomarker to predict CSF Aβ42/40 and Aβ PET VR status. We calculated the Odds Ratio (OR) for men and women and we additionally tested the interaction term between sex and each plasma biomarker. **Results:** Plasma p-tau217 and GFAP were higher in women compared to men (p-tau217: Mean[SD]women =0.15 [0.08] and Mean[SD]men=0.14 [0.05]; GFAP Mean[SD] women=144.63[62.53] and Mean [SD] men=129.22[60.05]; all P<0.05). We first assessed the biomarker performance to discriminate CSF Aβ42/40 positivity. In women, plasma p-tau231 had the highest AUC (0.771), followed by plasma Aβ42/40 (0.737) and GFAP (0.736), whilst highest sensitivity and NPV were rendered by plasma GFAP (S=0.728; NPV=0.821), p-tau231 (S=0.679; NPV=0.821), Aβ42/40 (S=0.630; NPV=0.803) and NfL (S=0.709; NPV=0.791). Conversely, in men, plasma Aβ42/40 showed the highest AUC, sensitivity and NPV (AUC=0.771, S=0.796 and NPV=0.855). None of the plasma biomarkers alone improved the performance of risk factors (age and APOE status) neither in women nor in men. The addition of plasma Aβ42/40, p-tau217, p-tau231 or GFAP significantly improved the performance of risk factors in women (Padj<0.01), but in men this was only achieved by plasma Aβ42/40 (Padj=0.008). For the discrimination of Aβ PET VR positivity, plasma p-tau217 rendered the highest AUC in both sexes (AUCwomen=0.843; AUCmen=0.764). In women, plasma p-tau217 also showed the highest sensitivity and NPV (S=0.885, NPV=0.977) while in men, those were highest for Aβ42/40 (S=0.938; NPV=0.976). When combined with risk factors, both plasma p-tau217 and Aβ42/40 significantly improved the performance of risk factors alone in women (Padj<0.05), but none of the combinations improved the risk factors model performance in men. Logistic regression results showed a trend to significant interactions between sex and plasma GFAP (P=0.056) and plasma p-tau231 (P=0.099) for the prediction of CSF Aβ status. Stratified analyses revealed that these two biomarkers had a higher OR in women (plasma p-tau231 OR[CI]=3.97[2.55-6.58] and plasma GFAP OR[CI]=3.15[2.09- 4.99]) than in men (plasma p-tau231 OR[CI]=2.08 [1.41-3.20] and plasma GFAP OR[CI]= 1.58[1.07-2.44]). Sex did not modify plasma biomarkers capacity to predict Aβ PET VR positivity. **Conclusion:** While in women p-tau231, GFAP and Aβ42/40 show similar performances, in men Aβ42/40 was shown to be the most accurate biomarker for the discrimination of CSF Aβ42/40 status. To discriminate Aβ PET VR status, plasma p-tau217 is the most accurate biomarker in both sexes. Our results suggest the sex differences might be more pronounced in the discrimination of CSF Aβ42/40 status than Aβ PET status, and therefore at the earliest stage of the preclinical AD continuum. Overall, there are sex differences in the levels and the diagnostic properties of AD plasma biomarkers that, if confirmed and replicated in further studies in comparable cohorts, can have important implications for the implementation and use of plasma biomarkers for clinical trials.

LP66- BASELINE PLASMA PTAU181 IMPROVES PREDICTION OF COGNITIVE DECLINE IN AMYLOID POSITIVE SUBJECTS WITH MILD COGNITIVE IMPAIRMENT. V. Devanarayan[1], P. Sachdev[1], A. Charil[1], A. Koyama[1], L. Reyderman[1], C. Swanson[1], H. Hampel[1], M. Irizarry[1], S. Dhadda[1], L. Kramer[1] *(1. Eisai, Inc. - Nutley (United States))*

Background: Blood-based tests for screening and monitoring patients in Alzheimer's disease (AD) clinical trials would be more convenient, faster and cost-effective. Plasma pTau181 has been shown in recent studies to be a good marker of brain amyloid burden. This research evaluated the use of baseline ptau181 as a prognostic predictor of cognitive decline (CD) in amyloid positive (A+) subjects with mild cognitive impairment (A+ MCI) over a typical 18-month duration of a clinical trial. **Methods:** Training cohort (TC) for constructing the signatures to predict CD comprised of 135 A+ MCI placebo subjects from two clinical trials. Two independent validation cohorts for testing the performance of these signatures included 115 and 203 A+ MCI subjects respectively from placebo arm of another clinical trial (VC-1) and fromADNI (VC-2). Plasma pTau181 was measured using Simoa assay at three different sites, and were normalized to have similar means and variances to make them

comparable across cohorts. TC and VC-1 included 18-month clinical follow-up, and VC-2 included 3 to 10-year follow-up. Change in clinical dementia rating sum of boxes (CDR-SB) of at least 1 was considered as faster CD. Signatures for predicting CD were constructed using Bayesian elasticnet, regularized random forests, and gradient boosting algorithms. Additional signatures were derived for assessing the added value of ApoE4 status, cognitive function assessments and brain volumetric measures from magnetic resonance imaging (MRI). Demographics (age, gender and body mass index) were considered in all evaluated signatures. Performance of these signatures was first assessed via 10 iterations of 10-fold stratified cross-validation within TC, and then tested in VC-1 and VC-2. Results from the best performing algorithm were reported. **Results:** Bayesian elastic net algorithm yielded signatures with optimal prediction performance. For predicting the 18-month CD, baseline plasma pTau181 achieved similar performance as baseline cognitive function , with area under the receiver operating characteristic curve (ROC-AUC) of 64.9% and 70.9%, respectively, in VC-1 ($p = 0.199$) and 65.3% and 66.7%, respectively, in VC-2 ($p = 0.395$). Adding ApoE4 count did not improve the prediction performance. When pTau181 was added to baseline cognitive function, ROC-AUC increased significantly from 70.9% to 74.7% in VC-1 ($p = 0.002$) and from 66.7% to 71.1% in VC-2 ($p < 0.001$). When pTau181 was added to baseline cognitive function and volumetric MRI features, ROC-AUC increased marginally from 77.2% to 79.2% in VC-1 ($p = 0.180$) and from 76.1% to 77.2% in VC-2 ($p = 0.227$). For predicting 36-month clinical progression from A+ MCI to mild AD in VC-2 (ADNI), adding baseline plasma pTau181 to baseline cognitive function significantly improved the prediction performance, with ROC-AUC increasing from 72.3% to 79.1% ($p < 0.0001$), and similarly when added to both the baseline cognitive function and volumetric MRI features, the ROC-AUC improved from 84.7% to 87.5% ($p = 0.04$). **Conclusions:** These results demonstrate the potential of baseline plasma pTau181 as a screening marker for idenfying A+ MCI subjects with faster cognitive decline over a typical 18-month duration of a clinical trial, with the performance improving significantly when combined with baseline cognitive function. Plasma pTau181 also improves the prediction of progression of MCI subjects to AD when combined with baseline cognitive function and/or volumetric MRI features.

LP67- ASSOCIATION OF CIRCULATING BRAIN-ENRICHED MICRORNAS WITH DEMOGRAPHIC AND CLINICAL FACTORS IN A4 SCREENING PLASMA SAMPLES FROM COGNITIVELY NORMAL INDIVIDUALS.

M. Keifer[1], K. Sheinerman[2], V. Tsivinsky[3], B. Martine[2], R. Rissman[4], S. Umansky[2] *(1. DiamiR Biosciences - San Francisco (United States), 2. DiamiR Biosciences - Monmouth Junction (United States), 3. DiamiR Biosciences - Boston (United States), 4. University of California San Diego School of Medicine - San Diego (United States))*

Background: Reliable and minimally invasive diagnostic tools are needed to better characterize patients with early stages of cognitive impairment. DiamiR's approach combines targeted, quantitative analysis of circulating brain-enriched and inflammation-associated microRNAs (miRNAs) with an algorithm classifier. miRNAs are small non-coding regulatory RNA molecules that modulate gene expression and whose levels change in disease. Certain miRNAs are enriched in specific organs and tissues, including different brain regions. Previously we reported differentiation between cognitively normal controls and mild cognitive impairment (MCI)/Alzheimer's disease (AD) study participants with a panel of 24 brain-enriched and inflammation-associated miRNAs detectable in plasma. Based on these 24 miRNAs the company is developing a molecular diagnostic assay, CogniMIR, for use in clinical trials and broader clinical practice. **Objectives:** The main objective of the present study was to evaluate correlations and associations between the 24 miRNAs, enriched in specific brain regions, present in synapses and detectable in blood plasma, and demographic and clinical factors known to be associated with AD, such as age, sex, amyloid status, APOE genotype, p-tau and neurofilament light (NfL), in 299 plasma samples collected during screening for the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) prevention study. **Methods:** The 299 plasma samples were collected from cognitively normal study participants during the screen3 of the A4 study. Specifically, blood was collected into purple-capped K2EDTA tubes (BD part#3666643) and placed on ice. Samples were centrifuged for 15 min at 2000xg using refrigerated centrifuge (4˚C). Plasma supernatant was aliquoted (0.5-ml aliquots) into Sarstedt tubes (cat# 72.730.217) and frozen at -80˚C. Samples with signs of hemolysis were excluded. Plasma levels of 24 pre-specified miRNAs were measured by individual quantitative RT-PCR. RNA was extracted from freshly thawed 0.5 ml aliquot of plasma using a TRIzol treatment and silica (Ambion Glass Fiber Microcolumn). Single target qRT-PCR was performed using the TaqMan® Reverse Transcription Kit and miRNA-specific stem-loop primers (Thermo Fisher Scientific). The RT step was performed in triplicate, and 2-μl plasma equivalents were present in a final PCR. The analysis was conducted with the use of the algorithms and software developed at DiamiR. Our biomarker is a ratio between two miRNAs; this "pair" approach reduces variability and enhances specificity and sensitivity of the biomarker, which is especially important when detecting gradual changes caused by a slowly developing pathology. Effective miRNA pairs are combined into classifiers. Two thresholds of determining amyloid positivity status based on PET SUVR measures were used: 1.15 as an original inclusion criteria in the A4 study, and 1.33, as more recently proposed in the literature. Plasma p-tau181 and NfL levels were measured at Quanterix with the Simoa system. **Results:** The analysis showed statistically significant correlations of specific miRNA biomarker pairs with markers of AD, including in amyloid-positive and APOE4-carrier high-risk, clinically relevant group. In accordance with our earlier data and literature data, the correlations are significantly improved by sex-stratification of study participants. miRNA pairs and SUVR correlation plots in amyloid positive/negative, APOE4 carriers/non-carriers, and male/female subgroups demonstrate strong correlations with $r = 0.33$ to 0.59; $p = 0.034$ to < 0.001. In amyloid positive/negative subgroup, APOE4 carriers are effectively separated from APOE4 non-carriers by select miRNA classifiers. Separation of APOE4 carriers from non-carriers is improved in subgroups stratified by sex. The best separation is observed within sex-stratified amyloid positive subgroup with AUC = 0.88 for males and AUC = 0.86 for females. Correlations between other measured parameters, including p-tau181 and NfL, with each other will be presented. **Conclusion:** The results generated in this study indicate that levels of cell-free miRNA biomarker candidates have a strong potential to be used in combination with other AD markers and risk factors to better characterize preclinical AD patients. A confirmatory analysis with additional well-characterized samples is underway. **Acknowledgment/Support:** We thank the A4 Study Team for providing the plasma samples and associated data for this project. This project

was supported by the Alzheimer's Drug Discovery Foundation (ADDF) Diagnostics Accelerator.

LP68- AGE DEPENDENCY OF PLASMA B-AMYLOID MEASURED BY FULLY AUTOMATED AND HIGHLY SPECIFIC IMMUNOASSAYS IN A JAPANESE COHORT STUDY (SESSA). K. Ishiki[1], M. Moniruzzaman[2], Y. Yano[2], K. Kondo[2], A. Kadota[2], M. Miura[1], S. Iwanaga[1], M. Nishimura[3], H. Ueshima[2], K. Miura[2] *(1. Central Research Laboratories, Sysmex Corporation - Kobe (Japan), 2. NCD Epidemiology Research Center (NERC), Shiga University of Medical Science - Otsu (Japan), 3. Molecular Neuroscience Research Center, Shiga University of Medical Science - Otsu (Japan))*

Background: In recent years, blood-based plasma β-amyloid (Aβ) has been increasingly studied as a potential biomarker of Alzheimer's disease (AD) because it is less invasive, more cost-effective, and easily accessible. Mounting evidence shows that the ratio of plasma Aβ1-42 to Aβ1-40 (Aβ42/Aβ40) is highly concordant with amyloid PET status, suggesting that it may reflect the brain Aβ pathology. Besides amyloid pathology in the brain, other risk factors for AD development are known, most notably age. Considering the use of plasma Aβ for the enrollment of subjects for clinical trials or for diagnostic adjunct purposes, it is important to understand the association between age and plasma Aβ. Because many disease-modifying therapies currently under development target the early stages before the onset of AD, it is necessary to understand the age dependency of plasma Aβ in older adults with normal cognitive function. However, several studies have reported conflicting results regarding the age dependence of plasma Aβ levels. Aβ is known to be unstable in the blood, and various factors at the time of blood collection are known to influence levels of blood Aβ. Such factors may influence the contralateral results on age dependency so far. Currently, the technique of canceling the effect by taking the ratio as Aβ42/Aβ40 is often used. On the other hand, when trying to understand the age-dependency of Aβ40 and Aβ42 alone, the handling of samples during blood collection requires rigor. **Objectives:** In this study, we aimed to examine the age-dependency of plasma Aβ40 and Aβ42 in a general Japanese male population using samples collected under a uniform protocol. **Methods:** The Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) is an ongoing epidemiological study in a general population randomly selected from Kusatsu City (Japan) residents at baseline (2006–2008). The second survey was performed between 2010 and 2014 and a total of 853 men aged 46–83 participated in medical examination. After an overnight fast of at least 12 hours, we collected blood samples by venipuncture and stored them at -80 degrees Celsius until measurement. For sample collection, blood collected in a collection tube containing EDTA was mixed by gently inverting several times, then stored on ice until centrifugation. All centrifuges were performed at 4 degrees Celsius, 3000 rpm, for 15 minutes. The time from blood collection to centrifugation was within 90 minutes. After centrifugation, plasma was rapidly stored in a freezer in 500 mL aliquots. Plasma Aβ40 and Aβ42 were measured using a fully automated immunoassay platform (HISCLTM series) in 2021. Both Aβ40 and Aβ42 were measured twice, and the average was used for analysis. We evaluated the age-dependency of Aβ40 and Aβ42 based on the measurement results of 822 participants, excluding 31 participants for whom measurements could not be performed. For this purpose, we divided participants into 5 age groups at 10 years intervals and examined the age dependency of Aβ40, Aβ42, and Aβ42/Aβ40 ratio by the Kruskal-Wallis test. **Results:** The mean (SD) age of the participants was 69.3±7.7 years. The mean (SD) values (in pg/mL) were 181.87±33.51, 20.47±4.28, and 0.113±0.015 for Aβ40, Aβ42, and Aβ42/Aβ40 ratio, respectively. There were significant differences in both Aβ40 and Aβ42 ($p < 0.001$) across the age groups, but not for Aβ42/Aβ40 ratio ($p = 0.307$). The change per year of age was 0.88 for Aβ40 ($p<0.001$) and 0.05 for Aβ42 ($p=0.005$), showing a significant increase by age. On the other hand, the change per year of age was -0.0002 for Aβ42/Aβ40 ratio ($p<0.001$), showing a significant decrease by age. **Conclusion:** Our results showed that plasma Aβ40 and Aβ42 increase in an age-dependent manner, while the Aβ42/Aβ40 ratio decreases in an age-dependent manner. This age-related change in plasma Aβ levels may be due to changes in production or functional changes in the blood-brain barrier. However, compared with the age-dependent changes in Aβ40 and Aβ42, the age-dependency of Aβ42/Aβ40 ratio was more gradual, with no significant differences found in the analysis divided into 5 age groups. It may suggest that age dependence may be reduced by using the Aβ42/Aβ40 ratio. Although the present results were based only on men and limited to the Japanese population, they suggest that using appropriate sample handling protocols and measurement methods may be able to assess the relationship between plasma Aβ and other factors. To further our understanding of plasma Aβ, an assessment of the association with cognitive function and other AD risk factors, as well as in women and other races, is warranted in the future.

LP69- A FULLY-AUTOMATED AND SCALABLE PLASMA PHOSPHO-TAU181 ASSAY FOR ALZHEIMER'S DISEASE. E.N. Wilson[1], C.B. Young[1], M. Vandijck[2], J.P. Quinn[3], C.H. Van Dyck[4], A. Nairn[4], S. Sha[1], V.W. Henderson[1], F.M. Longo[1], M.D. Greicius[1], A.D. Wagner[1], T. Wyss-Coray[1], K.L. Poston[1], E.C. Mormino[1], K.I. Andreasson[1] *(1. Stanford University - Stanford (United States), 2. Fujirebio NV - Ghent (Belgium), 3. Oregon Health & Science University - Portland (United States), 4. Yale University - New Haven (United States))*

Background: The advent of disease modifying therapies for Alzheimer's disease has ushered in a new era of AD treatment -- highlighting the need for biomarkers for early detection and treatment monitoring. Such biomarkers should be accessible and scalable for widespread implementation. Plasma P-tau181 is an accessible blood-based biomarker sensitive to AD during the preclinical phase. However, current commercially-available and prototype plasma p-tau181 assays have limited accessibility, throughput, and/or scalability that impede widespread implementation. **Objectives:** Our objective was to assess the diagnostic and prognostic performance of a high-throughput and fully-automated Lumipulse plasma p-tau181 assay for the detection of AD as determined clinically or with biomarkers. **Methods:** Plasma samples were obtained from the Stanford University Alzheimer's Disease Research Center (ADRC) and the Stanford Aging and Memory Study (SAMS). The study cohort included clinically unimpaired individuals (CU, n = 498) and patients with mild cognitive impairment (MCI, n = 110) or AD dementia (n = 78) were. In addition to its ability to predict longitudinal cognitive and functional change, we evaluated the discriminative accuracy of the Lumipulse plasma p-tau181 assay (modified from CSF version) for clinical AD diagnosis, its association with amyloid and tau concentrations in CSF. **Results:** The fully-automated Lumipulse Plasma p-tau181 assay showed robust clinical performance in differentiating AD dementia from CU participants (AUC 0.959). Plasma

p-tau181 levels were associated with CSF measures of amyloid and tau. Plasma p-tau181 significantly increased over time in CU and AD diagnostic groups. Baseline plasma p-tau181 predicted change in MoCA and change in CDR Sum of Boxes over follow-up of up to a 5-years. In addition, our studies revealed genetic, demographic and clinical variables correlating with plasma p-tau181 that may confound its interpretation in the context of AD. **Conclusion:** These results demonstrate that the Lumipulse plasma p-tau181 assay is a scalable, fully-automated and commercially available plasma p-tau test for AD – features supporting its implementation in early disease detection, therapeutic monitoring, and in clinical trials.

LP70- PLASMA P-TAU181 IN THE MULTIDOMAIN ALZHEIMER PREVENTION TRIAL (MAPT). N. Coley[1,2], H. Zetterberg[3], S. Guyonnet[1,2], P. De Souto Barreto[1,2], K. Blennow[3], N. Ashton[3], S. Andrieu[1,2], B. Vellas[1,2] *(1. INSERM, University of Toulouse - Toulouse (France), 2. Toulouse University Hospital - Toulouse (France), 3. University of Gothenburg - Gothenburg (Sweden))*

Background: Multidomain interventions may have a beneficial effect on cognitive function, especially in at risk populations, but their effects on Alzheimer's disease (AD) biomarker trajectories have not yet been well studied. Previously, expensive and/or burdensome procedures were required to measure AD biomarkers but reliable blood-based assays have recently been developed. Like CSF p-tau, and in contrast to PET tau biomarkers, plasma p-tau is known to be elevated in early stages of AD, and fluid tau biomarkers have been suggested to be preferential for monitoring intervention effects in clinical trials. Although CSF p-tau may be a closer indicator of brain processes than peripheral measures, plasma biomarkers offer huge advantages in the clinical trial setting in terms of cost and burden, thus enabling their measurement in larger numbers of participants. To our knowledge, plasma p-tau181 has not yet been evaluated in a multidomain prevention trial setting. **Objectives:** Our objectives were to (1) assess the effects of a multidomain intervention, omega-3 supplementation, and both interventions combined, compared to placebo, on 3-year change in plasma p-tau 181; and (2) assess intervention effects on 3-year change in a composite cognitive score (the MAPT primary outcome) in participants with abnormal baseline p-tau181. **Methods:** MAPT was a 3-year randomized controlled prevention trial involving 1680 community-dwelling individuals aged 70 and older with memory complaints, a limitation in one instrumental activity of daily living (IADL) and/or slow walking speed (≤ 0.8 m/s). Participants also had to be free of dementia at baseline, with a Mini Mental State Examination (MMSE) score ≥24, and have no difficulties in basic ADL. Participants were randomized into 4 groups, receiving a multidomain lifestyle intervention (group-based cognitive training, advice and education (including personalized action plans) on physical activity and nutrition, and an annual preventive consultation), omega-3 fatty acid supplementation, both interventions combined, or placebo for 3-years. The trial's primary outcome measure was a composite cognitive score calculated as the average of z-scores for the following tests: MMSE orientation items, Free and Cued Selective Reminding Test (sum of free and total recall scores), category fluency and Digit Symbol Substitution Test. For the present analysis, we included a subsample of participants (n=527) with plasma p-tau 181 measured in stored blood samples taken at baseline and 3-years. **Results:** In the total sample, median (IQR) p-tau181 concentrations were similar at baseline and 3 years. Baseline p-tau181 was significantly higher in older participants (median [IQR] p-tau181 (pg/ml): 11.6 [10.4-21.9] in participants aged 85 and older; 10.1 [7.9-13.0] for age 80-84y; 9.0 [7.0-12.5] for age 75-79y; 8.3 [6.2-11.2] for age 70-74y; p<0.001), men (10.0 [7.5-12.6] versus 8.4 [6.5-11.5]; p=0.001), APOE4 carriers (9.8 [7.5-12.5] versus 8.4 [6.6-11.8]; p=0.039), those with renal dysfunction (10.1 [7.4-12.8] versus 8.6 [6.6-11.6]; p=0.039), and those with a positive PET amyloid scan (11.0 [7.7-13.0] versus 7.9 [6.0-10.9]; p<0.001), but did not differ by baseline CDR score or BMI. Amongst the 505 participants with p-tau181 data at both baseline and 3-years, there were no significant differences in baseline characteristics between randomization groups. Preliminary analyses suggested no significant change in p-tau181 between baseline and 3-year follow-up in any of the groups, and no significant between-group difference in change. Between-group differences in cognitive change by baseline p-tau status will be presented. **Conclusion:** In our prevention trial setting, expected associations were found between plasma measures of p-tau 181 and socio-demographic, clinical, and biological characteristics. Preliminary analyses suggested no change in p-tau181 over time, and no between-group differences in change. Full results will be presented and implications for future trials will be discussed.

LP71- THE EFFECT OF NEPRILYSIN INHIBITION ON ALZHEIMER'S DISEASE PLASMA BIOMARKERS: RESULTS FROM A RANDOMIZED CONTROLLED TRIAL EVALUATING SACUBITRIL/VALSARTAN IN COGNITIVELY UNIMPAIRED INDIVIDUALS AT RISK FOR HEART FAILURE. W.S. Brum[1], K.F. Docherty[2], N.J. Ashton[1], S. Janelidze[3], P.S. Jhund[2], O. Hansson[3], H. Zetterberg[1], J.J.V. Mcmurray[4], K. Blennow[1] *(1. Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg - Mölndal (Sweden), 2. BHF Glasgow Cardiovascular Research Centre, School of Cardiovascular and Metabolic Health, University of Glasgow - Glasgow (United Kingdom), 3. Clinical Memory Research Unit, Faculty of Medicine, Lund University - Lund (Sweden), 4. New British Heart Foundation Cardiovascular Research Centre, University of Glasgow - Glasgow (United Kingdom))*

Background: In the amyloid cascade hypothesis, amyloid-β (Aβ) accumulation is a critical early event in the development of Alzheimer's disease (AD), and targeting brain Aβ has long been a focus of AD clinical trials. In 2015, sacubitril/valsartan was approved by the FDA for the treatment of heart failure (HF) with reduced ejection fraction. Sacubitril acts by inhibiting neprilysin, an enzyme responsible for degrading various vasoactive peptides including the natriuretic peptides. However, neprilysin is also involved in degrading Aβ species. Therefore, this approval raised the theoretical concern that sacubitril/valsartan treatment could potentially increase the risk of developing AD secondary to Aβ accumulation. To address this concern, the FDA ordered a trial evaluating the effect of sacubitril/valsartan on cognition and Aβ positron emission tomography (PET) in HF patients. The PERSPECTIVE trial (NCT02884206) reported no differences in cognitive function or cerebral Aβ deposition over 3 years of sacubitril/valsartan treatment compared with valsartan alone. While this robustly supports the neurocognitive safety of long-term neprilysin inhibition, its effect on high-performing AD blood biomarkers has not been reported in PERSPECTIVE. Imaging and fluid biomarkers offer complementary information on AD pathophysiology, with studies indicating that

plasma biomarkers of brain amyloidosis (Aβ42/Aβ40) and downstream tau pathology (p-tau) become abnormal several years earlier than Aβ-PET, and non-AD-specific biomarkers of neurodegeneration (neurofilament light; NfL) and glial activation (glial fibrillary acidic protein; GFAP) also provide relevant brain health information. Importantly, patients with HF often present some degree of cognitive impairment and have an increased risk of developing dementia. Thus, evaluating the effect of sacubitril/valsartan on AD blood biomarkers is needed, both for complementary neurocognitive safety information and to evaluate whether this treatment could be a potential confounding factor when interpreting AD blood tests. **Objectives:** To evaluate the effect of one-year treatment with sacubitril/valsartan compared with valsartan alone (i.e., the addition of neprilysin inhibition) on AD blood biomarkers in individuals with asymptomatic left ventricular systolic dysfunction late after myocardial infarction. **Methods:** Plasma-EDTA samples were collected at baseline, 6 months, and 12 months in a prospective, multicenter, double-blind, placebo-controlled, randomized clinical trial evaluating the effect of sacubitril/valsartan (target dose 97/103mg twice daily) compared with valsartan (target dose 160mg twice daily) on ventricular remodeling in cognitively unimpaired individuals with asymptomatic left ventricular systolic dysfunction at least 3 months following myocardial infarction (NCT03552575). With the Simoa technology, we measured Aβ42, Aβ40, Aβ42/Aβ40, GFAP, and NfL (Quanterix Neurology-4-Plex-E kit), and p-tau231 and p-tau181 with validated in-house assays (University of Gothenburg). Measurements for p-tau217 are ongoing (Lilly; Meso-Scale Discovery). Biomarker outcomes at 12 months were analyzed using linear regression models adjusting for randomized treatment and baseline biomarker values. **Results:** A total of 93 patients were randomized and 92 completed the trial (sacubitril/valsartan: n=46; valsartan: n=46; mean age, 60.7±10.4 years). Sacubitril/valsartan, compared with valsartan, increased levels of Aβ42, giving an adjusted between-group difference in change from baseline of +2.3 pg/mL (95% CI 1.8 to 2.7; p<0.001), and for Aβ40, +108.4 pg/mL (95% CI 96.4 to 120.3; p<0.001), and reduced the Aβ42/Aβ40 ratio in -0.020 (95% CI -0.022 to -0.018; p<0.001). At 12 months, these corresponded to mean fold-changes, compared to valsartan, of +31% for Aβ42, +100% for Aβ40, and -35% for Aβ42/Aβ40. No significant group-differences in change from baseline were observed for p-tau231 (p=0.94), p-tau181 (p=0.48), GFAP (p=0.47), or NfL (p=0.56). **Conclusion:** Plasma Aβ biomarkers were substantially altered by sacubitril-valsartan treatment, with no changes observed in biomarkers of tau pathology, glial activation, or neurodegeneration. We interpret the changes in Aβ as a non-pathological pharmacodynamic effect, caused by reduced peripheral neprilysin activity. While the Aβ42/Aβ40 ratio is low in AD patients mostly due to pathological reductions in Aβ42, the reduction in the ratio observed with sacubitril/valsartan reflected increases in both Aβ42 and Aβ40, with a greater increase in Aβ40 driving this reduction. Given the reassuring findings of the PERSPECTIVE trial and data from several studies indicating that peripherally injected Aβ42 doesn't reach the central nervous system, it is unlikely that higher circulating Aβ levels have any deleterious effect on patients receiving sacubitril/valsartan. The absence of increases in other biomarkers, especially p-tau231 and p-tau181, further supports the neurocognitive safety of sacubitril-valsartan, since p-tau biomarkers are highly associated with Aβ pathology and anti-Aβ drug trials have reported reductions in blood p-tau levels over the same duration of our study. Importantly, our results suggest that plasma Aβ blood tests for brain amyloid risk prediction will be confounded in patients receiving sacubitril/valsartan, potentially leading to false-positive results. Furthermore, these results add to the literature that changes in plasma Aβ levels with drug treatments (e.g., BACE1 inhibitors) may not translate to a corresponding effect on brain Aβ aggregation or cognitive changes. To our knowledge, this is the first reported drug-interaction contraindication for an AD blood test, which, alongside well-described robustness issues for plasma Aβ, further supports p-tau as the most reliable AD blood biomarker.

LP72- SIMULTANEOUS MASS SPECTROMETRIC QUANTIFICATION OF MULTIPLE TAU SPECIES IN BLOOD SHOWS DIFFERENTIAL ASSOCIATION WITH AMYLOID AND TAU PATHOLOGY. L. Montoliu-Gaya[1], A.L. Benedet[1], A. Vrillon[2], C. Tissot[3], W.S. Brum[1], N.J. Ashton[1], J. Lantero-Rodriguez[1], G. Brinkmalm[1], J. Nilsson[1], H. Zetterberg[1], J. Gobom[1], C. Paquet[2], P. Rosa-Neto[3], K. Blennow[1] *(1. Department of Psychiatry and Neurochemistry, Institute of Neuroscience & Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden. - Gothenburg (Sweden), 2. Cognitive Neurology Center, GHU Nord APHP Hospital Lariboisière Fernand Widal, Université de Paris, Paris, France. - Paris (France), 3. Translational Neuroimaging Laboratory, McGill Centre for Studies in Aging, McGill University, Montreal, Quebec, Canada. - Montréal (Canada))*

Background: With the emergence of several immunotherapies which efficiently remove Aβ aggregates from the brain, and a very active drug development pipeline, the need for blood biomarkers to facilitate participant recruitment and monitor disease progression in Alzheimer´s disease (AD) clinical trials is even more pressing. While a single biomarker (e.g., p-tau231 or p-tau217) may work well to identify Aβ pathology for trial recruitment or AD in clinical practice, they provide little information on disease stage. Further, biomarkers are needed to better reflect key pathophysiological processes related to the drug target, or mechanisms putatively downstream of the drug target (e.g., tau pathology). Therefore, a method which systematically measures multiple p-tau and non-phospho tau species in a single-shot analysis, not dependant on antibody affinity or immunoassay platform, will give greater insight into stage-specific changes which are critical to monitor pathology changes in drug response and disease development in clinical management. **Objectives:** To simultaneously quantify the plasma concentration of six different phosphorylated (p-tau 181, 199, 202, 205, 217 and 231), and two non-phosphorylated, tau peptides using a targeted Mass Spectrometric (MS) method to determine disease stage-specific changes and the link of each tau specie with amyloid and tau pathologies. **Methods:** Tau enrichment prior to MS analysis was performed by immunoprecipitation, using a combination of several non-phospho-tau antibodies, followed by tryptic digestion. A parallel reaction monitoring method with Orbitrap MS was used to measure the levels of targeted peptides. We analysed a total of 224 samples from two centres, the BioCogBank Paris Lariboisière cohort (France) and the TRIAD cohort (Canada). In TRIAD, we tested the association of the biomarkers with Aβ and tau pathologies, indexed by [18F]AZD469 and [18F]MK-6240, respectively. **Results:** All p-tau, except p-tau202, and non-phospho peptides showed significantly higher levels in Aβ and tau positive (A+T+) individuals compared to A-T- participants (p<0.001), with the highest fold-changes observed for p-tau205 (4.4), p-tau217 (4.3) and p-tau231 (2.5). In addition, p-tau181, p-tau205, p-tau217

and p-tau231 showed significant changes from A+T- to A+T+ (p<0.001). Plasma p-tau217 and p-tau205 were site-specific phosphorylations that showed higher correlations with Aβ PET global SUVR (p-tau217, r=0.81, p<0.001; p-tau205, r=0.71, p<0.001), yet p-tau231 was the epitope with significantly higher levels with lower thresholds of amyloid PET signal. Voxel-based analyses were conducted to study regional brain correlations with each plasma tau peptide. No association between Aβ-PET and p-tau199, p-tau202, tau212-221 or tau195-209 was observed. P-tau205 and p-tau231 presented Aβ-PET uptake in the medial frontal and cingulate cortices, the precuneus, as well as the temporal lobes. P-tau217 showed the strongest associations with [18F]AZD4694 throughout the whole cortex (p<0.001). Plasma p-tau217, and to a lesser extent p-tau231 and p-tau205, were the site-specific phosphorylations that showed higher correlations with tau PET global SUVR (p-tau217, r=0.7, p<0.001; p-tau231, r=0.53, p<0.001; p-tau205, r=0.53, p<0.001). Correlations with tau PET uptake depending on the Braak staging, showed that p-tau205 and p-tau217 associated more with Braak stages III&IV (r=0.8, p<0.001; and r=0.81, p<0.001), while p-tau231 had higher correlations with Braak I&II (r=0.59, p<0.001) and decreased with increasing Braak. Regarding tau PET uptake, non-significant associations were observed with p-tau199, p-tau202 or tau212-221. P-tau181 and tau195-209 presented [18F]MK6240 retention in the precuneus, and temporal lobes and p-tau231, in the precuneus, cingulate cortex as well as the temporal lobes (p<0.001). P-tau217 and p-tau205 presented the strongest correlations with [18F]MK6240, throughout the whole cortex (p<0.001). Finally, we performed regression models, using either only amyloid PET signal (A), only tau PET signal (T), both amyloid and tau density (A+T), or both A and T including their interaction term (AxT). Plasma p-tau205, p-tau217 and p-tau231 were the phosphorylations better explained by the models. P-tau231 was similarly mediated by A alone (r=0.34, AIC=-155) and the combination A+T (r=0.36, AIC=-154). P-tau217 presented a higher correlation in the association A+T (r=0.73, AIC=-205), superior to A (r=0.67, AIC=-199) and T alone (r=0.69, AIC=-204), although not significant in the latter. Finally, p-tau205 was equally explained by T (r=0.64, AIC=-311) and the combination A+T (r=0.64, AIC=-310), and showed less association to amyloid plaque density (r=0.5, AIC=-302). **Conclusion:** We have developed an immunoprecipitation-mass spectrometry method to simultaneously quantify six different phosphorylated (p-tau 181, 199, 202, 205, 217 and 231), and two non-phosphorylated tau species in plasma. Our results indicate that plasma p-tau217, p-tau231 and p-tau205 are the site-specific blood phosphorylations that better reflect amyloid and tau pathologies, although with different emergence along the AD continuum. P-tau231 was more associated with Aβ pathology and might be the first to emerge, followed by p-tau217 influenced by both amyloid and tau, and finally p-tau205 increases might be weighted towards tau accumulation. A comprehensive understanding of the pathological information that each blood p-tau reflects is paramount to decide which blood biomarker to use in each stage of the disease and to guarantee a correct read-out in clinical trials for anti-Aβ and anti-tau therapies. *The presenter author declares no conflict of interest.

LP73- CEREBROSPINAL FLUID PROTEOMICS REVEAL 5 MOLECULAR SUBTYPES IN ALZHEIMER'S DISEASE: IMPLICATIONS FOR PERSONALISED TREATMENT.

B. Tijms[1], W. Van Der Flier[1], C. Teunissen[1], J. Vijverberg[1], Y. Pijnenburg[1], E. Birkeland[2], F. Berven[2], P.J. Visser[1]
(1. Amsterdam UMC, location VUmc - Amsterdam (Netherlands), 2. University of Bergen - Bergen (Norway))

Background: Alzheimer's disease is heterogenous in underlying pathophysiology. This may have profound implications for therapy as specific subtypes may need different treatments. We previously identified three AD subtypes based on CSF proteomics (Tijms Brain 2020). One subtype was characterized by increased amyloid metabolism and aberrant neuronal plasticity; one subtype showed evidence of innate immune activation; and one subtype had blood-brain barrier dysfunction. Aim of the present study was to discover other AD subtypes in a large independent data set of 609 individuals in which we measured 1059 proteins in CSF. **Objectives:** 1. To study whether the 3 subtypes in previous work could be replicated in an independent dataset; 2. To find novel subtypes by increasing sample size and number of proteins measured compared to the previous studies. **Method:** We selected 419 AD individuals with at least abnormal CSF abeta42 and 187 controls (normal cognition and normal AD biomarkers) from Alzheimer center Amsterdam studies. With 16-plex TMT-MS we detected 3987 proteins in CSF, of which we clustered 1059 proteins with complete observations that differed between AD and controls (all p<.05). Subtypes were compared on 2906 proteins with at least 10 observations per subgroups. Potential upstream transcription factors associated with the molecular subtypes were identified with ENRICHR. **Results:** We found 5 subtypes with distinct protein profiles. Three subtypes were highly concordant with our previously observed subtypes (subtype 1a, 1b and 2b). Two subtypes were new: One showed proteasome dysfunction (1c) and the other showed impaired choroid plexus functioning (2a). Subtype 1a individuals (n=137, 32%) had increased levels of 877 proteins that were associated with neuroplasticity and increased amyloid processing (as indicated by high abeta40 and BACE1 levels). REST and SUZ12 were potential upstream drivers. Subtype 1b individuals (n=124, 30%) had increased levels of 988 proteins that were associated with neuronal plasticity and inflammation with SOX2 as potential upstream driver. Subtype 1c individuals (n=24, 6%), had increased levels of 517 proteins that were associated with neuroplasticity, retromer complex and proteasome dysfunction. These proteins were associated with TAF1 and MYC as potential upstream drivers. Subtype 2a individuals (n=78, 19%,) showed increased levels of 469 proteins, of which 45% were expressed by the choroid plexus (e.g., TTR). These proteins converged on NFE2L2. Subtype 2b individuals (n=56, 13%) showed increased levels of 649 proteins that were in part associated with blood-brain barrier leakage. These proteins converged on ERG1 and ESR1 as potential upstream drivers. **Conclusion:** In this new dataset we replicated three AD subtypes, and detected two novel subtypes. Subtypes differed in the processes involved, including neuronal plasticity, amyloid processing, immune system activation, proteasome function, choroid plexus function and blood-brain barrier function. All these processes have previously been implicated in AD pathophysiology and our findings suggest that specifc subgroups of AD patients show dysregulation of distinct processes. This indicates that treatment may need tailoring according to AD subtype, which can be detected in the CSF. For example, BACE inhibitors may be useful in subtype 1a only.

Intervention with antibodies may be in particular effective in subtype 2b (blood-brain barrier dysfunction) as the permeability of the blood-brain barrier in this subtype may allow increased Igg levels in the brain. Future studies are needed using data or samples from trials to test whether AD subtypes are associated with treatment response.

LP74- EFFECTS OF PRE-ANALYTICAL PARAMETERS ON PLASMA B-AMYLOID LEVEL. K. Ishiki[1], K. Yamashita[1], S. Watanabe[1], M. Miura[1], S. Iwanaga[1], T. Sato[1] *(1. Central Research Laboratories, Sysmex Corporation - Kobe (Japan))*

Background: Blood-based biomarkers of Alzheimer's disease (AD) are expected to be promising tools for assisting diagnosis in combination with conventional biomarkers such as neuroimaging and cerebrospinal fluid (CSF) biomarkers. In particular, the ratio of plasma β-amyloid1-42 (Aβ42) to β-amyloid1-40 (Aβ40) is known to be associated with brain Aβ pathology. Therefore, it could assist in the selection of the candidates for clinical trials of disease-modifying therapies targeting Aβ. We have developed assays that can specifically measure Aβ40 and Aβ42 in plasma using a fully automated immunoassay platform, the HISCLTM series. The assay showed high performance for predicting brain Aβ pathology defined by amyloid positron emission tomography (PET). However, it is widely recognized that plasma Aβ peptides are unstable molecules, and thus the measured values are affected by pre-analytical parameter such as external factors, measurement equipment and sample handling. Especially, blood collection and storage conditions in sample handling affect the quality of plasma Aβ levels, leading to false selection. Therefore, clarification of the influence of pre-analytical parameters on plasma Aβ levels measured by our assay is required to obtain reliable data in clinical trials. **Objectives:** The purpose of this study was to clarify the effect of pre-analytical parameters on plasma Aβ levels measured by HISCL series. **Methods:** Whole blood samples were collected in K2EDTA tubes from healthy volunteers. After centrifugation, plasma Aβ40 and Aβ42 levels were immediately measured using the HISCL series and plasma Aβ42/Aβ40 was calculated. We compared the impacts of the 11 pre-analytical parameters such as duration between blood collection and centrifugation at room temperature (RT) or 4°C, the interval between plasma storage at RT or 4°C before measurement, the number of freeze/thaw (F/T) cycles, the conditions of thawing, the length of time that the plasma was thawed before measurement, the types of tubes and manufacturers for storing plasma, the tip type using plasma separation, and the number of tube transfers on plasma Aβ42/Aβ40. **Results:** Plasma Aβ42/Aβ40 levels remained unchanged after 2 hours at RT and 6 hours at 4°C after blood collection. After the plasma separation, it is unaltered even after 18 hours of storage at 4°C. Longer sample storage time and higher storage temperature after plasma separation tended to affect the reduction of the plasma Aβ42/Aβ40 ratio, but did not have an effect beyond our established criteria. The time for holding the thawed plasma at RT was also investigated, and no difference was detected until 4 hours. For the freezing samples, up to three F/T cycles did not significantly change the Aβ42/Aβ40 ratio compared to the reference value. Thawing at RT and 37°C were also used to assess the thawing state. The 37°C conditions were verified using a water bath, a dry block incubator, and an air incubator. Furthermore, neither of the thawing conditions affects the Aβ42/Aβ40 values. The Aβ42/Aβ40 values are unaffected by tube manufacturer, tip type, or tube transfer up to one time. **Conclusion:** In this study, we evaluated the influences of 11 pre-analytical parameters on plasma Aβ42/Aβ40 ratio measured by HISCL series. In our evaluation, the sample storage time and temperature after plasma separation were the most influential factors in plasma Aβ42/Aβ40 ratio. These results were consistent with the previous reports of pre-analytical handling using another assay platform. This study will contribute to the determination of pre-analytical handling for plasma Aβ measurement using HISCL. By establishing pre-analytical handling based on the findings of this study, the high amyloid PET predictive performance we have shown so far could be achieved in clinical trials.

LP75- EFFECT OF A 1-YEAR NUTRITIONAL BLEND SUPPLEMENTATION ON PLASMA P-TAU181 LEVELS AMONG COMMUNITY-DWELLING OLDER ADULTS: A SECONDARY ANALYSIS OF THE NOLAN STUDY. K. Giudici[1], S. Guyonnet[1,2], C. Cantet[1,2], P. De Souto Barreto[1,2], K. Blennow[3,4], H. Zetterberg[3,4], C. Boschat[5], J. Hudry[5], S. Andrieu[2,6], B. Vellas[1,2], J. Schmitt[5,7,8] *(1. Institute of Aging, Gerontopole of Toulouse, Toulouse University Hospital - Toulouse (France), 2. CERPOP UMR1295, University of Toulouse III, Inserm, UPS - Toulouse (France), 3. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg - Mölndal (Sweden), 4. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 5. Société des Produits Nestlé SA, Nestlé Research - Lausanne (Switzerland), 6. Department of Epidemiology and Public Health, Toulouse University Hospital - Toulouse (France), 7. Singapore Institute of Food and Biotechnology Innovation, Agency for Science, Technology and Research - Singapore (Singapore), 8. Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research - Singapore (Singapore))*

Background: Observational studies and some randomized controlled trials have suggested that nutritional supplementation could be a possible intervention pathway to prevent cognitive decline and Alzheimer's disease (AD). As measuring amyloid-β and tau markers in the brain and in cerebrospinal fluid (CSF) is complex, plasma versions of such biomarkers have emerged as more accessible alternatives with comparable capacity of predicting cognitive impairment. **Objectives:** This study aimed to evaluate the effect of a 1-year intervention with a nutritional blend on plasma p-tau181 levels (a marker of cerebral tau phosphorylation) of community-dwelling older adults. Effects were further assessed in exploratory analyses within sub-cohorts stratified according to apolipoprotein E (APOE) ε4 status. **Methods:** A total of 289 participants ≥70 years (56.4% female, mean 78.1 years, SD = 4.7) of the randomized, double-blind, multicenter, placebo-controlled Nolan trial had their plasma p-tau181 assessed using a Single molecule array assay, and daily took either a nutritional blend (composed of 50 mg of thiamin, 15 mg of riboflavin, 25 mg of niacin, 23 mg of pantothenic acid, 18 mg of pyridoxine, 0.15 mg of biotin, 0.4 mg of folic acid, 0.5 mg of cobalamin, 82.6 mg of vitamin E, 500 mg of vitamin C, 15 µg of vitamin D, 85 mg of choline, 80 µg of selenium, 3 g of citrulline, 700 mg of eicosapentaenoic acid – EPA and 770 mg of docosahexaenoic acid – DHA) or placebo for 1 year. The blend (or placebo) was characterized by two soft gel capsules (with 775 mg filling each) and by one powdered sachet of ≈ 15 g, to be mixed in 120 mL of cold water. Recruitment started in December 2016 and ended in January 2018. Follow-up ended in February 2019. Efficacy analyses were done on a modified intention-to-treat (mITT) basis (i.e., including all randomly assigned participants with plasma p-tau181 measured at baseline who completed at least

one post-baseline visit). Linear mixed effects regression (with a random subject intercept and, if significant, a random linear slope and a random center intercept) adjusted on baseline data were performed in the mITT population in order to determine the effect of intervention, compared to placebo, on plasma p-tau181 levels. **Results:** At baseline, plasma p-tau181 did not differ between treatment groups at baseline (intervention: 14.1 pg/mL, SD = 6.0 vs. control: 13.3 pg/mL, SD = 5.6, p = 0.262), and was higher among subjects ≥85 years, male, APOE ε4 carriers, with CDR score 0.5 and amyloid-positive. After 1-year, both groups presented a significant increase in plasma p-tau181 values, with no effect of intervention (between-group difference: 0.27 pg/mL, 95%CI: -0.95, 1.48; p = 0.665). The allele APOE ε4 was identified among 24.7% of the sample (n = 68), and did not differ between groups (intervention: 21.9% vs. control: 27.5%; p = 0.279). Separate analyses according to APOE ε4 status mostly provided similar findings to the observed among the total studied population, with no differences in plasma p-tau181 changes between groups (difference in between-group differences over time for APOE ε4 carrier vs. non-carrier: 2.28 pg/mL, 95%CI: -0.58, 5.13; p = 0.118). **Conclusions:** We have shown that a 1-year supplementation with a nutritional blend composed of several vitamins and minerals was not able to mitigate the increase in plasma p-tau181 levels among community-dwelling older adults. Considering the novelty of the hypothesis tested in the present study, additional RCT with longer follow-ups and including other p-tau biomarkers are needed, and may contribute to a better understanding if (and how) nutritional supplementation may be able to protect brain health and cognitive function through impacting tau accumulation and amyloidosis. Together with other advances in the field targeting lifestyle approaches, this would enable not only setting nutritional strategies for optimizing brain health and preventing or slowing the development of neurodegenerative diseases, but also to reduce the need of drugs and expensive treatments. **Conflict of interest** (presenting author): None.

LP76- A NOVEL ACCESSIBLE AND SCALABLE ASSAY FOR PTAU217 IN BLOOD. S. Portbury[1], I.V.E.R. Verberk[2], S.S.A. Bayoumy[2], W. Van Der Flier[2], J.E.R.O.E. Vandrabrant[3], C.T.E.U. Teunissen[2], E.R.I.K. Stoops[3], A. Jeromin[1] *(1. ALZpath - Carlsbad, Ca (United States), 2. Amsterdam UMC - Amsterdam (Netherlands), 3. ADX Neurosciences - Gent (Belgium))*

Background: Blood-based biomarkers that can accurately report Alzheimer's disease (AD) pathophysiology are urgently required to aid in the diagnostic process in primary and secondary clinical care. Blood-based biomarkers are non-invasive in nature, considered to be more cost-effective compared with current assessment methods, and they do not require specialized centers. As a result, blood-based biomarkers allow for large population screening and scalability in clinical care. Plasma measures of phosphorylated tau have recently demonstrated high diagnostic accuracy in differentiating AD from non-AD neurodegenerative disorders, in several clinical trials that used neuropathological post-mortem measurements to validate AD diagnosis. Of promise is pTau217, where tau is phosphorylated at Thr217. Accordingly, ALZpath has developed a pTau217 monoclonal antibody for use in ELISA assays. The Alzpath monoclonal antibody provides the advantage of being highly scalable through expression in mammalian cells and it shows excellent lot to lot consistency. **Objectives:** ALZpath completed extensive fit for purpose assay development to establish an accessible, robust and scalable plasma-based ultra-sensitive assay, utilizing a proprietary monoclonal pTau217 antibody. **Methods:** In partnership with two independent contract research organizations (CROs), ALZpath has developed and evaluated reagents for pTau217 using various detection antibodies and calibrators across different immunoassay platforms. An ultra-sensitive blood-based ELISA assay, using a peptide calibrator, has been developed on the semi-automated single-molecule array Simoa® platform. **Results:** The identified clone 30H10 is highly specific to phosphorylation at residue 217 and does not bind to either phosphorylated residues 181, 231 or non-phosphorylated tau. ALZpath has successfully completed a fit for purpose validation of pTau217 assay in EDTA plasma. The Alzpath ptau217 Simoa® assay shows good precision (inter-day CVs of less than 12 %) and good sensitivity with a functional lower limit of quantification of 0.260 pg/ml. Parallelism/dilutional linearity is within the 80-120 % range. In an initial evaluation of the ALZpath pTau217 assay performance in plasma (n = 80) and CSF (n = 42), across healthy volunteer and AD participants the protein was measured in 90% of all samples with an intra-assay %CV below 10%. The ALZpath pTau217 assay demonstrated a functional (in matrix) lower limit of quantitation (LLOQ) of 0.26 pg/mL and strong linearity within 80-120% of acceptance criteria. In the subset of 40 control and 40 AD participants (70% female, 30% male), the ALZpath pTau217 assay had a 91% likelihood of accurately identifying AD (AUC = 0.91 (0.85-0.98)) with a 4.2-fold change in AD when compared with controls. The capability of the ALZPath pTau217 assay to differentiate AD exceeded the AUCs of the commercial Simoa® pTau181 based assay (abstract submitted, Bayoumy et al). **Conclusion:** The generated data demonstrate that the ALZpath plasma pTau217 assay is a potentially scalable reagent with high specificity for pTau217. ALZpath has established a fit-for-purpose validated Simoa® assay for pTau217 in blood with robust precision, and diagnostic accuracy in AD, compared to controls based on clinical diagnosis. ALZpath is partnering with a global network of collaborators to establish the clinical performance of the ALZpath pTau217 assay to screen and diagnose AD in both memory and primary care clinics. Cohorts selected have enrolled deeply phenotyped participants across various stages of AD and integrate multimodal biomarker assessments and evaluation of the importance of comorbidities. Based upon these results we intend to further validate the ALZpath Dx as a laboratory-developed test (LDT) for clinical use, and establish clinical evidence in different diagnostically relevant diverse populations with co-morbidities. **Conflicts of interest:** Andreas Jeromin PhD is an employee of Alzpath and an adviser to Quanterix. Stuart Portbury is an employee of ALZpath.

LP77- LONGITUDINAL ASSOCIATIONS OF CHANGES IN BLOOD-BASED MARKERS FOR NEURODEGENERATIVE DISEASES IN CLINICAL TRIALS ON ALZHEIMER'S DISEASE. D. Li[1], M. Glittenberg[1], D. Salisbury[1], V.F. Lin[2], F. Yu[3] *(1. University of Minnesota - Minneapolis (United States), 2. Stanford University - San Francisco (United States), 3. Arizona State University - Jedwards1@usf.edu (United States))*

Background: Blood-based amyloid-b (Ab) 42/40 ratio, tau phosphorylated at amino acid 181 (p-tau 181), glial fibrillary acidic protein (GFAP), and neurofilament light (NfL) are markers for brain Aβ pathology, tau pathology, reactive astrocyte, and neurodegeneration, respectively. These blood-based markers (BBMs) are poised to revolutionize the diagnostic and prognostic work-up of Alzheimer's disease (AD), as well as to improve the design of interventional trials as (pre)screeners

to identify individuals with AD, provided the AD status is later confirmed with positron emission tomography (PET) or cerebrospinal fluid (CSF) testing. However, these BBMs are yet to be used as primary endpoints in clinical trials, because longitudinal associations between changes in these BBMs and changes in imaging measures, pathology, or cognition in AD remain unclear. **Objectives:** As a step toward establishing blood-based Aβ42/Aβ40, p-tau 181, GFAP and NfL as primary endpoints in clinical trials, we examined longitudinal associations of changes in these BBMs in three randomized controlled trials in AD (Active Mind Trial, ACT Trial, FIT-AD Trial). The purpose of this study was to examine (1) cross-sectional associations amongst plasma Aβ42/Aβ40, p-tau 181, GFAP and NfL; (2) associations amongst longitudinal changes in plasma Aβ42/Aβ40, p-tau 181, GFAP and NfL (baseline as reference) and their baseline levels; (3) longitudinal associations amongst changes in Aβ42/Aβ40, p-tau 181, GFAP and NfL. **Methods:** The Active Mind Trial is an adaptive randomized controlled trial (RCT) that tests 3- month cognitive training combinations for enhancing instrumental activities of daily living among persons with mild cognitive impairment (MCI). The ACT Trial is a 2x2 factorial RCT to test the efficacy and synergistic effects of a 6-month aerobic exercise and cognitive training regimen on cognition and relevant mechanisms in older adults with amnestic MCI. The FIT-AD Trial was a 2-parallel group RCT that examined the effects of 6- month aerobic exercise on cognition and hippocampal volume in older adults with mild-to-moderate AD dementia. Active Mind Trial collected plasma samples at baseline (n=62) and 3 months (n=52); the ACT Trial at baseline (n=53), 3 (n=44), 6 (n=37), 12 (n=17), and 18 months (n=16); FIT-AD Trial at baseline (n=26), 3 (n=23) and 6 months (n=25). BBMs were measured using Quanterix SiMoA assays, except no p-tau 181 for the ACT Trial and no GFAP for the FIT-AD Trial. Because these plasma biomarker levels were not directly comparable across cohorts, we conducted linear regression models, adjusting for age and sex, within each cohort. **Results:** The mean (SD) age and % of female of the Active Mind, ACT, FIT-AD participants at baseline were 71.2 (5.8) years and 44%; 73.5 (5.6) and 49%; 77.6 (6.9) and 34%; respectively. None of the plasma biomarkers was significant different across time points in any of the three cohorts except p-tau 181 between baseline and 3-months in the FIT-AD Trial (mean [SD] of p-tau 181 at baseline and 3-months: 2.55 [1.37] pg/mL and 2.62 [1.29] pg/mL; p-value =0.0484). Because of this, we conducted cross-sectional association analysis by combining data of all time points within each cohort. Significant cross-sectional associations between plasma Aβ42/Aβ40 and GFAP, NfL, or p-tau 181 (standardized coefficient bs in the range of -0.38 to -0.31 and p-values 3.39 ´ 10-5 to 6.20 ´ 10-4) were generally weaker than the associations amongst plasma p-tau 181, GFAP, and NfL (b in the range of 0.60 to 0.77 and p-values 6.86 ´ 10-21 to 2.44 ´ 10-13). Significant cross-sectional association for plasma GFAP and NfL (b= 0.38 and p-value =2.36 ´ 10-4) and for plasma p-tau 18 and NfL (b= 0.62 and p-value =0.01) were replicated in the ACT and in the FIT-AD, respectively. Amongst the associations of all 3-month changes in plasma Aβ42/Aβ40, p-tau 181, GFAP, and NfL and their baseline levels, only greater 3-months increase in plasma Aβ42/Aβ40 was significantly associated with lower baseline Aβ42/Aβ40 in all three cohorts (bs in the range of -0.48 to 0.312 and p-values in the range of 0.023 to 0.042). When longer follow-up data were available in the ACT and FIT-AD, only 6-months increase in plasma p-tau 181 was significantly associated with lower baseline Aβ42/Aβ40 (b=0.538 and p-value=0.022) in the FIT-AD. Lastly, greater 3-month increases in plasma GFAP were significantly associated with greater 3-month increase in plasma NfL in the Active Mind (b= 0.397 and p-value 00038). The significant longitudinal association between changes in plasma GFAP and changes in plasma NfL was replicated in the ACT Trial at 3-month (b= 0.52 and p-value 0.007) but not at 6-month (b=0.409 and p-value=0.074). **Conclusion:** The observation that older adult with lower baseline plasma Aβ42/Aβ40 ratio had greater increase in plasma Aβ42/Aβ40 ratio at 3 months (baseline as reference) is most likely explained by regression to mean. Longitudinal associations in 3-month increases in plasma GFAP and in plasma NfL in the two independent cohorts suggests a strong coupling of neuron and astrocyte. Our study data potentially supports the use of changes in plasma GFAP and in plasma NfL as potential surrogate endpoints in clinical trials of AD, although the caveats are both changes in NfL and in GFAP are not specific for AD and can be related to other co-existing pathology (e.g., cerebrovascular pathology).

LP78- PLASMA P-TAU AND NFL POTENTIAL UTILITY AS SURROGATE BIOMARKERS IN PREVENTIVE CLINICAL TRIALS. P.L. Ferreira[1], J.P. Ferrari-Souza[1], C. Tissot[2], B. Bellaver[1], D.T. Leffa[1], G. Povala[1], F.Z. Lussier[1], J. Therriault[2], J.P. Soucy[2], S. Gauthier[2], V.L. Villemagne[1], P. Rosa-Neto[2], T.K. Karikari[1], T.A. Pascoal[1] *(1. Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA. - Pittsburgh (United States), 2. Department of Neurology and Neurosurgery, Psychiatry and Pharmacology and Therapeutics, McGill University, Montreal, QC (Canada))*

Background: Recently, the preclinical stage of Alzheimer's disease (AD) has become a focus of clinical trials based on the assumption that better therapeutic outcomes can be achieved before the onset of Aβ and tau pathologies, cognitive decline and major neurodegeneration. The preclinical AD key features are the presence of abnormal markers of Aβ, and tau tangles accompanied by the absence of cognitive symptoms. While presenting an elevated risk for cognitive decline, the vast majority of these individuals will remain clinically stable during typical clinical trial periods (12- to 24-month follow-up). This challenges the use of changes in cognitive measures as a single primary outcome in therapeutical trials using cognitively unimpaired (CU) individuals. In this context, using surrogate biomarkers to evaluate disease progression is crucial. Plasma and positron emission tomography (PET) biomarkers have already been proposed to monitor participants' disease progression in preventive clinical trials targeting CU individuals. However, while longitudinal changes in plasma phosphorylated tau 181 (p-tau181) and neurofilament light (NfL) correlate with AD progression, it is unknown whether these changes can be used to monitor drug effects in preventive clinical trials. **Objective:** Here, we tested the utility of plasma p-tau181 and NfL as surrogate biomarkers for clinical trials targeting CU older individuals. **Methods:** We evaluated 257 CU older individuals with available Aβ-PET (18F-florbetapir uptake) at baseline and longitudinal (up to 24-months) plasma p-tau181 and NfL measures from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Aβ positivity was conferred based on Aβ-PET composite standardized uptake value ratio (SUVR) greater than 1.11, following previous validation studies. We used the SUVR value and equations previously established by the ADNI PET core to transform the Aβ-PET SUVR to the Centiloid scale. We calculated the estimated sample size needed for a clinical trial testing a hypothesized 25% drug effect on longitudinal reduction in biomarkers with 80% power at alpha level 0.05 on reducing changes in plasma biomarkers. Using

data from a previous study (PMID: 29538647), we assessed changes in tau-PET (18F-flortaucipir uptake) or structural MRI (tensor-based morphology cortical volume) to calculate samples size and prices of trials using neuroimaging for surrogacy. **Results:** We demonstrated that longitudinal changes in plasma NfL were associated with age, whereas changes in plasma p-tau181 with progression to MCI. We found that therapeutic clinical trials using plasma biomarkers over 24 months would require 78% (n = 8,884) and 63% (n = 3,448) smaller sample sizes than 12-month trials for plasma p-tau181 and NfL, respectively. The use of Aβ positivity, in comparison to including the whole population, for population enrichment reduced the sample size of 24-month trials by 43% (n = 5,040) for p-tau181 and by 17% (n = 2,868) for NfL. Notably, using intermediate levels of Aβ (20-40 Centiloid units) as an enrichment strategy, rather than merely Aβ positivity, the sample size was reduced by 73% (n = 2,432) for p-tau181 and 59% (n = 1,396) for NfL over 24-months. The use of APOE ε4 carriership did not reduce sample sizes for p-tau181 and NfL over 24 months. We evaluated drug effects greater than 25% (used in this study), and our findings suggested that the sample size would reduce if we considered medications with larger effect sizes. For example, a ~50% drug effect on either p-tau181 or NfL reduction would lead to the need for a total of ~1,000 individuals for a clinical trial using plasma biomarkers as a surrogate outcome. When calculating the cost of biomarkers-only, the cost of using plasma is lower for p-tau181 (7-fold at 24 months) and similarly for NfL than the cost of using neuroimaging biomarkers for surrogacy. On the other hand, the total estimated trial cost when selecting an Aβ-positive population, considering surrogate biomarkers plus other related tests (such as costs of the definition of Aβ-PET positivity and cognitive assessment), is higher (more than 5-fold at 12 months and 2-fold at 24 months) using plasma than neuroimaging biomarkers for surrogacy. However, when we estimated the total cost of a trial including only individuals with intermediate Aβ levels, the cost was similar when using plasma and neuroimaging biomarkers for surrogacy. **Conclusion:** Our results suggest that plasma p-tau181 and NfL could potentially be used to monitor large-scale population interventions in CU Aβ-positive individuals. Additionally, we demonstrated that selecting individuals with intermediate levels of Aβ (20-40 Centiloid) is the most cost-effective population enrichment strategy tfor clinical trials using plasma biomarkers as surrogate marker.

LP79- FOSGONIMETON PROVIDES CONGRUENT BENEFIT ON DIVERSE BIOMARKERS OF NEURODEGENERATION, SIGNIFICANTLY CORRELATING WITH A COMPOSITE CLINICAL SCORE OF COGNITION AND FUNCTION IN ALZHEIMER'S DISEASE.

H. Moebius[1], K.B. Ooi[1], M. Hale[1], S. Setti[1], K. Kleist[1], C. Bernick[2] *(1. Athira Pharma - Bothell (United States), 2. Cleveland Clinic Lou Ruvo Center for Brain Health - Las Vegas (United States))*

Background: The pathophysiology of Alzheimer's disease (AD) dementia is multifactorial and the resulting cognitive and functional decline debilitating. AD has been associated with oxidative stress, inflammation, vascular insufficiency, metabolic dysfunction, and specific proteotoxicity. Despite this complex mechanism of the disease, clinical research in AD has been dominated by mechanisms that target proteotoxicity alone. Additional approaches that address other, known contributory factors of AD pathophysiology may provide much-needed improvements in functional and cognitive outcomes. The MET receptor and its ligand hepatocyte growth factor (HGF), which are both expressed in neurons and glia throughout the nervous system, activate a broad range of intrinsic cellular pathways that support function and homeostasis. MET expression is markedly reduced in AD. Fosgonimeton, a small-molecule positive modulator of the HGF/MET system, was evaluated in subjects with mild-to-moderate AD in the randomized, 6-month, double-blind, placebo-controlled, phase 2 ACT-AD study (NCT04491006*). Here we present additional fluid biomarker analyses. **Objectives:** To evaluate changes from baseline in plasma biomarkers at Week 26 of fosgonimeton treatment compared with placebo in subjects with mild-to-moderate AD enrolled in the ACT-AD study and assess multifactorial correlations with the global statistical test (GST), a composite score informed by both ADAS-Cog11 and instrumental activities of daily living (iADL). **Methods:** Blood samples were drawn from subjects providing consent at baseline (before treatment start; N=77) and at visit 8 (Week 26 of treatment). Whole blood was collected into EDTA sample tubes, on ice, then plasma was isolated following centrifugation. Initial biomarkers assessed include neurofilament light chain (NfL, an indicator of ongoing neurodegeneration), glial fibrillary acidic protein (GFAP, an indicator of microglial activation), chitinase-3-like protein 1 (YKL-40, a marker of neuroinflammation), and amyloid beta 40 and 42 (Aβ40, Aβ42). All were normalized to baseline. NfL was measured using the Simoa NF-light Advantage assay (Quanterix 103186); Aβ40, Aβ42, and GFAP were measured using the Simoa Neurology 4-Plex E assay (Quanterix 103670); and YKL-40 was measured using the U-PLEX Human YKL-40 assay (MSD K151VLK). Least squares mean differences (fosgonimeton vs placebo, without background therapy) and 95% confidence intervals (CIs) were calculated for change from baseline at Week 26, and analysis of variance was performed to determine treatment impact. Effects on plasma biomarker changes were evaluated while considering several factors (eg, ApoE4 genotype) and covariates (eg, baseline age, clinical dementia rating health status, and Mini-Mental State Exam (MMSE) score). Due to the limited trial size, results are represented for pooled active arms vs. placebo, without background therapy. **Results:** Baseline levels of all biomarkers were similar between treatment groups, and biomarker levels indicative of AD proteinopathy were in keeping with literature data for the "probable AD" target population recruited according to McKhann et al. 2011. NfL was elevated on average at baseline (20.8 pg/mL, SE 1.6); subjects receiving fosgonimeton showed a statistically significant change from baseline compared to placebo (−7.9 pg/mL, SE 2.7, p=0.0059). Across diverse biomarkers, fosgonimeton-treated subjects consistently showed directionally favorable improvements from baseline compared with placebo: GFAP (−29.3 pg/mL, SE 28.6, p=0.312); YKL-40 (−34.9 ng/mL, SE 26.5, p=0.195); and Aβ42/40 ratio (0.0066, SE 0.0035, p=0.064). ApoE4 carrier status, MMSE at baseline, sex or age did not affect these results. To confirm the correlation of biomarkers and clinical endpoint, data from the modified intent-to-treat study population from ACT-AD were analyzed; the composite endpoint GST, a pre-specified secondary analysis, informed by both ADAS-Cog11 and iADL, proved to be highly correlated with the change in NfL (r=0.46, P=0.0011) and GFAP (r=0.30, P=0.0394). **Conclusion:** In this first-ever randomized, double-blind, 6-month trial of a novel small molecule positive modulator of the HGF/MET neurotrophic system, fosgonimeton, a statistically significant benefit on NfL, and descriptive, congruent GFAP and YKL-40 plasma concentration improvements were observed, which could be consistent with a neuroprotective effect of this novel intervention and the

multimodal mechanism of action. These clinical findings are consistent with preclinical results of fosgonimeton-induced neuroprotection in various animal models of proteotoxicity and neurodegeneration. The significant correlation of NfL and GFAP benefit with the composite clinical endpoint, GST, informed by ADAS-Cog11 and iADL, further supports the translation and clinical relevance. *The ACT-AD trial is supported by a grant from the National Institute on Aging of the National Institutes of Health under award number R01AG06268. The information presented here is solely the responsibility of Athira and does not necessarily represent the official views of the National Institutes of Health.

LP80- IN AN OPTIMIZED CSF COLLECTION PROTOCOL THE PTAU181/AB1-42 RATIO INCREASES PREANALYTICAL VARIABILITY OVER MEASURING AB1-42 ALONE. R. Esquivel[1], S. Ho[2], J. Darrow[2], A. Calabro[1], P. Thakker[2], S. Gannon[1], F. De Simone[1], A. Moghekar[2] *(1. Fujirebio Diagnostics Inc - Malvern (United States), 2. Johns Hopkins School of Medicine - Baltimore (United States))*

Background: Core cerebrospinal fluid (CSF) biomarker concentrations for β-amyloid1-42 (Aβ1-42) β-amyloid1-40 (Aβ1-40), and ptau181 are valuable in the diagnosis of Alzheimer's Disease (AD). Specifically, when used in a ratio Aβ1-42/Aβ1-40 and ptau181/Aβ1-42 have shown high concordance with amyloid PET. However, questions remain on the robustness of these ratios when used in clinical routine due to the tendency of amyloid to adsorb to surfaces causing amyloid loss that may result in misdiagnosis. Stringent handling procedures of CSF have been proposed to reduce amyloid loss including the use of a single polypropylene tube type. The proposal of a single tube complicates CSF collection and creates doubt in results obtained from alternative tube types. **Objective:** In this study the effect of varying polypropylene tube type within clinical routine on amyloid concentration using Aβ1-42/Aβ1-40 and ptau181/Aβ1-42 ratios was evaluated in freshly collected CSF. The utility of the ratios to correct for pre-analytical variability and bring concentrations within +/- 5% of baseline as indicated by recently published Alzheimer's Association International Guidelines for CSF handling was examined. **Methods:** Fresh CSF samples were collected in Sarstedt polypropylene tubes 72.703.600 (tube A), 62.610.018 (tube B) and 63.614.699 (tube C) from patients at the Johns Hopkins Center for CSF Disorders and subjected to laboratory specific protocols. Aβ1-42, Aβ1-40, and ptau181 concentrations were measured using the Lumipulse G1200 (Fujirebio Diagnostics Inc., Malvern, PA). Tubes were filled to 80% fill volume and CSF was analyzed post centrifugation (2000 xg, 10 minutes, 5 ± 3°C). Extended sample cap contact was evaluated by storing samples upright or upside down at 4°C for 1 week or upright or upside down at -80°C for 1 month. Tube C was also filled at 100% upright or upside down at 4°C for 1 week. **Results:** Amyloid concentration at 4°C did not significantly change based on tube type even when stored upside down for 1 week. Notably, at 4°C in tube C, the ptau181/Aβ1-42 ratio mean values fell outside of the acceptance criteria when stored upright (mean: 5.5% CI 3.8% – 7.2%) and upside down (mean: 7.1% CI: 4.2% - 10.0%) although individual amyloid proteins Aβ1-42 (mean: -3.3% CI: -7.0 – 0.4) and Aβ1-40 (mean: -0.1 CI -4.1%-3.9%) and ptau181 (mean: 2.3% CI -1.9% - 6.5%) did not. This was true at both 80% and 100% fill volume. The Aβ1-42/Aβ1-40 ratio remained within the acceptance criteria at 4°C for tube C upright (mean: -3.2 CI -4.6% - -1.8%) and upside down (mean: -3.0% CI -4.3% - -1.6%). At -80°C ptau181 in tube B upright (mean: -6.3% CI-12.0% - -0.5%), Aβ1-42 in tube C upright (mean: -6.6% CI -12.5% - -0.7%) and upside down (mean: -9.3% CI -18.3% - -0.3%) and Aβ1-40 upside down (mean: -5.6% CI-14.8% - 3.6%) fell outside of the acceptance criteria. The Aβ1-42/Aβ1-40 ratio compensated for the amyloid loss in tube C (upright mean: -3.2% -6.8% - 0.4%; upside down mean: -3.9% CI -8.1 – 0.3%) and remained within the acceptance criteria for tube B. Although, the ptau181/Aβ1-42 ratio remained within the acceptance criteria for tube B it fell out of the acceptance criteria for Tube A upside down (mean: 6.7% CI 1.9% - 11.5%) and Tube C upright (mean: 7.5% CI -0.3% - 15.3%) and upside down (mean: 6.6% CI -2.3% - 15.6%), despite individual proteins falling within the criteria for tube A. **Conclusion:** In this study no significant differences were observed between polypropylene tubes and between fresh and frozen samples when using the Aβ1-42/Aβ1-40 ratio. Individual amyloid proteins and the ptau181/Aβ1-42 ratio did have significant variability dependent on tube type and handling. Variability of ptau181/Aβ1-42 was higher in all three tubes after storage at -80°C. As Tube A had the least variability when measuring individual analytes it is recommended for -80°C storage. While it is known Aβ1-42 generally decreases in concentration due to handling, a small, and generally not significant increase in ptau181 concentration is also observed. Due to this trend, the ptau181/Aβ1-42 ratio may amplify preanalytical variability even when amyloid loss is minimal. Measuring the Aβ1-42/Aβ1-40 ratio and ptau181 as an individual analyte may provide most consistent results in studies relying on biobanked samples. In clinical routine the Aβ1-42/Aβ1-40 ratio is also preferable to minimize the impact of deviations from an optimized collection and handling protocol on patient diagnosis.

LP81- ANALYTICAL FEASIBILITY OF COMPOSITE PLASMA PHOSPHORYLATED TAU AND AB BIOMARKER FOR PREDICTING AMYLOID PET POSITIVITY. A.W. Bannon[1], W.Z. Potter[2], S. Zicha[3], L.M. Shaw[4], H. Zetterberg[5], Z.S. Saad[6], J. Dage[7], I. Dobler[8], D.L. Raunig[9], K. Ferber[10], C.E. Rubel[10], S.E. Schindler[11], M. Baratta[3], E.A. Meyers[12], E.G. Rosenbaugh[13] *(1. AbbVie - North Chicago (United States), 2. Subject Matter Expert (United States), 3. Takeda, Pharmaceutical Company Ltd. - Cambridge (United States), 4. Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania - Philadelphia (United States), 5. Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at University of Gothenburg - Mölndal (Sweden), 6. Neuroscience Biomarkers, Janssen Research and Development LLC - La Jolla (United States), 7. Stark Neurosciences Research Institute at Indiana University School of Medicine - Indianapolis (United States), 8. Takeda, Pharmaceutical Company Ltd - Cambridge (United States), 9. Takeda, Pharmaceutical Company Ltd. - Cambridge (United States) - Cambridge (United States), 10. Biogen - Cambridge (United States), 11. Department of Neurology,Washington University School of Medicine - St. Louis (United States), 12. Alzheimer's Association - Chicago (United States), 13. Foundation for the National Institutes of Health - North Bethesda (United States))*

Background: The FNIH Biomarkers Consortium Plasma Aβ Project has recently published on the performance of six plasma Aβ amyloid assays (i.e., Aβ42/40) to predict amyloid PET status using samples from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Zicha et. al., 2022). Results from the study indicated that a model including age and APOE genotype predicted amyloid status with an area under the curve (AUC) of 0.75. Aβ42 and Aβ40 readouts from three assays improved

AUCs to 0.81, 0.81, and 0.84 (P < .05, uncorrected for multiple comparisons). Recent published findings have suggested that plasma phosphorylated Tau (pTau) measures perform comparably to plasma Aβ measures in predicting amyloid PET status. The current study measured pTau181 in the same ADNI plasma sample set using four different immunoassays and assessed the ability of plasma pTau181 to predict amyloid PET status alone or in combination with plasma Aβ data. **Objectives:** This study aimed to assess the ability of plasma pTau181 and plasma Aβ to discriminate between amyloid PET positive and negative compared to plasma Aβ, age and APOE genotype. **Methods:** Four plasma pTau immunoassays were selected for this study based on assay design and analytical performance criteria: ADx Neurosciences pTau181 Simoa, Fujirebo Lumipulse G pTau 181 Plasma, Quanterix Simoa® pTau 181V2 Advantage, and Roche Diagnostics Elecsys Phospho-Tau (181P) Plasma. The sample set from ADNI consisted of 121 plasma samples with corresponding amyloid PET (florbetapir, FBP) with 49.6% considered Aβ+: cognitively normal (CN) n = 49 (36.7% Aβ+), mild cognitive impairment (MCI) n = 54 (48.2% Aβ+), and Alzheimer's Disease (AD) n = 18 (88.9% Aβ+). Laboratory personnel were blinded to the clinical data during sample testing, and the data analysis was performed with blinding to the assay platforms. Diagnostic performance for determining amyloid PET positivity was assessed using Receiver Operating Characteristic curve analysis for pTau181 or in combination with Aβ42/40. All models included age, and APOE genotype. Importantly, the study was not powered for a head-to-head comparison to determine a superior assay. **Results:** The plasma pTau181 concentrations positively correlated with FBP standardized uptake value ratio (SUVR) values, or in other words, elevated plasma pTau181 correlated with higher amyloid burden. The four plasma pTau181 assays predicted amyloid PET status with AUCs ranging from 70-84%. For the plasma Aβ assays alone, the AUCs in this same cohort ranged from 64-81%. The addition of pTau181 to a model using Aβ42/40, age and APOE genotype marginally improved the AUC by approximately 4%. However, the resultant AUC was comparable to that from models without the Aβ42/40 data, suggesting that the observed increase in AUC may be caused by a greater AUC for plasma pTau-181 in this dataset. **Conclusion:** Overall, based on this relatively small ADNI cohort, plasma pTau181 measures predicted amyloid PET status at least comparably to plasma Aβ42/40 measures. The addition of pTau181 to models including Aβ42/40, age and APOE genotype marginally improved the AUC by approximately 4%; however, validation in an independent dataset is needed to determine whether this moderate improvement is idiosyncratic to this sample set. The project team will evaluate each of the plasma pTau181 assay's ability to predict tau positivity status from tau PET as well as CSF measures in future analyses and consider other pTau assays. Furthermore, an assessment of inter-assay correlations for pTau181 and FBP PET SUVR measures will be performed. **Reference:** Zicha S., Bateman R., Shaw L.M., Zetterberg H. et. al., Alzheimer's Dement., 2022 Jul 12. doi: 10.1002/alz.12697.

LP82- THE DEVELOPMENT OF AN AUTOMATED EEG-BASED MACHINE LEARNING PIPELINE FOR THE DETECTION OF ALZHEIMER'S DISEASE, A PROOF-OF-CONCEPT STUDY FOR CLINICAL TRIAL BIOMARKERS.

N. Chedid[1] *(1. SynapseBio Inc - New York (United States))*

Background: Electroencephalography (EEG) is a promising digital biomarker modality for Alzheimer's disease (AD) that is a non-invasive, cost-effective, repeatable, language-free, culturally fair, mobile, and brain-based screening tool that could uniquely show therapeutic target engagement in the brain at a high temporal resolution. Although EEG offers promise as a solution addressing many of the shortcomings of other diagnostic modalities for AD, EEG contain extra-cranial artifacts (most commonly eye movements and muscle contractions) that are potentially confounding and that are visually identified based on qualitative criteria. Additionally, while machine learning (ML) models have been applied to EEG to develop prediction models, many caveats exist with prior approaches, including long EEG epochs and the use of high-density EEG systems, a challenge for high throughput screening, lack of clarity around the artifact removal process, and use of computationally heavy approaches such as graph theory and 'black box' ML models that undermine explainability. **Objectives:** To develop an automated EEG-based ML pipeline for the detection of AD that solves the following problems simultaneously: (1) Lack of automation and unbiased removal of artifacts, (2) dependence on a high level of expertise in data pre-processing and ML for non-automated processes, (3) need for relatively large sample sizes and accurate EEG source localization using high density systems, (4) and reliance on black box ML approaches such as deep neural nets with unexplainable feature selection. **Methods:** EEGs (xx min resting state, eyes closed, xx channels) were collected from 23 healthy subjects and 18 patients with AD. EEG data was transformed from the time domain to the frequency domain. Low quality channels were removed. Our proprietary automated support-vector machine pipeline further detected and removed artifacts. Power spectral density (PSD) analysis was performed, and PSD features were selected for ML based on statistical analysis. These features were input into a logistic regression model. **Results:** We reached a mean accuracy of 81 % on the entire dataset for classifying subjects as healthy or with AD (AUC: 86 %, precision: 78 %, recall: 75 %). **Conclusion:** In summary, we developed a fully automated discrimination process for AD based on brief epochs of resting-state EEG using low-density channel montage, an end-to-end automated analysis pipeline for data preprocessing, and statistically guided feature extraction, leading to explainable ML classification with high accuracy. The novelty in our approach is twofold: 1) "transparent" ML techniques as opposed to black box deep learning methods, and 2) preprocessing EEG signals in an automated manner to remove artifacts such that our results are reproducible, rigorous, and scalable. These two novel aspects allowed us to obtain proof of concept data in a relatively small sample size. Our current and future work entails applying this automated pipeline to develop biomarkers to enhance safety, patient selection, and assessment of treatment efficacy in AD clinical trials. **Disclosures:** Nicholas Chedid is an employee of SynapseBio Inc.

LP83- TOWARDS IMPLEMENTATION OF PLASMA PHOSPHO-TAU 181 AS A SCREENING TOOL FOR PATIENT RECRUITMENT. A. Emersic[1], B.E. Kirsebom[2,3], W.S. Brum[4,5], M. Wettergreen[6,7], B. Winblad[8,9], K. Blennow[10,11], M. Gregoric Kramberger[1, 12], T. Fladby[6,13] *(1. Department of Neurology, University Medical Centre - Ljubljana (Slovenia), 2. Department of Neurology, University Hospital of North Norway - Tromsø (Norway), 3. Department of Neurology, Medical faculty, University of Ljubljana - Ljubljana (Slovenia), 4. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Clinical Neurochemistry Laboratory, The Sahlgrenska Academy at the University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Gothenburg (Sweden), 5. Department of Psychology, Faculty of Health Sciences, UiT, The Arctic University of Norway - Tromsø (Norway), 6. Department of Neurology, Akershus University Hospital - Lørenskog (Norway), 7. Institute of Clinical Medicine, University of Oslo - Lørenskog (Norway), 8. Department of Neurobiology, Care Sciences and Society, Division of Neurogeriatrics Karolinska Institutet - Stockholm (Sweden), 9. Clinical Molecular Biology (EpiGen), University of Oslo - Oslo (Norway), 10. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Clinical Neurochemistry Laboratory, The Sahlgrenska Academy at the University of Gothenburg - Gothenburg (Sweden), 11. Karolinska University Hospital - Stockholm (Sweden), 12. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Gothenburg (Sweden), 13. Universidade Federal do Rio Grande do Sul (UFRGS) - Porto Alegre (Brazil))*

Background: Success of clinical trials in Alzheimer's disease (AD) is largely depended on recruitment of eligible participants with underlying AD pathophysiology. Although currently available biomarkers have greatly improved the diagnostic accuracy of AD, they either require invasive lumbar puncture (LP) or costly neuroimaging procedures, which make them inconvenient for broader community screening. With the arrival of disease modifying therapies, easily available tools to facilitate early AD diagnosis are all the more needed. Plasma phospho-tau (p-tau) 181 has been shown to accurately predict AD pathology in memory-clinic cohorts, however little is known about its performance in general population settings. **Objective:** We aimed to evaluate plasma p-tau 181 potential to identify individuals at early asymptomatic or symptomatic stage of AD within the Precision Medicine Interventions in Alzheimer's Disease (PMI-AD, JPND2019-466-236) project and its open house initiative for community-based screening. In line with PMI-AD objectives, further clinical evaluation and participation in early therapeutic intervention is now offered to the individuals with increased risk for developing AD dementia. **Methods:** Participants: Pre-screening of 147 subjects between 55-80 years was done at the Department of Neurology, University Medical Centre Ljubljana, Slovenia. The AD8 Dementia Screening Interview, as well as Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Hospital Anxiety and Depression Scale (HADS) were used to assess mental status and detect potential anxiety or depression. Individuals with cognitive complaints in recent 3-5 years, who were independent in daily activities, could undergo MRI protocol and did not fulfil any of the exclusion criteria (dementia diagnosis or treatment, psychiatric disorders, known malignancy or previous stroke) could enter the screening with blood withdrawal. Blood analysis and prediction of amyloid positivity. P-tau 181 measurements and APOE genotyping was done at the University of Oslo, Akershus University Hospital. Plasma p-tau181 concentrations were measured with the single molecule array assay on the Simoa SR-X analyzer (Quanterix). Amyloid Aβ positivity based on CSF Aβ42/40 status was predicted using previously validated cut-off (>1.628 pg/ml) within the Dementia Disease Initation (DDI) cohort. Additionally, accuracy in detection of underlying AD (CSF Aβ42/40 positivity) was assessed for a prediction model with plasma p-tau 181 and APOE status, developed in the DDI dataset. Different specificity-based thresholds of the model were evaluated in comparison with plasma p-tau 181 positivity alone as potential strategies to guide and optimize further study enrollment. CSF sampling and study enrollment. Participants with plasma p-tau 181 above the threshold underwent LP and confirmatory CSF analysis. CSF AD biomarkers, total tau, p-tau 181 and Aβ42/40 ratio were measured using the Innotest (Fujirebio) immunoassays. Amyloid β positivity as defined by CSF Aβ42/40 ratio < 0.07 (previously validated cut-off) was necessary for further study enrollment. **Results:** Twenty-three individuals (16%) were excluded at pre-screening and among the rest blood collection with APOE genotyping and plasma p-tau 181 measurement was so far done in 86 (57 women). Median age of already screened individuals was 71 years (range 59-80 years), their MMSE and MoCA scores were 28.6 ± 1.2 and 26.4± 1.8 (mean ± SD). Fifty-three (62%) had plasma p-tau 181 above the screening cut-off and proceeded to LP for CSF AD biomarkers evaluation. By the end of September 2022, altogether 18 LP were performed and in 9 (50%) reduced CSF Aβ42/40 ratio was confirmed. Using a prediction model with plasma p-tau 181 and APOE status, estimated probabilities of underlying AD (CSF Aβ positivity) in already screened cases (n=86) were 40%, 34% and 19 % at the 85%, 90% and 95% specificity thresholds, respectively. Based on the CSF results in a small subgroup (n=18), only the stringent 95% specificity threshold would have substantially reduced our rate of Aβ-negative CSF results. At the same time, a third who turned out to be CSF Aβ positive would not have been screened with probability cut-offs, indicating a further need for confirmatory CSF testing. **Conclusions:** Our preliminary results demonstrate about 50% of concordance between plasma p-tau 181 and CSF Aβ positivity in this community-based cohort. A prediction model with plasma p-tau 181 and APOE status could reduce the rate of Aβ-negative CSF results, however some of the eligible individuals would not have been able to proceed to therapeutic intervention. Further studies should address applicability of plasma p-tau 181 for screening as well as combinations of different blood-based biomarkers that might be need to reliably predict AD in general population. **Acknowledgements:** The project was funded by the Ministry of Education, Science and Sport, Slovenia and the Norwegian Research council, JPND/PMI-AD (NRC 311993).

LP84- LEUKOCYTE-DERIVED RATIOS ARE ASSOCIATED WITH DEMENTIA. Y.N. Kim[1,2], S. Arif[2] *(1. Boston University - Boston (United States), 2. DotHouse Health - Boston (United States))*

Dementia is divided into late-onset (LOD) and early-onset dementia (EOD)(age <65). Studies showed that leukocyte-derived ratios could represent inflammation markers for cognitive decline in LOD. A recent study in our health center showed that they could also be markers for EOD. This study was an extension of our previous study to evaluate the relevance of these markers in EOD and LOD. We identified 86 community-dwelling patients seen at the cognitive assessment clinic in a community health center from 1/2021-4/2022 through chart review. Four patients were excluded as CBC results were unavailable. Forty-six patients were diagnosed

with dementia (EOD 8 patients, LOD 38 patients), and 27 patients had MCI (early-onset 9 patients, late-onset 18 patients). Nine patients had normal results. (age < 65 2 patients, age ≥ 65 7 patients) In this study, the control group was patients who were not diagnosed with dementia (normal results and MCI diagnoses), and we divided patients into two groups based on their age(<65 or ≥ 65) and compared each group with their control groups. We collected complete blood count (CBC) and calculated lymphocyte-to-monocyte ratio(LMR), neutrophil-to-lymphocyte ratio(NLR), and platelet-to-lymphocyte ratio(PLR). In the younger population, neutrophils, monocytes, and eosinophil counts were not likely associated with EOD, but NLR, LMR, and PLR seem related to EOD. NLR and PLR again suggested this relation when comparing the EOD group with the early onset MCI group. In the older population, most markers were likely unrelated to LOD diagnosis. Still, eosinophil counts and hemoglobin levels were highly likely associated with LOD (P value: 0.0224(eosinophils), 0.005(hemoglobin)). CBC is a widely available test that can be done quickly in the outpatient setting. If CBC can predict the likelihood of developing dementia, it will tremendously help our practice for risk assessment and diagnosis of dementia. Our study suggested that low NLR, PLR, and high LMR were associated with EOD, and high eosinophil counts and high hemoglobin levels were very likely related to LOD. Because different markers were associated with dementia depending on its onset, different pathophysiology may play a role in EOD and LOD. More extensive cohort studies are needed to investigate this further.

LP84A- THREE GROUP CLASSIFICATION OF PARTICIPANTS BASED ON FULLY AUTOMATED PLASMA B-AMYLOID MEASUREMENTS TO ACHIEVE HIGH POSITIVE AND NEGATIVE PREDICTIVE VALUES. K. Yamashita[1], M. Miura[1], K. Nagai[2], D. Verbel[3], S. Iwanaga[1], T. Sato[1], T. Yoshida[4], A. Iwata[5] *(1. Central Research Laboratories, Sysmex Corporation - Kobe (Japan), 2. Japan and Asia Clinical Development Department, Eisai Co., Ltd - Tokyo (Japan), 3. Biostatistics, Eisai Inc. - Nutley (United States), 4. Sysmex Corporation - Kobe (Japan), 5. Department of Neurology, Tokyo Metropolitan Geriatric Hospital and Institute of gerontology - Tokyo (Japan))*

Background: Blood-based biomarkers that can predict brain β-amyloid (Aβ) status are in high demand not only for the recruitment of participants into Alzheimer's disease (AD) clinical trials but also for ensuring that appropriate AD patients can receive disease-modifying therapies in the future as they become available. Recently, we reported that plasma Aβ1-42 (Aβ42) to Aβ1-40 (Aβ40) ratio measured by our fully automated immunoassay platform (HISCLTM series) predicted brain Aβ status defined by amyloid positron emission tomography (PET) as assessed by Centiloids (CL). Area under the curves of 0.932 and 0.922 were obtained in two clinical studies (discovery and validation studies). In the previous analysis, we determined a cut-off value of 0.102 using the Youden index in the discovery study. Using this cut-off value, we achieved high negative predictive value (NPV) of 97.6% and 94.0%, and moderate positive predictive value (PPV) of 80.6% and 79.6% in the discovery and validation studies, respectively. Considering use in the screening of participants for clinical trials, higher PPV would be preferable. In this study, we combined discovery and validation studies to one dataset, and classified participants into three groups (positive, intermediate, and negative Aβ groups) depending on their plasma Aβ42/Aβ40 ratio, in order to improve PPV of our plasma Aβ assay. **Objectives:** To evaluate the performance of our plasma Aβ42/Aβ40 ratio in predicting amyloid PET status upon classifying participants into three groups. **Methods:** Plasma Aβ40 and Aβ42 were measured using a fully automated immunoassay platform in a set of plasma samples sourced from participants in the screening phase of the elenbecestat Phase 3 program. Participants were clinically diagnosed with mild cognitive impairment and mild dementia. In this analysis, we combined datasets from previously reported discovery and validation studies to make one dataset that included 172 amyloid PET positive participants and 199 negative participants. Brain Aβ status was determined by amyloid PET scans as assessed by the Centiloid method (cut-off value defined previously as 32.21 CL). Here, we determined the cut-off value of our plasma Aβ42/Aβ40 ratios that would result in a PPV of 90.0% or more. We then utilized this cut-off value and the prior reported cut-off value of 0.102 as the thresholds to divide participants into positive, intermediate, and negative Aβ groups. **Results:** A cut-off value of 0.092 was determined based on the criteria to achieve a PPV of at least 90.0%, and we used this cut-off value and 0.102 to classify participants into positive (≤ 0.092), intermediate (> 0.092 and ≤ 0.102), and negative (> 0.102) Aβ groups. In this analysis, PPV in positive Aβ group was 90.1% while NPV in the negative Aβ group was 95.8%. In intermediate Aβ group, 68.4% corresponded to amyloid PET positive participants. **Conclusion:** Our Aβ assay achieved PPV and NPV ≥ 90% by classifying participants into the three groups. Majority of participants were classified as positive or negative Aβ groups by plasma Aβ42/Aβ40 ratio, indicating that our assay may contribute to reduce amyloid PET scan or CSF Aβ testing, which could be helpful in applications such as the recruitment step of clinical trials.

CLINICAL TRIALS: COGNITIVE AND FUNCTIONAL ENDPOINTS

P126- VISIT-TO-VISIT BLOOD PRESSURE VARIABILITY AND COGNITION IN THE SPRINT MIND TRIAL. I. Sible[1], D. Nation[2] *(1. USC - Los Angeles (United States), 2. Uc Irvine - Irvine (United States))*

Background: Blood pressure (BP) variability (BPV) is an emerging risk factor for cognitive impairment, dementia, and cerebrovascular disease, independent of traditionally studied average BP levels, but relationships with cognition in the context of antihypertensive strategies remain unclear. **Objectives:** We examined whether visit-to-visit BPV is related to cognitive change based on antihypertensive treatment type. **Methods:** In this post hoc analysis of the SPRINT MIND trial, 2348 participants underwent 4 BP measurements over a 9-month period after treatment randomization (standard vs intensive BP lowering) and ≥ 1 neuropsychological evaluation thereafter. Participants underwent cognitive testing at study baseline and every two years during the planned 4-year follow-up. Primary outcomes for the present study were standardized composite scores for processing speed (Trail Making Test parts A and B, Digit Symbol Coding) and executive function (Trail Making Test part B minus part A, Digit Span). Linear mixed models investigated relationships between BPV, antihypertensive treatment group, and time on cognitive scores. **Results:** Elevated BPV was associated with the fastest decline in processing speed (ß = -.06 [95% CI -.12, -.01]; p = .03) and executive function (ß = -.09 [95% CI -.18, -.001]; p = .048) in the standard treatment group only. BPV was not significantly related to cognitive scores in the intensive treatment group.

Conclusion: Elevated BPV remains a risk factor for cognitive impairment despite strictly controlled BP levels, in the standard treatment group. Declines were observed in processing speed and executive function, domains often impacted by cerebrovascular disease and may underpin risk for dementia and cerebrovascular disease associated with BPV. Additionally, BPV is easily accessible and widely available in a number of clinical settings, underscoring the utility of BPV as a vascular risk factor linked with cognitive impairment and dementia. The authors have no conflicts of interests to disclose.

P127- CLASSIFICATION AND PREDICTION OF DIFFERENT COGNITIVE TRAJECTORIES IN COGNITIVELY NORMAL ELDERLY. Y.J. Kim[1], S.E. Kim[2], A. Hahn[3], S.H. Cho[4], D.L. Na[1], J.P. Kim[1], H. Jang[1], H.J. Kim[1], J. Chin[1], S.W. Seo[1] *(1. Samsung Medical Center - Seoul (Korea, Republic of), 2. Haeundae Paik Hospital - Busan (Korea, Republic of), 3. Johns Hopkins Bloomberg School Of Public Health - Baltimore (Korea, Republic of), 4. Chonnam National University Hospital - Chonnam (Korea, Republic of))*

Background: Aging-related health issues are receiving more spotlights as aging-related diseases are projected to be higher societal and economic burdens. In fact, Alzheimer's disease (AD) is one of the major causes of disability and dependency of the elderly population. Therefore, early diagnosis and intervention are critical to reduce all the burdens of AD. **Objectives:** This study aims to investigate cognitive trajectory of cognitively normal (CN) elderly using Preclinical Alzheimer Cognitive Composite (PACC) in Alzheimer's Disease Neuroimaging Initiative (ADNI) and explore how the risk factors impact cognitive trajectory. **Methods:** Data were obtained from the ADNIMERGE dataset of the ADNI database and from the Samsung Medical Center (SMC) for external validation. A total of 407 CN participants from ADNI database were included in the current study, and they had at least 2 follow-ups of cognitive assessment. We used the ADNI-modified PACC with trial-making test B time to completion (mPACCtrt) as the cognitive endpoint. We tested whether there were distinct growth patterns in cognitive trajectory of the CN elderly using the latent growth mixture modeling and developed the prediction model, a nomogram. Also, 285 CN participants from SMC were examined to check whether the trajectory modeling we built is reliable. **Results:** There were two latent classes in the cognitive trajectories of the CN elderly; a 'stable group' (86.2%) and a 'declining group' (13.8%) in ADNIMERGE dataset. The results of the external validation analysis also revealed similar patterns. The logistic regression model (Model 1) showed that higher age (OR = 1.092, 95% CI = 1.013-1.177), presence of APOE ε4 allele (OR = 2.692, 95% CI = 1.208-6.003), and lower hippocampal volume (HV) (OR = 0.465, 95% CI = 0.239-0.906) were predictive of cognitive decline. After adding the information of AV45 SUVR to independent variables (Model 2), higher AV45 SUVR (OR = 1.703, 95% CI = 1.374-2.111), and decreased HV (OR = 0.396, 95% CI = 0.189-0.831) predicted fast decline, but the effects of older age and APOE ε4 carrier disappeared. Finally, prediction models of cognitive decline showed fair to good discrimination and calibration capabilities (C-statistic = 0.74 for model 1, 0.84 for model 2). **Conclusion:** Our study provides novel insights into the different cognitive trajectories among CN participants. Furthermore, the prediction model could facilitate the classification of CN participants, which could be employed in future primary prevention trials. **Competing interests:** The authors declare that they have no conflict of interest.

P128- WHAT'S IN A SCORE: COMPARING AND ALIGNING SCORES BASED ON ITEM RESPONSE THEORY AND CLASSICAL TEST THEORY FOR THE AMSTERDAM INSTRUMENTAL ACTIVITIES OF DAILY LIVING QUESTIONNAIRE. M. Dubbelman[1], M. Postema[1], R. Jutten[2], J. Harrison[1], C. Ritchie[3], B. Schalet[4], C. Terwee[5], W. Van Der Flier[1], P. Scheltens[1], S. Sikkes[1] *(1. Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam Umc Location Vumc - Amsterdam (Netherlands), 2. Department Of Neurology, Massachusetts General Hospital, Harvard Medical School - Boston (United States), 3. University Of Edinburgh - Edinburgh (United Kingdom), 4. Department Of Medical Social Sciences, Feinberg School Of Medicine, Northwestern University - Chicago (United States), 5. Amsterdam Umc Location Vumc, Epidemiology And Data Science, Amsterdam Umc - Amsterdam (Netherlands))*

Background: Early along the Alzheimer's disease continuum, individuals may develop difficulties performing cognitively complex 'instrumental activities of daily living' (IADLs) such as doing grocery shopping and using a computer. Performance of IADLs is a clinically relevant outcome measure often captured using patient- or observer-reported outcome measures. These outcome measures may be scored using classical test theory (CTT), which holds that an observed total score is the sum of a person's true score (ability) and random error of measurement, regardless of ability. Item response theory (IRT) is a more advanced scoring method which assumes that measurement error varies across the scale. IRT also accounts for varying properties of items, such as discriminative ability (how well an item can distinguish between individuals with good or poor ability on the construct) and location on the scale (or, how difficult an item is). As such, IRT-based scores may provide a more precise reflection of a person's true ability. It has been suggested that IRT-based scores may be less biased than CTT-based scores when estimating change in a construct, potentially increasing responsiveness. The Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q) is an extensively validated functional outcome measure which was developed using IRT and has both CTT-based and IRT-based scoring available. **Objective:** We aimed to compare and align IRT-based with CTT-based scores of impairment in everyday functioning, as measured with the A-IADL-Q. **Methods:** We included 2,295 participants, 2,032 (89%) of whom were cognitively normal. Others had subjective cognitive decline (n=93, 4%), mild cognitive impairment (n=79, 3%), or dementia (n=91, 4%). A completed A-IADL-Q was available for all participants. We computed IRT-based scores, which follow a normal distribution centered around a mean of 50 with a standard deviation of 10 and with higher scores representing better functioning, as well as CTT-based scores, which range from 0 to 100 with higher scores representing more impairment. IRT-based scores are calculated using an algorithm, whereas CTT-based scores are the average of all item scores. We then compared CTT-based and IRT-based score distributions and discriminative ability between diagnostic groups using linear regressions and investigated floor and ceiling effects. We subsequently compared change over time between scoring methods using linear mixed models adjusted for age, sex, and education, in a subgroup of 1,415 individuals who had longitudinal data available (mean follow-up 1.4 ± 0.6 years). **Results:** IRT-based and CTT-based scores correlated strongly (Pearson's r = -0.92, 95% confidence interval = [-0.93, -0.91]). A total of 1,622 individuals (71%) had a CTT-based score of 0, indicating no impairment, while only 54 individuals (2%) had an IRT-based score of 70, indicating no impairment. Linear

mixed models showed that both CTT-based and IRT-based scores showed change in everyday functioning over time in the whole sample. IRT-based scores deteriorated modestly but significantly in cognitively normal older adults (B = -0.15, 95%CI = [-0.28, -0.03]), while CTT-based scores showed no significant change (B = 0.20, 95%CI = [-0.02, 0.41]). In the clinical groups, both CTT-based and IRT-based showed significant change over time, with similar effect size in the whole group. In more advanced disease stages, CTT-based scores showed larger effects. Mean-to-standard deviation ratios (MSDRs) were marginally larger for CTT-based scores. We aligned CTT-based and IRT-based scores using 150,000 simulated responses to the A-IADL-Q. The mean and range of IRT-based scores were computed for each unique CTT-based score and the mean was aligned with the CTT-based score. We created a crosswalk table that can be built into an electronic case report file so IRT-based scores can automatically be derived from CTT-based scores. **Conclusion:** IRT-based scores of the A-IADL-Q have several advantages over CTT-based scores, including the absence of a ceiling effect and slightly superior responsiveness in preclinical disease stages. With the alignment of the CTT-based and IRT-based scores, made possible by the similarities in measurement properties of the two scoring methods, IRT-based scores can be approximated using the more straightforward CTT-based scoring method. This may be useful when calculation of IRT-based scores is impractical and allows all A-IADL-Q scores to be placed on a single scale, regardless of scoring method.

P129- SLOWING OF ALZHEIMER'S DISEASE PROGRESSION WITH NEUROAID. C.L.H. Chen[1], Y. Pokharkar[2], N. Venketasubramanian[3] *(1. National University of Singapore - Singapore (Singapore), 2. Singapore Clinical Research Institute - Singapore (Singapore), 3. Raffles Hospital - Singapore (Singapore))*

Background: Slowing disease progression in Alzheimer's Disease (AD) remains challenging and research has focussed on targets with potential disease-modifying therapeutic effects. Moreover, drug combinations may be needed for a multifactorial approach to the treatment of AD which has complex underlying mechanisms. NeuroAiD-II (MLC901) is a formulation containing extracts from nine herbal components, which is marketed in some countries for recovery in stroke and traumatic brain injury (TBI). MLC901 has biological effects on neuroprotection and neuroregeneration as well as clinical benefits on functional and cognitive recovery in stroke and TBI. Clinical studies have been conducted in patients with mild to moderate AD, mild cognitive impairment, vascular cognitive impairments no dementia and vascular dementia (1, 2). The promising results of the ATHENE (Alzheimer's Disease THErapy with NEuroaid) study (NCT03038035) suggested a disease slowing effect with MLC901 as an add-on treatment in subjects with mild to moderate AD. However, the full effect of MLC901 as disease-modifying treatment may have been reduced by non-compliance and missing data (1). **Objectives:** The objective of this exploratory analysis is to assess over 12-month period the disease modification effect of MLC901 as an add-on therapy in mild to moderate AD using an alternative linear mixed effect model. **Methods:** All subjects from ATHENE, a randomized double-blind placebo-controlled delayed-start clinical trial in mild to moderate AD, were included in the analysis. At study entry, subjects were stable on standard treatment (acetylcholinesterase inhibitors or memantine) which was continued throughout the study according to the treating physician's judgement. Subjects were randomized to receive MLC901 (early-starters) or placebo (delayed-starters) for 6 months, followed by a further 6 months when all subjects received MLC901. The Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog) scores were measured at 3, 6, 9 and 12 months. Comparison between early-starters and delayed-starters was performed using a linear mixed effect model with repeated measurements adjusted for treatment, visit, treatment by visit interaction and baseline ADAS-Cog score. The adjusted mean difference (MD) with 95% confidence interval (CI) and p-value (P) were calculated for ADAS-Cog change from baseline at months (M) 9 and 12. The analyses were conducted on both intention-to-treat (ITT) and per-protocol (PP) populations. **Results:** 125 subjects were included in this exploratory analysis. At baseline, mean ADAS-Cog scores were not significantly different (31±12 and 29±10) in early-starters and delayed-starters. Early-starters were significantly different compared to delayed-starters in mean change from baseline ADAS-Cog scores at M9 in both ITT (MD: -3.67 [95% CI: -6.06, -1.28]; P=0.003) and PP analyses (MD: -3.93 [95% CI: -6.99, -0.86]; P=0.013). A significant difference in change in ADAS-Cog score was also observed at M12 only in the PP analyses (MD: -4.30 [95% CI: -8.38, -0.22]; P=0.039). **Conclusions:** This exploratory alternative analysis confirmed a difference between early-starters and delayed-starters on ADAS-Cog suggesting either a prolonged symptomatic effect of MLC901 or slowing of disease progression in subjects on early treatment with MLC901 as an add-on to standard therapy. The treatment effect was most substantial at M12 in patients who were compliant to the study medication and study completers, as shown in PP analysis. The previously available preclinical and clinical data, along with the recent promising ATHENE study results suggest that the next step in the clinical development of MLC901 in AD should be to design a larger clinical study of a longer duration with added biomarkers to demonstrate a disease modification effect in AD. **References:**
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P130- A MULTICENTER, PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED INVESTIGATION OF SAFETY AND EFFICACY OF NILOTINIB BE IN EARLY ALZHEIMER'S DISEASE (NILEAD). Y. Torres-Yaghi[1], M. Sabbagh[2], C. Hoyt[3], K. Guedes[3], F. Pagan[1], R. Turner[1], J. Ahn[1], C. Moussa[1] *(1. Georgetown - Washington, DC (United States), 2. Barrow - Phoenix, AZ (United States), 3. Keiferx - Washington, DC (United States))*

Background: Nilotinib BE is a new formulation of the same active pharmaceutical ingredient (API), nilotinib (tasigna, Novartis), that has significant clinical use in over 6000 patients with Chronic Myelogenous Leukemia (CML). KeifeRx in collaboration with Sun Pharmaceuticals Research Industry will evaluate the efficacy of Nilotinib BE in individuals with Early Alzheimer's Disease (EAD) by determining the superiority of Nilotinib BE compared with placebo on the change in the

Clinical Dementia Rating–Sum of Boxes (CDR-SB) from Baseline to 18 months (Week 72) of treatment. We hypothesize that Nilotinib BE will halt cognitive decline in EAD. KeifeRx will conduct a phase 3 multicenter, placebo-controlled study that will enroll a total of approximately 1275 subjects and will include a Core Study that will enroll approximately 425 subjects who will be randomized to the placebo group (arm A) and 425 subjects to each of the Nilotinib BE, 84mg (arm B) and 112mg (arm C) groups. A Biomarker Sub-study will also enroll approximately 180 subjects (60 subjects per group), who will be randomized for the CSF biomarker sub-study at Baseline and 18 months (Week 72). Additional, approximately 164 subjects (48 per group) will be randomized to the imaging sub-studies, including amyloid PET, tau PET and vMRI, at Baseline and 18 months (week 72). Nilotinib BE is an oral drug that has significant advantages compared to intravenously administered treatments. Not only the convenience of oral administration favors Nilotinib BE, but also the known safety profile of Nilotinib in CML and in neurodegenerative diseases compared to the serious adverse effects of infusions, mainly Amyloid Related Imaging Abnormalities (ARIA).

P131- SUBJECTIVE ILLNESS REPRESENTATIONS IN AN EARLY-STAGE ALZHEIMER´S DISEASE POPULATION: PSYCHOMETRIC PROPERTIES OF THE RADIX QUESTIONNAIRE. A. Villarejo-Galende[1], E. García-Arcelay[2], G. Piñol-Ripol[3], A. Del Olmo-Rodríguez[4], F. Viñuela[5], M. Boada[6], E. Franco-Macías[7], A. Ibañez De La Peña[8], M. Riverol[9], J. Maurino[2] *(1. Department Of Neurology, Hospital Universitario 12 De Octubre - Madrid (Spain), 2. Medical Department, Roche Farma - Madrid (Spain), 3. Unitat Trastorns Cognitius, Hospital Universitari De Santa Maria - Lleida (Spain), 4. Department Of Neurology, Hospital Universitario Dr. Peset - Valencia (Spain), 5. Department Of Neurology, Hospital Universitario Virgen Macarena - Sevilla (Spain), 6. Ace Alzheimer Center Barcelona - Barcelona (Spain), 7. Department Of Neurology, Hospital Universitario Virgen Del Rocío - Sevilla (Spain), 8. Centro De Investigación De Parkinson, Policlínica Guipúzcoa - San Sebastián (Spain), 9. Department Of Neurology, Clínica Universidad De Navarra - Pamplona (Spain))*

Background: Patients' beliefs and expectations about a disease influence their emotional reactions and coping resources, and have been associated with quality of life and treatment adherence. Identifying and understanding patients' representations of Alzheimer´s disease (AD) can be useful for the early implementation of individualised interventions to improve their ability to live well with their disease. The Representations and Adjustment to Dementia Index (RADIX) is a self-report instrument validated in patients with mild-to-moderate dementia to assess their understanding of the condition and its consequences in five components: identity, cause, disease course, possibilities for controlling the disease, and practical and emotional consequences. However, it has not been evaluated in patients with early-stage AD. **Objectives:** The aim of this study was to assess the dimensional structure and item distributions of the RADIX in early AD. **Methods:** A non-interventional, cross-sectional study was conducted at 21 Memory clinics in Spain. Patients aged 50-90 years, diagnosed with prodromal or mild AD (NIA/AA criteria), a Mini-mental State Examination (MMSE) score ≥ 22, and a Clinical Dementia Rating-Global score (CDR-GS) of 0.5 or 1.0 were recruited. For practical (4 items) and emotional (5 items) consequences, responses to the RADIX questions are rated on a 4-point scale (from strongly disagree to strongly agree) and can be summed to give an overall score and then divided by 4 and 5 to give the mean score, respectively. Higher scores indicate greater negative consequences. A non-parametric item response theory procedure, Mokken analysis, was performed to assess the underlying dimensional structure and scalability of items and overall questionnaire. Each item was required to have a scalability coefficient (Hi) of ≥ 0.30 and an overall scale scalability index (H) of ≥ 0.30. A confirmatory factor analysis (CFA) was also run to check the two-dimensional structure originally described with practical and emotional consequences as latent variables underlying the RADIX measure. Associations between the RADIX and the generic Brief Illness Perception Questionnaire (B-IPQ) and Quality of Life in Alzheimer´s Disease scale (QoL-AD) were analysed using Spearman´s rank correlations. All analyses were performed with JASP (v 0.14.1) and R (v 4.0.3) using the mokken and lavaan libraries. **Results:** A total of 146 patients were studied. Mean (SD) age was 72.3 (7.0) years and 50.3% were female. Mean duration of AD was 1.4 (1.8) years. Mean MMSE score was 24.6 (2.1) and 87.2% had a CDR-GS score of 0.5. One hundred sixteen (79.4%) participants were aware of their condition and sixty-six (44.3%) used the term AD when asked if they knew their specific diagnosis. The most frequent causes assigned by patients as responsible for their condition were ageing and brain changes. Mean practical and emotional consequences RADIX scores were 1.8 (0.6) and 2.2 (0.8), respectively. The RADIX showed high reliability (Cronbach's alpha = 0.86). Mokken analysis indicated its items fitted to a unidimensional scale with an overall scalability coefficient which agrees with a moderate scale (H = 0.45). Analyses also showed RADIX was consistent with the monotone homogeneity model and appropriate to order persons across the latent trait assessed. The CFA analyses were consistent with both a unidimensional model (CFI=0.96; RMSEA=0.09; SRMR=009) and the two-dimensional model previously described (CFI=1; RMSEA=0, SRMR=0.06). The linear correlation between Mokken item scalability coefficients and standardised loadings from the unidimensional CFA was 0.98 ($p<0.0001$), meaning that both procedures agree when ordering the items of the RADIX scale. RADIX total score correlated significantly with the emotional representation ($r = 0.48$, $p < 0.001$) and cognitive representation ($r = 0.31$, $p < 0.001$) of the B-IPQ, whereas correlation was practically null with the illness comprehensibility ($r = -0.07$, $p = 0.43$). Practical and emotional consequences RADIX scores showed a significant negative correlation with QoL-AD score ($r = -0.39$ and -0.41, respectively; $p<0.0001$). **Conclusions:** The RADIX showed appropriate psychometric characteristics and may constitute a valuable disease-specific addition to understand illness perceptions in earlier stages of AD.

P132- IMPACT OF DISEASE PROGRESSION ON DEPENDENCY IN PATIENTS WITH MILD AND MODERATE ALZHEIMER DISEASE. W. Ye[1], J. Chandler[1], X. Mi[2], A. Tockhorn-Heidenreich[1], J. Johnston[1], E. Doty[1] *(1. Eli Lilly And Company - Indianapolis (United States), 2. Techdata Services Company - King Of Prussia (United States))*

Background: Dependence on others to carry out everyday activities as Alzheimer's Disease (AD) progresses is associated with greater care partner burden, higher societal costs and lower quality of life for patient and care partner. The impact of cognitive and functional decline on dependency in early symptomatic AD has not been well characterized. Understanding progression of dependency across the disease spectrum may further support the value assessment of disease

modifying treatment. **Objective:** We evaluated dependency in everyday activities in a sample of mild and moderate AD patients over 18 months and estimated the potential impact of a 20-30% slowing of disease progression. **Methods:** Participants with amyloid positivity in the placebo arms of the EXPEDITION1, 2 and 3 randomized placebo-controlled studies of solanezumab in mild and moderate AD (NCT00904683, NCT01900665 and NCT00905372) were used in these post-hoc analyses. IADRS (a composite score of Alzheimer's Disease Assessment Scale Cognitive subscale ADAS-Cog14 and Alzheimer's Disease Cooperative Study- instrumental Activities of Daily Living (ADCS-iADL) and Clinical Dementia Rating Scale (CDR-SB) were used to measure disease progression. Six dependence levels (DL) (0-5; 0-no care needs; 3-extensive home care services; 5-nursing home) were derived from ADCS-ADL using a previously validated algorithm. DL was dichotomized into DL ≤ 2 or > 2, where DL > 2 indicates need for extensive home care or full-time care. Mixed-model repeated measures (MMRM) analyses were conducted to estimate least squares mean change (LSMC) and standard error (SE) from baseline for measurements. A logistic regression model was used to assess the likelihood of reaching DL >2 at 18 months with IADRS or CDR-SB change from baseline as the predictor, adjusting for age, baseline dependency level, investigator, and concomitant AChEI and/or memantine use at baseline (yes/no). Separate models were fitted for mild and moderate AD. The predicted mean probability of reaching DL >2 at 18 months was estimated using prespecified values (20% and 30%) of slowing of disease progression. Odds ratios (OR) with 95% confidence interval (CI) of reaching DL>2 were estimated relative to natural disease progression. **Results:** 1278 study patients (1204 mild and 74 moderate AD) had mean age (Standard Deviation (SD)) 73.5 (8.06) years and 58.5% female. Moderate AD patients had greater DL than mild AD at baseline (average (SD) 2.5(0.8) and 2.1(0.9), respectively. The average (SD) IADRS and CDR-SB were 105.5 (14.21) and 3.90 (1.93) for mild AD and 85.3 (18.29) and 5.70 (2.30) for moderate AD. The mean changes in IADRS and CDR-SB from baseline to 18 months were statistically significant for both groups with IADRS and CDR-SB LSMC (SE) -14.78 (0.55) and 2.16 (0.09) for mild AD and -24.09 (2.43) and 4.26 (0.38) for moderate AD, respectively. Over 18 months, the proportion of patients reaching DL> 2 increased for both groups (from 24.8% at baseline to 41.9% at 18 months in mild AD, and from 37.8% to 68.2% in moderate AD). For mild AD, a 14.78-point worsening in IADRS led to a predicted probability of reaching DL >2 of 0.41 for progression over 18 months. Compared to the observed progression, delaying progression by 20% or 30% could lower that probability to 0.35, or 0.33 and make it 21% or 30% less likely to reach DL> 2 with OR (95% CI) 0.79 (0.76, 0.82), or 0.70 (0.66, 0.74), respectively. For moderate AD, a 24.09-point worsening in IADRS could has a predicted probability of reaching DL >2 of 0.91 over 18 months. Delaying progression by 20% or 30% could lower the probability of reaching DL >2 to 0.86 - 0.82 and make it 41-54% less likely reaching DL>2 with OR (95% CI) 0.59 (0.40, 0.88) to 0.46 (0.26, 0.82). A 2.16-point worsening for mild AD and 4.26-point for moderate AD in CDR-SB led to a predicted probability of reaching DL >2 of 0.38 and 0.81 over 18 months. Compared to the observed progression over 18 months, delaying progression by 20% or 30% could lower the predicted probability of reaching DL>2 to 0.34 or 0.32 for mild AD and 0.72 or 0.66 for moderate AD, respectively and make it 16%-24% less likely for mild AD with OR (95% CI) 0.84 (0.81, 0.86) or 0.76 (0.73, 0.80) and 40%-54% less likely for moderate AD with OR (95% CI) 0.60 (0.42, 0.86) to 0.46 (0.27, 0.80) to reach DL >2, respectively. **Conclusion:** Moderate AD patients had greater levels of dependency than mild AD patients and dependence levels increased over 18 months for both groups. Treatments that slow disease progression in early symptomatic AD have the potential to delay patients' need for more extensive home care or assisted living seen in moderate AD. Full COI disclosure will be on the 2nd slide of the presentation or in the poster presentation.

P133- THE RESPONSIVENESS OF COGNITIVE AND FUNCTIONAL OUTCOME MEASURES IN PRECLINICAL ALZHEIMER'S DISEASE: IMPLICATIONS FOR TRIAL DESIGN. M. Dubbelman[1], H. Hendrikse[1], L. Ottenhof[1], E. Vijverberg[1], N. Prins[2], L. Kroeze[1], A. Van Harten[1], B. Van Berckel[1], J. Harrison[1], W. Van Der Flier[1], S. Sikkes[1] *(1. Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam Umc Location Vumc - Amsterdam (Netherlands), 2. Brain Research Center - Amsterdam (Netherlands))*

Background: Cognitive and functional outcome measures that are sensitive to the earliest cognitive changes in preclinical Alzheimer's disease (AD) are essential for demonstrating treatment efficacy in secondary prevention trials. We hypothesized that the sensitivity of outcome measures may differ according to biomarker inclusion criteria, such as amyloid and/or tau positivity, or apolipoprotein (APOE) ε4 carriership. **Objectives:** To determine the sensitivity of numerous cognitive and functional outcome measures, commonly used in clinical practice, within various biomarker groups. **Methods:** We included 551 participants with subjective cognitive decline (61.8±8.6 years, 44% female) from the observational Amsterdam Dementia Cohort. All had longitudinal cognitive assessments and baseline biomarker data, Mini-Mental State Examination (MMSE) ≥26, and Geriatric Depression Scale <6. We created different (overlapping) target groups, based on inclusion criteria in secondary prevention trials of preclinical AD: (1) amyloid positive as determined by positron emission tomography scans or in cerebrospinal fluid (CSF) (n = 106), (2) p-tau positive as determined by CSF phosphorylated (p-)tau levels (n = 120), (3) both amyloid and p-tau positive (n = 47), (4) APOE ε4 carriers (n = 156) and (5) APOE ε4 carriers who are also amyloid positive (n = 64). Linear mixed models were used to investigate the sensitivity to change of seventeen standardized cognitive outcome measures, including the MMSE, immediate and delayed recall on word list learning and logical memory tests, the Trail Making Test, Stroop Color-Word Test, Letter Digit Substitution Test, semantic and phonetic fluency tests, digit span backwards, and the Boston Naming Test. The Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q) was used as a functional outcome. All test scores are presented as higher reflecting better performance. Time in years served as the main variable of interest of which we report standardized coefficients reflecting standard deviation decline per year, adjusting for sex, education, and baseline age. We also investigated composites based on the Preclinical Alzheimer Cognitive Composite (PACC5) and the Cognitive-Functional Composite (CFC). Finally, we limited study follow-up duration to a maximum of 18 months, in line with the typical minimum duration of a phase III trial. **Results:** Based on the full follow-up duration (mean = 3.9 ± 2.9 years, range 0.4–18.9 years), the amyloid and p-tau positive group showed the largest number of cognitive tests that show significant change over time with the largest effects (14/17, 82%) with standardized coefficients ranging from -0.70 to -0.24). The responsiveness of cognitive outcomes was lower among APOE ε4 carriers, with 9/17 responsive tests (53%; standardized coefficients ranging

from -0.30 to -0.13) showing change over time. The phonetic fluency improved among APOE ε4 carriers (standardized coefficient = +0.10). In the amyloid positive group, 11/17 cognitive outcome measures (65%) were responsive to change (standardized coefficients ranging from -0.47 to -0.21) and in the p-tau positive group 10/17 cognitive tests (59%) were responsive, with standardized coefficients ranging from -0.39 to -0.14. In amyloid positive APOE ε4 carriers, 9/17 cognitive outcome measures showed significant change over time, with standardized coefficients ranging from -0.41 to -0.17. Functional impairment, as measured with the A-IADL-Q was responsive in all target groups except the p-tau only group (standardized coefficients ranging -0.16 for APOE ε4 carriers to -0.70 for amyloid and p-tau positive individuals). The PACC5 and CFC were responsive to change over time all but one group, with standardized betas ranging from -0.22 (p-tau only) to -0.60 (p-tau and amyloid) and -0.20 (p-tau only) to -0.48 (p-tau and amyloid), respectively. Both composites did not show change over time among APOE ε4 carriers. With the follow-up duration limited to a maximum of 18 months, most cognitive tests were no longer responsive to change over time. Moreover, the direction of changes reversed, indicating improvements over time. The A-IADL-Q did not show change over time in any group, nor did the CFC. The PACC5 showed improvements in the p-tau only group (standardized coefficient = 0.10) and among APOE ε4 carriers (standardized coefficient = 0.06). **Discussion:** We demonstrated that commonly used cognitive outcome measures, as well as a functional outcome measure, can capture cognitive decline in preclinical AD, specifically over longer follow-up times and in individuals who are included in a more advanced pathological disease stage (i.e., those who are both amyloid and tau positive). However, with a limited study duration of 18 months or shorter, as well as among APOE ε4 carriers, responsiveness was considerably lower. Our findings have important implications for trial design, to the extent that either longer study durations, more sensitive outcome measures, or more specifically targeted study populations may be required to adequately investigate potential treatment effects. We propose that outcome measures be selected to be appropriate to the target population and that trial duration be determined by the required rate of decline.

P134- THE EFFECT OF DIETARY HABIT ON THE PROGRESSION OF ALZHEIMER'S DISEASE: A CREDOS (CLINICAL RESEARCH CENTER FOR DEMENTIA OF SOUTH KOREA) STUDY. Y.K. Minn[1], S.H. Choi[2] *(1. Kangnam Sacred Heart Hospital, Hallym University - Seoul (Korea, Republic of), 2. Inha University Medical Center - Inchon (Korea, Republic of))*

Background: The social costs associated with AD increase as dementia severity increases. Despite extensive research in the field of dementia, few drugs prevent the progression of AD. Alternative therapies, including non-pharmacological approaches, are still needed not only for the prevention of dementia but also for the stage of dementia. It is well-known that specific diet patterns, such as a Mediterranean diet, slow the development of dementia. However, dietary patterns are reflective of nations' unique cultures and are difficult to artificially change. Both healthy and unhealthy eating habits exist even within the same culture. In addition, the effects of dietary habit on progression of on dementia patients remain unknown. **Objectives:** In this study, we aimed to investigate what dietary habits are associated with progression of dementia over three years from Alzheimer's disease dementia patients enrolled in the Clinical Research Center for Dementia of South Korea (CREDOS) study (November 2005 to January 2015), a hospital based multi-center registry project (1). **Methods:** We selected mild to moderate Alzheimer disease patients with a Clinical Dementia Rating (CDR) scale of 2 or less from the CREDOS study. We included probable AD patients using criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association, and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Mini-Dietary Assessment Index for Koreans was initially assessed (2). A subject was asked to check, in their answers, either 'always', 'usually', or 'rarely', reflected by a score 5, 3, and 1 (5 means good habit, 1 means bad habit). The CDR-Sum of Box, the Caregiver-Administered Neuro Psychiatry Inventory (CGA-NPI), Seoul-Instrumental Active Daily Living(S-IADL) and a global composite score (NTB-Z) were checked for up to three years. For un-adjustment analysis, mixed model as applied, A two-way layout model with repetition was selected. ANOVA and $\chi 2$ test were used to testing the heterogeneity of well-known risk factor for dementia between each group. A mixed model analysis was performed again by correcting the disturbance variable that was found to be meaningful in the above step. **Result:** A total of 705 patients with mild to moderate AD were enrolled. In the un-adjustment linear mixed models, some good diet habit (Q2, eat foods made of meat, fish, eggs, beans, or tofu at least 3-4 times daily, Q7, add salt or soy sauce to food, when eating and Q10, eat all food evenly without being picky eaters) showed positive effect. In Q2, score 5 and score 3 showed lower CGA-NPI than score 1. In Q7, score 3 showed good effect on NTB-Z, CGA-NPI and S-IADL but only CGA-NPI showed good effect on score 5. In Q10, score5 showed good effect on CDR-SB and S-IADL than score 1 but score 3 did not showed good effect. Male, high education, current smoker, current drinking low GDS-15 and high MMSE participants had good dietary habits. After adjustment, Q7 and Q10 showed good effect on dementia progression. In Q7, CDR-SB, NTB-Z, S-IADL and CGA-NPI showed good effect on score 3 but only CDR-SB and CGA-NPI showed good effect on score 5. In Q10, the score5 group showed better effects than the score1 group for 3 years on CDR-SB and S-IADL. Conclusion: Good dietary habits, especially eating less salt and evenly without being picky eaters, have good effects on dementia, even after adjusting for major risk factors linked to dementia. It is important not only to find and consume special foods that are good for dementia, but eating less salty and eating the foods evenly under given environment is helpful for dementia. **References:** 1. Park HK, Na DL, Han S-H, et al. Clinical Characteristics of a Nationwide Hospital-based Registry of Mild-to-Moderate Alzheimer's Disease Patients in Korea: A CREDOS (Clinical Research Center for Dementia of South Korea) Study. Journal of Korean Medical Science. 2011;26(9):1219-1226. 2. Kim W, Cho M, Lee H. Development and validation of mini dietary assesment index for Koreans. KoreanJ Nutr. 2003;36(1):83-92.

P135- LENGTH OF ADMINISTRATION OF ADAS-COG AND CDR ASSESSMENT IMPACTS DATA QUALITY. B. Echevarria[1], S. Negash[1], L. Wolf[1], R. Blattner[1], J. Giuffrida[1], S. Gamazo Navarro[1], V. Cimermanova[1], C. Randolph[1] *(1. WCG Clinical Endpoint Solutions - Hamilton (United States))*

Background: Administration of both structured (ADAS-Cog) and semi-structured (CDR) clinician administered outcome assessments (COA) utilized in Alzheimer disease (AD) clinical trials can significantly vary among study sites and raters. This variability in administration of key outcome measures can undermine the detection of a treatment effect

in a randomized clinical trial and may also be a contributing factor in failures and inconclusive results recently seen in AD trials. Administration time of outcome measures that is either too short or too long may be linked to poor rater performance or contribute to decreased subject performance. In this project we examined whether assessments that are duration outliers (either too short or too long) result in higher rates of scoring discrepancies and/or are deemed to not meet assessment quality expectations when reviewed by a team of highly trained and calibrated independent clinicians. **Objectives:** In this study we aim to evaluate whether ADAS-Cog and CDR assessments that are too short or too long result in a higher number of scoring errors and/or quality failures when they are independently reviewed by highly trained and calibrated clinicians. **Methods:** Aggregated data from 18 multinational clinical trials of Early Symptomatic and Mild to Moderate AD were analyzed. ADAS-Cog and CDR assessments conducted by site raters were independently reviewed via audio recording. Site raters underwent a rigorous pre-screening, qualification, and certification process prior to being added to studies. A total of 43,590 reviewed assessments were evaluated. Separate analyses were conducted for each study population and scale in four cohorts: Early Symptomatic/CDR (n = 23,536), Mild-to-Moderate/CDR (n = 5,025), Early Symptomatic/ADAS-Cog (n = 8,971), Mild-to-Moderate/ADAS-Cog (n = 6,058). Scale duration groups in each cohort were classified based on percentile rank, where assessments in the top 10 % of the cohort were classified as High Duration, bottom 10% as Low Duration, and the remaining assessments as Expected Duration. Rates of scoring discrepancies as well as quality failures were compared across Duration groups in each cohort. **Results:** Group differences were observed in both ADAS-Cog and CDR groups. One-way ANOVAs comparing the Duration groups in ADAS-Cog revealed significantly worse performance in High Duration group than Expected Duration for both discrepancy rates (Early Symptomatic: $df = 2$, $F = 44.52$, $p < .0001$; Mild-to-Moderate: $df = 2$, $F = 10.18$, $p < .0001$) and quality failures (Early Symptomatic: $df = 2$, $F = 61.18$, $p < .0001$; Mild-to-Moderate: $df = 2$, $F = 11.61$, $p < .01$). For the CDR, significantly worse performance was observed in Low Duration group than Expected Duration for both discrepancy rates (Early Symptomatic: $df = 2$, $F = 47.77$, $p < .0001$; Mild-to-Moderate: $df = 2$, $F = 7.16$, $p < .0001$) and quality failures ($df = 2$, $F = 204.11$, $p < .0001$; Mild-to-Moderate: $df = 2$, $F = 48.68$, $p < .0001$). **Conclusion:** Results indicate that unusually long duration assessments with the ADAS-Cog are associated with significantly increased score discrepancies across disease severities. Unusually short or unusually long ADAS-Cog administration times were also associated with a more modest increase in administration errors, more evident in the early symptomatic subjects than in subjects with mild-moderate dementia. For the CDR, unusually long duration of assessment was not associated with an increase in either scoring errors or administration errors, but unusually short duration of assessment was associated an increase in both scoring and administration errors, evident across disease severity.

P136- A RANDOMIZED STUDY TO EVALUATE THE EFFICACY OF DONEPEZIL IN IMPROVING VISUOSPATIAL ABILITIES IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT USING EYE-TRACKER.

K. Ko Woon[1], W. Qi[2], K. Se Hee[3], S. Byoung-Soo[1] *(1. Department of Neurology, Jeonbuk National University Medical School and Hospital - Jeonju (Korea, Republic of), 2. Jeonbuk National University Medical School - Jeonju (Korea, Republic of), 3. Biomedical Research Institute of Jeonbuk National University Hospital - Jeonju (Korea, Republic of))*

Background: Cholinesterase inhibitors (ChEIs) decrease long-term cognitive decline in patients with Alzheimer's disease (AD); however, there is little evidence that ChEIs affect cognitive test scores in patients with mild cognitive impairment (MCI). Conventional endpoints, such as cognitive tests or clinical rating scores, may lack the sensitivity to subtle treatment effects in participants with MCI. Therefore, there is an immediate need to refocus on direct physiological assessments to detect the effects of ChEIs in patients with MCI due to AD. **Methods:** We propose a randomized controlled trial to evaluate the effect of donepezil, a ChEI, on patients with MCI due to AD. We plan to recruit 78 participants (39 in each arm) with MCI who had amyloid positron emission tomography (PET)-positive results for this open-label study. To evaluate subtle differences, we will measure eye-tracking metrics and digital pen data while participants perform the simplified Rey Complex Figure (RCFT) and clock drawing tests. The primary outcome is a change in the ratio of the number of fixations (working space/perceptual space) performed using the simplified RCFT, from baseline to 12 weeks, as assessed using eye-tracking metrics. The secondary outcomes are changes in general cognition, clinical severity, activities of daily living, and visuospatial function assessed using standard rating scores and digital pen data. The analyses of the primary and secondary outcomes will be based on the difference in changes during follow-up between the donepezil and control groups using the t-test or Mann-Whitney U test, as well as adjusting for baseline values. **Results:** Our preliminary results showed a tendency for the ratio of the number of fixations (working space/perceptual space) to increase in the donepezil group compared to the control group ($p = 0.036$). **Discussion:** This study is designed to determine whether eye-tracking metrics can detect the effect of donepezil on visuospatial dysfunction more sensitively in patients with MCI. It is expected that multimodal data, such as eye-tracking and digital pen data, may provide helpful biomarkers for identifying subtle changes that are difficult to measure using conventional methods. This research was supported by Eisai Korea Inc.

P137- A PHASE 2B, RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFECTS OF SAGE-718 IN PATIENTS WITH ALZHEIMER'S DISEASE: STUDY DESIGN.

A. Koenig[1], T. Lago[1], J. Johannesen[1], S. Li[1], E. Freitag[1], J. Wald[1], K. Paumier[1], M. Quirk[1], J. Doherty[1] *(1. Sage Therapeutics, Inc. - Cambridge, Massachusetts (United States))*

Background: Alzheimer's disease (AD) is a common neurodegenerative illness associated with cognitive impairment and loss of independence, accounting for 60–70% cases of dementia globally (1). Both executive functioning (eg, problem solving) and learning and memory deficits that are associated with AD occur early in the disease (2). Approved therapies for mild cognitive impairment (MCI) or mild dementia associated with AD have modest efficacy, and their use may be limited by side effects (3). There is unmet need for effective treatments

that address early cognitive decline and impairment in daily functioning in patients with AD. N-methyl-D-aspartate receptors (NMDARs) are critical for neuronal network stabilization and are involved in many cognitive and behavioral processes (4, 5). NMDAR dysfunction has been implicated in multiple neuropsychiatric conditions (6). SAGE-718 is a novel NMDAR positive allosteric modulator that is being investigated by Sage Therapeutics for the treatment of cognitive impairment associated with AD and other neurodegenerative disorders. Treatment with SAGE-718 demonstrated improved performance on cognitive tests vs placebo following a ketamine challenge in a study of healthy volunteers (7). In the Phase 2, open-label, signal-finding LUMINARY Study (NCT04602624), SAGE-718 was generally well tolerated and associated with improved performance on cognitive tests in patients with MCI or mild dementia due to AD (n=26). Based on these preliminary results, a randomized, double-blind, placebo-controlled study to evaluate the effect of SAGE-718 on cognitive performance in patients with MCI or mild dementia due to AD was planned. **Objectives:** To describe the design of a randomized, double-blind, placebo-controlled study to evaluate the effect of SAGE-718 on cognitive performance in patients with MCI or mild dementia due to AD. **Methods:** Approximately 150 patients will be enrolled across 40 sites in the United States. Eligible patients are aged 50–80 years meeting diagnostic criteria for AD with a baseline Montreal Cognitive Assessment (MoCA) score of 15-25, a baseline Clinical Dementia Rating (CDR) score of 0.5 to 1.0 (inclusive), and a memory box score ≥0.5 will be randomized to receive either oral SAGE-718 or placebo. The primary endpoint is the change from baseline to Day 84 in the Wechsler Adult Intelligence Scale Fourth Edition-IV (WAIS-IV) Coding Test (total correct). The secondary endpoints are safety and tolerability and number of study withdrawals due to treatment-emergent adverse events (TEAEs). Other exploratory cognitive and functional endpoints will also be evaluated. The study design includes a 3-week screening period, a 1-week baseline period, a 12-week treatment period, and a 4-week follow-up period. During the initial 6 weeks of the treatment period, patients in the SAGE-718 arm will receive an initial dose of SAGE-718 (Days 1 to 42), then during the next 6 weeks of treatment, patients will receive a lower dose of SAGE-718 (different dose; Days 43 to 84). The dose regimen is selected to provide optimal pharmacokinetic exposures that are similar to those achieved in prior studies that demonstrate target engagement. Matching placebo will be given throughout the entire treatment period (12 weeks). At scheduled clinic visits during the treatment period, cognitive performance, safety, efficacy, and adherence will be assessed. Study initiation is planned for late 2022. **Conclusion:** This randomized, double-blind, placebo-controlled study is intended to evaluate the safety and effects on cognitive performance of SAGE-718 in patients with MCI or mild dementia due to AD. The results of this study are expected to inform the potential of SAGE-718 for the treatment of cognitive impairment associated with AD. **References:** 1. Sharma K. Mol Med Rep. 2019;20(2):1479-1487. 2. Weintraub S, et al. Cold Spring Harb Perspect Med. 2012;2(4):a006171. 3. Han JY, et al. Alzheimer Dis Assoc Disord. 2019;33(2):87-94. 4. Ghanavati E, et al. Cereb Cortex. 2022. 5. Li F, et al. N Engl J Med. 2009;361(3):302-303. 6. Paoletti P, et al. Nat Rev Neurosci. 2013;14(6):383-400. 7. Koenig A, et al. ACNP 58(th) Annual Meeting: Poster Session I. Neuropsychopharmacology. 2019;44(Suppl 1):78-229. **Funding Source:** This study was sponsored by Sage Therapeutics, Inc. **Acknowledgments:** We would like to thank the patients and their families for helping us reimagine brain health. Medical writing and editorial support were provided by Symbiotix, LLC, funded by Sage Therapeutics, Inc. AK, TL, JJ, SP, SL, EF, JW, KP, MQ, and JD are employees of Sage Therapeutics, Inc., and hold stock or stock options. **Note:** SAGE-718 is an investigational drug and is not approved by the FDA or any other regulatory agency as safe and effective for any use.

P138- BRINGING MEANING TO PERSONALISED BRAIN HEALTH: A TOOL THAT EMPOWERS INDIVIDUALS TO DEFINE AND MONITOR PERSONALLY MEANINGFUL CHANGE. S. Saunders[1], D. Bates[2], A. Bharija[2,3], J. Gomes-Osman[2,4], S. Luz[1], G. Muniz-Terrera[1], Á. Pascual-Leone[2,5], C. Ritchie[1] *(1. Centre for Clinical Brain Sciences, University of Edinburgh, UK - Edinburgh (United Kingdom), 2. Linus Health Inc., Boston, MA, USA - Boston (United States), 3. Department of Medicine, Division of Primary Care and Population Health, Stanford Medicine, Stanford, USA - Stanford (United States), 4. Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA - Miami (United States), 5. Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA - Boston (United States))*

Background: In the early stages of Alzheimer's disease (AD), the aim is to maintain brain health by preventing entirely, or delaying significantly, the development of symptoms. However, it is essential to demonstrate an intervention delivers a meaningful outcome for the patient. Therefore, it is critical to associate most commonly used outcome measures in clinical trials (i.e., biomarkers and symptoms) with outcomes that are relevant for the individual patient and account for the change in treatment priorities over time. To fill this knowledge gap, researchers at the University of Edinburgh have partnered with Linus Health to create a tool for capturing personally meaningful outcomes to monitor functional trajectory, and importantly, treatment effects over time. **Objectives:** Our aim is to create a tool to easily capture what aspects are most important for individuals to retain should their brain health deteriorate through conditions like AD. The presentation aims to (1) to update on the latest results of the electronic Person Specific Outcome Measure (ePSOM) programme, reporting findings from a large UK-wide survey on what outcomes matter to people when developing new treatments for AD and (2) outline a development plan to validate a new digital tool to capture and monitor personally meaningful outcomes in Brain Health. Method: The UK-wide survey (conducted Aug 2019 – Nov 2019) probed individuals to define most important individual priorities in five domains of Brain Health (Everyday functioning; Enjoying life; Thinking abilities; Relationships and Social interactions; Sense of identity). These data were collected using primarily free text responses, alongside relevant clinical and demographic data. We used natural language processing (NLP) techniques to analyse the data. We report findings from a subgroup analysis which includes individuals with a self-reported neurodegenerative disease diagnosis (primarily Mild Cognitive Impairment (MCI) or AD) whereby we conducted comparisons with an age and gender matched control group. We also describe the development and validation plan for a tool aimed at capturing personally meaningful outcomes for use in clinical trials as adjunct to biomarker, cognitive and functional endpoints. Importantly, this tool has the potential to create a critical anchor for personalised interventions by allowing individuals to define 'what does treatment success look like for them? **Results:** The ePSOM survey was filled in by n=5808 respondents across the UK, with over 80,000 free text responses of what outcomes matter to individuals. The automated

NLP analysis resulted in 184 unique themes of importance about Brain Health across the whole data set. A sub-set of n=167 respondents (2.9%) (women n = 91, men n = 69, other n = 7) had received one of our pre-defined neurodegenerative disease diagnoses: most commonly MCI n = 52, 1.1%; or Alzheimer's disease n = 48, 1.0%. Several thematic clusters were significantly more important for the target diagnostic group, e.g.: Expressing opinions; and less important, e.g., Cognitive Games. **Conclusion:** The person specific digital tool developed by our team invites each person using the tool to first define their brain health priorities. While deriving a numeric score is less central in clinical practice than in regulatory trials where a change of score indicates improvement/decline/no change over time, this 'personal outcomes tool' allows patients to define the most important outcomes against which we should measure treatment success. It also informs the most appropriate interventions so that the person can 'be the best version of themselves', i.e., a truly personalised medicine approach. For instance, if a patient defines driving as the key outcome, then as well as personalised interventions to maintain brain health and risk factor modification, the person may also be directed to 'coaching' for driving to build resilience with driving, maintain confidence and develop new skills that helps keep them driving for as long as possible. By employing NLP of either speech or text, we ensure every outcome recorded is unique to that individual and immune to cultural/language biases inherent with tools using pre-defined items. In clinical trials, there is much value for such a tool in parallel with biological measures of AD and provide a secondary endpoint to offer further proof of drug effectiveness, from the study participant's point of view. The ePSOM programme results to date suggest that outcomes that matter shift along the preclinical, prodromal and dementia continuum. This has important implications for the development of outcome measures that may be used in long-term clinical monitoring and interventional studies that may last several years. Our personalised medicine approach could have value more broadly in other diseases which affect brain health.

P139- DEMENTIA CONVERSION RATE DIFFERENCES BETWEEN PATIENTS WITH HIGH- AND LOW-RISK AMNESTIC MILD COGNITIVE IMPAIRMENT IN THE REAL-WORLD: A PROSPECTIVE, MULTICENTER, OBSERVATIONAL STUDY. H. Jang[1], D. Na[2], J. Kwon[3], M. Park[4], Y. Moon[5], J. Lee[6], K. Park[7], A. Lee[8], H. Cho[9], J. Lee[10], B. Kim[11], K. Park[12], B. Lee[13], H. Choi[14], K. Jieun[15], N. Jung[16]
(1. Samsung Alzheimer's Convergence Research Center, Samsung Medical Center - Seoul (Korea, Republic of), 2. Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine - Seoul (Korea, Republic of), 3. Department of Neurology, Changwon Fatima Hospital - Changwon (Korea, Republic of), 4. Department of Neurology, Yeungnam University College of Medicine - Daegu (Korea, Republic of), 5. Department of Neurology, Konkuk University Medical Center, Konkuk University School of Medicine - Seoul (Korea, Republic of), 6. Department of Neurology, Jeju National University College of Medicine - Jeju (Korea, Republic of), 7. Department of Neuroscience, Cognitive Disorders and Dementia Center, Dong-A University College of Medicine and Institute of Convergence Bio-Health - Busan (Korea, Republic of), 8. Department of Neurology, Chungnam National University School of Medicine - Daejeon (Korea, Republic of), 9. Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine - Seoul (Korea, Republic of), 10. Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine - Seoul (Korea, Republic of), 11. Department of Neurology, Chonnam National University Medical School & Hospital - Gwangju (Korea, Republic of), 12. Department of Neurology, College of Medicine, Gachon University Gil Hospital - Incheon (Korea, Republic of), 13. Department of Neurology, Hallym University College of Medicine - Seoul (Korea, Republic of), 14. Department of Neurology, Hanyang University Guri Hospital - Guri (Korea, Republic of), 15. Department of Medical, Eisai Korea Inc. - Seoul (Korea, Republic of), 16. Department of Neurology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine - Yangsan (Korea, Republic of))

Background: Amnestic MCI (aMCI), a subtype of MCI associated with significant decline in memory with no impairment in activities of daily living, may represent the prodromal state of Alzheimer's disease, with a greater risk of conversion to dementia. As aMCI is a heterogeneous clinical entity, prediction of conversion to dementia in aMCI is difficult but important in the real-world setting. Among clinical variables, neuropsychological profiles are significantly associated with dementia conversion; therefore, a nomogram to predict dementia conversion in aMCI was developed to incorporate various major neuropsychological indices. However, this nomogram has not yet been validated to predict dementia conversion in a real-world setting. **Objective:** The primary objective was to determine and compare the conversion rates of high- and low-risk MCI patients using a nomogram that incorporated Seoul Neuropsychological Screening Battery (SNSB) test results from multiple centers. The secondary objectives were (1) to evaluate neuropsychological test score changes, including those of the SNSB-dementia version (SNSB-D) total score, Clinical Dementia Rating Sum of Boxes (CDR-SB), and the Short Form of Geriatric Depression Scale (SGDS), and (2) to evaluate changes of structural magnetic resonance imaging (MRI) measures including cortical atrophy index, hippocampal volume, and cortical thickness between the high- and low-risk groups after 1 and 2 years. **Methods:** This prospective, multicenter, observational study was conducted at 14 study sites in South Korea. Patients were classified as having either high-risk or low-risk MCI according to their

nomogram result. When applying the nomogram, the model without APOE genotype data (Model 1) was used to predict high-risk and low-risk groups considering age and SNSB features (modality of memory impairment [visual, verbal, or both], severity of memory impairment [early or late], and multiplicity of cognitive domains involved [single or multiple]). Based on these features, the predicted probability for dementia conversion was calculated using the nomogram, where the upper and lower 30% were categorized as high-risk and low-risk MCI groups, respectively. Data were collected at Visit 1 (Day 0, time of obtaining informed consent), Visit 2 (Month 12), and Visit 3 (Month 24) using case report forms. The primary endpoint was the differences of conversion rates to dementia between high- and low-risk MCI subgroups, according to the definition of dementia based on the CDR-SB (scores ≥3) and Korean version of the Instrumental Activities of Daily Living (K-IADL) scores ≥0.4. Changes in neuropsychological test scores and structural MRI measures at 1 and 2 years were also compared between high- and low-risk groups. **Results:** In total, 195 patients were included: 97 and 98 in the high-risk and low-risk groups, respectively. Of these, 160 patients, 77 and 83 in the high-risk and low-risk groups, respectively, completed the 2-year follow-up. CDR-SB, SNSB-D, and K-IADL scores; cortical atrophy index; temporal thickness; and hippocampal volume at baseline were significantly different between the high-risk and low-risk groups. The dementia conversion rate overall was 24.7% (39/158); in the high-risk group, 46.1% (35/76); and in the low-risk group, 4.9% (4/82) at the 2-year follow-up. The mean changes from baseline in CDR-SB, SNSB-D, and K-IADL scores and cortical atrophy index at 1 and 2 years were significantly different between the groups. The mean change from baseline at 1 year in temporal thickness and hippocampal volume was significantly larger in the high-risk group than in the low-risk group, while the mean change from baseline at 1 and 2 years in parietal thickness was larger in the high-risk group than in the low-risk group. Finally, significant differences between converters and non-converters in the high-risk group were noted for baseline CDR-SB and K-IADL, but no differences were noted in age, sex, or education. Linear mixed model analysis showed that CDR-SB and SNSB-D at 1 and 2 years were significantly different between converter and non-converter subgroups. **Conclusions:** The conversion rate to dementia after 2 years was greater in high-risk MCI patients than in low-risk MCI patients as determined by the nomogram. In addition, the high-risk MCI group showed worse cognition and neurodegeneration trajectory than the low-risk MCI group. This nomogram is a clinically useful predictor of conversion to dementia that categorizes patients into high-risk and low-risk groups.

P140- PREDICTING TAU PET SIGNAL IN PRODROMAL-TO MILD ALZHEIMER'S DISEASE FROM SPEECH BIOMARKERS AND MACHINE LEARNING.

M.M.M. Mina[1], J.T. Troeger[1], L.S. Schwed[1], N.L. Linz[1], S.S. Bohórquez[2], S.H. Hashemifar[2], T.B. Boggiano[3], E.T. Teng[2]
(1. ki:elements - Saarbruecken (Germany), 2. Genentech Inc - San Francisco (United States), 3. F. Hoffmann-La Roche Ltd - Basel (Switzerland))

Background: In Alzheimer's Disease (AD), the amount and extent of deposition of tau protein correlates with the severity of cognitive and functional impairment, and behavioral symptomatology. However, assessing cerebral tau levels currently requires PET imaging or lumbar punctures, which may be costly, inaccessible, and/or less acceptable for AD patients. Therefore, alternative approaches to estimating brain tau levels may have utility for facilitating decentralized trial designs, higher frequency intra-trial monitoring, or accelerated screening funnels at scale. In this context, speech-based digital measures have great potential as they offer remote assessment, pose lower participant burden, and can be collected frequently at low cost. **Objectives:** To examine whether cerebral tau pathology measured with tau PET can be modeled through speech biomarkers. **Methods:** We performed cross-sectional analyses of baseline assessments from the Phase 2 Tauriel study of semorinemab (an anti-tau antibody) in prodromal-to-mild AD (NCT03289143) in a subset of right-handed English-speaking participants recruited from sites in the United States (N=86, 59% female). Speech data were collected from recordings of the semi-structured Clinical Dementia Rating (CDR) interview with study participants, then processed by the ki:e speech pipeline, which extracts features that have construct validity with cognitive subdomains such as memory and language. Several machine learning models, including Support Vector Regressor, Random Forest Regressor, and Extra Trees Regressor, were trained on those features to predict [18F]GTP1 standardized uptake value ratio (SUVR) in left-hemisphere domain-specific brain regions of interest (ROIs) from the Hammers atlas for language (parahippocampal gyrus, inferior middle temporal gyrus, anteromedial temporal lobe, inferior frontal lobe, lateral inferior parietal lobe, posterior temporal), bilateral ROIs for memory (caudate nucleus, hippocampus, middle frontal gyrus, parahippocampal gyrus, inferior middle temporal gyrus, anteromedial temporal lobe), and whole cortical gray matter. For each model, we used feature selection based on mutual information to optimize performance with the most relevant features. Furthermore, we trained the same models using cognitive scores (including Repeatable Battery for the Assessment of Neuropsychological Status [RBANS] and Alzheimer's Disease Assessment Scale-Cognitive subscale [ADAS-Cog13]) as input to predict [18F]GTP1 SUVR. We used a leave-one-out cross validation to maximize training data while still maintaining testing on the whole population. Speech features were also checked for correlation with cognitive scores, including ADAS-Cog13 and CDR-sum of boxes (SB). **Results:** Speech biomarkers consistently showed better performance relative to cognitive scores in predicting [18F]GTP1 SUVR in ROIs that correspond to language and memory function. Our model on speech features achieved a R2 equal to 0.22, 0.17, and 0.17 for the middle frontal gyrus, inferior frontal lobe, and whole cortical gray ROIs, respectively. Models derived from speech features yielded R2 values that are on average 41% larger than those achieved with the same models derived from cognitive scores. Importantly, incorporating speech features with cognitive scores improves model performance by increasing R2 up to 0.38. Speech biomarkers also moderately correlated with scores on the ADAS-Cog13 (r=-0.22) and CDR-SB (r=-0.39). **Conclusion:** The results show that speech biomarkers have the potential to predict cerebral [18F]GTP1 SUVR related to severity of cognitive impairment in prodromal-to-mild AD. Potential future applications include more rapid population-wide screening for trial inclusion, more frequent estimates of underlying cerebral tau burden during trials, and diagnostic screening to facilitate appropriate use of approved disease modifying therapeutics. **Conflicts of interest:** N.L. & J.T. are shareholders of ki:elements. N.L., J.T., M.M. & L.S. are employees of ki:elements. S.S., S.H. & E.T. are employees of Genentech Inc. T.B. is an employee of F. Hoffmann-La Roche Ltd.

LP85- A MULTICENTER, RANDOMISED, OPEN-LABEL, PROSPECTIVE STUDY TO ESTIMATE THE ADD-ON EFFECTS OF MEMANTINE AS EBIXA® ORAL PUMP (SOLUTION) ON LANGUAGE IN MODERATE TO SEVERE ALZHEIMER'S DISEASE PATIENTS ALREADY RECEIVING DONEPEZIL (ROMEO-AD). H.J. Kim[1], H.J. Han[2], Y. Shim[3], B.C. Kim[4], K.H. Park[4], S.Y. Moon[5], S.H. Choi[6], D.W. Yang[7], B. Yoon[8], E.J. Kim[9], J.H. Jeong[10], S.H. Han[11] *(1. Professor of Neurology Department of College of Medicine, Hanyang University - Seoul (Korea, Republic of), 2. Department of Neurology, Myongji Hospital, Hanyang University College of Medicine - Seoul (Korea, Republic of), 3. Department of Neurology, The Catholic university of Korea Eunpyeong St. Mary's Hospital - Seoul (Korea, Republic of), 4. Department of Neurology, Chonnam National University Medical School - Seoul (Korea, Republic of), 5. Department of Neurology, Ajou University School of Medicine - Seoul (Korea, Republic of), 6. Department of Neurology, Inha University School of Medicine - Seoul (Korea, Republic of), 7. Department of Neurology, The Catholic University of Korea, Seoul St. Mary's hospital - Seoul (Korea, Republic of), 8. Department of Neurology, Konyang University College of Medicine - Seoul (Korea, Republic of), 9. Department of Neurology, Pusan National University Hospital - Seoul (Korea, Republic of), 10. Department of Neurology, Ewha Womans University Seoul Hospital - Seoul (Korea, Republic of), 11. Department of Neurology, Konkuk University College of Medicineb - Seoul (Korea, Republic of))*

Objectives: It is a multicentre, randomised, open, and prospective study to evaluate the effectiveness of speech function in additional treatment of memantine (memantine solution) in moderate to severe Alzheimer's disease patients taking donepezil. **Methods:** There are two groups: Drug trial group is donepezil + memantine (memantine solution) and the Control group is the Donepezil only administered group. Patients in the test group should increase the dose of memantine by 5 mg/day per week for the first 4 weeks and maintain it at 20 mg/day until the end of administration. **Results:** Out of 188 participants, 24 participants dropped out, and the other 164 participants completed the final research process. As the primary outcome, K-WAB had an increase in scores in both groups compared to baseline, but was not statistically significant with a p-value of 0.678. After 12 weeks, donepezil treatment groups presented higher K-MMSE and lower CDR-SB score compared with combination donepezil with memantine, indicating better cognitive and functional status. However, this effect did not sustain until 24 weeks. Combination group presented slowly progressed in the clinical course ($P < 0.0001$). The secondary outcome, Relevant Outcome Scale for Alzheimer's Disease (ROSA), was found in patients with donepezil. As compared with those who were assigned to receive combinations, patients had scores on the ROSA that were higher by an average of 4.6 points. NPI-Q index improved compared to baseline in both groups. The SIB scale did not change significantly compared to the study baseline. **Conclusions and Relevance:** Although several clinical studies have reported significant improvement in speech function after administration of memantine, clinical studies on speech function improvement in Alzheimer's disease patients are still insignificant. There are no studies worldwide on the effect of donepezil and memantine on language function in combination treatment in moderate and severe stages of AD. Therefore, the effect on speech function in add-on therapy of memantine (memantine solution) was evaluated in moderate to severe AD patients who are taking Donepezil at a stable dose. Although it did not show superior effectiveness in the memantine add-on over the Donepezil monotherapy group, memantine is effective in improving behaviour symptoms in patients with moderate or severe stage of AD.

LP86- EFFECTIVENESS OF VORTIOXETINE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND EARLY DEMENTIA: THE MEMORY STUDY. M.C. Christensen[1], S.N. Schmidt[1], I. Grande[2] *(1. H. Lundbeck A/S - Valby (Denmark), 2. Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM - Barcelona (Spain))*

Background: Major depressive disorder (MDD) is a prevalent recurring psychiatric condition associated with cognitive and functional disabilities. Comorbid dementia worsens the prognosis in patients with MDD. Vortioxetine, a multimodal antidepressant, has demonstrated efficacy and safety in adults and the elderly population with MDD, including patients with comorbid Alzheimer's disease (AD), showing improvement in cognitive performance and depressive symptoms. **Objectives:** To evaluate the effectiveness of vortioxetine flexible dose during 12 weeks of acute treatment of depressive symptoms in patients with MDD and early dementia. **Methods:** In this interventional, open-label, single-group, 12-week study, vortioxetine was administered orally starting at 5 mg/day from baseline to week 1 and increased to 10 mg/day at week 1. After week 1, the dose could be increased to 20 mg or decreased to 5 mg based on investigator judgment and patient response. Safety follow-up occurred up to 4 weeks after last treatment or withdrawal. Patients aged 55–85 years diagnosed with recurrent MDD (onset before age 55) and comorbid dementia diagnosed at least 6 months prior to screening were enrolled. Eligible patients required a baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score of ≥26 (moderate to severe depression) and a Mini-Mental State Examination (MMSE-2) score of 20–24 (mild dementia). The primary endpoint was change from baseline to week 12 in MADRS total score analyzed using a mixed model for repeated measurements. Secondary endpoints included change from baseline to week 12 in Digit Symbol Substitution Test (DSST) cognitive performance, Rey Auditory Verbal Learning Test (RAVLT) to assess memory, Instrumental Activities of Daily Living (IADL) for functioning, and Bath Assessment of Subjective Quality of Life in Dementia (BASQID). Change from baseline in IADL total score (dichotomized) was analyzed by sex. Subgroup analysis assessed severity of depression using MADRS total score in patients with AD, baseline DSST total score below average, and MMSE as a covariate. Safety and tolerability were assessed at week 12. **Results:** 83 patients were enrolled, and the full analysis set consisted of 82 (98.8%) patients. The majority were female (65.9% [n=54]) and White (95.1% [n=78]); mean age was 70.3 (n=82) years, and the most common type of dementia was AD (42.7% [n=35]). All 82 patients received vortioxetine 5 mg/day between baseline and week 1, 79 (100%) patients received vortioxetine 10 mg/day between weeks 1 and 4, 52.6% (n=40/76) received vortioxetine 20 mg/day between weeks 4 and 8, and 47.2% (n=34/72) of patients remained on vortioxetine 20 mg/day between weeks 8 and 12. Mean (SE) change from baseline to week 12 MADRS total score (n=70) was −12.4 (0.78; 95% CI, −14.0, −10.9; $P<0.0001$), indicating significant improvement in symptoms of depression. The standardized effect sizes for change from baseline to week 12 DSST total and RAVLT total scores (n=70) were 0.65 (least squares [LS] mean 4.9; SE, 0.90; $P<0.0001$) and 0.28 (LS mean 2.1; SE, 0.90; $P=0.0199$), respectively, exceeding clinically relevant effect sizes of 0.2, indicating cognitive improvement from baseline.

Change from baseline to week 12 BASQID total score converted to percentages (n=72; LS mean 10.2; SE, 1.25; 95% CI, 7.8, 12.7; P<0.0001) showed a significant improvement in subjective quality of life. In the subgroup of patients with DSST total score <1 SD below DSST score at baseline, mean (SE) change from baseline to week 12 MADRS total score was −9.6 (2.56 [n=6; 95% CI, −15.94, −3.30]). Mean (SE) change from baseline to week 12 MADRS total score using MMSE-2 as a covariate was −12.4 (0.79 [n=70; 95% CI, −14.01, −10.86]). Mean (SE) change from baseline to week 12 IADL total scores in female and male patients was 0.26 (0.12 [n=48; 95% CI, 0.03, 0.50]) and 0.02 (0.24 [n=25; 95% CI, −0.47, 0.51]), respectively, indicating significantly better improvement in daily functioning among women (P=0.0308). At week 12, IADL (polytomous) scales for ability to handle finances, ability to use telephone, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, and shopping were rated "1" by 18.8% (n=13), 49.3% (n=34), 43.5% (n=30), 27.5% (n=19), 42.0% (n=29), 42.0% (n=29), 50.7% (n=35), and 23.2% (n=16) of patients, respectively. Mean (SE) change from baseline to week 12 MADRS total score in patients with AD was −11.97 (1.22 [n=31; 95% CI, −14.42, −9.51]) and with other types of dementia was −13.15 (1.0 [n=39; 95% CI, −15.20, −11.09]). A total of 39 (47.6%) patients reported 60 occurrences of adverse events. **Conclusion:** Vortioxetine 10–20 mg at a starting dose of 5 mg for the first week demonstrated effectiveness in reducing symptoms of depression, improving cognitive performance in patients with MDD and comorbid early dementia, and was well tolerated. Approximately 50% of patients were treated with 20 mg by end of treatment. A consistent improvement in MDD symptom severity over time was demonstrated among patients with AD. Overall improvement in daily functioning was demonstrated through the IADL scores. **Disclosures:** MCC and SNS are employees of H. Lundbeck A/S. IG is an advisor, consultant, and/or speaker for Lundbeck, Otsuka, ADAMED, Angelini, CasenRecordati, Ferrer, and Janssen Cilag, and has received research funding from the Institut de Salud Carlos III, Ministry of Economy and Competitiveness, Spain.

LP87- ASSESSING CLINICALLY MEANINGFUL FUNCTIONAL OUTCOMES IN PRECLINICAL ALZHEIMER'S DISEASE. C. Romano[1], G. Novak[2], J. Choi[3], S. Qin[1], D. Henley[2], M. Donohue[3], G. Romano[4], R. Raman[3], R. Amariglio[5], P. Aisen[3], R. Sperling[5] *(1. RTI-HS - Research Triangle Park (United States), 2. Janssen - Titusville (United States), 3. USC - San Diego (United States), 4. Alector - San Francisco (United States), 5. Harvard - Boston (United States))*

Background: Rigorously developed and highly sensitive composite neurocognitive measures have been created to assess very subtle changes in cognition related to preclinical Alzheimer's Disease (AD). An example of these instruments includes the Preclinical Alzheimer Cognitive Composite (PACC) which is comprised of four scales that assess episodic memory, executive function and global cognition. Similar to cognition, subtle functional decline occurs in cognitively unimpaired individuals who later progress to MCI or AD dementia. Highly sensitive functional measures may capture these subtle changes and may help to define clinically meaningful clinical trial outcomes in preclinical AD. Janssen Research & Development LLC and Shionogi and Co Ltd were developing atabecestat, a nonselective oral BACE-1 and BACE-2 inhibitor. A phase 2b/3 confirmatory registration trial (the EARLY trial) was conducted to evaluate efficacy and safety of atabecestat for slowing cognitive decline in preclinical AD and was terminated prior to completion. This study included several functional measures: the Cognitive Function Index (CFI), the Cognitive Function Index Acute (CFIa), the Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument (ADCS-ADL-PI), the State-Trait Anxiety Inventory-6 item version (STAI-6) and the Geriatric Depression Scale (GDS), in addition to neurocognitive assessments; the PACC and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). **Objectives:** Objectives of this research were to interrogate screening data collected in the EARLY trial to examine the relationship between functional measures and amyloid status, and to examine the relationship between functional and cognitive measures. These data will be useful to guide selection of clinically meaningful functional endpoints in future clinical trials. **Methods:** The analysis population included any participant screened for the EARLY study with amyloid status, based on either PET or CSF, and with any one of the following assessments: the self and study partner versions of the CFI (14 items to assess change over past 1 year across a 3 point scale), the CFIa (a modified version of the CFI with an expanded Likert scale and current recall period), the ADCS-ADL-PI (18 items across a 4 point scale, including 3 high-level function items), STAI-6 (6 items assessed with a 4 point scale) and the GDS-short form (15 items with a dichotomous response scale), in addition to the PACC and RBANS. Screening demographics were summarized by amyloid eligibility group, with frequencies and percentages for categorical variables, and mean and standard deviation for continuous data. Comparisons between groups (where sufficient data) were performed using t-tests for continuous variables, and Pearson's chi-squared test for categorical data. Analysis of covariance (ANCOVA) models were used to examine the difference in functional measures between amyloid groups controlling for pre-specified covariates of age, gender and education. Pearson correlation coefficients were used to examine the cross-sectional relationship between the functional and cognitive measures. **Results:** The analysis sample included a total of 3,686 participants. Of these, 756 (21%) were Aβ+, 2182 (59%) were female, 2721 (74%) were married, and 3472 (94%) had a high school or greater education; 1154 (32%) were identified as APOE e4 carriers. Controlling for age, sex and education, scores were significantly higher (worse) for Aβ+ than Aβ- on the CFIa self [2.09 (CI 1.28 – 2.91), p<0.001] and study partner [1.91 (CI 1.09 – 2.73), p < 0.001], and on the CFI self [0.74 (CI 0.27 – 1.21), p=0.002] and study partner [0.56 (CI 0.13 – 0.99), p=0.011], but not for the ADCS-ADL-PI, GDS, or STAI. In Aβ+ participants, Pearson correlations to the PACC were moderate with the CFI (self and study partner, -0.31 and -0.34 respectively), moderate to small with the ADCS-ADL-PI (self and study partner, 0.33 and 0.25 respectively), and small with the CFIa (self and study partner, -0.20 and -0.28, respectively). Correlations of the RBANS were small with the CFI, CFIa, ADCS-ADL-PI and the STAI (range r= 0.10 – 0.23). The corresponding correlations were generally smaller among Aβ- individuals, except for a moderate correlation between the PACC and the ADCS-ADL-PI (0.34 for both self and study partner). Correlations between the CFI and CFIa were strong (ranging 0.59 to 0.67) and were similar between participant and study partner. **Conclusions:** In this cross-sectional assessment, self and study partner rated versions of the CFI and CFIa were sensitive to amyloid status, and the CFI and ADCS-ADL-PI-self demonstrated generally moderate relationships ($|r| \geq 0.30$) to the PACC. While CFI and CFIa were well-correlated, the level of correlation did not indicate a redundancy between measures indicating these tools may measure different aspects of function. Results of this analysis provide important information

on the sensitivity of these functional assessments to amyloid pathology and to neurocognitive assessment. Exploration of these relationships may provide valuable insight into clinically meaningful interpretation of clinical trial study endpoints. Longitudinal assessment of these measures will provide further discernment as to whether these functional measures may detect change over time.

LP88- CHARACTERIZING COGNITIVE CHANGES IN EARLY-STAGE ALZHEIMER'S DISEASE USING LATENT COGNITIVE MEASURES FROM THE ADNI DATASET. J. Bock[1,2], J. Hara[1,3], D. Fortier[1], B. Albala[4,5] *(1. Embic Corporation - Newport Beach (United States), 2. Dept. of Cognitive Sciences, University of California at Irvine - Irvine (United States), 3. Pickup Family Neuroscience Institute, Hoag Memorial Hospital - Newport Beach (United States), 4. UCI Center for Clinical Research - Irvine (United States), 5. UCI School of Medicine - Irvine (United States))*

Background: Many Alzheimer's disease (AD) drugs in development target early stages and could potentially enable AD patients to preserve cognitive abilities and quality of life. However, because cognitive deficits are more subtle in earlier stages, establishing meaningful cognitive treatment effects has become an increasingly difficult challenge for trial sponsors. Drug developers have shown an historical bias in favor of robust batteries (e.g., ADAS-Cog) that test many cognitive domains, including some that are often unaffected in the early stages of AD, and have used rudimentary analytic methods to score these batteries. The inclusion of tests on which all subjects are likely to perform well dilutes signals from wordlist memory (WLM) tests that are more sensitive to early signs of decline due to AD, and using weighted summary scores, even on the most well-designed tests, masks insightful information in response data. The dataset from the Alzheimer's Disease Neuroimaging Initiative (ADNI) contains latent cognitive measures that quantify the underlying cognitive processes of encoding and retrieval. Constructed from these cognitive measures are behavioral measures that quantify probability of recall. One composite measure, M2, is comprised of encoding and retrieval processes involved in immediate recall and correlates closely with performance on immediate free recall (IFR) tasks. Another, M3, is comprised of encoding and retrieval processes involved in delayed recall and correlates with delayed free recall (DFR) tasks. Contrary to directly-observed behaviors (e.g., number of words recalled), these two measures of recall probability are more directly influenced by the processes that underlie behavior and are more sensitive to change. **Objective:** To compare sensitivity to progressive cognitive decline between generalized probability of recall (M measures) and the traditional summary score approach, using WLM test data obtained from the ADNI database. Methods: Item response data was obtained from ADAS-Cog WLM tests (n = 10,933) performed between the years of 2005 and 2021 on subjects (n = 2,348) enrolled in the ADNI, along with their demographics, AD biomarkers, Clinical Dementia Rating-Global Score (CDR-GS), and latent cognitive measures for each WLM test. The subjects were assigned to one of the three groups based on the number of available WLM tests (>=2), the CDR, and ATN status (amyloid, tau, neurodegeneration) via CSF. Since biomarkers were not assessed at each visit, ATN status was assumed to persist for ADAS-Cog assessments within 2 years if an update in status was not available. Stable CN (S-CN; n subjects=155, n assessments=581): CDR 0 and ATN- at baseline with subsequent CDR 0 following 2 years. Slow-progressing MCI (SP-MCI; n subjects=215, n assessment=942): CDR 0.5 and ATN+ at baseline with subsequent CDR 0.5 following 2 years. Fast-progressing MCI (FP-MCI; n subjects=133, n assessments=506): CDR 0.5 and ATN+ at baseline with subsequent CDR 1 or greater following 2 years. Four mixed fixed- and random-effects regression models were generated, each to examine one of the cognitive performance outcome measures: IFR summary scores, DFR summary scores, M2, and M3. Fixed predictors in all models were demographics, ADAS-Cog wordlist, group, and years of follow-up within each group. Random-effects predictors were per-subject intercept variance within each group. Data included in initial analyses was limited to the first 2 years of follow-up, while further analyses utilized the full dataset. Standardized coefficients of slopes were compared between SP-MCI and FP-MCI groups within each measure; they were also compared between measures (IFR vs. M2 and DFR vs. M3) within each group. **Results:** Initial models predicted the corresponding cognitive performance measures (all p's < .001). Intercept coefficients for SP-MCI and FP-MCI groups showed significant difference from the S-CN (reference) group (all p's < .001): IFR (-5.72 [SE=0.40] and -8.68 [SE=0.49] words, respectively), DFR (-3.57 [SE=0.21] and -5.13 [SE=0.21] words), M2 (-.113 [SE=.008] and -.183 [SE=.011] points), and M3 (-.140 [SE=.009] and -.210 [SE=.009] points). Per-year slope coefficients for SP-MCI and FP-MCI groups showed significant decline over time (all p's < .001): IFR (-0.69 [SE=0.13] and -1.30 [SE=0.16] words, respectively), DFR (-0.37 [SE=0.06] and -0.56 [SE=0.07] words), M2 (-.022 [SE=.003] and -.048 [SE=.004] points), and M3 (-.018 [SE=.003] and -.029 [SE=.003] points). Tests of the Z statistic for comparison of standardized coefficients showed significant differences between slopes across years for SP-MCI and FP-MCI groups within each measure (all p's < .01). Within the FP-MCI group, comparison between measures showed a significantly steeper slope for M2 than for IFR (Z = 2.07, p = .038). This trend was corroborated more prominently in analyses of the longer-followed, full data set. **Conclusion:** In early AD clinical trials, when disease progression and cognitive symptoms are mild, demonstrating cognitive benefits of treatment will require the most precise definition of change over time. This study demonstrates that latent cognitive measures, derived from ADAS-Cog WLM test data, are significantly more sensitive than summary scores both for differentiation of CN, slow-progressing MCI, and fast-progressing MCI subjects and for measurement of decline over time.

LP89- NEUROGENESIS HYPOTHESIS WITH A CASE STUDY- PHASE 2A CLINICAL TRIALS RESULTS OF NA-831 FOR THE TREATMENT OF ALZHEIMER'S DISEASE. M. Kurkinen[1], L. Tran[1] *(1. Biomed Industries, Inc. - San Jose (United States))*

In the hippocampus, new neurons are generated throughout life via a process called adult hippocampal neurogenesis (AHN). In mild cognitive impairment (MCI) and mild to moderate AD (early AD), AHN is reduced suggesting that AHN impairment compromises hippocampal function. Accordingly, augmenting AHN could help prevent or slow cognitive decline in MCI and early AD. NA-831 is a small drug molecule, which activates synaptic AMPA receptors, and increases the expression of BDNF (brain derived neurotrophic factor). BDNF is crucial in synaptic plasticity, learning and memory formation in the hippocampus. NA-831 restores neurogenesis by increasing the number of DCX+PCNA+ neuroblast cells. A randomized clinical trial of NA-831 was conducted in 56 patients including 32 patients with MCI, who received 10 mg of NA-831 or placebo orally per day; and 24 patients with

mild and moderate AD, who received 30 mg of NA-831 or placebo orally per day for 24 weeks. **Results:** NA-831 provided a significant delay in cognitive decline in MCI as measured by ADAS-Cog-13, an average score difference of 3.4 compared to placebo (p = 0.01; ITT) after 24 weeks of treatment. Similarly, NA-831 delayed cognitive decline in early AD, an average score difference of 4.1 com-pared to placebo (p = 0.001; ITT). CIBIC-Plus showed 78 % of the study participants receiving NA-831 improved (p = 0.01; ITT). NA-831 was well-tolerated at 30 mg/day for 24 weeks, and no serious adverse events were observed. The Neurogenesis Hypothesis, and details of these Phase 2A clinical trials will be presented and discussed.

LP89A- COGNITIVE COMPOSITE OUTCOME MEASURES FOR CLINICAL TRIALS: CAN YOU HAVE TOO MUCH OF A GOOD THING? X. Wang[1], D. Jacobs[1], D. Salmon[1], H. Feldman[1], S. Banks[1], S.D. Edland[1] *(1. University of California San Diego - La Jolla (United States))*

Background: Cognitive composite outcomes measures are receiving increasing attention as endpoint for clinical trials. For example, the Preclinical Alzheimer Cognitive Composite (PACC) is an outcome measure designed for clinical trials targeting the preclinical to early stages of Alzheimer's disease. The PACC is calculated as the weighted linear sum of four validated neuropsychometric instruments, the Mini-Mental State Examination, Logical Memory Paragraph Recall, Free and Cued Selective Reminding Test, and Digital Symbol Substitution Test. As of July of 2022, 20 clinical trials listed in clinicaltrials.gov report a PACC as the primary or secondary cognitive outcome measure. Moreover, there is an active literature describing variants of the PACC, including modified PACCs with less than or more than four components. **Objectives:** The performance of composite outcome measures such as the PACC is determined by the pattern of covariance of change of the component measures forming the composite. As we have previously shown by formal mathematical derivation and computer simulations, individual component measures used in a composite may actually reduce the efficiency and statistical power of clinical trials using the composite (Ard et al., Pharm Stat. 2015;14(5):418-26). It is important to understand the potential loss of power resulting from this phenomenon. **Methods:** We used standard power calculation formulas informed by longitudinal cohort studies to investigate the performance of cognitive composites as endpoints for clinical trials targeting prodromal Alzheimer's disease. To investigate the performance within elderly persons with amnestic mild cognitive impairment we used longitudinal data from the National Alzheimer's Coordinating Center (NACC) (n=1333 participants, age > 60, mean age 75.3 (standard deviation(SD) 7.3), 46.0% female, 41.6% with an APOE E4 allele). Only three instruments comparable to the components of the PACC are available in this dataset, the Mini-Mental State Examination, WAIS Digital Symbol Substitution Test, and Logical Memory IIA Test. We used these components to calculate a three-item NACC-PACC. Sample size estimates for powering clinical trials using the full NACC-PACC were compared to sample size estimates for the NACC-PACC with a component removed. Power calculations assumed a two-sample t-test with equal allocation to arms, power of 80%, type 1 error of 5%, and equal standard deviation of change in treatment and placebo. **Results:** The mean three year change in the three-item NACC-PACC was 1.20 with an SD of change of 2.38. Using these parameters, a three year clinical trial powered to detect a 50% reduction in mean change would require 246 subjects per arm. The two-item PACC formed by removing the Logical Memory component has a mean three year change of 1.14 (SD 1.95) and would require 186 subjects per arm to detect a 50% slowing of progression. **Conclusions:** Cognitive composites with fewer components and greater statistical power are preferred. The specific PACC variant investigated here is not proposed for an active clinical trial and therefore the findings presented here have no direct clinical relevance. However, this example definitively illustrate a potential problem of composite instruments. There is no guarantee that adding more components will improve the performance of a PACC. Careful examination of pilot data, including examination of reduced forms of the proposed composite, is warranted. To support this examination, we describe methods for identifying component measures that reduce the overall performance of proposed cognitive composite outcome measures.

COGNITIVE ASSESSMENT AND CLINICAL TRIALS

P141- SKT SHORT COGNITIVE PERFORMANCE TEST FOR THE DETECTION OF EARLY COGNITIVE DECLINE – DATA FROM INTERNATIONAL VALIDATION STUDIES. M. Stemmler[1] *(1. University Of Erlangen-Nuremberg - Erlangen (Germany))*

Background: The SKT (= Syndrom-Kurztest; Erzigkeit, 2001) is a short cognitive performance test for the assessment of cognitive decline in older adults. The SKT, which is available in five parallel testing forms, takes about 10-15 minutes for its administration. The test consists of nine subtests assessing memory (three subtests) and attention/speed of information processing (six subtests). Factor analyses suggested that the SKT also taps executive functioning. The SKT was newly scaled using a regression-based norming (cf. Crawford & Garthwaite, 2006). The total score in accordance with the new German norms varies from 0 to 18 (Stemmler, Lehfeld & Horn, 2015). A traffic light system was developed based on optimal cutoffs for the discrimination between three diagnostic groups (cognitively healthy, mild cognitive impairment (MCI) or dementia). Summary scores between 0 and 4 suggest normal cognitive aging or cognitive health (green), scores between 5 and 10 suggest MCI (yellow), and scores above 11 are likely to represent pathological cognitive decline probably due to dementia (red). The regression-based norming was repeated in English speaking countries (Stemmler, Poon & Schneider, 2021) and in China (Lu, Hu, Stemmler & Guo). The testing material, which is almost culture free, was only slightly adapted for the Chinese culture. **Objectives:** To show the test and measurement equivalence of the SKT for the three different versions. **Methods:** In a multicenter study data from cognitively unimpaired volunteers aged 60 to 96 years were collected. Next to descriptive statistics, multiple regressions and of confirmatory factor analysis (CFA) were calculated. **Results:** Data from three culturally different cohorts were analyzed: n = 1054 from German-speaking centers, n = 285 from English-speaking centers, and n = 288 from China. Female adults were always in the majority, 60% (China) and 56% (German and English samples); the mean age varied between 68.1 years (China), 71.5 years (German sample) and 74.1 years (English sample); the mean IQ-value point ranged from 8.74 (China) via 10.7 (German sample) to 11.2 (English sample). Despite the found sample variations, the descriptive statistics suggested large similarities. In all cultures age, intelligence and gender were the most important predictors for assessing cognitive performance. In all samples

the Subtest VII Reversal Naming revealed the largest explained variance based on R2. The CFAs compared the German factor solution to the English and Chinese dataset. Goodness of fit indices suggested high measurement equivalence. **Conclusion:** The SKT can be applied to German, English and Mandarin speaking older adults across the world. **Conflicts of Interest:** The international standardizations were supported by Dr. Willmar Schwabe Pharmaceutics, Karlsruhe, Germany. SKT copyright belongs to Andreas Erzigkeit, owner of Geromed Ltd. (Spardorf, Germany; info@geromed-gmbh.de). Mark Stemmler received fees from Geromed Ltd. for scientific advice. **References:** Erzigkeit H. A short cognitive performance test for assessing deficits of memory and attention – User's manual. Geromed; 2001. Crawford, J. R. & Garthwaite, P. H. Comparing patients' predicted test scores from a regression equation with their obtained scores: A significance test and point estimate of abnormality with accompanying confidence limits. Neuropsychology 2006, 20, 259–271. Stemmler M, Lehfeld H, & Horn R. SKT Manual. 4th extended and revised edition. Spardorf: Geromed; 2015. Lu, Y., Hu, J., Stemmler, M. & Guo, Q. Validation of Chinese Version of SKT (Syndrom Kurztest): A Short Cognitive Performance Test for the Assessment of Memory and Attention. Diagnostics 2021, 11(12), 2253. Stemmler, M, Schneider, S. M. V. & Poon, L. W. The Application of the SKT Short Cognitive Performance Test to English-Speaking Populations. Psych 2021, 3(4), 717-727.

P142- IMPACT COGNITIVE ASSESSMENT: WHAT ARE WE MEASURING. J. Gyurke[1], P. Schatz[2] *(1. Riverside Insights - Lutz (United States), 2. Saint Joseph's University - Philadelphia (United States))*

Background: Evaluation of neurocognitive status has evolved significantly throughout the past several decades, including a transition from paper-based to computer-based assessment measures. This transition has created an increasing demand for a computerized neurocognitive battery that is practical, cost effective, and efficient for healthcare professionals to utilize, especially when assessing large numbers of individuals. The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT, Version 4) is designed to meet these demands while maintaining high standards for reliability, validity, sensitivity, and specificity. Within the elderly population, increased variability in measures of reaction time, working memory, and fluid intelligence has been consistently found in early research (Hale, Myerson, Smith, and Poon 1988; Morse 1993). In this regard, assessment of these domains using ImPACT Version 4 should show similarly increased variability in the Verbal Memory and Reaction Time composites. Complicating interpretation of test data in this age group, poor performance may be attributed to a number of factors such as health conditions (i.e., age related cognitive decline, Parkinson's, etc.) or medication. In addition to increased variability, it also generally accepted that as individuals age, there is an age-appropriate level of cognitive decline in performance. The specific nature of cognitive decline is less well understood, as performance in different domains does not decline at the same rate within and across subjects. Such variability can complicate the assessment and classification of cognitive status, as tools that provide a single summary score often overlook cognitive issues that might occur in broader performance domains. This is particularly important when trying to qualify potential subjects for clinical trials. **Objectives:** The purpose of this study was to: 1) document normative, age-related neurocognitive performance changes across 10-year age bands (between 40 and 80) on measures of memory and response time, 2) establish construct validation of ImPACT as a valid measure of memory and response time in individuals ages 60-80, and 3) establish test-retest reliability of the measure in individuals ages 60-80. **Methods:** All measures in all samples were administered by neuropsychologists who were trained in test administration. All tests were administered according to standard procedures outlined in the associated Administration and Scoring Manuals. Normative sample: A normative sample of 1,680 individuals (964 males and 725 females), ages 40-80, completed the ImPACT Version 4. Dependent measures include 4 composite scores: Verbal Memory, Visual Memory, Visual Motor Speed, and Reaction Time. Construct Validation Sample: A sub-sample of 71 individuals (45 males and 26 females), ages 60-80 years old (mean= 67.27, SD=4.92) completed the construct validity study. The normative sample completed only the ImPACT Version 4, whereas the construct validation sample also completed widely utilized and previously validated instruments of Memory and Motor Speed, select subtests of the Hopkins Verbal Learning Test (HVLT), Brief Visuospatial Test-Revised (BVMT-R), and Symbol Digit Modalities Test (SDMT), and ImPACT Version 4 were administered within the same session. Test-Retest Sample: A sub-sample of 93 individuals (62 males, 31 females), ages 60-80 (mean age=68.18, SD=5.1 years), completed the ImPACT Version 4 across an average range of 30 days (mean=16.04, SD=8.65). Intraclass Correlations (ICCs) were calculated to examine test-retest reliability for the component tests across the time periods, along with Reliable Change Indices (RCI) to document the percentage of cases revealing change that exceeded a 95% confidence interval (CI). **Results:** Normative Data: ImPACT Version 4 performance reflected age-related changes across the 40-49, 50-59, 60-69, and 70-80 age bands, with decreased memory performance and slower speed of response time across all 4 ImPACT Version 4 Composite Scores. In addition, variability in response time increased along with age. Construct Validation: Results revealed that the ImPACT Verbal and Visual Memory Composite scores correlated with both the HVLT and BVMT-R, as well as the SDMT Memory Sub-scales (significant at $p<.001$) which represent measures of verbal and visual memory. ImPACT Motor Speed and Reaction Time Composite Score both correlated with the SDMT Total Correct Subscales, which represents a measure of psychomotor coding speed. Test-Retest: Intra-class correlation coefficients reflected stability across the test-retest period: Verbal Memory=.88, Visual Memory=.73, Visual Motor Speed=.91, Reaction Time=.65. Reliable Change Indices revealed only 1% of cases exceeded the 95% CI for Visual Memory and Visual Motor Speed (both 94% within the 95% CI), whereas 98% of cases fell within the 95% CI for Verbal Memory and 97% of cases for Reaction Time. **Conclusions:** These correlations provide validation for ImPACT as a measure of Verbal and Visual Memory and psychomotor speed, and support its use for assessment of speed and accuracy of neurocognitive performance in individuals 60-80 years of age. These findings support the use of ImPACT as a measure that should be considered when in-person or remote assessment of cognitive functioning is required.

P143- VALIDATION OF AN OBJECTIVE, SPEECH-BASED OBJECT CONTENT SCORE FOR MEASURING DISEASE PROGRESSION IN AD. J. Robin[1], M. Xu[2], M. Detke[3], W. Simpson[2] *(1. Winterlight Labs - Vancouver (Canada), 2. Winterlight Labs - Toronto (Canada), 3. Detke Biopharma Consulting - Indianapolis (United States))*

Background: Speech and language changes are well-known to occur in AD, with patients frequently described as having "empty speech" lacking in information content. Novel tools to objectively measure speech and language content can help to quantify this clinical symptom and provide measures of disease severity and progression. By using a picture description task and natural language processing analyses, we developed an object content score to measure the information provided when describing a picture. In this study, we collected brief picture description speech assessments over the course of a 48 week AD clinical trial, which were administered via a tablet and took less than five minutes to complete. In this study, we validate the object content score by examining its progression within the placebo arm of the 48 week study period and correlations with other clinical scores. **Objective:** The objective of this study was to validate the use of an objective, speech-based object content score for tracking disease progression in Alzheimer's Disease (AD). **Methods:** 148 English-speaking participants with mild-to-moderate AD who were randomized into the placebo arm of a clinical trial completed an app-based speech assessment at their baseline visit. Follow up assessment occurred at 12-weeks (n = 128), 24-weeks (n = 125) and 48-weeks (n = 98). Speech assessments were administered by a trained rater during a clinical visit. Each speech assessment included two picture description tasks: open-ended speech tasks in which participants are shown a line drawing of a scene and asked to describe it. Participants use their own words to describe the picture and have no time limit or feedback. Speech recordings were captured by the device's microphone and processed using the Winterlight speech analysis platform. Text transcripts were generated for every recording and objective measures of information content were automatically computed based on custom natural language processing algorithms, reflecting how many items in the picture were correctly described. Object content scores were averaged across the two pictures at each assessment. **Results:** Object content scores were found to show significant decline over the course of the study at the group level, consistent with disease progression (estimated slope of change = -0.06, $t = -5.02$, $p < 0.001$). To test the validity of object content scores compared to standard trial endpoints, we computed correlations between object content scores and scores of cognition and function at baseline. Object content scores had significant correlations with baseline scores of cognition and function, including the ADAS-Cog ($r = -.29$, $p < 0.001$), the MMSE ($r = .24$, $p = 0.003$), ADCS-ADL ($r = .23$, $p = 0.005$), and a weak association with the CDR-SB ($r = -.16$, $p = 0.06$). Change in object content scores from baseline to endpoint (48-weeks) also had significant correlations with change in clinical scores, including the ADAS-Cog ($r = -.35$, $p < 0.001$), the MMSE ($r = .36$, $p < 0.001$), ADCS-ADL ($r = .29$, $p = 0.004$), but not the CDR-SB ($r = -.17$, $p = 0.10$). **Conclusions:** This study provides initial validation of a speech-based, objective measure of information content as a measure of disease severity in AD. We found that in a placebo group of individuals with mild-to-moderate AD, object content scores showed significant decline over 48 weeks, consistent with disease progression. Concurrent validation of object content scores showed moderate correlations with standard trial endpoints. Notably, the strongest correlations were with the cognitive scales, suggesting that object content scores were most related to other measures of cognition. In comparison, the object content score was derived from an app-based speech assessment, which took less than 5 minutes to complete and required minimal instruction or training. Digital speech-based measures have the potential to reduce patient burden and improve sensitivity in assessing AD in future trials.

P144- RELATIONSHIP BETWEEN TELOMERE SHORTENING AND EARLY SUBJECTIVE DEPRESSIVE SYMPTOMS AND COGNITIVE COMPLAINTS IN OLDER ADULTS. S.H. Koh[1], M.H. Han[1], E.H. Lee[1], H.H. Park[1], S.H. Choi[2] *(1. Hanyang University - Seoul (Korea, Republic of), 2. Inha University - Incheon (Korea, Republic of))*

Background: Telomere length (TL) has been reported to be associated with depression and cognitive impairment in elderly. Early detection of depression and cognitive impairment is important to delay disease progression. Therefore, we aimed to identify whether TL is associated with early subjective depressive symptoms and cognitive complaints among healthy elderly subjects. **Methods:** This study was a multicenter, outcome assessor-blinded, 24-week, randomized controlled trial (RCT). Measurement of questionnaire and physical activity scores and blood sample analyses were performed at baseline and after six months of follow-up in all study participants. Linear regression analyses were performed to identify whether early subjective depressive symptoms, cognitive complaints, and several blood biomarkers are associated with TL. **Results:** Altogether, 137 relatively healthy elderly individuals (60–79 years old) were enrolled in this prospective RCT. We observed an approximate decrease of 0.06 and 0.11−0.14 kbps of TL per one point increase in the geriatric depression scale and cognitive complaint interview scores, respectively, at baseline and after six months of follow-up. We also found an approximate decrease of 0.08−0.09 kbps of TL per one point increase in interleukin (IL)-6 levels at baseline and after six months of follow-up. **Conclusion:** Our study showed that both early subjective depressive symptoms and cognitive complaints were associated with a relatively shorter TL in relatively healthy elderly individuals. In addition, based on our findings, we believe that IL-6 plays an important role in the relationship between shortening TL and early subjective depressive symptoms and cognitive complaints.

P145- ACCURACY OF AUTOMATED SCORING OF WORD RECALL ASSESSMENTS. R. Kindellan[1], C. Fidalgo[1], W. Simpson[1], J. Robin[1] *(1. Winterlight Labs - Toronto (Canada))*

Background: Natural language processing tools can be used to automate and standardize the scoring of clinical assessments. Many cognitive assessments used as endpoints in Alzheimer's disease (AD) trials require manual scoring and review which can be costly and time consuming. Developments in natural language processing technology can be leveraged to develop automated and objective tools to generate text transcripts and produce scores for cognitive assessments. As a proof of concept, we tested an automated method to score the word recall portion of the ADAS-Cog, a standard endpoint in AD research. **Objective:** The objective of this study was to develop and test a method to automatically score the word recall portion of the ADAS-Cog assessment. **Methods:** Audio recordings of the ADAS-Cog from 23 older adult volunteers were collected. Audio recordings were manually split into the subsections of the ADAS-Cog assessment. The first trial of the word recall portion was transcribed using automatic speech recognition

(ASR) software from Amazon Web Services (AWS) Transcribe. AWS ASR was preconfigured based on the expected ADAS-Cog word list to increase accuracy. Each recording was also manually transcribed and scored. Scores for the word recall portion were computed by counting how many words per trial were correctly recalled (out of a possible 10). Scores were compared to evaluate agreement using intraclass correlations and by comparing mean values. **Results:** There was 100% agreement between the manual transcription and scoring with the original clinical scoring of the assessment. In comparison, the automated scoring had an intraclass correlation of 0.87 ($p < 0.01$), indicating good agreement with the human-rated scores. Out of 23 samples, scores were identical on 9 assessments. Automated scoring tended to underestimate scores compared to the human raters, with an average score of 5.43 (SD = 2.25) compared to an average score of 6.31 (SD = 2.23) based on the human scoring. Underestimations tended to be due to incorrect transcriptions due to substitutions of similar sounding alternate words (e.g. "annual" instead of "animal"). **Conclusions:** This study demonstrates how scoring of word recall tasks can be automated using natural language processing tools. Tools such as these could be used to automate and increase the efficiency of quality assurance and review of clinical assessments conducted as part of trials. In this study, we found that preconfigured automated systems approached human accuracy, although still tended to underestimate scores due to transcription errors. Future work to refine the use of ASR to evaluate clinical endpoints includes optimizing ASR accuracy by filtering noise before processing samples and further customizing language models to suit the datasets at hand, as well as exploring the use of ASR in other elements of cognitive assessments, to provide more efficient and scalable scoring methods.

P147- PRE-SCREENING EARLY AD TRIAL POPULATIONS OVER THE TELEPHONE USING A SPEECH BIOMARKER FOR COGNITION — PRELIMINARY RESULTS FROM AUTONOMY PHASE 2 AD TRIAL RECRUITMENT. S. Ruhmel[1], J. Tröger[2], N. Linz[2], J. Herrmann[2], M. Quiceno[1], K. Langel[3] *(1. Janssen Research & Development, LLC (United States), 2. ki:elements - Saarbrücken (Germany), 3. Janssen-Cilag (Spain))*

Background: Optimizing enrollment duration is one of the major challenges in Alzheimer's Disease (AD) trials especially targeting early stages of the disease. Cost-efficient pre-screening could drastically enhance screen-in rate and accelerate early AD trials. We present results from the pre-screening in AUTONOMY Phase 2 early AD trial using a pre-screener based on the ki: elements (ki:e) speech biomarker for cognition (SB-C) which is automatically collected over a phone bot system and integrated into a state-of-the-art electronic patient recruitment funnel. **Objectives:** The project set out to evaluate in the real environment an approach to scalable pre-selection of suitable participants for an early AD trial over the telephone using a speech biomarker for cognition. **Methods:** The AUTONOMY Phase 2 early AD trial (ClinicalTrials.gov: NCT04619420) expands traditional site-based enrollment with a global outreach strategy targeting a broad population. For selected sites in the US, the ki:e SB-C is integrated into an electronic patient recruitment funnel and automatically collected on the phone through robot calls to outreach responders. The ki:e SB-C leverages speech gathered during word list learning, semantic verbal fluency, and free speech tasks, then automatically extracts up to 100 explainable speech features composing three subdomain scores for episodic memory, executive function and processing speed. Subsequently, subdomain scores are merged into one overall cognition score. The SB-C is developed for automatic deployment over ordinary landline telephone using a 10 minute phone-bot assessment protocol. After completing the call which automatically collects the ki:e SB-C, responders are classified into referrals (possible MCI) and non-referrals (either healthy or dementia) based on a pre-screening engine that uses the SB-C and its subscores as input. To evaluate performance of this pre-screening approach, the pre-screening engine does not affect the actual invitation to the on-site screening in AUTONOMY. **Results & Conclusion:** The pre-screening system has been deployed since July 2022 and automated pre-screening calls will be conducted at a rate of 5 responders per week. Therefore, we will be able to present interim results from about 100 first responders evaluating the SB-C-based pre-screening performance in a real-world deployment to identify suitable MCI candidates for a clinical trial. .

P148- THE DIFFERENCE IN TRAJECTORIES ACCORDING TO EARLY AMYLOID ACCUMULATION IN NORMAL COGNITIVE ELDERLY. Y.J. Kim[1], M.Y. Chun[1], H. Jang[1], H.J. Kim[1], J.Y. Seo[1], S.W. Seo[1] *(1. Samsung Medical Center - Seoul (Korea, Republic of))*

Background: Amyloid-β (Aβ) accumulation, a major biomarker in Alzheimer's disease (AD), induces tau accumulation, eventually resulting in cognitive decline. However, Aβ trajectory in cognitively normal participants has not been extensively investigated. Modeling the Aβ trajectory remains an important goal, as future treatments targeting Aβ are expected to develop. **Objectives:** Through a longitudinal study on amyloid changes in normal elderly people, we investigated whether they might be divided into the normal aging group and the pathological group with increased amyloid. We also compared the differences between the groups according to the patterns of Aβ accumulation. **Methods:** We included 297 subjects from the Alzheimer's Disease Neuroimaging Initiative database, which showed normal cognition. All subjects underwent neuropsychological test (mPACCdigit and mPACCtrt), apolipoprotein E (APOE) genotype test, brain MRI, and an average of 3.03 follow-ups 18F-florbetapir (AV45) PET scans. The original dataset was divided by 6:4 to create a training set (n=178) and a validation set. Latent Class Growth Analysis (LCGA) was used for statistical analysis. A linear mixed-effects model was used to analyze longitudinal changes in hippocampal volume and cognition analysis. **Results:** By applying LCGA to the training set and increasing the number of classes from 1 to 5, the slope shapes were tested from linear to cubic function. Considering the information criterion and interpretability, we determined that the 3-class model was the most suitable, and high entropy of 0.979 was shown: class 1 (non-accumulating group; n=117, 65.7%), class 2 (increasing group; n=46, 25.8%), and class 3 (high accumulating group; n=15, 8.4%). The increasing group, which converted from amyloid-negative to positive, had more APOE ε4 carriers and a higher tau burden than the non-accumulating group. In longitudinal analysis, the high accumulating group showed the steepest decline, and the increasing group showed a steeper decline than the non-accumulating group in cognition (mPACCdigit, $p < 0.001$; mPACCtrt, $p < 0.001$). **Conclusion:** Our study showed the heterogeneity of Aβ accumulation trajectories according to aging in the normal cognitive elderly. Heterogeneity of Aβ accumulation and early detection of the Aβ converter group may be helpful in the early diagnosis and treatment of AD. **Key words:** Alzheimer's disease, Latent class

growth analysis, Amyloid, Positron emission tomography, Longitudinal study

P149- RATER ERROR PATTERN ON THE CDR OUTCOME ASSESSMENT IN ALZHEIMER'S DISEASE CLINICAL TRIALS. J. Barbone[1], E. Barney[1], J. Crome[1], R. Leventhal[1], L. Kingery[1], S. Wacker[1] *(1. Cogstate - New Haven (United States))*

Background: The Clinical Dementia Rating Scale (CDR) is a global staging measure used to characterize cognitive performance across six functional domains, often used as primary outcome in Alzheimer's Disease clinical trials to provide meaningful information about effects of investigational therapies on patients' cognitive decline. The CDR is administered in a semi-structured interview format with the patient and an informant, and scored in a semi-objective fashion, with data quality heavily dependent on rater's clinical interviewing skill set and competency with scoring the instrument. Standardized training protocols and in-study data monitoring programs are routinely used to calibrate clinical raters to this nuanced scale with the goal to reduce rater error rates. Analysis of rater performance can enhance understanding of error pattern and inform rater training programs. **Objectives:** - Understand pattern of rater error; - Inform rater training programs to improve impact on rater performance. **Methods:** Completed CDR administrations were reviewed by calibrated, expert neuropsychologists and flagged for incidents of raters' deviation from administration gold standards, proper recording of participants' responses, and accuracy in applying scoring rules. Data source review process involved evaluation of test forms, documentation of participant responses and audio recordings of assessment sessions, and was highly standardized to ensure consistent approach across reviewers. **Results:** A total number of 3987 individual CDR administrations were reviewed across three multi-country programs. 44% of reviewed CDR administrations were flagged for at least one rater error. Administration (29%) and recording errors (24%) were more common than scoring (13%) or other (8%) errors. Most common errors flagged were related to raters' general clinical interviewing skill sets, like following standardized questions with appropriate probing when needed, inquiring about concrete examples of reported behaviors, querying clinically inconsistent information to distinguish between current and premorbid functioning in order to score the most appropriate rating for a patient's level of cognitive functioning. Individual review items with the highest rate of error (in 15% of administrations) showed inconsistent adherence to administration guidelines specifically in the personal care domain, where the rater must solicit enough information in questioning to distinguish between physical and cognitive limitations as barrier to effective functioning. Of note also was incomplete response recording in the judgment and problem-solving section, where raters often marked an answer choice without documenting the actual patient response (in 12% of administrations). **Conclusions:** Close monitoring of error patterns in rater performance illuminated areas of difficulties in raters' clinical skill sets. Understanding the source of errors is paramount to inform rater selection and rater training programs. Administering the semi-structured CDR interview requires a seasoned tool kit of general clinical skills to obtain the rich, clinical information and concrete examples necessary to arrive at an accurate severity rating, and falling short of interviewing gold standards seemed to drive a majority of rater error. Results support the need to recruit highly qualified raters, equipped with excellent core clinical skills, and an increased emphasis on clinical interviewing tools as part of study calibration for raters in training to support clinical AD trials.

P150- PRELIMINARY PSYCHOMETRIC AND CLINICAL VALIDATION OF INFORMATION PROCESSING SPEED IN EARLY ALZHEIMER'S DISEASE USING A SMARTPHONE-BASED REMOTE ASSESSMENT. A.M. Wolfer[1], I.T. Kurniawan[1], K.I. Taylor[1], F. Lipsmeier[1], T.M. Perumal[1] *(1. Roche Pharma Research And Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 - Basel (Switzerland))*

Background: Digital biomarkers potentially enable the remote assessment of cognitive and functional impairments in clinical trial participants' daily lives at a higher frequency than standard in-clinic neuropsychological assessments. Early stages of Alzhiemers disease (AD) are marked by a disproportionate slowing of information processing speed (Nestor 1991) which may be measured using a simple smartphone-based cognitive task. Here, we present an assessment of psychomotor speed, called Information Processing Speed (IPS), designed to be regularly self-administered over the course of a trial. IPS has two components, a baseline digit-digit matching task measuring motor speed, and a digit-symbol substitution task measuring psychomotor processing speed. We report the preliminary validation and psychometric properties of the IPS assessment in a cohort of amyloid negative healthy individuals (HC), individuals with amyloid negative and positive subjective cognitive decline (SCDn and SCDp), and amyloid positive early AD (eAD) verified by a PET-scan. **Objectives:** The objectives were to investigate the feasibility of remote IPS self-administration in participants with eAD, SCD, and HC and to establish the reliability and validity of IPS metrics. **Methods:** 123 adults were enrolled as a part of a Proof-of-Concept (POC) study for Alzheimer's Digital Assessment Suite (AD-DAS) (https://www.isrctn.com/ISRCTN17035495): 31 HC, 31 SCDn, 31 SCDp and 30 eAD. During this multicentre observational study, each participant was provided with a provisioned smartphone and instructed to execute 9 IPS assessments over the course of 30 days. IPS is a smartphone-based task designed to assess attention, visual scanning behavior and psychomotor speed, based on the Symbol Digit Modalities Test (SDMT). Participants were instructed to use a digit-symbol key to select the correct digit for every presented symbol. The task lasted 90s. Baseline speed was evaluated using a simple digit-digit matching task lasting 15s, during which participants were instructed to select the number from the keypad that matched the number shown on screen. Feasibility was evaluated as the proportion of completed IPS tasks relative to the 9 total scheduled IPS tasks. Two IPS performance metrics were estimated. Baseline motor speed was quantified with the number of correct answers provided in digit-digit matching (DD15). Psychomotor speed was quantified with the number of correct answers provided in digit-symbol matching (DS90). Intraclass Correlation Coefficients (ICC) tested the reliability of IPS metrics. Preliminary clinical validity (i.e., association with Digit-Symbol Coding Test (DSCT) and Trail Making Test (TMT)) and groups validity was evaluated using a linear modeling framework. Linear models predicting performance metrics of interest were fitted with age, sex, education level, ethnicity, study site and application version as covariates, and group to test known-groups validity and clinical comparator to test clinical validity. The specific contribution of either the group or the clinical comparator variables to the model was evaluated using the Bayesian Information Criteria (BIC)

explaining the improvement in the decreased model error variance. As the POC study was not powered to identify cross-sectional differences between groups, all p-values reported are nominal and not corrected for multiple comparisons. **Results:** Out of 123 participants, 97.5% completed the POC study (n=120), and these participants completed 88.9% of assigned IPS (corresponding to 8/9 expected) tests with no difference in adherence between groups (F=0.88, p<0.45). DD15 and DS90 metrics showed excellent reliability (ICC=0.82, ICC=0.92 respectively). DS90 significantly distinguished between Non-eAD and eAD participants (p<0.001, partial r2=0.112). DD15 was associated with the total number of correct answers in DSCT (p<0.05, r2=0.91) and the time taken to complete the TMT-A (p<0.001, r2=0.186). DS90 was associated with the total number of correct answers in DSCT (p<0.001, r2=0.267), and time taken to complete TMT-A (p<0.001, r2=0.182) and TMT-B (p<0.001, r2=0.239). **Conclusions:** Remote self-assessments offer the possibility to characterize study participants in an ecologically valid environment and at a higher frequency, yet require validation against standard clinical outcomes in cognitively impaired populations. Our results demonstrate that a smartphone-based IPS task can be successfully self-administered by cognitively healthy participants and individuals in the eAD spectrum, with high adherence to the study protocol. IPS metrics differentiated between participants with objective dementia and other study groups. Finally, we demonstrated good reliability of IPS metrics and preliminary clinical validity of IPS measurements compared with DSCT and TMT-B/A. IPS aims to provide a remote clinically meaningful characterization of a participant's cognitive impairment to support drug trials in preclinical and early AD. **References:** Paul G. Nestor, Raja Parasuraman & James V. Haxby (1991) Speed of information processing and attention in early Alzheimer's dementia, Developmental Neuropsychology, 7:2, 243-256.

P151- RATER ERROR PATTERN ON THE MMSE AND ADAS-COG OUTCOME ASSESSMENTS IN ALZHEIMER'S DISEASE CLINICAL TRIALS. S. Wacker[1], J. Barbone[1], E. Barney[1], J. Cromer[1], L. Kingery[1], R. Leventhal[1] *(1. Cogstate - New Haven (United States))*

Background: Cognitive assessments are critical in understanding the effects of investigational therapies in Alzheimer's Disease (AD) clinical trials. Cognitive outcome measures, like the widely-used ADAS-Cog and MMSE tests, are complex and their use can be vulnerable to variability in test administration and scoring. Rigorous data quality programs in the form of thorough rater training and close monitoring of in-study administrations, with the goal to reduce rater error rates, are paramount to ensure optimal reliability and validity of clinical outcome data. **Objectives:** Understand pattern of comon rater error. Inform training programs to improve impact on rater performance. **Methods:** Completed administrations of Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) from multi-national clinical trials were reviewed by calibrated, expert neuropsychologists, and flagged for incidents of raters' deviation from administration gold standards, proper recording of participants' responses, and accuracy in applying scoring rules. Data source review process involved evaluation of test forms, rater notes, documentation of participant responses and audio recordings of assessment sessions and was highly standardized to ensure consistent approach across reviewers. **Results:** A total number of 8298 scale administrations were reviewed across three programs, including 3832 individual administrations of ADAS-Cog and 4466 individual administrations of MMSE. In 53% of ADAS-Cog reviews and 47% of MMSE reviews at least one item was flagged for rater error. Errors of administration were the most common errors across both scales (48% of ADAS-Cog reviews and 37% of MMSE reviews), over errors of response recording and scoring. Across both scales raters fell short of administration guidelines on delivery of introductory questions (21% error on ADAS-Cog open-ended conversation that precedes the first cognitive task and is intended to elicit an adequate sample of spontaneous speech; 12% error on MMSE introductory memory questions). Reviewers also identified raters' deviations from standardized task directions, when instructing and especially when prompting the patient. **Conclusion:** Close monitoring of error patterns in rater performance revealed areas of difficulties in raters' clinical skill sets. Understanding the source of errors is paramount to inform rater training programs and to prevent administration errors. Those aspects of scale administration requiring a solid tool kit of general clinical skills, such as guiding unstructured, open-ended conversations and delivering task instructions and prompts that are appropriate for a participant's specific response or behavior, appear to be challenging for some raters. These monitoring results support the continued need for data quality monitoring programs to improve the conduct of cognitive assessments in-study, as well as the need for stringent rater qualification criteria, and increased focus on applied clinical interviewing skills as part of rater training.

P152- PRELIMINARY PSYCHOMETRIC AND CLINICAL VALIDATION OF EXECUTIVE FUNCTION IN EARLY ALZHEIMER'S DISEASES USING A SMARTPHONE-BASED ASSESSMENT. I.T. Kurniawan[1], A.M. Wolfer[1], C. Chatham[1], E. Aponte[1], S. Holiga[1], T.M. Perumal[1], K.I. Taylor[1] *(1. Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124 - Basel (Switzerland))*

Background: Early treatment initiation for Alzheimer's Disease (AD) relies on timely detection at the preclinical and early stages. Validated in-clinic assessments demonstrate important neuropsychological signs of preclinical AD, including executive dysfunction 2 years prior to diagnosis. Digital remote monitoring may accelerate efforts to detect and track subtle cognitive changes via more frequent at-home assessments. However, these remote monitoring tasks require validation against standard clinical outcome measures and relevant biomarkers. **Objectives:** We present preliminary psychometric and clinical validity of Tilt Task (TT), a novel gamified smartphone-based assessment of executive function. This cognitive task was part of the AD digital assessments suite (AD-DAS) administered in a multicenter cross-sectional proof-of-concept study (POC) with healthy controls (HC), participants with subjective cognitive decline (SCD) and with early AD (eAD). The SCD group included individuals without and with beta amyloid (SCDn, SCDp, respectively) as assessed with amyloid Positron Emission Tomography (PET). **Methods:** 123 adults (aged 65 or above) were enrolled: 31 HC, 31 SCDn, 31 SCDp and 30 eAD. Groups were demographically comparable (https://www.isrctn.com/ISRCTN17035495; Perumal, et al., 2021). Each participant received a preconfigured smartphone for unsupervised at-home TT testing once a day for 9 consecutive days. TT was developed based on principles of the Trail-Making Test (TMT) and Stroop tests and named after the response modality: tilting the smartphone to move a ball towards a target

location (north, east, south, or west). TT consists of five levels of increasing difficulty, whereby the next level is administered only if fewer than 3 errors are committed. Level 1 is a motor baseline task where participants see only one target. In level 2, participants hit numbers in squares in ascending order. Normalized by level 1, level 2 measures the ability to "stay-on-set". Level 3 recapitulates level 2 except for trials when the ball changes to a star (50% chance), during which participants tilt in the opposite direction to hit the target. Normalized by level 2, level 3 measures "simple response inhibition". In level 4, participants alternately hit a number in a square and a letter in a circle in ascending order. Normalized by level 2, level 4 measures "set shifting". Level 5 recapitulates level 4, but with an opposite-tilt component. Normalized by level 4, level 5 measures "complex response inhibition". Intraclass Correlation Coefficients (ICC) tested the reliability of TT metrics. Linear mixed models including age2, sex, years of education, study site, and session number as covariates and participant as a random intercept evaluated the group effect on total scores, reflecting maximum level reached (range from 0-5), and group effects at each level on normalized accuracy and response times (RT; log-transformed). Standardized regression coefficients (β) and the significance p-values for simple contrasts against eAD are reported. Spearman's correlations (ϱ) tested for relationships between TT and TMT metrics. **Results:** 84.45% of scheduled TT sessions were completed (corresponding to 7.6/9 expected sessions). There was no difference in TT adherence between groups, $F=1.52$, $p>0.22$. Out of 120 participants that completed the study, 5 failed to complete at least 1 TT session and were therefore excluded from TT analyses (final n=115). 11% of participants did not reach level 2, 24% level 3, 69% level 4, and 87% level 5. Total score, and normalized accuracy and log-transformed RT at levels 1-3 showed moderate to good reliability (ICC 0.52-0.89). Group differences were observed in total scores, accuracy, and log-transformed RTs. Compared to HC and SCDn, eAD group had lower total scores than SCDn ($\beta=0.52$, $p<0.007$) but not HC ($p>0.1$), lower accuracy at levels 2-3-4 for both groups (smallest $\beta=0.19$, $p<0.02$), and slower response times at level 2 for SCDn ($\beta=0.2$, $p<0.02$) but not HC ($p>0.07$). Time taken to complete TMT-A correlated with level 2 log(RT) ($\varrho=0.26$, $p<0.006$), but time taken to complete TMT-B did not correlate with level 4 log(RT) ($\varrho=0.11$ $p>0.39$). We will report group contrasts compared to eAD and explore correlations between TT performance and Magnetic Resonance Imaging (MRI) measures of brain integrity. **Conclusions:** Clinical AD research requires reliable and valid measures of executive function. The TT was designed as a self-administered frequent and in-depth assessment of executive function at participants' homes. The present findings demonstrate some group differences and preliminary clinical validity of digital performance metrics of executive function, namely poorer abilities to stay-on-set, inhibit responses, and shift mental sets in individuals on the early AD spectrum. Together with metrics from other cognitive tasks a composite score of cognitive functioning may support the identification of target subgroups of AD fast progressors and ultimately provide remote, clinically meaningful outcome measures for future clinical trials in preclinical and early AD.

P153- PRELIMINARY PSYCHOMETRIC AND CLINICAL VALIDATION OF VISUOSPATIAL WORKING MEMORY DEFICITS IN EARLY ALZHIMER'S DISEASE MEASURED WITH A SMARTPHONE BASED DIGITAL ASSESSMENT.

E.A. Aponte[1], K.I. Taylor[1], A.M. Wolfer[1], C. Chatham[1], T.M. Perumal[1] *(1. Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124 - Basel (Switzerland))*

Background: The preclinical and early clinical stages of Alzheimer's disease (AD) are chiefly characterized by deficits in episodic and semantic memory, yet other cognitive domains such as working memory may also be affected in the initial phases of the disorder. Scalable digital solutions offer the opportunity to quantify and track subtle changes in cognition remotely with a minimal burden to participants. Here, we present the preliminary clinical validation and psychometric properties of the gamified visuospatial working memory task Find the Egg (FtE) in healthy controls (HC), participants with subjective cognitive decline (SCD) and with early AD (eAD). The SCD group included individuals with and without beta amyloid (SCDp, SCDn, respectively) as assessed with amyloid Positron Emission Tomography (PET). **Objectives:** The objectives are to: (i) evaluate the feasibility of remote FtE self-assessments in healthy elderly, and in preclinical and early clinical stages of AD, (ii) identify the performance metrics that best differentiate between groups, and (iii) determine the reliability of these metrics. **Methods:** 123 adults of age 65 and older participated in a proof-of-concept (POC) study (https://www.isrctn.com/ISRCTN17035495) and were stratified in 4 groups: HC (31), SCDn (31), SCDp (31), and eAD (30). 120 participants successfully completed the study. 4 participants did not take part in FtE testing. During the course of an FtE session, a variable number of items (chickens) were displayed on the screen of the provisioned smartphone. Participants were instructed to search for targets (eggs) hidden behind the items by tapping on them and to avoid perseverative searching of locations where targets had already been found, or discovered not to be present. Depending on participants' ability, they could reach any of 6 levels of difficulty, each corresponding to 4, 6, 8, 10, and 12 items on the screen. At the end of each session, the difficulty of the task was automatically calibrated by reducing the number of items presented during the next testing session according to participants' performance. FtE was administered on nine days over the course of a month. Feasibility was examined with adherence metrics, and performance with five additional metrics: within- and between-search error rate, maximum difficulty level reached, and two computational metrics: total working memory (TWM) and attention level. TWM was estimated by extending Cowan's K. This score represents the average number of items that an individual can simultaneously hold in working memory. Attention level is an index of how often participants make errors likely due to attention slips. The current report focuses only on the computational performance metrics to illustrate our most recent progress. All features were analyzed with a linear model with age, sex, education, site, and ethinicity as covariates. Differences between groups were computed using exploratory, unpaired t-tests. Reliabilities between the first and second half of the study were quantified with intra-class correlation coefficients (ICC). Because the study was not powered to detect cross sectional differences between groups, all p-values should be considered exploratory and nominal, and were not corrected for multiple comparisons. **Results:** On average, participants with FtE data (n=116) completed 85% of the assigned testing sessions.

Adherence did not differ across groups (F=0.26, p>0.82). Each session lasted around 91s (± 59s). Ten participants were excluded from further analyses because they completed fewer than 5 sessions (n=5) or because their within-search error rate was above 2 standard deviations (SD) of the entire group mean (n=5). For the computational analysis, one eAD participant was excluded because their performance was 4 SD above the entire cohort. TWM significantly differentiated eAD from HC (t=3.1; p<0.003) and SCDn participants (t=2.5, p<0.013). SCDp had lower TWM compared to HC (t=-2.21, p<0.029). Overall, TWM followed the expected pattern across groups (mean and standard error): HC: 5.1 (0.2) > SCDn 4.9 (0.2) > SCDp 4.5 (0.2) > eAD 4.3 (0.5). There were no significant differences between groups related to attention level (F=2.0,p>0.11).Only TWM showed moderate to good reliability (ICC=0.72). Attention level displayed poor reliability (ICC=0.44). **Conclusion:** Find the Egg is a nove smartphone test of visuospatial working memory. Collecting high quality data with self-administered cognitive tests over the course of a clinical trial can be challenging, especially in elderly populations with memory impairments. Our results demonstrate the feasibility of self-administered FtE in this population. Importantly, FtE imposed minimal burden on participants, with sessions lasting on average less than 2 minutes. Although not part of the core deficits associated with eAD, we found impairments in visual working memory in early AD compared to amyloid negative individuals (HC and SCDn). In conclusion, FtE is a promising digital technology task that may enable the measurement of subtle changes in visual working memory in eAD.

P154- THE PHASE 2 LUMINARY TRIAL ASSESSING SAGE-718 IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT OR MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE.

A. Koenig[1], S. Malhotra[2], J. Wald[1], J. Petrillo[1], K. Paumier[1], J. Johannesen[1], S. Li[1], M. Quirk[1], E. Freitag[1], J. Doherty[1] *(1. Sage Therapeutics, Inc. - Cambridge, Massachusetts (United States), 2. Neuro-Behavioral Clinical Research, Inc. - North Canton, Ohio (United States))*

Background: Cognitive impairment has a profound impact on the lives of patients with Alzheimer's disease (AD) and their care partners. It is well-established that the early stages of AD are often characterized by memory impairment. However, a growing body of evidence indicates that executive dysfunction is also associated with early AD, which impacts the ability to perform complex activities, leaving a marked reduction in patients' quality of life.1-5 There are no approved therapies to address cognitive impairment in nondemented patients with AD; approved therapies for dementia have limited efficacy in early cognitive impairment and are associated with substantial side effects.6 Novel strategies to treat cognitive impairment early in the course of AD are needed.6 N-methyl-D-aspartate receptors (NMDARs) play a critical role in neuronal network stabilization and are involved in many cognitive and behavioral processes. Additionally, NMDAR dysfunction has been implicated in multiple neurodegenerative disorders.7 SAGE-718 is a novel NMDAR positive allosteric modulator that is being investigated for the treatment of cognitive impairment in patients with neurodegenerative diseases such as AD. **Objectives:** The primary objective was to evaluate the safety and tolerability of orally administered SAGE-718 in patients with mild cognitive impairment (MCI) or mild dementia due to AD. Other objectives included the plasma pharmacokinetic (PK) profile of SAGE-718 following daily administration for 14 days and evaluating the effect of SAGE-718 on cognitive performance in patients with MCI or mild dementia due to AD. **Methods:** LUMINARY (NCT04602624) was an open-label, Phase 2 study evaluating SAGE-718 (3 mg QD for 14 days) in patients with AD. Patients (aged 50–80 years) were included if they had a memory complaint, a diagnosis of AD-related MCI or mild dementia confirmed by a Clinical Dementia Rating Scale (CDR) score of 0.5 or 1.0 with a memory box score of ≥0.5, essentially preserved activities of daily living, a score of 15-24 on the Montreal Cognitive Assessment (MoCA) at screening, normal premorbid intelligence quotient (IQ) at screening, and a reliable study partner willing to support the patient during the study. Patients were excluded from the study if they had any medical or neurological condition (other than AD) that might be contributing to the participant's cognitive impairment or history of cognitive decline; any medical condition that could account for the observed cognitive impairment (excluding abnormalities consistent with underlying AD pathology); or current or recent suicidality. The study design included a 2-week screening period, a 1-week baseline period, a 2-week treatment period, and a 2-week off-drug follow-up period. The primary endpoint was safety and tolerability of SAGE-718 (treatment-emergent adverse event incidence through Day 28). Secondary endpoints included other safety outcomes. The effects of SAGE-718 on cognitive performance and functional outcomes were also analyzed. **Results:** Twenty-six patients with AD (69.2% female; mean age 67 years), and a mean±SD MoCA of 20.7±2.61 were enrolled. Most patients (23/26) had a global CDR score of 0.5. Eight TEAEs were reported in 7 (26.9%) patients; all were mild/moderate; 6 events were treatment related, but none resulted in study drug discontinuation or study withdrawal. No serious adverse events or deaths were reported. We have previously reported that after completion of dosing at Day 14, improvements from baseline were observed on tests of executive functioning (Digit Symbol Substitution and Multitasking), tasks of learning and memory (Pattern Recognition Memory and Verbal Recognition Memory tests), and that MoCA improvement (+2.3 points vs baseline) was observed at Day 28. No changes in attention/psychomotor speed were observed, consistent with the profile of SAGE-718 observed to date. Here we present results from additional executive functioning tests (One Touch Stockings, Spatial Working Memory, and 2-Back tests) showing improvement from baseline at Day 14, noting that an overall trend of improved performance from baseline at Day 14 was observed across all tests of executive functioning. **Conclusions:** In patients with MCI or mild dementia due to AD, SAGE-718 was generally well tolerated and associated with improvement across multiple measures of executive functioning and learning and memory. The improvement in cognitive performance was largely consistent with previous results from clinical studies assessing SAGE-718 in patients with cognitive impairment due to Parkinson's disease or due to Huntington's disease. These results support further investigation of SAGE-718 for the treatment of cognitive impairment associated with AD and other neurodegenerative diseases. A randomized placebo-controlled trial to further evaluate the effect of SAGE-718 on cognitive function in patients with AD is planned. **References:**

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American Academy of Neurology Annual Meeting. April 2-7, 2022, Seattle, Washington. **Funding Source:** This study was sponsored by Sage Therapeutics, Inc. **Acknowledgments:** We would like to thank the patients and their families for helping us reimagine brain health. Medical writing and editorial support were provided by Symbiotix, LLC, funded by Sage Therapeutics, Inc. AK, JW, JP, KP, JJ, SL, MQ, EF, and JD are employees of Sage Therapeutics, Inc., and hold stock or stock options. SM is an employee of Neuro-Behavioral Clinical Research, Inc. **Note:** SAGE-718 is an investigational drug and is not approved by the FDA or any other regulatory agency as safe and effective for any use.

P155- LONGITUDINAL EVOLUTION OF FINANCIAL CAPACITY AND CEREBRAL TAU AND AMYLOID BURDEN IN COGNITIVELY NORMAL OLDER ADULTS, MILD COGNITIVE IMPAIRMENT, AND ALZHEIMER'S DISEASE DEMENTIA.

K. Mimmack[1], E. Sprague[2,3], R. Amariglio[1,2,3], P. Vannini[1,2,3], G. Marshall[1,2,3] *(1. Department of Neurology, Massachusetts General Hospital, Harvard Medical School - Boston (United States), 2. Department of Neurology, Brigham and Women's Hospital, Harvard Medical School - Boston (United States), 3. Center for Alzheimer Research and Treatment - Boston (United States))*

Background: Financial capacity, which describes both an individual's financial reasoning as well as their ability to perform certain financial tasks such as balancing a checkbook and making change, is an instrumental activity of daily living that can majorly impact independence and autonomy in older adults. Financial capacity can be measured with the Financial Capacity Instrument – Short Form (FCI-SF), a performance-based assessment which has been associated with the buildup of Alzheimer's Disease (AD) pathology in the brain, specifically cortical tau and amyloid, but this relationship has only recently begun to be examined longitudinally. **Objectives:** This study aimed to investigate whether greater baseline cortical tau and amyloid burden was associated with worsening financial capacity over time across the AD spectrum. **Methods:** This study consisted of 490 older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI), including 285 CN, 173 MCI, and 32 AD dementia who underwent flortaucipir tau positron emission tomography (PET) imaging and yearly FCI-SF exams, and a subset of 305 participants who additionally had florbetapir amyloid PET imaging. Separate linear mixed-effects models were run predicting longitudinal FCI-SF total score from baseline tau, baseline amyloid, and their interaction, all adjusted for age, gender, verbal intelligence (the American National Adult Reading Test), and cognition (Rey Auditory Verbal Learning Test total learning score and Trail Making Test Part B). Models were run on the whole sample, CN, and symptomatic (MCI and AD dementia combined) groups separately. A secondary analysis examined tau and amyloid in relation to only the composite checkbook subtask of the FCI-SF. A pivoted log+1 transformation was applied to FCI-SF scores for model fit, and confirmatory untransformed models were run additionally. P-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method. **Results:** The total sample was 51% female and 93% White, with a mean age of 74.0 (SD = 7.8), mean 16.6 (SD = 2.5) years of education, and total follow-up time ranging between 0.8 and 4.6 years (mean = 2.3, SD = 1.0). FCI-SF total scores for CN participants were clustered near the perfect score and were mostly stable, while the symptomatic group showed a wide range of scores which tended to worsen steeply over time. In the full sample, worsening financial capacity (FCI-SF total score) over time was significantly associated with greater baseline entorhinal ($t = 3.39$, $p = 0.004$), inferior temporal ($t = 4.26$, $p < 0.001$), and supramarginal tau burden ($t = 2.81$, $p = 0.02$) after correction for multiple comparisons. Within CN participants, significance was found in the inferior temporal ($t = 3.55$, $p = 0.003$), precuneus ($t = 2.48$, $p = 0.049$), supramarginal ($t = 3.43$, $p = 0.004$), and dorsolateral prefrontal cortex (DLPF) ($t = 2.88$, $p = 0.02$) regions, while in the symptomatic group, no regions were significant. No significant effect of amyloid over time or three-way interaction between amyloid, tau, and time was found. For the composite checkbook subtask of the FCI-SF, worsening financial capacity over time was significantly associated with greater inferior temporal ($t = 2.67$, $p = 0.03$) tau burden in the whole sample. No significance was found in the symptomatic or CN groups alone. **Conclusion:** Greater cerebral tau burden was associated with worsening financial capacity over time. This effect was most prominent in CN participants, which could be due to the smaller sample size of the symptomatic group, limiting its statistical power. With the strength of its relationship with AD biomarkers in CN participants, the FCI-SF may be a valuable tool in early detection of AD and a sensitive, clinically meaningful marker of early decline in clinical trials. Further research should continue the investigation of the longitudinal relationship between financial capacity and AD biomarkers, including in more diverse groups than our overwhelmingly White and highly educated sample to better represent the general population.

P156- POTENTIAL INFLUENCE OF COGNITIVE HETEROGENEITY IN A CLINICAL TRIAL FOR MILD-TO-MODERATE PROBABLE ALZHEIMER'S DEMENTIA.

D. Jacobs[1], Y. Qiu[2], D. Salmon[1], K. Messer[1], L. Donahue[3], S. Kaplita[3], I. Qureshi[3], H. Feldman[1] *(1. University of California San Diego - La Jolla (United States), 2. School of Statistics, East China Normal University - Shanghai (China), 3. Biohaven Pharmaceuticals, Inc - New Haven (United States))*

Background: We previously identified and validated two distinct cognitive profiles among persons with mild-to-moderate probable Alzheimer's dementia (AD) in two independent cohorts from the National Alzheimer's Coordinating Center (NACC) who satisfied inclusion criteria for a typical AD clinical trial.1 Approximately 80% of participants exhibited a "typical" AD cognitive profile on the NACC Neuropsychological Test Battery (NACC-NTB), with greater impairment of episodic and semantic memory than other cognitive functions, while approximately 20% had an "atypical" profile characterized by comparable impairment across cognitive domains. Cognitive profiles were stable over time and had similar prevalence of AD pathology at autopsy. The atypical profile was associated with younger age, male sex, lower probability of APOE-e4, less severe global dementia, higher depression scores, slower cognitive decline, and lower Braak stage at autopsy but not with a higher prevalence of non-AD pathology. Here we apply this classification approach in a randomized clinical trial (RCT) for treatment of mild-to-moderate AD. **Objectives:** (1) To replicate and validate in a RCT cohort our previously published decision rule which identified two distinct cognitive subtypes within mild-to-moderate AD; (2) To determine whether cognitive subtypes differ in disease course or treatment response in a 48-week trial. **Methods:** 350 persons with mild-to-moderate probable AD were enrolled in T2 Protect AD, a phase 2, 48-week, multicenter, double-blind, placebo controlled RCT of the

glutamate modulator, troriluzole (NCT03605667). Detailed trial methods and results are provided elsewhere.2 ADAS-Cog-11 and CDR sum of boxes (CDR-SB) were co-primary outcomes. The NACC-NTB was administered at baseline and end-of-study as an exploratory outcome. Sixteen participants missing follow-up or cognitive test data were excluded from these analyses, leaving n=334. Principal component analysis (PCA) was used to identify cognitive profiles in T2 Protect AD baseline NACC-NTB data, and concordance between these results and subtype classification using our previously published rule1 was examined. Statistical models were used to explore associations of cognitive subtype (determined by our published rule) with participant characteristics, AD biomarkers, and trial outcome measures; all models included an indicator for treatment arm. **Results:** Consistent with our previous findings, PCA identified two distinct cognitive profiles: a "typical" profile with greater impairment of episodic and semantic memory than other cognitive functions (N=282; 84%) and an "atypical" profile with comparable impairment across cognitive domains (N=52; 16%). Concordance between T2 PCA results and classification based on our previously described rule1 was high for the typical (98%) and atypical (82%) subgroups. As in our previous study, the atypical profile was associated with lower prevalence of APOE-e4 (50% vs. 69.5%; p<.01) and less severe global dementia (results reported as mean+SD) (ADAS-Cog 22.0+8.01 vs. 26.8+7.96; p<.001; CDR-SB 5.1+2.17 vs. 6.8+2.47; p<.001; MMSE 21.3+3.97 vs. 19.0+3.67; p<.001). Atypicality was also associated with greater baseline hippocampal (2.80+0.47 vs. 2.47+0.44; p<.001) and entorhinal cortex (2.26+0.46 vs. 1.96+0.41; p<.001) volumes, and with lower plasma GFAP (354.28+139.78 vs. 409.34+176.66; p<0.05) and total tau (1.98+0.75 vs. 2.44+1.31; p<0.05). Groups did not differ in plasma Aβ40/Aβ42 ratio (p=0.92); p-tau-181 (p=0.39); or NFL (p=0.87). After controlling for appropriate covariates in a mixed-effects repeated measures model, the three-way interaction between treatment arm, cognitive subtype, and time was not significant (p=0.152 for ADAS-Cog change and 0.367 for CDR-SB change). After dropping interaction terms with treatment arm from the model, the 2-way interaction between cognitive subtype and time remained nonsignificant (p=0.273 for ADAS-Cog change and p=0.098 for CDR-SB change). **Conclusion:** These results replicate our previous findings1 of two distinct cognitive profiles in mild-to-moderate probable AD and extend these findings to those enrolled in a RCT. The typical vs. atypical cognitive subgroups differed in some disease biomarkers at baseline (hippocampal and entorhinal atrophy, plasma GFAP, and total tau levels), but not others (plasma Aβ40/Aβ42 ratio, p-tau-181, or NFL). In contrast to our previous study, the typical and atypical subgroups did not differ in rate of decline on cognitive or functional outcome measures over the course of this 48-week trial, perhaps due to a shorter time period, smaller sample size, or slightly younger age and greater baseline global impairment in this trial cohort. Typical and atypical subgroups did not differ in response to treatment. These findings suggest that cognitive subtype had minimal consequences on the results of this RCT in mild-to-moderate probable AD. Impact of cognitive heterogeneity on RCTs may depend on the specifics of trial design (e.g., entry criteria, duration, and endpoints) as well as the treatment and its therapeutic target. **References:** Qiu Y, et al. Cognitive heterogeneity in probable Alzheimer disease: Clinical and neuropathologic features. Neurology.2019;93(8):e778-90. Feldman H, et al. T2 Protect AD: Results of a 48-Week Randomized Clinical Trial of Troriluzole in Mild-to-Moderate Alzheimer's Disease. JPAD.2021;8(4):s46. **Acknowledgements:** The trial was funded and sponsored by Biohaven Pharmaceuticals, Inc. and undertaken through a cooperative agreement with the UC San Diego Alzheimer Disease Cooperative Study (ADCS).

P157- IMPACT OF DIFFERENT RATES OF DISEASE PROGRESSION IN INDIVIDUALS WITH AMYLOID POSITIVE ALZHEIMER'S DISEASE - FINDINGS FROM THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE.

J.M. Chandler[1], M. Georgieva[2], U. Desai[2], N. Kirson[2], W. Ye[1], A. Gomez-Lievano[2], A. Hilts[3], D. Eid[2], A. Zhao[2], T. Schilling[1] *(1. Eli Lilly and Company - Indianapolis (United States), 2. Analysis Group - Boston (United States), 3. Groupe d'Analyse - Montréal (Canada))*

Background: The heterogeneity in the rate of disease progression among individuals with Alzheimer's disease (AD) has been well-documented. However, few studies have comprehensively assessed the implications of differential rates of disease progression in individuals with AD on longitudinal outcomes. A better understanding of the associations between initial rates of progression and cognitive and functional outcomes over time could help interpretation of clinical trial findings for treatments with potential to slow AD disease progression. **Objectives:** This study aimed to describe the underlying characteristics and long-term outcomes associated with different rates of disease progression as defined by the annualized change in Clinical Dementia Rating scale Sum of Boxes (CDR-SB) score, among amyloid-positive individuals with AD. An additional objective of the study was to estimate the effect of hypothetical reduction in change in CDR-SB on other outcomes over time. **Methods:** This retrospective observational study used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database in the United States and Canada (09/2007-03/2022). Subjects with a clinical assessment of mild cognitive impairment (MCI), early MCI, late MCI, or AD/dementia were included; first observation with such diagnosis was defined as the index date. Eligible subjects were further required to have at least two visits after the index date with complete information on demographics, cognitive, and functional outcomes. Amyloid positive status was defined as cerebrospinal fluid amyloid-beta <192 pg/ml, florbetapir positron emission tomography (PET) global cortical uptake >1.11 standardized uptake value ratio (SUVR), or florbetaben PET global cortical uptake >1.08 SUVR. Eligible subjects were stratified into mutually exclusive cohorts based on the median positive annualized change (1.0 point) in CDR-SB score between the index visit and the first subsequent visit as follows: No progression (change≤0), Slower progression (0<change≤1.0 points), and Faster progression (change>1.0 points). For each cohort, the CDR-SB scores, Mini-Mental State Examination (MMSE) scores, Alzheimer's Disease Assessment Scale Cognitive Subscale 13 (ADAS Cog-13) scores, and Functional Activities Questionnaire (FAQ) scores were described at index and each subsequent visit for up to four years. In addition, analysis of covariance (ANCOVA) on complete data will be conducted to assess the effect of change in CDR-SB score (as a continuous measure) on changes in MMSE, ADAS Cog-11, and ADAS Cog-13 scores over the follow-up period. All models will adjust for patient characteristics and scores at index. **Results:** Of the 495 eligible subjects, 233 (47.1%) were classified in the No progression, 131 (26.5%) in the Slower progression, and 131 (26.5%) in the Faster progression cohort over one year post-index. Demographic characteristics at index were similar across cohorts. Among all subjects, the mean±SD age at index was 73.5±7.3 years and 59.0% were males. At index, subjects in the

Faster progression cohort were more likely to have a diagnosis of dementia than those in other cohorts: 27.5% vs. 14.6% for No progression and 19.1% for Slower progression. In addition, the Faster progression cohort had higher CDR-SB score (2.4±1.5 vs. 1.9±1.4 for No progression and 2.0±1.5 for Slower progression), lower MMSE scores (25.8±2.5 vs. 27.2±2.4 and 26.8±2.5 for the No and Slower progression cohorts, respectively), and higher ADAS Cog-13 scores (23.5±7.8 vs. 16.2±7.4 and 19.9±6.6 for the No and Slower progression cohorts, respectively) at index. The mean±SD FAQ scores were 7.8±6.8 (with 38.2% having FAQ≥9, an indication of impaired function and possible cognitive impairment) vs. 3.5±4.8 (15.5% had FAQ≥9) and 5.2±5.4 (25.2% had FAQ≥9) for the Faster, No and Slower progression cohorts, respectively. Over time, all cohorts progressively developed cognitive and functional impairment; however, the Faster progression one continued to experience worse outcomes compared with the other cohorts. By the fourth visit after the index, the CDR-SB score for the Faster progression cohort increased by 4.9 points on average, compared with 0.5 and 2.7 points for the No and Slower progression cohorts, respectively. The corresponding ADAS Cog-13 score increases were 10.0, 0.5, and 6.5 points, respectively. Nearly 60% of the Faster progression cohort had FAQ scores ≥9 compared with 20.5% and 47.7% among the No and Slower progression, respectively. Estimates from the ANCOVA models are under analysis and will be presented during the scientific congress. **Conclusion:** Despite similar demographic characteristics at baseline, amyloid-positive individuals with faster progression in CDR-SB early in the disease trajectory have higher disease severity at index and continue to experience worse outcomes over time than those with more gradual change in this metric. Conclusions from the ANCOVA models will be presented during the scientific congress. Full COI disclosure will be on the 2nd slide of the presentation or in the poster presentation.

P158- CAUSAL IN SILICO PATIENT MODELS CAN INFORM ALZHEIMER'S DISEASE PATIENT IDENTIFICATION AND ENDPOINT SELECTION FOR EARLY-STAGE CLINICAL TRIALS.

S.Y. Shin[1], S. Deepanshi[1], A. Bharthur[1], T. Oakland[1], J. Latourelle[1] *(1. GNS Healthcare - Somerville, Ma (United States))*

Background: The high cost of conducting clinical trials means that suboptimal trial design adds significant risk to developing a new drug. Clinical trial simulation shows promise as a tool to allow drug developers to test different trial designs in silico prior to enrollment. GNS Healthcare's in silico Alzheimer's disease (AD) patient model combines multi-omic, imaging and clinical profiles from patients diagnosed with AD and mild cognitive impairment (MCI) from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The ability of these models to provide patient-level predictions of disease progression over time makes them a powerful tool for optimizing trials, especially in the critical earliest stages of disease progression. **Objective:** Here we describe the utility of our in silico AD patient models, AD Gemini, in design of trials, through understanding of the expected progression of individual patients at different disease stages for different cognitive measure. Use of the models will allow researchers to identify the fastest progressing patient subsets for outcomes of interest in their study. **Methods:** After data processing, the training data for the primary in silico patient model included 317 samples (with 29 AD, 191 MCI, 97 Controls) and 57,792 features from WGS, DNA methylation, Microarray Gene Expression, Metabolites, MRI and PET imaging, CSF biomarkers, demographics, medication and selected cognitive endpoints measured over time. All the -omics measures were obtained from whole-blood. Nine cognitive endpoints were evaluated (ADAS13, ADAS11, ADAS3, CDR-SB, CDR-SB-Cog, mPACCdigit, mPACCtrailsB, FAQ, MMSE) for both baseline and rate of change, estimated as the slope in the generalized linear mixed model on repeated measurements). A second in silico patient model was built in parallel from the independent multi-omic, longitudinal ANMerge data (with 71 AD, 63 MCI, 65 Controls) with complementary available omics features (e.g. metabolites in ADNI and proteins in ANMerge). Each in silico patient is comprised of an ensemble of Bayesian network models built from the training data. A Bayesian network model is a directed graphical representation of relationships between variables where each node is a variable and each arrow is a conditional dependency. Given this, our approach can simulate the causal effect of a given upstream variable on an outcome of interest by estimating the outcome changes conditional on fixed upstream values while appropriately adjusting for all the other covariates laying on the paths across all the networks. **Results:** The ADNI-based in silico patient models had strong predictive performance across a variety of cognitive outcomes, both at baseline and for progression-rate. Specifically, the proportion of variability explained by the model (measured by R2) in the full training set ranged from 0.57 (for CDR-SB) to 0.71 (for mPACCtrailsB) for the progression endpoints. Cross-validation test set R-squared values were similarly high with an average 0.1 decrease in R2 observed. This decrease is likely due to sample size reduction in the nested CV models, rather than overfitting bias, as evidenced by comparison of top predictors across the models. The predictive performance was further evaluated in the AD and MCI subsets, to specifically assess how well fast progressing patients could be identified at different disease stages. For MCI, the best predicted progression-rate endpoints included mPACCtrailsB (R2=0.63), mPACCdigit (R2= 0.60), and ADAS13 (R2= 0.61), while the least well predicted endpoints were CDR-SB (R2= 0.5) and FAQ (R2= 0.49). In comparison, for the smaller sub-cohort of AD patients, the most robustly predicted progression-rate endpoints were CDR-SB (R2= 0.39) and CDR-SB-Cog (R2= 0.38). While CDR-SB showed a higher R2 in MCI than AD, the reduced performance in AD group is likely from the reduced sample, and so the relative ranking of the measures within each subset is more appropriate to determine the optimum endpoints in each disease stage. Thus, we confirmed the relative effectiveness of the CDR measures in the AD cohort in the independent ANMerge-based model which included more comparable numbers of MCI and AD patients. In that model, the R2 for CDR-TOTAL progression was 0.72 for AD patients and 0.44 for MCI. **Conclusion:** These results highlight the relative utility of different measures in different disease stages, suggesting that PACC tests are more suitable for early detection of cognitive impairment whereas CDR tests are best to monitor progression rates once the dementia developed. This study is limited by the small samples sizes once looking at the stratified analyses and inability to directly validate the models with the independent data sets due to differences in data. It does however demonstrate the robustness of the causal in silico patient approach despite underlying data differences. Further work will also allow understanding the relative contributions to the predictive ability of each model dependent on different data modalities (including comparison of utility of metabolomics in ADNI and proteomics in ANMerge models). Use of these in silico patient models for identification of fast progressing patients can greatly enhance particularly in critical early stages of disease.

P159- CLINICAL PREDICTORS FOR CONVERSION TO ALZHEIMER'S DEMENTIA IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT USING AMYLOID PET IMAGING : INTERIM RESULTS. K.W. Park[1], S.J. Kim[1], D.Y. Kang[2], Y.J. Jeong[2] *(1. Department of Neurology, Dong-A University College of Medicine - Busan (Korea, Republic of), 2. Department of Nuclear Medicine, Dong-A University College of Medicine - Busan (Korea, Republic of))*

Background and Objective: Alzheimer's dementia (AD) has different pathogenesis and progression than dementia caused by other causes, and various studies have been conducted to target and treat it. In particularly, patients with mild cognitive impairment (MCI) are a clinically important group as they are at increased risk for the progression to AD, typically 10-15% per year. One of the predictive biomarkers of identifying AD, amyloid positron emission tomography (PET) is being used as an imaging test to overcome the accuracy of clinical diagnosis. Amyloid PET, which imaging beta-amyloid protein, is positive in the earlier stage of disease. Therefore? it is useful for clinically discriminating dementia before symptoms appearing. In this prospective study, we determined the rate of conversion to Alzheimer's dementia between the two groups based on amyloid PET positivity. and investigated the clinical predictors for conversion to Alzheimer's Dementia in Patients with Mild Cognitive Impairment Using Amyloid PET Imaging. **Methods:** Individuals aged 50 and above with consistent cognitive complaints without significant impairment of activities of daily living (ADL) were eligible of the study. Subjects with MCI according to Petersen's criteria underwent neurologic examinations, laboratory test including ApoE genotyping, detailed neuropsychological tests, brain magnetic resonance imaging (MRI) and amyloid PET which was assessed by florbetaben (18F), flutemetamol (18F) and FC119S (18F). They have been clinically evaluated at baseline and followed up at least in one-year visit. Group comparisons and association analysis were performed using SPSS (version 26.0). Prognostic model was constructed with Cox proportional hazards regression analysis to predict progression to AD. **Results:** We consecutively recruited 50 patients who were clinically diagnosed with MCI and 42 subjects were included in the study (M:F 16:26, Age 71.36±6.92 years, Education 10.10±3.41 years). 19 of 42 (45.2%) subjects showed positive amyloid depositions, and we compared two groups according to amyloid PET positivity. The basic demographics were not significantly different between two groups except for Korea Instrumental Activities of Daily Living (KIADL) in baseline (p=0.006) and 1 year follow up study (p=0.003). 4 of 19 (21.1%) subjects with amyloid PET positive clinically converted to AD during follow up (mean duration 17.95±4.34 months) (p=0.158). Meanwhile, 5 of 42 patients (11.9%) were converted to Alzheimer's disease, and the remaining group of MCI was compared with the group who converted to AD. There were not significantly different between two groups, but Clinical Dementia Rating-Sum of box (CDR-SOB) score was higher in AD group at baseline (p=0.015). Also, Mini-Mental State Examination (MMSE), Global Deterioration Scale (GDS) and CDR-SOB score were higher in AD group compared MCI group in 1 year follow up study. The effect of independent variables on progression to AD was analyzed using multivariate Cox proportional hazards regression. As a result, higher CDR-SOB score was considerably related to increased risk of AD conversion (hazard ratio 6.740, 95% confidence interval, 1.461-31.094, p=0.014). **Conclusion:** In this prospective study, patients with MCI who were amyloid PET-positive were more likely to progress to Alzheimer's disease than patients who were amyloid PET-negative, but long-term follow-up was required. In addition, the group who converted to AD had higher CDR-SOB score than the stable MCI group at baseline and had higher MMSE, GDS, and CDR-SOB score in the 1-year follow-up period. We found that the CDR-SOB score was significantly considered as a clinically valuable prognostic predictor of disease progression from MCI status to AD.

P160- CLINICAL TRAJECTORY OF PRECLINICAL AD OVER 36 MONTHS IN THE CHARIOT STUDY. G. Novak[1], S. Baker[1], K. Karcher[1], D. Henley[1,2], C. Udeh-Momoh[3], O. Robinson[4], G. Price[3], T. Watermeyer[5], C. Ritchie[5], L. Middleton[3,4] *(1. Janssen R&D - Titusville, Nj (United States), 2. Indiana University School of Medicine - Indianapolis, In (United States), 3. Imperial College Healthcare NHS Trust - London (United Kingdom), 4. AGE Research, School of Public Health, Imperial College of London - London (United Kingdom), 5. Edinburgh Dementia Prevention, Centre for Clinical Brain Sciences, University of Edinburgh - Edinburgh (United Kingdom))*

Background: Longitudinal studies in cognitively unimpaired individuals with biomarker evidence of Alzheimer's pathology suggest that they show a greater rate of decline in performance on tests of memory and executive function, relative to individuals without such evidence. The recent shift towards preventative strategies in early-stage disease requires clinical trials with sensitive outcome measures suitable for detection of therapeutic effect. The ongoing CHARIOT-PRO Substudy aims to estimate the rate of cognitive change in the early Alzheimer's pathological continuum, comparing individuals with and without baseline biomarker evidence of amyloid deposition (Aβ+ and Aβ-, respectively) over a 4.5 year follow up. The COVID-19 pandemic necessitated a shift to remote cognitive assessments over several months in 2020-2021. Here we present clinical outcome data through 36 months, comparing Aβ+ and Aβ- participants in both remote and in-person testing conditions. **Objectives:** To compare longitudinal cognitive performance in unimpaired Aβ+ and Aβ- individuals, using the Preclinical Alzheimer's Cognitive Composite (PACC). To assess whether the PACC's association with amyloid status remained evident under remote (rather than in-person) testing conditions. **Methods:** Healthy, cognitively unimpaired individuals (60-85 years), with Clinical Dementia Rating (CDR) scale = 0, underwent amyloid assessment via PET or lumbar puncture; approximately equal numbers of Aβ+ and Aβ- individuals were enrolled. Cognitive outcomes were assessed with the PACC, comprised of the Free and Cued Selective Reminding Task (FCSRT; total + free recall), Logical Memory II (LMII) from the Wechsler Memory Scale, Coding, and the Mini-Mental State Exam. The PACC was calculated as the sum of the z scores for each component calculated relative to the baseline mean and standard deviation for the entire sample. The PACC was obtained in screening and at baseline, and every 6 months thereafter. During the pandemic, remote assessments were conducted by videoteleconference. Verbal stimuli were presented by computer audio or phone. Visual stimuli were displayed via webcam or Power- Point and responses were recorded on forms unsealed at the time of the visit and were captured as screenshots by raters. Change from baseline was analyzed using a mixed effects model for repeated measures (MMRM) with amyloid status (negative, positive), visit, education level (9-12 years, college), APOE ε4 status (non-carrier, carrier) and visit-by-amyloid status interaction as factors, and age, hippocampal volume, and baseline value as

covariates. Changes from baseline were calculated separately for remote and in-person testing in Aβ+ and Aβ- participants and were summarized with descriptive statistics. **Results:** A total of 258 Aβ+ and 261 Aβ- participants were enrolled in the study. At baseline, Aβ+ participants were older (mean (sd): Aβ+ =72.4y (5.7) vs Aβ- = 70.4y (5.3), p<0.00001), were more likely to be ApoE ε4 carriers (Aβ+ = 55.6% vs Aβ- =23.0%, p<0.001), and had lower scores on the PACC (Aβ+ = -0.40 (2.6) vs Aβ- =0.39 (2.7), p=0.001). Due to Covid-19, in-person visits were suspended from March 2020 to May, 2021. During these 14 months, 364 remote PACC assessments for Month 18, 24, 30, and 36 visits were carried out. As participants were at various timepoints in the study, the proportion of remote assessments within each visit window increased from 45 (9.6%) at Month 18 to 154 (44%) at Month 36. Performance on the PACC surpassed baseline at every visit in both groups with maximum mean change at Month 18 of +1.15 (Aβ-) and +0.64 (Aβ+). There was greater improvement for Aβ- than for Aβ+ participants at every visit, with statistically significant differences 18 months (LS mean difference [SE] = 0.39 [0.18], p=0.032), 30 months (0.54 [0.22], p=0.016), and 36 months (0.84 [0.20], p<0.001). Differences between Aβ+ and Aβ- in mean change from baseline were approximately the same magnitude for those that had in-person assessment (+1.03 Aβ- vs. +0.15 Aβ+ at Month 36) vs those that were tested remotely (+1.19 Aβ- vs. +0.37 Aβ+ at Month 36). Across both amyloid groups, mean PACC scores were lower at Month 18 for participants that had remote testing (0.04 Aβ-; -1.04 Aβ+) compared to those that had in-person testing (1.80 Aβ-; 0.51 Aβ+) but were comparable between the testing conditions at Months 24, 30, and 36. The difference at Month 18 appeared to arise from lower performance in coding and on the MMSE for remote testing, with minimal difference apparent for the FCSRT and the LMII. **Discussion:** In these cognitively unimpaired individuals, performance on the PACC improved over 36 months, though to a significantly greater extent in Aβ- than Aβ+ participants, consistent with differential practice effects previously reported on the first 2 administrations of the RBANS in this cohort. Though there were differences in performance between remote and in-person testing, the effects of amyloid status were similar in magnitude in both testing conditions. These findings highlight the value of the PACC as a sensitive measure for clinical trials and raises important consideration regarding remote versus in-person cognitive testing.

P161- IMPACT OF DIFFERENT RATES OF DISEASE PROGRESSION IN INDIVIDUALS WITH AMYLOID POSITIVE ALZHEIMER'S DISEASE - FINDINGS FROM THE NATIONAL ALZHEIMER'S COORDINATING CENTER.

J.M. Chandler[1], M. Georgieva[2], U. Desai[2], N. Kirson[2], W. Ye[1], A. Zhao[2], D. Eid[2], A. Gomez-Lievano[2], A. Hilts[3], T. Schilling[1] *(1. Eli Lilly and Company - Indianapolis (United States), 2. Analysis Group - Boston (United States), 3. Groupe d'Analyse - Montréal (Canada))*

Background: The heterogeneity in the rate of disease progression among individuals with Alzheimer's disease (AD) has been well-documented. However, few studies have comprehensively assessed the implications of differential rates of disease progression in individuals with AD on longitudinal outcomes. A better understanding of the associations between initial progression rates and cognitive, functional, and neuropsychiatric outcomes over time could help interpretation of clinical trials findings for treatments with potential to slow AD disease progression. **Objectives:** This study aimed to describe the underlying characteristics and long-term outcomes associated with different rates of disease progression as defined by the annualized change in Clinical Dementia Rating scale Sum of Boxes (CDR-SB) score, among amyloid-positive individuals with AD. An additional objective of the study was to estimate the effect of hypothetical reduction in change in CDR-SB on other outcomes over time. **Methods:** This retrospective observational study used data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) in the United States (06/2005-11/2021). Subjects with a clinical assessment of mild cognitive impairment or dementia and CDR-SB score 0.5-9.0 (inclusive; first visit defined as the index date) were included in the study. Eligible subjects were further required to have primary or contributing etiologic diagnosis of AD on at least half of the visits, including the most recent visit after the index date, and have at least two visits after the index date with complete information on demographics and outcomes of interest. Amyloid positive status was defined as either abnormally elevated amyloid on positive emission tomography scan or abnormally low amyloid in cerebrospinal fluid ante-mortem; or frequent density of neocortical neuritic plaques or Braak stage for neurofibrillary degeneration of Stage V or Stage VI post-mortem. Eligible subjects were stratified into mutually exclusive cohorts based on the median positive annualized change (2.0 points) in CDR-SB score between the index visit and the first subsequent visit as follows: No progression (change≤0), Slower progression (0<change<2.0 points), Median progression (2.0-point change), and Faster progression (change>2.0 points). For each cohort, the cognitive, functional, and neuropsychiatric outcomes were described at index and each subsequent visit for up to five years. In addition, analysis of covariance (ANCOVA) on complete data will be conducted to assess the effect of change in CDR-SB score (as a continuous measure) on changes in Mini-Mental State Examination (MMSE), Functional Activities Questionnaire (FAQ), and Neuropsychiatric Inventory-Questionnaire (NPI-Q) scores over the follow-up period. All models will adjust for patient characteristics and scores at index. **Results:** Of the 1,263 eligible subjects, 474 (37.5%) were classified in the No progression, 297 (23.5%) in the Slower progression, 213 (16.9%) in the Median progression, and 279 (22.1%) in the Faster progression cohort over one year post-index. Demographic characteristics and comorbidity profiles at index were similar across cohorts. Among all subjects, the mean±SD age at index was 72.7±9.7 years and 55.3% were males. The most common comorbidities at index were hypercholesterolemia (54.7%), psychiatric disorders (49.4%), and hypertension (48.5%), and 62.7% had at least one copy of APOE e4 gene. At index the Faster progression cohort had higher CDR-SB score (4.9±2.1 vs. 3.6±2.0 for No, 3.7±2.1 for Slower, and 3.5±2.2 for Median progression), higher FAQ score (15.7±7.1 vs. 9.4±7.1, 10.2±7.4, and 10.7±7.7 for the No, Slower, and Median progression respectively), and higher NPI-Q scores (4.5±4.0 vs. 3.5±3.5, 3.5±3.3, and 3.5±3.7 for the No, Slower, and Median progression cohorts). Additionally, fewer subjects in the Faster progression cohort were able to live independently (17.6% vs. 39.2%, 34.3%, and 36.6% among the No, Slower, and Median progression cohorts). Over time, all cohorts progressively developed cognitive and functional impairment; however, the Faster progression one continued to experience worse outcomes compared with the other cohorts. By the fifth visit after the index, the CDR-SB score for the Faster progression cohort increased by 11.4 points on average, compared with 6.6, 8.3, and 9.7 points for the No, Slower, and Median progression cohorts, respectively. Nearly 75% of the Faster progression cohort was

completely dependent compared with 28.3%, 34.0%, and 49.3% among the No, Slower, and Median progression, respectively. The neuropsychiatric outcomes at five years post-index were similar for all cohorts. Estimates from the ANCOVA models are under analysis and will be presented during the scientific congress. **Conclusion:** Despite similar demographic and comorbidity profiles at baseline, amyloid-positive individuals with faster progression in CDR-SB early in the disease trajectory have higher disease severity at index and continue to experience worse outcomes over time than those with more gradual change in this metric. Conclusions from the ANCOVA models will be presented during the scientific congress. Full COI disclosure will be on the 2nd slide of the presentation or in the poster presentation.

P162- RESCREENING ON RBANS DELAYED MEMORY INDEX? FORGET ABOUT IT! M.N. Sabbagh[1], W. Michalak[2], C.T. Hansen[2], L.L. Raket[2], C.A. Wichmann[2], A. Clark[2] *(1. Barrow Neurological Institute - Phoenix, Arizona (United States), 2. Novo Nordisk A/S - Søborg (Denmark))*

Background: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Delayed Memory Index (DMI) is frequently used to screen patients for early Alzheimer's Disease trials. An RBANS DMI score ≤85 is typically used to select a patient population with cognitive impairment and increased likelihood of being amyloid positive, and thus avoid unnecessary amyloid PET scans and lumbar punctures. Trial investigators may consider some patients who do not meet the RBANS DMI ≤85 cut-off to otherwise have Alzheimer's Disease, but it is unclear if they would meet eligibility criteria if rescreened at a later date. We sought to gain a better understanding of RBANS DMI trajectory over time and how, in combination with other Alzheimer's Disease trial inclusion criteria, such as clinical scale scores, it relates to amyloid positivity. **Objectives:** To help inform trialists about the potential value of rescreening patients who initially fail RBANS DMI inclusion criteria, in order to aid trial recruitment. **Methods:** We conducted an analysis of data from the European Prevention of Alzheimer's Dementia (EPAD) database. A study population was identified with the following criteria at baseline: 1) age 50–85 years; 2) no dementia diagnosis from the participant's physician; 3) a Mini-Mental State Examination (MMSE) score ≥22; and 4) data on RBANS DMI. Data were stratified by RBANS DMI score at baseline (≤85, 86–95, and >95) and characterized in relation to distribution of age, ethnicity, amyloid positivity, ApoE genotype, MMSE and Clinical Dementia Rating (CDR) global score. RBANS DMI trajectories were visualized by spaghetti plots and modeled (mixed model with participants as random effects, and time, and time interaction with baseline RBANS DMI as fixed effects) using available longitudinal data to estimate average change from baseline to 6 and 12 months in the total population and by baseline RBANS DMI group. Logistic regressions were performed to determine the odds and probabilities for participants with baseline RBANS DMI 86–95 of meeting: A) the RBANS DMI cut-off of ≤85 at rescreening; B) criteria A + CDR global ≥0.5; and C) criteria B + being amyloid positive. These outcomes were assessed at 6 and 12 months, respectively. The proportion of participants with an RBANS DMI score ≤85 at 6 months was also assessed with different baseline RBANS DMI thresholds for rescreening. **Results:** Of the 2,096 participants in the database, 1,965 fulfilled the four inclusion criteria at baseline. Of these, 1,731 also had data on CDR global and amyloid status. For those who were assessed at both baseline and 6 months, 1,551 participants also had CDR and amyloid data. At baseline, amyloid positivity rates were 58.3% (147/252), 36.7% (76/207), and 28.5% (362/1,272) for RBANS DMI scores of ≤85, 86–95, and >95, respectively. Amyloid positivity increased to 73.4% (n=116/158) among participants with both RBANS DMI score ≤85 and CDR global score ≥0.5. There was large variability in the change in RBANS DMI scores over time, with a median change of 2.0 (interquartile range: –5.0; 9.0) at 6 months. For participants with baseline RBANS DMI scores of 86–95 (N=207), there was also no clear trend in RBANS DMI values at 6 and 12 months. It was estimated that 15% of participants would progress from RBANS DMI scores of 86–95 at baseline to ≤85 at 6 months, with 8% also achieving the CDR global criteria and 5% also being amyloid positive. This implies a need to rescreen approximately 7 participants with a baseline RBANS DMI of 86–95 to identify one participant fulfilling criteria A, 13 participants to meet criteria B, and 20 participants to meet criteria C. Modeling data for a 12-month follow-up resulted in similar findings. Regardless of the baseline RBANS DMI threshold used to rescreen, no more than 16% of participants would progress to a score of ≤85 at 6 months. The mixed model indicated that participants with baseline RBANS DMI scores <109 are likely to have a positive change in RBANS DMI and participants with scores >109 are likely to have a negative change. These findings could suggest an effect of regression to the mean. **Conclusion:** In this study, there was a large degree of variability in RBANS DMI scores, with no trend in the scores over time. Only a small proportion of participants not meeting the initial RBANS DMI criteria progressed to meet the RBANS DMI threshold of ≤85 at 6 and 12 months, and fewer still also met other common trial inclusion criteria. This indicates that there is limited value in rescreening patients based on their RBANS DMI score. **Conflicts of Interest:** MNS serves as a consultant to Novo Nordisk. However, MNS received no remuneration for participating in this project. WM, CTH, LLR, CAW, and AC are employees of Novo Nordisk A/S, and CTH also holds stocks in Novo Nordisk.

P163- PREDICTORS OF MEMORY IMPAIRMENT IN MILD COGNITIVE IMPAIRMENT WITH LOW MINI-MENTAL STATE EXAMINATION RECALL SCORES. S.Y. Ryu[1], S.B. Lee[1], T.J. Lee[1], Y.J. Jung[1] *(1. The Catholic University of Korea, Daejeon St. Mary's Hospital - Daejeon (Korea, Republic of))*

Background: Alzheimer's disease (AD) is the main cauase of cognitive impairment in late-life, and the typical early presentation of AD in older aduts is amnestic cognitive impairment. Mini-Mental State Examination (MMSE) is widely used in screening cognitive impairment in elderly and includes recall item that measures memory. **Objectives:** The aim of this study was to examines if low MMSE recall scores would be associated with verbal memory impairment in individuals with mild cognitive impairment (MCI). **Methods:** 158 MCI subjects with low MMSE recall scores (MMSE recall subscore <= 1) (mean age: 74.28 ± 6.67 years) were included in this study. The participants underwent clinical assessments and completed detailed neuropsychological tests. The participants were divided into two groups according to Seoul Vebal Learning Test Delayed Recall (SVLT DR) scores: normal verbal memory performance (SVLT DR >= -1.0 SD) vs low verbal memory performance (SVLT DR < -1.0 SD) groups. Group comparisons between normal and low verbal memory performance were performed. **Results:** Low verbal memory performance group (n = 91) was older and had more males than normal verbal memory performance group (n = 67). For MMSE items, low

verbal memory performance group had lower MMSE time orientation subscores and higher MMSE language subscores than normal verbal memory performance group. The results for MMSE time orientation remaind significant after adjusting age, sex, education. There were no differences in MMSE total scores, other MMSE items, instrumental activities of daily living, clock drawing tests or depressive symptoms between the two groups. **Conclusion:** In MCI individuals with low MMSE recall scores, low verbral memory performance was associated with lower MMSE time orintation scores, compared to the normal vermal memory performance group. These results suggest that more consideration for MMSE sub-items would be helpful for the clinical evaluation of individuals with MCI at first step.

P164- INCREASED NUMBERS OF MODIFIABLE DEMENTIA RISK FACTORS AMPLIFY ADVERSE EFFECTS ON COGNITION ACROSS THE ADULT LIFESPAN. A. Laplume[1], L. Mcketton[1], B. Levine[1,2?3], A. Troyer[4,5], N. Anderson[1,2,6] *(1. Rotman Research Institute, Baycrest Health Sciences - Toronto (Canada), 2. Department of Psychology, University of Toronto - Toronto (Canada), 3. Department of Medicine (Neurology), University of Toronto - Toronto (Canada), 4. Department Of Psychology, University Of Toronto - Toronto (Canada), 5. Neuropsychology and Cognitive Health Program, Baycrest Health Sciences - Toronto (Canada), 6. Department of Psychiatry, University of Toronto - Toronto (Canada))*

Background: Prior studies showed that modifiable lifestyle behaviours can reduce dementia risk by 40%, however their prevalence and association with cognition extending to early adulthood is not well understood. Growing evidence suggests that age related cognitive decline begins in younger adults, which extends the critical period for targeting risk factors from older to early adulthood. **Objectives:** We sought to build on previous work to test whether prevalence of modifiable risk factors for dementia and their dose-response relationship with cognition is moderated by age. **Methods:** We used a large web-based dataset on participants who completed a free, self-administered online assessment (the Cogniciti Brain Health Assessment) that is psychometrically validated, and demonstrated adequate internal consistency, test-retest reliability, alternate version reliability, construct validity and adequate convergent validity when compared to clinician-administered neuropsychological tests of the same constructs. Moreover, the test was designed to be suitable for older adults and provides greater sensitivity at the high end of function than the Montreal Cognitive Assessment, offering sensitivity to assess a relatively healthy sample. Our sample included a dataset of N = 93,363 assessment attempts. After extensive data cleaning, associations between eight modifiable risk factors for dementia (low education, hypertension, hearing loss, traumatic brain injury, alcohol or substance abuse, diabetes, smoking, and depression) and cognition were examined using polynomial regression analyses in this online sample (N = 22,117, aged 18-89). **Results:** Our results extend previous findings to show that risk factors are more prevalent as age increases and show a larger dose-response association with cognition as age increases. Older adults (ages 66-89) had more risk factors than middle-aged (ages 45-65) and younger adults (ages 18-44). Polynomial regression revealed each additional risk factor was associated with a drop in cognitive performance (equivalent to three years of aging), with a larger association as age increased. Adults with no risk factors in their 40s-70s showed similar cognitive performance to people 10 or 20 years younger with many risk factors. **Conclusion:** Dementia has a long preclinical period which highlights the need to study risk factors and cognitive impacts long before a clinical diagnosis of dementia. We found that modifiable dementia risk factors may be more important than age in predicting cognitive performance.

P165- FEASIBILITY, RELIABILITY, AND VALIDITY OF REMOTE SMARTPHONE DATA COLLECTION IN FRONTOTEMPORAL DEMENTIA USING THE ALLFTD MOBILE APP. A. Staffaroni[1], J. Taylor[1], A. Clark[1], H. Heuer[1], A. Wise[1], M. Manoochehri[2], L. Forsberg[3], C. Mester[3], M. Rao[3], D. Brushaber[3], J. Rojas[1], J. Kramer[1], B. Boeve[3], H. Rosen[1], A. Boxer[1] *(1. UCSF - San Francisco (United States), 2. Columbia University - New York (United States), 3. Mayo Clinic - Rochester (United States))*

Background: The successful identification of safe and effective therapies for frontotemporal dementia (FTD) is contingent on validated clinical trial endpoints that are capable of efficiently capturing the clinical heterogeneity of FTD. Moreover, FTD is relatively rare and affected individuals are geographically dispersed, making recruitment challenging. Clinical trials in the familial forms of FTD, for example, will likely require global recruitment. Remote assessment tools could address these challenges and potentially enable decentralized clinical trials. We developed the ALLFTD Mobile App, a smartphone application that includes assessments of cognition, speech/language, and motor functioning, to address some of these . There is a dearth of information about the feasibility, reliability, and validity of remote smartphone assessment in FTD. **Objectives:** The objectives were to determine the feasibility of implementing a remote smartphone data collection protocol in a multicenter FTD research study and evaluate the reliability and validity of the smartphone cognitive measures. **Methods:** A diagnostically mixed sample of 207 participants with FTD or from familial FTD kindreds (CDR®+NACC-FTLD=0 [n=91]; CDR®+NACC-FTLD=0.5 [n=39]; CDR®+NACC-FTLD≥1 [n=39]; unknown [n=38]) were asked to remotely complete a 25-35 minute smartphone assessment battery three times over two weeks. The battery included five executive functioning (EF) tests and an adaptive memory test. They also completed surveys about their experience interacting with the app. We analyzed adherence (percentage of available measures that were completed) and user experience. We evaluated split-half reliability using the first available assessment for each participant. We assessed test-retest reliability across all available assessments. To establish evidence for construct validity, linear models tested the association of the smartphone tests with gold-standard neuropsychological outcomes (UDS3-EF composite & CVLT-SF Immediate Recall), a measure of disease severity (CDR®+NACC-FTLD Box Score), and regional gray matter volumes. **Results:** Participants completed 70% of tasks. Those that completed at least one set of assessments reported that the instructions were understandable (93%), considered the time commitment acceptable (97%), and were willing to complete additional assessments (98%). Split-half reliability was excellent for the executive functioning tasks (r's=0.93-0.99) and good for the memory test (r=0.78). Test-retest reliabilities ranged from acceptable to excellent (intraclass correlations: 0.70–0.96). Smartphone EF measures were strongly associated with the UDS3-EF composite (ß's=0.6–0.8, all p<.001), and the memory test was strongly correlated with total immediate recall on the CVLT-SF (ß=0.7, p<.001). Worse performance on all tests was associated with greater disease severity (ß's=0.5–0.7, all p<.001). Poorer performance on the smartphone EF tasks was associated

with lower frontoparietal/subcortical volume (ß's=0.4–0.6, all p<.015) and worse memory scores with lower hippocampal volume (ß=0.5, p<.001), controlling for total intracranial volume. **Conclusion:** These results indicate that remote digital data collection in FTD research is feasible and acceptable. These findings also support the reliability and validity of the ALLFTD Mobile App cognitive tests. Future studies will aim to understand the validity of these measures for early detection of symptoms and longitudinal monitoring. **Conflicts of Interest:** The authors declare no conflicts of interest relevant to the current work.

P166- CALCULATING GENERALIZED RECALL PROBABILITY USING DIGITAL COGNITIVE BIOMARKERS DERIVED FROM WORDLIST MEMORY TEST ASSESSMENT. J. Hara[1,2], J. Bock[1,3], K. Shah[4], D. Fortier[1], M. Lee[3] *(1. Embic Corporation - Newport Beach (United States), 2. Pickup Family Neuroscience Institute and Hoag Center for Research and Education, Hoag Memorial Hospital - Newport Beach (United States), 3. Dept. of Cognitive Sciences, University of California at Irvine - Irvine (United States), 4. University of California at Berkeley - Berkeley (United States))*

Background: Digital cognitive biomarkers (DCBs) quantify underlying, unobservable (latent) cognitive processes that are fundamental to cognitive function and that animate the cognitive domains of memory, orientation, and verbal fluency. DCBs of encoding and retrieval can be generated with a hierarchical Bayesian cognitive processing (HBCP) model, applied to item response data from commonly used wordlist memory (WLM) tests of learning and recall. Seven base DCBs have been well validated, each representing probability of information processed through different encoding (N1, N2, N3, or N4) or retrieval (R1, R2, or R3) paths and three distinct storage states (pre-task, transient, or durable storage states). While these base DCBs provide granular insight into cognitive function, additional measures that quantify the probability of recall from various storage states are valuable to bridge between underlying processes (encoding and retrieval) and observed behaviors (e.g., word recall). A generalized probability of recall, which includes the combination of encoding and retrieval processes that result in successful recall across WLM test tasks, can be constructed from base DCBs subsequent to modeling. Such additional measures can provide deeper insight into observed behavior and could aid in interpreting and communicating cognitive changes during clinical trials or in clinical settings. **Objective:** To calculate and validate additional measures that use digital cognitive biomarkers of encoding and retrieval to represent the probability of recall from transient and durable storage states for immediate and delayed recall. **Methods:** In calculating generalized probability of recall, the seven base DCBs were first generated on item response data from the ADAS-Cog WLM tests (n = 10,933) performed between the years of 2005 and 2021 on subjects (n = 2,348) enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Their demographics and clinical diagnoses were also obtained. The HBCP model that generates these DCBs uses a multinomial processing tree to calculate the probability that each encoding or retrieval process is used during each learning and recall task of the WLM test. A post-modeling calculation was performed to summate the probabilities across the tree for the subsets of processes involved in recall from transient storage on immediate recall tasks, from durable storage on immediate recall tasks, and from durable storage on delayed recall tasks, generating M1, M2, and M3, respectively. These M parameters were calculated for each of the ADAS-Cog WLM test assessments and were visually compared to total word recall for each immediate and delayed recall task and all tasks combined. After randomly assigning 20% of the sample to a training subsample, we evaluated a pair of logistic regression models to compare subject assessments with diagnosis of mild cognitive impairment (MCI) to cognitively normal (CN) and compare dementia due to Alzheimer's disease (AD) to MCI, respectively. Demographics and all three M parameters were included as predictors, and we used backward elimination of non-significant predictors. On the testing subsample (the remaining 80% of the sample), we plotted receiver operating characteristic (ROC) curves and obtained classification accuracy for both diagnosis pairs. **Results:** Visual comparison of M parameters and total word recall showed a clear curvilinear relationship. Both logistic regression models were significant (p's < .001), with pseudo R2 = .23 for classification of MCI from CN and .38 for AD from MCI. The ROC AUCs = .79 and .88, respectively, and with a cutoff of .51 and .53, classification accuracies = 72.05% and 81.39%, respectively. **Conclusion:** The results demonstrate that the underlying cognitive processing parameters, when summated as a probability of recall from pre-task, transient, or durable storage states, highly resemble observed behavior of total word recall for each of the immediate and delayed recall tasks. This reinforces the accuracy of the base DCBs and validates the generalized measures of recall probability (M1, M2, M3) as predictors of observed behavior. Furthermore, these measures demonstrate predictive accuracy for classifying individuals according to AD impairment severity, based on a single assessment. Such measures are beneficial for characterizing subjects during the enrollment stage of clinical trials and for comparing treatment arms in clinical research.

P167- DIGITAL COGNITIVE BIOMARKERS FOR THE ADAS-COG WORD RECALL TEST: ACCURACY AND VALIDITY OF CLASSIFYING COGNITIVE IMPAIRMENT. J. Bock[1,2], J. Hara[1,3], D. Fortier[1], T. Mangrola[1], W. Shankle[1,2,3], M. Lee[2] *(1. Embic Corporation - Newport Beach (United States), 2. Dept. of Cognitive Sciences, University of California at Irvine - Irvine (United States), 3. Pickup Family Neuroscience Institute, Hoag Memorial Hospital - Newport Beach (United States))*

Background: In Alzheimer's disease (AD) clinical trials, episodic memory performance is frequently assessed with wordlist memory (WLM) tests during enrollment and/or as an outcome measure for individuals who are cognitive normal (CN) or who have mild cognitive impairment (MCI) or AD dementia. Most commonly, the total number of words recalled across tasks is used to score performance. However, this approach fails to use the majority of information available in a WLM test and is often insufficient for characterizing subtle cognitive changes. This is especially true in CN and MCI stages and when measuring changes in underlying cognitive processes that may be differentially affected by the course of AD. As the focus of AD clinical trials shifts toward prevention, pre-clinical, or MCI-stage AD, there is a vital need to quantify episodic memory more precisely, enabling more accurate classification of impairment. Digital cognitive biomarkers (DCBs) quantify underlying, unobservable (latent) cognitive processes, fundamental to cognitive function. We generate DCBs of encoding and retrieval with a hierarchical Bayesian cognitive processing (HBCP) model, applied to item response data from commonly used multi-task WLM tests of learning and recall. There are seven base DCBs, each representing probability

of information processed through different encoding (N1, N2, N3, or N4) or retrieval (R1, R2, or R3) paths and three distinct storage states (pre-task, transient, or durable storage states). These DCBs provide new, granular, and insightful measures of cognitive function. There are several commonly used WLM tests, including the AVLT, CVLT, EVLT, CERAD, and ADAS-Cog. While these tests share a common test administration paradigm, consisting of multiple learning and recall tasks (immediate and delayed), the ADAS-Cog employs a shuffled wordlist presentation, whereby each of the 10 words in the wordlist are presented in a different order during each of the three learning tasks. Since shuffling the presentation order of words eliminates the serial position effects of primacy and recency on encoding (which is a loss of available information), generating DCBs for this test paradigm requires modeling the item-level responses with a distinct approach compared to that used for fixed-order tests. **Objective:** To validate generation of DCBs with ADAS-Cog WLM tests by comparing outcomes across individual assessments according to clinical diagnoses. **Methods:** Item response data was obtained from ADAS-Cog WLM tests (n = 10,933) performed between the years of 2005 and 2021 on subjects (n = 2,348) enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI), along with their demographics and clinical diagnoses (CN, MCI, and AD). An HBCP model was used to evaluate individual WLM assessments, independent of all other assessments being modeled. To enable characterization of latent processes with a single ADAS-Cog WLM test, three modifications were made that distinguish the model from that used for fixed order tests: 1) Bayesian prior distributions of DCBs were obtained through modeling of 77,000 subjects who were assessed with the EVLT, separated across female and male, low and high education, and ages 40 to 85, and individual ADAS-Cog assessments use the appropriate prior distribution for their demographic group; 2) position-specific parameters are used for each word, dependent on task; and 3) word-specific encoding and retrieval probability penalties were calculated and are applied to modeling recall. The resulting DCB posterior distribution means were examined to characterize patterns in cognitive performance and, after randomly assigning 20% of the sample to a training subsample, we evaluated a pair of logistic regressions to compare MCI to CN and AD to MCI subject assessments, respectively. Demographics and all seven DCBs were included as predictors, and we used backward elimination of non-significant predictors. On the testing subsample (the remaining 80% of the sample), we plotted receiver operating characteristic (ROC) curves and obtained classification accuracy for both diagnosis pairs. **Results:** DCB posterior distribution means, when grouped according to diagnosis, showed clear decline in cognitive processing ability with increasing severity and clear separation among groups. Both logistic regression models were significant (p's < .001), with pseudo R2 = .24 for classification of MCI from CN and .38 for AD from MCI. The ROC AUCs = .79 and .88, respectively, and with a cutoff of .58 for both models, classification accuracies = 71.89% and 81.18%, respectively. **Conclusion:** This demonstration of accurate classification of cognitive impairment by diagnosis with DCBs, generated from item response data of individual assessments with established priors, obtained from a large population across demographic groups, validates our HBCP modeling approach on the ADAS-Cog WLM test. Because these DCBs characterize underlying cognitive processes, this enables more granular classification, pertaining to encoding and retrieval specifically, than total word recall can provide. Furthermore, it enables comparison of individual episodic memory performance across WLM tests, whether word presentation order is shuffled or fixed. This is valuable to clinical trial recruitment, enrollment, and outcome measurement by providing expanded information about subject cognition prior to and during study.

P168- A NOVEL 2-MINUTE HIGH-FREQUENCY ASSESSMENT OF EPISODIC MEMORY, SHOWS DIURNALITY, TIME VARYING PATTERNS IN FATIGUE AND MOOD WHICH BECOME MORE TIGHTLY COUPLED WITH AGE.

A.L. Anwyl-Irvine[1], A. Kaula[1], N. Taptiklis[1], C. Nathan[1], F. Cormack[1] *(1. Cambridge Cognition - Cambridge (United Kingdom))*

Background: A decline in episodic memory is a strong marker of neurodegenerative diseases such as Alzheimer's. As such measuring, this faculty has potential for early detection of disease processes. This makes tasks which measure this an important target for cognitive assessment. Yet measures of memory can show variability across time, both in a linear way (e.g., neurodegeneration or recovery) and a stationary way (e.g., morning-afternoon patterns). Far from being noise, this information may offer more statistical power and insight into an individual's life. High-frequency assessments, therefore, present a tempting opportunity to capture this rich information. Such a measure of episodic memory must involve recalling what, when and where some percept occurred. Additionally, to promote patient compliance with many sessions, it should ideally be easy to understand, brief, and compatible with mobile devices. Here we present such a tool, assessing memory for objects on a screen (what) in a specific order (when) and in a specific location (where). We show initial data in two healthy samples (n=133, 117) with a wide age range to evaluate appropriateness as a candidate tool in patient populations. **Objectives:** To present a novel, brief, high-frequency assessment of episodic memory. Assess the overlap of test-metrics with existing measures of memory. Test the compliance, learning curve and time-varying properties of the assessment metrics. Show if these co-vary with Age, time-of-day, fatigue and mood, as requirements before testing this task in a patient population. **Methods:** The task consists of a learning phase where participants see a sequence of four items (animal emoji) in a specific order and location, and then are asked to replicate the item order and location by dragging and dropping these items on-screen. A recall phase follows a minimum 12-hour delay, with replication of the earlier response. Each session takes less than 2 minutes. The first phase supplies visual short term memory metrics of spatial and order precision, with the second phase capturing these metrics as indications of long-term episodic memory. Participants were recruited online and tested remotely on their own devices. Experiment 1 (n=133, 18-68 y/o) is a cross-sectional study investigating age and comparing a single-use version of the task with established assessments (CANTAB Paired Associate Learning/PAL, Spatial Span/SSP). Adjusted Pearson's r is used to assess the association between task metrics and age. Dominance analysis is used to compare variance unique and shared with existing measures. In Experiment 2 (n=117, 23-79 y/o) the novel task was repeated morning and afternoon for 7 days, alongside momentary mood, fatigue, and sleep ratings, and a more comprehensive battery of CANTAB tasks at the last timepoint. Diurnality was tested using one-sample t-tests. Group-level temporal patterns between metrics and momentary ratings are analysed using repeated-measures correlations (RMCOR), individual differences in these patterns and Age are modelled using individual partial-correlations to conduct a Monte-Carlo permuted multi-level General Linear Model

(GLM). **Results:** Experiment 1 revealed that CANTAB measures and novel spatial and order metrics were correlated with age (r=.20 to r=.37, adjusted P= <.05). Multiple regression showed models with PAL total error score and delayed novel spatial metrics were significantly predictive of age (t= -4.08, 3.17, p <.005). The dominance analysis revealed novel immediate precision overlapped with existing measures in predicting age, while delayed precision had more unique variance (4.6% vs 0.62% unique sample variance explained in age, accounting for PAL). Experiment 2 showed compliance of 75% over 14 time points, with no evidence of learning curves. Morning scores were significantly higher for delayed spatial precision and order (order: t(88)=8.388, p<.001, d=0.89; spatial: t(88)=3.93, p<.001, d=0.42) suggesting sensitivity to memory consolidation. Delayed order was significantly coupled with fatigue ratings across time (rmcorr=-.098, adjusted p <.05). Individual differences GLM revealed that both coupling between mood and delayed order recall significantly (beta=.06, MontecarloP <.05), and fatigue and immediate order recall (beta=.059, MontecarloP <.05), increased with age. **Conclusion:** This short, high-frequency assessment of episodic memory displays promising characteristics, with no learning curve, allowing assessment from the first instance. Firstly, participants' performance declines with age, in a similar pattern to more established measures. Secondly, it shows acceptable compliance over many sessions. Thirdly the temporal patterns are potentially sensitive to memory consolidation, fatigue and mood. Finally, we show that these temporal patterns also vary with Age. Future research will now involve gathering high-frequency data from different patient populations.

LP90- ACHIEVING 98% SCORING ACCURACY IN A NOVEL VOICE-BASED MULTI-DAY LEARNING PARADIGM. N. Taptiklis[1], A. Kaula[1], H. Tseng[1], F. Cormack[1]
(1. Cambridge Cognition - Cambridge (United Kingdom))

Background: Remote deployment of cognitive assessment makes high-frequency assessment feasible, enabling the use of novel paradigms to measure aspects of cognitive performance that cannot be addressed in a single timepoint assessment. Recently, remote testing approaches have been used in Alzheimer's Disease (AD) studies to measure participants' learning of stimuli over multiple timepoints, with the slope of their 'learning curve' being the prime outcome measure of interest. Verbal assessments of memory are frequently used in trials of AD. There is increasing interest in employing speech recognition technology to automate the delivery and scoring of these assessments. Automated speech recognition (ASR) technology reported word error rates in some cases approach 3% on test data sets but are significantly impacted by audio quality and background noise. By combining the output from multiple ASRs, it is possible to increase the accuracy of the automated scoring. An automated verbal stimuli learning paradigm could be a sensitive measure of memory function in clinical trials. However remote deployment of automated verbal assessments of learning depends on the ability to accurately score verbal responses in potentially noisy environments on a wide range of participant devices. **Objectives:** We were interested in exploring the feasibility of using remote automated verbal testing to measure a participant's ability to learn verbal stimuli over multiple testing days using the Neurovocalix (NVx) verbal cognitive platform. The NVx platform can be configured to employ multiple ASR engines to improve scoring accuracy. We were interested in both the scoring accuracy of individual ASR engines, the overall accuracy of the aggregate system, and in understanding how the performance of individual ASR engines contributed to the overall system performance. We were also interested in understanding participant compliance. **Methods:** 20 older adults were recruited aged from 65 to 79 (M=10). Participants performed the assessments on their own devices at home. Participants were invited to perform a verbal learning task once a day for five days. The task consisted of a single attempt at Verbal Paired Associates with eight pairs of words. The task was modified so that from the second day, the recall phase was administered prior to the presentation phase of the same word pairs, in order to measure participants ability to learn the word pairs over the course of the study. The NVx platform was configured to use five ASR engines: Google Speech, IBM Speech US, IBM Speech GB, Amazon Transcribe and Amazon Lex. Amazon Lex and the IBM ASR engines were configured to bias recognition in a keyword list consisting of the 8 word pairs. All participant responses were manually reviewed, with the performance of each ASR being recorded, as well as whether the system correctly scored each utterance. Poor noise quality and other observations were recorded. **Results:** Participants performed in total 96 testing sessions (96% compliance), yielding 720 individual verbal responses (utterances). We found a 98% scoring accuracy, with 704 out of 720 utterances correctly scored by the system. Of the 16 incorrectly scored utterances, 11 were false positives (where the system scored an incorrect response as correct) and five were false negatives (where the system scored a correct response as incorrect). Seven of the 11 false positives were driven by Amazon Lex, which is the ASR configured with the highest degree of bias towards target words. We examined the contribution of individual ASRs to the overall accuracy of the system. In 12 cases only a single ASR correctly scored the utterance, including eight utterances which were only scored correctly due to the biased Amazon Lex engine. We explored system accuracy considering all possible combinations of the five ASR engines we deployed. The highest accuracy for a single ASR was .951 for Google Speech. In this study, the best performing combination of ASRs was Google Speech, IBM US, Amazon Transcribe and Amazon Lex which would have achieved an accuracy of .981, slightly higher than the deployed combination of five ASRs used in the trial, due to a single false positive from IBM GB. We found both word and participant effects on system accuracy, with the word 'matter' most likely to be mis-heard by participants. Six of the false positives appeared to be due to participants mis-hearing the target word, and responding with a phonetically similar word, which was interpreted as the target word by the biased ASR engines. Arguably, in the context of a memory test a human rate would score these as correct as well. **Conclusion:** This small study suggests that automated remote verbal assessment of learning over multiple timepoints is feasible. By aggregating the results of multiple ASR engines, the system achieves very high accuracy (98%) even when testing is conducted in noisy home environments on devices with poor quality audio. The novel verbal learning paradigm would appear acceptable to participants, achieving 96% compliance, and all participants completing at least four testing sessions.

LP91- SEX DIFFERENCES IN THE ASSOCIATION BETWEEN TAU PET AND COGNITION IN PRECLINICAL AD (A4 STUDY). X. Wang[1], E. Sundermann[1], S. Banks[1]
(1. University of California, San Diego - San Diego (United States))

Background: Sex differences in tau pathology and cognitive resilience have been reported in preclinical AD, with cognitively

normal, amyloid-positive women showing higher regional tau PET levels and better verbal memory than men. Regional tau PET signal has been associated with subtle decrements in cognitive performance in preclinical AD. We are interested in how the associations between tau and cognitive measures differ by sex in preclinical AD. **Objectives:** The aim of this study was to detect the sex differences in the associations between tau PET and cognitive outcomes in preclinical AD. **Methods:** We included 343 cognitively unimpaired amyloid-positive individuals (205 women, 138 men) from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study who self-identified as non-Hispanic white and had available 18F-flortaucipir PET data. Participants completed the neuropsychological tests of Computerized Cognitive Composite (C3) at the first screening visit (Visit 1) and an alternative C3 within 90 days (mean = 55 days) at the study eligibility visit (Visit 3) before study eligibility disclosure. Preclinical Alzheimer's Cognitive Composite (PACC) were also completed at their first screening visit. Standardized uptake value ratio (SUVR) images were created using the inferior cerebellum grey matter as the reference region. A composite meta temporal region (entorhinal, amygdala, fusiform, inferior temporal and middle temporal region defined by Freesurfer) was the region of interest (ROI) in this study. We applied linear regression models to detect the sex differences in PACC and C3 components (Visit 1 and Visit 3), adjusting for age and education. Using linear regression models with an interaction term (tau SUVR in the meta temporal ROI by sex), we assessed the interaction effects between sex and tau SUVR in the meta temporal ROI on PACC and C3 components (at Visit 1 and Visit3), adjusting for age and education. Sex-stratified analyses were conducted to probe significant tau by sex interaction effects. **Results:** Women outperformed men on PACC ($P < 0.001$) and its components: Mini-Mental State Examination (MMSE) ($P = 0.001$), Digit-Symbol Coding Test (DSC) ($P < 0.001$), and Free and Cued Selective Reminding Test–Free + Total Recall (FCSRT96) ($P < 0.001$). For C3 components, women performed better than men on first letter name recall (FNLT) (Visit 1: $P < 0.001$, Visit 3: $P = 0.008$), face-name matching (FNMT) (Visit 1: $P = 0.006$) and face recognition (FSBT) (Visit 1: $P < 0.001$, Visit 3: $P < 0.001$). However, men outperformed women on Detection (DET)-reaction time (RT) (Visit 1: $P = 0.007$, Visit 3: $P = 0.048$). There were significant interactions effects between sex and tau in the meta temporal ROI on PACC component: DSC (interaction $\beta = -1.974$, SE = 0.895, $P = 0.028$) and C3 components: DET RT (Visit 1: interaction $\beta = 0.202$, SE = 0.101, $P = 0.046$), One-Card Learning (OCL) RT (Visit 1: interaction $\beta = 0.207$, SE = 0.097, $P = 0.033$; Visit 3 interaction $\beta = 0.182$, SE = 0.091, $P = 0.045$). After sex stratification, higher levels of tau in the meta temporal ROI were associated with poor cognitive performance specifically in women: DSC score ($\beta = -1.669$, SE = 0.542, $P = 0.002$), DET RT (Visit 1: $\beta = 0.089$, SE = 0.057, $P = 0.117$), OCL RT (Visit 1: $\beta = 0.172$, SE = 0.056, $P = 0.002$; Visit 3: $\beta = 0.115$, SE = 0.051, $P = 0.026$), not in men (Ps>.05). **Conclusion:** Our results suggest that sex differences in early AD might be due to higher amounts of tau in women's brains with stronger relationships with certain tests in women. These findings have important implications for how cognition is assessed in sex-specific tau-targeted preventive AD clinical trials. **Conflict of Interest and Disclosure Statement**: Xin Wang, Dr. Sundermann and Dr. Banks have no relevant disclosures.

LP92. STEPPED-ASSESSMENT FOR COGNITIVE SCREENING AND EVALUATION: MEMTRAX-COGNIFIT.

C. Ashford[1], J. Clifford[2], M. Bergeron[3], J. Andoni[4], J. Ashford[5], C. Rodriguez[6] *(1. MemTrax, LLC - Redwood City (United States), 2. College of San Mateo - San Mateo (United States), 3. University of Hartford - Hartford (United States), 4. Nebriia University - Madrid (Spain), 5. Stanford - Palo Alto (United States), 6. CogniFit, Inc. - Madrid (Spain))*

Background: Cognitive and functional impairment are stigmata of dementia, traumatic brain injury, and many other conditions affecting mental processing. Neuropsychologists use paper and pencil tools and questionnaires for estimating cognitive function. However, this methodology is time-consuming, expensive, subject to rater variations and biases, and is not amenable to monitoring change over time. New directions are needed for neurocognitive assessment. With the advent of computerized cognitive testing, cognitive tests can be quickly implemented, providing robust information and rapid reporting of brain function, allowing frequent repetition within minutes. Brief computerized tests can provide rapid (< 2 minutes), accurate, reliable measures of memory and executive function, with processing speed in these domains precisely quantified. For example, MemTrax can be repeated frequently and indefinitely to screen for cognitive impairment and assess treatment and clinical trial outcomes. Other tests are computerized cognitive batteries that can assess performance of numerous cognitive domains, supplemented by questionnaires to assess daily function. CogniFit, can provide such information in a wide variety of domains, so that the underlying pathology can be precisely characterized. **Objective:** Describe one on-line computerized tool for screening and another for assessment of cognitive impairment. **Methods:** MemTrax is a rapid on-line test using a continuous recognition paradigm, assessing visual information processing, episodic memory, and recognition accuracy and speed: https://pubmed.ncbi.nlm.nih.gov/?term=memtrax&sort=date. CogniFit Cognitive Assessment Battery (CAB)® PRO (FDA Registration Number: 3017544020) is an extended computerized battery providing physical, psychological, and social function estimates. CogniFit PRO is a comprehensive online neuropsychological battery of 17 non-invasive tests that provide a broad, objective, and precise assessment of 22 well-documented cognitive skills. CogniFit is broadly used and implements state-of-the-art cognitive science, psychometrics and technology: https://pubmed.ncbi.nlm.nih.gov/?term=cognifit&sort=date. **Results:** MemTrax can be repeated frequently to provide indices of change over time. This 50 picture-based MemTrax has a variable N-back design developed to measure episodic memory and processing speed impairments associated with early AD; but it is useful for related conditions. MemTrax has been implemented and utilized online in different countries and on various platforms, available in 120 languages: http://www.memtrax.com and www.memtrax.com.cn. Administered to a senior cohort in an independent-living elderly population in the Netherlands and another group in China, MemTrax was more efficient than the Montreal Cognitive Assessment (MoCA) with similar clinical efficacy. MemTrax is used by the Brain Health Registry: https://www.brainhealthregistry.org and the Alzheimer's Foundation of America: https://AFAmemorytest.com. MemTrax has been performed by over one million individuals on-line, and performance data in different settings has generated several reference norms. The performance measures, percent correct, percent hits, percent correct rejections, and response time, can be translated into the

summary score and 4 of the component scores of the Montreal Cognitive Assessment (MoCA), with equal or better ROC measures for distinguishing normal cognitive function and mild cognitive impairment in less time, in any locale. CogniFit has 24/7 online availability, unlimited locations, and cost-efficiency, making it an ideal tool for clinical practice and research. Backed by highly accurate psychometrics, intelligent data science and advanced automation systems, CogniFit makes cognitive measurement and delivery of individual and group data effortless, instantaneous, and accessible. The reference normative dataset behind (CAB)® PRO matrix used 1,282,242 unique subjects (711,262 females, 570,980 males) ages 7-85 years. The Cognitive Assessment Battery (CAB)™ has been validated using construct and convergent validity. For details: https://www.cognifit.com/cab. The CogniFit assessment is designed for people ≥ 7 y/o and takes 30 to 40 minutes, on a computer, tablet, or smartphone. CogniFit's automated platform facilitates individual and large-scale data collection and allows for simultaneous large-scale testing. Quantitative results report a global score for gauging overall cognitive function, individual scores on 22 cognitive skills, and a well-being score. The CogniFit Cognitive Assessment Battery (CAB)® assessment has a Validity Index of its measurements. The system detects absent-minded performance and asks the users to pay more attention. With corrected behavior, the variables measured during the task are considered valid. Otherwise, the variables measured are considered invalid, and reported. CAB accurately captures human cognitive development across lifespan, using normative data to depict cognitive growth during childhood, peak of cognitive abilities in young adulthood, and the progressive cognitive decline associated with ageing. For both tests, deeper analysis can be provided by artificial intelligence/machine learning, and with the capacity to assemble very large data sets of information, progressively more salient interpretations will become available. However, clinician oversight of the assessment continuum remains essential to confirm results and provide safety assurances. Moreover, stepped assessment combines an initial brief test (e.g., MemTrax) for initial broad cognitive screening, potentially providing an indication of the need for more comprehensive evaluation (e.g., CogniFit), including an in-depth series of measurements. **Conclusion:** This presentation outlines an initial screening test which can lead to a broad evaluation of brain function with biological, psychological, and social components. MemTrax and CogniFit are effective for screening and longitudinal assessment of cognitive function for clinical and research purposes.

BEHAVIORAL DISORDERS AND CLINICAL TRIALS

P169- A PROOF-OF-CONCEPT STUDY TO EVALUATE EFFICACY OF NANOLITHIUM ON THE PROGRESSION OF NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH MILD-TO-SEVERE ALZHEIMER'S DISEASE.

M. Soto[1], S. Guilliot[2], P.J. Ousset[1], D. Angioni[1], N. Sastre Hengan[1], J.C. Maurel[2], J. Touchon[3] *(1. Department Of Geriatrics, Gerontopole, University Hôpital Toulouse, France - Toulouse (France), 2. Medesis Pharma - Baillargues (France), 3. Montpellier School Of Medecine; University Of Montpellier - Montpellier (France))*

Background: In mild-to-severe forms of AD, neuropsychiatric symptoms (NPS) are frequent and highly disabling. There is currently no specific treatment for these symptoms. Lithium has been the mainstay of bipolar disorder (BP) treatment for many years. There is currently a renewed interest in lithium's utility for the treatment of not only BP but also of neurodegenerative diseases, mainly due to in vitro and in vivo studies supporting the potential neuroprotective effect of lithium through multiple intersecting mechanisms. However, the narrow therapeutic window of lithium hampered its development in neurodegenerative diseases. Study drug: Medesis Pharma has applied the Aonys® technology to lithium. The Aonys® delivery system allows a significant decrease of the lithium dose (1.8 mg Li / 0.18 mEq per day; minimal dose used in clinical practice: 10 mEq / day) while allowing enhanced CNS uptake, optimizing lithium therapeutic window. Nanolithium is administered as a buccal mucosa deposit, structured in HDL lipoprotein in contact with apoproteins A1 in mucosa, protected plasma transport in HDL lipoprotein, intra-cellular delivery by HDL receptors and distributed in all cells of the whole body. An efficacy study for depression was conducted in behavioral test mimicking depression in wild type mice. Nanolithium induced a significant antidepressant-like effect after treatment at a dose 400 times lower than a lithium solution inducing the same effect. No drug-related mortality or clinical signs were observed in these experimental conditions. In rodent studies Nanolithium showed equivalent efficacy and lower toxicity than an oral solution of lithium. Pharmacology studies in AD transgenic rat model (McGill-R-Thy1 APP), after 8-week treatment at a low dose of lithium (0.04 mg Li/kg/ day), Nanolithium was shown to reverse many of the key AD pathologic hallmarks (cognitive deficit, BACE1 activity, neurogenesis, level of toxic Aβ42 peptides, etc) as well as cognitive symptoms at the early stages of the disease. In preclinical toxicology studies and phase 1 study in healthy volunteers, Nanolithium was well tolerated with no SAEs. **Objectives:** To evaluate the clinical safety and efficacy on NPS and on neuroprotection of NanoLithium in patients with mild-to-severe AD. **Study Design:** A prospective, multicenter Phase II study with a first randomized, placebo-controlled, parallel-group, double-blind 3 months period followed by an open-label trial period of 9 months. Primary outcome will be to evaluate the clinical efficacy of Nanolithium versus placebo, on the NPS progression between baseline and 12 weeks based on total NPI-12 score. Secondary outcomes includes assessment of the clinical safety of Nanolithium administered during 48 weeks; evaluation of the efficacy of Nanolithium over 48 weeks on progression of cognitive performances (CDR, MMSE, ADL), progression of NPS (score on each NPI-12 item and agitation based on NPI-C-IPA scale), progression of cortical hypometabolism in parieto-temporal regions (PET-FDG); evidence of potential disease-modifying effect of Nanolithium on the progression of AD pathophysiological biological peripheral biomarkers (Protein β-amyloid, Neurofilaments, BDNF, pTau protein) and nonspecific biomarkers (inflammatory cytokines); and to assess treatment compliance. Main inclusion criteria include patients between 50 and 90 years inclusive, patient with sufficient clinical and paraclinical information for the diagnosis of AD, patient presenting clinically significant BPSD requiring medication in the opinion of the study physician (NPI ≥ 4 in at least one item of NPI-12), patients with a MMSE score from 10 to 26). **Statistical Method:** Sixty-eight patients will be randomly assigned to two treatment arms, with a 1:1 randomization ratio: 34 patients will be assigned to the NanoLithium arm and 34 patients to the placebo arm. Analysis of the primary endpoint: NPI-12 total score change from inclusion to 12 weeks of treatment will be presented by randomization arm and overall. Comparison between randomization arms will be done

using an ANCOVA analysis (LS-means, the CI and the adjusted differences between arms and p-value) adjusted on center, sex, age, severity of the disease based on MMSE, education level and other comorbidities. Analysis of secondary endpoints will be performed overall and by arm. **Conclusion:** Study has been initiated in 6 centers in France, primary outcomes at 12 weeks intermediate analysis are expected beginning of 2023, final outcomes are expected end of 2023 - Beguining of 2024.

P171- SAFETY AND TOLERABILITY OF BREXPIPRAZOLE FOR THE TREATMENT OF AGITATION IN ALZHEIMER'S DEMENTIA: POOLED RESULTS FROM THREE PHASE III TRIALS. D. Lee[1], M. Slomkowski[1], N. Hefting[2], D. Chen[1], K. Larsen[2], E. Kohegyi[1], M. Hobart[1], A. Shah[1], A. Estilo[1], M. Panni[1], A. Farovik[2], M. Miguelez[1], P. Such[2], G. Grossberg[3] *(1. Otsuka Pharmaceutical Development & Commercialization Inc. - Princeton, New Jersey (United States), 2. H. Lundbeck A/S - Valby, Copenhagen (Denmark), 3. Department of Psychiatry and Behavioral Neuroscience at Saint Louis University School of Medicine - St Louis, Missouri (United States))*

Background: Despite the high burden of agitation in Alzheimer's dementia (AAD) (1), there are no FDA-approved pharmacological treatments for the management of AAD. Certain medications, including antipsychotics, are commonly prescribed off-label to help control agitation symptoms. However, the use of off-label therapies is hindered by relatively poor adherence, and safety and tolerability concerns (2). Atypical antipsychotics carry an FDA boxed warning for mortality in elderly patients with dementia, due to analyses that show an increased risk of death versus placebo (3). Brexpiprazole, which has shown good tolerability in schizophrenia and major depressive disorder (4, 5), has been investigated as a potential therapy for AAD. **Objectives:** To assess the safety and tolerability of brexpiprazole in patients with AAD based on the combined results of three Phase III trials. **Methods:** Data were pooled from three 12-week, randomized, double-blind, placebo-controlled, parallel-arm trials of brexpiprazole versus placebo in patients with AAD (ClinicalTrials.gov identifiers: NCT01862640 [6], NCT01922258 [6], NCT03548584). Two of the trials evaluated fixed doses of brexpiprazole (0.5, 1 or 2 mg/day [0.5 mg/day arm discontinued], and 2 or 3 mg/day), whereas the other trial investigated a flexible dose (0.5–2 mg/day). The primary objective of these trials was to assess efficacy on agitation symptoms (reported elsewhere). Safety was assessed as a secondary objective using standard variables, including treatment-emergent adverse events (TEAEs). For this post hoc analysis, data for all brexpiprazole groups were pooled, as were data for placebo groups. **Results:** Overall, 658 patients were randomized to brexpiprazole, and 389 patients randomized to placebo. At baseline, mean age was 73.5–74.2 years, and mean time since diagnosis of Alzheimer's disease was 28.2–35.6 months, depending on the trial and randomized treatment group. A total of 655 patients were exposed to ≥1 dose of brexpiprazole, and 388 patients to ≥1 dose of placebo. The majority of patients had ≥42 days' exposure to study drug (95.1% for brexpiprazole, and 96.9% for placebo). Across all three trials, the incidence of TEAEs was 51.1% with brexpiprazole, with no notable differences between doses, and 45.9% with placebo. Serious TEAEs were experienced by 6.4% of patients receiving brexpiprazole and 4.1% of patients receiving placebo; TEAEs leading to discontinuation were experienced by 6.3% of patients receiving brexpiprazole compared with 3.4% receiving placebo. TEAEs that occurred in ≥2% of patients receiving brexpiprazole and more than in placebo-treated patients were insomnia (3.7% versus 2.8%), somnolence (3.4% versus 1.8%), nasopharyngitis (2.7% versus 2.6%), and urinary tract infection (2.6% versus 1.5%). Other TEAEs of interest in this patient population include falls (1.7% [brexpiprazole] versus 2.6% [placebo]), metabolism and nutrition disorders (3.5% versus 4.4%), sedation (0.3% versus 0%), and extrapyramidal disorder (0.8% versus 0%). No extrapyramidal symptom-related TEAEs occurred in ≥2% of patients receiving brexpiprazole and more than in placebo-treated patients. The mean change from baseline to last visit in body weight was 0.1 kg with brexpiprazole and -0.2 kg with placebo. The incidence of ≥7% increase in body weight from baseline was 1.7% with brexpiprazole and 0.8% with placebo. The mean change from baseline to last visit in Mini-Mental State Examination Total score was 0.21 with brexpiprazole (mean baseline 14.6) and 0.14 with placebo (mean baseline 14.9). Six patients receiving brexpiprazole (0.9%) and one patient receiving placebo (0.3%) died during the double-blind treatment period; none of these deaths were considered by the investigator to be related to brexpiprazole. **Conclusion:** Based on pooled results from three Phase III trials, brexpiprazole was well tolerated in patients with AAD, and had a clinical safety profile consistent with that of brexpiprazole in other indications. Brexpiprazole-treated patients had a similar incidence of sedation, extrapyramidal disorder, death, falls, and metabolic TEAEs compared with placebo, and no worsening of cognition. **References:** 1. Khoo et al. The impact of neuropsychiatric symptoms on caregiver distress and quality of life in persons with dementia in an Asian tertiary hospital memory clinic. Int Psychogeriatr 2013;25(12):1991–1999. 2. Antonsdottir et al. Advancements in the treatment of agitation in Alzheimer's disease. Expert Opin Pharmacother 2015;16(11):1649–1656. 3. Jeste et al. ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology 2008;33(5):957–970. 4. Kane et al. Overview of short- and long-term tolerability and safety of brexpiprazole in patients with schizophrenia. Schizophr Res 2016;174(1–3):93–98. 5. Thase et al. Efficacy and safety of brexpiprazole as adjunctive treatment in major depressive disorder: overview of four short-term studies. Expert Opin Pharmacother 2019;20(15):1907–1916. 6. Grossberg et al. Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. Am J Geriatr Psychiatry 2020;28(4):383–400.

LP93- EFFECTS OF BREXPIPRAZOLE ON SEVERITY OF AGITATION IN ALZHEIMER'S DEMENTIA: AN ANALYSIS OF CLINICAL GLOBAL IMPRESSION DATA FROM TWO PHASE III FIXED-DOSE TRIALS. D. Lee[1], M. Slomkowski[1], N. Hefting[2], D. Chen[1], K. Larsen[2], E. Kohegyi[1], M. Hobart[1], A. Shah[1], A. Estilo[1], M. Panni[1], A. Farovik[2], M. Miguelez[1], P. Such[2] *(1. Otsuka Pharmaceutical Development & Commercialization Inc. - Princeton, New Jersey (United States), 2. H. Lundbeck A/S - Valby, Copenhagen (Denmark))*

Background: Neuropsychiatric symptoms of Alzheimer's dementia, including agitation, are among the most difficult and stressful aspects of the disease for patients and caregivers (1). Agitation is a prevalent clinical manifestation of the illness (2, 3). Currently, there are no FDA-approved pharmacological treatments for the management of agitation in Alzheimer's dementia (AAD). Brexpiprazole, which acts on noradrenergic, serotonergic, and dopaminergic neurotransmitter systems (4), has been investigated as a potential AAD therapy. The

brexpiprazole AAD trials employed the 7-point Clinical Global Impression – Severity of illness (CGI-S) and Clinical Global Impression – Improvement (CGI-I) scales as secondary efficacy endpoints – simple, easy-to-use, and well-established clinician-rated measures of symptom severity and improvement, respectively (5). **Objectives:** To evaluate Clinical Global Impression data from two Phase III fixed-dose trials of brexpiprazole in patients with AAD. **Methods:** Three Phase III, 12-week, randomized, double-blind, placebo-controlled, parallel-arm trials of brexpiprazole versus placebo in patients with AAD have been conducted (ClinicalTrials.gov identifiers: NCT01862640 [6], NCT01922258 [6], NCT03548584). In those trials, the primary endpoint was the change in Cohen–Mansfield Agitation Inventory (CMAI) Total score from baseline to Week 12, and the key secondary endpoint was change in CGI-S score, as related to agitation, from baseline to Week 12. CGI-I response rate (defined as a CGI-I score of 1 [very much improved] or 2 [much improved]), was also assessed. One trial investigated flexible doses of brexpiprazole (0.5–2 mg/day), and the other two investigated fixed doses of brexpiprazole (0.5, 1 or 2 mg/day [0.5 mg/day arm discontinued], and 2 or 3 mg/day). The present post hoc analysis evaluates data from the two fixed-dose trials. **Results:** In the first fixed-dose trial, in the brexpiprazole 2 mg/day group, no patients had a CGI-S score of 1 (normal, not at all ill) or 2 (borderline mentally ill) at baseline compared with 17.5% at Week 12; in the placebo group, no patients had a CGI-S score of 1 or 2 at baseline compared with 10.2% at Week 12. In the same trial, in the brexpiprazole 2 mg/day group, 8.7% of patients had a CGI-S score of 6 (severely ill) or 7 (among the most extremely ill) at baseline compared with no patients at Week 12; in the placebo group, 7.6% had a CGI-S score of 6 or 7 at baseline compared with 0.8% at Week 12. On the change from baseline to Week 12 in CGI-S score, as related to agitation, numerical improvement was observed with brexpiprazole 2 mg/day versus placebo (nominal p=0.16). In the same trial, CGI-I response rate at Week 12 was 49.3% with brexpiprazole 2 mg/day and 45.8% with placebo. In the second fixed-dose trial, in the brexpiprazole 2 or 3 mg/day group, 0.4% of patients had a CGI-S score of 1 or 2 at baseline compared with 11.9% at Week 12; in the placebo group, no patients had a CGI-S score of 1 or 2 at baseline compared with 5.9% at Week 12. In the same trial, in the brexpiprazole 2 or 3 mg/day group, 9.8% of patients had a CGI-S score of 6 or 7 at baseline compared with 1.0% at Week 12; in the placebo group, 9.5% had a CGI-S score of 6 or 7 at baseline compared with 2.9% at Week 12. Brexpiprazole 2 or 3 mg/day was superior to placebo in change from baseline to Week 12 in CGI-S score, as related to agitation (p=0.0078). In the same trial, CGI-I response rate at Week 12 was 52.4% with brexpiprazole 2 or 3 mg/day and 40.5% with placebo. **Conclusion:** In patients with AAD, brexpiprazole 2 or 3 mg/day was associated with overall improvement in Clinical Global Impression, as related to agitation, compared with placebo. **References:** 1. Antonsdottir et al. Advancements in the treatment of agitation in Alzheimer's disease. Expert Opin Pharmacother 2015;16(11):1649–1656. 2. Halpern et al. Using electronic health records to estimate the prevalence of agitation in Alzheimer disease/dementia. Int J Geriatr Psychiatry 2019;34(3):420–431. 3. Fillit et al. Impact of agitation in long-term care residents with dementia in the United States. Int J Geriatr Psychiatry 2021;36(12):1959–1969. 4. Maeda et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin–dopamine activity modulator. J Pharmacol Exp Ther 2014;350(3):589–604. 5. Guy. ECDEU Assessment Manual for Psychopharmacology, Revised. Rockville, MD: National Institute of Mental Health, 1976. 6. Grossberg et al. Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. Am J Geriatr Psychiatry 2020;28(4):383–400.

HEALTH ECONOMICS AND CLINICAL TRIALS

P172- HEALTH ECONOMIC CONSIDERATIONS IN THE DEVELOPMENT OF A PREVENTIVE ALZHEIMER'S TREATMENT.

M.A.T.T.K. Mattke[1], K.K. Jun[1], S. Chu[2], M. Hanson[1], E. Reiman[3], J. Kordower[4] *(1. University Of Southern California - Los Angeles (United States), 2. Cornell University - Ithaca (United States), 3. Banner Alzheimer's Institute - Phoenix (United States), 4. Arizona State University - Tempe (United States))*

Background: Multiple amyloid-targeting drugs are currently in late-stage clinical trials of a preventive indication, i.e., identification and treatment of preclinical Alzheimer's disease (AD). With the large patient pool, the potential cost to ascertain the AD pathology and the cost of treatment, careful consideration needs to be given which diagnostic pathway and which treatment cost would represent adequate value for money. **Objectives:** To project the cost per avoided case of progression to symptomatic AD under different assumptions for cost and performance of diagnostic tests and cost and effectiveness of treatment as well as the yield of the diagnostic process, i.e., the share of truly diseased persons, who were correctly identified. **Methods:** Using a Markov model and published estimates for prevalence of preclinical AD and annual progression to MCI, we project the disease trajectory of 2022 U.S. cohort age 50 to 79 without cognitive impairment (n=95 million) in the absence of treatment. For the counterfactual scenario of a disease-modifying treatment, we assume that all persons would receive a one-time blood test for the AD pathology at a cost of $75 and that a subset of persons with a positive test result would go to confirmatory testing before treatment while the others would go directly to treatment. Lifetime treatment cost would be $2,500 per person. Confirmatory testing would be done with PET scans (40%, cost of $4,000) and CSF analysis (60%, cost of $500). We calculate the cumulative number of avoided symptomatic AD cases over 20 years. **Results:** Without treatment, 13% of people (n=12.1 million) would become cognitively impaired over 20 years. Assuming a blood test with specificity and sensitivity of 80% and use of confirmatory testing in 25% of test-positive subjects, 18.0% of cognitively unimpaired persons (n=17.5 million) would be identified and treated with a false-positive rate of 16.5%. A treatment that reduced progression risk from cognitively unimpaired to impaired stages of AD by 30% would prevent 14.9% of cases (n=1.8 million) of incident developing symptomatic AD at a cost of $52,026 per case avoided and overall cost of $4,128 per person over 20 years. **Conclusion:** At the stated assumptions, prevention of symptomatic AD entails costs in line with established preventive interventions, such as prophylactic ICD implantation for patients at elevated risk of sudden cardiac death (~$27,000 per life-year saved) and anticoagulation for stroke (16,675 per case avoided with abixaban and $36,777 with dabigatran). Ongoing work will look into overall net cost, i.e., considering cost offsets from reduced progression. and cost-effectiveness under a range of assumptions, such as treatment cost and effectiveness, and explore alternative detection approaches, such as periodic use of blood tests in those with initially negative results.

P173- LONG-TERM CARE INSURANCE SERVICE UTILIZATION PATTERN ACCORDING TO CLINICAL FACTORS OF DEMENTIA. J.H. Lee[1] *(1. National Health Insurance Service Ilsan Hospital - Goyang-Si (Korea, Republic of))*

Background: After the opening of the Dementia Prevention Center at Ilsan Hospital in Korea, we plan to produce basic data for establishing a strategy for providing long-term care benefits for dementia patients by analyzing the use of medical and long-term care services according to various clinical factors including the severity of Dementia. **Method:** Information on patients who received cognitive function tests such as K-MMSE and neuropsychological test battery was collected at Ilsan Hospital. Based on this patient group, the National Health Insurance service's customized DB and the elderly's long-term care DB information were joined to verify the patient's medical records and investigate the use of the elderly's long-term care benefits. **Result:** A total of 1921 patients people were diagnosed with dementia at Ilsan Hospital in Korea, from 2011 to 2018, and 391 patients (20.35 %) were classified as long-term care rating judges, 76 patients (3.96%) were undecided, and 1454 patients (75.69 %) were not applied. Statistically significantly, the number of patients diagnosed with dementia in Ilsan Hospital also increased from 2011 to 2018, and the number of dementia rating groups increased continuously, especially after the introduction of the special dementia grade in 2014. 75.69 % of the patients diagnosed with dementia at Ilsan Hospital are not applied for long-term care insurance for the elderly, and they are showing a relatively young age and high level of education. Cognitive function tests in hospitals also reflect the severity and frequency of patients and the suffering of their guardians when assessing neurological behavioral abnormalities. However, currently, the evaluation score for long-term care service for the elderly are judged only by the presence or absence of symptoms, so it is considered necessary to take countermeasures as it shows differences in hospital examination results and the results of long-term care service evaluation. **Conclusion:** It is necessary to identify the long-term care benefits required for each characteristic of dementia patients, to indirectly verify the validity of the current benefit system by current status, and to develop policies to establish long-term care benefit types and service strategies for individual characteristics of dementia patients

P174- THE IMPACT ON R&D INVESTMENT OF THE CMS NATIONAL COVERAGE DETERMINATION FOR AMYLOID-DIRECTED MONOCLONAL ANTIBODIES IN ALZHEIMER'S DISEASE. D. Schulthess[1], H. Bowen[2] *(1. vital transformation - Wezembeek Oppem (Belgium), 2. Queens University - Charlotte (United States))*

Background: This study investigates the potential impact of the recent National Coverage Determination (NCD) by The Centers for Medicare & Medicaid Services (CMS) on willingness of investors to continue to fund the development of new treatments in Alzheimer's Disease. CMS will only cover FDA approved monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (AD) under Coverage with Evidence Development (CED) in "CMS approved randomized controlled trials." **Objectives:** This analysis measures the potential impact of this NCD, using assumptions based on the current draft language and historical data about AD R&D trials and investments, based on current clinical development time, that the NCD will add 3 or more years to the time it takes for an AD asset to see any return on investment. **Methods:** Starting from 1993, a cohort of clinical trials for the treatment of Alzheimer's Disease (AD) was extracted – 551 trials in total. All early stage investments, venture funding, grants, IPOs, and deals involving clinical research in AD were obtained by the date secured and then linked to the specific asset/company that entered into AD RCTs for FDA approval – 729 individual financing rounds and 287 deals in total. The length of time from launch to conclusion of an AD trial was calculated for the entire historical cohort, and the increase of time, increase of costs, and reductions of revenue caused by the CMS draft decision was incorporated into our assessment. The impacts of the CMS draft decision were applied to a revised estimate for ROI, taking into consideration several scenarios for reduced revenue relative to patent life. **Results:** Of the programs currently in development – if the proposed NCD was in place at the time of program initiation, 93% of investments would have had negative ROI and therefore would not have likely been made. A three year delay in market access also finds that existing clinical development programs would likely be halted based on a logistical regression model ($p < 0.0001$) - 78% of the change in the probability of having a positive or negative ROI is determined solely by the decision made by CMS (i.e. the G2 Statistic). Given the current trends in declining AD developments before the CMS coverage decision, an >80% decline in the number of trials with a positive ROI if the CMS guidance is implemented, i.e. with a delay of 3 years, assuming those trials are stopped, brings active clinical developments from 30 to 3. **Conclusions:** Given their high failure rate, a delay of three or more years in the marketing authorization of new Alzheimer's therapies renders the majority those under clinical investigation financially untenable, according to our model. The decision to potentially overturn an FDA decision further adds uncertainty to investors, as the evidence challenges to other neurological disorders is similar to that of Amyloid Beta based treatments. Even though the proposed CMS guidance applies specifically to amyloid-targeting antibodies, it introduces material risks to the ROI calculations for other assets in development, including other Alzheimer's treatments as well as neurology more broadly, and all products approved under the accelerated approval pathway. The proposed guidance puts at risk the entire US Government's strategy to create incentives via the prescription drug benefit to promote the adaption of targeted therapies, orphan drugs, and difficult areas of research such as neurological disorders. CMS' guidance, if implemented, will have cooling effect on R&D, and funds will likely move to larger indications with lower risk profiles; it will push risk capital and biopharma away from areas of high unmet medical needs, into other 'me too' categories not seen since the 1990s. The use of accelerated approvals is vital to the financial viability of treatments with challenging economics such as orphan diseases and hard to treat neurological disorders; ultimately, these policies were put in place to promote the development of cures in clinical areas with the most challenging science with high probabilities of failure – the effect of this guidance, if implemented, will be less innovation where it is needed most. **Disclosure:** Vital Transformation, an international health economics and strategy consultancy, was asked to conduct an analysis of the impact of CMS' draft decision on Amyloid Beta reimbursement under evidence on the biopharmaceutical innovation ecosystem, and specifically the impact on investment and new drug pipeline development in Alzheimer's Disease. The opinions included in this work are those of Vital Transformation, LLC, and not necessarily those of the project's sponsor, Biogen. The analysis was performed by Vital Transformation Consulting Economist Dr Harry P. Bowen and Vital Transformation Managing Director Duane Schulthess.

The raw data behind this research can be found here. https://onedrive.live.com/?cid=fd1ceff1664dae51&id=FD1CEFF1664DAE51%2125067&authkey=!AAF8X-0iJeq24Aw.

P175- BRIDGING CLINICAL TRIALS AND HEALTH ECONOMIC MODELS IN ALZHEIMER'S DISEASE.

L. Jonsson[1], R. Handels[2], C. Green[1] *(1. Karolinska Institutet - Stockholm (Sweden), 2. Maastricht University - Maastricht (Netherlands))*

Background: Evidence on cost-effectiveness of novel disease-modifying therapies (DMT) for Alzheimer's disease (AD) is of increasing importance for patient access. Clinical trials do not fully capture the health economic (HE) consequences of DMT, such as potential effects on long-term disease progression, institutionalization rates or mortality. Decisions on reimbursement and introduction of these treatments in routine care are therefore to large extent informed by evidence from modelling studies, where trial data is combined with data on long-term disease progression, quality of life and costs of care in different disease stages. However, clinical trials are not primarily designed to provide input to HE models, and HE models are usually based on data sources with different characteristics from clinical trials in terms of patient populations, endpoints and other factors. In this study we identify challenges with incorporating efficacy data from clinical trials in HE models and provide best practice recommendations for reducing these issues. **Methods:** The International PharmacoEconomic Collaboration on Alzheimer's Disease (IPECAD) conducted a series of workshops with research groups developing HE models in AD, to systematically characterize methodological approaches to HE modeling and benchmark results from these models in standardized scenarios. We reviewed published HE models in AD and contrasted the characteristics of these models with study design specifications of recent late-stage clinical trials of AD DMT to highlight potential issues with incorporating efficacy data from clinical trials into existing HE models. **Results:** We identified a number of areas of challenges as outlined below. Endpoints and scales: HE models are developed from observational studies that often include different endpoints and scales compared to clinical trials. Mapping between scales used in the trials and scales used in models can introduce considerable uncertainty. Multiple effect domains: Treatment effects can in HE models be represented either through a single domain (e.g. cognition), or on multiple domains (e.g. cognition / function / behaviour). Decision on which effect domains to include are often made post-hoc when trial outcomes are known. If effects are represented on multiple domains, the method for translating trial efficacy data into effects applied in the HE model becomes increasingly complex and sensitive to methodological choices. The use of composite endpoints carries the additional risk of spurious correlations between treatment effects and HE outcomes. It is plausible that the treatment may (mainly) have an effect on one subdomain of the composite endpoint, while the correlation with costs and quality of life outcomes may (mainly) be driven by other subdomains. Estimating treatment efficacy: There are important differences between standard biostatistical methods for clinical trial data analysis and the methods used in HE modeling. HE models often categorize patients into disease states rather than utilizing clinical scales as continuous variables. This facilitates the analysis of disease progression as well as calculation of costs and utilities. Estimating treatment effects for integration in HE models therefore involves post-hoc analysis of the trial data outside of the statistical analysis plan. This means that methodological decisions may not receive the same level of scrutiny and there may be higher risk of the methodological choices affecting the results. Patient population: Clinical trials are typically designed to optimize the probability of observing a treatment effect, rather than estimating the size of the potential treatment effect in a routine care population (which is typically the focus of HE modeling). Translating the effects of a trial into what might be effects in a broader, real-world unselected population might be accomplished by an adjustment process (e.g. weighting the trial sample based on the covariate profile in relation to a general patient population), though this has rarely been done in practice in past economic evaluations. **Conclusions:** Challenges involved in implementing efficacy data from clinical trials into HE models is an important source of uncertainty around the value of new AD therapies. The design of future clinical trials of DMT need to take into account the need to generate data to populate HE models. Pre-specifying analyses of trial data for HE modeling purposes can reduce uncertainty and improve confidence in results used for reimbursement decision making.

LP94- A MORE PRECISE DIAGNOSIS BY MEANS OF AMYLOID-PET CONTRIBUTES TO DELAYED INSTITUTIONALIZATION, LOWER MORTALITY AND REDUCED CARE COSTS IN A TERTIARY MEMORY CLINIC SETTING.

W. Van Der Flier[1], I. Van Maurik[1], H. Broulikova[1], A. Mank[1], E. Bakker[1], A. De Wilde[2], F. Bouwman[1], A. Stephens[3], B. Van Berckel[1], P. Scheltens[1] *(1. Amsterdam UMC - Amsterdam (Netherlands), 2. EQT Life Sciences - Amsterdam (Netherlands), 3. Life-MI - Berlin (Netherlands))*

Introduction: Previous studies demonstrated the diagnostic value of AD biomarkers in terms of clinicians' confidence in the clinical diagnosis and impact on patient management. A more precise diagnosis could have long term health benefits as a result of arranging more proper care, but such clinical utility not yet been demonstrated. We aimed to study the effects of a more precise diagnosis – by means of amyloid-PET – on institutionalization, mortality, and health-care costs. **Methods:** Between October 27, 2014 and December 31, 2016, we offered amyloid-Positron Emission Tomography (PET) to all patients as part of their diagnostic work-up. Patients who accepted to undergo amyloid-PET (n=449) were propensity score matched with patients without amyloid-PET (n=571, i.e. no-PET). Matched groups (both n=444; 64±8yrs, 40%F, MMSE 25±4, 38% SCD, 19%MCI, 43%dementia) were compared on rate of institutionalization, mortality and health-care costs in the years after diagnosis. **Results:** Amyloid-PET patients had a lower risk of institutionalization 10% (n=45) vs. 21% (n=92); HR=0.48 [0.33-0.70]) and mortality rate (11% (n=49) vs. 18% (n=81)); HR=0.51 [0.36-0.73]) over a four year period, and less health-care costs in the years after diagnosis compared to matched no-PET patients (β=-4573·49[-6524·76: -2523·74], p-value<0·001). **Conclusion:** We show that memory clinic patients who had a more precise diagnosis and were better informed based on amyloid PET, had more beneficial long term outcomes in terms of institutionalization, death and health-care costs, which may translate into considerable cost savings on a macro-economic level. Randomized trials are required to validate these findings.

LP95- ECONOMIC BURDEN OF DAILY TRANSITIONS TO LATER STAGES OF AD DEMENTIA IN THE US.

M. Razavi[1], W. Herring[2], C. Gillis[3], N. Maserejian[3], P. Pemberton-Ross[4], M. Nejati[3] *(1. Schneider Institutes for Health Policy and Research, Brandeis University - Waltham (United States), 2. RTI Health Solutions - Research Triangle Park (United States), 3. Biogen - Boston (United States), 4. Biogen - Baar (Switzerland))*

Background: The economic burden associated with inefficiencies and waste in the US healthcare system ranges from $760 to $935 billion annually (1). Certain categories of healthcare inefficiencies, such as missed prevention opportunities, leave a significant impact on society from both health and economic perspectives (2). In the context of health economics, prevention of a chronic condition includes opportunities to slow disease progression. In patients with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) or AD dementia, the costs of potential missed prevention opportunities correspond to the economic burden associated with progression to later stages of AD. **Objectives:** To estimate the economic burden of daily transitions to later stages of AD in the US. **Methods:** A comprehensive literature review was conducted to estimate the number of patients transitioning to the next stage of AD severity and the associated costs. Using a funnel-based approach, we first estimated the number of biomarker-positive MCI due to AD and AD dementia cases in the US among those ≥50 years old. Starting with the Centers for Disease Control and Prevention WONDER data in the population ≥50 years old, we applied age- and race/ethnicity-stratified estimates of the prevalence of all-cause MCI or AD dementia clinical syndrome from a recent study in individuals ≥65 years old (3). In those <65 years old, literature on MCI prevalence was limited and estimates were derived from 2 additional sources (4, 5). Likewise in AD, estimates in individuals <65 years old were sourced from the Alzheimer's Association (6). We then estimated the number of all-cause MCI cases that would be clinically attributable to AD (7) and the proportion of AD cases by dementia severity (mild, moderate, severe) (8). Finally, we estimated the number of these cases likely to be amyloid-positive using results from the Amyloid Biomarker Study (9). Annual transition probabilities from the National Alzheimer's Coordinating Center (10) were applied to the amyloid-positive case estimates, and these counts were used to approximate the number of daily transitions from each stage to the next advanced stage of AD severity. Next, we identified direct medical, nonmedical, and unpaid caregiving costs in the US by disease stage. The GERAS-US study (11) was selected as the most appropriate source of costs in patients with MCI due to AD and mild AD dementia. Costs for moderate and severe AD dementia were estimated using between-stage ratios from an observational study (12). Both studies relied on the Resource Utilization in Dementia questionnaire (13) and US-specific unit costs to estimate care costs. For the proportion of patients in institutional settings (14), direct medical costs were assumed to equal costs in the community, direct nonmedical costs were obtained from the Genworth Cost of Care Survey (15, 16) and unpaid caregiving costs were set to 44% of those in the community based on results from the What Matters Most study (17). Costs were inflated to 2021 US dollars where required (18, 19). **Results:** The economic burden associated with progression of AD was estimated using the number of patients who transition from one stage to the next each day. Progression of 5792 patients from MCI due to AD to mild AD dementia per day accounted for the highest burden with an incremental daily cost of $323,891 (approximately $118 million per year). Likewise, the burden associated with daily transitions from mild to moderate AD dementia (n=2308) and from moderate to severe AD dementia (n=1438) were $88,747 and $143,923, respectively. Cost of progression to more advanced stages of AD dementia might be even higher when including transitions of >1 stage annually or when accounting for the potential impact of AD caregiving on a caregiver's direct medical costs (11). Results should be considered in the context of limitations of the available data. **Conclusion:** The estimated daily impact of disease progression to later stages of AD on a population-level in the US is associated with significant economic burden that represents potential missed prevention opportunities. Any timely intervention that slows the progression could substantially mitigate the economic and health burden of AD in the US. **References:** 1. Shrank WH, et al. JAMA. 2019. 2. Berwick DM, et al. JAMA. 2012. 3. Rajan KB, et al. Alzheimers Dement. 2021. 4. Petersen RC, et al. Neurology. 2018. 5. Lopez-Anton R, et al. Acta Psychiatr Scand. 2015. 6. Alzheimer's Association. Alzheimers Dement. 2019. 7. Knopman DS, et al. Alzheimers Dement. 2016. 8. 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EPIDEMIOLOGY AND CLINICAL TRIALS

P176- IDENTIFICATION OF MEDICAL CONDITIONS AS RISK FACTORS FOR MILD COGNITIVE IMPAIRMENT – A US CLAIMS DATABASE STUDY.

G. Li[1], T. Nicola[2], B. Richard[3], G. James[4], H. David[5], D.S. Susan[6], H. Harald[6] *(1. Eisai Inc - Hillsborough (United States), 2. Rome University - Rome (Italy), 3. Eisai Inc - Basel (Swaziland), 4. Miami University - Miami (United States), 5. Janssen - Indianapolis (United States), 6. Eisai Inc - Nutley (United States))*

Introduction: Early identification of Alzheimer's disease (AD) is crucial for increasing the likelihood of effective treatment outcomes. As novel therapeutic strategies for AD emerge, targeting accurate and timely detection and diagnosis of early AD becomes increasingly relevant, particularly at the prodromal, symptomatic, mild cognitive impairment (MCI) stage. The MCI detection rate using clinical assessment by primary care physicians has proven woefully insufficient and can be as low as 6%. We aimed to determine: a) whether medical conditions commonly known to be AD risk factors are also risk factors for MCI, b) how well do these risk factors discriminate MCI individuals from non-MCI controls, and c) what specific medical conditions are the risk factors for MCI incidence. **Methods:** Using data from MarketScan, a US claims database, we performed a retrospective analysis that included a cohort of 5185 MCI individuals without an established dementia diagnosis aged 50 years or older. An additional 15555 subjects were included as controls (no MCI nor dementia diagnosis) and were matched on age, sex, and geographic region. A literature review was conducted to identify a list of medical conditions including cardiovascular, thyroid, and metabolic disease, and central nervous system/psychiatric disorders previously associated with risk for AD. A medical condition was considered a risk factor if it appeared in the MCI cohort

with a statistically significantly higher frequency compared to the control cohort. Both logistic regression model and extreme gradient boosting (XGBoost), a machine learning method, were applied to discriminate MCI from control subjects. To apply the XGboost approach the dataset was split into a training (20%) and test (80%) set. This approach addressed the potential collinearity issue among medical conditions. **Results:** Twenty-five medical conditions were found to have a statistically significantly higher frequency in the MCI cohort compared to controls and therefore, were considered MCI risk factors. Five of them with a frequency >10% in MCI and an odds ratio > 2 were: depression, stroke / transient ischemic attack (TIA), obstructive sleep apnea, insomnia, and hearing loss, with odds ratio of (MCI vs Control) 3.8 (95%CI = 3.5-4.1), 3.3 (95%CI = 3.0-3.6), 2.9(95%CI = 2.7-3.1), 2.7 (95%CI = 2.4-2.9), and 2.1 (95%CI = 1.9-2.3), respectively (p's <0.0001). Across three age groups (55-64 years, 65-79 years, and ≥80 years), for every medical condition, the odds ratios (MCI vs Control) decreased as age increased, e.g., the 3 age groups had odds ratios of 6.4 (95%CI = 5.4-7.5), 3.0 (95% CI = 2.6-3.5), 2.1 (95%CI = 1.8-2.5) in stroke/ TIA; and 4.4 (95%CI = 4.0-4.9), 3.1 (95% CI=2.7-3.6), 2.9 (95% CI =2.4-3.6) in depression. Further, the logistic regression model reached an AUC of 0.71 in discriminating MCI individuals from controls. In comparison, the XGBoost approach reached an AUC = 0.94 on the training set and AUC = 0.75 on the test set. Based on performance as measured by AUC in both approaches, the importance of age in the MCI prediction was found to be higher for the younger age group. The two leading MCI risk factors for all age groups were depression and stroke/ TIA. **Conclusion:** The results from both traditional logistic regression and XGBoost approaches are consistent. MCI individuals show a different medical condition profile compared to controls. The risk factors for AD were also found to be risk factors for MCI. Evaluation of medical condition profiles has the potential to formulate accurate MCI discrimination and hence to identify individuals at high risk of developing MCI.

P177- SAFETY OF FLUORINE 18-LABELED AMYLOID TRACERS: PHARMACOVIGILANCE VALIDATION USING A LARGE REAL-WORLD DATABASE. K. Sato[1], Y. Niimi[2], R. Ihara[3], K. Suzuki[4], A. Iwata[3], T. Iwatsubo[1] *(1. University Of Tokyo - Tokyo (Japan), 2. University Of Tokyo Hospital - Tokyo (Japan), 3. Tokyo Metropolitan Geriatric Medical Center Hospital - Tokyo (Japan), 4. National Defense Medical College - Saitama (Japan))*

Background: Amyloid PET has been widely used as one of the gold standards to screen positive amyloid accumulation in brain to identify individuals who are eligible for Alzheimer's disease (AD) prevention trials (1, 2). Its PET tracers are fluorine 18-labeled tracers including florbetapir (AmyvidTM), flutemetamol (VizamylTM), or florbetaben (NeuraCeqTM). Because these amyloid tracers are drugs not for treatment of AD but rather for diagnosis/screening of AD pathology, they should require higher level of safety when compared to disease-modifying therapies for AD itself. Indeed, these amyloid tracers are reported as generally safe: their known potential adverse events (AEs) are limited to a few numbers of mild and acceptable ones such as injection site reaction, hypertension, flushing, or headache (2). **Objectives:** Along with the expanding increase in the number of individuals screened by amyloid PET for AD clinical trials, we need to validate whether there may be any rare but serious AEs that could not be identified at the pre-marketing clinical trials. For this purpose, in this study we analyzed potential AEs of amyloid tracers using the FDA Adverse Event Reporting System (FAERS) database that contains a very large number of case reports with potential drug AEs. **Methods:** This study was approved by the University of Tokyo Graduate School of Medicine institutional ethics committee [ID: 11754-(1)]. Informed consent was not required for this type of study. On March 2022, from the FDA's website (https://www.fda.gov) we downloaded patient data that were reported between 2012 and 2021. In our analysis, we included only reports that were classified as 'primary suspected' and 'secondary suspected' as to the suspected causality between the AE and the drug. In addition, we included only reports that were reported from medical doctor, pharmacist, or other medical staffs, but not from lawyers or consumers. We classified each case report based on the following binomial factors: 'with' or 'without' exposure to the use of sold amyloid tracers (i.e., florbetaben, florbetapir, or flutemetamol), and 'with' or 'without' the development of each of the AEs which are determined by the Medical Dictionary for Regulatory Activities (MedDRA). Since there were no cases reporting AEs following the use of florbetaben, so we only included florbetapir or flutemetamol as amyloid tracers to consider here. To evaluate the degree of self-reporting, for each of the included tracers (florbetapir or flutemetamol) we calculated the reporting odds ratio (ROR) using a logistic regression model targeting the development of AE of interest and including age, sex, and the exposure to the tracer of interest (in binary) as explanatory varaibles. The ROR was calculated only for AEs which were reported twice or more (i.e., $n \geq 2$) following the use of each amyloid tracer. When the p-value of the AE term in the derived logistic regression model was less than 0.05, the AE was considered to be significantly highly reported following the use of the amyloid tracer, compared with the report of the same AE following the use of any other drugs. **Results:** As a result, our analysis included 3,792,541 unique AE case reports following the use of any drugs. Among them, there were 50 AE cases with the exposure to florbetapir (n = 11) or flutemetamol (n = 39), and these cases were generally in their 70's. The frequency of reported AEs in cases with exposure to amyloid tracers was low (i.e., 4 at best), and 'Hypertension' (adjusted ROR = 53.4, $p < 0.001$) was the only significantly highly reported AE in cases with florbetapir, and those with flutemetamol had the significant reporting of 'Blood pressure increased' (adjusted ROR = 18.0, p = 0.008), 'Flushing' (adjusted ROR = 44.7, $p < 0.001$), and 'Headache' (adjusted ROR = 14.8, p = 0.001). **Conclusion:** These results showed a statistically significant association (albeit marginal) between the use of amyloid tracers and a few of AEs, all of which are well-known as mild and acceptable AEs with the use of amyloid tracers (2). In addition, no any other AEs were suggested as potential unrecognized AEs of amyloid tracers. Despite the limitations that our approach has due to some bias that derived from the nature of self-reporting database, the major strength of our study is that it was based on a database that includes global real-world data from a very large number of patients. These results might provide some supportive evidence as to the safety of amyloid tracers, and would be of help for researchers to further facilitate current AD prevention trials. **References:** 1. Barthel H, Sabri O. Clinical Use and Utility of Amyloid Imaging. J Nucl Med. 2017 Nov;58(11):1711-1717. 2. Filippi L, Chiaravalloti A, Bagni O, Schillaci O. 18F-labeled radiopharmaceuticals for the molecular neuroimaging of amyloid plaques in Alzheimer's disease. Am J Nucl Med Mol Imaging. 2018 Aug 20;8(4):268-281.

P178- DIAGNOSIS AND CLINICAL TRIAL RECRUITMENT OF PATIENTS WITH EARLY ONSET ALZHEIMER'S DISEASE IN CLINICAL PRACTICE: SINGLE CENTER EXPERIENCE IN JAPAN. M. Kurihara[1], R. Ihara[1], K. Ishibashi[2], K. Ishii[2], K. Kanemaru[1], A. Iwata[1] *(1. Department Of Neurology, Tokyo Metropolitan Geriatric Hospital And Institute Of Gerontology - Tokyo (Japan), 2. Research Team For Neuroimaging, Tokyo Metropolitan Geriatric Hospital And Institute Of Gerontology - Tokyo (Japan))*

Background: Early onset Alzheimer's disease (EOAD) is a devastating condition that presents with cognitive decline before the age of 65 years. Sporadic EOAD is more common than autosomal dominant AD (ADAD) due to PSEN1, PSEN2, and APP mutations. Most of the current clinical trial recruitment focuses on patients with ADAD or sporadic patients above a certain age, such as 50 or 55 years, and young patients are often excluded due to different clinical characteristics and course of disease. Recruitment of patients with sporadic EOAD for clinical trials can be difficult because there is no framework focusing on the recruitment of this patient group, at least in Japan. **Objectives:** This study aimed to summarize the characteristics of patients with EOAD diagnosed in clinical practice and to consider problems in clinical trial recruitment. **Research setting:** The Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology is a community-based hospital located in urban Tokyo that provides clinical care and conducts research focusing on age-related medical conditions, including AD and other cognitive disorders. Although the Japanese national insurance covers only cerebrospinal fluid (CSF) p-tau181 as an AD biomarker to date, we conduct amyloid PET and CSF biomarker analyses, including Aβ42 in patients with suspected EOAD after obtaining informed consent. Since the last author A.I., a neurologist specializing in general neurology and cognitive disorders, moved to this institution in April 2020, the institution started to participate in three international randomized controlled trials for AD and also started to introduce clinical trials conducted at other institutions if deemed appropriate. **Methods:** We retrospectively reviewed all patients who underwent amyloid PET from April 2020 to April 2022, and included patients with EOAD based on the results of [11C] Pittsburgh compound B, [18F] THK5351, and [18F] FDG PET imaging. CSF biomarker analyses were also conducted in patients who consented. Clinical information, test results, and information on clinical trial enrollment were extracted through a chart review. Variables are summarized as mean ± standard deviation or median (full range). **Results:** From April 2020 to April 2022, out of approximately 1300 new patients who presented to the last author's clinic, 175 had cognitive disorders, and 82 had AD. There were 13 patients with EOAD (15.9%), all of whom had biomarkers confirmed by PET imaging. The mean age at symptom onset was 54.9 ± 5.7 years old, and 38.5% of patients were female. While 61.5% had a family history of dementia, none had an obvious family history of EOAD. Three of the 11 patients tested were APOE ε4 homozygotes (27.3%) and one patient was APOE ε4 heterozygote (9.1%). The median duration from symptom onset to the first hospital visit was 6 (3-60) months, and the median duration from the first visit to referral to our hospital was 3 (0-38) months. Twelve patients (92.3%) were referred from another hospital or clinic, including tertiary care hospital and private specialty clinic. At the time of presentation to our hospital, the disease stage was mild cognitive impairment in 4 patients (30.8%), mild dementia in 9 patients (53.8%), and moderate dementia in 2 patients (15.4%). The median MMSE score was 24 (11-29). The median number of comorbidities was 1 (0-2). Available clinical trial information was provided to eight patients (61.5%), and seven patients of interest were introduced to nearby study sites. Two were introduced to a phase 1 trial, four were introduced to a phase 2 trial, and two were introduced to a phase 3 trial. The only patient who declined the proposal was due to relocation to a rural area. The reasons for unavailability of a suitable clinical trial were advanced stage (n = 2), young age (n = 1, 46 years old), multiple cortical superficial siderosis (n = 1), and the absence of an appropriate study partner (n = 1). **Conclusion:** We summarized the characteristics of patients with biomarker-confirmed EOAD diagnosed during clinical practice at our institution. Although the timing of referral to our hospital varied widely, most patients were in the early symptomatic stage and had few comorbidities. Most patients were willing to participate in a clinical trial after being given information on clinical trials in 2020. Patients with sporadic EOAD also have a great interest in clinical trials and should have the opportunity to obtain information on available clinical trials.

P179- TREATMENT STATUS OF ALZHEIMER'S DEMENTIA USING COMMON DATA MODEL IN SOUTH KOREA. S. Jeong Yun[1], J. Jae-Won[1,2] *(1. Kangwon National University Hospital - Chuncheon (Korea, Republic of), 2. Kangwon National University College of Medicine - Chuncheon (Korea, Republic of))*

Background: Medications for dementia are prescribed to patients with Alzheimer's dementia (AD) widely in South Korea. **Objectives:** The aim of this study was to assess the treatment pattern of anti-dementia medication in AD using standardized manner at multiple hospitals. **Methods:** The status of medical management in patients with AD was analyzed using a standardized data format that the Observational Medical Outcome Partnership Common Data Model from five hospitals were used in this study. The anti-dementia treatment data from datasets during 2009–2020 and the medication usage status was analyzed with regarde to persistence and treatment trends for 12 years. **Results:** Among the 8653 patients withnewly diagnosed AD, donepezil was the most commonly prescribed anti-dementia medication (4218; 48.75%), followed by memantine (1565; 18.09%), rivastigmine (887; 9.33%), and galantamine (494;5.19%). The rising prescription trend during observation period was found only with donepezil. Thetreatment pathways for the three cholinesterase inhibitors combined with N-methyl-d-aspartatereceptor antagonist were different according to the drugs (18.5%; donepezil; 26.1%; rivastigmine,and 16.1%; galantamine). A 12-month persistence analysis showed values of about 50%for donepezil and memantine and approximately 40% for rivastigmine and galantamine. **Conclusion:** There were differences in persistence and the prescribing pattern among anti-dementia medications from database using the Observational Medical Outcome Partnership Common Data Model in South Korea.

P180- GLOBALIZATION OF ALZHEIMER DISEASE CLINICAL TRIALS: RECOMMENDATIONS FOR TRIAL IMPLEMENTATION IN LOW- AND MIDDLE-INCOME COUNTRIES. J. Llibre-Guerra[1] *(1. Washington University School Of Medicine In St.louis - St. Louis (United States))*

Background: Alzheimer's disease and related dementias (ADRD) have emerged as a global priority, and the need for therapies that could delay or stop AD progression is urgent. Despite the increase in the number of clinical trials in AD over the last decade, ethnoracially diverse individuals and

populations from low- and middle-income countries (LMIC) remain underrepresented in ADRD trials. Globalization of ADRD trials is key to addressing context-specific questions related to biological and non-biological variations that may exist across populations. **Objectives:** We aimed to determine the global distribution of dementia clinical trials and provide recommendations for implementing ADRD clinical trials in LMICs. **Methods:** A two-step strategy was utilized. The first step aimed to determine the global distribution of dementia clinical trials. Our primary data sources to identify trial distribution in LMICs included ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform. Data analysis included the number of clinical trials per country, regional distribution, funding source, and regional annual growth rate relative to dementia estimates. The second step aimed to identify existing barriers and provide recommendations for conducting dementia clinical trials in LMICs via expert consensus. **Results:** Over the last two decades, 1237 ADRD modifying therapies (ADRD-DMT) have been tested in 74 countries for a total of 3467 clinical trials. Among those, 3065 (88.4%) clinical trials were conducted in high-income countries and 405 (11.6%) in developing countries. 78.8% of all clinical trials were conducted in Europe and North America. LMICs had the lowest annual trial density (2000-2021) despite the relatively large population living with dementia. Experts' consensus (including pharma representatives, clinical researchers, and government representatives) provided guidance on barriers and recommendations for trial implementation. **Conclusion:** Although LMICs countries bear the most significant burden of ADRD, less than 15% of ADRD clinical trials are conducted in developing countries; failing to include the true diversity of the population facing ADRD. We identified several barriers to successfully implementing the ADRD trial globally, including lack of investment due to limited commercial opportunities, resource limitations, poor efficiency of regulatory systems, and unresolved operational complexities.

P181- THE MINORITY REPORT: AN UPDATE ON MINORITY RECRUITMENT FROM A LARGE SITE IN CENTRAL FLORIDA. S. Torres[1], S. Baez-Torres[1], S. Cassidy[1], B. Lenox[1], S. Stanton[1], J. West[1] *(1. K2 Medical Research, LLC, Orlando (United States))*

Participation in Clinical Trials for Alzheimer's Disease have led a very small numer of minority and underserved population over the past 30 years. In many registration trials the number of participants that randomize have been lower than 2% of the total number of people in the the study. K2 Medical Research is large clinical trial netowrk in Central Florida with 4 sites between Orlando, FL and The Villages. In 2022, the site has been able to enroll 1326 patients worried about or diagnosed with MCI and/or Alzheimer's Disease. The site has 50% minority staff and is able to speak spanish, creole, french, and arabic. There have been 726 partcipants enrolled in Clinical Trials for Alzheimer's Disease, which represents 53%. The epdeiolgy in Central Florida is 60% Caucasian, 22% Balck, 35% Hispanic, and 12% other. This presentation will outline the path to success to enroll particpants of minority representation.

P182- GENERALIZABILITY OF COGNITIVE RESULTS FROM CLINICAL TRIAL PARTICIPANTS TO OLDER ADULT POPULATION: ADDRESSING EXTERNAL VALIDITY. V. Aslanyan[1], H.N. Hodis[1,2,3], J. St. John[1,2], N. Kono[1,2], V. Henderson[4], W.J. Mack[1] *(1. Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California - Los Angeles, CA (United States), 2. Atherosclerosis Research Unit, Keck School of Medicine, University of Southern California - Los Angeles, CA (United States), 3. Department of Medicine, Keck School of Medicine, University of Southern California - Los Angeles, CA (United States), 4. Department of Epidemiology and Department of Neurology and Neurological Sciences, School of Medicine, Stanford University - Stanford, CA (United States))*

Background: Generalizability of findings from a randomized clinical trial (RCT) refers to the ability of extending these findings from the trial sample to a target population, the population from which the sample is drawn. Single-site RCTs may recruit a nonrepresentative sample from the target population, often due to sociodemographic differences attributed to location-specific recruitment practices. RCTs often exclude participants with comorbidities that may be of interest. Trial criteria and recruitment practices introduce external bias and limit the generalizability of RCT findings. Statistical approaches using the probability of sampling individuals provide a basis for generalizability of outcomes from trial populations. These approaches assign greater weights to the randomized participants with lower probability of trial participation. The assessment of generalizability is crucial for post-hoc analyses from RCTs, thus differences between randomized and non-randomized participants from the target population should be properly adjusted before performing such analyses. **Objectives:** To generalize cross-sectional findings from clinical trials conducted at the Atherosclerosis Research Unit (ARU), University of Southern California. As an illustration, the relationship between cognition and depression, a modifiable risk factor for Alzheimer's disease, will be assessed using the cohort with and without adjustment for differences from the target population. **Methods:** Female clinical trial participants were recruited for four RCTs (B-Vitamin Atherosclerosis Intervention Trial (BVAIT), Women's Isoflavone Soy Health (WISH) trial, Early versus Late Intervention Trial with Estradiol (ELITE), and the Nattokinase Atherothrombotic Prevention Study (NAPS)). All participants had similar cardiovascular profiles and were screened against diabetes and clinical symptoms of cardiovascular disease. Global, verbal memory, executive function, and visual memory composite cognitive scores were derived from the battery of fourteen neuropsychological tests. Participants' demographic and health data were collected during screening. Non-randomized participants were selected from the Health and Retirement Study (HRS), a representative sample of older adults. This HRS sample was surveyed in 2016 and consisted of female participants with complete demographic and health profiles. A logistic regression prediction model was used to estimate the probability of being randomized into the trials. Participants' weight of generalizability was determined from these probabilities using inverse probability weighting. Linear regression was used to estimate the magnitude of the association between depression (measured using Center for Epidemiological Studies-Depression (CESD) scale) and cognitive performance. The depression—cognitive function associations were adjusted for age, race/ethnicity, APOE4 carrier status, and education. **Results:** 3180 female survey

participants from HRS and 1309 trial participants from ARU (196 from BVAIT, 343 from WISH, 607 from ELITE, and 163 from NAPS) were selected for the current study. Randomized participants had statistically significant differences from non-randomized participants in all sociodemographic and basic health variables used in the prediction model (age, sex, education, marital status, race/ethnicity, body mass index, blood pressure and blood cholesterol). The prediction model had a sensitivity of 0.87 and specificity of 0.84 at the empirical optimal cutpoint of 0.30, and the area under the curve was 0.93. Weights were calculated from the inverse probability of belonging to the randomized cohort estimated in the prediction model. Weights for the randomized cohort followed a skewed distribution (median weight=1.35, IQR=1.07, range: 1.00—488.26). There was no significant depression—global cognition relationship in the randomized sample (β=-0.004 per 1-unit CESD scale increase, 95% Confidence Interval (CI) (-0.01, 0.003), p=0.25). After applying weights from the prediction model, a unit increase in CESD scale corresponded a mean decrease of global cognition score of 0.017 (95% CI: (-0.025, -0.01), p<0.001). Similarly, while the relationship between depression and verbal memory score was not significant (β=-0.003 per 1 unit increase, 95% CI: (-0.009, 0.002), p=0.24), the relationship was statistically significant after applying the weights (β=-0.019 per 1 unit increase, 95% CI: (-0.025, -0.012), p<0.001). The relationship between depression and executive function was statistically significant using both approaches (β=-0.006 per 1 unit increase in cohort, 95% CI: (-0.01, -0.001), p=0.017; β=-0.006 per 1 unit increase using weights, 95% CI: (-0.012, -0.001), p=0.023). The relationship was not significant for visual memory using both approaches (β=-0.001 per 1 unit increase in cohort, 95% CI: (-0.003, 0.006), p=0.58; β<-0.001 per 1 unit increase using weights, 95% CI: (-0.005, 0.004), p=0.9). Overall, findings from the cohort without any adjustments tended to misalign with accumulated evidence and confirmed previous findings only after adjustments for representation. **Conclusions:** Combining modeling the probability of trial participation with modeling the expectation of the outcome results in less biased estimates from specialized trial cohorts. This approach helps generalize findings from the cohort to a target population in a less biased manner, weighting participants according to the probability of being selected into the trial if they were coming from the target population, which is calculated using a representative reference cohort. The current study presents an example where previously confirmed findings were not present in a non-representative trial cohort but were evident after weighting the participants to make the cohort generalizable. Authors report no conflict of interests.

P184- PREVALENCE ESTIMATIONS FOR THE ALZHEIMER'S DISEASE CONTINUUM IN THE US HEALTH AND RETIREMENT STUDY. A.A. Tahami Monfared[1,2], Q. Zhang[1], A. Chandak[3], A. Khachatryan[4], L. De Benedetti[5], N. Hummel[6] *(1. Eisai Inc. - Nutley (United States), 2. Biostatistics and Occupational Health, McGill University - Montreal (Canada), 3. Certara Inc. - New York (United States), 4. Certara Ltd. - Sheffield (United Kingdom), 5. Certara Canada Corporation - Montreal (United States), 6. Certara GmbH - Lörrach (Germany)))*

Background: Alzheimer's disease (AD) prevalence data by severity across the AD continuum, including mild cognitive impairment (MCI), is limited. These prevalence estimates are important for health services planning and the development of new disease-modifying therapies targeting different stages of the disease. **Objective:** To estimate prevalence of MCI, mild, moderate and severe AD in a representative sample of the US population. **Methods:** Data from the Health and Retirement Study (HRS) was used. The HRS provides a representative sample of the US population containing data for Americans over 50 years old, with more than 43,000 individuals interviewed to date. Interviews are conducted bi-annually. The three most recent time points were assessed: surveys collected in 2014, 2016 and 2018. AD patients were identified in two ways: they were included (1) if they reported an AD diagnosis (diagnosis-based approach), or (2) if they were considered as having AD based on their cognitive performance, at or before the considered time points (cognitive performance-based approach). MCI patients were identified by their cognitive performance only. MCI and AD severity staging was assessed using a crosswalk from results of the modified telephone interview of cognitive status (TICS-m) to the mini-mental state examination (MMSE). For the diagnosis-based approach, the prevalence was estimated by dividing the number of patients with self-reported diagnosis by the total number of survey respondents. For the cognitive performance-based approach, the prevalence for MCI or AD was estimated by dividing the number of patients with TICS-m score ≤ 22 (i.e., a TICS-m score satisfying at least MCI) by the total number of survey respondents that had TICS-m scores available. Prevalence estimates were also pooled across 2014-2018. Severity distribution among the patients identified through the two methods were assessed by year and pooled. **Results:** With the diagnosis-based method, 2%, 1%, 1% patients were identified as having AD in 2014, 2016 and 2018, respectively (3% pooled). Overall, these AD patients were 80.0 years old (SD=9.8) at their first survey between 2014-2018, 63% female, and 17% passed college or above. Severity distributions among patients with available TICS-m scores were as follows: 27%, 27% and 46% for mild AD in 2014, 2016 and 2018, respectively (32% pooled); 43%, 38% and 36% for moderate AD in 2014, 2016 and 2018, respectively (39% pooled); and 31%, 35% and 18% for severe AD in 2014, 2016 and 2018, respectively (29% pooled). With the cognitive performance-based method, 55%, 51%, 44% were identified as having AD or MCI in 2014, 2016 and 2018, respectively (61% pooled). Overall, these MCI or AD patients were 70.9 years old (SD=11.8) at their first survey between 2014-2018, 57% female, and 27% passed college or above. Severity distributions among patients with available TICS-m scores were as follows: 44%, 47% and 53% for MCI in 2014, 2016 and 2018, respectively (41% pooled); 29%, 29% and 31% for mild AD in 2014, 2016 and 2018, respectively (30% pooled); 23%, 22% and 15% for moderate AD in 2014, 2016 and 2018, respectively (25% pooled); and 4%, 3% and <1% for severe AD in 2014, 2016 and 2018, respectively (4% pooled). **Conclusions:** There is a discrepancy in AD prevalence estimations using self-reported diagnoses of AD vs. using cut-offs of TICS-m, with the latter identifying higher proportion of MCI or mild AD cases. Both methods bear potential limitations: while AD diagnoses may be under-reported, especially in early stages of the disease, identification based on TICS-m relies on the score cut-offs that were benchmarked using MMSE and are not validated. Due to missing data, the final sample for prevalence estimation is quite small especially for severity specific prevalence. As a result, the prevalence rates based on HRS are likely subject to sizable error variability. Depending on the method of identification used in this study, approximately one-third of the patients had mild AD and almost half of the patients had MCI. This suggests the need for effective clinical interventions to prevent or slow the progression of this disease.

P185- ASSOCIATION BETWEEN A/T/N PROFILES AND MORTALITY IN PATIENTS WITH COGNITIVE DISORDERS. M. Régy[1,2], A. Dugravot[1], B. Hanseeuw[3], J. Dumurgier[1] *(1. CRESS U1153 Epidemiology of Ageing and neurodegenerative diseases (Inserm) - Paris (France), 2. Brain Ageing Lab (Catholic University of Louvain - Brussels (Belgium), 3. Brain Aging Lab (St-Luc Hospital) - Bruxelles (Belgium))*

Background: Alzheimer's disease (AD) is the 5th leading cause of death for people aged 65 years and older. The A/T/N classification has been proposed as an unbiased definition of AD with markers of Aβ deposition (A), pathologic tau (T), and neurodegeneration (N), based on CSF or PET biomarkers assessment. **Objectives:** Few is known about the relationship between A/T/N status and the risk of mortality, therefore we here report the association between A/T/N profiles and mortality, in a large population of patients with cognitive disorders consulting in a memory clinic. **Method:** Our study used data from the BioCogBank Study, including patients explored for cognitive disorders in Lariboisiere hospital (Paris, France), followed up to 15 years. All participants underwent a lumbar puncture in clinical setting, with the assessment of the levels of CSF total tau (t-tau), phosphorylated tau (p-tau) and amyloid-beta 42 (aβ42). Vital status on July 1st, 2020 was recorded for each participant using French open data on mortality. Individuals were categorized according to their A/T/N profiles based on their level of CSF aβ42 or aβ42/40 ratio, p-tau and t-tau. Short term (5 years) and long term (15 years) Kaplan Meier and multivariate Cox analyses were performed with A-/T-/N- subjects as reference. **Result:** Among the 1353 patients included (mean age: 68 years old, 53% of women, mean MMSE score: 22.6), 262 died during the follow-up. At 5 years of follow-up, A-/T-/N+ individuals showed the highest risk of mortality in Kaplan Meier and adjusted Cox analyses (HR (IC) = 2.83 (1.25-6.42)). At 15 years of follow-up, patients in the AD spectrum had an higher mortality risk with a gradient effect between A-/T+ (HR: 1.63 (1.04-2.58)), A+/T- (HR: 1.96 (1.29-2.99)), and A+/T+ individuals (HR: 2.25 (1.55-3.27)), compared to A-/T-/N- patients. Adjustments on potential confounders had little impact on these associations. **Conclusion:** This study shows the association between A/T/N profiles and mortality in a large population of patients explored for cognitive disorders. At short term, patients with isolated evidence of neurodegeneration showed the higher mortality rate. At long term, patients with the AD profile (A+/T+) had the highest mortality rate.

P186- ULTRA HIGH RISK AND HIGH PREDICTABILITY OF ALZHEIMER'S DISEASE ONSET IN PEOPLE WITH DOWN SYNDROME: IMPLICATIONS FOR CLINICAL TRIALS. J. Fortea[1,2,3], A. Lleo[1,2], A. Bejanin[1,2], M.F. Iulita[1,2] *(1. Memory Unit and Biomedical Research Institute Sant Pau (IIB Sant Pau), Neurology Department, Hospital de la Santa Creu i Sant Pau - Barcelona (Spain), 2. Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED) - Madrid (Spain), 3. Barcelona Down Medical Center, Fundació Catalana Síndrome de Down - Barcelona (Spain))*

Background: Down syndrome is the most frequent cause of intellectual disability and a genetically determined form of Alzheimer's disease. Alzheimer's disease has near full penetrance in this population, and the natural history of clinical and biomarker changes is very similar to that of autosomal Alzheimer's disease. However, age at onset is considered variable and the longitudinal age-associated risk of progression to symptomatic Alzheimer's disease has not been established. **Objectives:** To assess the variability in symptom onset of Alzheimer's disease dementia in Down syndrome in comparison with autosomal dominant Alzheimer's disease, and to provide the 5-year progression rate to symptomatic Alzheimer´s disease at different ages. **Methods:** We extracted data from two systematic reviews and meta-analyses to investigate the age at onset of Alzheimer's disease dementia in Down syndrome and in autosomal dominant Alzheimer's disease. We compared the 95% prediction intervals, the coefficients of variation and the span of age at onset in the two forms of the disease. We analysed the clinical change to symptomatic Alzheimer's disease in adults with Down syndrome in a large population cohort of 607 adults with Down syndrome with at least 6 months of follow-up from the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI). **Results:** The estimate of age at onset in adults with Down syndrome was 53.8 (95%CI, 53.1 to 54.5) years (n=2595). Coefficients of variation and 95% prediction intervals of age at onset were comparable to those reported in autosomal dominant Alzheimer's disease. In our cohort study of cognitive stable adults with Down syndrome, we found a high age-dependent risk to develop symptomatic Alzheimer's disease at 5 years: 0.1% [0-1.8%] for <40 years; 21.1% [8.0-32.5%] for 40-44 years; 41.4% [23.1-55.3%] for 45-49 years and 57.5% [38.2-70.8%] for >50 years. **Conclusion:** Down syndrome is probably the best population in which to perform Alzheimer's disease prevention trials due to its high prevalence and the ultra-high risk to develop symptomatic Alzheimer´s disease at a predictable age.

LP96- ASYMPTOMATIC EXTRACRANIAL CAROTID ATHEROSCLEROSIS AND ITS ASSOCIATION WITH INCIDENT ALZHEIMER'S DEMENTIA. F. Vitali[1], I. Bolakale-Rufai[1], G. Branigan[1], J. Arias[1], E. Reinman[1], R. Brinton[1], C. Weinkauf[1] *(1. University of Arizona - Tucson (United States))*

Background: Dementia is a major cause of disability and dependency among older people worldwide. Growing evidence suggests that vascular diseases contribute to the development and progression of cognitive dysfunction. Symptomatic extracranial carotid atherosclerosis resulting in stroke or transient ischemic attack has been well defined as a risk for dementia. However, the relationship between asymptomatic extracranial carotid arterial disease(aECAD) and dementia is not well established. **Objective:** Our study aims to determine the association of aECAD with incident Alzheimer's dementia (AD) in a cohort of patients. **Methods:** Longitudinal data were obtained from the Mariner insurance claims data set which contains over 122 million patients from private and Medicare insurance in the United States. The data set was queried retrospectively for patients with a first diagnosis of aECAD from 2010 to Q2 of 2018. Only patients that were continuously enrolled for at least 3 years prior to the index date were included. Population with no diagnosis of aECAD 6 months after 1st claim was selected as the control group. Patients who were 45 years or older with no previous diagnosis of dementia at the index date were included in our study and followed up for an outcome of AD. Propensity score matching was performed to adjust for vascular comorbidities that were confounding factors. Demographic and incidence statistics were analyzed using unpaired 2-tailed t-tests or $\chi 2$ tests, as appropriate, to test the significance with $P < .05$ considered statistically significant. **Results:** 784,062 patients were included in our study. The age of patients ranged from 65-80years with a mean [SD] age of 59.5[4.05] years. 52.9% of the patients were female. The mean duration of follow-up before

the AD diagnosis was 4.8years. 8736 out of 247,119(1.55%) patients with aECAD and 8015 of 536,943(0.92%)without aECAD developed AD respectively. After a propensity score match of the aECAD group versus the control group (without aECAD), 247,119 patients with aECAD and without aECAD were included in the final analysis. Over the period of follow-up, 5041(2.04%) patients with aECAD and 4187(1.69%) without aECAD developed AD. Unadjusted, aECAD was associated with a risk of incident dementia. (RR: 2.29, 95% C.I: 2.20-2.38, p<.001). After matching the population for covariates, the group with a diagnosis of aECAD had a significantly higher risk of Alzheimer's disease compared to the group without aECAD (RR: 1.2, 95% CI, 1.15-1.25 P<.001). **Conclusions:** This study suggests that aECAD increases the risk of incident Alzheimer's dementia by 20%. Well-designed prospective studies will further aid our understanding of the interaction between the two conditions. Defining the contribution of aECAD to Alzheimer's disease is compelling because effective treatments exist for aECAD yet are not currently offered for AD risk reduction. **Declaration of Conflicts:** Authors have no conflict of interest to declare at this time.

ANIMAL MODEL AND CLINICAL TRIAL

P187- THE PROBUCOL IN ALZHEIMER'S TRIAL: A DOUBLE-BLIND RCT INVESTIGATING COGNITIVE OUTCOMES, CEREBRAL AMYLOID AND BRAIN MORPHOMETRY BASED ON POSITIVE PROOF-OF-CONCEPT PRECLINICAL FINDINGS.

J. Mamo[1], R. Clarnette[2], V. Lam[1], M. Bynevelt[3], G. Watts[4], C. Orr[4], P. Loh[4], C. Reid[1], S. Dhaliwal[1], S. Robinson[1], R. Takechi[1], R. Adam[5], M. Vaccarezza[1] *(1. Curtin University - Perth (Australia), 2. Australian Alzheimer's Research Foundation - Perth (Australia), 3. Sir Charles Gardiner Hospital - Perth (Australia), 4. University of Western Australia - Perth (Australia), 5. University of Queensland - Perth (Australia))*

Background: Several lines of study suggest that peripheral metabolism of amyloid beta (Aß) is associated with risk for Alzheimer disease (AD). In blood, greater than 90% of Aß is complexed as an apolipoprotein, raising the possibility of a lipoprotein-Aß mediated axis for AD risk. To test the indicated hypothesis, we engineered C57BL/6J mice to synthesise human Aß only in liver (hepatocyte-specific human amyloid (HSHA) strain). HSHA mice with synthesis of lipoprotein-human Aß restricted to liver had marked neurodegeneration concomitant with capillary dysfunction, brain parenchymal extravasation of lipoprotein-Aß and neurovascular inflammation. HSHA mice also showed impaired performance in the passive avoidance test, suggesting impairment in hippocampal-dependent learning. Transmission electron microscopy showed marked neurovascular disruption in HSHA mice. Probucol, a historic cholesterol lowering agent was found to profoundly suppress the synthesis and secretion of lipoprotein-Aß. In HSHA mice, provision of probucol completely prevented cognitive dysfunction. Collectively, the preclinical studies provided the primary foundation to establish a clinical trial exploring the putative efficacy of Probucol to stabilize cognitive decline in Alzheimer's. **Objectives:** The Probucol in Alzheimer's (PIA)-Study (ACTRN12621000726853) will evaluate the efficacy of 2x daily 250 mg probucol provided as Lorelco™ on cognitive performance in Alzheimer's patients over a 102 week treatment period. Evaluate cerebral amyloid abundance in the brain of Alzheimer's Disease patients treated with probucol. Evaluate the Mesial temporal lobe (hippocampus and entorhinal cortex via Scheltens grading) in Alzheimer's Disease patients treated with Lorelco™. Activities of daily living will be assessed using the Alzheimer's Disease Co-operative Study Mild Cognitive Impairment Activities of Daily Living scale (ADCS-MCI-ADL24). Depression, anxiety, and stress will be assessed using Depression Anxiety Stress Scale (DASS-21). **Conclusion:** Exaggerated peripheral metabolism of lipoprotein-Aß may be a risk factor for Alzheimer's that can be positively regulated with provision of probucol.

P188- A NOVEL SMALL MOLECULE INHIBITOR REDUCES TOXIC AMYLOID OLIGOMERS TO RESCUE DISEASE IN AD MICE.

V. Mathur[1], K. Burk[1], X. Liu[2], S. Gaikwad[3], R. Kayed[3], M.T. Bowers[2], K. Planey[1], A. Singh[1] *(1. Acelot Inc. - Santa Barbara (United States), 2. Department of Chemistry and Biochemistry, University of California - Lubbock (United States), 3. Departments of Neurology & Neuroscience & Cell Biology & Anatomy, University of Texas Medical Branch - Galveston (United States), 4. Acelot Inc - Santa Barbara (United States))*

Background: Alzheimer's disease (AD) is associated with the deposition of insoluble aggregates of amyloid beta 1-42 (Abeta42) fragment of amyloid precursor protein (APP) and hyperphosphorylated Tau protein which further causes neuronal loss and inflammation in the central nervous system. What causes damage in AD is still debated, however small oligomers, but not higher order aggregates, are shown to be associated with toxicity leading to neuronal death. While Abeta42 and Tau are being tested as individual targets, a combination therapy is not tested and might prove beneficial. **Objectives:** To show in vitro potency and mechanism of action of Acelot's novel small molecule AC0203, determine pharmacokinetic properties and target engagement in vivo and to show efficacy in 3xTg mouse model of AD. **Methods:** Using our joint pharmacophore space (JPS) machine learning platform, we have identified novel small molecules that bind to multiple amyloid oligomers. We now show in vitro mechanism of action using ion mobility -mass spectrometry (IM-MS) for Abeta42 and cellular target engagement for Tau using oligomer toxicity assay. Lastly, we show drug efficacy in vivo using 3xTg mouse model of AD which has both Abeta and tau pathologies. **Results:** We show that AC0203 targets both Abeta42 and tau oligomers. IM-MS shows that Abeta42 peptide forms dimers to dodecamers in vitro. Either coincubation with AC0203 or incubation post oligomerization, reduces oligomers and increases Abeta42 monomers in solution. Additionally, AC0203 rescues Tau oligomer dependent rat primary neuronal toxicity suggesting that the drug is cell permeable and potent in neuronal cells. Furthermore, AC0203 rescues Tau oligomer dependent electrophysiological defects in mouse hippocampal brain slices. Orally administered AC0203 is well tolerated in mice and is detected in the brain for up to 24 hours. Lastly, AC0203 rescues certain behavioral deficits in 3xTg mouse model of AD. **Conclusion:** AC0203 is a clinical candidate drug with good pharmacokinetic properties and brain penetration that targets toxic forms of both Abeta42 and Tau. We show that AC0203 inhibits toxic amyloid oligomers in vitro, reduces oligomer dependent neuronal toxicity, partially rescues oligomer associated nerve conduction and rescues behavioral defects in 3xTg AD mice. **Conflict of Interest:** AS, KP, KB, VM are founder/board member/employed by and hold stock options for Acelot Inc.

P189- T-TYPE CALCIUM CHANNEL MODULATOR AD101 IMPROVES COGNITIVE FUNCTION IN ANIMAL MODELS OF MEMORY AND LEARNING IMPAIRMENT AND PROVIDES A RATIONALE FOR THE POTENTIAL CLINICAL USE OF AD101 IN THE SYMPTOMATIC TREATMENT OF ALZHEIMER'S DISEASE. J. Burmeister[1], S. Gauthier[2], S. Rogers[1] *(1. AmyriAD Pharma, Inc. - Los Angeles (United States), 2. McGill University - Montréal (Canada)*

Background: AD101 is a novel synthetic compound in development as an orally administered treatment for probable AD. After AD101 showed potential effects in animal models of learning and memory function in phenotypic screening, a series of investigations in animal models for normal aging, memory and learning impairment, and Alzheimer's Disease were performed. While AD101 stimulates the presynaptic release of acetylcholine in hippocampal neurons, some these studies suggested other additional mechanisms of action which potentially contribute to its beneficial effects on learning and memory function. **Objectives:** Summarize the effects of AD101 on learning and memory function in animal models for normal aging, induced memory and learning impairments and Aβ and tau dependent models. Describe combined effects of AD101 administration with available therapies such as cholinesterase inhibitors and memantine. **Methods:** Review of previously published and unpublished nonclinical studies. **Results:** Initial dose finding studies in rodents investigated doses of AD101 ranging from 0.001 to 1.0 mg/kg. The behavioral outcome measures used were the Novel Object Recognition (NOR), the Passive Avoidance (PA), the Radial Arm Maze (RM) and the Morris Water Maze Task (WWM). In normally aged rats (22 months) treatment with AD101 for 23 days elicited increased exploratory preference over untreated rats in the NOR task. Monotherapy with memantine 10 mg/kg as a positive control produced a significant effect over the untreated group as well, whereas the combination of AD101 and memantine produced the highest effect size. The effects of AD101 were explored further using learning and memory impairments induced either chemically or via neuronal lesioning: After muscarinic blockade via scopolamine administration AD101 (doses > 0.001 mg/kg) significantly attenuated step-through latencies in the passive avoidance task. While in the positive control group a significant effect was seen after administration of 0.1 mg/kg donepezil, combination treatment of donepezil and AD101 produced higher effect sizes. Glutamatergic blockage via oral administration of 0.2 mg/kg MK-801 significantly reduced step-through latency in the passive avoidance task. A single dose administration of 0.1 mg/kg but not of 1 mg/kg AD101 significantly ameliorated step-through latency. 7 days of exposure to methamphetamine-induced significant impairments of recognition memory in the NOR. Those effects were attenuated by administration of 1μg/kg AD101. While AD101 administration was increased hippocampal phosphorylated ERK1/2 levels treatment effects, were negated by pretreatment with a ERK kinase inhibitor SL327. Administration of the dopamine D1 receptor antagonist, SCH23390 and the NMDA receptor antagonist MK-801 blocked the ameliorating effect of AD101 effect as well. These results suggest that indirect activation of ERK1/2, as well as modulation of dopaminergic (D1) and glutamatergic (NMDA) pathways may contribute to the effects of AD101 on learning and memory function. Neuronal lesioning: Lesioning of the Nucleus Basalis Magnocellularis (NBM) with ibotenic acid or lesioning via intracerebroventricular Aβ25-35 Injections both led to reduced step-through latencies in the PA task in the rat. These impairments were partially mitigated by AD101 administration (0.01 and 0.1 mg/kg in the NBM model and 0.1 and 1 mg/kg in the Aβ25-35 model which led to prolonged step-through latencies in the PA task 14 days after NBM lesioning and 4 days after the Aβ25-35 injection. Models dependent on Aβ and tau were used to investigate the potential effects of AD101 on AD hallmark features and associated neurobehavioral problems: Intracerebroventricular Infusion of Aβ1-40 in rats produced deficits in the step-through latency in the PA task which were fully reversible by administration of 0.01 and 0.1 mg/kg AD101. This improvement was later shown to be associated with a reduction in Aβ accumulation. Senescence Accelerated Mouse-Prone 8 (SAMP8) mice are a mouse strain that, via a spontaneous gene mutation, develops age-related deficits in learning and memory along with an accelerated accumulation of Aβ-like deposits in brain tissue. SAMP8 mice were investigated at 12 months age. In the NOR untreated SAMP8 mice demonstrated an expected decrease in exploratory preference while treatment withAD101 (0.0015 to 0.14 mg/kg/day) attenuated this effect and significantly increased exploratory preference. LaFerla triple transgenic Mice (3xTG) are an animal model for AD in which AD neuropathological features such as Aβ-plaques, neurofibrillary tangles and neurobehavioral problems are expressed in an age dependent manner. After two months of treatment with AD101 3xTG mice were assessed using the Morris Water Maze. During retention testing at 24- and 72-hours animals treated with AD101 required significantly less time to reach the former platform. **Conclusion:** AD101 demonstrated beneficial effects on learning and memory function in animal models of normal aging, impaired learning and memory function and Alzheimer's Disease.

P190- EFFECTS OF T-TYPE CALCIUM CHANNEL MODULATOR AD101 ON THE ACCUMULATION OF BETA AMYLOID, TAU AND POLYUBIQUITINATED PROTEINS IN ANIMAL MODELS OF ALZHEIMER'S DISEASE. J. Burmeister[1], S. Gauthier[2], S. Rogers[1] *(1. AmyriAD Pharma, Inc. - Los Angeles (United States), 2. McGill University - Montréal (Canada))*

Background: AD101 is a first-in-class small molecule with demonstrated positive effects on learning and memory function in animal models for both normal aging and Alzheimer's Disease (AD). While AD101 modulates T-type voltage gated calcium channels and thus stimulates the presynaptic release of acetylcholine in hippocampal neurons, further studies investigated the potential role of AD101 in protein processing and accumulation as potential contributors to its clinical effects. **Objectives:** Summarize the effects of AD101 on Beta Amyloid and Tau aggregation, Amyloid Precursor Protein processing and modulation of proteasomal and lysosomal protein degradation. **Methods:** Review of sponsored and previously unpublished in-vitro and in vivo animal studies of AD models conducted as part of a collaboration with UC Irvine led by Kim Green, Ph.D. **Results:** In vitro studies using protein quantification via ELISA showed that AD101 reduces Amyloid-beta (Aβ) 1-42 in Neuro2a neuroblastoma cells and both Aβ 1-40 and 1-42 in primary neuronal cultures derived from transgenic mice overexpressing APP. These results were reproduced in several studies using brain tissue of LaFerla triple transgenic mice (3xTgAD) of varying age (12-24 months). A similar effect was eventually reported from brain tissue analyses derived from Cynologus monkeys. Western-blots derived from the same 3xTgAD mice demonstrated a decrease in C99 and C83 c-terminal APP fragments as signs of altered APP processing via

α- and β-secretase. Further Western-blot analyses demonstrated a reduction of beta-secretase (BACE) and alpha-secretase pro-enzyme (pro-ADAM) as well. Immunohistochemical staining with H7 anti-human tau monoclonal antibody of hippocampal brain section from 3xTgAD mice treated with AD101 showed a clear reduction of pathological tau staining in comparison to controls. Further experiments were conducted to assess whether changes in protein degradation may contribute to the reductions in Aβ and Tau protein concentrations. Changes in the ubiquitin-proteasome pathway were assessed with Western-blot analyses using an anti-ubiquitin antibody: 12-month-old 3xTgAD mice that had been treated with 5/mg/kg/day ST101 over 2 months have shown a consistent and profound reduction of polyubiquitinated protein concentrations. While long term treatment with AD101 in younger 3xTgAD mice of 3 months demonstrated similar effects in the 1mg/kg/day dose group after 10 months of AD101 administration, shorter treatments durations (3 months) and higher doses (5 mg/kg/day) showed negative results. Functional studies of proteins involved in autophagy and lysosomal degradation (LC3, Cathepsin D, Becllin 1 and LAMP2A) have not been conducted, however Western Blot analysis did not suggest significant changes in the concentrations of these proteins. Follow-up experiments showed that AD101 reduces ubiquitinated proteins in other models (C57 and SAMP8 mice) as well. **Conclusion:** These series of studies demonstrate that there are potential mechanisms of action of AD101 targeting protein processing and degradation in neuronal cells. The reduction of polyubiquitinated proteins could be a result from increased rates of proteasomal degradation. Alongside the known effect of AD101in increasing cholinergic neurotransmission, enhanced removal of nonfunctional proteins known to be associated with AD and other neurodegenerative diseases may contribute to the beneficial treatment effects of AD101 in AD.

LP97- MODULATION OF PERIPHERAL MONOCYTES BY A PROTEOSOME-BASED ADJUVANT (PROTOLLIN) FOR THE TREATMENT OF ALZHEIMER'S DISEASE.

P. Kolypetri[1], L. Liu[1], E. Solana[1], C. Gauthier[1], T. Singhal[1], S. Gale[1], T. Chitnis[1], D. Selkoe[1], H. Weiner[1] *(1. BWH - Boston (United States))*

Background: Amyloid beta (Aβ) accumulation is considered the primary initiating event in Alzheimer's disease (AD) pathogenesis. Our previous work has shown that nasal administration of Protollin - a proteosome-based adjuvant acting as a TLR2/TLR4 agonist - leads to reduction of insoluble, fibrillar and soluble Aβ accumulation in the brains of young and old AD mice (1-4). **Objectives:** We investigated the effects of nasal Protollin on activation and recruitment of peripheral monocytes in the brains of APP/PS1 mice as well as their ability to clear Aβ and improve cognitive behavior. We also investigated transcriptional and functional changes in blood CD14+ monocytes from early AD patients receiving nasal Protollin as part of a phase 1 single ascending dose trial at Brigham and Women's Hospital. **Methods:** APP/PS1, APP/PS1-CCR2RFP+/- and APP/PS1-CCR2RFP/RFP transgenic mice received nasal Protollin. Transcriptional profiling of FACS-sorted monocytes from cervical lymph nodes (CLN), spleen and bone marrow (BM) was performed by bulk RNA sequencing and differentially expressed (DE) genes were analyzed by Ingenuity Pathway Analysis (IPA). Quantification and visualization of brain infiltrating immune cells was performed by multi-color flow cytometry and confocal imaging. Quantification of brain Aβ was performed using ELISA and immunofluorescence staining. Assessment of the cognitive abilities of mice was examined using the Y-maze, Morris water maze and Barnes maze tests. Single-cell (sc)-RNAseq analysis of mouse brain cells from Protollin and PBS-treated mice was examined using the 10x Genomics Chromium technology. The phagocytic ability of blood CD14+ monocytes from AD patients was assessed by an in vitro phagocytosis assay and gene expression was analyzed by qPCR. **Results:** We examined the in vivo effect of nasal Protollin on peripheral monocytes from APP/PS1 mice and we found that certain monocytes from CLN, spleen and BM of Protollin treated-mice acquired tissue-specific signatures with DE genes involved in cell migration, complement activation, Aβ clearance and M2 polarization pathways. In the brains of treated mice, analysis of infiltrating immune cells showed a selective, increased recruitment of certain monocytes, located adjacent to Aβ aggregates. We also investigated which brain cortical cells undergo transcriptional changes after monocyte infiltration and identified unique subsets of glial and choroid plexus epithelial cells expressing high levels of genes affecting neuronal growth and function, in brains of Protollin-treated mice. We also addressed whether monocytes from treated mice are sufficient to promote Aβ clearance and improve the cognitive behavior of APP/PS1 mice following an adoptive transfer approach. APP/PS1 mice receiving Protollin-treated monocytes had improved performance in the Y-maze, Morris water maze and Barnes maze tests as well as lower levels of brain Aβ compared to control mice. In parallel, blood CD14+ monocytes from an AD patient receiving Protollin (days 1 and 14) had increased phagocytic ability against Aβ1-42 in a dose-dependent manner as well as differential expression of phagocytosis-related genes compared to monocytes from placebo treated subjects. Currently, we are investigating transcriptional profiles of blood CD14+ monocytes from these patients using bulk RNA and (sc)-RNAseq. **Conclusion:** Our data demonstrate that nasal Protollin induces: 1) tissue-specific transcriptional changes in peripheral monocytes which infiltrate in the brains of APP/PS1 mice promoting Aβ clearance and improving cognitive deficits; 2) generation of unique glial and choroid plexus epithelial cell subsets promoting neuronal growth and function in the cortex of Protollin-treated APP/PS1 mice and 3) an increase in the phagocytic ability of blood CD14+ monocytes against Aβ1-42 from nasal Protollin-treated AD patients plus alterations in the transcriptional profile of blood monocytes. A phase 1 single ascending dose trial of nasal Protollin in early AD is in progress. Given its safety profile and immune effects in both animal models and human AD subjects, Protollin represents a novel immunologic approach for the treatment of AD. 1. D. Frenkel, R. Maron, D. S. Burt, H. L. Weiner, Nasal vaccination with a proteosome-based adjuvant and glatiramer acetate clears beta-amyloid in a mouse model of Alzheimer disease. Journal of Clinical Investigation 115, 2423-2433 (2005). 2. D. Frenkel et al., A nasal proteosome adjuvant activates microglia and prevents amyloid deposition. Ann. Neurol. 63, 591-601 (2008). 3. D. Frenkel et al., Scara1 deficiency impairs clearance of soluble amyloid-beta by mononuclear phagocytes and accelerates Alzheimer's-like disease progression. Nat Commun 4, 2030 (2013). 4. V. Lifshitz et al., Immunotherapy of cerebrovascular amyloidosis in a transgenic mouse model. Neurobiol. Aging 33, 432 e431-432 e413 (2012). The authors declare there is no conflict of interest. Jiangsu Nhwa Pharmaceutical (NHWA) and I-Mab Biopharma (I-Mab) are responsible for the development, manufacturing and marketing of the immune modulator Protollin.

LP98. AN EFFICACIOUS THERAPY FOR ALZHEIMER DISEASE ALREADY EXISTS, AND IT IS COMMERCIALLY EXPLOITABLE. D. Dolcetta[1], S. Giovagnoli[2], D. Roberto[3] *(1. Istituto di Neuroscienze di Rosà - Vicenza (Italy), 2. Department of Pharmaceutical Sciences, University of Perugia, Italy - Perugia (Italy), 3. Dep of Biochemistry, Desio Hospital - Brianza (Italy))*

Background: Since 2010 (Caccamo et al, JCB 2010) oral administration of rapamycin has been shown to allow the prevention of cognitive impairment of many mouse models of dementia (Spilman P, et al, PLoS One. 2010; Lin AL, et al, J Cereb Blood Flow Metab. 2017; Tramutola A, et al, BMC. 2018). This seems to be mainly due to the pro-autophagic effect obtained with the inhibition of m-TOR: cognitive maintenance or recovery is accompanied by a significant reduction in Aβ intracellular storages. However, Caccamo, unlike many others, has shown not to prevent decay, but, by administering rapamycin at the onset of memory disturbances, to recover an already evident and measurable cognitive deficit. In other words, she demonstrated that it is possible to recover an already established initial dementia. Subsequent studies have shown that initial memory deficits could be due to an initial toxic effect of Aβ on synapses: adminisdtrating rapamycin in this phase, the stimulation of autophagy progressively enables neurons to degrade Aβ. It reduces its intraneuronal accumulations and recovers neuronal and synaptic health. Only later in the clinical progression, the Aβ accumulation would cause neuronal death with irreversible loss of the ability to store new memories. Rapamycin therapy is effective only if performed prior to the formation of Ab plaques. After this stage, the effect of functional recovery disappears (Majumder et al, PLoS One 2011). Two clinical trials are finally underway (NCT04200911 & NCT04629495) with oral rapamycin in AD: their aim is to replicate Caccamo's results on patients. In our opinion, these trials carry two main limitations: 1) the administered doses cannot be maximal, due to the serious metabolic and immunosuppressive side effects that rapamycin causes: this involves very long expected administration protocols (many months, years), while patients' decay is often rapid. 2) Rapamycin and many other mTOR inhibitors are no longer patent protected, so they have no commercial interest at all. We instead chose to give a high-dose mTOR inhibitor via intra-cerebroventricular (ICV) route of administration. It is good to remember that AD is a local, organ-specific disease: why to bear heavy systemic side effects (immunosuppressive and metabolic) if they can be avoided with a local and short administration? In some fortunately rare clinical conditions affecting sometimes children (e.g. cerebral lymphomas resistant to maximal doses of oral or parenteral administration of anticancer drugs) ICV administration has now become a routine and safe clinical practice, even if used for long periods (Peyrl et al, J Neurooncol 2014). In our strategy its invasiveness had the advantage of allowing both the administration of high local doses with limited systemic immunosuppression, and for a short period. We then administered ICV the most thermostable mTOR-Inhibitor we had (everolimus) for 12 days, in the Caccamo's model (3xTg-AD mouse), at the same age (6 months), when the animals had an already serious decay, although initial (in short, mice with MCI). Unfortunately everolimus (although more stable than rapamycin) was still very unstable at body temperature (BT). This means that over the 12 days the drug gradually declined and eventually disappeared. Despite the short administration, which in the first days was at high doses, we obtained a surprising recovery (cognitive and pathological), and even more lasting than expected (Cassano et al, Exp Neurol 2019). This last unexpected observation will be deepened in the future. However, the lack of a thermostable formulation made our strategy clinically inapplicable. It was absolutely necessary to develop a new formulation of mTOR-inhibitors resistant at BT, which would allow ICV administration of known and reproducible doses of mTOR-Inhibitors, lasting several days in the ICV administration devices. We then made and patented it (WO2021205297 (A1) - 2021-10-14). This patent, applicable to mTOR-Inhibitors, has been filed in the EU, US, China, Canada and India. Now, after a short in vivo preclinical validation, this new formulation will be ready to reach the bedside. **Objectives:** We aim to exploit the pro-autophagic activity of mTOR inhibitors and replicate, in 10 patients with initial AD, what we observed in 3xTg-AD mice (Cassano et al, Exp Neurol 2019). **Methods:** Everolimus was loaded in distear oylphosphatidylethanolamine-polyethyleneglycole 2000 (DSPE-PEG2000) micelles by the thin layer method. The compounds were dissolved in chloroform. The solvent was evaporated at r.t. under nitrogen stream and vacuum dried for 1 hour. Micelle formation was obtained by hydration of the thin layer with an Everolimus physiologic solution. **Results:** We have developed a micellar formulation stable at BT for over 15 days, and then decaying quite slowly (PCT: WO2021205297 (A1) — 2021-10-14). Moreover, the already known biocompatibility, its ease of production, storage, and preparation for use are also interesting features. **Conclusion:** Despite the need of a further in vivo preclinical validation of the formulation, it has been bridged the missing step towards the clinical translation of the local administration of mTOR inhibitors strategy in AD and other neurodegenerative proteinopathies.

PROOF OF CONCEPT/TRANSLATIONAL RESEARCH FOR ALZHEIMER DRUG DEVELOPMENT INTERVENTIONS

P191- A COMBINATION OF PET TRACERS SERVES AS A POTENTIAL TRIAL BIOMARKER FOR EQUILIBRATIVE NUCLEOSIDE TRANSPORTER 1 (ENT1) INHIBITION TREATMENT OF ALZHEIMER'S DISEASE. C.P. Chang[1,2], C.W. Wu[1,2], C.Y. Lin[1,2], K.C. Wu[1,3], H.H. Yeh[4], C.Y. Wu[5], C.C. Weng[6], L.W. Hsin[3], C.J. Lin[3], Y. Chern[1,2] *(1. Biomedical Translation Research Center, Academia Sinica - Taipei (Taiwan, Republic of China), 2. Institute of Biomedical Sciences, Academia Sinica - Taipei (Taiwan, Republic of China), 3. School of Pharmacy, National Taiwan University - Taipei (Taiwan, Republic of China), 4. Brain research center, National Yang Ming Chiao Tung University - Taipei (Taiwan, Republic of China), 5. Department of Biomedical Imaging and Radiological Sciences, National Yang Ming Chiao Tung University - Taipei (Taiwan, Republic of China), 6. Department of Medical Imaging and Radiological Sciences, Chang Gung University - Taoyuan (Taiwan, Republic of China))*

Background: Alzheimer's disease (AD), the major cause of dementia, is a substantial healthcare burden for aging societies. To date, the treatment of AD remains to be an unmet medical need. The major pathogenic hallmarks of AD include extracellular amyloid plaques and intracellular neurofibrillary tangles in the brain. However, additional variables (e.g., stress, diet, concurrent disease, and other drugs) may also contribute to the disease progression and/or affect the efficacy of the treatments. In recent years, imaging- and blood-based biomarkers have also been actively investigated to facilitate the developments of sensitive assessment for the early detection and progression of AD. Another major pathological feature of AD is energy dysfunction associated with mitochondrial

impairment and reduced ATP production. We have previously demonstrated that a novel inhibitor of equilibrative nucleoside transporter 1 (ENT1), (J4) can prevent and reverse AD pathology via modulating the adenosine homeostasis, which is tightly linked to the energy metabolism in the brain. Targeting the adenosine metabolism thus becomes a new strategy for the development of AD treatments. To this end, we aimed to develop suitable biomarker(s) for J4 and/or energy-related treatments for AD. **Objectives:** We set out to identify the proper biomarker(s) for J4, an orally active ENT1 inhibitor by non-invasive positron emission tomography (PET) scans in AD mouse models. **Methods:** Two distinct AD mouse models (APP/PS1 for amyloidosis and THY-Tau22 for tauopathy) with the onset of memory deficiency at the age of 6 months were employed. To examine the therapeutic effects, mice were treated with J4 (3 mg/kg/day) in drinking water containing 1% HPβCD at the late disease stage (10-12 months old) for one month. We monitored the therapeutic efficacy of J4 in vivo using PET images including mitochondria-, FDG-, amyloid-, and Tau-PET in this preclinical study. **Results:** Our results showed that one-month treatment with J4 rescued cognitive decline and impaired spatial memory in symptomatic APP/PS1 and THY-Tau22 mice. In addition, J4 treatment elevated the mitochondria- and FDG-PET signal in the brain of AD mice, indicating that J4 ameliorated the impairments of mitochondria and glucose metabolism. Moreover, reduction of Aβ and tau deposition by J4 administration could be observed not only by immunofluorescence staining but also by the amyloid- and Tau-PET imaging in APP/PS1 and THY-Tau22 mice, respectively. **Conclusion:** Data from the present study showed that oral administration of J4 after the onset of cognitive decline provided therapeutic effects against AD pathology. In addition, a combination of PET images (e.g., mitochondria-, FDG-, amyloid-, and Tau-PET) may serve as biomarkers for the assessment of for AD progression. **Conflict of interest statement:** Yijuang Chern holds patents on J4 for the treatment of neurodegenerative diseases.

P192- XANAMIA PHASE 1B TRIAL WITH XANAMEM® ACHIEVES PRIMARY ENDPOINTS: RESULTS AND STRATEGIC UPDATE. M. Woodward[1], P. Rolan[2], M. Roesner[2], J. Taylor[2], T. Miller[2], P. Maruff[3] *(1. Aged Care Research And Memory Clinic, Austin Health - Melbourne (Australia), 2. Actinogen Medical - Sydney (Australia), 3. Cogstate Ltd - Melbourne (Australia))*

Background: Xanamem® is a potent and selective inhibitor of 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1), which catalyzes the conversion of cortisone to cortisol. In the brain, 11β-HSD1 is highly expressed in regions such as the hippocampus, frontal cortex, and cerebellum. There is evidence from studies in animals and in humans linking elevated cortisol with cognitive dysfunction and neurotoxicity. Thus, reducing cortisol levels in the brain is considered an important therapeutic goal in the treatment of Alzheimer's Disease (AD) and other conditions where cognitive impairment and cortisol excess is a major component of the disease. Nonclinical and clinical studies to date indicate that Xanamem offers potential to be rapidly cognitive enhancing and disease modifying. **Objectives:** The results of the recently completed XanaMIA Part A Phase 1b trial, which aimed to understand the minimally effective dose of Xanamem for effects on cognition, will be presented. A strategic update on the development of Xanamem will also be presented. **Methods:** XanaMIA Part A was a double-blind, placebo-controlled, dose-ranging Phase 1b study to assess the efficacy, pharmacodynamics, and safety of Xanamem in healthy older volunteers. Participants were randomized to receive either 5 mg Xanamem (n=36), 10 mg Xanamem (n=34), or matching placebo (n=37) orally for 6 weeks. Primary objectives were safety of the 2 dose levels, pharmacodynamics of the adrenocorticotropic hormone response, and effects on cognition, using the Cogstate Cognitive Test Battery (CTB) with International Digit Symbol Substitution Test – Symbols (IDSST-S). The study was designed to measure effect sizes in cognition, rather than statistical significance. Effect sizes vs. placebo were estimated from modeled data as Z scores and raw data as Cohen's d statistics. The a priori criterion for effect detection was Cohen's $d \geq 0.3$ in one or more tests. **Results:** Xanamem was safe and well-tolerated over the 6-week treatment period in this cognitively normal population aged 50-80 years (mean age 64 years, mixed female and male population). There were no treatment-related serious adverse events, and other predominantly mild adverse events were generally equally distributed across the 3 groups (including placebo). Both 5 mg and 10 mg dose levels showed pharmacodynamic activity by raising mean ACTH by 2.03 to 2.35 times, respectively, principally within the normal laboratory range and to a similar extent as higher doses in prior studies. Clinically significant improvements were seen in the Cogstate CTB with both doses for the three domains making up an attention composite, including working memory. This included improvement in the visual attention domain with 5 mg at the end of treatment, achieving the a priori primary endpoint criterion of Cohen's $d > 0.3$ (Cohen's $d = 0.32$, $Z = 1.97$, $p < 0.05$). Improvements were not seen in those domains making up a memory composite or the IDSST-S. The cognitive findings were consistent with those seen with a 20 mg dose in a prior randomized trial and with the high brain activity seen at 5 mg and 10 mg doses in a Positron Emission Tomography (PET) study. **Conclusion:** The XanaMIA Part A trial met its primary objectives, demonstrating rapid improvements in cognition for attention tests, pharmacodynamic activity on ACTH and good tolerability. While the cognition data were somewhat variable, the pattern of response was consistent with results from the prior randomized trial. These results strongly support continuation of the Xanamem Phase 2 trial program using a dose range ≤ 10 mg. The XanaMIA Part B Phase 2 trial will assess the effect of Xanamem on cognition in participants with early AD.

P193- LEVERAGING UNTAPPED NATIONAL SYNERGIES TO ACCELERATE REPRESENTATION OF HISPANIC/LATINOS IN CLINICAL TRIALS ON DEMENTIA: THE PROGRESS OF THE NEW CONSORCIO BETWEEN THE NATIONAL ASSOCIATION OF HISPANIC NURSES AND THE ALZHEIMER'S ASSOCIATION. E. Portacolone[1], A. Perez[2], C.V. Hill[3], J.C. Rojas[1] *(1. University California San Francisco - San Francisco (United States), 2. Penn University - Philadelphia (United States), 3. Alzheimer's Association - Chicago (United States))*

Background: Most efforts to recruit Hispanic/Latinos into clinical trials on dementia have typically leveraged community engagement strategies via partnerships with local community-based organizations (CBOs). Local organizations - churches, community clinics, advocacy organizations – have helped increase recruitment of Hispanic/Latinos. However current approaches to community engagement are labor- and time-intensive and limited to specific geographic areas such as particular cities. Nevertheless, many trusted CBOs

have an infrastructure at both national and local levels, thus, a key missed opportunity is the inadequate leveraging of this infrastructure to facilitate recruitment. For example, the National Association of Hispanic Nurses (NAHN) has a national office, including 49 chapters and 1,834 members. The Alzheimer's Association (ALZ) has 77 chapters nationwide. As a result, our research will test the hypothesis that partnering with organizations with national reach and trusted by local Latino/Hispanic communities can provide the infrastructure needed to rapidly implement scalable recruitment strategies nationwide. Specifically, in the summer of 2021 we established a research recruitment Consorcio driven by Latino/Hispanic stakeholders involving NAHN and the ALZ; both organizations found to be trusted in focus groups that included 178 Latinos. First activities included establishing a Consorcio Advisory Group including leaders of NAHN and ALZ (n=8) advised by a Community Experts Group of Latinos/Hispanic community members (n=16). The first 9 months of the Consorcio were devoted to identifying synergies, establishing decision-making procedures, and developing a common message with the support of a senior Latina messaging designer. The next phase will include testing the efforts of the Consorcio in the Ahead A3-45 clinical trial, a large clinical trial partially funded by the NIA testing an anti-amyloid therapy for Alzheimer's disease prevention. Specifically, we will implement the Consorcio intervention in 4 sites of the clinical trial and we will compare recruitment metrics with 4 other comparable sites with usual activities. The intervention will include the presence of an outreach specialist supporting NAHN and ALZ to increase awareness among Latino/Hispanic communities of the importance of participating in clinical trials and the risks and benefits involved in participating in the Ahead clinical trial. The intervention involves: local presentations, radio shows, Facebook posts, flyers, and ads in the news, and a website. To assess the effectiveness of the intervention we will draw from mixed methods. Specifically, we will analyze: 1) recruitment metrics of sites receiving the intervention vs. those using usual recruitment activity in the Ahead A3-45 clinical trial, and; 2) experiences and perceptions of the recruitment process from semi-structured interviews with research team of the trial and Latino community members who choose to enroll, or not, in this trial. The results will help accelerate critical participation of Latinos in dementia research. Our approach can be replicated in other sites nationwide and adapted to accelerate recruitment of other racial/ethnic minorities and other underrepresented groups into clinical trials on dementia.

P195- ASTROCYTIC REGULATORY MECHANISM ON PM2.5-INDUCED NEURONAL CELL DEATH AND NEUROINFLAMMATION. S.H. Han[1], R.E. Kim[2], K.J. Kwon[2,3] *(1. Department Of Neurology, Konkuk Hospital Medical Center, 120-1 Neungdong-Ro, Gwangjin-Gu - Seoul (Korea, Republic of), 2. Department Of Neuroscience, School Of Medicine, Konkuk University - Seoul (Korea, Republic of), 3. Department of Neurology, Konkuk Hospital Medical center, 120-1 Neungdong-ro, Gwangjin-Gu - Seoul (Korea, Republic of))*

Background: Several evidences demonstrated that PM2.5 exposure is associated with increased risk of neurological disorders. including Alzheimer's disease (AD), Parkinson's disease (PD), and other forms of neurodegenerative diseases, but the underlying pathological mechanisms are not clear. Chlorophyll is a green pigment found in plants, which is packed with a range of powerful nutrients. This pigment is reported to prevent cancer, aging and neurological disorder such as AD based on the potent antioxidant properties. **Objective:** The aim of this study is to investigate whether chlorophyll can prevent PM2.5-induced neuronal cell death through the alteration of neurotoxic reactive astrocytes. **Methods:** In this regard, we examined 1) the mRNA expression of inflammatory mediators including iNOS, IL-1b, TNFa, TGFb and PAI-1, 2) nitric oxide (NO) and reactive oxygen species (ROS) production, and 3) phagocytotic function using pHrodo dyes in rat cultured astrocytes cells. We used a well-characterized Diesel particulate matter, PM2.5, from SIGMA-Aldrich. Results: PM2.5 increased NO and ROS production in C6 glioma cells and iNOS, IL-1b and TNFa mRNA expression. However, chlorophyll attenuated PM2.5-induced iNOS and reactive astrocytes markers expressions and prevented neuronal cell death in rat primary cortical neurons. Our results show that PM2.5 can induce neurotoxic reactive astrocytes leading to neurotoxicity, and that chlorophyll can prevent the neurotoxicity with reduction in astrocyte activation. **Conclusion:** These results demonstrate the potential beneficial effects of chlorophyll against air pollutant exposure (PM2.5)-associated neurodegenerative disease, such as AD. **Funding Source:** This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2019M3C7A1031455 and 2022R1A2C1005917) and by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (2017M3A9G2077568).

P196- IMPACT OF SEMAGLUTIDE IN AMYLOID POSITIVITY (ISAP): PROTOCOL FOR A RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL IN AMYLOID POSITIVE INDIVIDUALS. I. Koychev[1], A. Adler[1], P. Edison[2], B. Tom[3], J. Milton[1], J. Butchart[4], A. Hampshire[2], C. Marshall[5], E. Coulthard[6], H. Zetterberg[7], F. Cormack[8], C. Mummery[9], R. Holman[1] *(1. University of Oxford - Oxford (United Kingdom), 2. Imperial College London - London (United Kingdom), 3. University of Cambridge - Cambridge (United Kingdom), 4. Royal Devon University Healthcare NHS Foundation Trust - Exeter (United Kingdom), 5. Queen Mary University of London - London (United Kingdom), 6. University of Bristol - Bristol (United Kingdom), 7. University of Gothenburg - Gothenburg (United Kingdom), 8. Cambridge Cognition - Cambridge (United Kingdom), 9. University College London - London (United Kingdom))*

Background: Alzheimer's Disease (AD), characterised by synaptic dysfunction and neurodegeneration, is thought to be mediated by the accumulation of amyloid plaques and tau neurofibrillary tangles in the brain. The latter drives neurodegeneration modulated by neuroinflammation. Treatment approaches aimed directly at amyloid and tau have been largely disappointing. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may offer novel mechanisms to delay or even prevent neurotoxicity in individuals at-risk for developing AD. GLP-1 is an incretin hormone produced by intestinal enteroendocrine L-cells which enhances insulin release and reduces glucagon release-responses. Preclinical studies have shown that GLP-1 RA administration is associated with decreased AD protein and neuroinflammatory burden, improved blood-brain-barrier integrity, and improved memory function. Pooled data from three double-blind, randomised, GLP-1 RA placebo-controlled Cardiovascular Outcome studies in patients with type 2 diabetes mellitus (T2DM) of liraglutide and semaglutide have shown in post-hoc analyses that GLP-1 RA treatment reduced the risk of developing all-cause-dementia, an exploratory endpoint, compared with

placebo, over a 3.6-year follow-up period (hazard ratio 0.47, 95% CI 0.25–0.86). Additionally, the REWIND trial showed that another GLP-1 RA, dulaglutide, reduced cognitive impairment compared with placebo, in patients with T2DM. These data suggesting GLP-1 RAs may be beneficial in AD led us to investigate whether semaglutide could reduce the accumulation of cortical tau protein and neuroinflammation in individuals at risk of developing AD (defined as being amyloid positive in the brain by imaging). This mechanistic study will complement data from two semaglutide compared with placebo phase 3 trials (EVOKE and EVEOKE+) which investigate modification of Alzheimer's disease effects in patients diagnosed with dementia or mild cognitive Impairment. **Objectives:** Primary: To investigate the difference in effect of oral semaglutide versus placebo on tau accumulation in preclinical AD. Secondary: To assess the safety and effect of oral semaglutide versus placebo on measures of neurodegeneration, neuroinflammation and AD pathology in blood, cognition, quality of life, physical activity and circadian rhythm. **Methods:** The Impact of Semaglutide in Amyloid Positivity (ISAP) trial is an investigator-led randomised, double-blind, placebo-controlled, superiority study of oral semaglutide. It will randomise 88 individuals aged 55 years or above with no or mild cognitive impairment and amyloid positivity in the brain assessed through positron emission tomography (PET). T2DM Individuals will comprise up to 30% of the randomised sample. Participants with low affinity binding variant of the rs6971 allele of the Translocator Protein 18 kDa (TSPO) gene will be excluded, as this could affect interpretation of their TSPO PET scans. Following a screening visit and assessment for amyloid positivity, eligible participants attending their baseline visit will be randomised in an overall 1:1 ratio to semaglutide or placebo and booked for tau and TSPO PET scans prior to initiating study treatment. MRI data will be collected at the TSPO PET scan using a combined PET-MRI machine. Baseline physical activity and cognitive data will be collected using a wrist-worn actigraph and from CANTAB (in-clinic) and Cognitron cognitive battery (remotely) respectively. Oral semaglutide or placebo will be started at 3mg once-daily and be escalated at four-weekly increments, to 7mg and then 14mg. Participants will attend safety visits at weeks 4, 8, 26 and 39 to assess tolerability of medication and obtain blood samples to measure AD biomarkers. All cognitive assessments will be repeated at week 26. Last study visit will be at Week 52, when all baseline measurements will be repeated. **Results:** Recruitment is projected to take 15 months, commencing in Q2 2022. The primary analysis will be an intention-to-treat analysis of the mean annualized change in PET tau standardized uptake value ratio, comparing the semaglutide and placebo groups. Results are expected in 2024. **Discussion:** Mechanisms for the potential disease modifying action of GLP-1 RAs with regard to AD remain unclear. As therapies targeting AD core pathology have yet to achieve clinical efficacy, efforts to develop alternative treatment approaches have intensified. GLP-1 RAs appear to be a promising option with semaglutide being trialled in two phase 3 studies (EVOKE and EVOKE+) of people with early AD. This investigator-initiated trial will complement on-going research by offering insights into the potential pathophysiological mechanisms through which GLP-1 RA may offer a treatment option for Alzheimer's disease across the disease spectrum.

P197- THE NOVEL FKBP51-HSP90 INTERACTION INHIBITOR ATTENUATES HIGH-FAT-INDUCED COGNITIVE IMPAIRMENT. B. Winblad[1], L. Wang[1], J. Wojcieszak[1], R. Kumar[1], P. Pavlov[1] *(1. Karolinska Institutet - Stockholm (Sweden))*

Background: Obesity increases the risk of type 2 diabetes mellitus and Alzheimer disease. Heat shock protein 90 (Hsp90) co-chaperone FK506-binding protein 51 (FKBP51) is and important regulator of metabolic and cognitive dysfunction. FKBP51 knockout mice are resistant to diet-induced obesity, exhibit elevated glucose and insulin tolerance, and have less endogenous tau. FKBP51 overexpression preserves tau and impairs spatial reversal learning and memory. Our group has identified a new family of FKBP51 inhibitors that can disrupt FKBP51-Hsp90 interactions. A previous study has shown that our inhibitors can dose-dependently reduce lipid accumulation in adipocytes differentiated from primary human mesenchymal stem cells and stimulate neurite outgrowth in differentiated neuroblastoma SH-SY5Y cells. **Objective:** This study aims to investigate the potential roles of FKBP51-Hsp90 interaction inhibitors on metabolic and cognitive dysfunction in vivo. **Methods:** Pharmacokinetic study: Plasma and brain samples were ocollected and analyzed by liquid chromatography-mass spectrometry. High-fat diet (HFD) study: Male C57BL/6J mice were fed either chou diet or HFD for 4 weeks and then treated with vehicle or inhibitor E8 (20 mg/kg, Sc) and their respective diets for another 4 weeks. Behaviors, body composition measurements by EchoMRI, fasting glucose/insulin detections and glucose/insulin tolerance tests were performed during the last week. Hippocampus was collected for western blot, RNA sequencing and quantitative real-time PCR analysis. **Results:** After subcutaneous injection, E8 can be quickly absorbed into the blood and penetrate the blood-brain barrier. In HFD model, E8 can attenuate the impairment of locomotor activity and short-term memory. But it could neither reduce body weight gain, nor improve insulin sensitivity and glucose/insulin tolerance. In the hippocampus, E8 reduces the elevated p-tau (Ser214)/tau levels induced by HFD but does not show any effects on insulin signaling. It suggests that E8 reverses the behavioral impairments independently of metabolic regulation in vivo. The underlying mechanisms were further investigated by RNA sequencing and quantitative real-time PCR analysis. **Conclusion:** We showed that inhibiting FKBP51-Hsp90 interactions with small molecules provides novel therapeutic targets on cognitive dysfunction in obesity. **Disclosures:** The authors declare no conflict of interest. **Key words:** cognition; FK506-binding protein 51; inhibitor; high-fat diet; obesity.

P198- INTRACELLULAR AB ACCUMULATION IN HIPPOCAMPAL NEURONS LEADS TO ENDOSOMAL/LYSOSOMAL LEAKAGE. S. Schedin Weiss[1], Y. Gao[1], L.O. Tjernberg[1] *(1. Karolinska Institutet - Solna (Sweden))*

Background: Alzheimer disease (AD) is characterized by plaques loaded with accumulated amyloid β-peptide (Aβ) and neurofibrillary tangles composed of tau. Still, the molecular details behind AD are largely unknown. However, intracellular levels of Aβ containing 42 amino acids (Aβ42) has been shown to correlate with AD neuropathology (1). Using super-resolution microscopy, we have identified different pools of Aβ42 in hippocampal neurons (2, 3). We hypothesize that some intracellular pools of Aβ42 are physiologically relevant whereas other pools are toxic. As an important source of intracellular Aβ, extracellular Aβ can be internalized and accumulated in endocytic vesicles. Previously, we treated

hippocampal neurons with Aβ42 monomers and detected Aβ42 oligomerization in the late endosomes/lysosomes by using Förster resonance energy transfer (FRET) live cell imaging (4). However, it is still unknown how intracellular aggregated Aβ causes toxicity to the cells. In this study, we investigate whether low extracellular Aβ42 levels can be endocytosed and accumulated in late endosomes/lysosomes to a high concentration and cause endosomal/lysosomal membrane permeabilization in primary neurons. **Objectives:** Our aim is to – at a cellular level – further understand the uptake and subcellular polymerization of Aβ and explore the mechanisms of cytotoxicity of intracellular Aβ in neurons. Our overarching goal is to specifically use intracellular Aβ as a target for pharmaceutical intervention of AD. **Methods:** Hippocampal neurons were isolated from E16-17 C57BL/6 mice embryo brains and cultured for 21 days in vitro. Neurons were treated with monomeric Aβ42 with or without fluorescent labels at different concentrations for different time periods in an acute or chronic model. Intracellular accumulation of Aβ42, taken up from the medium, was monitored over time by lattice light sheet microscopy. Aβ42 concentrations in neuronal vesicles were determined by live cell imaging by using confocal microscopy. Immunocytochemistry and Airyscan microscopy were used to detect the loss of endosomal/lysosomal integrity in neurons. Results: Monitoring uptake of Aβ42 during 24 h showed that the majority of Aβ42 was transported to the soma region where it accumulated in late endosomes/lysosomes. Treatment with 1 nM Aβ42 for 20 days caused three orders of magnitude higher concentrations in late endosomes/lysosomes as compared to the cell culture medium. Accumulated Aβ42 induced endosomal/lysosomal leakage when Aβ42 concentration reached micromolar levels in those vehicles. **Conclusion:** These data suggest that extracellular Aβ42 is endocytosed, gradually accumulates in late endosomes/lysosomes where it polymerizes and damages vesicle integrity. The damaged vesicle may release Aβ42 and other lysosomal components into the cytosol and thus generate toxicity. We therefore consider the late endosomal/lysosomal pool of aggregated Aβ42 as a target for AD treatment. **References:** 1. Hashimoto, M., et al., Analysis of microdissected human neurons by a sensitive ELISA reveals a correlation between elevated intracellular concentrations of Abeta42 and Alzheimer's disease neuropathology. Acta Neuropathol, 2010. 119(5): p. 543-54. 2. Yu, Y., et al., Neuronal Abeta42 is enriched in small vesicles at the presynaptic side of synapses. Life Sci Alliance, 2018. 1(3): p. e201800028. 3. Yu, Y., et al., A Super-Resolved View of the Alzheimer's Disease-Related Amyloidogenic Pathway in Hippocampal Neurons. J Alzheimers Dis, 2021. 83(2): p. 833-852. 4. Gao, Y., et al., Live Cell FRET Imaging Reveals Amyloid beta-Peptide Oligomerization in Hippocampal Neurons. Int J Mol Sci, 2021. 22(9).

P199- ALZ-201, A MONOCLONAL ANTIBODY THERAPY FOR SPECIFIC NEUTRALISATION OF TOXIC AMYLOID-B IN ALZHEIMER'S DISEASE. A. Sandberg[1] *(1. Alzinova AB - Gothenburg (Sweden))*

Background: The conspicuous plaques in Alzheimer' disease (AD) brains are mainly deposits of insoluble fibrillar assemblies of the peptide amyloid-β (Aβ). These assemblies are effectively targeted by monoclonal antibodies (mAb) exhibiting selectivity for aggregated forms of Aβ (aducanumab, lecanemab, and gantenerumab) or specificity for pyroglutamated forms (donanemab). Plaques are, however, not nearly as toxic as some soluble oligomeric forms of Aβ and clinical benefits of plaque reduction are very modest. The oligomer-targeting vaccine candidate ALZ-101 (NCT05328115) was therefore used to develop a murine mAb, ALZ-201, as a potential therapy capable of specifically targeting toxic oligomeric Aβ thereby avoiding binding to plaques and non-aggregated Aβ altogether. We here show data on how this antibody was developed, characterised, validated, and humanised in preparation for clinical trials on AD patients. **Objective:** Develop mAb ALZ-201 as a potential AD therapy. **Methods:** Monoclonal murine ALZ-201 was purified from a mouse hybridoma isolated after vaccination with ALZ-101. Conformational specificity for oligomeric Aβ was confirmed with ELISA against various non-aggregated and aggregated forms of the peptide and therapeutic potential investigated using human AD brain extracts and automated high content microscopy analysis of primary mouse neuron cultures in vitro, as previously reported. A chimeric antibody, chALZ-201, with backbones for human IgG1 HC constant region and human kappa LC constant region was then designed and transiently expressed in CHO cells. Binding specificity of chALZ-201 was verified and benchmarked with biosimilars of aducanumab, lecanemab, and gantenerumab using ELISA against different aggregated forms of Aβ. Further humanisation of ALZ-201 resulted in several promising candidates. Biacore analysis was used to determine the binding affinity towards the stabilised oligomer antigen in vaccine ALZ-101. **Results:** ALZ-201 was isolated as a murine IgG3 and found to be truly specific, not just selective, for structured oligomers as opposed to control antibody 6E10 which was reactive towards all forms of the peptide. Murine ALZ-201 and chALZ-201 did exhibit a small yet statistically significant difference in EC50 for the oligomeric form by 29 ng/mL (95% CI, 22.3267 to 35.9192, $p<0.0001$), but did not bind any other conformations of the peptide, indicating that the antigen-binding properties are retained in the chimeric human IgG1 variant of murine ALZ-201. In contrast, aducanumab, lecanemab, and gantenerumab had similar affinities for all different conformations of the peptide. Biacore measurements demonstrated that chALZ-201 had high affinity for ALZ-101 oligomers, with a binding off-rate (koff) of 4.67x10-4 s-1 and a binding constant of 1.56 nM (humanised variants had similar values). Furthermore, our studies indicate that very few species of Aβ are ALZ-201 reactive. In actively aggregating Aβ42, for instance, these "ALZ-201 reactive oligomers" reach a maximum of 39.4 ± 5.6 ng/mL after 20 min after which they slowly disappear over the course of 40 min as the rate of fibrillisation increases. This corresponds to only 0.047% of all Aβ42. As previously shown, similar results were found when immunodepleting AD brain extracts with ALZ-201, which did not significantly impact the measured amounts of Aβ. Remarkably, immuno-depletion of AD brain extracts with ALZ-201 efficiently neutralised the Aβ-mediated neurotoxicity in these extracts to a similar extent as 4G8 (removes all Aβ) despite the low abundance of "ALZ-201 reactive oligomers". **Conclusion:** Our studies confirm the binding specificity of the unique mAb ALZ-201, which recognises a conformational epitope on the stabilised oligomer antigen in vaccine ALZ-101 and a subset of synthetic Aβ42 oligomers. We previously demonstrated that ALZ-201 specifically binds to a toxic species in post-mortem AD brain extracts to cause a positive physiological and protective impact on the integrity and morphology of mouse neurons. Biosimilars of aducanumab, lecanemab, and gantenerumab, on the other hand, were here shown to exhibit no conformational preference for Aβ, indicating that their weak binding to non-aggregated forms stem almost exclusively from fast binding off-rates. Consequently, these antibodies will target plaques with high

functional affinity because plaques are likely to be the largest multivalent Aβ structures in the brain. Given the modest clinical effect plaque reduction has on pathology, next generation anti-Aβ therapies ought to instead focus on antibodies that are truly specific for toxic forms of soluble oligomeric Aβ. To this end, a lead humanised candidate of ALZ-201 is now in preparation for clinical trials on AD patients.

P200- REDUCING TOXIC AMYLOID-B OLIGOMERS IN AD THROUGH PRECISE TARGETING OF THE MOLECULAR MECHANISMS OF OLIGOMER FORMATION WITH SMALL MOLECULE INHIBITORS. J. Habchi[1], K. Jenkins[1], S. Pandey[1], R. Staats[1], S. Sarwat[1], B. Mannini[1], X. Yang[1], L. Rajah[1], S. Cohen[1], S. Brewerton[1], A. Plowright[1] *(1. Wren Therapeutics Limited - Cambridge (United Kingdom))*

Background: Oligomeric forms of Aβ, as opposed to monomers or large fibrils and plaques, have been shown to have wide-ranging neurotoxicity and underlie the onset and progression of Alzheimer's Disease. These Aβ oligomers bind directly to membranes and receptors, disrupt key cellular and neuronal functional pathways, and cause neuronal death, but have so far proved challenging to target with conventional drug discovery approaches. Using the framework of "chemical kinetics", we have mapped the key molecular mechanisms that generate oligomers: primary nucleation (where several monomers come together to form an oligomer) and secondary nucleation (where oligomer formation is catalysed and accelerated by the presence of Aβ fibrils / plaque). Here, we present initial data with small molecule oligomer inhibitors, discovered using our proprietary drug discovery platform, that precisely target these molecular mechanisms of oligomer generation. This unique approach is designed to inhibit both intracellular and extracellular sources of toxic Aβ oligomer species, to address neurodegeneration across progressive stages of AD, and is distinct from conventional antibody approaches that focus on clearing fibrils and plaques in the extracellular space. **Objectives:** To develop potent and precise inhibitors of oligomer generation from both primary and secondary nucleation of Aβ, examine their effect on Aβ aggregation, and investigate their therapeutic efficacy in a range of pre-clinical models. **Methods:** In vitro screening and validation assays were used to screen and characterise compounds that inhibit Aβ aggregation, starting from recombinant human Aβ(1-42) in monomeric form. These assays were carried out in a range of conditions (different buffers, protein mutants and isoforms, with and without the presence of pre-formed fibrils, as well as using human patient brain tissue to seed in vitro aggregation). Following compound optimisation including potency, oral pharmacokinetics and brain penetration, the effect of these compounds was explored in several translational models: transgenic, human-Aβ-expressing C. elegans; iPSC-derived glutamatergic neurons and a transgenic mouse model (APPSL). In the transgenic C. elegans model, animals expressing human Aβ in their muscular cells were grown on media dosed with WTX in the nM to mM range. Measurements of aggregated Aβ in the head region of the C. elegans and phenotypic motility (the "bends per minute" seen in the animals) were taken and compared to those for untreated and wild type animals. In the iPSC-derived glutamatergic neuron model, differentiated cells were incubated with Aβ monomer, pre-formed fibrils, or a combination of monomer and pre-formed fibrils (where oligomer generation is expected to be high), in the absence or presence of WTX. The cells were then stained and their levels of synapsin and aggregated Aβ (pFTAA) quantified. In the APPSL mouse model, 6-month old male transgenic mice were treated orally for 8 weeks with a daily dose of 100mg/kg WTX. Whole brain hemispheres from treated and control mice were homogenised and the oligomer levels in each mouse were quantified using a proprietary ELISA-based assay. **Results:** Wren has discovered and developed extremely potent small-molecule inhibitors of Aβ oligomer generation from primary and secondary nucleation, with up to 96% inhibition of each mechanism in vitro. This inhibition is conserved across different conditions and forms of Aβ, and is highly specific to Aβ vs other aggregating proteins. In C. elegans, aggregate levels in treated animals were reduced to those seen in wild-type animals, with a 75% recovery in motility phenotype vs untreated animals. In iPS cells, WTX treatment significantly reduced Aβ aggregate levels in cells insulted with a combination of monomer and fibrils, along with a significant recovery in synapsin levels, indicative of a recovery in synaptic function. In the APPSL mouse model, daily treatment with 100mg/kg WTX was well tolerated and provided consistent and robust pharmacokinetics throughout the study duration. In this model WTX reduced oligomer levels by 69% vs vehicle mice. **Conclusion:** We have demonstrated a robust platform for the discovery and development of precise and potent small molecule inhibitors of Aβ oligomer generation. We have shown that these small molecules are potent inhibitors of oligomer generation across a range of different in vitro conditions and assays, and that they can be optimised to enable the reduction of both oligomer and aggregate levels, with a clear link to functional benefit, across multiple translational models.

P201- THE BROMODOMAIN AND EXTRATERMINAL DOMAIN PROTEIN INHIBITOR APABETALONE INHIBITS THE NEUROTOXIC KYNURENINE PATHWAY IN MONOCYTES AND BRAIN ENDOTHELIAL CELLS. S. Wasiak[1], L. Fu[1], S.D. Stotz[1], D. Gilham[1], L.M. Tsujikawa[1], C.D. Sarsons[1], J. Kroon[2], E.S.G. Stroes[2], N.C.W. Wong[1], M. Sweeney[3], J. Johansson[3], E. Kulikowski[1] *(1. Resverlogix - Calgary (Canada), 2. University of Amsterdam - Amsterdam (Netherlands), 3. Resverlogix - San Francisco (United States))*

Background: The kynurenine pathway (KP) is activated in several neurodegenerative and neuropsychiatric disorders including Alzheimer's disease. During chronic inflammation, multiple cell types express KP enzymes, with monocytes being the most active producers of KP metabolites. Proinflammatory cytokines induce the expression of two KP rate-limiting enzymes: indoleamine 2,3-dioxygenase 1 (IDO1) responsible for the conversion of tryptophan to kynurenine, and kynurenine 3-monooxygenase (KMO) that facilitates conversion of kynurenine into 3-hydroxykynurenine. These three metabolites can cross the blood brain barrier where they are processed by brain cells into neuroactive molecules, the ratio of which can either be neuroprotective or neurotoxic. The kynurenine-to-tryptophane ratio, an indicator of IDO1 peripheral activity, is elevated in patients with neurodegenerative disease. Reducing the activity of the KP pathway in the circulation favorably alters the ratio of KP metabolites in blood and the brain and has been shown to improve disease outcomes in mouse models of Huntington's disease and Alzheimer's disease. **Objectives:** Epigenetic regulators bromodomain and extraterminal domain (BET) proteins control responses to cytokines in monocytes, endothelial cells and hepatocytes. Here, we tested the ability of a clinical-stage BET inhibitor (BETi) apabetalone (also called RVX-208) to counter the cytokine-dependent production of KP enzymes and kynurenine in cultured cells. **Methods:** The monocyte-like THP-1 cell line, the hCMEC/D3 human brain

endothelial cell line, primary human monocytes, hepatocytes and whole blood were treated with apabetalone and/or TNFα+IFNγ or IFNγ alone (10 ng/mL, 4 to 48h). mRNA levels measured by real time PCR or gene expression microarrays. Intracellular proteins were measured by flow cytometry. KP metabolite levels in cell culture media were measured using ELISAs (ImmuSmol) or UHPLC-MS/MS (biocrates). **Results:** In primary human monocytes, IDO1 mRNA was undetectable in basal conditions. Stimulation with IFNγ strongly induced its transcription (>300-fold), which was largely countered by cotreatment with apabetalone (-62% at 5 μM, -95% at 25μM, 4h). In TNFα+IFNγ stimulated THP-1 cells, apabetalone reduced IDO1 mRNA (-62% at 5 μM, -90% at 25 μM, 4h) and protein (-36% at 5 μM, -80% at 25μM, 24h) levels and countered the accumulation of kynurenine in the cell supernatant (-30% at 5μM and -70% at 25μM, 24h). In IFNγ-treated primary monocytes, apabetalone (25μM, 24h) completely reversed tryptophan consumption and reduced kynurenine accumulation in the cell culture supernatant (-85%), resulting in lower kynurenine-to-tryptophane ratio (-87%). These results show that BETi reduced IDO1 activity in monocytes. In human brain microvascular endothelial cells, which form the blood brain barrier, apabetalone downregulated the cytokine induced IDO1 mRNA (-44% at 5μM, -85% at 25μM, 24h) and protein (-58% at 5μM, -85% at 25μM, 24h) levels, as well as kynurenine production (-50% at 25μM, 24h). Finally, apabetalone reduced non-stimulated KMO levels in ex vivo treated human whole blood (-60% at 5 μM, -74% at 20μM, 24h, n=3 donors), primary monocytes (-80% at 25μM, 4h, n=10 donors) and hepatocytes (-70% at 30μM, 48h, n=2 donors). Cytokine-mediated KMO induction in THP-1 cells was also countered by apabetalone at both gene (-41% at 5μM, -90% at 25μM, 24h) and protein (-60% at 25μM, 24h) level. **Conclusions:** Apabetalone decreases proinflammatory activation of the KP in vitro in multiple cell types. These findings provide mechanistic insights to the beneficial effects of apabetalone on cognition that were recently demonstrated in a phase 3 clinical trial (BETonMACE): diabetic coronary artery disease patients with baseline MoCA scores ≤21 experienced a significant 1.8-unit improvement in MoCA scores following apabetalone treatment versus placebo (p=0.02) over 24 months. **Conflicts of Interest:** SW, LF, SCS, DG, LMT, CDS, NCWW, MS, JOJ, EK are employed by Resverlogix and hold Resverlogix stock. JK and ESGS have no competing interests.

P202- A NOVEL THERAPEUTIC APPROACH TO TREAT ALZHEIMER'S DISEASE: THE BRAIN-SPECIFIC SIGNAL PEPTIDE PEPTIDASE-LIKE 2B (SPPL2B). S. Tambaro[1], R. Maccioni[2], C. Travisan[3], S. Zerial[3], A. Wagener[4], Y. Andrade-Talavera[1], F. Picciau[2], C. Grassi[5], G. Chen[6], A. Fisahn[1], B. Schröder[7], P. Nilsson[1] *(1. Department of Neurobiology, Care Sciences and Society (NVS) Division of Neurogeriatrics, Karolinska Institutet - Solna (Sweden), 2. Department of Biomedical Sciences, Neuroscience and Clinical Pharmacology, University of Cagliari - Cagliari (Italy), 3. Department of life science, University of Trieste - Trieste (Italy), 4. Interdisciplinary center for Neuroscience, Heidelberg University - Heidelberg (Germany), 5. Department of Pharmacy and Biotechnology, University of Bologna - Bologna (Italy), 6. Department of Biosciences and Nutrition, Karolinska Institutet - Huddinge (Sweden), 7. Institute of Physiological Chemistry, Technische Universität Dresden - Dresden (Germany))*

Background: Alzheimer's disease (AD) is a multifactorial disorder in which the abnormal brain production of amyloid β-peptide (Aβ) plays a crucial role in the disease onset. Identifying new proteins and pathways involved in the Aβ cascade is essential to providing novel, effective therapeutic targets. The intramembrane enzyme signal peptide peptidase-like 2 b (SPPL2b), which belongs to the same protein family as Presenilin, is a new potential target since it is involved in the proteolysis of the AD-related proteins: TNF-alpha and BRI2, implicated in the inflammatory response and Aβ production, respectively. The SPPL2b substrate BRI2 is considered an anti-Alzheimer gene that negatively regulates Aβ production by binding to APP and inhibiting its secretase processing by secretases. SPPL2b modulates the APP-BRI2 interaction by cleaving BRI2 in its transmembrane region. Most importantly, it has been reported that SPPL2b levels drastically increase in the early stage of AD. SPPL2b localizes in the cell membrane and is expressed predominantly in the hippocampus and cortex, suggesting a role of SPPL2b in learning and memory. **Objectives:** Based on these findings, we believe that the SPPL2b enzymatic activity may play an essential role during AD pathogenesis. In the present study, we investigated the expression levels and the pathogenic role of SPPL2b in AD. **Methods:** For this purpose, the pathophysiological role of SPPL2b in Aβ metabolism was evaluated in vitro by using human cell lines stably expressing APP (SH-SY5Y and HEK293), mouse primary neuronal cell cultures, and acute mouse brain slices. Furthermore, we evaluated the SPPL2b expression in the new state-of-the-art App knock-in AppNL-G-F AD mouse and human postmortem AD brain tissues. **Results:** The overexpression of human APP in SH-SY5Y cells leads to an increase in the levels of SPPL2b. A biphasic expression of SPPL2b was observed in SH-SY5Y cells upon treatment with Aβ42. In brain slices-maintained ex vivo, Aβ42 exposure induced a strong up-regulation of SPPL2b. SPPL2b expression was also evaluated in the AD mouse model AppNL-G-F. Interestingly, an increased level of SPPL2b was observed in the cortex in the early stage of the AD-associated Aβ pathology of 3 months old AppNL-G-F mice. However, at 22 months of age, when Aβ pathology is severe and accompanied by neuroinflammation in this mouse model, SPPL2b protein expression was significantly lowered compared to control mice. Similarly, a significantly decrease in SPPL2b was also observed in human AD samples at Braak stages V and VI. Furthermore, immunofluorescence staining showed that SPPL2b is expressed in neurons and glia deposited in the Aβ plaques in AppNL-G-F but not in astrocytes. Further, the overexpression of SPPL2b in human cells led to an increase in APP cleavage by cleaving Bri2, whereas neurons derived from SPPL2b knock-out mice exhibited lower APP cleavage, reinforcing the involvement of SPPL2b in the APP processing. **Conclusions:** These results strongly support the involvement of SPPL2b in AD pathology. Most importantly, Aβ42 directly effects SPPL2b expression, inducing a vicious cycle where Aβ42, SPPL2b, BRI2, and APP are involved. Our findings show that SPPL2b is increased in the early stages of AD, indicating its involvement in the pathogenesis of the disease by promoting both the inflammatory (TNF-alpha cleavage) and amyloidogenic pathway (BRI2 cleavage). In a global scenario characterized by the urgent need to identify novel strategies to prevent and counteract AD progression, this study points out the importance of SPPL2b. This data provides an incentive to explore more the SPPL2b role in AD and eventually develop selective inhibitor compounds targeting SPPL2b. In this context, the systemic administration of SPPL2b inhibitors/modulators in mouse AD models will be necessary to evaluate the potential of targetting SPPL2b for treating AD. Furthermore, the brain-specific expression and the few substrates related to SPPL2b may lower the risk of side effects in pharmacological treatment.

P203- INCREASED CSF-DECORIN PREDICTS BRAIN PATHOLOGICAL CHANGES DRIVEN BY ALZHEIMER'S AB AMYLOIDOSIS. R. Jiang[1], U. Smailovic[1], H. Haytural[1], B. Tijms[2], H. Li[1], G. Shevchenko[3], J. Gobom[4], S. Nyström[5], P. Hammarström[5], S. Syvänen[3], H. Zetterberg[4], B. Winblad[1], J. Bergquist[3], P. Jelle Visser[2], P. Nilsson[1] *(1. Karolinska Institutet - Stockholm (Sweden), 2. Amsterdam UMC - Amsterdam (Netherlands), 3. Uppsala University - Uppsala (Sweden), 4. Sahlgrenska Academy at the University of Gothenburg - Gothenburg (Sweden), 5. Linköping University - Linköping (Sweden))*

Background: Alzheimer's disease (AD) is caused by amyloid-beta (Aβ) amyloidosis which starts 20 years before onset of clinical symptoms. Biomarkers reflecting early events in the development of the pathology are needed for early diagnosis, prevention, and treatments. **Objectives:** AD brains are characterized by extracellular Aβ deposition and autophagy dysregulation. Here we aimed at deepening the understanding of how these brain pathologies translate to the CSF to identify potential biomarkers by combining preclinical and clinical data. **Methods:** We used two state-of-the-art App knock-in AD mouse models, AppNL-F and AppNL-G-F, exhibiting AD-like Aβ pathology to analyze how the brain pathologies translate to CSF proteomes by label-free mass spectrometry (MS). The mouse CSF proteomes were further stratified to a previous CSF proteome dataset obtained from patients across the AD spectrum in the large human European Medical Information Framework for Alzheimer's Disease Multimodal Biomarker Discovery (EMIF-AD MBD) cohort (n = 310). Correlations of newly identified CSF proteins were performed with CSF-Aβ, CSF-tau and CSF-t-tau, followed by receiver operating characteristic (ROC) analysis. **Results:** The label-free MS identified several extracellular matrix (ECM) proteins as significantly altered in App knock-in mice. The mouse CSF proteomes were compared with previously reported human CSF MS results acquired from patients across the AD spectrum. Intriguingly, the ECM protein decorin was similarly and significantly increased in both AppNL-F and AppNL-G-F mice, strikingly already at three months of age in the AppNL-F mice and preclinical AD subjects having abnormal CSF-Aβ42 but normal cognition. Notably, in this group of subjects, CSF-decorin levels positively correlated with CSF-Aβ42 levels indicating that the change in CSF-decorin is associated with early Aβ amyloidosis. In addition, CSF-decorin highly correlated with both CSF-t-Tau and CSF-p-Tau. Importantly, ROC analysis revealed that CSF-decorin can predict a specific AD subtype having innate immune activation and potential choroid plexus dysfunction in the brain. Consistently, in AppNL-F mice, increased CSF-decorin correlated with both Aβ plaque load and with decorin levels in choroid plexus. In addition, a low concentration of human Aβ42 induces decorin secretion from mouse primary neurons. Interestingly, we finally identify decorin to activate neuronal autophagy through enhancing lysosomal function. Altogether, the increased CSF-decorin levels occurring at an early stage of Aβ amyloidosis in the brain may reflect pathological changes in choroid plexus, present in a subtype of AD subjects. **Conclusions:** Decorin has the potential to be a CSF biomarker for early Aβ amyloidosis and may reflect changes in choroid plexus.

P204- ANTIBODIES GENERATED AGAINST AN AB-DERIVED OLIGOMER: EFFORTS TOWARD A NOVEL ALZHEIMER'S DISEASE IMMUNOTHERAPY. C.M. Parrocha[1], A. Kreutzer[2], J. Pascual[3], C. Stringer[3], J. Nguyen[1], A. Ith[1], E. Head[3], J. Nowick[1,2] *(1. Department of Pharmaceutical Sciences, University of California Irvine - Irvine (United States), 2. Department of Chemistry, University of California Irvine - Irvine (United States), 3. Department of Pathology and Laboratory Medicine, University of California Irvine - Irvine (United States))*

Background: β-Amyloid (Aβ) peptide vaccines are promising therapeutics against Alzheimer's disease (AD) which rely on the generation of antibodies after an endogenously administered Aβ antigen. These newly generated anti-Aβ antibodies neutralize endogenous targets of interest that are similar to the antigen. Thus far, there are no Aβ peptide vaccine candidates that have received FDA approval. Current Aβ peptide vaccine clinical candidates rely on non-conformationally defined fragments of full-length Aβ as the antigen. However, these fragments could self-aggregate into heterogeneous higher orders of assembly which may lead to inconsistent treatments and potentially harmful side effects. Due to their cytotoxic properties, Aβ oligomers are strong contributors to the progression and pathogenesis of AD, as they induce cognitive impairment, and inhibit long-term potentiation. For this reason, Aβ oligomers have become an attractive target for novel peptide vaccines and immunotherapies. However, Aβ oligomers are an elusive species; there is no structural definition for Aβ oligomers due to their diversity in size, heterogeneity, and propensity to self-assemble into fibrils. To study the properties of Aβ oligomers, we generated synthetic peptides derived from fragments of full-length Aβ that share properties similar to Aβ oligomers. These Aβ-derived oligomers are well characterized by X-ray crystallography, SDS-PAGE, size exclusion chromatography, cytotoxicity assays on SHSY-5Y human neuroblastoma, and incorporate native residues that stabilize their higher order assemblies. In our extensive collection of Aβ-derived oligomer peptide models, the 4AT-L Aβ-derived oligomer contains the most native residues of full-length. Our aim was to generate a novel peptide vaccine with 4AT-L that ameliorates AD pathology in the 5xFAD transgenic mouse model and could serve as a potential new therapeutic against AD. **Objectives:** We hypothesized that 4AT-L would stimulate the production of antibodies that target endogenous Aβ and may lead to amelioration of cognitive impairment and pathology in the 5xFAD AD transgenic mouse model. As a proof of concept, rabbit polyclonal antibodies were generated against 4AT-L creating the 4AT-L polyclonal antibody (pAbs) to determine if these can recognize Aβ ex vivo by immunofluorescent microscopy. Using the same immunization strategy we generated rabbit polyclonal antibodies to immunize C57BL/ mice and obtained antibody titers similar to those reported in literature for other preclinical AD vaccine studies. Once the immunizations strategy was confirmed via antibody titers in C57BL/6, 5xFAD mice were immunized with previously reported immunization regime. After the mice had grown into their pathology (ca. 8 months) memory, cognition, and reduction in Aβ loads, will be accessed by a battery of behavior assays as well as histology and biochemical assays. **Methods:** 4AT-L is the product of three macrocyclic peptide monomers that are covalently stabilized into a trimer with disulfide bonds. To assess if 4AT-L can stimulate the production of 4AT-L pAbs rabbits were immunized with 4AT-L by Pacific Immunology (Ramona, CA). 4AT-L pAbs were then sent to the

Nowick Group for affinity purification. Immunofluorescence microscopy on brain samples from 5xFAD mice and people with AD was used to determine if antibodies generated from 4AT-L recognize Aβ ex vivo. Optimal vaccine regime and formulation was determined in C57BL/6. 5xFAD received interperitoneally injections of 100 mg of 4AT-L conjugated to Keyhole limpet Hemocyanin and formulated with AddaVax™ once every 28 days for a total of five immunizations. **Results:** Preliminary studies indicate that rabbits immunized with 4AT-L sustained a strong immune response (reported antibody titer >1:5000). Through immunofluorescent staining, the 4AT-L pAb, recognizes Aβ pathology brain samples of 5xFAD mice as well as people with AD and people with Down Syndrome and AD. We have additionally observed that 4AT-L recognizes cerebral amyloid angiopathy, which is the accumulation of Aβ within blood vessel walls, a pathology highly prevalent in people with Down Syndrome and AD. C57BL/6 immunized with 4AT-L demonstrated a sustained immune response with antibody titers as high as ca. 1:1000. 5xFAD mice immunized using the same vaccine approach with antibody titers as high as approaching 1:2000. Behavior assays assessing for improvement in memory and cognition will begin in June 2022. **Conclusion:** Based on preliminary data, the 4AT-L pAb recognizes pathology in brain samples of 5xFAD mice, as well as people with AD and people with Down Syndrome and AD. Further characterization of the polyclonal antibody will be performed to determine the potential of the polyclonal antibody as a tool to better understand the molecular basis of AD, and isolate monoclonal antibodies for potential passive immunotherapy studies. Both C57BL/6 and 5xFAD mice generated literature precedent antibody titers against 4AT-L which may infer an amelioration of AD pathology in 5xFAD mice. This body of work is not yet published, and final results will be presented at CTAD.

LP99- REDUCTION OF PLASMA P-TAU181 FROM A PHASE1A RANDOMIZED TRIAL OF NNI-362 IN A HEALTHY AGED POPULATION CONSISTENT WITH AMELIORATION OF TAU HYPERPHOSPHORYLATION IN HUMAN DIFFERENTIATED NEURON CULTURES.

R. Turner[1], M. Mielke[2], J. Kelleher-Andersson[3] *(1. Georgetown Univ. - Washington, Dc (United States), 2. Mayo Clinic - Rochester, Mn (United States), 3. Neuronascent, Inc. - Clarksville, Md (United States))*

Background: NNI-362 is a novel small molecule discovered by phenotypic screening of compounds that have neuroprotective capacity and promote new neurons from endogenous human neural progenitor cells. A placebo-controlled, double-blind Phase 1a trial* examined the safety and tolerability of NNI-362, as well as a pharmacodynamic outcome - the level of plasma p-tau181 - a blood-based biomarker of Alzheimer's disease (AD) pathology. **Objectives:** The aim of this study was to determine the safety, tolerability, and biomarker effects of NNI-362 in a first-in-human study of healthy aged subjects, and to relate biomarker outcomes to preclinical efficacy models. **Methods:** Oral NNI-362 and matching placebo were formulated by Parexel (Glendale, CA). Healthy, cognitively-unimpaired individuals (age 50-72) were randomized at a 1:3 ratio to placebo:drug, with the sponsor, PI, and subjects all blinded. Duplicate frozen plasma samples were analyzed (blinded to treatment) at Mayo Clinical Laboratories (MN) from the placebo group and the two highest SAD/MAD dose arms of 120 and 240 mg NNI-362. Levels of plasma p-tau181 were determined using a SimoaTM HD Analyzer (Lot Number 503008) with an Advantage V2 Kit. Calibration curves of p-tau181 ranged between 0.00-74.6 pg/mL. Plasma biomarkers were examined at pre-treatment (baseline), day 15 (12 h post final dose), and day 16 (24 h post final dose). Statistical analyses examined a change from the pre-treatment level of p-tau181. **Results:** NNI-362 treatment was safe and well-tolerated in cognitively unimpaired older individuals. NNI-362, at the two highest multi-doses, 120 mg and 240 mg, significantly reduced plasma p-tau181 in participants compared to pre-treatment levels ($p<0.0012$ and $p<0.0009$, respectively), while on average no change occurred in subjects receiving placebo (Chengxie Xiong, Ph.D. - Lily Consultants). These results are consistent with a reduction of tau phosphorylation by NNI-362 in vitro using differentiated human neural progenitor cells (Lonza, MD) stimulated by Ab25-35 exposure. **Conclusion:** These findings suggest that even in a small number of healthy older subjects, oral NNI-362 appeared safe and well-tolerated, and reduced plasma p-tau181 levels - a blood-based biomarker of AD pathology. Further study, including a Phase 2 trial of NNI-362, are warranted in individuals with neurodegenerative tauopathies including AD. *NIA grant-R01AG056561 (PI-JKA). **COI statement:** RST is a consultant for Neuronascent, Inc. and Re:Cognition Health; Georgetown University receives research funding from Lilly, Biogen, Eisai, Novartis, Roche, Genentech, Janssen, and Alector.

LP100- INHIBITION OF EQUILIBRATIVE NUCLEOSIDE TRANSPORTER 1 (ENT1) INHIBITOR AS A NOVEL THERAPEUTIC TREATMENT TO RESCUE ALZHEIMER'S DISEASE PATHOLOGY AND COGNITIVE IMPAIRMENT.

C.W. Wu[1,2], C.P. Chang[1,2], C.Y. Lin[1,2], K.C. Wu[2,3], H.H. Yeh[4], C.J. Lin[2,3], Y. Chern[1,5] *(1. Institute of Biomedical Sciences, Academia Sinica - Taipei (Taiwan, Republic of China), 2. Biomedical Translation Research Center, Academia Sinica - Taipei (Taiwan, Republic of China), 3. School of Pharmacy, National Taiwan University - Taipei (Taiwan, Republic of China), 4. Brain research center, National Yang Ming Chiao Tung University - Taipei (Taiwan, Republic of China), 5. Biomedical Translation Research Center - Taipei (Taiwan, Republic of China))*

Background: Alzheimer's disease (AD) is the most prominent neurodegenerative disease in aging societies and generates a significant burden on the healthcare system. Abnormal protein aggregations (e.g., extracellular amyloid plaque and intracellular neurofibrillary tangles) are commonly observed in the brain of AD patients, and cause AD pathogenesis including neuritic dystrophy, synapse loss, microgliosis, astrogliosis, and cognitive impairment. To date, most of the potential AD treatments in clinical trials were designed based on the amyloid hypothesis and tauopathy. Effective drugs that ameliorate the symptoms or progression of AD remain to be found. Therefore, new drug targets for AD are urgently needed. The adenosinergic system is dysregulated in AD. Adenosine is an important homeostatic building block of many important metabolic pathways, which modulates physiological functions in the central nervous system. Equilibrative nucleoside transporter 1 (ENT1) is a bidirectional transporter that transports adenosine in a concentration-dependent manner. Our previous study demonstrated that inhibition of ENT1 before the disease onset prevents cognitive dysfunction of two AD mouse models, which further support that targeting the adenosine homeostasis may become a new strategy for the development of AD treatment. **Objectives:** We set out to characterize an orally active small compound (designed J4) that inhibits ENT1 in the blockage of the amyloid-

and tau-related pathologies of AD. **Methods:** Two distinct AD mouse models (APP/PS1 for amyloidosis and THY-Tau22 for tauopathy) with the onset of memory deficiency at the age of 6 months were employed. To examine the therapeutic effects, mice were treated with J4 (3 mg/kg/day) in drinking water containing 1% HPβCD at the late disease stage (10-12 months old) for one month. The cognitive functions of AD mice and their littermate controls were examined using the Morris water maze task. The mitochondrial mass, neuroinflammation, and abnormal protein aggregations (e.g., Aβ and tau deposition) were evaluated by biochemical and pathological analyses (including positron emission tomography, immunofluorescence staining, and western blot analysis). **Results:** Our results showed J4 exhibited superior profiles in pharmacokinetics (including decent oral bioavailability, good exposure to the brain, and low potential for drug-drug interaction) and safety (no obvious toxicity during high-dose repeated treatments and a low binding affinity to hERG). One-month treatments with J4 in symptomatic APP/PS1 and THY-Tau22 mice rescued cognitive decline and impaired spatial memory. In addition, J4 treatment ameliorated the mitochondria loss and energy deprivation accompanied by the reduction of Aβ and tau deposition, oxidative stress, and neuroinflammation of APP/PS1 and THY-Tau22 mice at the symptomatic phase. **Conclusion:** Data from the present study showed that modulation of adenosine homeostasis by J4 provided beneficial effects in two AD models at the symptomatic stage, supporting that targeting adenosine metabolism is a novel and effective therapeutic strategy for AD.

LP101- CHARACTERIZING THE MOLECULAR DETERMINANTS OF THE LECANEMAB PARATOPE BINDING SITE BY COMBINING IN SILICO PREDICTION AND IN VITRO FAB ANALYSIS ON AD BRAIN EXTRACTS. J.P. Bellier[1], L. Liu[1], D.J. Selkoe[1] *(1. Brigham and Women's - Boston (United States))*

Background: In Alzheimer's disease (AD), soluble amyloid beta-protein (Aβ) aggregates have been reported to be more neurotoxic than insoluble aggregates. Some Aβ antibodies have been developed to include these diffusible forms of Aβ. Lecanemab (BAN2401) is a humanized IgG1 version of the mouse monoclonal antibody mAb158 directed against early, more soluble Aβ aggregates. Lecanemab is said to bind preferentially to Aβ assemblies referred to as protofibrils or soluble oligomers and to a lesser extent to insoluble amyloid fibrils. Phase II clinical trials showed that lecanemab was well tolerated and, at the highest doses, lowered brain amyloid levels and appeared to slow cognitive decline. In the absence of structural details regarding lecanemab binding to its antigens, the basis of the molecular interaction that defines its binding site (paratope) remains to be determined. **Objectives:** Here, we investigated the molecular determinants of the binding site between lecanemab and Aβ using complementary in silico prediction and in vitro biochemical analysis. **Methods:** MOE software (Molecular Operating Environment, Chemical Computing Group) was used to predict the 3-dimensional structure from the publicly available amino acid sequence of lecanemab. The resultant in silico structural model was then analyzed to identify amino acid residues potentially involved in binding (i.e., hydrophobic and electrostatic patches in CDR regions of lecanemab). Next, E.coli were used to express and purify Fab fragments of both lecanemab and certain engineered variants in which predicted key amino acid residues potentially involved in binding Aβ were mutated to alanines. Brain extracts from AD patients were then used in indirect ELISAs to examine the criticality of the mutated lecanemab residues for degree of binding to Aβ. We further used Fabs of lecanemab or its engineered mutants coupled with well-established Aβ antibodies in sandwich ELISAs to assay both Aβ-rich AD brain extracts and recombinant Aβ peptide fragments of varying lengths. **Results:** Lecanemab antibody structure was predicted from its primary sequence. Analysis of this structural model identified amino acid residues that may be involved in the binding site (paratope). Lecanemab Fab as well as Fab mutants of the predicted paratope residues were produced and analyzed for their binding abilities to native AD brain extracts, thereby confirming the role of the predicted residues in the binding site. Further, indirect ELISAs using lecanemab Fab as capture antibody and established Aβ antibodies as detectors indicated that lecanemab competed with the binding sites of several known antibodies that recognize the middle region of Aβ. Immunoassays using corresponding synthetic Aβ fragments confirmed these observations. **Conclusion:** In silico prediction of the structural details of Lecanemab provided a useful starting point that could be tested and confirmed in vitro via the expression of WT and mutant Fabs of lecanemab. The molecular determinants of the Aβ binding site as well as the antigen regions where they bind were characterized. **Disclosures:** D.J.S. is a director and consultant of Prothena Biosciences. All other authors declare no competing interests.

LP102- EFFECTS OF THE P38A KINASE INHIBITOR NEFLAMAPIMOD ON THE BASAL FOREBRAIN, ASSESSED BY STRUCTURAL MRI, IN ALZHEIMER'S DISEASE (AD). J. Alam[1] , C.P. Lin[2], S. Noteboom[2], N. Prins[3], F. Barkhof[4], L. Jonkman[2], M. Schoonheim[2] *(1. EIP Pharma - Boston (United States), 2. Amsterdam UMC, Location VUmc, Vrije Universiteit Amsterdam, Department of Anatomy and Neurosciences, Amsterdam Neuroscience - Amsterdam (Netherlands), 3. Brain Research Center - Amsterdam (Netherlands), 4. Amsterdam UMC, Location VUmc, Vrije Universiteit Amsterdam, Department of Radiology and Nuclear Medicine, Amsterdam Neuroscience - Amsterdam (Netherlands))*

Background: The rationale for developing acetylcholinesterase inhibitors (AChEIs) in the 1990s was the "cholinergic hypothesis", a pathogenic model based on Alzheimer's disease (AD) being associated with loss of neurons producing acetylcholine in the basal forebrain (i.e., "basal forebrain cholinergic neurons", BFCNs). However, with not treating the underlying degenerative process, merely compensating for it, the efficacy of AChEIs was found to be transient and cholinergic-directed therapeutics research fell into the background. With the development of MRI techniques to evaluate the degenerative process in the basal forebrain, there is an increasing recognition that basal forebrain degeneration is an early event in AD and is a driver of neurodegeneration in the cortex, including in the temporal lobe, (Nat Commun. 2016, 7:132492016;; Brain. 2020, 43:993-1009; Brain, 2022;145:2869–2881). Further, with this understanding there has been a resurgence of interest in therapeutics research directed at BFCN degeneration (JPAD, 2019, 6:2-15; Neuropsychopharmacol, 2022;47,405-406). The p38α kinase inhibitor neflamapimod acts on molecular mechanisms underlying cholinergic degeneration, including reducing the expression of BACE1, and restores the number & morphology of BFCNs in Ts2 (Down Syndrome) transgenic mice (Nature Commun, 2022;13:5308). In addition, in a phase 2a clinical-study in dementia with Lewy bodies (DLB), neflamapimod improved BFCN-associated clinical outcomes (Nature Commun, 2022;13:5308). Recently, MRI-

based volumetry (as a measure of atrophy) of the Nucleus basalis of Meynert (NbM) within the basal forebrain has been correlated to clinical outcomes in AD, PD and DLB (Neurology, 2022 98:e947-e957; Brain 2021 36:611-621;Brain Comm, 2022, 4:fcac013; Brain, 2022;145:2869–2881). Herein, we retrospectively assessed MRI scans obtained in a previously reported phase 2a pilot clinical study of neflamapimod in AD (ACTN, 2018;5:464–473), utilizing analytic techniques to assess NbM volume that were not available at the time of the study was originally conducted. **Objectives:** To evaluate the effect of neflamapimod on basal forebrain cholinergic degeneration in AD, as assessed by structural MRI. **Methods:** Blinded longitudinal study of neflamapimod (40mg BID or 125 mg BID) in patients with amyloid-PET documented early AD (MMSE 20-28). Structural (3D T1 Isotropic) MRI was obtained before, and after 12 weeks treatment (n=13 participants). NbM volume was assessed using a probabilistic atlas and followed over time. **Results:** At baseline, mean NbM volume was 353(SD=33) mm3. At the end-of-treatment, NbM volume increased significantly from baseline (p=0.025), with a mean 3.2%(SEM=0.7) increase for the study overall, and 8 of 13 participants showing >3% increase in NbM volume. As previously reported, global brain volume was decreased by a mean 0.6%(SEM=0.2). Analyses by dose group will be conducted after ongoing additional analyses are complete. **Conclusion:** Neflamapimod treatment is associated with increasing NbM volume, suggesting p38α kinase inhibition positively impacts the cholinergic degenerative process in AD. The results are in line with the recently reported preclinical mechanistic results in Ts2 mice, in which neflamapimod increased the number and size of cholinergic neurons in the basal forebrain (Nature Commun, 2022;13:5308). In addition, an effect of neflamapimod on NbM volume is consistent with results of a separate clinical trial of neflamapimod in AD (Alz Res Ther, 2021;27:106) in which compared to placebo, neflamapimod significantly lowered CSF levels of total tau, a reported CSF biomarker of NbM atrophy Neurology 2020 Jan 7;94:e30-e41). Further evaluation of this potential effect of neflamapimod on the basal forebrain in placebo-controlled clinical trials in AD and other diseases in which the basal forebrain is impacted (e.g., dementia with Lewy bodies) is warranted. Correlation between clinical outcomes with effects on NbM volume in such studies would inform on the relative contribution of cholinergic deficits (vs. atrophy in other brain regions) to the clinical expression of disease in such disorders.

LP103- CONNECTIVITY-BASED AMYLOID-TAU INTERACTION MODEL: STAGES, STRATIFICATION, AND PREDICTION OF CLINICAL BENEFIT. W.J. Lee[1], J. Brown[2], H.R. Kim[3], R. La Joie[2], H. Cho[4], C.H. Lyoo[4], G. Rabinovici[2], W. Seeley[2], J.K. Seong[1,5] *(1. Neuroxt, Inc. - Seoul (Korea, Republic of), 2. University of California, San Francisco - San Francisco (United States), 3. Seoul Women's University - Seoul (Korea, Republic of), 4. Gangnam Severance Hospital - Seoul (Korea, Republic of), 5. Korea University - Seoul (Korea, Republic of))*

Background: With the emergence of disease-modifying treatments for Alzheimer's disease (AD), there is a critical need to understand the molecular anatomical progression of AD. This information will inform disease pathogenesis and may enhance patient selection for specific therapies. Researchers have proposed that brain amyloid-beta (Ab) deposition triggers tau neurofibrillary tangles to spread beyond the medial temporal lobe and into the heteromodal neocortex, but to date it has remained unclear how this might occur when Ab and tau deposition begin within spatially disparate brain regions. **Objectives:** We aimed to discover: (1) How brain connectivity enables Ab to interact with tau before tau spreads beyond the medial temporal lobe, (2) When and why AD tauopathy propagates throughout the neocortex, (3) Why Ab-lowering drugs have shown only modest clinical benefit, even when Ab-lowering is achieved, and (4) An image-based algorithm to identify who is most likely to benefit from Ab-lowering drugs across the full AD clinical spectrum from cognitively normal (CN) to mild cognitive impairment (MCI) to dementia. **Methods:** We included participants from two non-overlapping datasets. The discovery dataset was derived from the ADNI cohort and included patients with AD-type dementia (n=11), MCI (n=94), and CN (n=187). The validation dataset included participants clinically diagnosed at Gangnam Severance Hospital, South Korea: 96 CN, 84 MCI, and 71 AD-type dementia patients. All participants underwent structural MRI, amyloid-PET, and tau-PET. Our stratification algorithm proposes two important transitions during the natural history of AD, based on: (1) remote connectivity-based Ab-tau interaction in the lateral entorhinal cortex (EC) and (2) local Ab-tau interaction within the inferior temporal gyrus (ITG). To examine each subject's status with respect to these transitions, we computed two quantitative scores. The first was computed using the EC remote Ab influence metric, derived as a weighted sum of regions' connectivity to the EC multiplied by the Ab SUVR in those regions, and the EC tau W-score. Similarly, for the second score, the ITG local amyloid SUVR was multiplied by the ITG tau W-score. We then applied a threshold to each score to classify each subject into one of four groups: (1) least affected by the tau pathology ("tau-negative") in EC, (2) subthreshold EC remote Ab-tau interaction despite the presence of EC tau ("latent tau"), (3) suprathreshold EC remote Ab-tau interaction but subthreshold ITG local Ab-tau interaction ("spreading tau"), and (4) suprathreshold ITG local Ab-tau interaction ("propagating tau"). **Results:** Plotting EC remote and ITG local Ab-tau interaction metrics using cross-sectional and longitudinal data demonstrated a fundamental arc of disease progression reflecting sequential occurrence of two interactions across and within individuals. The EC remote Ab influence metric was determined through the EC-connected regions including fusiform gyrus, parahippocampal gyrus, precuneus, posterior cingulate gyrus, parietooccipital sulcus, and hippocampus. Quadratic regression models based on the mean (left/right) cross-sectional values fit both datasets well (ADNI: R2 = 0.664, Korean: R2 = 0.652). Using this stratification method, subjects assigned to the "spreading tau" group fall just before or shortly after the tau deposition exhibits a nonlinear acceleration[SB1] , whereas those designated "propagating tau" are nearly all found within and beyond the acceleration phase. As expected, longitudinal subjects within the "spreading" and, in particular, "propagating tau" groups showed dramatically greater whole-brain annualized tau accumulation. For both datasets, most CN subjects were assigned to the "tau-negative" or "latent tau" group, but 17.1% of Ab+ subjects were stratified to one of the more advanced groups. In symptomatic subjects, patients with MCI were more often classified as having "spreading tau" (14.4%; 9.2% in AD) whereas the AD group showed the most "propagating tau" group (78.5%; 46.7% in MCI). Interestingly, 11% of Ab+ pre-symptomatic subjects were classified as having "spreading tau", which implies that amyloid-lowering drug could be suitable for participants without cognitive deficits. **Conclusion:** Expert recommendations for the use of the amyloid-lowering drug, aducanumab, emphasize the importance of positive AD

biomarkers and a clinical label of MCI or mild dementia. The model-driven subject stratification method presented here overlays inconsistently on the biomarker-anchored clinical groupings conventionally used in AD clinical trials. These findings raise the possibility that molecular-anatomical disease staging may outperform clinical labels in predicting clinical responsiveness to amyloid-lowering drugs and other AD therapies. **References:** 1. Wha Jin Lee, Jesse A. Brown, Hye Ryun Kim, Renaud La Joie, Hanna Cho, Chul Hyoung Lyoo, Gil D. Rabinovici, Joon-Kyung Seong, and William W. Seeley. "Regional Aβ-tau interactions promote onset and acceleration of Alzheimer's disease tau spreading", Neuron, 2022.

LP104- MRI-BASED REAL-WORLD IMPLEMENTATION FOR PREDICTING REGIONAL TAU PATHOLOGY AND ITS APPLICATION TO AMYLOID-LOWERING TREATMENT INDICATION. W.J. Lee[1], H. Cho[2], C.H. Lyoo[2], J.K. Seong[1,3] *(1. Neuroxt, Inc. - Seoul (Korea, Republic of), 2. Gangnam Severance Hospital - Seoul (Korea, Republic of), 3. Korea University - Seoul (Korea, Republic of))*

Background: Most of the recent clinical trials of Ab-lowering therapies have shown only modest clinical benefit even when Ab-lowering is achieved. The Phase 3 studies of Aducanumab in early Alzheimer's Disease (AD) (EMERGE and ENGAGE) and the Phase 2b study of Lecanemab in early AD (BAN2401-G000-201) show inconsistent clinical benefits of Ab-lowering treatments, while the Phase 2 proof-of-concept trial of Donanemab (TRAILBLAZER-ALZ (NCT03367403)) proves to slow progression of early symptomatic AD. The major change in TRAILBLAZER-ALZ study is the tau-based inclusion criteria in the patient selection scheme. Moreover, the exploratory sub-group analysis shows that the lower third sub-group among selected patients shows the best clinical benefits, which strongly implies that early tau may represent an important treatment window for Ab-lowering drugs. **Objectives:** Although tau burden provides an important indication for Ab-lowering treatments, like all PET techniques, its clinical utility in medical practices has been limited due to cost, availability, and safety regarding radiation exposure. We therefore aim to develop (1) an MRI-based algorithm to predict regional tau accumulation level, (2) a brain connectivity-based prediction method for future cortical atrophy, and (3) a fully automated system for calculating global tau eligibility scores to identify patients who are most likely to benefit from Ab-lowering drugs in AD clinical trials. **Methods:** We included participants from Gangnam Severance Hospital, South Korea: 74 cognitively normal (CN), 61 amnestic mild cognitive impairments (MCI) due to AD, and 38 AD-type dementia patients. All participants underwent two structural MRI scans separated by a 2-year interval, as well as18F-florbetaben PET for Ab and 18F-flortaucipir PET for tau. Standardized uptake value ratio (SUVR) values were obtained from PET images using Desikan-Killiany cortical atlas with the cerebellar crus as the reference region. These values were then converted to W-scores based on amyloid-negative controls as reference. Cortical atrophy patterns were extracted for each participant using FreeSurfer. Correlation-based brain connectivity was then constructed between follow-up structural MRI and baseline tau PET. Specifically, a connectivity weight between brain regions i and j was defined as a partial correlation between baseline tau burden at brain region i and follow-up cortical atrophy at brain region j. This connectivity encodes a region-wise association of baseline tau burden and future cortical atrophy, which well represents an ATN downstream hypothesis. We then employed this connectivity for predicting baseline tau pathology using follow-up structural MRI. Finally, follow-up tau pathology was again predicted using the baseline tau information by employing a simple linear regression model. The efficacy of the proposed model was validated using a 5-fold cross validation scheme. The predicted tau burden was further applied to Ab-lowering treatment indication: A global tau eligibility score was calculated similarly to the previous PERSI-based methods, and the performance was compared with the results from the TRAILBLAZER-ALZ study. Using the same stratification method with the previous study, subjects were assigned to either "low tau" group, "intermediate tau (inclusion window)" group, and "high tau" group. **Results:** The predicted follow-up tau burden exhibited significant regional correlations (r=0.69 [0.61-0.74], median [IQR]) with the original tau burden, which appears to be particularly higher in AD-related regions like the entorhinal cortex (r=0.78, left/right mean), inferior parietal lobe (r=0.77), precuneus (r=0.76), and inferior temporal gyrus (r=0.76). Within each amyloid-positive subject, the predicted and original values were also highly correlated (r=0.71 [0.56, 0.81], median [IQR]). Global tau scores, computed from the predicted tau burden, fitted scores from original burden well (R2=0.51), showing high performance in treatment window determination as compared to the TRAILBLAZER-ALZ study. The "low tau" group was classified from the other two groups with an area under the receiver operating characteristic curve (AUC) of 0.83, and the "high tau" group was classified from the other two groups with an AUC of 0.92. **Conclusion:** We believe AD is indeed an Ab-triggered tauopathy and that Ab-lowering trials have shown modest and inconsistent benefits due to problems concerning patient selection. Considering the identification of optimal patients who are most likely to benefit from Ab-lowering drugs, neurofibrillary tangles (NFTs) formed by tau are highly predictive indicators for treatment window. In this study, we proposed a brain connectivity-based algorithm for predicting tau pathology using only structural MRI and validated its performance. The predicted tau pathology was further utilized to find an optimal treatment window based on clinical trial results of the previous TRAILBLAZER-ALZ study. These findings raise the possibility that MRI-based real-world implementation may outperform clinical labels in predicting clinical responsiveness to Ab-lowering therapies.

LP105- HYDROXYLATED DOCOSAHEXAENOIC ACID AS AN ALTERNATIVE THERAPEUTIC APPROACH FOR ALZHEIMER DISEASE IN TERMS OF EFFICACY AND SAFETY. V. Llado[1,2], S. Parets[2,3], J. Cabot[2,3], M. Miralles[2,3], M.A. Fiol-Deroque[2], L. Trujillo-Estrada[4], P. Fernández-García[3,5] X. Busquets[2], A. Gutiérrez[4], P.V. Escribá[3,6], M. Torres[6] *(1. Laminar Pharma Inc - Acton, Ma (United States), 2. Laboratory of Molecular Cell Biomedicine, University of the Balearic Islands - Palma (Spain), 3. R&D Department, Laminar Pharmaceuticals - Palma (Spain), 4. Department of Cell Biology, University of Malaga, CIBERNED, IBIMA - Málaga (Spain), 5. Laboratory of Molecular Cell Biomedicine, University of the Balearic Islands - Palma (Spain) - Palma (Spain) - Palma (Spain), 6. Laboratory of Molecular Cell Biomedicine, University of the Balearic Islands - Palma (Spain) - Palma (Spain))*

During the last 20 years, a multitude of molecules has been designed to halt or delay AD-related neurodegeneration. So far, only aducanumab (passive immunotherapy against β-amyloid peptide -Aβ-) has recently obtained accelerated approval by the FDA (Food & Drug Administration) amidst great controversy due to poor clinical evidence regarding

efficacy in preventing AD-related cognitive decline. Most of these molecules were designed based on the «amyloid cascade hypothesis» that assumes Aβ aggregation as a primary cause of this pathology. Unfortunately, AD is a complex disorder whose pathophysiological basis is not well understood yet. In the present work, we introduce 2-hydroxy-docosahexaenoic acid (DHA-H) as a promising alternative therapeutic approach for AD. Oral administration of DHA-H to a transgenic model of AD (5xFAD mice) prevents cognitive, synaptic, and neuronal degeneration in both, animals treated early (from 2 to 6 months of age) or late (from 8 to 12 months). These effects are accompanied by increased neuronal cell proliferation in the hippocampus, suggesting that part of its neuroprotective effect might be mediated by restoration of neurogenesis up to healthy levels. On the other hand, tau protein phosphorylation and Aβ accumulation revealed a significant brain reduction in animals under treatment with DHA-H, as compared to untreated control. All these results together indicate that DHA-H administration must preserve neuronal density. The latter has also been demonstrated in cell models, where DHA-H prevents neuronal death induced by oligomeric Aβ or NMDA (N-Methyl-D-Aspartate)/Ca-mediated excitotoxicity. In terms of safety, 90-day repeated-dose regulatory toxicology in rats revealed that NOAEL for DHA-H must be established at ca. 280 mg/kg/day which is equivalent to ca. 45 mg/kg/day in humans (conversion based on Body Surface Area). At this dose, minimum acanthosis/hyperkeratosis (without erosions or edema) were observed, and these alterations were considered non-adverse events. No increased incidence or severity of these gastric lesions were observed during the recovery period. On the other hand, the minimal effective dose in mice was defined at 20 mg/kg/day which is equivalent to 1.6 mg/kg/day in humans. This data points towards a large therapeutic window and a good safety profile for DHA-H for clinical trials in humans. COI: Victoria Llado holds an employment agreement and is a directors board member of Laminar Pharma Inc, subsidiary of Laminar Pharmaceuticals which is the company responsible for DHA-H development.

LP105A- RIGOR AND REPLICATION IN ALZHEIMER'S THERAPEUTIC DEVELOPMENT: A CASE STUDY.

A. Heilbut[1], J. Brodkin[2], P. Markey[3], E. Milioris[4] *(1. Logphase Research - New York (United States), 2. Behavioral Instruments - New Jersey (United States), 3. Berlin (Germany), 4. London (United Kingdom))*

Background: Alzheimer's disease (AD) presents an enormous unmet medical need which incentivizes research and development of novel therapeutic candidates. Early identification of drug candidates and clinical trials destined to fail would allow more effective public and private research investment, and ensure that patients volunteer to participate in clinical trials that are likely to offer benefit, are scientifically informative, and are ethical. **Objectives:** We sought to develop a framework to predict likelihood of success for clinical trials of novel therapeutics based on comprehensive, rigorous, independent evaluation of preclinical and clinical data, together with targeted experimental replication of key biological claims. As a case study, we assessed Simufilam, a novel drug candidate currently in Phase 3 trials for AD (NCT04994483, NCT05026177). **Methods:** We systematically reviewed the Simufilam literature, including post-publication reviews, to assess the quality of biological (1,2,3) and clinical (4,5) evidence for this drug candidate. We then employed isothermal titration calorimetry (ITC) to experimentally measure for the first time the binding enthalpy of both Simufilam and Naloxone to their reported molecular target, the VAKGL peptide, in an attempt to recapitulate their discovery and validate the biochemical basis for Simufilam as a drug targeting Filamin-A (1,2). While there are no other known interactions between any small molecules and VAKGL or other pentapeptides available as positive controls, we also measured binding between Carbonic Anhydrase II (CAII) and its well-characterized inhibitor Acetazolamide to validate our technical capability to measure high-affinity interactions by ITC. **Results:** A thorough evaluation of both pre-clinical and early-stage clinical data identified concerns with statistical analysis and presentation, biochemistry methods, biophysics, thermodynamics, pharmacokinetics, and inconsistencies with expected human physiology across many of the experiments and trials critical to motivating Simufilam development. Using ITC, we failed to observe any evidence for binding of either Naloxone or Simufilam to their previously reported high affinity target, the VAKGL pentapeptide, and no difference between ITC thermograms when Simufilam was mixed with VAKGL versus a negative control VAAGL peptide. In contrast, the enthalpy of Acetazolamide binding with CAII was easily and reproducibly detected. **Conclusion:** Careful independent re-evaluation of preclinical and early clinical literature about a novel therapeutic identified potential scientific problems of relevance to later clinical programs. Focused biophysical experiments provided further validation of these concerns. The apparent absence of binding of Simufilam to its purported molecular target has important implications for the interpretation of published preclinical studies, potential efficacy, and future clinical development of this molecule. This case study demonstrates the value of independent, rigorous scientific evaluation and replication to maximize success rate and integrity for all trials of experimental Alzheimer's therapeutics. **References:**

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DIGITAL HEALTH / E-TRIALS

P205- ASSESSMENT OF DEEP LEARNING ALGORITHM OF DIAGNOSING ALZHEIMER'S DISEASE WITH KOREAN ELDERLY. J.B. Bae[1], J.W. Han[1], K.W. Kim[1,2,3,4], J.S. Kim[2,5] *(1. Department Of Neuropsychiatry, Seoul National University Bundang Hospital, Gyeonggido, Korea - Seongnam (Korea, Republic of), 2. Institute of Human Behavioral Medicine, Seoul National University Medical Research Center, Seoul, Korea - Seoul (Korea, Republic of), 3. Department of Psychiatry, Seoul National University, College of Medicine, Seoul, South Korea - Seoul (Korea, Republic of), 4. Department of Brain and Cognitive Science, Seoul National University College of Natural Sciences, Seoul, South Korea - Seoul (Korea, Republic of), 5. Department of Neuropsychiatry, Seoul National University Bundang Hospital, Gyeonggido, Korea - Seongnam (Korea, Republic of))*

Background & Objectives: Although the number of the people with Alzheimer's disease (AD) is increased year by year, most hospitals, specialized in diagnosis and management of AD, are centralized in urban areas despite that AD is more prevalent in rural areas. Despite the fact that the MRI unit is constantly increasing worldwide, lack of specialists on AD may miss the timing of diagnosis of AD that must be quick and accurate. Our previously developed deep learning algorithm is capable of diagnosing AD using brain MRI. In this study, we investigated whether the VUNO Med-DeepBrain AD (DBAD) using brain MRI can be employed as a decision support service on the diagnosis of AD in the hospital. **Methods:** The study included 98 elderly subjects with 60 or older from the visitors to the Seoul Asan Medical Center and the Korea Veteran Health Service. We administered a standard diagnostic assessment for AD including standardized diagnostic interview, neuropsychological test, laboratory test, acquisition of T1-weighted MRI and amyloid PET at Seoul National University Bundang Hospital and considered as golden diagnosis. DBAD and three panels of medical experts (ME) diagnosed subjects whether normal cognition (NC) or AD using only T1-weighted MRI. We estimated sensitivity, specificity and accuracy of the diagnoses made by the DBAD and ME using receiver operating characteristic curve analysis. **Results:** DBAD classified 37 subjects as AD (DBAD-AD) and the rest as NC (DBAD-NC). Among 37 DBAD-AD subjects, 17 were finally diagnosed as AD in the standard diagnostic assessment. Among 61 DBAD-NC subjects, 47 were diagnosed as NC with Aβ-. On the other hand, ME classified 36 subjects as AD (ME-AD) and the rest as NC (ME-NC). Among 36 ME-AD subjects, 15 were finally diagnosed as AD in the standard diagnostic assessment. Among 62 ME-NC subjects, 47 were diagnosed as NC with Aβ- negative in the standard diagnostic assessment. The sensitivity (93.3% for DBAD and 80.0% for ME), specificity (85.5% for DBAD and 85.5% for ME) and accuracy (87.1% for DBAD and 84.3% for ME) of both DBAD and ME on diagnosing AD were comparable, however, DBAD showed trend of being higher than ME in every analysis. **Conclusion:** We assessed that DBAD has identical diagnostic capability to AD specialists. It approved DBAD is able to assist doctors in diagnosing AD.

P206- A CASE-CONTROL CLINICAL TRIAL ON THE DIAGNOSTIC PERFORMANCE FOR ALZHEIMER'S DISEASE OF A DEEP LEARNING-BASED CLASSIFICATION SYSTEM USING BRAIN MAGNETIC RESONANCE IMAGING OF KOREAN ELDERLY. J.S. Kim[1,2], J.B. Bae[1], S. Lee[3], J.W. Han[4], K.W. Kim[2,4,5] *(1. Department Of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, Korea - Seongnam (Korea, Republic of), 2. Institute of Human Behavioral Medicine, Seoul National University Medical Research Center, Seoul, Korea - Seoul (Korea, Republic of), 3. Department Of Electrical And Computer Engineering, Seoul National University, Seoul, Korea - Seoul (Korea, Republic of), 4. Department Of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, Korea - Seoul (Korea, Republic of), 5. Department of Psychiatry, Seoul National University, College of Medicine, Seoul, South Korea - Seoul (Korea, Republic of))*

Background: A deep learning-based classification system (DLCS) which uses structural brain magnetic resonance imaging (MRI) to diagnose Alzheimer's disease (AD), was developed in a previous recent study. Here, we evaluate its performance by conducting a single-center, case-control clinical trial. We retrospectively collected T1-weighted brain MRI scans of subjects who had an accompanying measure of amyloid-beta(Aβ) positivity based on a 18F-florbetaben positron emission tomography scan. The dataset included 188 Aβ-positive patients with mild cognitive impairment or dementia due to AD, and 162 Aβ-negative controls with normal cognition. We calculated the sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver operating characteristic curve (AUC) of the DLCS in the classification of Aβ-positive AD patients from Aβ-negative controls. The DLCS showed excellent performance, with sensitivity, specificity, positive predictive value, negative predictive value, and AUC were 85.6% (95%CI, 79.8–90), 90.1% (95%CI, 84.5–94.2), 91.0% (95%CI, 86.3–94.1), 84.4% (95%CI, 79.2–88.5), and 0.937 (95%CI, 0.911–0.963), respectively. The DLCS shows promise in clinical settings, where it could be routinely applied to MRI scans regardless of original scan purpose, to improve the early detection of AD.

P207- THE EFFECT OF HOME-BASED COGNITIVE TRAINING USING WORKBOOK AND TABLET PC IN PRESENILE DEMENTIA PATIENTS. J. Kwon[1], K. Lee[2], T.Y. Kim[3], T.K. Eom[1] *(1. Department Of Neurology, Changwon Fatima Hospital - Changwon (Korea, Republic of), 2. Department Of Neurology, Samsung Medical Center - Changwon (Korea, Republic of), 3. Department Of Neurology, Busan Wilis Hospital - Busan (Korea, Republic of))*

Background: Although, the effectiveness of cognitive training has previously been established, adherence or maintenance to these program is difficult to achieve due to the lack of validated and convenient tools and programs. Furthermore, presenile dementia patients are usually physically normal but their welfare programs are overlooked compared to senile patients. The aims of this study are to evaluate the effects of home-based cognitive training and usefulness of workbook and tablet personal computer focusing on presenile dementia patients. **Materials and Methods:** We enrolled 48 dementia patients who met the predefined inclusion criteria from two dementia outpatient clinics. Finally, 34 presenile dementia patients (age; 63.03±4.58, 16 men and 18 women, educational attainment; 10.03±4.30 years, CDR sum of box; 3.21±1.97, MMSE; 21.74±5.24, ADAS-Cog_total; 20.12±8.13, K-IADL; 0.43±0.36) were randomly assigned to a 12-week

scheduled cognitive training program using either an workbook (W group age; 62.53±4.03, 9 men and 10 women, educational attainment: 10.05±3.05, CDR_SOB; 3.68±2.07, MMSE; 21.42±5.46, ADAS-Cog_total 20.95±8.49, K-IADL; 0.50±0.40) or tablet personal computer (T-group age; 63.67±5.26, men 7 and women 8, Education; 10.00±5.63, CDR_SOB; 2.60±1.71, MMSE; 22.13±5.11, ADAS-Cog_tatal; 19.07±7.81, K-IADL; 0.33±0.29). All patients underwent 1 hour/day for 5 days/week of training with support from their caregiver. During the program, levels of difficulties were adjusted according to rater's regular measurement. Before and after the training program, all patients were tested for MMSE, CDR-SB, IADL and ADA-Cog. **Results:** On ADAS-cog tests, patients showed improvement post training (p=0.021). T group showed more improvement in CDR-SB than W group (P=0.01). In subgroup analyses including subdomain, there were no significant differences between pre and post tests. All patients and caregivers were well-tolerated for 12 weeks. **Conclusion:** We suggest that cognitive training using workbook and tablet personal computer is a well-tolerated and comparable tool for presenile dementia patients and their caregivers.

P208- EFFICACY OF THE 'FINGER-TO-BRAIN' GAME ON COGNITIVE FUNCTION OF OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT: A RANDOMIZED CONTROLLED CROSSOVER TRIAL. J.W. Han[1,2], D.G. Moon[1], J.U. Shin[1], Y. Park[3], M.J. Kwon[3], H.I. Kim[3], W. Moon[1], D.J. Oh[2,4], J.B. Bae[1,2], K.W. Kim[2,3,5] *(1. Department Of Neuropsychiatry, Seoul National University Bundang Hospital - Seongnam-Si (Korea, Republic of), 2. Department of Psychiatry, Seoul National University College of Medicine - Seoul (Korea, Republic of), 3. Department Of Brain And Cognitive Science, Seoul National University College Of Natural Sciences - Seoul (Korea, Republic of), 4. Department Of Psychiatry, Smg-Snu Boramae Medical Center - Seoul (Korea, Republic of), 5. Department Of Neuropsychiatry, Seoul National University Bundang Hospital - Seongnam-si (Korea, Republic of))*

Background: We developed the Finger to Brain (F2B) which is a functional game app for training memory and executive function. The F2B consists of eight games that are organized in usual daily life of community-dwelling older adults so that the training effect is more likely to be generalized in real life. **Objectives:** We investigated the efficacy of the F2B on cognitive function and functional activity of brain in older adults with mild cognitive impairment (MCI). **Methods:** This study was a single-center, double-blind, randomized, placebo-controlled, two-period, crossover trial. Sixty-four participants with MCI aged 60 years or older were randomized into the F2B group or the Mock intervention (MI) group. The MI consists of reading articles on health and web surfing that are incorporated as a sub-menu in the F2B app so that the participants were blinded to intervention type. Each participant was asked to play the F2B or the MI for 15 minutes or longer per session, five sessions per week for eight weeks. After a four-week washout period, each participant began an alternative treatment for the next eight weeks. The primary outcome measure was the Cognitive Subscale of Alzheimer's Disease Assessment Scale (ADAS-COG) and the secondary outcome measures were Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS) and functional near-infrared spectroscopy (FNIRS). All measures were administered at the beginning of the trial (week 0), and after the first treatment period (week 9) and the second treatment period (week 21). We performed an intention-to-treat analysis using linear mixed modeling. This study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital. **Results:** Of 64 randomized participants, 60 completed the study. There were no significant differences in the changes of ADAS-COG, MMSE, and GDS scores between the F2B and MI groups (p=0.215 for ADAS-COG, p=0.168 for MMSE, p=0.974 for GDS). However, the F2B group showed significantly lower oxyHb while the MI group showed increased oxyHb during the verbal fluency task and encoding/immediate recall task after intervention in frontal cortex (p=0.025 in right middle frontal, p=0.047 in right superior frontal, p<0.001 in right medial superior frontal, during verbal fluency task; p=0.027 in right superior frontal, during encoding task; p=0.003 in right superior frontal, p=0.009 in left medial superior frontal, during immediate recall task). There were no F2B-related adverse events. **Conclusion:** The F2B for eight weeks showed comparable efficacy on cognition to active control (reading and web-surfing). However, the F2B may increase the neural efficiency of the frontal cortex in performing semantic and episodic memory. (Trial registration: Clinical Research information Service No.: KCT0005061)

P209- FEASIBILITY, ACCEPTABILITY, AND ADHERENCE OF A REMOTE SMARTPHONE-BASED SELF-ASSESSMENT OF COGNITION, FUNCTION, AND BEHAVIOR IN EARLY ALZHEIMER'S DISEASE. T.M. Perumal[1], A. Wolfer[1], M. Veloso[2], I.T. Kurniawan[1], G. Keita[3], N. Hagenbuch[4], B. Shi[5], F. Orfaniotou[6], D. Watson[7], M. Boada Rovira[8], K.I. Taylor[2] *(1. Roche Pharma Research And Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 Basel, Switzerland - Basel (Switzerland), 2. Roche Pharma Research And Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 - Basel (Switzerland), 3. Cytel Inc., Wilmington Del Usa, Succursale De Meyrin, Route De Pre-Bois 20, C.p. 1839, Ch-1215 - Geneve (Switzerland), 4. Global Product Development Data And Statistical Sciences, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 - Basel (Switzerland), 5. Global Product Development Medical Affairs, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 - Basel (Switzerland), 6. Global Product Development, Personalized Healthcare, Digital Health, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 - Basel (Switzerland), 7. Alzheimer's Research And Treatment Center - Wellington (United States), 8. Networking Research Center On Neurodegenerative Diseases (ciberned), Instituto De Salud Carlos Iii - Madrid (Spain))*

Background: Trials in early Alzheimer's disease (eAD) require the quantification of cognitive and functional progression. This is traditionally accomplished with in-clinic standard neuropsychological assessments administered via trained clinical professionals. Digital health technologies (DHT) tools now offer the possibility to collect complementary cognitive and functional information remotely and frequently. Online cognitive testing in lieu of in-person testing at site visits during the COVID-19 pandemic demonstrated the importance and feasibility of remote monitoring of cognition in clinical trials. Compared with traditional in-clinic assessments, remote assessments via DHTs enable the collection of a broader palette of cognitive and functional measures at higher frequency and in patients' home environments. However, these must demonstrate acceptability and participant adherence, as well as validation against standard clinical outcome measures and relevant biomarkers, before their broader use in clinical trials. **Objectives:** The objectives were to determine the feasibility, acceptability, and adherence to remote monitoring via the AD Digital Assessment Suite (AD-DAS) in the AD continuum.

Methods: AD-DAS comprises 9 active tasks of cognitive and motor functioning and four survey questionnaires installed on a preconfigured study smartphone, along with a passive monitoring of behavior in daily life measured using sensors in participants' own smartphones. The 9 active tasks measure episodic memory, conceptual fluency and logical memory, executive functioning based on principles of the Trail-Making Test (TMT) and Stroop interference test, visuospatial working memory, attention and visual scanning behavior based on the Symbol Digit Modalities Test (SDMT), dual-task gait, semantic memory, psychomotor speed and language, and simple motor dexterity and reaction time. 4 survey questionnaires queried sleep quality, sociability, mood and orientation in time. Aspects of social cognition and functioning in daily life were measured with an optional smartphone application on participants' own smartphones. This application quantified participants' gait, life space, and sociability as measured by app usage from application logs. Participants included 32 amyloid PET negative healthy controls (HC Aβ-), 61 participants with subjective cognitive decline (SCD) (i.e., 31 SCDn who are Aβ- and 30 SCDp who are Aβ+) and 30 individuals with early Alzheimer's disease (eAD Aβ+). They were recruited in two countries (USA and Spain) across 5 sites in 2 languages (English and Spanish) as part of the multicenter cross-sectional Proof-of-Concept (POC) study (https://www.isrctn.com/ISRCTN17035495). Participants aged 65 and above underwent amyloid PET Aβ +/- classification and MRI for measurement of brain atrophy. All completed a battery of standard in-clinic neuropsychological, motor, activities of daily living, and health-related assessments. All 123 participants were instructed to perform a subset of 9 different active smartphone tasks and 4 survey questionnaires daily on the AD-DAS for a period of 28 days remotely without supervision. Participants acceptability and perceived difficulty of the AD-DAS tasks were assessed using an end-of-study visit questionnaire. **Results:** The primary results showed ~98% feasibility (i.e., 120 out of 123 participants successfully completed the study). Among the 120 who completed the study, the median adherence, defined as at least one task completed on a given day, was ~96% (i.e., corresponding to ~27 days) in the 28-day remote monitoring period. More than 85% of respondents rated their experience of using the study smartphone and the AD-DAS as 'good' or 'very good' on a 5-point Likert scale. Over 89% of participants agreed that the task instructions were clear and easy to follow. Participants took part in remote assessments for an average of 10.9 minutes per day, and the majority (~91%) rated their perceived burden as acceptable. No differences were observed in feasibility (percent completed: HC: 97%, SCDn: 100%, SCDp: 100%, eAD: 93%), adherence (median (standard deviation) HC: 89% (±30%), SCDn: 96% (±24%), SCDp: 96% (±12%), eAD: 96% (±15%)), and acceptability (all groups' median Likert rating 4/5, i.e. 'good') between groups. Little impact from the COVID19 pandemic was observed. Preliminary validity analyses indicate that age, sex, education, and site impact the cognitive and functional measures collected in the study. **Conclusions:** Primary outcomes of the AD-DAS POC study show excellent feasibility, good acceptability, and good adherence to performing remote cognitive and functional assessments in individuals on the early AD spectrum. This study shows the promise of using remote DHT to measure cognition and function in the real-world, without relying on participant or caregiver recall, and with relatively low burden to the trial participants. The AD-DAS aims to support future clinical trials by identifying target populations, stratifying subgroups of fast progressors, and providing sensitive cognitive measures of disease progression, to ultimately provide clinically meaningful outcomes for observational and interventional trials in preclinical and early AD.

P210- EFFECT OF INTERNET-BASED MINDFULNESS TRAINING ON COGNITIVE AND PSYCHOLOGICAL WELL-BEING AND EEG BRAIN ACTIVITY IN THE ELDERLY: PRELIMINARY RESULTS. S. Galluzzi[1], M. Lanfredi[1], A. Chiesa[2], C. Festari[1], S. Meloni[1], R. Rossi[1], E. Tomasoni[1], D. Moretti[1], M. Pievani[1] *(1. IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli - Brescia (Italy), 2. Istituto Mente e Corpo and Associazione di Psicologia Cognitiva - Scuola di Psicoterapia Cognitiva - Bologna, Rome (Italy))*

Background: As the worldwide population of older adults will rapidly increases in the coming years, effective strategies are needed to maintain cognitive and psychological well-being. Mindfulness training (MT) has been proposed as an efficacious way to enhance cognition and regulate emotion. **Objectives:** Aim of the study is to evaluate cognitive, psychological, and electrophysiological effects of a standard 8-week MT delivered via a live internet-based videoconference in healthy older adults. **Methods:** Fifty older adults aged 60 to 75 years took part in a standardized MT program consisting of 2-hour group sessions that were delivered at weekly intervals for 8 weeks. A comprehensive cognitive (verbal memory, attention and executive functions) and psychological (anxious and depressive symptoms, dispositional mindfulness, worries, emotion regulation strategies, wellbeing, interoceptive awareness, sleep) evaluation and EEG recording were collected at pre- and post-MT and at 6-month follow-up. Data were analyzed using an intention-to-treat approach by a linear mixed model. Estimated mean and standard error were reported, with age, gender and education as covariates. **Results:** The participants had 14+5.2 years of education and were predominantly women (74%). Eight out of 50 participants (16%) withdrew due to personal or medical problems. Only one subject was lost at 6-month follow-up. We found significant improvement between pre- and post-MT on California Verbal Learning Test, immediate recall (50.3+1.2 vs 54.4+1.3, p=.04), short and long delayed cued recall (11.4+.3 vs 12.7+.3, p=.004, and 11.5+.3 vs 12.6+.3, p=.046, respectively) and on Multidimensional Assessment of Interoceptive Awareness, self-regulation (2.4+.1 vs 3.1+.1, p<.0005). These improvements remained significant at 6-month follow-up (p<.01 for all scales). In a subgroup of 20 consecutive participants, EEG alpha1 and alpha3 frequencies increased from pre- to post-MT (p<.05). **Conclusion:** Our preliminary results suggest that MT has positive effects on cognitive and psychological features in healthy older adults, even when delivered in an internet-based format. Moreover, the electrophysiological results suggest that the mechanism of action of MT might involve a modulation of alpha power. No conflict of interests to declare.

P211- INCREASING STUDY POWER VIA FREQUENT SPEECH-BASED ASSESSMENTS OF COGNITION. G. Stegmann[1], S. Hahn[1], J. Liss[1], V. Berisha[1], K. Mueller[2] *(1. Arizona State University and Aural Analytics - Scottsdale, Az (United States), 2. University of Wisconsin - Madison - Madison, Wi (United States))*

Background: With an increase in clinical trials targeting patients early in their disease course comes challenges in trial design. Powering a trial focused on traditional biomarkers in early-stage patients requires large sample sizes and lengthy

trials, with significant consequences for recruitment and retention. To address these problems, there is interest in novel biomarkers that are more sensitive than traditional biomarkers and can be measured frequently, at low cost to patient and trial sponsor. One way to increase the power, and therefore decrease the sample size requirement for a clinical trial, is by collecting data at more frequent time intervals. Rutkove et al (2020) demonstrated how frequent sampling of both traditional and digital biomarkers improved the ability to detect small changes in disease progression. Frequent data collection is made feasible if the participants are measured remotely. Stegmann et al. (2022) demonstrated that speech samples could be collected outside of the clinic, without clinical supervision, and that it was possible to use it to measure cognitive function. The authors used transcripts from healthy and cognitively impaired participants performing the Cookie Theft picture description to automatically extract a speech-based measure of communicative efficiency, Semantic Relevance, and showed that it correlated with the Mini Mental State Exam. Speech is therefore a promising candidate biomarker for measuring clinically-relevant changes to cognition in a low-burden manner. **Objective:** In our study, we used Semantic Relevance as the cognitive outcome of interest, and the model described in Stegmann et al. (2022), to show the relationship between power and speech sampling frequency in participants with mild cognitive impairment. **Methods:** A power analysis was conducted using the longitudinal parameter estimates from Stegmann et al. (2022). In the published article, a growth curve model (longitudinal mixed-effects model) was estimated such that the longitudinal change in a Semantic Relevance was modeled for participants from different levels of cognitive impairment. The parameter estimates from the mild cognitive impairment participants' longitudinal model were used as the basis for the power analysis. The power analysis was performed through a simulation study. In the simulation study, a treatment and a control group were generated. The control group followed the longitudinal decline according to the parameter estimates obtained from the article, and the treatment group declined 10%, 30%, 50%, and 75% slower than the control group. Sample sizes of N = 100, 125, and 150 participants per group were generated for a hypothetical 2-year study. Finally, sampling frequencies of 15 (every 15 days), 30, 60, 90, 180, and 365 were generated. For each combination of simulation conditions, the slopes were estimated for each participant, and a two-sample t-test was used to estimate the mean difference in slopes between the two groups. 200 replicates were performed for each simulation condition, and the proportion of replicates where the t-test was significant was used to compute the power to detect the treatment effect. **Results:** The power (proportion of replicates with significant differences between the two groups) was calculated for each simulation condition. The power increased as the differences between the hypothesized treatment and control group increased, but more importantly, the power increased substantially as the sampling frequency increased. For example, for an effect size of 50% difference in mean slope between a treatment and control group of 100 participants per group, the power to detect a significant effect was 14% when sampling every 365 days, and it increased to 71% when sampling every 15 days. **Conclusion:** This study highlights the value of frequent sampling in clinical trials as a way to increase the power to detect significant treatment effects. An added benefit of this approach is that participants do not need a clinic visit for data to be obtained, and this also reduces participant burden and attrition. **References:** Rutkove, S. B., Narayanaswami, P., Berisha, V., Liss, J., Hahn, S., Shelton, K., Qi, K., Pandeya, S., & Shefner, J. M. (2020). Improved ALS clinical trials through frequent at-home self-assessment: A proof of concept study. Annals of Clinical and Translational Neurology, acn3.51096. Stegmann, G., Hahn, S., Bhandari, S., Kawabata, K., Shefner, J., Duncan, C.J., Liss, J., Berisha, V., Mueller, K. (2022). Automated semantic relevance as an indicator of cognitive decline: Out-of-sample validation on a large scale dataset. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 14. **Conflicts of Interest:** Visar Berisha and Julie Liss are co-founders of Aural Analytics. Gabriela Stegmann and Shira Hahn are employed by Aural Analytics. **Acknowledgements**: This work was supported by NIH SBIR (1R43DC017625-01), NSF SBIR (1853247), NIH R01 (5R01DC006859-13), NIA/NIH R01 (AG027161, AG054059, AG070940), Prime award SPA00001764/ASUB00000177.

P212- A MULTIMODAL DEEP LEARNING APPROACH TO PREDICTION OF COGNITIVE DECLINE AND ITS POTENTIAL APPLICATION IN CLINICAL TRIALS FOR ALZHEIMER'S DISEASE.

C.H. Wang[1], Y.Z. Li[1], H. Yamaguchi[2], H. Tachimori[3], A. Sekiguchi[4], Y. Yamashita[2] *(1. Imaging Technology Center, FUJIFILM Corporation - Kanagawa (Japan), 2. Department of Information Medicine, National Institute of Neuroscience, National Center of Neurology and Psychiatry - Tokyo (Japan), 3. Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology and Psychiatry - Tokyo (Japan), 4. Department of Behavioral Medicine, National Institute of Mental Health, National Center of Neurology and Psychiatry - Tokyo (Japan))*

Background: For decades, numerous efforts were made for Alzheimer's disease therapeutics, but almost all the clinical trials failed to show their effects on slowing or halting cognitive decline. Among several challenges in such trials, one came into notice recently but have not been investigated thoroughly yet is that the large variation of cognitive decline speeds in individuals may result in uneven distributions of fast and slow cognitive decliners in treatment and placebo groups allocated in randomization. This may strongly influence the outcome of a trial aimed at preventing cognitive decline. **Objectives:** The objective of this study is to propose a novel approach to reduce allocation bias in randomization by introducing a prediction artificial intelligence (AI) technology based on deep learning, and then demonstrate the effectiveness of the proposed approach by simulation. **Methods:** A hybrid multimodal deep learning model consisting of deep neural networks (DNNs) and a linear support vector regression (SVR), was developed to predict CDR-SB changes during the trial period. The prediction was based on T1-weighted MRI images and non-image information including APoE4, MMSE, FAQ and ADAS-cog available at baseline. The DNNs were trained to automatically extract features from sub-regions related to cognitive decline, such as hippocampus and anterior temporal lobes and the SVR was trained to predict CDR-SB changes using image features extracted by DNNs together with non-image information. The model was trained, validated and test using samples from longitudinal data in NA-ADNI dataset selected with following criteria's: (1) a clinical diagnosis of mild cognitive impairment (MCI) or Alzheimer's dementia (AD) with MMSE score ≥24; (2) amyloid-beta positive in CSF or PET imaging; (3) a global CDR scale of 0.5; (4) with information needed for model training and a 1.5 to 2 years follow up CDR-SB available. A total of 1194 samples of 506 participants were used for training, validation and test of the model, and 506 samples at the baseline visit of each participant were used for

randomization simulation. Predictions of CDR-SB changes were obtained from the test sets in a participant-based 10-fold cross-validation test setting. Simulations of randomization were carried out to mimic a typical phase II trial with a sample size of 300. A simple randomization and stratified ones using APoE4, CSF Amyloid beta-42, MMSE, ADAS-cog and AI predictions of CDR-SB changes as stratification indices were considered. While the former directly allocated participants into treatment and placebo, the later separated participants into subgroups according to stratification indices and then did allocation in each subgroup. With each randomization method, 300 participants were randomly selected and allocated to treatment and placebo groups. The mean of actual CDR-SB changes in each group were calculated, and their difference was regarded as allocation bias caused by randomization methods. For each method, the simulation was repeated 10000 times to get a distribution of allocation biases. **Results:** The mean and standard deviation of CDR-SB changes of the 506 samples used for simulation are 0.978 and 1.899 respectively. The mean absolute error (MAE) of AI predictions is 1.074 (0.892 for 95% of inners of distribution of actual CDR-SB changes and 4.567 for %5 outers). The correlation coefficient of AI predictions and actual values is 0.580 (0.620 for inners and -0.036 for outers). Deviations of the distributions of allocation biases brought by simple and stratified randomizations were 0.221 and 0.213, 0.203, 0.202, 0.199, 0.175 for APoE4, Amyloid beta-42, MMSE, ADAS-cog, AI predictions respectively. Compared with simple randomization, stratified randomization using AI predictions could reduce the allocation bias by 20.8%. As allocation biases can also be reduced by increasing sample size, reduction in allocation bias by a specific randomization method means it can reduce sample size needed to assure that there was actually an effect in the treatment when a same outcome was obtained. For example, provided that a moderate outcome of 0.3 on CDR-SB decline slowing was obtained, the minimum sample size needed to assure the effect of the treatment was not null, that is, the outcome was not purely due to the allocation bias, with a confidence over 95% for above randomization methods are 618, 572, 539, 525, 503 and 390, respectively. Using AI predictions can reduce the sample size by 37% compared to simple randomization. Randomization using ground truth of CDR-SB changes resulted in 71.5% and 85.3% reduction in bias deviation and sample size respectively, that implies a large potential of using AI predictions in randomization. **Conclusion:** We proposed a hybrid multimodal deep learning model to predict CDR-SB changes and a novel stratified randomization method using its prediction outputs. Simulation results showed effectiveness and big potential of using AI predictions in randomization. In the future, salvages of some failed trials may be possible if we re-evaluate them using a much less biased allocation obtained by randomization method based on AI prediction. All authors have no conflict of interest to disclose.

P213- PRELIMINARY RESULTS OF A DIGITAL PILOT TO IMPROVE AD TRIAL RETENTION BY MANAGING CAREGIVER STRESS. R. Laird[1,2], J. Branning[1] *(1. ClinCloud Clinical Trials - Viera (United States), 2. Navigating Aging Needs LLC - Orlando (United States))*

Background: Clinical research activity directed toward an increased understanding of and cure for Alzheimer's disease (AD) represents a critical advance in providing relief for the 6 million patients and families impacted. The FDA has approved four drugs with 411 active clinical trials in 2022. The study design for most AD trials requires a subject/study-partner dyad for the trial duration, which averages 18 months. Retention of subjects and study partners in these long trials is challenging given the realities of disease progression; the likelihood of the subject's cognitive, physical, and emotional decline; and the potential for health or other stressors affecting study partner participation. In many trial dyads, study partners are also engaged as Family Caregivers (FCs) for the subject. This dynamic adds a unique set of responsibilities and stressors that increase the risk of trial withdrawal. The average retention rate for mild cognitive impairment (MCI) AD trials is 71.6%, mild-to-moderate AD trials 77.7%, and moderate-to-severe and severe AD trials 75.4%. Each early termination reduces overall study scientific potential and is costly to trial sponsors. The replacement costs for a patient who drops out average $19,533. Failure to retain patients and caregivers is costly and delays 80% of clinical trials by at least a month, causing potential losses of $600,000 to $8M daily. To address this problem, ClinCloud Clinical Trials partnered with Navigating Aging Needs LLC (NAN) to pilot a virtual FC support service focused on improving retention rates for AD trials and stabilizing or reducing the perceived burden of stress on FCs. **Objectives:** To explore the potential to increase the rate of study completion and reduce early termination due to caregiver stress in AD clinical trials by stabilizing or reducing the burden of stress for "study partners," typically FC of patients with AD. **Methods**: -Family caregivers volunteering as study partners in phase 3 trials from two key sponsors were offered a 12-month subscription to the Navigating Aging Needs (NAN) Program. - Sponsors funded subscription costs through invoiceable retention fees per each randomized subject. Subscriptions included weekly Zoom sessions with a personal NAN Navigator (licensed social worker). - The initial meeting between each FC and social worker consisted of an assessment that included 80 questions on the AD patient's medical, emotional, social, and legal/financial well-being and the validated battery of 12 questions comprising the Zarit Burden Scale. - Following the initial meeting, the social worker provided the FC with a plan that identified areas of risk that "need attention" or "may need attention," along with resources to address identified needs. - For the following six months, the social worker met with the FC weekly to guide how to resolve areas identified as high-risk and discuss other relevant issues as they arose. - At each session, FCs were queried about their current satisfaction of clinical trial participation. As needed the social worker engaged site personnel to mitigate areas identified as "stress of participation." - The social worker re-assessed the family caregiver's Zarit Burden Score twice, after three months and six months of guidance and support. - FCs had access to and round-the-clock availability of resources on the nanforcaregivers.com website. **Results:** Data are available for the first six FC to enter the pilot. (We continue to enroll additional family caregivers in this ongoing program.) Initial results demonstrate a positive impact of the NAN program with no instances of drop-out due to FC stress and two instances of reducing FC "stress of participation." Five of the six family caregivers showed stable Zarit Burden Scale scores. Caregiver engagement was high for virtual sessions, website use, and open rate for NAN support materials. **Conclusion:** Providing support to FC shows signs of reducing study drop-out due to related to FC stress, supporting retention in clinical trials by monitoring "stress of participation" and intervening as needed, and stabilizing perceived burden of stress. Based on these early results, NAN and ClinCloud are working together to expand the number of FC enrolled and the duration of support. They will continue to monitor the impact of this intervention and

plan to expand the program to address both recruitment and retention needs.

P214- BRAIN NETWORK DIFFERENCE BETWEEN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE DEMENTIA USING EEG. H. Yuseong[1], B. Kyoungwon[2], P. Ukeob[1], Y. Byoung Seok[2], K. Seung Wan[1] *(1. iMediSync Inc. - Seoul (Korea, Republic of), 2. Yonsei University College of Medicine - Seoul (Korea, Republic of))*

Background: Alzheimer's disease (AD) is the most common neurodegenerative disease characterized by progressive memory impairment along with neuropsychiatric symptoms. Early detection of the disease in mild cognitive impairment (MCI) or prodromal AD stage is important for effective treatment and the proper use of expected disease modifying therapies. Proven biomarkers for AD including CSF amyloid β and amyloid positron emission tomography imaging, which are invasive or expensive, have restrictions on access in clinical environment. Electroencephalography (EEG) is one of the general methods to explore brain activities. It can inspect the change in brain activity in the real time with inexpensive equipment, so it is commonly used in the clinical environment and several studies proposed various EEG features as a biomarker for brain disorder. **Objectives**: In this paper, we investigated the difference between AD dementia and MCI by using brain functional network from EEG. Global efficiency and clustering coefficient calculated from brain functional network were adopted to compare AD and MCI. By using two features representing integration and segregation of the network, we propose a new biomarker that could find out the difference between MCI and AD dementia compared to cognitive normal case. **Materials and Methods**: The EEG data of 66 AD dementia (72.3 ± 7.0 years) and 55 MCI (70.8 ± 5.0 years) subjects were used in this paper. The same number of age and sex controlled normal subjects were selected among the dataset of iMediSync to compare AD dementia and MCI. EEG recorded more than 2 minutes with eye closed resting state was used to construct the brain functional network. Each EEG signal was pre-processed using 1-45 Hz band pass filter and time-series rejection. Also, to remove the remaining artifact signal, we adopted independent component analysis (ICA). The filtered EEG signal was decomposed and the artifacts were excluded. EEG recorded from 19 channels (international 10-20 system) was converted to 68 cortical regions of interest (ROIs) using standardized low resolution brain electromagnetic tomography (sLORETA). The functional connectivity was calculated from these 68 ROIs, which was imaginary part of coherence (iCoh). Finally, the brain functional network was constructed from the iCoh values between 68 ROIs. Before investigating the brain functional network, we firstly divide the brain regions to the subregions. The whole brain regions were divided into the three functional subregions: default mode network, central executive network, salience network and six regional subregions: left frontal, right frontal, left temporal, right temporal, left parietal-occipital, right parietal-occipital lobes. Then, except the top 25% iCoh values, the remainder was removed to construct partially connected network. To compare AD dementia and MCI group with normal control group, we used two network features, which were global efficiency and clustering coefficient. Two features were selected to compare integration and segregation of the network, respectively. **Results**: Global efficiency of AD dementia group was lower than that of normal control group in all subregions. On the other hand, clustering coefficient of two groups showed the opposite result, which is higher in AD dementia. Especially, the network features of DMN and both lateral temporal lobes were significantly distinguished. Global efficiency of DMN (0.077 ± 0.015 / 0.097 ± 0.017, AD dementia and normal control respectively), left temporal lobe (0.075 ± 0.026 / 0.109 ± 0.022) and right temporal lobe (0.073 ± 0.025 / 0.105 ± 0.025) showed statistically significant (< 0.01). Clustering coefficient of DMN (0.507 ± 0.046 / 0.442 ± 0.045), left temporal lobe (0.479 ± 0.044 / 0.457 ± 0.042) and right temporal lobe (0.457 ± 0.043 / 0.427 ± 0.059) also showed the same results (< 0.01). Both features of MCI group were greater compared to the normal control group. Overall results of clustering coefficient were similar to that of AD dementia. In case of global efficiency, MCI group showed rather higher values than normal control group. The most significant difference was both lateral frontal lobes that is nearly the same with normal in AD dementia results. Global efficiency of left frontal lobe (0.096 ± 0.026 / 0.079 ± 0.018, MCI and normal control respectively) and right frontal lobe (0.095 ± 0.027 / 0.079 ± 0.018) showed statistically significant (< 0.01). **Conclusion**: In this study, we found different brain network change between normal control, patients with MCI and AD dementia. Noninvasive EEG biomarker would be used as a possible source for AD biomarkers for early detection of AD.

P215- USING ECOLOGICAL MOMENTARY ASSESSMENT TO MEASURE REAL-WORLD EFFECTS OF A COMBINED COMPUTERIZED COGNITIVE AND FUNCTIONAL SKILLS TRAINING PROGRAM IN MILD COGNITIVE IMPAIRMENT. P. Harvey[1] , P. Kallestrup[1] , S. Czaja[3] *(1. University of Miami Miller School of Medicine - Miami (United States), 2. i-Function - Miami (United States), 3. Weill Cornell Medical Center - New York (United States))*

Background: Pharmacological treatments for Mild Cognitive impairment (MCI) have not been particularly successful, leading to attempts to use computerized cognitive training (CCT) to improve cognition and functioning. Studies of CCT have had some success in healthy older people with normal cognition (NC) and MCI, but one of the major concerns in CCT is generalization to real-world functioning. As a result, computerized technology-based skills training systems have been developed. Recent studies have reported that combining commercially available CCT (Brain HQ) and computerized functional skills assessment and training (FUNSAT) software leads to gains in both the ability to perform everyday functional skills and in cognitive performance, across both NC and MCI populations (Czaja et al, 2020). The combination of CCT and FUNSAT led to synergistic gains in both cognition and functional skills compared to training with just one strategy (Harvey et al., 2022). However, in those studies, despite considerable improvements in MCI in both cognition and functional skills performance, training was conducted in person and real-world transfer was not assessed. The current study uses a fully remotely delivered CCT and FUNSAT platform for monitored at-home training, combined by daily ecological momentary assessment (EMA) paging. EMA pages query the performance of both training and untrained technology related skills. **Objectives:** The objectives are: 1: to examine the efficacy of remotely delivered cognitive and functional skills training for performance on computerized measures of cognition and functional skills in rigorously diagnosed participants with MCI across two different training conditions; 2: to examine real-world transfer of these training gains using EMA. **Methods:** 120 participants with MCI (Defined with the Jak-Bondi criteria) and 60 NC constitute the sample. 50% of the participants in

both groups are being fully assessed and trained in Spanish. 50% of the MCI participants were randomized to FUNSAT alone while 50% receive combined training. All NC receive FUNSAT alone for development of training norms. Outcomes are measured with training gains on the training software (time to completion of the tasks and errors), performance on measures of untrained cognitive abilities (Brief Assessment of Cognition) untrained functional skills (Virtual Reality Functional Capacity Assessment Tool), and real-world functioning assessment with daily EMA. EMA surveys query performance of trained tasks and untrained but related technology-focused tasks. FUNSAT training tasks include ATM, Ticket Kiosk, Telephone Voice Menu, Medication Management, and Internet Banking and Shopping. Training in FUNSAT alone includes two 1-hour training sessions per week for 12 weeks. Combined treatment includes a training burst of 4 weeks with twice-weekly BrainHQ followed by 8 weeks of FUNSAT training. Participants who master individual tasks graduate and no longer train. End of training, 3 month, and 6 months outcomes are measured. Participants were all provided with a Chromebook device, along with accounts and passwords for accessining training software. Data plans were also provided if needed. EMA surveys were also launched on the same device. **Results:** As of the present time, 120/180 cases have been assessed at baseline and randomized. This includes 55 NC participants and 65 MCI participants, of whom 32 are randomized to combined training and 33 to FUNSAT alone. 27 NC and 23 MCI participants have completed training. All participants have been recruited in the past 5 months, so the study will be done by November. Percentage improvement in time to completion from baseline to end of training across the 6 tasks in MCI participants ranges from 41% to 56% across the tasks, with tasks that were more difficult at baseline improving more. For example, it took MCI participants 1303 seconds on average to complete the 6 online-banking subtasks at baseline; endpoint performance averaged 620 seconds. There are no differences in training gains associated with combined vs. FUNSAT only training. NC participants had equivalent improvements, although they performed about 1.0 SD better at baseline, typically mastered the tasks somewhat more rapidly, and more commonly graduated before completion of the full complement of 24 training sessions. Number of errors improved even more, with all tasks showing a minimum improvement in error rates of 80% across participant groups and training conditions. Thus, training results were similar to the previous study. For EMA data, participants were paged every day (Monday through Saturday) and asked to respond to three surveys per week. Adherence to EMA surveys averaged three surveys per week, suggesting that participants were adhering as instructed. A total of 1142 EMA surveys were answered to date. Changes in EMA-assessed activities were detected. The proportion of surveys where the respondents reported using the internet since the last survey (outside of third training) increased by 35% over the 12 weeks of the study. Increases were greatest in the first 3 weeks. Specific internet related activities increased by more, including accessing social media, which doubled in frequency. Nontrained, but technology focused, activities also increased. There was a 54% increase in the proportion of surveys where respondents reported that they had sent a text message since the last survey and a 20% increase in the proportion of surveys reporting mobile phone use. **Conclusions:** A fully remotely deliverable functional skills and CCT training program is feasible and shows evidence of efficacy consistent with our previous study. Training related gains across technology-related task domains were consistent with prior results. Again, CCT plus FUNSAT led to synergistic gains, in that equivalent functional skills gains over the training period were achieved with only 8 weeks of FUNSAT training following a 4-week burst of CCT. EMA assessment of everyday activities manifested excellent adherence and generated a large survey database. Importantly, participants were found to engage in activities that were related to their training and also to engage in other technology-related activities that were untrained.

P216- THE EFFECTS OF HOME-BASED COGNITIVE INTERVENTION WITH CHAT-BOT ON BRAIN FUNCTION IN PATIENTS WITH AMNESTIC MILD COGNITIVE IMPAIRMENT. G.H. Kim[1], B. Kim[1], J.H. Jeong[1] *(1. EwhaW. University - Seoul (Korea, Republic of))*

Background and Purpose: Cognitive intervention (CI) has been known to improve cognition and to delay cognitive decline in patients with mild cognitive impairment. The purpose of this study was whether our newly developed, home-based CI with a chat bot for 12 weeks changed brain function and cognitive performance in patients with amnestic mild cognitive impairment(MCI). **Methods:** A single-blind randomized controlled trial was conducted in 72 patients with amnestic MCI. Participants were randomized into the two groups: the CI with chat bot (CI) (n=36) group and waitlist control group without CI (Control) (n=36) groups. A total of 13 chat-bot based CI programs were developed targeting for attention, memory, visuospatial, calculation, language and frontal executive functions. The CI comprised 30-min-session per day for 12 weeks. The primary outcome was the changes in brain function measured by resting state electroencephalogram (EEG), which was measured in eyes open and eyes closed conditions for 3 minutes each, with a 19-channel wireless EEG device. The secondary outcome was the changes of cognitive function measured using the Cambridge Neuropsychological Test Automated Battery. **Results:** There were no baseline demographic and clinical differences between the CI and the control groups. EEG analysis after 12-week showed increased beta wave on the frontal areas in the CI group, while decreased beta wave on the frontal areas in the control group. In addition, CI group also demonstrated improvement in attention domain compared to the control group. **Conclusions:** Considering that increased beta wave is associated with attention performance, our results suggest that the 12 week home- based CI with chat bot could help improve brain function in patient with MCI.

P217- REMOTE COMPUTER-BASED COGNITIVE TRAINING: SHORT- AND LONG-TERM BENEFITS ON COGNITION AND DAILY LIVING IN PATIENTS WITH ALZHEIMER'S DISEASE. S. Dimachki[1] , F. Tarpin-Bernard[2], S. De Chalvron[2], B. Croisile[3], H. Chainay[1] *(1. Laboratoire d'Étude des Mécanismes Cognitifs, Université Lyon 2 - Lyon (France), 2. Scientific Brain Training SA - Lyon (France), 3. Service de Neuropsychologie, Centre Mémoire de Ressource et de Recherche de Lyon, Hôpital Neurologique - Lyon (France))*

Introduction: Considering increasing occurrence of neurodegenerative disorders in older adults, such as Alzheimer's disease (AD), and in the absence of effective drug treatment, cognitive training appears to be a promising alternative for improving cognitive functioning and daily living. The efficacy of cognitive training in patients with AD is still under the debate regarding the best methodological approaches to optimize the training outcomes, commitment, and motivation. The computer-based cognitive training (CBCT) provides wide variety of well-calibrated exercises

easily adaptative to each patient. The short- and long-term benefits of CBCT first shown in healthy older adults have also been proven in patients with AD and MCI. Overall, studies recommend early intervention with 30 minutes to 1 hour sessionseveral times a week. Such recommendations are hard to apply as most people will only consult when symptoms become more pronounced and high-frequency cognitive training protocols require frequent travels between home and speech-language pathologists' (SLP) offices. The patients' compromised autonomy . and many health problems are additional difficulties leading to training interruptions. One way of circumventing these problems is to design remote CBCT sessions. Our main hypothesis is that remote CBCT is an effective way to increase the cognitive and psychological benefitsthrough increased frequency of training. **Objectives:** The aim of this study was to examine short- and long-term benefits of CBCT at home in patients with mild to moderate AD, as a complement to the training in SLP's offices. The secondary purpose was to study training frequency required to obtain noticeable effects. **Material and Method:** The study followed a conventional protocol used to evaluate cognitive and psychological benefits of CBCT. A multicenter study was conducted in SLP's offices. Because of COVID pandemic, only a limited number of patients have been included. Twelve women and 12 men (n=24) diagnosed with AD according to DSM-V criteria (MMSE mean = 26.25; SD = 3.06) were included for 8-month duration protocol. They gave their informed consent to participation to this study, which obtained the authorization of the national ethical committee CPP Sud Méditerranée III (Nr. 2019-A00458-49) and was registered on clinicaltrials.gov (NCT04010175). Patients received CBCT for 4 months under one of three conditions: (1) in SLP's office once a week (REG – regular group), (2) in SLP's office once a week plus once at home (MFG - moderate frequency group), and (3) in SLP's office once a week plus three times at home (HFG – high frequency group). The trainings' content in SLP office and at home were identical. Eight SLP's offices (inclusion centres) were pseudo-randomly assigned into training frequency groups. During the CBCT patients performed a series of short exercises targeting memory, executive functions, processing speed, visuospatial abilities for 45 minutes using the Happyneuron Professional software (https://www.happyneuronpro.com). To test the training's effect, three types of instruments were used: experimental tasks, neuropsychological tests, and questionnaires. The primary measures were patients' scores in executive and working memory experimental tasks. The secondary were patients' scores in neuropsychological tests and questionnaires. These measures were performed at 3-point: T1 (pre-training), T2 (post-training) and T3 (3-month post-training). Because the inclusion of expected number of patients per group was not possible due to the pandemic COVID-19 the innovative statistical approach was used to analyse the data. Sequence analyzes (Abbott & Tsay, 2000) was performed based on an event: the number of exercises carried out and of a state (scores obtained each time) to identify typical trajectories, these trajectories were then compared to the three groups and with well-being scores. We used R software with TramMineR. Depending on the exercises type (executive or working memory) between two and three typical trajectories came out. In a case of two trajectories, one has shown an absence of progress and the second a progression. In the case of three trajectories, one has shown an absence of progress, one a slight progress and another one a real progress. For well-being, three trajectories were observed: one without progression, another with a small progression and comprising undulations (progression, regression, progression) and a third where the progression was more important and more linear. The pre-post-training comparisons have shown significantly more important improvement in working memory and executive functions (inhibition) in HFG group than two other groups. This study shows the progression with training and some of the benefits of training on cognition and well-being in patients with Alzheimer's disease.The main limitation of the study is a small number of patients included to the study due to the health crisis. However, this work opens a new way to identify parameters for optimizing the CBCT (selection of exercises, adaptation of difficulty levels and frequency of training). **Key words:** Alzheimer's disease, MCI, computer-based cognitive training, at home cognitive training, cognitive benefits, daily living. **Competing interests' statement:** Franck Tarpin-Bernard and Bernard Croisile are cofounders and shareholders of SBT Humans Matter.

P218- TAKING CARE OF FAMILY DEMENTIA CAREGIVERS: A QUALITATIVE EXAMINATION OF PATIENT PERSPECTIVES AND PERCEIVED HEALTH OUTCOMES AFTER RECEIVING USUAL CARE AND AFTER A DIGITALLY SUPPORTED CARE MANAGEMENT PROGRAM. O.A. Klein[1], A. Karras[2], W. Hoffmann[3,4], S. Teipel[1,2], I. Kilimann[1,2] *(1. Deutsches Zentrum fuer Neurodegenerative Erkrankungen - Rostock (Germany) - Rostock (Germany), 2. Clinic for Psychosomatics and Psychotherapy, University Medical Center Rostock - Rostock (Germany), 3. Deutsches Zentrum fuer Neurodegenerative Erkrankungen - Greifswald (Germany), 4. Institute for Community Medicine, Section Epidemiology and Community Health, University Medicine Greifswald - Greifswald (Germany))*

Background: Almost two-thirds of people with dementia (PwD) living at home receive care from a family or other informal caregiver. For caregivers this often results in a workload comparable or above a full-time position. Evidence shows that family caregivers experience increased physical, psychological, emotional, and social stress which, in the long term, results in adverse health outcomes. The development of effective healthcare and support management for family caregivers is vital. **Objectives:** Therefore, our aim was to examine and compare the perceptions of participants who received a digitally supported care management program with those who received usual care. **Methods:** This study was embedded within a large, multi-center cluster randomized controlled trial (GAIN study) examining the effectiveness of a care management program for family caregivers of people with dementia. Ethical approval has been obtained from the Ethical Committee of the University Medicine Greifswald (Registry number BB 120/2019). The trial is still ongoing and registered at ClinicalTrials.gov (NCT04037501). Data collected through 30 semi-structured telephone interviews with participants of the GAIN trial will be recorded, transcribed and analyzed using framework analysis. Based on previous research, we developed two semi-structured interview schedules, each tailored to the content of the group (control or intervention). Both interview schedules (control and intervention) covered participants' health, care situation and responsibilities, use of medical and non-medical services (before and during the trial), changes regarding their health and wellbeing in the past six months, and any feedback based on their experience of being involved in the trial. Participants in the control group were also asked about their experience and thoughts on being part of the control group. Participants in the intervention group were

asked about their perspectives on the most and least useful aspects of the GAIN care management program, the impact the intervention had on their health and daily life activities after the trial, the participants' experience and thoughts on being part of the intervention group, as well as participants' overall experience of the care management program. **Results:** To date we have interviewed 27 participants, out of which 11 belonged to the control group and 16 to the intervention group with the majority being female. We have started the analysis of the transcripts. Complete results will be available and presented at the conference. **Conclusion:** The results of this interview study will be useful in informing and better understanding the results of the GAIN trial. In addition, the results will further improve the care management program developed as part of the trial and will be useful for future trials.

P219- INTUITION: A BRAIN HEALTH STUDY USING MULTIMODAL DIGITAL BIOMARKERS TO DECIPHER COGNITIVE PROFILES OF INDIVIDUALS AT-RISK FOR ALZHEIMER'S AND RELATED DEMENTIAS. M. Butler[1], A. Porsteinsson[2], S. Kenny[1], H. Lenyoun[3], M. Hobbs[1], R. Brown[1], M. Bianchi[3], J. Williams[1], A. Gabelle[1], S. Belachew[1], I. Intuition Study Scientific Committee[1] *(1. Biogen - Cambridge (United States), 2. University of Rochester Medical Center - Rochester (United States), 3. Apple - Cupertino (United States))*

Background: Identifying individuals at-risk for Alzheimer's disease (AD) and related dementias is critical for early diagnosis, monitoring, and treatment. Emerging digital health technologies offer unique opportunities to describe and decipher cognitive trajectories in at-risk populations. Consumer-grade digital devices can unobtrusively trace real-world behaviors and generate digital signatures of everyday cognition. Passive and active data collection with digital tools may open new avenues for early detection in non-clinical settings and expand the scope and scale of screening for cognitive decline. Remote and frequent cognitive sampling allows for increased spatiotemporal resolution at an individual level and has the potential to optimize prediction of clinical progression in a robust, dynamic fashion. Development and validation of personalized digital tools may equip and empower patients to track cognitive wellness and promote societal awareness of brain health. **Objectives:** The co-primary objectives of the INTUITION study are to (1) develop real-world high-accuracy classifier models that distinguish cognitive impairments from healthy aging to promote screening and monitoring of people at-risk to develop AD and related dementias, and (2) to construct a trackable cognitive health score. The secondary aims are to predict cognitive decline and risk of conversion to mild cognitive impairment (MCI) in healthy and subjective cognitive complaint (SCC) populations. In a subset of participants, AD-biomarkers define the at-risk populations and will be used to assess classifier selectivity for suspected underlying pathology. **Methods:** The INTUITION study (NCT 05058950) is a two-year observational digital study enrolling 23,000 U.S.-based participants aged 21 to 86 years of age inclusive, including healthy controls, SCC, and MCI. The study launched in September of 2021 and continues recruitment in 2022. This virtual app-based study uses multimodal sensor devices, including an iPhone and Apple Watch, for longitudinal data collection from consenting participants. The study has been designed with privacy, control, and transparency in mind as well as data security. Device use is coupled with passive sensor-based monitoring in conjunction with validated cognitive tests and behavioral surveys. The sources of passive data collected from the study specific app using Apple Watch and iPhone cover multiple domains, including motor and autonomic function, diurnal rhythms, speech and language, social function, and everyday cognition. We aim to demonstrate the utility of using data from features derived from sensor streams to distinguish cognitive status between cognitively intact participants and those with MCI. Those features which drive model outputs will be mapped to cognitive outcome measures with the purpose of deriving a trackable cognitive health score. There are two study arms with a design to support the development of a classifier model which is both accurate and generalizable. In one study arm, model accuracy will be appraised in subjects with recently established cognitive status based on expert clinical evaluation, phenotyping, and AD-biomarkers. In the second study arm, a larger population-based cohort will provide data to understand classifier model generalizability. In this arm cognitive status is established by self-report and the confidence in cognitive status labeling is adjudicated by tele-research evaluation. Cognitive assessments are deployed at monthly and quarterly intervals using neuropsychological methods adapted for virtual research and with a high-frequency, repeated measurement approach. Cognitive test selection was designed to probe the integrity of learning and memory, processing speed, attention, executive and visuospatial function. App-based administration of validated surveys occurs at regular intervals and covers multiple domains, including mood, sleep, diet, substance use, exercise, quality-of-life, stress and discrimination, self-efficacy, medical history, medications, risk-factors for dementia, global cognitive health, and instrumental activities of daily living. **Results:** The INTUITION study is currently enrolling and is proceeding along expected timelines with full enrollment expected before the end of 2022. Baseline characteristics and cognitive profiles of the whole population and subgroups of interest (e.g., SCC, MCI) will be presented at the conference. We will provide preliminary results of the normative cognitive data of the population both with and without cognitive complaints across the aging spectrum from the third to ninth decades of life. **Conclusions:** The INTUITION study is the first digital health and medicine study of this scope and will provide a large and comprehensive dataset of passive and active digital biomarker assessments on participants with and without vulnerability to cognitive decline due to AD or other underlying disease processes.

P220- COGNITIVE HEALTH IN UNDERREPRESENTED POPULATIONS: EARLY LEARNINGS FROM THE INTUITION BRAIN HEALTH STUDY. R. Au[1], M. Butler[2], H. Lenyoun[3], S. Kenny[2], R. Brown[2], P. Saha-Chaudhuri[2], M. Bianchi[3], J. Williams[2], A. Gabelle[2], S. Belachew[2], I. Intuition Study Scientific Committee[2] *(1. Boston University School of Medicine - Boston (United States), 2. Biogen - Cambridge (United States), 3. Apple - Cupertino (United States))*

Background: An evolving challenge for clinical research is how to recruit and retain demographically diverse populations. Barriers and facilitators to participate in research are complex and influenced by a host of factors, such as the burden of travel to study sites or schedule flexibility. It remains to be seen how digital, de-centralized studies might transform the engagement landscape for research that aims to enroll cohorts reflective of large, heterogeneous populations, such as those in the United States. Given the rapid growth and ubiquity of digital devices in everyday life, research that utilizes real-world consumer technology offers the possibility to overcome

traditional obstacles to join research. Strategies to lower barriers to participation aim to enroll representative study populations, deliver increasingly generalizable results, and promote a culture of equitability. Cognitive health in underrepresented populations is less studied and this area of unmet need is due at least in part to challenges related to accessibility of research. Given that socioeconomic factors are associated with vulnerability to cognitive decline and potential determinants of health, then research to characterize risks to brain health ought to utilize tactics to enroll representative populations. **Objectives:** The INTUITION study (NCT 05058950) is an observational two-year virtual study in adult residents of the United States aged 21 to 86 years, and with the goal to enroll 23,000 individuals that are stratified into cohorts based on age and risk of cognitive decline. The aim is to develop real-world high-accuracy classifiers that distinguish cognitive impairment from healthy aging, and to construct a trackable cognitive health score. Recruitment and engagement strategies have been deployed to enroll a diverse study population, including 20% or greater participants who self-report ethnicity as Hispanic/Latino or self-report race as Asian, Black/African American, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, or other/multi-racial. Additional recruitment goals are to enroll individuals with a range of educational attainment, regional geographical diversity, and to maintain a relative balance in the male-to-female ratio. **Methods:** The study recruitment strategy includes multiple channels, such as email/direct mail campaigns, paid search and social media, word-of-mouth, and event-based outreaches in collaboration with patient advocacy groups. This virtual study uses an iPhone and Apple Watch to collect digital multimodal longitudinal data from consenting participants. The study has been designed with privacy, control, and transparency in mind as well as data security. Device use is collected via passive sensor-based monitoring through the study specific app, and this is coupled with validated cognitive tests and behavioral surveys. Cognitive assessments are served at monthly and quarterly intervals and measure different neuropsychological domains, such as episodic learning and memory, working memory, psychomotor and processing speed, sustained attention, executive and visuospatial function. App-based administration of validated surveys occurs at regular intervals and covers multiple areas, including psychosocial function, nutrition, substance-use, sleep, physical activity, stress, discrimination, medical and cognitive history, prescription and supplemental medications, and global function. We will compare the recruitment strategies and evaluate the adherence to digital tool use with a focus on data from underrepresented populations by age group and cognitive status. Descriptive and summary statistics are used to evaluate the demographic data. **Results:** The study launched in September 2021 and as of June 2022, the INTUITION study has successfully enrolled more than 80% of its total target population. The population contains individuals with varying degrees of risk for cognitive decline and 75% of the participants are over the age of 50 years. The study is on track to meet and possibly exceed enrollment goals with respect to racial/ethnic diversity and spread in educational attainment. The study is also achieving geographic diversity in terms of regional representation from across the United States. The most successful recruitment strategies include word-of-mouth and direct email campaigns that draw from focused databases of individuals with interest to participate in research. At the conference, up-to-date study population characteristics will be shared in addition to an assessment of the recruitment strategies used to enroll a diverse population. Cognitive, clinical, and behavioral profiles will be presented, as well as early learnings from passive and active data collection. **Conclusions:** The INTUITION study has the potential to demonstrate that virtual studies can readily enroll individuals from generally underrepresented populations. A diverse U.S.-based population continues to enroll in this large-scale observational study. De-centralized studies leveraging digital health technology tools such as the INTUITION study so far appear to lower barriers for individuals to participate and may offer the potential to enroll populations that accurately reflect the diverse constitution of the larger society.

P221- ANALYZING FACIAL EXPRESSIONS AND POSES CAPTURED DURING VIDEO CHATS FOR EARLY IDENTIFICATION OF MCI - PROOF OF CONCEPT STUDY: I-CONECT PROJECT. M. Alsuhaibani[1], A. Pourramezan Fard[1], H. Dodge[2,3], M. Mahoor[1] *(1. School of Electrical and Computer Engineering, University of Denver - Denver (United States), 2. Layton Aging and Alzheimer's Disease Center, Oregon Health & Science University - Portland (United States), 3. Oregon Center for Aging and Technology (ORCATECH), Oregon Health & Science University - Portland (United States))*

Background: Artificial Intelligence algorithms such as Computer Vision (CV) might be able to detect early cognitive declines by analyzing facial expressions and movements captured during casual video chats. **Objectives:** In this study, we have utilized deep-learning-based CV techniques to extract facial features in facial videos of older adults with two cognitive statuses (those with normal cognition (NCO) and mild cognitive impairments (MCI) and then used extracted features to distinguish subjects with MCI from NCO. **Methods:** Data: Data came from the facial videos collected in the Internet-Based Conversational Engagement Clinical Trial (I-CONECT) (NCT02871921), the behavioral intervention randomized controlled trial aimed to examine the effect of increased social interactions through video chats on cognitive functions. The socially isolated older subjects aged 75 were recruited and the experimental group conversed with trained conversational staff 4 times per week for 6 months and 2 times per week for additional 6 months using internet webcam. Over 6000 files of 30 minutes long video chat sessions were recorded with each session discussing a different topic. In this proof of concept study, we extracted 18 videos where the elderly discussed their summertime memories with the conversational staff. These videos were selected based on the video quality (brightness of the screen, no eyeglasses, acceptable distance between face and camera, and visibility of the subject's face during the video). Two third of the 18 subjects were clinically diagnosed as MCI with the rest being NCO. The detail of the study protocol for this intervention was published elsewhere (Yu et al., 2021). **Analyses:** We first analyzed the videos using our deep neural models on a frame level to detect the subjects' faces in the videos, and then recognize facial attributes/features. The videos have variable frame rates, but we extracted the faces using a fixed frame rate among all videos. Currently, two types of features are extracted: Head Pose (HP) and Facial Emotion Recognition (FER). HP has three values representing the Yaw, Pitch, and Roll of the subject's head movement. FER contains seven values that represent probabilities of six basic emotions (Happy, Sad, Surprise, Fear, Disgust, Anger) and neutral. We investigated several machine learning approaches to analyze the features but two models gave the best classification accuracies: Support Vector Machine (SVM) with Radial Basis Functions (RBF) and Random Forest (RF). We trained SVM and RF models

using the cross-validation technique, where one subject data is left for testing and the remaining for training. We trained the models at the frame level and then use them to classify each frame whether belong to the MCI group or the NCO group. The model determined the subject's cognition status based on pose, FER, fusing of HP, and FER. We also explored the average of FER for all frames of the same subjects. **Results:** The evaluation metrics are accuracies, F1 score, and the Area Under the Curve (AUC). The HP data shows a promising classification result of the subjects' cognitive status. The best model had 83.3%, 0.889, and 0.75 for accuracy, F1 score, and AUC, respectively, using Head Pose (HP). On the other hand, the accuracies are 66.7% for the 18 subjects if we use FER data. Thus, the HP features have carried more information about the subjects' cognitive status. **Conclusion:** The Head Pose features extracted using Computer Vision provided reasonable discriminatory ability in distinguishing those with MCI from NCO. In this proof of concept study, we limited the conversational session to one theme where all discussed the same topic. In the next study, we plan to apply our method to more diverse sessions utilizing all the recorded video chats could improve the generalizability of our results.

P222- USING AI AND NATURAL LANGUAGE PROCESSING ALGORITHMS TO SCREEN OLDER ADULTS WITH MILD COGNITIVE OR EARLY ALZHEIMER'S DISEASE. S. Melgar-Donis[1,2], J. Siewierski[3], R. Zandie[1,3,] D. Pittman[1], L. Chileshe[1], H. Abdollahi[3], M. Habibi[3], B. Soicher[3], E. Emamian[3], M. Mahoor[3,4] *(1. University of Denver - Denver (United States), 2. DreamFace Technologies, LLC, 3. DreamFace Technologies, LLC - Centennial, Co (United States), 4. Univesrity of Denver - Denver (United States))*

Background: Cognitive impairment, a known precursor to Alzheimer's disease/related dementias (AD/ADRD), is many times not recognized in early stages. This might be due to many barriers to early detection of ADRD that can delay diagnosis and treatment. One of the main barriers is a lack of trained staff at care facilities, coupled with an increasing number of residents to care for. This situation adds strain to an already diminishing caregiver population. Along with an ongoing senior caregiver shortage, the pandemic has revealed an unmet need for caring for those with MCI and dementia. A suggested method of doing this is by care communities and independent living communities implementing memory screening programs and employing a systematic use of a screening tool, which has been shown to be one of the best ways for people to get referrals for neuropsychological evaluation and testing. In this study, we evaluate the feasibility of the MyRyan App to monitor the language and cognitive function in older adults with Mild Cognitive Impairment (MCI) and early AD/ADRD. MyRyan is an interactive mobile software application developed at DreamFace Technologies, LLC. It is designed in the form of a photo-realistic and engaging virtual agent that is used for meaningful daily conversation. It is designed to improve the psychological well-being and loneliness in individuals with MCI and AD/ADRD by giving seniors the opportunity to engage in dynamic conversation about topics consistent with the aging population demographic. It is a tool that is not only engaging for daily use but also uses state-of-the-art Artificial Intelligence (AI), including speech recognition, natural language processing (NLP) and deep machine learning algorithms, to assess mild cognitive impairment in participants according to Saint Louis University Mental Status Exam (SLUMS) screening tool. **Objective:** With this pilot study we demonstrate the need for a low-barrier screening tool for mild cognitive impairment and how an AI based application can serve this purpose. We used the MyRyan App to evaluate the effectiveness of such a screening tool in our study. This abstract presents the results of our clinical trial on a group of participants with MCI and early AD/ADRD on evaluating how automated AI/NLP algorithms can score cognitive impairment. **Methods:** We designed and conducted a pilot/feasibility study for the MyRyan App and recruited 12 older adults (average age: 76.92 years, std: 4.93 years; 8 Females) who participated in the study, six with MCI and six with early-stage AD/ADRD (12 participants total) living in three different independent living facilities located in Denver Metro areas. Participants interacted with MyRyan in two sessions over a period of three weeks. Each participant spent between 25-30 minutes interacting with MyRyan in every session. Participants conversed with MyRyan about different topics of interest and at the end completed the Cookie Theft Picture description. For the picture description test, we transcribed the speech automatically and ran it through our Deep Neural Network Model (A Transformer model call RoBERTa) where the model assigned a score between 0 to 1 indicating whether the participant has dementia and cognitive impairment. In training the RoBERTa model, we used the University of Pittsburgh (Pitt) dataset, the largest publicly available language dataset on dementia and AD/ADRD, containing transcripts and audio files of 3,228 conversations from a normal control group and 19,305 conversations from a population with probable dementia, administered by the Alzheimer and Related Dementias Study at the Pitt School of Medicine. The participants were able to interact with the application on two different visits to ensure variation in the picture descriptions. At the beginning of the first visit, the participants were administered the SLUMS as a benchmark to compare against our predicted results. **Results and Analyses:** Our prediction rate on the training set showed just under 90% accuracy, with a similar 80% prediction accuracy rate from the field results with a sample size of N = 12. These results are much higher than prediction rates found in other studies that use LASSO and tree-based classification methods. Furthermore, we fitted a linear regression model with the predicted dementia scores plotted against the participants' SLUMS (the lower the SLUMS score, the higher the cognitive impairment). The regression model shows that the SLUMS is inversely correlated with the model prediction ($R2 = 0.6001$). To measure user engagement in conversation, we used words per minute (WPM). We automatically counted the number of words per minute for each utterance (or interaction). Results show that on average, participants spoke 101 (STD = 37) WPM. According to the National Center for Voice and Speech, the average conversation rate for English speakers in the U.S. is about 150 WPM. Studies show that the WPM is slightly lower when people speak with a virtual agent (MyRyan is a virtual agent). In addition, 50% of the participants in our study have MCI or early-stage AD/ADRD, which is another factor that slows down speech rate. Results show that participants in our study are engaged in conversation with MyRyan. **Conclusion:** Based on these preliminary results, we believe that an AI-based mobile app such as the MyRyan App can provide a low-barrier testing tool to care providers and facilities that can be used as an objective and independent diagnostic tool for ADRD in aging populations. Use of such tools would aid in labor shortages of care givers and allow facilities to be able to provide better care for their residents. In addition to being a screening tool, the application can be engaging for users and can improve their quality of life.

LP106- DEVELOPMENT OF A MACHINE LEARNING MODEL TO DIAGNOSE DEMENTIA USING QUESTIONNAIRES ASSESSING SUBJECTIVE MEMORY COMPLAINTS AND DEPRESSIVE SYMPTOMS.

M. Kim[1], J. Hong[1], J. Park[1] J. Han[1], K.W. Kim[1] *(1. Seoul National University Bundang Hospital - Seongnam-Si (Korea, Republic of))*

Background: Rapid diagnosis of dementia in the early stages is a key factor in successful dementia management. Existing diagnostic methods such as cognitive tests, biomarkers, and brain imaging are expensive and time-consuming, limited in use in the clinical field. Dementia screening based on patient characteristics and self-report questionnaires is highly accessible and easily applied to the majority of the population in a very short time. However, the method of determining the risk of dementia based on the total score of the questionnaire or a specific risk factor showed low accuracy and sensitivity. In this study, we attempt to implement a dementia prediction model that learns dementia risk factors and clinical characteristics using a machine learning algorithm. **Methods:** Data were collected from a nationwide dementia cohort, which is the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD), and a retrospective cohort consisting of outpatient data from Seoul National University Bundang Hospital. A total of 28,001 people who completed the Subjective Memory Complaint Questionnaire (SMCQ) and the Geriatric Depression Scale (GDS) from the two cohort studies were included in this study. Several demographic variables and individual items of SMCQ and GDS were selected as input features to train the prediction model. Labeling the diagnosis of dementia was conducted through interviews with clinicians. Samples with even one missing value were excluded, and 5,730 participants were included for final model development. Five algorithms including logistic regression, support vector machine, random forest, XGBoost, and light gradient boosting machine were tried and hyperparameter tuning was conducted using GridSearchCV. The model with the highest area under receiver operating curve was selected as the best model. For model interpretation, the Shapley additive explanations (SHAP) analysis was performed on the model with the best predictive performance. By plotting a calibration curve, we identified the best-calibrated model. Ensemble model combining the most predictive model and calibrated model was created using the soft voting method. **Results:** Of the five individual algorithms, the model with the highest AUC was the XGBoost algorithm (AUC=0.928) and the best-calibrated model is logistic regression when checking calibration curves visually. The ensemble model combining with the XGBoost logistic regression model showed both higher predictive performance (AUC=0.929) and an improved level of calibration, compared with individual models. Age was the most predictive feature in the results of the XGBoost model interpretation analyses. Among the top 10 features, there were five items of SMCQ and two items of GDS. The education year was ranked third among the demographic variables. **Conclusion:** Our prediction model can successfully identify individuals with dementia with good calibration. This prediction tool can be used in clinical trials to enroll individuals who are more likely to diagnose dementia. Using our model, clinicians can identify individual dementia risk factors and establish treatment strategies accordingly. Future clinical trials are needed to prove the efficacy of our algorithm in the early prediction of dementia and the establishment of treatment strategies.

LP107- THE COMMUNITY ENGAGED DIGITAL ALZHEIMER'S RESEARCH (CEDAR) STUDY: DIGITAL ENGAGEMENT STRATEGIES TO INCREASE ADRD RESEARCH PARTICIPATION OF BLACK AMERICANS.

A. Aaronson[1,2,3], M. Ashford[1,2,3], D. Zhu[4], H. Cham[4], C. Conti[1,2,3], X. Deng[4], R. Alaniz[5], R.S. Mackin[2,3], M. Weiner[1,2,3], D. Byrd[6], R.W. Turner[7], C. Hill[8], R. Nosheny[2,3], M. Rivera Mindt[4,9] *(1. Northern California Institute for Research and Education (NCIRE), Department of Veterans Affairs Medical Center - San Francisco (United States), 2. Veterans Affairs Advanced Research Center - San Francisco (United States), 3. University of California, San Francisco - San Francisco (United States), 4. Department of Psychology, Latin American Latino Studies, African and African American Studies, Fordham University - New York (United States), 5. Alaniz Marketing - Novato (United States), 6. CUNY, Queens College - Queens (United States), 7. George Washington University - Washington (United States), 8. Alzheimer's Association - Chicago (United States), 9. Department of Neurology, Icahn School of Medicine at Mount Sinai - New York (United States))*

Background: Underrepresented populations (URPs), including Black older adults, experience significant inequities in Alzheimer's disease and related dementias (ADRD) prevalence, incidence, and outcomes. However, ADRD research studies and clinical trials fail to adequately include Black American older adults. Community Engaged Research (CER) is an evidence-based approach for improving URP engagement in ADRD research, but CER strategies often lack scalability to the national level. As internet usage among URP older adults increases, internet-based research demonstrates promise as a feasible, valid approach for engaging and longitudinally assessing Black older adults. **Objectives:** The CEDAR study aims to develop, deploy, and evaluate a culturally informed, digital platform utilizing a CER approach, to increase the engagement (i.e., longitudinal task completion) of Black American adults included in the Brain Health Registry (BHR) and in additional ADRD clinical research. **Methods:** BHR is a public, online registry consisting of over 100,000 members. BHR aims to recruit, screen, and longitudinally monitor participants for aging and cognitive-related research. BHR participants are also referred to other research studies. BHR participants complete a sequence of well-validated, unsupervised, online self-report questionnaires and cognitive tests. A subpopulation of BHR participants who self-identify as Black/African American and who agreed to be contacted about future research opportunities were recruited to join CEDAR via automated email invitations describing the study. After signing an electronic informed consent, all enrolled participants were directed to a 5–15-minute online survey about motivators (i.e., reasons to participate in research) and barriers (i.e., obstacles that make participation challenging) to BHR participation, as well as preferences for communication channels and engagement methods. All participants were invited to volunteer for a Community Science Partnership Board (CSPB). All participants were encouraged to complete BHR questionnaires, including the Everyday Cognition Scale (ECog), and cognitive tests, including the Cogstate Brief Battery, MemTrax Memory Test, and Cambridge Cognition Paired Associates Learning. In collaboration with a marketing team and the CSPB, we developed and deployed a series of engagement strategies and materials to address barriers to research participation, including (1) compensation for task completion, (2) culturally informed websites, email campaigns, and social media posts, and (3) written and video testimonials from CEDAR participants and investigators. We compared the demographics, cognitive profile, and baseline BHR task

completion rates between enrolled CEDAR participants and those invited to join CEDAR who did not enroll. We used independent sample t-tests to compare group means for continuous variables and reported Cohen's d as effect size. For categorical variables, we used Chi-square tests if ≤ 20% of expected cell counts were less than 5 and reported Cramer's V as effect size. Otherwise, Fisher's exact tests were used if > 20% of expected cell counts were less than 5. **Results:** Out of 3,738 participants who received invitations to join CEDAR, 364 (9.74 %) expressed interest in enrolling by clicking on the email study link, and 349 (9.34%) enrolled. 210 (5.62%) of enrolled participants completed the barriers and motivators survey, and 134 (3.58%) indicated interest in joining the CSPB. Compared to those who did not enroll in CEDAR, those who enrolled were significantly older (mean age in years = 58.29, SD 11.49 vs mean 54.08, SD 13.02), had higher educational attainment (mean education in years = 16.25, SD 2.4 vs mean 15.40, SD 2.52), and a higher percentage of self-reported family history of AD (41.83% vs 28.09%). Those who enrolled in CEDAR had significantly lower subjective cognitive decline (self-report ECog score) compared to those who did not enroll (mean 1.39, SD 0.44 vs mean 1.49, SD 0.52). Among all Black BHR participants invited to join CEDAR, 100% completed at least the BHR initial questionnaire, 4.12% completed all tasks, 53.18% completed at least one BHR cognitive test, 11.08% attempted to complete one BHR test but encountered technical difficulties, and 4.95% have an enrolled study partner. Compared to those who did not enroll, those enrolled in CEDAR had a significantly higher percentage of: participants completing all BHR tasks (22.42% vs 1.92%), participants completing at least one cognitive test (76.83% vs 49.66%), participants attempting a cognitive test but encountering technical difficulties (17.88% vs 10.12%) and participants with an enrolled study partner (17.88% vs 3.36%). The CSPB convened on a quarterly basis and consists of 19 BHR members, 6 CEDAR investigators, and 1 marketing professional. The CSPB provided guidance and iterative feedback on URP recruitment and engagement strategies, participant communications, and methods for building trust and relationships with community-based organizations. **Conclusion:** These findings demonstrate that culturally informed strategies created through a CER approach are a feasible, scalable strategy to increase engagement of Black participants in an online ADRD-related research registry. Future efforts should evaluate the effectiveness of the individual engagement strategies deployed. Furthermore, CEDAR participants were 84.53% female and had mean education of 16.25 years. Strategies should be developed for recruiting and engaging Black men and Black individuals with lower educational attainment.

LP108- QUESTIONNAIRE-BASED COMPUTER ASSISTED DIAGNOSIS (CADX) IS USEFUL FOR IDENTIFYING ALZHEIMER'S DISEASE. T. Daly[1], D. Weisman[2] *(1. Sorbonne Université - Paris (France), 2. Abington Neurological Associates - Abington (United States))*

Background: Memory and cognitive disorders are underdiagnosed and the failure to recognize them is a missed opportunity for treatment, diagnosis and inclusion in research. Computer Assisted Diagnosis (CADx) may be a simple tool for assisting the identification of subjects with Alzheimer's disease (AD) and mild cognitive impairment (MCI) compared with normal elder controls. **Objectives:** Our study validated the diagnoses of memory complaints with a questionnaire-based CADx against gold standard same day diagnosis. **Methods:** The CADx is a web based memory/cognitive screening program (Cogminder.com). The study used prospective data entry from caregivers entering subject information into a computerized expert system that renders a report. We validate this report by comparing the report with standard diagnosis based on same day history and physical. All patients were seen in a private neurology office. **Results:** 319 patients with cognitive complaints who presented with a caregiver were included. Out of the 319, 253 (79.3%) were properly diagnosed and 31 (9.7%) were misdiagnosed by the system. Of the misdiagnoses, a total of 10 (3.1%) were considered "near misses" (for example, a clinical diagnosis DLB and AD overlap vs a CADx of AD only) and 21 (6.6%) were considered wrong (clinical diagnosis of normal cognition, CADx of MCI). Indeterminate results occurred in 27 (8.5)% of cases (computer data was at odds with itself, leading to indeterminate CADx) and the results were appropriately held in 8 (2.5%) cases due to the presence of suicidality. Features independently associated with increased misdiagnosis and near misses were presence of any historical confounder (odds ratio, 3.49; 95% confidence interval, 1.58 to 7.73, sig P= 0.0020) including psychiatric background, severe neuro-psychiatric symptoms, medical comorbidities, and English as second language. The clinical diagnosis of Alzheimer's disease was associated with better CADx performance (Odds ratio 0.41, 95% CI: 0.18 to 0.95, P = 0.0383) compared to normal, MCI, DLB. **Conclusion:** The CADx was particularly efficient at assisting clinical diagnosis of AD, suggesting its usefulness as an extender support system within general practice. Confounders and non-AD clinical diagnoses were associated with misdiagnoses and future studies will be necessary to help refine the accuracy of CADx and improve its implementation in clinical practice.

LP109- ADVANCING MEASUREMENT IN ALZHEIMER'S DISEASE AND RELATED DISORDERS THROUGH DIGITIZING ASSESSMENT OF MEANINGFUL ASPECTS OF HEALTH. P. Griffiths[1], C.Y. Wu[2], D. Stefko[3], L. Cesnakova[4], J. Goldsack[5] *(1. The Digital Medicine Society - Saumur (France), 2. The Digital Medicine Society - Portland (United States), 3. The Digital Medicine Society - Nashville (United States), 4. The Digital Medicine Society - Prague (Czech Republic), 5. The Digital Medicine Society - Sarasota (United States))*

Background: To assess the impact of an intervention on a patient's life, measurement must go beyond biological and clinical assessment of Alzheimer's Disease and Related Dementias (ADRD). Alongside this important work, the impact on the patient's lived experience needs to be appraised. Meaningful aspects of health (MAH) are the elements of the disease that a patient wants to prevent, does not want to worsen, or wants to improve. MAHs are typically expressed in the patient's own words and the context of their daily life. MAHs are the basis for measuring what is important to patients. In the case of ADRD, it is critical to understand what the care partner and the clinician consider meaningful. This will allow researchers to find an intersection between all three stakeholders, allowing for measurement of ADRD which is directly translatable to the patient's lived experience. Furthermore, given the global nature of clinical research, identifying MAHs that transcend language, culture, and place is essential. **Objectives:** To perform a systematic literature review of existing qualitative studies and summarize the frequently mentioned MAH at ADRD disease stages across people with different roles. To provide the basis for ongoing work led by a pre-competitive collaboration hosted by the Digital Medicine Society (DiMe) to develop a core set of high-value, globally

relevant digital measures of ADRD. **Methods:** A systematic literature search was conducted using the PubMed and Embase databases (PROSPERO: CRD42022342748). The searches were limited to articles published from 2002 to present (past 20 years). A total of 2,113 titles and abstracts were reviewed independently by 2 researchers for screening. A third reviewer reconciled discrepancies between the 2 screeners. Of the 2,113 titles and abstracts, 65 publications were selected for the full-text review. From the full-text screening, 32 articles were identified for the final data extraction, including 2 systematic review articles, 1 non-English article, and 4 articles hand-searched from the included systematic review articles. **Results:** Most articles were on Alzheimer's disease/mild cognitive impairment (MCI) (n = 19), followed by Lewy body disease (LBD) (n = 5) and mixed etiology disease (n = 3). No articles on frontotemporal dementia or vascular dementia alone were identified for inclusion. Most studies were conducted in North America (n = 9) and Europe regions (n = 9), followed by Asia (n = 3), mixed regions (n = 3), Africa (n = 1), Australia (n = 1), and South America (n = 1). Thirteen studies recruited dyads cohort (adults with ADRD and care partners), 13 studies recruited each role alone (n = 6 for adults with ADRD, n = 6 for care partners, n = 1 for clinicians), and only 2 studies recruited all three roles. Nearly half of the studies (48%) determined the ADRD diagnosis through hospitals and clinics (electronic medical records, physician referral etc). More than one-third of the studies (39%) recruited adults with mixed ADRD severities. Among the 30 original research articles, the most frequently reported meaningful outcomes were mental health (depression, anxiety et.; n = 21), followed by activities of daily living (n = 20), psychiatric symptoms (n = 15), communication/conversations (n = 14), memory (n = 13), behavior problems (n = 13), sleep (n = 13), self-care/hygiene (n = 13), and behavior change (n = 13) across studies. While adults with ADRD had mentioned mobility/ physical health, socialization, and recognizing names/people as important concepts, caregivers did not mention them as often across studies. Instead, 67% of articles that recruited caregivers mentioned behavior problems as a relevant concept. Communication/conversations (67%), psychiatric symptoms (50%), and sleep (44%) were frequently reported in articles targeting adults with moderate/severe AD but sparsely reported in MCI/mild AD articles (38%; 13%; 13%). Safety, medication management, comorbidity, and visual problems were only mentioned in articles targeting moderate/severe AD, but not MCI/mild AD. **Conclusion:** From the initial results arising from this literature review, we identified common elements of ADRD that 1) matter to patients, care partners and clinicians, and 2) transcend language, culture, and place. These relate to depression and anxiety, and sleep. We also discovered differences across these stakeholder groups. For example, patients place more emphasison mobility, physical health, socialization and recognizing names and people for patients, whereas care partners are more likely to prioritize behavior problems. There is limited available information for MAHs important to clinicians. This work will be used to develop a mixed methods survey to help address gaps in the MAH in ADRD for each of these three stakeholders and will be conducted across five countries. This work will allow us to understand which may be most appropriate to target with emerging digital health technologies, and to explore how these MAH could be parameterised for digital measurement in a way that is interpretable and useful for patients, care partners and clinicians. The overarching goal is to find meaningful digital measures that can be used to support drug development and clinical practice, the world over.

AD CLINICAL TRIALS AND COVID-19

LP110- SUSTAINED ACCELERATED COGNITIVE DECLINE IN OLDER ADULTS AS A RESULT OF THE COVID-19 PANDEMIC: ANALYSIS OF THE PROTECT UK STUDY DATA. A. Corbett[1], C. Ballard[1], B. Creese[1], A. Hampshire[2], D. Aarsland[3], H. Brooker[1] *(1. University of Exeter - Exeter (United Kingdom), 2. Imperial College London - London (United Kingdom), 3. King's College London - London (United Kingdom))*

Background: The full impact of the COVID-19 pandemic on public health is yet to be fully understood. Whilst the direct long-term health effects of SARS-CoV-2 infection are increasingly being recognised there is little understanding of the wider impacts of the pandemic conditions on public health. The societal restrictions during the first year of the pandemic hold the potential for considerable detriment to cognitive and mental health, particularly since major dementia risk factors such as exercise and dietary habits were impacted during this period. The longitudinal PROTECT study offers a unique means of exploring the impact of the pandemic on cognition in older adults. **Methods:** This is a longitudinal analysis of data from 3412 people aged 50 and over in the PROTECT study using computerised neuropsychology data and online self-report data collected before the pandemic (March 2019-2020) and during its first year (March 2020-March 2021) and second year (March 2021-2022). Cognitive trajectory was compared across the three time periods using ANCOVAs. Additional sub-group analyses were conducted in people with Mild Cognitive Impairment (n=147) and self-reporting Covid-19 infection (n=752), and an exploratory regression analysis identified lifestyle and medical factors associated with change in cognitive trajectory. **Findings:** Both executive function and working memory trajectories showed significant worsening across the whole cohort (p=0.0006) and sub-groups in the first year of the pandemic. This worsening was sustained in the second year (p=0.043). Regression analysis indicated that exercise, alcohol use and mental health significantly contributed to these declines, with sustained impacts in people with MCI and Covid-19 in the second year. **Interpretation:** The pandemic conditions have resulted in a significant worsening of cognition in older adults, driven by major dementia risk factors. The sustained decline highlights the need for public health interventions to mitigate the potential for dementia risk, particularly in people with MCI where conversion to dementia is likely within five years. The findings emphasise the need to consider long-term intervention for people with Covid-19 to support cognitive health in the long-term.

LETTER TO THE EDITOR: CASSAVA SCIENCES RESPONSE TO CTAD ABSTRACT LP105A. R. Barbier *(Cassava Sciences, Inc., Austin, TX, (USA))*

Dear Editor, We are developing simufilam, a novel drug candidate, for mild-to-moderate Alzheimer's disease. We appreciate the opportunity to respond to CTAD abstract LP105A (J Prev Alz Dis 2022;9(S1):S51-S248). **The Abstract Does Not Describe an Attempt to Replicate Prior Experiments:** First, the title refers to the "replication" of experiments, but the authors do no such thing. Rather, they describe a one-off experiment using a different measurement technique. That is not "replication." Second, the binding affinity of simufilam was previously established using two reliable techniques: competitive binding and direct binding to the full protein, either purified or in tissue (1). The authors describe a third

technique, isothermal titration calorimetry (ITC). In their hands, ITC generated incongruous results. The authors' incongruous result does not nullify two prior experiments. The meaning of the authors' results is inconclusive, at best. **The Reliability of Data Is in Doubt:** First, the authors could only have used adulterated simufilam. Simufilam is a proprietary compound not authorized for manufacture, sale or use in the US and countries where it is patented. Any drug not manufactured in compliance with cGMP regulations is "adulterated" under the law. Adulterated simufilam may be sold illegally on-line, but an illegal manufacturer/seller of adulterated simufilam is unlikely to comply with FDA regulations that assure identity, strength, quality, and purity. In addition, a drug must be authenticated by independent, third-party certification to ensure manufacturing standards are met. The authors' use of adulterated simufilam sourced from an unauthorized vendor raises questions about data reliability. Second, the abstract does not describe an appropriate positive control. A negative experimental result is significant and reliable if compared to a positive result from a positive control. The authors do not, however, describe a positive control showing a small molecule binding to a short peptide using ITC. Instead, they reference a small molecule binding to its whole protein target (carbonic anhydrase II). Third, ITC is a sensitive research technique, and results depend strongly on the chosen experimental parameters (2). Different values of enthalpies (the total heat energy of a system) can be obtained with different instruments and different setting parameters. ITC results are affected by numerous factors, including choice of buffer, solvent, pH and concentration; presence of impurities; equilibration temperature; saturation of the signal; and computational methodologies. Any one of these experimental factors can contribute variability to the data or lead to unclear results. **Conclusion:** Abstract LP105A does not nullify two prior experiments relating to simufilam. The authors used adulterated simufilam to conduct their experiment. Their experiment lacks an appropriate positive control. They engaged in patent infringement. They failed to disclose all conflicts of interest. The abstract must be read in this context. As recently highlighted by the Journal of Clinical Investigation, everyone should be concerned "when whistleblowers profit from allegations of scientific misconduct" (3). **Conflict of Interest:** Remi Barbier is President, CEO, Chairman and a shareholder of Cassava Sciences, Inc. Cassava Sciences has filed a defamation lawsuit against the authors of this abstract and other defendants in US federal court alleging dissemination of false information about simufilam. **References:** 1. Wang, HY, et al. PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis. Neurobiol Aging 55, 99-114 (2017). 2. Medoš, Ž., Čobanov, I., Bešter-Rogač, M. et al. Usually overlooked problems related with measurements of high-heat effects using power compensation isothermal titration calorimetry. J Therm Anal Calorim 145, 87–96 (2021). https://doi.org/10.1007/s10973-020-09663-2. 3. McNally EM. Conflicting interests: when whistleblowers profit from allegations of scientific misconduct, J Clin Invest. 2022;132(21):e166176. https://doi.org/10.1172/JCI166176

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