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Editorial

Are We There Yet (and How Do We Get There…)?

R.A. Sperling

Corresponding Author: Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA USA, reisa@bwh.harvard.edu

Following nearly three decades of controversial and often disappointing clinical trial results, the reports over the past year have finally yielded consistent results that the Alzheimer's disease (AD) field is on the right track in the pursuit of slowing the progression of the pathophysiological process and clinical symptoms of AD. The Phase 3 trial results from two anti-amyloid monoclonal antibodies, lecanemab (1) and donanemab (2), demonstrated marked reduction in amyloid PET levels and moderate slowing of cognitive and clinical decline in the early stages of symptomatic AD. Although there remains some debate about the cost-effectiveness and clinical meaningfulness of the effect size, it is now clear that aggressive reduction of fibrillar forms of amyloid-β can modulate the clinical course of AD.

Although there will certainly be ongoing discussion regarding potential advantages of one antibody versus another, the consistency of the findings across lecanemab and donanemab, as well as the results from less successful anti-amyloid monoclonal antibody programs, point to several key findings that should guide our future work. First, the amount of amyloid plaque reduction, as estimated by PET imaging, appears to be an important factor. It remains unclear whether it is the total amount or rate of amyloid clearance or the percentage of individuals who fall to below the somewhat arbitrary "amyloid negative" level that drives the clinical effect. There is not yet a dependable correspondence at the individual participant level that can accurately predict the degree of clinical slowing for a given rate or level of amyloid decrease. Nevertheless, a consistent pattern emerges across the programs that links greater reduction in amyloid PET signal below baseline levels to better clinical response. It is also possible that although amyloid PET tracers primarily bind amyloid-β in its fibrillar forms in plaques and cerebral amyloid angiopathy, that the clinical response is due to associated reduction of "toxic halos" of soluble oligomeric forms or rebalancing clearance pathways that could augment reduction of multiple forms of amyloid-β. While there are differences in the intended targets of these monoclonal antibodies, specifically that donanemab was engineered to bind to pyroglutamate modified N-terminus amyloid-β present in plaque, lecanemab was designed to have high affinity to soluble large molecular weight amyloid-β protofibrils, aducanumab and gantenerumab show the highest binding to fibrils, whereas solanezumab and crenezumab bind primarily to monomeric forms of amyloid-β, however, potential differences regarding the specificity of the in vivo mechanisms of each of these antibodies in the living human brain and their effects on synaptic function, tau aggregation and neurodegeneration, remain to be fully elucidated.

Interestingly, one of the areas with somewhat less consistent findings was the effects on tau PET imaging outcomes, despite similar range of slowing cognitive and clinical decline. Lecanemab reported slowing of the rate of tau PET increases in multiple temporal lobe composites in the treated group compared to placebo, whereas donanemab did not find evidence of treatment effects on tau PET in the pre-specified frontal composite (based on Phase 2 data) or global tau PET measures. This discrepant finding with donanemab is an apparent paradox given the evidence from observational studies that tau PET measures track clinical progression reasonably closely during the early symptomatic stages of AD. These differences could be due to multiple technical factors, including different tau PET tracers and/or different processing and regional analytic approaches, in addition to the possibility that the anti-amyloid antibody mechanism of action could have differential effects on tau aggregation and propagation. Fortunately, ongoing analyses of both datasets will be presented at CTAD this year and should yield further insights into these apparent discrepancies.

Another area that requires more research and understanding is amyloid related imaging abnormalities or ARIA (5) – as these phenomena remain the dose-limiting adverse event, and the presence of >4 microhemorrhages at screening (ARIA-H) means that many patients will not be eligible to receive immunotherapy. The data are becoming clearer that aggressive amyloid clearance is associated with ARIA, particularly among IgG1 antibodies. ARIA with edema (ARIA-E) and ARIA-H are hypothesized to share a common pathophysiology related to cerebral amyloid angiopathy (CAA), but the role of perivascular inflammation and/or direct removal of amyloid from vessels remains to be determined. The timing of ARIA-E which occurs after the first few treatments with

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most but not all anti-amyloid monoclonal antibodies may provide clues. Although the number of APOE ε4 alleles and C-max dose of antibody confer the highest risk for ARIA edema/effusion (ARIA-E), we still do not fully understand why a small percentage of individuals become symptomatic. Slow accumulation of microhemorrhages is observed more commonly over the course of AD in the absence of treatment, particularly among APOE ε4 carriers, but the very rare occurrence of macrohemorrhage continues to be of concern. Studies with titration regimens and subcutaneous administration are ongoing to evaluate potential reduction in risk of both forms of ARIA.

The second consistent finding across these programs is that earlier intervention within the range of symptomatic AD patients was associated with greater clinical benefit. This pattern was clear both across and within programs, whether "earlier" was defined as earlier clinical stage (MCI vs. mild dementia), lower baseline amyloid PET centiloid values across programs, earlier clinical stage (MCI vs. mild dementia), or lower tau PET levels at baseline. This finding is particularly remarkable as the cognitive and clinical outcomes utilized in these programs were developed primarily for tracking mild-moderate dementia progression and may be less powerful in detecting decline at earlier clinical stages of disease, supporting the hypothesis that anti-amyloid intervention may be more efficacious when initiated as early as possible.

The anti-amyloid trials in the asymptomatic or "preclinical" stages of AD, however, have not yet succeeded in slowing subtle cognitive decline in either autosomal dominant or sporadic AD (3, 4). These studies have demonstrated that rate of cognitive decline is associated with the baseline level of amyloid burden even at this very early stage of disease, but unfortunately, the majority of these secondary prevention trials tested anti-amyloid approaches that did not substantially decrease amyloid PET from baseline levels. Ongoing trials in preclinical AD are testing antibodies with proven potent amyloid reduction, including lecanemab in the AHEAD Study (clinicaltrials.gov/ct2/show/NCT04468659) and donanemab in the TRAILBLAZER-Alz-3 Study (clinicaltrials.gov/ct2/show/NCT05026866). These studies will test the hypothesis that marked reduction of amyloid burden started prior to clinical impairment can more substantially impact the curve of cognitive and functional decline. The recent advances in AD blood-based biomarkers are already serving to improve the efficiency of screening for these preclinical AD trials and are likely to serve as primary outcome measures in future prevention trials.

In addition to intervening at much earlier stages of AD, additional work is needed to further impact slowing of progression during the clinical stages of AD. We must redouble our efforts to better understand the contributions to cognitive decline in more diverse, representative cohorts, as it is becoming clear that there may be different rates of amyloid pathology prevalence across races and potentially across ethnicities, and that multiple factors may impact higher risk of dementia among communities of color. The success of the recent anti-amyloid monoclonal antibody trials will now spawn the first combination trials of amyloid and tau therapeutics (6), as well as other approaches, including amyloid therapeutics tested in combination with agents aimed at reduction of vascular and metabolic risk, and neuroprotective mechanisms. We must also invest in therapeutic approaches that will be lower cost and more widely accessible around the world than frequent antibody intravenous infusions, including subcutaneous formulations, active immunization, and potential oral agents. This has been a very exciting year indeed, but we must build rapidly on our new knowledge and accelerate our efforts to prevent further cognitive and functional decline in the tens of millions around the world at risk for developing dementia due to AD and those already suffering from the devastating consequences of these symptoms.

Conflict of Interest: RAS has served as a paid consultant for AC Immune, Acumen, Alector, Bristol Myers Squibb, Genentech, Ionis, Janssen, Oligomerix, Prothena, Roche and Vaxxinity. She receives trial funding from Eisai and Eli Lilly for public-private partnership clinical trials and receives grant funding from the National Institute on Aging/National Institutes of Health, GHR Foundation, and the Alzheimer's Association.

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ABSTRACTS

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Symposia

S1- THE EFFECTS OF RACE AND GENDER ON AMYLOID POSITIVITY

Introduction : Determining amyloid status in different racial, ethnic, and gender groups. Suzanne Schindler *(Washington University St. Louis, St. Louis, MO (United States))*

Background: Research studies, clinical trials, and clinical care require biomarkers of Alzheimer disease (AD) brain pathology that perform consistently across racial, ethnic, and sex or gender groups. However, some studies indicate that biomarker levels may vary by race, ethnicity, and sex or gender groups, even after adjusting for key covariates. Further, the relationships between biomarkers, and between biomarkers and cognitive outcomes, may vary by these groups, potentially leading to disparities that could impact the diagnosis and care of patients. **Methods:** Epidemiological studies of dementia prevalence by race, ethnicity, and sex or gender will be reviewed. Research studies comparing AD biomarkers in different groups will be described, including their limitations. The apparent discrepancies between population-based studies of dementia and AD biomarker research studies will be highlighted, including potential reasons for these differences. Approaches to interpreting biomarker levels across groups will be discussed. **Results:** Epidemiological studies indicate that self-identified Black or African American and Hispanic individuals have a higher prevalence of dementia than Non-Hispanic White individuals. The prevalence of dementia also varies by sex and gender in some studies but not others. Notably, these studies do not routinely include AD biomarker testing, so it is unknown whether reported dementia is related to AD, alternative etiologies, or mixed etiologies. In a seeming discrepancy, Black and Hispanic individuals in some AD research studies have a lower frequency of amyloidosis, as well as a lesser degree of amyloidosis. Studies have also found differences by sex or gender in some AD biomarkers but not others. There are multiple potential reasons for seemingly conflicting findings in population-based studies of dementia and AD biomarker research studies, including biases in recruitment, different frequencies of dementia not caused by AD in different groups, and differential associations between biomarkers and AD pathology that may be mediated by social determinants of health and/or medical conditions. **Conclusions:** Accurate determination of amyloid status across racial, ethnic, and gender groups will be increasingly important for equitable care of patients with dementia. Early studies have significant limitations that make understanding group differences challenging. The AD field would benefit from larger studies that include biomarker testing, especially with blood-based biomarkers that are more accessible and acceptable to individuals in minoritized groups. Data on social determinants of health and medical conditions will also be essential to understanding the appropriate interpretation of biomarker results. The use of biomarker cut-offs based on race have historically led to unintended negative consequences, so interpretation of biomarker results based on the factors underlying group differences (e.g., differential rates of renal clearance) may be preferable. Additionally, some biomarker tests may perform more consistently across groups, reducing or eliminating the need for covariate adjustment. Overall, awareness and understanding of the associations between biomarkers and groups may improve understanding of AD and enable greater accuracy of biomarker testing in all individuals. **Key words:** Race, ethnicity, sex, gender, biomarkers, amyloid. **Disclosures:** SES served on a scientific advisory board for Eisai.

Presentation 1: Amyloid PET results from the GAP Bio-Hermes study: initial findings on differences between racial and ethnic groups, Robin Wolz[1], Lynne Hughes[2], Richard Manber[1], Richard Mohs[2], John Dwyer[2], Douglas Beauregard[2] *(1. IXICO - London (United Kingdom), 2. Global Alzheimer's Foundation - Washington (United States))*

Background: The FDA has set out plans to improve enrolment of traditionally under-represented racial and ethnic groups in Alzheimer's disease (AD) clinical trials [1]. Differences in amyloid PET positivity (Aβ+) and standardized uptake value ratio (SUVR) between racial and ethnic groups have been reported, but with inconsistent findings [2-4]. Systematic disparities in confounding effects (e.g. co-pathology, genetic risk factors) complicate interpretation, and site-specific acquisition differences have been suggested as potential source of bias [4]. The GAP Bio-Hermes study has enrolled 945 study volunteers across 16 US sites: 398 cognitively normal subjects, 293 with MCI and 254 with mild Alzheimer's disease. The study has recruited 23% percent from traditionally underrepresented communities. **Methods:** Florbetapir PET was collected on all study subjects following central site qualification. Visual read was performed centrally through the VisQ process [5] in the MIM Software [6], where SUVR is considered by a reader to perform classification into Aβ+ or Aβ-. 924 subjects were included in the analysis: 104 Black or African American, 803 White and 16 Asian subjects. 89% participants identified as Not Hispanic or Latino and 11% identified as Hispanic or Latino. Excluded cases did not identify as one of the three racial groups, or one or more of the assessments required for the analysis was not available. Comparison of Aβ status and SUVR was performed between the racial and ethnic groups as well as between different ApoE groups: ε4-non-carriers (N=579), ε4-carriers (one or two ε4 alleles, N=345), ε4 homozygotes (two ε4 alleles, N=51)). Analysis was performed in the full cohort and in the subset of 398 healthy subjects. Average MMSE was 26.7 ± 2.9 (healthy sub-group: 28.4 ± 1.5) and average age was 72.0 ± 6.7 (70.3 ± 6.5). **Results:** All presented results are statistically significant. Other comparisons described in Methods did not show statistically significant difference. Aβ+ proportion is 37% in the overall cohort and 22% in the cognitively normal sub-group. Aβ+ proportion in ε4-non-carriers, ε4-carriers and ε4 homozygotes is 22% (cognitively normal sub-group: 14%), 62% (39%), 88% (78%), respectively. Aβ+ proportion in Black or African American population and White population is 29% and 38% respectively. Mean SUVR is 1.16 in the overall cohort and 1.07 in the cognitively normal sub-group. Mean SUVR in ε4-non-carriers, ε4-carriers and ε4 homozygotes is 1.08 (healthy sub-group: 1.03), 1.29 (1.16), 1.41 (1.34), respectively. The Aβ+ group in the White population shows higher SUVR than the Aβ+ group in the Black or African American population; the Aβ- group shows lower SUVR in the White population. **Conclusion:** The presented findings extend previous results on the comparability of amyloid PET results between racial groups. Additional analysis will be performed to inform the design of increasingly diverse AD clinical trials and procedures that enable reproducible and robust PET data collection and interpretation in those trials. **Key words:** Amyloid PET, ApoE, SUVR, VisQ, under-represented populations. **Disclosures:**

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Robin Wolz and Richard Manber are employees of IXICO. Lynne Hughes, Richard Mohs, John Dwyer, Douglas Beauregard are employees of the Global Alzheimer's Platform Foundation. **References:** 1. FDA Guidance for Industry, 2022. https://www.fda.gov/media/157635/download; 2. Wilkins et al; JAMA Neurol. 2022;79(11):1139-1147 https://jamanetwork.com/journals/jamaneurology/fullarticle/2796653; 3. Deters et al; Neurology. 2021 Mar 16; 96(11): e1491–e1500. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8032379/; 4. Gleason et al; Alzheimer's Dement.2022;18:1545–1564. [https://alz-journals.onlinelibrary.wiley.com/doi/pdf/10.1002/alz.12511]; 5. Harn et al; Clin Nucl Med. 2017 Aug;42(8):577-581; 6. MIM Software Package [https://www.mimsoftware.com/]

Presentation 2: Race and Sex Effects on Rates of Amyloid Positivity in Real-World Memory Care: Insights from IDEAS and New IDEAS, Charles Windon[1], Maria Carillo[2], Peggye Dilworth-Anderson[3], Constantine Gatsonis[4], Emily Glavin[5], Lucy Hanna[6], Bruce Hillner[7], Andrew March[5], Sid O'bryant[8], Robert Rissman[9], Barry Siegel[10], Karen Smith[1], Christopher Weber[2], Consuelo Wilkins[11], Gil Rabinovici[1] *(1. Memory and Aging Center, UCSF Weill Institute for Neurosciences, University of California, San Francisco - San Francisco (United States), 2. Alzheimer's Association - Chicago (United States), 3. Gillings School of Global Public Health, University of North Carolina-Chapel Hill - Chapel Hill (United States), 4. Department of Epidemiology and Biostatistics, Brown University School of Public Health - Providence (United States), 5. American College of Radiology - Reston (United States), 6. Center for Statistical Sciences, Brown University School of Public Health - Providence (United States), 7. Department of Medicine, Virginia Commonwealth University - Richmond (United States), 8. Institute for Translational Research, University of North Texas Health Science Center at Fort Worth - Fort Worth (United States), 9. Department of Physiology and Neuroscience, Alzheimer's Therapeutic Research Institute, Keck School of Medicine of the University of Southern California - San Diego (United States), 10. Mallinckrodt Institute of Radiology, Washington University in St Louis - St. Louis (United States), 11. Department of Medicine, Division of Geriatric Medicine, Vanderbilt University Medical Center - Nashville (United States))*

Background: The New IDEAS study is evaluating the impact of beta-amyloid PET on clinical management and diagnosis among cognitively impaired, ethnoculturally diverse Medicare beneficiaries from across the United States. Black/African American and Latino/a/x (heretofore LatinX)/Hispanic participant enrollment is emphasized, given underrepresented populations only constituted ~10% of the original IDEAS study cohort. **Methods:** New IDEAS is an observational, open-label, longitudinal cohort study that will enroll 7,000 Medicare beneficiaries (minimum 2,000 Black/African American and 2,000 LatinX/Hispanic individuals) with MCI or dementia at ~150 memory clinics across the US between 2020-2024. Participants are classified at presentation clinically as "typical", memory-predominant MCI/ dementia suggestive of Alzheimer's Disease, and "atypical", where non-memory symptoms predominate, significant comorbidities may be contributing, mixed disease may be present, and clinical course is divergent. Study procedures in New IDEAS follow the design of the original IDEAS study, though New IDEAS includes an optional blood plasma sample collection. The study features a community engagement approach led by Vanderbilt University, University of North Carolina and the Alzheimer's Association. Efforts began with identification of major metropolitan regions with large numbers of potential participants followed by deployment of sustained local regional efforts (i.e., trainings, tailored recruitment, etc.). Structural barriers to research participation (i.e., lack of transportation) have also been addressed. **Results:** A total of 139 dementia practices, 237 dementia specialists, and 91 PET facilities have participated in New IDEAS. Among dementia practices, 27.3% (38/139) are solo practices, 42.4% (59/139) group practices, 17.3% (24/139) university based, and 13.0% (18/139) hospital based. Dementia specialists' fields of expertise include Neurology (87.8%, 208/237), Psychiatry (4.6%, 11/237), and Geriatrics (7.9%, 18/237). Most PET facilities (84.6%, 77/91) are independent, though 15.4% (14/91) are hospital-based. As of May 30, 2023, 4293 unique individuals have registered for the study and 3432 amyloid PET scans completed and assessed. Blood sample collection participation has totaled 2811 consented individuals and 866 collected samples. Median age of registered participants is 75 (35-98) years and 55.6% (2387/4293) are female. Median MMSE score is 26 (0-30) for participants with MCI and 20 (0-27) for participants with dementia. Representation among ethnocultural groups is notable for: Black/African American individuals 22.5% (966/4293), LatinX/Hispanic individuals 20.1% (863/4293), all other individuals 57.4% (2464/4293). A total of 3415 individuals have successfully completed amyloid PET scan and been assessed clinically with 63% (2128/3415) having MCI and 37.7% (1287/3415) having dementia. Rates of amyloid positivity are higher in atypical vs typical syndromes (combined MCI and dementia) across all groups: Black/African American 68.4% vs 47.8%; Latinx/Hispanic 66.1% vs 54.4%; all others 70.8% vs 63.0%. By ethnocultural group, 60.7% (425/700) of Black/African American and 61.6% (364/591) of LatinX/Hispanic individuals are amyloid positive compared to 68.4% (1449/2117) of all other individuals. In the original IDEAS study, 53.8% of Black/African American and 54% of LatinX/Hispanic individuals were amyloid positive compared to 62.7% of White individuals. **Conclusion:** New IDEAS has demonstrated large-scale enrollment of ethnoculturally diverse individuals in a study to better evaluate the clinical utility of beta-amyloid PET is possible and will advance our understanding imaging biomarkers in a real-world setting. **Key words:** Amyloid, PET, New IDEAS. **Clinical Trial Registry:** NCT04426539; https://clinicaltrials.gov/. **Disclosures;** Dr Windon reported grants from the Alzheimer's Association and the National Institutes of Health and has received honorariums from the American Academy of Neurology and LCN. Ms Glavin, Ms Hanna, Mr March, and Dr Gatsonis reported funding from the American College of Radiology. Dr Carrillo, Dr Griffin, and Dr Weber are employed by the Alzheimer's Association. Dr Dilworth-Anderson reported funding by the American College of Radiology, the National Institutes of Health, the National Center for Advancing Translational Sciences, and the University of North Carolina Chapel Hill. Dr Hillner reported receiving grants and clinical trial support from the American College of Radiology and the Alzheimer's Association. Dr O'Bryant reported multiple grants from the National Institute on Aging as well as patents on precision medicine approaches to neurodegenerative diseases and holds an interest in Cx Precision Medicine. Dr Rissman reported grants from the National Institutes of Health and Alzheimer's Association. Dr Siegel reported grants from the American College of Radiology and nonfinancial support from the Alzheimer's Association during the conduct of the study and personal fees from the American College of Radiology (self and spouse), Avid Radiopharmaceuticals, Curium Pharma, Progenics Pharmaceuticals, American Medical Foundation for Peer Review & Education, Siemens

Healthineers (spouse), Capella Imaging, GE Healthcare, Lantheus Medical Imaging, Radiological Society of North America (self and spouse), ECOG-ACRIN Medical Research Foundation (spouse), Evicore Healthcare (spouse), and grants from Curium Pharma, Progenics Pharmaceuticals, ImaginAb, and Blue Earth Diagnostics outside the submitted work. Dr Wilkins reported grants from the National Institutes of Health, Patient-Centered Outcomes Research Institute, Robert Wood Johnson Foundation, American College of Radiology, and Alzheimer's Association. Dr Rabinovici reported grants from the National Institutes of Health, American College of Radiology, Alzheimer's Association, Rainwater Charitable Foundation, Avid Radiopharmaceuticals Inc, GE Healthcare, Life Molecular Imaging, and Genentech and personal fees from Alector, Eli Lilly, Johnson & Johnson, Genentech, and Roche and is Associate Editor of JAMA Neurology. **References:** Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. JAMA. 2019;321(13):1286-1294. doi:10.1001/jama.2019.2000; Wilkins CH, Windon CC, Dilworth-Anderson P, et al. Racial and ethnic differences in amyloid PET positivity in individuals with mild cognitive impairment or dementia: a secondary analysis of the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) cohort study [published online ahead of print, 2022 Oct 3]. JAMA Neurol. 2022;79(11):1139-1147. doi:10.1001/jamaneurol.2022.3157.

S2- DONANEMAB IN EARLY SYMPTOMATIC ALZHEIMER'S DISEASE: ADDITIONAL INSIGHTS FROM TRAILBLAZER-ALZ 2.

J.R. Sims[1], T. Iwatsubo[2], S.M. Greenberg[3,4], M. Mintun[1], A. Atri[5,6], J.A. Zimmer[1], C.D. Evans[1], M. Lu[1], Paul Ardayfio[1], J. Sparks[1], C. Battioui[1], A.M. Wessels[1], A. Atkins[1], S. Shcherbinin[1], H. Wang[1], E.S. Monkul Nery[1], E.C. Collins[1], D.A. Brooks[1] *(1. Eli Lilly and Company - Indianapolis, IN (United States), 2. Graduate School of Medicine, The University of Tokyo - Tokyo (Japan), 3. Harvard Medical School - Boston, MA, (United States), 4. Massachusetts General Hospital - Boston, MA, (United States), 5. Banner Sun Health Research Institute and Banner Alzheimer's Institute - Sun City and Phoenix, AZ, (United States), 6. Brigham and Women's Hospital - Boston, MA, (United States))*

Introduction: Positive Phase 3 outcomes [1] were reported from the TRAILBLAZER-ALZ 2 study evaluating donanemab as an investigational treatment for early symptomatic Alzheimer's disease (AD), replicating previously reported positive Phase 2 results from TRAILBLAZER-ALZ [2]. Donanemab treatment significantly slowed disease progression on multiple clinical scales including the integrated AD Rating Scale (iADRS) and Clinical Dementia Rating–Scale Sum of Boxes (CDR-SB), and rapidly and robustly reduced biomarkers associated with AD, including amyloid positron emission tomography (PET) and plasma P-tau217. Building on previous TRAILBLAZER-ALZ 2 publications with new insights, the symposium will feature presentations focused on amyloid-related imaging abnormalities (ARIA) risk, benefit prediction, and clinical relevance of donanemab treatment. **References:** 1. Sims, J. R., Zimmer, J. A., Evans, C. D., Lu, M., Ardayfio, P., Sparks, J., Wessels, A. M., Shcherbinin, S., Wang, H., Monkul Nery, E. S., Collins, E. C., Solomon, P., Salloway, S., Apostolova, L. G., Hansson, O., Ritchie, C., Brooks, D. A., Mintun, M., Skovronsky, D. M., & TRAILBLAZER-ALZ 2 Investigators (2023). Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA, 330(6), 512–527. https://doi.org/10.1001/jama.2023.13239; 2. Mintun, M. A., Lo, A. C., Duggan Evans, C., Wessels, A. M., Ardayfio, P. A., Andersen, S. W., Shcherbinin, S., Sparks, J., Sims, J. R., Brys, M., Apostolova, L. G., Salloway, S. P., & Skovronsky, D. M. (2021). Donanemab in Early Alzheimer's Disease. The New England journal of medicine, 384(18), 1691–1704. https://doi.org/10.1056/NEJMoa2100708

Presentation 1: ARIA Insights from the Donanemab Trials, Steven M. Greenberg

ARIA is an important safety concern of amyloid-targeting therapies. Improved understanding of risk factors for ARIA may help to inform individual benefit/risk of treatment as well as the underlying mechanism. To address this important topic, post-hoc analyses were performed with all donanemab exposures (N=2031) in completed Phase 2 and Phase 3 studies using TRAILBLAZER-ALZ (N=131; NCT03367403), TRAILBLAZER-ALZ 2 (N=853; NCT04437511), and a newly completed addendum (N=1047) to explore associations between ARIA−edema and effusions (ARIA-E) occurrence and patient characteristics. The addendum was a multicenter, open-label, Phase 3 addendum to TRAILBLAZER-ALZ 2 conducted to collect exposure and safety in participants with early symptomatic Alzheimer's disease (AD) with amyloid pathology. The addendum (NCT04437511) enrolled participants from 122 sites in the United States, Canada, and Japan. Enrollment in the addendum was based on amyloid PET imaging and unlike the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 studies, tau PET was not required for study entry; participants previously known to be tau PET negative (N=253) were included. All participants received donanemab every 4 weeks (w) for a maximum of 72w and stopped donanemab treatment if amyloid PET-based completion criteria were met (as previously defined [1, 2]. Baseline demographics for the addendum population were n=566 (54%) female, n=652 (62%) APOE ε4 carriers, and n=707 (67%) mild AD. Compared to previous trials, the addendum population had lower mean baseline amyloid level at screening (82.5 [SD 37.2] Centiloids compared to 107.6 [36.0] Centiloids in TRAILBLAZER-ALZ and 103.5 [34.5] Centiloids in TRAILBLAZER-ALZ 2), a higher proportion of Hispanic/Latino participants (11% [n=100] compared to 4% [n=5] in TRAILBLAZER-ALZ and 6% [n=35] in TRAILBLAZER-ALZ 2), and a higher proportion with MCI (33% [n=345] compared to 18.3% [n=24] in TRAILBLAZER-ALZ and 17% [n=146] in TRAILBLAZER-ALZ 2). For the addendum, ARIA-E occurred in 19.8% of participants (n=207 compared to 27.5% [n=36] in TRAILBLAZER-ALZ and 24% [n=205] in TRAILBLAZER-ALZ 2). Using an integrated dataset of donanemab exposures from TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2, and the addendum, machine learning approaches that included penalized regression and decision tree-based models were employed in a hypothesis-generating manner to determine possible variables associated with ARIA-E. Across 2031 donanemab exposures, baseline characteristics were analyzed. This presentation will share additional insights on the ARIA-E risk analyses. 1. Sims, J. R., Zimmer, J. A., Evans, C. D., Lu, M., Ardayfio, P., Sparks, J., Wessels, A. M., Shcherbinin, S., Wang, H., Monkul Nery, E. S., Collins, E. C., Solomon, P., Salloway, S., Apostolova, L. G., Hansson, O., Ritchie, C., Brooks, D. A., Mintun, M., Skovronsky, D. M., & TRAILBLAZER-ALZ 2 Investigators (2023). Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized

Clinical Trial. JAMA, 330(6), 512–527. https://doi.org/10.1001/jama.2023.13239; 2. Mintun, M. A., Lo, A. C., Duggan Evans, C., Wessels, A. M., Ardayfio, P. A., Andersen, S. W., Shcherbinin, S., Sparks, J., Sims, J. R., Brys, M., Apostolova, L. G., Salloway, S. P., & Skovronsky, D. M. (2021). Donanemab in Early Alzheimer's Disease. The New England journal of medicine, 384(18), 1691–1704. https://doi.org/10.1056/NEJMoa2100708

Presentation 2: Predicting Efficacy in Donanemab-Treated Participants, Mark Mintun

Results from the TRAILBLAZER-ALZ 2 study suggested that donanemab treatment slowed relative disease progression to a greater degree in participants with less advanced disease. To further investigate this hypothesis, post-hoc efficacy analyses were conducted to explore the following objectives: 1) disease slowing according to baseline tau PET as assessed using the iADRS and CDR-SB scales, 2) biomarkers of efficacy including amyloid clearance and change in P-tau217 in no/very low tau participants from the recent TRAILBLAZER-ALZ 2 addendum, and 3) the effect of additional baseline characteristics as predictors of donanemab treatment benefit, especially baseline disease stage and P-tau217, alone or in combination with other baseline characteristics. Disease stage modeling in the third objective was done by staging patients relative to each other and aligning their longitudinal trajectories of clinical scores along an estimated disease timeline by a latent-time mixed-effects model. Donanemab treatment effect, modeled as disease slowing, was allowed to depend on the predicted disease stage. Collectively, results that will be presented suggest that while donanemab is more efficacious in those early in the disease, there is still potential benefit for all candidates regardless of tau level or disease stage. Further evaluation of baseline characteristics may allow for better individualized estimates of treatment benefit.

Presentation 3: Clinical Relevance of Donanemab Treatment, Alireza Atri

Translating clinical trial findings into concepts that matter to patients and clinicians permits improved interpretation of treatment benefits. Surveys of patients with AD, their care partners, and clinicians, endorse the value of slowing disease progression to remain in earlier clinical stages of disease so patients can preserve greater independence and ability to participate in activities they find important [3]. This presentation will explore the impact of donanemab by evaluating the effects of donanemab treatment on individual item-measures of cognition and daily function and on risk of transition to more advanced clinical severity. In the TRAILBLAZER-ALZ 2 study, donanemab substantially slowed the rate of decline by 22-36% on both the iADRS and the CDR–SB. The iADRS and CDR-SB are comprised of items that assess cognition and daily function and can serve as indicators of global clinical severity. Analyses examining the relationship between disease severity and performance on individual iADRS items show that impairments in episodic memory (word recall, delayed word recall) present early, preceding broader impairments in cognition and memory-dependent instrumental activities of daily living (iADLs: talking about recent experiences related to reading and TV). Treatment with donanemab significantly slowed progression on these items. Furthermore, donanemab significantly slowed progression of more widespread deficits in iADLs (performing hobby, using appliance, being left at home) and multi-domain cognitive impairments in orientation and language. On the CDR-SB, donanemab treatment benefits were not limited to particular domains but showed significant and broad impact in slowing progression on all individual cognitive and functional domains (memory, orientation, judgment/problem solving, community affairs, home/hobbies, and personal care). Collectively, these results provide evidence of donanemab treatment effects across multiple cognitive and daily functions, both reducing the risk of transitioning into more severe stages of disease and allowing patients to engage in activities and maintain independence longer. **Reference**: 1. DiBenedetti, D. B., Slota, C., Wronski, S. L., Vradenburg, G., Comer, M., Callahan, L. F., Winfield, J., Rubino, I., Krasa, H. B., Hartry, A., Wieberg, D., Kremer, I. N., Lappin, D., Martin, A. D., Frangiosa, T., Biggar, V., & Hauber, B. (2020). Assessing what matters most to patients with or at risk for Alzheimer's and care partners: a qualitative study evaluating symptoms, impacts, and outcomes. Alzheimer's research & therapy, 12(1), 90. https://doi.org/10.1186/s13195-020-00659-6

S3- CLINICAL AND ATN BIOMARKER FINDINGS ON THE IMPACT OF AMYLOID REMOVAL IN A 10 YEAR PREVENTION TRIAL – THE DIAN-TU-001.

R. Bateman[1], E. Mcdade[1], G. Wang[1], N. Bartelemy[1], Y. Li[1], B. Gordon[1], T. Benzinger[1], L. Ibanez[1], S. Salloway[2], M. Farlow[3], D. Clifford[1], J. Llibre-Guerra[1], C. Supnet[1], C. Xiong[1], J. Hassenstab[1], A. Fagan[1], S. Mills[1], A. Aschenbrenner[1], R. Hornbeck[1], A. Santacruz[1], R. Yaari[4], G. Klein[5], R. Doody[5], M. Baudler[5], A. Atri[6] *(1. Washington University School Of Medicine - St. Louis (United States), 2. Butler Hospital and Warren Alpert Medical School of Brown University - Providence (United States), 3. Indiana University School of Medicine - Indianapolis (United States), 4. Eli Lilly and Company - Indianapolis (United States), 5. Hoffmann-La Roche - Basel (Switzerland), 6. Banner Sun Health Research Institute - Sun City (United States) On behalf of the DIAN-TU Study Team))*

Presentation 1: A comprehensive analysis of CSF tau following amyloid reduction recapitulates the tau-related staging of Alzheimer disease biomarkers, E. McDade *(Washington University School of Medicine - St. Louis (United States))*

Background: Recent studies of cerebrospinal fluid (CSF) tau-related biomarkers have indicated a sequential pattern of change in Alzheimer's disease (AD) starting with hyperphosphorylation of specific isoforms (p-tau217, p-tau231, p-tau181) increasing at the time that amyloid plaques appear followed by p-tau205 approximately 7 years before symptom onset, and then microtubule binding region (MTBR) 243 increasing near the time that clinical symptoms and tau-PET signal increase. We tested this observational AD pattern of soluble tau changes following treatment with two different amyloid immunotherapies, targeting plaque (gantenerumab) and targeting soluble amyloid-beta (solanezumab) in the Dominantly Inherited Alzheimer's Trial Unit (DIAN-TU). **Methods:** We measured the percent (%)phospho-tau/unphosphorylated tau of tau 217, 231, 181, and 205 and the concentrations of MTBR-243 with liquid chromatography mass-spectrometry in CDR 0 and > CDR 0 dominantly inherited AD (DIAD) mutation carriers (MCs) randomized to gantenerumab, solanezumab or a shared placebo at baseline, year 4, and also participants who enrolled in the open label extension period and were given 3-times higher dose of gantenerumab. A mixed model for repeated measures (MMRM) was used to assess each treatment compared to the pooled placebo group and DIAN natural history external control group, when available. The MMRM incorporated fixed effects such as baseline value, treatment arm, visit, and their respective interactions.

Additionally, it utilized an unstructured variance-covariance matrix to account for the correlations among repeated measures. Spearman correlations between soluble tau-biomarkers and amyloid-PET and tau-PET were performed to assess change in aggregated amyloid and tau with changes in soluble tau. **Results:** At year 4, PiB-PET levels were significantly reduced in gantenerumab treated MCs relative to placebo but not in solanezumab treated MCs. Related, early phase p-tau isoforms %p-tau217, %p-tau231, %p-T181,% p-tau153 all decreased substantially in gantenerumab treated MCs relative to placebo but not in solanezumab treated MCs. However, tau-PET values continued to increase for all groups over 4 years. Related, late phase tau isoforms (p-tau205, MTBR-243) levels were similar for both treated vs placebo at year 4. Similarly, the rate of change of early phase p-tau isoforms correlated strongly with the rate of change of PiB-PET but not tau-PET for all participants. For tau-PET change, the highest correlations were observed for late-phase soluble tau measures. **Conclusion:** Lowering of amyloid plaques with amyloid immunotherapy recapitulates the pattern of post-translational changes of tau in the CSF in DIAD, i.e. reduction of amyloid associated p-tau, but not later tau pathology changes. Early phase p-tau ratios changed with amyloid PET changes, in contrast, late phase p-tau205 and MTRB-243 matched tau-PET and cognitive decline changes, supporting the validation of these soluble tau measures as surrogates of amyloid pathology, neurofibrillary tau (NFT) and, potentially, cognitive decline respectively. Further studies of therapies that substantially lower NFT pathology are needed to better validate late phase soluble tau-related biomarkers. **Key words:** phospho-tau, autosomal dominant, gantenerumab, tau. **Clinical Trial Registry:** NCT01760005. **Disclosures:** RJB receives funding from the NIH, Roche, Lilly, Eisai, Biogen, Abbvie, Novartis, BMS and Janssen and is a co-founder of C2N Diagnostics. EMM received honoraria from Eisai and is an advisor for Lilly and Alector. GW is an advisor for Lilly and Alector.

Presentation 2: Examining Amyloid Reduction as A Surrogate Endpoint through Latent Class Analysis Using Clinical Trial Data for Dominantly Inherited Alzheimer's Disease, G. Wang *(Washington University School of Medicine - St. Louis (United States))*

Introduction: Increasing evidence suggests that amyloid reduction could serve as a plausible surrogate endpoint for clinical efficacy. Both the phase 3 lecanemab and donanemab trials led to robust amyloid removal, and significant treatment effects across multiple clinical endpoints; whereas in two identically designed phase 3 trials of gantenerumab with similar magnitude of amyloid removal, these effects did not achieve significance in their primary endpoint. These seemingly diverse results underscore the need for a comprehensive evaluation of amyloid PET reduction as a surrogate endpoint for clinical benefits. This report aims to investigate amyloid reduction as a surrogate endpoint by employing latent class (LC) analysis using clinical trials with non-significant overall effects in clinical endpoints. **Methods:** We applied the LC analysis to the longitudinal PiB PET data from the DIAN-TU-001 trial (N= 139). LC analysis aims to identify distinct subgroups with different properties that may impact the clinical treatment effects. It does not require prior specification of these properties; instead, it only requires determining the number of classes to be identified beforehand (three classes specified for this report based on the potential amyloid change during the follow-up). **Results:** LC analysis categorized participants into three classes using longitudinal amyloid PiB PET SUVR data: amyloid no change (rate of change: -0.009/year SUVR, N=47), amyloid reduction (-0.183/year SUVR, N=24), and amyloid growth (0.113/year SUVR, N=68). The amyloid-no-change class was at an earlier disease stage for amyloid amounts and dementia [baseline mean (SD) SUVR: 1.51 (0.47)]. Despite similar baseline characteristics, the amyloid-reduction class [baseline SUVR: 3.23 (0.96)] exhibited a numerical reduction in the annual decline rate compared to the amyloid-growth class [baseline SUVR: 3.28 (1.15)] across various measures: CDR-SB decline was reduced by 47.1% (0.74/year vs 1.40/year, p-value: 0.0499), MMSE decline by 31.9% (-1.37/year vs -2.01/year, p-value: 0.24), Digit symbol decline by 48.3% (-1.88/year vs -3.63/year, p-value: 0.11), ISLT decline by 56.7% (-0.21/year vs -0.48/year, p-value: 0.035), FAS decline by 40.1% (1.51/year vs 2.53/year, p-value: 0.089), and Tau PET SUVR by 44.5% (0.071/year vs 0.128/year, p-value: 0.066). Interestingly, these reductions are in line with the magnitudes observed with lecanemab and donanemab. Numerically the smallest progression was observed in NfL among the amyloid-reduction class. Furthermore, only the amyloid-reduction class displayed significant reductions in CSF p-tau181 and CSF total tau, highlighting the association of these biomarkers with amyloid PET reduction. **Conclusions:** Latent-class analysis indicates that amyloid reduction in the DIAN-TU study is associated with improved clinical outcomes even when the overall treatment effect is not significant in the primary endpoints. If the LC analysis can be validated in trials with larger sample sizes, it could play a crucial role in validating a surrogate biomarker. This validation, in turn, could significantly expedite the development of therapies for anti-amyloid drugs. The limitations of our LC analysis include the non-randomness of the model-determined classes, the need to pre-specify the number of classes, and the restricted sample size of the DIAN-TU study. **Key words:** Latent class analysis, amyloid, clinical endpoint. **Clinical Trial Registry:** NCT01760005. **Disclosures:** RJB receives funding from the NIH, Roche, Lilly, Eisai, Biogen, Abbvie, Novartis, BMS and Janssen and is a co-founder of C2N Diagnostics. EMM received honoraria from Eisai and is an advisor for Lilly and Alector. GW is an advisor for Lilly and Alector.

Presentation 3: Top-line results of gantenerumab amyloid removal in the prevention of symptom onset and dementia progression in the DIAN-TU, Randall Bateman *(Washington University School of Medicine - St. Louis (United States))*

Background: Amyloid-plaque removing monoclonal antibody therapies for Alzheimer's disease (AD) can slow progression in symptomatic AD, but the ability to prevent the onset of symptoms is unknown. In 2012, the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) launched a double-blind trial to evaluate the effects of amyloid-plaque removal on disease progression in dominantly inherited Alzheimer's disease (DIAD) participants transitioning to an open-label extension (OLE) of gantenerumab. The first long-term clinical, amyloid-plaque removal, and biomarker results of gantenerumab in individuals treated for up to 10 years will be presented. **Methods:** A double blind (DB) phase 2/3 trial with a common-close design ran from 2012 to 2019 (average treatment duration 5 years) with gantenerumab doses up to 1200 mg SQ q4 weeks, with a treatment gap period of approximately 1 year, before open-label treatment titrating up to 3000 mg SQ q4 weeks. The average OLE treatment was 2 years when an interim analysis was performed to determine the effects of gantenerumab in delaying symptom onset and

progression in asymptomatic participants at baseline. Cox proportional hazard ratio (HR) of the cohort vs. main set controls (DB phase participant in placebo arm who did not enroll in OLE plus external control data, n=74 asymptomatic and 70 symptomatic) was the primary outcome in three groups with different durations of treatment from 2-10 years. Baseline EYO was included as a covariate in the model. **Results:** For the primary analyses of baseline asymptomatic participants who received gantenerumab treatment in either DB phase or OLE phase (n = 53), the HR (95% CI) is 1.00 (0.47, 2.14) for time to first progression in CDR global, and 0.76 (0.45, 1.29) for time of recurrent progression in CDR-SB. For the longest treated baseline asymptomatic group (n = 22) with average duration of 8 years, the HR (95% CI) is 0.50 (0.17, 1.47) for CDR global and 0.50 (95% CI 0.25 to 0.99) for CDR-SB. For the OLE period, the shortest treated baseline asymptomatic group with average duration of 2 years (n=40), the HR (95% CI) is 1.3 (0.45, 4.04) for CDR global and 1.41 (0.59, 3.33) for CDR-SB. PIB-PET SUVR amyloid-plaque removal was dose-dependent, with approximately 3-fold greater rates of amyloid-plaque lowering by 3-times the dose, however, few reached amyloid-plaque negative levels. CSF biomarkers demonstrated amyloid-plaque biomarkers amyloid-beta 42/40, non-phosphorylated tau, and %p-tau217 ratio all decreased in a dose proportional manner related to amyloid removal. **Conclusions:** These findings indicate no overall effect in the treated group, but there may be delayed onset of symptoms and dementia progression in DIAD mutation carriers with long-term treatment of up to 10 years with high dose gantenerumab before symptom onset. However, the results of this complex study design and analyses preclude firm conclusions of clinical effect due to the OLE and external control design, limited numbers of participants, and potential sources of bias. Results from ongoing follow-up and treatment of this cohort, may guide analysis and designs for current and future prevention trials. **Key words:** Amyloid, biomarkers, treatment. **Clinical Trial Registry:** NCT01760005. **Disclosures:** RJB receives funding from the NIH, Roche, Lilly, Eisai, Biogen, Abbvie, Novartis, BMS and Janssen and is a co-founder of C2N Diagnostics. EMM received honoraria from Eisai and is an advisor for Lilly and Alector. GW is an advisor for Lilly and Alector.

S4- LECANEMAB FOR EARLY ALZHEIMER'S DISEASE:LONG-TERM OUTCOMES, PREDICTIVE BIOMARKERS AND NOVEL SUBCUTANEOUS ADMINISTRATION.

C. Van Dyck[1], K. Johnson[2], R. Sperling[2], M. Irizarry[3] *(1. Yale Alzheimer's Disease Research Center - New Haven (United States), 2. Harvard Medical School - Boston (United States), 3. Eisai Inc. - Nutley (United States))*

Presentation 1: Clarity AD: Review of the Mechanism-Based Rationale and Results of the Lecanemab Phase 3 Trial, Christopher van Dyck, David Li, Shobha Dhadda, Steven Hersch, Michael Irizarry, Lynn Kramer

Background: Lecanemab is an anti-amyloid monoclonal antibody that binds with highest affinity to soluble Abprotofibrils, which are more toxic than monomers or insoluble fibrils/plaque. In the phase 3 Clarity AD study, lecanemab demonstrated a consistent slowing of decline in clinical (global, cognitive, functional, and quality of life) outcomes, and reduction in brain amyloid in early Alzheimer's disease (AD). **Objective:** To provide an overview of the mechanistic and clinical rationale for development of lecanemab, including how lecanemab treatment impacts tau protein aggregates, a predictive biomarker for AD that is closely linked to emergence of neurodegeneration and manifestation of clinical symptoms. An overview of the mechanistic differences and their implications among anti-amyloid antibodies will also be presented. **Methods:** Clarity AD was an 18-month treatment (core study), multicenter, double-blind, placebo-controlled, parallel-group study with open-label extension (OLE) in patients with early AD. Eligibility criteria included being 50-90 years of age with a diagnosis of mild cognitive impairment or mild dementia due to AD with biomarker confirmed amyloid pathology. Eligible participants were randomized 1:1 to receive either placebo or lecanemab 10-mg/kg IV biweekly. The primary efficacy endpoint was change from baseline at 18 months in the Clinical Dementia Rating-Sum-of-Boxes (CDR-SB). Key secondary endpoints included change from baseline at 18 months in amyloid PET standardized uptake value ratio (in patients participating in the sub-study), Alzheimer's Disease Assessment Scale-Cognitive Subscale 14 (ADAS-Cog14), and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL). Subgroup analysis of low baseline tau was conducted (MK-6240 tau PET SUVr < 1.06). The OLE evaluates the long-term safety and tolerability of lecanemab 10 mg/kg biweekly in patients with early AD. **Results:** Overall, 1795 participants were randomized (lecanemab:898; placebo:897). Lecanemab treatment met the primary endpoint, reducing decline on the CDR-SB versus placebo at 18 months by 27.1% (difference: -0.45; P<0.001), with highly significant differences starting at six months. At 18 months, all key secondary outcomes favored lecanemab (P<0.001), reducing brain amyloid (difference: -59.1 [95%CI: -62.6, -55.6]), slowing cognition loss by 25.8% (ADAS-Cog14), and functional decline by 36.6% (ADCS-MCI-ADL). Lecanemab was generally well-tolerated, with an incidence of amyloid-related imaging abnormalities-edema (ARIA-E) of 12.6% for lecanemab and 1.7% for placebo (symptomatic: lecanemab:2.8%; placebo:0.0%). In the low tau subgroup, 60% of lecanemab participants had improvement on CDR-SB compared to 28% in placebo. Efficacy trends continued in the OLE, with no new safety signals. Indirect comparison between trials would suggest lecanemab has lower ARIA-E than some other published Ab immunotherapies even without titration. Incidence and timing of ARIA vary among treatments, possibly related to differences in binding profiles to soluble aggregated amyloid species, amyloid plaques, and vascular amyloid. **Conclusion:** Lecanemab demonstrated a consistent slowing of decline in clinical (global, cognitive, and functional) outcomes, and reduction in brain amyloid in early AD, including in low tau population. Targeting the protofibrils may provide an additional benefit by continuing to target Ab species and improve biomarkers even after clearance of amyloid plaques. **Key words:** Clarity AD, Lecanemab, Mechanism, Phase 3 Trial. **Conflicts of interest:** Christopher van Dyck is a consultant for Roche, Eisai, Cerevel, and Ono and receives research support from Biogen, Eisai, Roche, Genentech, Eli Lilly, Janssen, UCB, Cerevel, and Biohaven. David Li, Shobha Dhadda, Steven Hersch, Michael Irizarry, Lynn Kramer are employees of Eisai.

Presentation 2: Biomarker Assessments from Clarity AD: Downstream Implications of Targeting Protofibrils and Tau as a Predictive Biomarker, Keith Johnson, David Li, Shobha Dhadda, Pallavi Sachdev, Arnaud Charil, Michael Irizarry, Lynn Kramer

Background: Lecanemab is distinguished from other anti-amyloid antibodies in that it selectively targets large soluble

protofibrils relative to monomers (greater than 1000-fold over Aβ monomers), with preferential activity over insoluble fibrils (up to 10-fold over fibrils). Tau PET can be used to stage Alzheimer's disease and track progression. **Objective:** To present updated biomarker results from the Clarity AD trial, focusing on study outcomes stratified by the participants' level of the brain protein tau. Tau protein aggregates are a predictive biomarker for Alzheimer's disease that is closely linked to emergence of neurodegeneration and manifestation of clinical symptoms. The downstream implications of targeting protofibrils on tau pathophysiology will be discussed. **Methods:** Clarity AD was an 18-month, global, multicenter, double-blind study in individuals with early Alzheimer's disease. Eligible participants were randomized 1:1 to receive either placebo or lecanemab 10-mg/kg IV biweekly. The primary efficacy end point was change from baseline at 18 months in the Clinical Dementia Rating-Sum-of-Boxes (CDR-SB). Subgroup analysis of low baseline tau was conducted from patients who participated in an optional tau PET sub-study. **Results:** Lecanemab treatment impacted tau biomarkers across various biomarker platforms (CSF, plasma, imaging). Of the 342 patients in the tau PET substudy, 141 (41.2%) were low tau (MK-6240 tau PET whole cortical gray matter SUVr <1.06), 191 (55.8%) were intermediate tau (SUVr ≥1.06, ≤2.91), and 10 (2.9%) were high tau (SUVr >2.91). Lecanemab has downstream effects on tau pathology by PET and soluble measures of tau. In the low tau subgroup, lecanemab reduced decline on CDR-SB relative to placebo by -0.59 (549% improvement; p=0.022) at 18 months. In the low tau subgroup, 60% of lecanemab treated patients had improvement on CDR-SB (vs 28% on placebo) and 76% had no decline on CDR-SB (vs 55% on placebo) at 18 months. Lecanemab slowed tau pathology in temporal lobe (early Braak regions). In addition, lecanemab impacts different brain regions in low tau PET group vs intermediate tau PET group consistent with stage of disease. In those with low tau, lecanemab impacts medial temporal (which is the earliest tau region) tau progression, while in intermediate tau (which on average has tau already in temporal and parietal regions), lecanemab impacts tau progression on PET more broadly. **Conclusions:** Biomarker assessment results from Clarity AD show that lecanemab treatment has an overall effect on tau PET for all patients, arresting tau progression/spread in low tau patients and changing the tau accumulation trajectory in patients with higher tau levels. Results from Clarity AD in low tau subgroup supports earlier treatment with lecanemab. **Keywords:** Clarity AD, Lecanemab, Biomarkers, Tau, Protofibrils. **Conflicts of interest:** Keith Johnson has relationships with Siemens, Avid Radiopharmaceuticals/Lilly Healthcare, Janssen AI, Bayer, Navidea Biopharmaceuticals, and Piramal Healthcare. David Li, Shobha Dhadda, Pallavi Sachdev, Arnaud Charil, Michael Irizarry, Lynn Kramer are employees of Eisai.

Presentation 3: Lecanemab for the Treatment of Early Alzheimer's Disease: The Extension of Efficacy Results from Clarity AD, Reisa Sperling, David Li, Shobha Dhadda, Steven Hersch, Larisa Reyderman, Michael Irizarry, Lynn Kramer

Background: Lecanemab is a humanized IgG1 monoclonal antibody binding with high affinity to protofibrils of amyloid-beta (Ab) protein. In phase 3 development, lecanemab has been shown to reduce markers of amyloid in early symptomatic Alzheimer's disease and slow decline on clinical endpoints of cognition and function at 18 months. In the ongoing open-label extension (OLE) study, we evaluated whether the treatment benefits were maintained at 24 months and assessed the impact of baseline tau PET levels on the long-term treatment response. **Objective:** To report on initial findings from the OLE of the Clarity AD clinical trial efficacy results out to 24 months and to evaluate the long-term efficacy results categorized by baseline tau PET levels. **Methods:** Clarity AD is an 18-month treatment (core study), multicenter, double-blind, placebo-controlled, parallel-group study in patients with early AD. The trial also includes an OLE phase in which eligible patients who completed 18 months of study drug treatment had the option of enrolling. Assessments included the Clinical Dementia Rating-Sum-of-Boxes (CDR-SB), AD Assessment Scale-Cognitive Subscale 14 (ADAS-Cog14), Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL) and amyloid PET. Long-term efficacy beyond 18 months of lecanemab 10 mg/kg biweekly was evaluated in the OLE utilizing the same efficacy assessments as the core study (6-month data reported). Clinical and biomarker (PET, Ab42/40 ratio, and ptau181) outcomes were evaluated by examining the OLE results for patients receiving placebo in the core study followed by lecanemab in the OLE. Analyses of participants from the optional tau PET sub-study, initiated during the core study, were conducted to evaluate the OLE treatment response segmented by core baseline tau PET levels. **Results:** In the core study, a total of 1795 participants were enrolled, 898 assigned to lecanemab and 897 to placebo. Of the 1486 subjects that completed 18 months of the double-blind core study, 1385 participants enrolled in the OLE. Differences between treatment and placebo across clinical endpoints increased over time during the first 18 months, but then became parallel after initiation of lecanemab in the core placebo group from 18 to 24 months, consistent with a disease modifying effect. Biomarker changes were seen in as early as 3 months in newly treated lecanemab participants in the OLE. Across efficacy assessments participants with low tau at core baseline, initially assigned to lecanemab, continued to show benefit of lecanemab treatment beyond 18 months, and participants initially assigned to the placebo arm began to demonstrate evidence of benefit subsequent to lecanemab being started in the OLE. **Conclusions:** In initial data available from the Clarity AD OLE, treatment differences vs placebo observed in the core study were extended across clinical efficacy assessments at 24 months. These results are consistent with disease modification and support the initiation of treatment early in the disease. **Key words:** Clarity AD, Lecanemab, Long-term efficacy, Tau. **Conflicts of interest:** David Li, Shobha Dhadda, Steven Hersch, Larisa Reyderman, Michael Irizarry, Lynn Kramer are employees of Eisai.

Presentation 4: Preliminary Update on Lecanemab Safety in Clarity AD Open-Label Extension, Including Subcutaneous Formulation, Michael Irizarry, David Li, Shobha Dhadda, Steven Hersch, Larisa Reyderman, Lynn Kramer

Background: Lecanemab is an anti-amyloid antibody that has been approved by the United States FDA for treatment of early Alzheimer's disease (AD). Lecanemab 10 mg/kg every 2 weeks (Q2W) intravenously (IV) was shown in the Clarity AD trial to slow the progression of AD. Pharmacokinetic/pharmacodynamic (PK/PD) modeling demonstrated that lecanemab average steady-state concentrations (Cav,ss) are associated with amyloid plaque lowering and efficacy, while maximum steady-state concentrations (Cmax,ss) tended to be more strongly correlated with the incidence of amyloid-related imaging abnormalities-edema (ARIA-E). Lecanemab SC is being tested in the Clarity AD open-label extension (OLE) to test the

hypothesis that a subcutaneous lecanemab formulation with similar Cav,ss but lower Cmax,ss will have similar or better safety profile by lowering the rates of ARIA-E and infusion-related reactions. **Objective:** To provide an update on the safety profile of lecanemab, including and immunogenicity (neutralizing antibodies (Nab) and anti-drug antibodies [ADA]) assessments from the intravenous lecanemab clinical trials. In addition, a preliminary safety data update on the subcutaneous lecanemab formulation that is currently in development. **Methods:** Clarity AD is a phase 3 multicenter, double-blind, placebo-controlled, parallel-group study of 18-month treatment duration with OLE in patients with early AD with confirmed amyloid pathology. Eligible patients are randomized to placebo or 10 mg/kg biweekly initiated with full therapeutic dosing. Clinical assessments in both studies included Clinical Dementia Rating-Sum-of-Boxes (CDR-SB) and AD Assessment Scale-Cognitive Subscale 14 (ADAS-Cog14). A subcutaneous dose is under development based on PK/PD modeling and bioavailability data and is currently being assessed in a substudy of the OLE. ADA and NAb assays were developed and validated in accordance with FDA guidance and industry best practice and were performed using a tiered approach. **Results:** In the intravenous lecanemab Clarity AD phase 3 study, the incidence of treatment emergent positive ADA in lecanemab was 5.5%, respectively, with low titers. The incidence of ADA in phase 3 OLE study was 5.7%. The incidence of treatment emergent NAb positive was 4.1% in the phase 3 study, respectively, and characterized by low titers. ADA and NAb status did not meaningfully affect lecanemab serum concentration. The slowing of cognitive decline (CDR-SB and ADAS-Cog14) with lecanemab relative to placebo is not affected by the presence of ADA and NAb. The preliminary safety data on a subcutaneous formulation of lecanemab from the Clarity AD open-label extension study will be presented, including data on ARIA-E, ARIA-H, and other adverse effects. The potential for a subcutaneous formulation to have an improved safety profile and more patient friendly route of administration will be discussed. **Conclusions:** Based on the ADA profile and minimal impact of ADA on PK, PD, efficacy, and safety, lecanemab is a low-risk molecule for immunogenicity. The differential administration and PK profile of SC relative to IV is a potential basis for further improving the safety profile of lecanemab. Ongoing studies will confirm the safety and efficacy profiles of SC lecanemab. **Key words:** Lecanemab, Immunogenicity, Subcutaneous Formulation, Safety. **Conflicts of interest:** Michael Irizarry, David Li, Shobha Dhadda, Steven Hersch, Larisa Reyderman, Lynn Kramer are employees of Eisai.

S5- WHAT CAN WE LEARN FROM THE A4 STUDY? ASSOCIATIONS AMONG LONGITUDINAL COGNITIVE, FUNCTIONAL, BIOMARKER AND IMAGING OUTCOMES. R. Sperling[1], M. Donohue[2], R. Raman[2], K. Johnson[3], R. Yaari[4], K. Holdridge[4], M. Case[4], J. Sims[4], P. Aisen[2], on behalf of the A4 Study *(1. Brigham and Women's Hospital Harvard Medical School - Boston (United States), 2. Alzheimer Therapeutic Research Institute, University of Southern California - San Diego (United States), 3. Massachusetts General Hospital, Harvard Medical School - Boston (United States), 4. Eli Lilly and Co. - Indianapolis (United States))*

Background: The A4 Study was the first of its kind secondary prevention trial in cognitively unimpaired adults (ages 65-85) with elevated amyloid on PET, following individuals with cognitive, functional, biomarker, and imaging outcomes for up to 8 years across double-blind and open-label phases of the trial. The companion LEARN Study followed participants who did not show elevated amyloid on screening PET and underwent the same assessments with a similar schedule over up to 7 years. **Methods:** Eligibility criteria for both A4 and LEARN included CDR-Global Scale (CDR-GS)=0, MMSE≥25, WMS Logical Memory=6-18. Amyloid PET imaging with 18-F florbetapir was used to determine amyloid status. A4 eligibility required elevated amyloid (SUVr>1.15 or visual read positivity). Participants who did not show elevated amyloid were eligible to enroll in LEARN at participating sites. Amyloid PET was acquired at Baseline and approximately Week 240 at the end of the double blind-phase in A4 and equivalent timing in LEARN. Tau PET was acquired with 18-F flortaucipir PET in a subset of individuals in A4 and LEARN at Baseline, Months 18, 36, and 54. Plasma was collected at multiple visits to assess p-tau217 and other fluid biomarkers. The primary cognitive outcome was the Preclinical Alzheimer Cognitive Composite (PACC) assessed every 6 months. The computerized cognitive composite (C3) was collected using an iPad at Baseline, 3 months, 9 months alternating visits with the PACC. Multiple functional measures were assessed annually: including self and study partner Cognitive Function Index (CFI), Activities of Daily Living Scale (ADL), CDR-GS and CDR Sum of Boxes. **Results:** Additional fluid biomarker and imaging data are currently pending. Analyses of the relationship between longitudinal change in biomarkers, imaging, and cognition are ongoing, and detailed results will be provided to CTAD later this summer. Thus far, we have seen that baseline amyloid is strongly predictive of future decline on all cognitive and functional measures and will be exploring whether rate of amyloid accumulation is associated with rate of decline. We have observed that greater increase in tau PET (in medial temporal lobe and neocortical composites using template space) is associated with faster cognitive decline, and will be exploring the associations between change in individual anatomic tau PET measures and specific cognitive domains. We will also be investigating the relationship between change in p-tau217 with longitudinal tau PET and cognitive trajectories. In particular, we will evaluate whether early changes in plasma and imaging measures are predictive of longer term cognitive and functional outcomes at the stage of preclinical AD. **Conclusion:** The A4 and LEARN Studies offer a wealth of data to inform ongoing and future prevention trials in preclinical AD. In particular, the comparison of longitudinal cognitive, biomarker, and imaging trajectories across the two A4 amyloid positive treatment arms and LEARN amyloid negative group should prove useful in determining the most sensitive outcomes related to early amyloid and tau accumulation. Understanding the temporal relationship among longitudinal biomarker, imaging, cognitive and functional trajectories should serve to make future prevention trials more efficient. **Disclosures:** The A4 Study is a public-private partnership funded by the National Institute on Aging/NIH and Eli Lilly and Co. The LEARN Study was funded by the Alzheimer's Association, GHR Foundation, and other philanthropic donors. **ClinicalTrials.gov:** A4: NCT02008357 LEARN: NCT02488720

S6- IMPLEMENTING BLOOD BIOMARKERS IN CLINICAL PRACTICE AND TRIALS

Presentation 1: Defining the minimum acceptable performance of blood-based biomarkers of Alzheimer's disease for clinical use in symptomatic patients, S. Schindler[1], Ana C. Pereira[2], D. Galasko[3,4], S. Salloway[4], M. Suárez-Calvet[5,6], Oskar Hansson[7] *(1. Washington University School of Medicine, Department of Neurology, St. Louis (United States), 2. Icahn School of Medicine at Mount Sinai, Department of Neurology, New York, (United States), 3. University of California-San Diego, Department of Neurology, San Diego (United States), 4. Alpert Medical School of Brown University, Departments of Neurology and Psychiatry, Providence (United States), 5. Barcelona βeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona (Spain), 6. Hospital del Mar, Neurology Department, Barcelona (Spain), 7. Lund University, Clinical Memory Research Unit, Lund (Sweden))*

Background: The accurate diagnosis of symptomatic Alzheimer's disease (AD) requires biomarker testing, but financial costs and accessibility issues have limited the use of PET and CSF biomarkers in clinical care. The recent emergence of disease-modifying therapies (DMTs) for the treatment of patients with early symptomatic AD prompts the need for a more rapid diagnosis and is likely to increase the demand for biomarker testing by orders of magnitude. Blood-based biomarkers (BBMs) are uniquely suited to enable much higher volumes of biomarker testing, and they are also less invasive, more accessible, and may be less expensive than conventional AD biomarkers. BBMs have developed rapidly over the last several years and the accuracy of some BBMs may now be suitable for clinical use, but the minimum acceptable performance for BBMs must be defined. **Methods:** The Global CEO Initiative on Alzheimer's Disease (CEOi) convened virtual meetings in 2023 with the objective of preparing relevant stakeholders for the widespread adoption of BBMs in clinical practice. The minimum acceptable performance of BBMs for use in initial or secondary care as either a triaging test (initial BBM test with the plan for a confirmatory test if positive) or confirmatory test (BBM test without a subsequent test) were defined using amyloid PET as the reference standard and the diagnostic performance of clinically used CSF tests as a benchmark. **Results:** For triaging, the Workgroup concluded that a BBM test should have ≥90% sensitivity and ≥85% specificity for amyloid PET status, which is only slightly lower than FDA-approved CSF tests. For triaging, the performance of BBMs can only be slightly less accurate than CSF tests; otherwise, many amyloid positive patients with falsely negative BBM results would not be identified, or many amyloid negative patients with falsely positive BBM results would need confirmatory PET or CSF testing. For confirmation of amyloid pathology, the Workgroup concluded that BBMs should have ≥90% sensitivity and ≥90% specificity for amyloid PET status, which is equivalent to FDA-approved CSF tests. A major consideration was that BBMs must have accuracy equivalent to CSF tests for confirmation of amyloid pathology or clinicians would strongly prefer use of CSF tests, especially if treatment with a DMT were a consideration. The Workgroup further recommended that BBMs should have less than 5% discordance of positive and negative status when blood is collected and analyzed on different occasions, e.g., within 1-2 months. The performance values would ideally be derived from head-to-head studies comparing BBMs to CSF tests in classifying amyloid PET status in cohorts with characteristics closely matching the intended use population, and with appropriate sample sizes. **Conclusions:** Given the potential major implications of biomarker testing for patients, high standards of performance were set. Some BBMs have very high performance that may meet the standards recommended by the Workgroup, especially when using a two cut-point approach. Given the major capacity constraints and drawbacks of PET and CSF testing, integration of these high performance BBMs in clinical care may enable many more patients to access an accurate diagnosis and appropriate treatments. **Disclosures:** SES served on a scientific advisory board for Eisai. ACP served on a scientific advisory board for Sinaptica Therapeutics, as a consultant for Eisai, and is co-founder of Neurobiopharma, LLC. MSC has served as a consultant and at advisory boards for Roche Diagnostics International Ltd and Grifols S.L., has given lectures in symposia sponsored by Roche Diagnostics, S.L.U and Roche Farma, S.A., and was granted with a project funded by Roche Diagnostics International Ltd; payments were made to the institution (BBRC). DG has served as a consultant for Eisai, Biogen, GE Healthcare, Fujirebio, Roche Diagnostics, and is on the DSMB for Artery Therapeutics.

Presentation 2: A highly accurate blood test for Alzheimer's disease pathology has performance equivalent or superior to clinically used cerebrospinal fluid tests, N. Barthelemy[1,2*], G. Salvadó[3*], S. Schindler[1,2,4], Y. He[1,2], S. Janelidze[3], L. Collij[3], B. Saef[1], R. Henson[1], C. Chen[5], B. Gordon[5], T. Benzinger[5], J. Morris[1,4], N. Mattsson-Carlgren[3,6], S. Palmqvist[3,6], R. Ossenkoppele[1,7,8], E. Stomrud[3,6], R. Bateman[1,2,4**], Oskar Hansson[3,6**] *(*these authors contributed equally as first authors; **these authors contributed equally as senior authors and are co-corresponding authors, 1. Washington University School of Medicine, Saint Louis (United States), 2. The Tracy Family SILQ Center, Washington University School of Medicine, Saint Louis (United States), 3. Lund University, Clinical Memory Research Unit, Lund (Sweden), 4. The Knight ADRC, Washington University School of Medicine, Saint Louis (United States), 5. Department of Radiology, Washington University School of Medicine, Saint Louis (United States), 6. Memory Clinic, Skåne University Hospital, Lund (Sweden), 7. Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, (The Netherlands), 8. Amsterdam Neuroscience, Neurodegeneration, Amsterdam (The Netherlands))*

Background: As disease-modifying treatments for Alzheimer's disease enter the clinic, there is an urgent need to rapidly and accurately identify patients who could benefit from these treatments. We assessed whether a highly accurate blood test could identify individuals with amyloid plaques and tau tangles as accurately as clinically used cerebrospinal fluid (CSF) tests. **Methods:** Blood plasma samples were analyzed with mass spectrometry to quantify the ratio of tau phosphorylated at threonine 217 to non-phosphorylated tau levels (%p-tau217). Matched CSF samples were analyzed with clinically used FDA-approved automated immunoassays. The primary and secondary outcomes were detection of brain amyloid or tau pathology using PET imaging as the reference standard. **Results:** The Swedish BioFINDER-2 cohort included 1,422 individuals (mean age 69.3 years). The United States Knight ADRC cohort included 337 individuals (mean age 69.8 years). Plasma %p-tau217 was equivalent to FDA-approved CSF tests in classifying amyloid PET status, with an area under the curve (AUC) for both between 0.95-0.97. In cognitively impaired sub-cohorts (720 from BioFINDER-2 and 50 from the Knight ADRC), plasma %p-tau217 had an accuracy, positive predictive value and negative predictive value of 90% for amyloid PET

status. In the BioFINDER-2 cognitively impaired sub-cohort, plasma %p-tau217 outperformed CSF tests in classification of tau pathology (p<0.001, AUC 0.97). **Conclusions:** Blood plasma %p-tau217 demonstrates performance equivalent or superior to clinically used FDA-approved CSF tests in the detection of Alzheimer's disease pathology. Use of high accuracy blood tests in clinical practice would increase access to accurate AD diagnosis and AD-specific treatments. **Disclosures:** SES served on a scientific advisory board for Eisai. None of the other authors have anything to declare and have no conflicts associated with the presented data.

Presentation 3: Aβ42/Aβ40 and phospho-tau217 concentration ratios increase the accuracy of amyloid PET classification in preclinical Alzheimer's Disease, R. Rissman[1,2,3], O. Langford[2], R. Raman[2], M. Donohue[2], S. Abdel-Latif[2], M. Meyer[5], T. Wente-Roth[5], K. Kirmess[5], J. Ngolab[1], C. Winston[1], G. Jimenez-Maggiora[2], M. Rafii[2], P. Sachdev[4], T. West[5], K. Yarasheski[5], J. Braunstein[5], M. Irizarry[4], K. Johnson[6], P. Aisen[2], R. Sperling[7], on behalf of the AHEAD 3-45 Study team *(1. Department of Neurosciences, University of California, San Diego (United States), 2. Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego (United States), 3. Department of Neurosciences, University of California, San Diego and VA San Diego Healthcare System, La Jolla, (United States), 4. Eisai Inc, Nutley (United States), 5. C2N Diagnostics (United States), 6. Massachusetts General Hospital, Boston (United States), 7. Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston (United States))*

Background: We hypothesized that incorporating blood-based AD biomarkers such as tau and Aβ into screening algorithms would improve screening efficiency. **Methods:** Plasma Aβ, p-tau181, and p-tau217 concentration levels from AHEAD 3-45 study participants were measured using mass spectrometry. Tau concentration ratios for each proteoform were calculated to normalize for inter-individual differences. Receiver Operating Characteristic (ROC) curve analysis was performed for each biomarker against amyloid positivity, defined by >20 CL. A prediction model, Plasma Predicted Centiloid (PPC), was developed using a Mixture of Experts model and an analysis including tau concentration ratios into the existing predictive algorithm (Aβ42/Aβ40, Age and ApoE) for amyloid PET status. **Results:** We find that the Area Under the Receiver Operating Curve (AUC) was 0.89 for Aβ42/Aβ40, 0.77 for p-tau181/np-tau181, and 0.92 for p-tau217/np-tau217. The PPC, a predictive model including p-tau217/np-tau217, Aβ42/Aβ40, age, and ApoE improved AUC to 0.95. **Conclusion:** In conclusion we find that including plasma p-tau217/np-tau217 along with Aβ42/Aβ40 in predictive algorithms may reduce the screening burden of preclinical individuals into anti-amyloid clinical trials. **Disclosures:** None of the academics have anything to declare and have no conflicts associated with the presented data. KEY, JBB, TW, MRM, TWR and KMR are paid employees of C2N. PS and MI are paid employees of Eisai. The work was supported by NIH/NIA grants AG018440, AG058252, AG078109AG058533 and AG073979 to RAR, NIA ACTC U24 AG057437 to PSA and RAS. C2N Diagnostics was supported by the NIH R44 AG059489, BrightFocus Foundation grant CA2016636, The Gerald and Henrietta Rauenhorst Foundation, and the Alzheimer's Drug Discovery Foundation grant GC-201711-2013978.

S7- INTERCEPT-AD PHASE 1 INSIGHTS AND FINDINGS FROM THE INVESTIGATION OF ACU193, A MONOCLONAL ANTIBODY TARGETING SOLUBLE AB OLIGOMERS. M. Trame[1], M. Dodds[1], E. Cline[2], J. Moore[2], H. Zhang[2], R. Dean[2], J. Jerecic[2], G. Sethuraman[2], E. Siemers[2], T. Feaster[2], K. Sundell[2], V. Skljarevski[2], T. Poppe[3], S. Salloway[4] *(1. Certara - Boston (United States), 2. Acumen Pharmaceuticals - Charlottesville (United States), 3. Acumen Pharmaceuticals - London (United Kingdom), 4. Alpert Medical School of Brown University, Providence (United States))*

Presentation 1: Determination of target engagement at various doses of ACU193 in INTERCEPT-AD, M. Trame *(Certara, Boston (United States))*

Background: ACU193 is a humanized, affinity matured, IgG2 subclass monoclonal antibody that targets soluble amyloid beta oligomers (sAβOs). A phase 1 trial in participants with early Alzheimer's disease (AD; mild cognitive impairment or mild dementia due to AD) was recently completed and provides extensive dose-response information that can be used to determine doses for subsequent clinical trials. ACU193 was developed to target globular sAβOs. Given the unique target of ACU193, demonstration of target engagement in the central compartment and evaluation of dose responses were important aspects of this first-in-human trial, INTERCEPT-AD. **Methods:** Individuals with early AD were confirmed to have AD pathology using florbetapir positron emission tomography (PET) in this randomized, double-blind, placebo-controlled study. Part A was a single ascending dose (SAD) study of four cohorts randomized in a 6:2 ratio to ACU193 (2, 10, 25, or 60 mg/kg) or placebo. Part B was a multiple ascending dose (MAD) study of three administrations of study drug to each of three cohorts randomized in an 8:2 ratio to ACU193 (10 or 60 mg/kg every four weeks [Q4W] or 25 mg/kg every two weeks [Q2W]) or placebo. In addition to safety and tolerability endpoints, the study incorporated measures of ACU193 concentrations in cerebrospinal fluid (CSF) and assessment of change in amyloid plaque load based on PET imaging. An immunoassay was developed to detect ACU193 bound to oligomers; this measure served as the determinant of central target engagement. **Results:** Of the 65 participants randomized to study drug, 46 who were administered ACU193 and 14 who were administered placebo completed the study. CSF samples were obtained at baseline and Day 21 for SAD Cohorts 1 – 4, Day 70 for Cohort 5 (10 mg/kg Q4W), Day 63 for Cohort 6 (60 mg/kg Q4W), and Day 35 for Cohort 7 (25 mg/kg Q2W). A dose-proportional increase in target engagement was shown across the cohorts. An Emax model was derived comparing CSF concentrations of ACU193 to target engagement across doses. The model showed a clear relationship between CSF drug concentration and target engagement with an Emax of 23.6 AU/mL. For Cohorts 6 and 7, target engagement in CSF approached Emax. PET scans were obtained at screening and Day 42 (SAD cohorts 1-4), Day 70 for Cohort 5, Day 63 for Cohort 6, and Day 70 for Cohort 7. Treatment with ACU193 led to a nominally statistically significant reduction in amyloid plaque load in Cohorts 6 and 7. A 25% reduction in Centiloids was observed in Cohort 6 and a 20% reduction was observed in Cohort 7 (for both cohorts, p=0.01; baseline to endpoint within-group differences using a paired t-test). **Conclusions:** The INTERCEPT-AD results showed a clear dose response for target engagement, as determined by CSF concentrations of ACU193 bound to oligomers, approaching Emax with higher doses of ACU193. Additionally, with the two highest doses of ACU193

a decrease in plaque load based on PET was demonstrated. A larger study is being planned which will further assess safety, biomarkers, and clinical efficacy of ACU193. **Key words:** oligomer, ARIA, amyloid lowering, target engagment. **Clinical Trial Registry:** NCT04931459; https://clinicaltrials.gov

Presentation 2: Reduction in amyloid plaque load at higher doses of ACU193 in INTERCEPT-AD, Eric Siemers *(Acumen Pharmaceuticals, Inc, Charlottesville (United States))*

Background: ACU193 is a humanized, affinity matured, IgG2 subclass monoclonal antibody that targets soluble amyloid beta oligomers (sAβOs) for intravenous administration for the treatment of early Alzheimer's disease (AD; mild cognitive impairment [MCI] or mild dementia due to AD). Recent evidence suggests that sAβOs, including the globular soluble oligomers targeted by ACU193 and soluble linear protofibrils, are the most toxic Aβ forms. Soluble AβOs are known to impair synaptic function, induce tau hyperphosphorylation, and exacerbate inflammatory processes. An antibody that binds to sAβOs and neutralizes their effect may, therefore, prevent synaptic toxicity, inflammation, neurodegeneration, and ultimately cognitive impairment associated with AD. This mechanism of action differentiates ACU193 from a number of anti-Aβ antibodies, either in development or recently approved, which may directly target Aβ plaques. **Methods:** INTERCEPT-AD was a phase 1, first-in-human study of ACU193 in individuals with early AD (MCI or mild dementia due to AD) and PET-confirmed evidence of AD pathology. It was a randomized, double-blind, placebo-controlled study. Part A was a single ascending dose study of four cohorts randomized in a 6:2 ratio to ACU193 (2, 10, 25, or 60 mg/kg) or placebo. Part B was a multiple ascending dose study of three administrations of study drug to each of three cohorts randomized in an 8:2 ratio to ACU193 (10 or 60 mg/kg every four weeks [Q4W] or 25 mg/kg every two weeks [Q2W]) or placebo. Inclusion criteria for the study included a positive amyloid PET scan using florbetapir. SUVr values less than 1.0 were considered negative and greater than 1.2 were considered positive. For SUVr values of 1.0 – 1.2, a visual read was performed to determine amyloid status. **Results:** Of the 65 participants randomized, 62 received at least one dose of ACU193 or placebo. ACU193 was well tolerated. The most common treatment-emergent adverse events from all ACU193 dose groups combined were ARIA-E (10.4%), ARIA-H (8.3%), COVID-19 (6.3%), hypersensitivity (6.3%), bronchitis (4.2%), headache (4.2%), fall (4.2%) and post lumbar puncture syndrome (4.2%). Treatment with ACU193 led to a dose-related, nominally statistically significant reduction in amyloid plaque in higher dose cohorts as determined by an exploratory analysis of composite cortical PET images expressed in Centiloids. A 25% reduction was observed in Cohort 6 (60 mg/kg Q4W) at Day 63 and a 20% reduction was observed in Cohort 7 (25 mg/kg Q2W) at Day 70 (p=0.01 for both cohorts, baseline to endpoint within-group differences using a paired t-test). Some baseline amyloid plaque load values expressed in Centiloids were lower than those typically seen in other studies. **Conclusions:** The INTERCEPT-AD results confirmed the validity of sAβOs as a target in the treatment of AD. Potential explanations for the observed plaque reduction effect of ACU193 will be discussed. A larger study is planned to assess clinical efficacy of ACU193 and fully understand its effect on plaques. The relatively low Centiloid values seen at baseline in this study could be related to the PET evaluation method using both SUVr cut-offs and visual reads. **Key words:** oligomer, ARIA, amyloid lowering, target engagment. **Clinical Trial Registry:** NCT04931459; https://clinicaltrials.gov

Presentation 3: Characteristics of Participants in INTERCEPT-AD Who Did or Did Not Develop ARIA with ACU193, Stephen Salloway *(Alpert Medical School of Brown University, Providence (United States))*

Background: ACU193 is a humanized, IgG2 subclass monoclonal antibody that targets soluble amyloid beta oligomers (sAβOs). ACU193 is a promising approach for the treatment of Alzheimer's disease (AD) with evidence of significant amyloid plaque load reduction at higher doses and a differentiated rate of amyloid-related imaging abnormalities (ARIA). Treatment-related ARIA has been observed with numerous anti-amyloid immunotherapies and the ARIA patient profiles appear to differ for these anti-amyloid antibodies. We will present ARIA data from a robust phase 1 study of ACU193 INTERCEPT-AD in early AD. **Methods:** INTERCEPT-AD was a phase 1 randomized double-blind, placebo-controlled, single- and multiple-dose study investigating the safety, tolerability, and pharmacokinetics of intravenous ACU193 in mild cognitive impairment or mild dementia due to AD. The single ascending dose (SAD) portion included four cohorts receiving 2, 10, 25, or 60 mg/kg ACU193 (n=6 per cohort) or placebo (n=2 per cohort). The multiple-ascending dose (MAD) portion included three cohorts receiving three doses of ACU193 (n=8 per cohort) or placebo (n=2 per cohort): 10 mg/kg once every four weeks (Q4W), 60 mg/kg Q4W, and 25 mg/kg once every 2 weeks (Q2W). Both SAD and MAD portions of the study included routine MRI to monitor safety, including ARIA. Key inclusion criteria were 55-90 years of age, PET scan positive for brain amyloid, MMSE 18-30, and CDR-Global score 0.5 or 1.0. **Results:** At 17 sites in the U.S., 260 participants were screened, 65 were randomized, and 62 received at least one dose of ACU193 or placebo. There were no drug-related SAEs. There were five cases of ARIA-E: one case at 10 mg/kg followed the third administration of drug (7.1%), one at 25 mg/kg followed the second administration of drug (7.1%) and three occurred at 60 mg/kg (21.4%). For the 60 mg/kg group, two cases of ARIA-E were after a single dose and one case was after three administrations of drug. One case of ARIA-E that occurred after one administration of drug was symptomatic (60 mg/kg; 2.1%). Regarding APOE carriers, four of five cases of ARIA-E were in ε4 heterozygotes (47% of the study population) and none of the six ε4 homozygotes that received ACU193 developed ARIA-E, despite comprising 13% of the study population. An exploratory analysis of composite cortical PET imaging found baseline Centiloids for the five ARIA cases ranged from 69.2 to 111.2 and all cases resulted in an end-of-study change from baseline ranging from -10 to -47.4 percent. Clinical characteristics will be presented for those who did or did not develop ARIA-E including baseline plaque load, change in plaque load, target engagement, and presentation/time course. **Conclusions:** The INTERCEPT-AD study demonstrated five cases of ARIA-E in the 46 participants treated with ACU193. Four of the five cases of ARIA-E occurred in ε4 heterozygotes and none in ε4 homozygotes. There was a reduction in amyloid plaque at higher doses. A larger study is being planned which will further assess safety and clinical efficacy of ACU193. **Keywords:** oligomer, ARIA, amyloid lowering, target engagment. **Clinical Trial Registry:** NCT04931459; https://clinicaltrials.gov

Roundtables

ROUNDTABLE 1- NIA-AA REVISED CRITERIA FOR DIAGNOSIS AND STAGING OF ALZHEIMER'S DISEASE.

C. Jack[1], R. Sperling[2,3], O. Hansson[4], H. Snyder[5], L. Ryan[6]
(1. Mayo Clinic - Rochester (United States), 2. Brigham and Women's Hospital - Boston (United States), 3. Massachusetts General Hospital - Boston (United States), 4. Lund University - Lund (Sweden), 5. Alzheimer's Association - Chicago (United States), 6. National Institute on aging/NIH - Bethesda (United States))

Background: The National Institute on Aging and the Alzheimer's Association (NIA-AA) convened three separate work groups in 2011 [1, 2, 3] and single work group in 2018 [4] to create recommendations for the diagnosis and characterization of Alzheimer's disease (AD). The NIA-AA also convened a workgroup that published a consensus document on the neuropathological diagnosis of AD in 2012 [5]. Several core principles emerged from these efforts as fundamental tenets.These include, Alzheimer's disease (AD) should be defined biologically, not based on a clinical syndrome(s). The disease is a continuum that is first evident with the appearance of brain pathologic changes in asymptomatic individuals and progresses through stages of increasing pathologic burden eventually leading to the appearance and progression of clinical symptoms. The disease is diagnosed in vivo by abnormalities on core biomarkers. **Methods:** Developments in the field have necessitated the 2018 research framework are updated to reflect recent scientific advances. The first public presentation of the revised criteria occurred at AAIC 2023. At the same time, the workgroup released draft documents for public comment and input [6]. Since then, the workgroup has received comments, suggestions, feedback and have reviewed these for consideration, incorporation and/or clarification in the document. A revised draft will be released in late September or early October. **Results:** The draft document has since been updated based on feedback received. The updates to the criteria will be presented. **Conclusions:** This presentation will describe the current (post AAIC 2023) version of the revised criteria, which will be posted as an updated draft online for public comment through November 15, 2023 [6]. **Key words:** Alzheimer's disease, diagnosis, ATN, biomarkers, criteria, disease staging **Disclosures of panelists and session chairs:** CRJ is employee of Mayo Clinic; has received grant funding from the NIH; served on a DSMB for Roche pro bono (no payments to the individual or institution were involved). Also received funding from Alzheimer's Association for travel. He holds index funds. RS is employed by Brigham and Women's Hospital. She hasreceived grants/ contracts from ACTC, NIA, Eli Lilly,Alzheimer's Association and GHR, and Eisai. She has received consulting fees from AC Immune, Acumen, Alnylam, Bristol-Myers Squibb, Cytox, Genentech, Janssen, JOMDD, NervGen,Neuraly, Neurocentria, Oligomerix, Prothena, Renew, Shionogi,Vigil Neuroscience, Ionis, Vaxxinit and Alector. She has alsoreceived honoraria from Lahey Clinic Grand Rounds. OH:employed by Lund University; grants/ contracts from ADx, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio,GE Healthcare, Pfizer and Roche. Consulted with AC Immune,Amylyx, Alzpath, BioArctic, Biogen, Cerveau, Eisai, Eli Lilly,Fujirebio, Genentech, Merck, Novartis, Novo Nordisk, Roche,Sanofi, and Siemens. HMS: employed by Alzheimer's Association; spouse works for Abbott in unrelated field. The disclosures of full workgroup are at alz.org/nia-aa and will be displayed at session start. **References:** 1. McKhann et al. 2011 Alzheimer's & Dementia; 2. Knopmanet al. 2011 Alzheimer's & Dementia; 3. Sperling et al. 2011 Alzheimer's & Dementia; 4. Jack et al. 2018 Alzheimer's & Dementia; 5. Hyman et al. 2012 Alzheimer's & Dementia; 6. Alz.org/nia-aa, last accessed 8/31/23.

ROUNDTABLE 2- FORGING THE PATH FORWARD: CAPITALIZING ON RECENT ALZHEIMER'S MOMENTUM THROUGH STRATEGIC INVESTMENTS IN NOVEL THERAPEUTICS.

H. Fillit[1], P. Scheltens[2], S. Kohlhaas[3], J. Behr[4], J. Lewcock[5]
(1. Alzheimer's Drug Discovery Foundation - New York City (United States), 2. EQT Life Sciences - Amsterdam (Netherlands), 3. Alzheimer's Research UK -London (United Kingdom), 4. Dementia Discovery Fund - London (United Kingdom), 5. Denali Therapeutics - South San Francisco (United States))

There's no question we've entered a new era of Alzheimer's research, but what will the field look like in the year 2033? More importantly—how can we leverage our existing knowledge and recent progress to continue gaining momentum in the field over the next decade? While the first class of anti-amyloid therapies is on the market, these drugs are only effective in reducing cognitive decline by around 30%. Informed by success in other diseases of chronic aging, such as cancer, the goal is to develop multiple therapies that can be used in combination with one another and prescribed based on patients' individual biomarker profiles for a precision medicine approach. As such, advancements in the next class of novel therapeutics centered around the biology of aging will be crucial to halting cognitive decline altogether. As we look to develop this next generation of drugs, we've reached an inflection point where we must reimagine how we design and conduct clinical trials. For instance, a trial that takes a combination therapy approach and explores the benefits of the anti-amyloids, cholinesterase inhibitors and novel therapies has the potential to unlock an unprecedented reduction in cognitive decline. With over six million Americans living with Alzheimer's, there is a pressing need to develop new guidelines to accelerate these trials and streamline for efficacy, duration, and cost. It is our duty to continue building on the momentum of the past few years to ensure patients get new, more effective treatments faster than ever. This roundtable aims to catalyze a thought-provoking discussion around the vision for the future of Alzheimer's treatments, including the evolving role that biotech companies, pharma, VCs, and philanthropy will play in advancing the science and directing the funding as we look to create the path forward.

Oral Communications

OC01- CLINICAL EFFECTS OF LEWY BODY PATHOLOGY IN CLINICALLY UNIMPAIRED AND COGNITIVELY IMPAIRED INDIVIDUALS.

O. Hansson[1], S. Palmqvist[1], P. Parchi[2] *(1. Lund University - Lund (Sweden), 2. University of Bologna - Bologna (Italy))*

Background: Aggregates of misfolded α-synuclein are the underlying pathology of Lewy body (LB) disease. Little is known about the early effects of LB pathology in preclinical (i.e., pre-symptomatic) individuals. Further, there is poor knowledge about the independent clinical effects of Lewy body (LB) pathology in patients with cognitive decline, especially when coexisting with Alzheimer's disease (AD) pathology.

Methods: Here, we examined the effects of LB pathology using a cerebrospinal fluid α-synuclein seeding aggregation assay in 1,182 cognitively and neurologically unimpaired participants as well as 882 participants with mild cognitive impairment or dementia from the BioFINDER-1 and BioFINDER-2 studies. **Results:** In clinically unimpaired individuals, we found that 8% were LB-positive, 26% Aβ-positive (12% of those were also LB-positive), and 16% tau-positive. LB pathology had independent and significant negative effects on cross-sectional and longitudinal global cognition and memory. These were similar in magnitude to the effects of tau pathology and more pronounced than those of Aβ pathology. Participants with both LB and AD (Aβ and tau) pathology exhibited faster cognitive decline than those with just LB or AD pathology. LB, but not AD, pathology was associated with reduced sense of smell. In cognitively impaired individuals, we found that 23% of participants had LB pathology, of whom only 32% fulfilled clinical criteria of Parkinson's disease or dementia with Lewy bodies, and 54% exhibited AD pathology (amyloid-β+ and tau+). Within the LB-positive group, 48% also had AD-pathology. In the AD-positive group, 17% of patients with mild cognitive impairment and 24% of those with dementia were also LB-positive. LB pathology was associated with worse attention/executive, visuospatial, and motor function independently of AD pathology. Moreover, LB pathology was also independently associated with a faster longitudinal decline in all examined cognitive functions. **Conclusion:** This study highlights the cognitive effects of LB pathology, independent from AD pathology, in clinically unimpaired individuals, which will be important to consider for prognosis and design of both preclinical AD and LB disease trials. Further, analyzing LB status, in addition to amyloid-β and tau, in cognitively impaired individuals provides a better precision medicine approach identifying patient subgroups with different clinical trajectories.

OC02- NOVEL CSF TAU BIOMARKERS CAN BE USED FOR DISEASE STAGING OF SPORADIC ALZHEIMER'S DISEASE. G. Salvadó[1], K. Horie[2,3,4], N.R. Barthélemy[2,3], J.W. Vogel[1,5], A. Pichet Binette[1], C.D. Chen[6], B.A. Gordon[6], T.L.S. Benzinger[6,7], D.M. Holtzman[3,7], J.C. Morris[3,7], S. Janelidze[1], R. Ossenkoppele[1,8,9], S.E. Schindler[3,7], R.J. Bateman[2,3,7], O. Hansson[1,10] *(1. Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University - Lund (Sweden), 2. The Tracy Family SILQ Center, Washington University School of Medicine - St Louis (United States), 3. Department of Neurology, Washington University School of Medicine - St Louis (United States), 4. Eisai Inc. - Nutley (United States), 5. Department of Clinical Science, Malmö, SciLifeLab, Lund University - Lund (Sweden), 6. Department of Radiology, Washington University School of Medicine - St Louis (United States), 7. Charles F. and Joanne Knight Alzheimer Disease Research Center, Washington University School of Medicine - St Louis (United States), 8. Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc - Amsterdam (Netherlands), 9. Amsterdam Neuroscience, Neurodegeneration - Amsterdam (Netherlands), 10. Memory Clinic, Skåne University Hospital - Malmö (Sweden))*

Background: The biological staging of Alzheimer's disease (AD) can significantly enhance the diagnostic and prognostic evaluation of dementia, both in clinical practice and in the design of clinical trials. Our objective was to develop a staging system based on cerebrospinal fluid (CSF) biomarkers, which are more accessible and cost-effective compared to PET scans. However, before developing such a staging system, it was essential to determine whether a single staging system could capture variability in fluid biomarkers across all individuals, in opposition to what has been shown with tau-PET. **Methods:** We included 462 participants from the BioFINDER-2 cohort (Sweden), encompassing the entire AD spectrum as well as non-AD patients with available CSF biomarkers. To construct our CSF staging model, we utilized the Subtype and Stage Inference (SuStaIn) algorithm, a machine learning technique that models temporal progression patterns (stages) from biomarkers, with the possibility of multiple temporal patterns (subtypes). We examined the optimal number of CSF abnormality trajectories (subtypes) that best represented disease progression across all participants using cross-validation. Based on these findings, we developed a CSF staging model and compared it to other biomarkers, including Aβ- and tau-PET, as well as cognition, both in cross-sectional and longitudinal analyses. Finally, we assessed the prognostic value of our staging model in predicting clinical progression. The main results were validated in 220 participants from the Knight ADRC cohort (USA). **Results:** SuStaIn revealed that a single subtype and only five CSF biomarkers (in the following order: Aβ (Aβ42/40), phosphorylation occupancies of tau at residues 217 and 205 [pT217/T217 and pT205/T205], microtubule-binding region of tau containing residue 243 [MTBR-tau243], and total tau) were sufficient to create an accurate disease staging model. Increasing CSF stages (0-5) were associated with greater abnormality in other AD-related biomarkers, such as Aβ- and tau-PET, and aligned with different phases of longitudinal biomarker changes consistent with prevailing models of AD progression. Our staging model demonstrated high accuracy in predicting Aβ-PET status (CSF stage 2: AUC[95%CI]=0.96[0.93,0.98] and 0.89[0.85,0.94] for BioFINDER-2 and Knight ADRC, respectively) and tau-PET status (CSF stage 4: AUC[95%CI]=0.95[0.93,0.97] and 0.94[0.91,0.96]). Furthermore, it effectively discriminated between AD and non-AD cognitive impairment (BioFINDER-2: CSF stage 2: AUC[95%CI]=0.95[0.93,0.98]). Higher CSF stages were associated with an increased risk of clinical deterioration (CSF stages 4-5 vs. 1-3: HR[95%CI]=5.2[2.2,12.6] and 6.9[3.0,16.0]). **Conclusions:** Our findings suggest the existence of a distinct pathophysiologic molecular pathway that develops across all AD patients. A single CSF sample is sufficient to reliably indicate the presence of both AD pathologies and the degree and stage of disease progression. Therefore, our CSF staging model could facilitate the selection of optimal participants for specific AD clinical trials without relying on PET imaging. These results will gain even greater significance upon their transfer to plasma biomarkers. **Key words:** CSF staging; fluid biomarkers; selection of participants; prognosis. **Disclosures:** OH has acquired research support (for the institution) from ADx, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Amylyx, Alzpath, BioArctic, Biogen, Cerveau, Eisai, Eli Lilly, Fujirebio, Genentech, Merck, Novartis, Novo Nordisk, Roche, Sanofi and Siemens. JWV is supported by the SciLifeLab & Wallenberg Data Driven Life Science Program (grant: KAW 2020.0239). KH is an Eisai-sponsored voluntary research associate professor at Washington University and has received salary from Eisai. Washington University, RJB, and DMH have equity ownership interest in C2N Diagnostics. RJB. and DMH receive income from C2N Diagnostics for serving on the scientific advisory board. KH, NRB, and RJB. may receive income based on technology (METHODS TO DETECT MTBR TAU ISOFORMS AND USE THEREOF) licensed by Washington University to C2N Diagnostics. DMH may receive income based

on technology (ANTIBODIES TO MID-DOMAIN OF TAU) licensed by Washington University to C2N Diagnostics. RJB has received honoraria as a speaker, consultant, or advisory board member from Amgen and Roche. DMH is on the scientific advisory board of Genentech, Denali, and Cajal Neurosciences, and consults for Alector and Asteroid. NRB is co-inventor on the following US patent applications: 'Methods to detect novel tau species in CSF and use thereof to track tau neuropathology in Alzheimer's disease and other tauopathies' (PCT/US2020/046224); 'CSF phosphorylated tau and amyloid beta profiles as biomarkers of tauopathies' (PCT/US2022/022906); and 'Methods of diagnosing and treating based on site-specific tau phosphorylation' (PCT/US2019/030725). NRB may receive a royalty income based on technology licensed by Washington University to C2N Diagnostics.

OC03- THE ANTI-AMYLOID BETA «BRAIN SHUTTLE» ANTIBODY TRONTINEMAB RAPIDLY REDUCES AMYLOID PLAQUES IN PEOPLE WITH ALZHEIMER'S DISEASE. L. Kulic[1], F. Alcaraz[1], A. Vogt[1], C. Hofmann[1], P. Barrington[2], M. Marchesi[1], G. Klein[1], R. Croney[3], D. Agnew[3], J.A. Abrantes[1], S. Ahlers[4], P. Delmar[1], I. Wiesel[1], H. Svoboda[1] *(1. Roche - Basel (Switzerland), 2. TranScrip group - Wokingham (United Kingdom), 3. Roche - Welwyn (United Kingdom), 4. Excelya Germany GmbH - Mannheim (Germany))*

Background: Trontinemab is a bispecific 2+1 monoclonal antibody (mAb) under development for the treatment of Alzheimer's disease (AD). It combines by recombinant fusion an anti-amyloid beta antibody moiety with a transferrin receptor 1 (TfR1) binding "brain shuttle" module, enabling active receptor-mediated transport across the blood–brain barrier. In preclinical studies in nonhuman primates, trontinemab showed substantially improved exposure in the brain parenchyma compared with gantenerumab. In the first-in-human Phase (Ph) Ia single ascending dose study in healthy young volunteers (NCT04023994), a markedly increased cerebrospinal fluid (CSF)/plasma ratio was observed compared with typical mAbs. Trontinemab is currently under evaluation in the ongoing Ph Ib/IIa Brainshuttle AD study (NCT04639050) in participants with prodromal or mild-to-moderate AD. **Methods:** The Brainshuttle AD study is a randomized, double blind, placebo-controlled, multiple ascending dose global, parallel-group study designed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of trontinemab following intravenous infusion. The Brainshuttle AD study assesses whether faster and more extensive amyloid plaque clearance in participants with AD can be achieved through active TfR1 receptor-mediated transcytosis of an anti-amyloid mAb to the brain. Seven intravenous doses of trontinemab or placebo are being administered once every 4 weeks to participants aged 50 to 85 years with prodromal or mild-to-moderate AD, who are amyloid positive at baseline based on amyloid positron emission tomography (PET) (cut-off: >50 Centiloid units). The study consists of a continuous screening period (including a one week baseline period), a double-blind treatment period (28 weeks), and a safety follow-up period (28 weeks). It uses a staggered parallel-group design, with participants recruited in four planned sequential dose cohorts (selected dose levels: 0.2 mg/kg (cohort 1), 0.6 mg/kg (cohort 2), 1.8 mg/kg (cohort 3), and 3.6 mg/kg (cohort 4)). Sentinel dosing is being applied to each cohort. Amyloid plaque burden is being assessed by florbetapir and florbetaben PET imaging at screening, day 78 (only cohort 3 and cohort 4), and day 196. An interim analysis of the amyloid PET results was performed prior to escalating to the maximum dose level of 3.6 mg/kg (cohort 4). **Results:** The interim analysis for safety and amyloid PET was based on a data snapshot as of January 18, 2023. The safety results included blinded data from a total of 44 participants who received trontinemab or placebo. The vast majority of adverse events (AEs) were mild (grade 1) or moderate (grade 2) in severity. Consistent with previous results from the Ph Ia single ascending dose study of trontinemab, infusion related reactions (IRRs) were the most common treatment-emergent AEs. All IRRs were mild or moderate in severity. The interim amyloid PET results included data from 36 participants (11 men, 25 women) enrolled in cohorts 1 to 3, who underwent at least one post-baseline amyloid PET scan. A significant dose-dependent amyloid plaque lowering was observed across all three analyzed dose levels. In cohort 3 (1.8 mg/kg) a strong amyloid plaque reduction and amyloid PET negativity in several participants (cut off: <24 Centiloids) were documented already at day 78. Detailed interim data will be presented. **Conclusion:** Preliminary results from the ongoing Ph Ib/IIa Brainshuttle AD study of trontinemab suggest that rapid amyloid plaque clearance may be achieved at significantly lower dose levels than with typical anti-amyloid mAbs, in line with the TfR1-based brain shuttle platform approach. The preliminary safety, tolerability and pharmacodynamic data support further investigation of trontinemab as a potential next-generation amyloid targeting therapy for AD. **Clinical Trial Registry**: NCT04639050; https.://clinicaltrials.gov/ct2/show/NCT04639050?term=RO7126209&draw=2&rank=1. **Disclosures:** HS is a full-time employee of Roche Diagnostics GmbH and owns stocks in F. Hoffman-La Roche Ltd. IW is a full-time employee of and owns stock in F. Hoffman-La Roche Ltd. AV is a full-time employee and owns stock options in F. Hoffman-La Roche Ltd. PB is a Contractor of F. Hoffman-La Roche Ltd. LK is a full-time employee and owns stock in F. Hoffman-La Roche Ltd. CH is a full-time employee and owns stock in F. Hoffmann-La Roche Ltd. MA is a full-time employee and owns stock in F. Hoffman-La Roche Ltd. RC is a full-time employee and owns stock options in F. Hoffman-La Roche Ltd. GK is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd. FA is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd. DA is a full-time employee of and owns stock in F. Hoffmann-La Roche Ltd. PD is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd. MM and JAA are full time employees of F. Hoffmann-La Roche Ltd and may own company stock/stock options.

OC04- RAPID DETECTION OF THE EARLIEST AMYLOID-RELATED CHANGES IN MEMORY CONSOLIDATION: ASSESSMENT OF LEARNING USING DAILY DIGITAL TESTING. K. Papp[1], R. Jutten[1], D. Soberanes[1], E. Weizenbaum[1], S. Hsieh[1], C. Molinare[1], R. Buckley[1], R. Betensky[2], K. Johnson[1], D. Rentz[1], R. Sperling[1], R. Amariglio[1] *(1. Harvard Medical School - Boston (United States), 2. New York University - New York (United States))*

Background: The ability to detect and track subtle Alzheimer's disease (AD)-related cognitive decrements at the preclinical stage of disease, where treatments may be most effective, has been a significant challenge for the field. **Objective:** To determine whether assessing learning over days reveals AD-biomarker related alterations in memory consolidation in healthy older adults that are otherwise undetectable with single timepoint assessments. **Methods:** Participants completed the Multi-Day Boston Remote Assessment for Neurocognitive Health (BRANCH) for 10 min/

day on personal devices (i.e., smartphones, laptops) which captures the trajectory of daily learning of the same content on three repeated tests (Digit Signs Test, Groceries Test, Face-Name Associative Memory Exam). Overall learning is computed as an equally-weighted composite of accuracy across all three measures. Participants also completed standard in-clinic cognitive tests as part of the Preclinical Alzheimer's Cognitive Composite-(PACC-5), and additional challenging single timepoint memory tests. 123 participants underwent a PACC-5 follow-up after 1.07 (SD=0.25) years. **Results:** Participants included 164 cognitively unimpaired older adults (Mean Age=74.3 (SD=7.31, 60-91)). A total of 36 (21.9%) participants were classified as having elevated β-amyloid (Aβ+) and 128 (78%) classified as Aβ- using Positron Emission Tomography (PET) with 11CPittsburgh Compound-B (PiB). At the cross-section, there were no differences in performance between Aβ+/- participants on any standard in-clinic cognitive tests (e.g., PACC-5, challenging memory tests) or on Day 1 of Multi-Day BRANCH. Aβ+ participants exhibited diminished 7-day learning curves on Multi-Day BRANCH after 4 days of testing relative to Aβ- participants (Cohen's d=0.49, 95%CI=0.10-0.87). Diminished learning curves were also associated with greater annual PACC-5 decline (r=0.54, p<0.001). **Conclusions:** Very early Aβ-related memory alterations can be revealed by assessing learning over days, suggesting that failures in memory consolidation predate other conventional amnestic deficits in AD and are associated with prospective decline on standard neuropsychological testing. Repeated digital memory assessments, increasingly feasible and uniquely able to assess memory consolidation over short time periods, have the potential to be transformative for detection and tracking of cognitive change in preclinical AD.

OC05- CLINICAL OUTCOMES FROM A PHASE 3, RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF NE3107 IN SUBJECTS WITH MILD TO MODERATE PROBABLE ALZHEIMER'S DISEASE.
C. Reading[1], C. Ahlem[1], J. Palumbo[1], N. Osman[1], M. Testa[2], D. Simonson[1] *(1. BioVie Inc. - Carson City (United States), 2. Department of Biostatistics, Harvard T.H. Chan School of Public Health - Boston (United States), 3. Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School - Boston (United States))*

Background: Chronic inflammation is thought to induce insulin resistance (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 Alzheimer's disease (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 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. In a phase 2 study in patients with mild cognitive impairment, NE3107 was associated with neurophysiological and neuropsychological enhancements and improvements in biomarkers associated with neuroinflammation and AD. **Objectives:** This phase 3 study (NM101; NCT04669028) was designed to assess the efficacy, safety, and tolerability of NE3107 in subjects with mild to moderate probable AD (enrolling Aβ+ and Aβ− subjects). **Methods:** Subjects, aged 60-85 years, with mild to moderate probable AD were randomized to receive either 20-mg NE3107 BID or placebo for 30 weeks. The primary efficacy endpoint is change from baseline to week 30 in the Clinical Dementia Rating Sum of Boxes (CDR-SB). Secondary endpoints include the Alzheimer's Disease Assessment Scale Cognitive Subscale 12 (ADAS-Cog12) and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), additional neuropsychological assessments, and measures of glycemic control. Exploratory endpoints include inflammatory markers, neuroimaging and epigenetic changes. **Results:** The trial is fully enrolled (439 subjects) and the last subject visit with activity assessments is scheduled for September 26, 2023. The analysis of correlations between changes from baseline for assessments and metabolic inflammation parameters will remain blinded until the database is locked, but blinded correlations will be presented after the last subject's last assessment visit. Data presented will include frequency distributions and correlations for changes from baseline for CDR-SB, ADAS-Cog12, ADCS-CGIC, Mini-Mental State Exam, Alzheimer's Disease Cooperative Study – Activities of Daily Living, Amyloidβ 42/40 ratio, Apolipoprotein ε4 carriage, waist/hip ratio, weight, gender, age, mean amplitude of glycemic excursions (MAGE) from continuous glucose monitoring, C-reactive protein, monocyte chemoattractant protein-1, regulated upon activation, normal T cell expressed and secreted (RANTES), complement component C1q, hyperglycemia, Homeostatic Model Assessment 2-insulin resistance, fructosamine, hypertension, hypercholesterolemia, hypertriglyceridemia, volumetric magnetic resonance imaging, F18-fluorodeoxyglucose positron emission tomography, neuropsychiatric inventory depression, anxiety, irritation, sleep, and appetite. **Conclusion:** Using well-established assessments for neuropsychological function and a variety of metabolic parameters, this study aims to establish the potential therapeutic efficacy, cognitive improvements, and safety profile associated with NE3107 treatment in patients with mild to moderate AD. **Funded by:** BioVie Inc. **Disclosures:** MAT has received grant support from BioVie Inc. CLR, CA, JMP, and NO are employees of BioVie Inc. DCS has nothing to disclose.

OC06- PLASMA P-TAU217 FACILITATES A TWO-PHASE SCREENING APPROACH FOR PARTICIPANT SELECTION INTO ANTI-AMYLOID TRIALS.
N. Mattsson-Carlgren[1], L. Collij[1,2], A. Pichet Binette[1], R. Ossenkoppele[1,2], R. Smith[1], O. Strandberg[1], S. Palmqvist[1], E. Stomrud[1], N. Ashton[3], K. Blennow[3], S. Janelidze[1], O. Hansson[1] *(1. Lund University - Lund (Sweden), 2. Amsterdam UMC - Amsterdam (Netherlands), 3. University of Gothenburg - Gothenburg (Sweden))*

Background: The rapid development of blood-based biomarkers (BBM) for Alzheimer's disease (AD) to detect amyloid-β (Aβ) and phosphorylated tau (P-tau) proteinopathy has further facilitated their implementation in clinical trial design. The Donanemab TRAILBLAZER trial required participants to be Aβ-positive based on PET and to have a specific range of tau-PET burden1. To facilitate this inclusion criteria, we aim to investigate the use of plasma biomarkers as a pre-screening tool in a two-phase approach. **Methods:** We included 912 subjects (SCD:N=215, MCI:N=355, Dementia;N=342) from the Swedish BioFINDER-2 study with available [18F]RO948-PET quantification using the multi-block barycentric discriminant analysis (MUBADA) region-of-interest (ROI) from the phase-2 Donanemab trial; a voxel-wise map that optimally discriminates between Aβ-positive clinically defined

MCI and AD dementia patients against Aβ-negative cases2. Participants were classified as low (SUVRMUBADA<1.10), intermediate (1.10<SUVRMUBADA>1.46) or high tau burden (SUVRMUBADA>1.46). Measures of plasma P-tau217, P-tau181, P-tau231, NTA, GFAP, and NfL were determined. Aβ-status was defined using either [18F]flutemetamol amyloid-PET (N=505) or CSF Aβ42/40 (N=407). Youden index was used to define optimal cut-points. Logistic regression was performed to predict Aβ and tau-PET status and compared to 3 machine learning approaches, namely random forest classification, extreme gradient boosting, and support Vector Machine with radial basis function kernel. **Results:** Among all study participants, 58.8% were Aβ-positive and of those, 275 (51.3%) had low, 145 (27.1%) had intermediate, and 116 (21.6%) had high tau-PET burden. P-tau217 was the best individual biomarker to predict Aβ-status (AUCtraining=0.96; AUCtest=0.93) and therefore used for subsequent analyses. Phase 1 of participant selection entailed identification of Aβ-positive subjects, while minimizing the need for confirmation testing through CSF or PET. We implemented a two-cut point or "gray-zone" strategy, which yielded a combination of two pTau217 cut-points (pTau217log: low=-0.731, high=-0.607, 12.7% of test-set fell within this range) with a sensitivity/specificity of 0.93/0.91, respectively. In the test-set (N=181), this strategy classified 29.9% as true negatives, 4.5% as false positives, 9.4% as false negatives, and 55.8% as true positives for Aβ-status. Thus, the algorithm resulted in identifying 39.3% of subjects not suitable for trials requiring Aβ-positivity. Phase 2 entailed identification of Aβ-positive participants with the highest tau-PET burden (SUVRMUBADA>1.46), that would require subsequent tau-PET imaging for confirmation. Logistic regression showed that pT217 alone resulted in the highest AUC (training=0.89; test=0.90). The range of "saved scans" went from 37.1% (at cut-point corresponding to the lowest level of plasma pTau217 among MUBADA-high subjects) to 100% (highest possible cut-point for P-tau217, i.e., no cases undergo tau-PET). More specifically, a cut-point for FNR0.05 in the training set achieved FNR 3.3% in the test set and resulted in 54.5% saved scans. Thus, the two-phase approach resulted in 72.3% (1–((1-0.393)*(1-0.545))=0.723) "saved" tau-PET scans overall, compared to doing tau PET in the entire sample. **Conclusions:** Plasma P-tau217 facilitates a two-phase screening approach, first excluding Aβ-negative subjects and second identifying participants likely to have high tau-PET burden. Plasma P-tau217 may be used as a first-line screening tool in processes for decision-making about start of treatment with anti-amyloid immunotherapies in Alzheimer's disease. **References:** 1. Mintun MA, Wessels AM, Sims JR. Donanemab in Early Alzheimer's Disease. Reply. N Engl J Med 2021;385:667. 2. Pontecorvo MJ, Devous MD, Kennedy I, et al. A multicentre longitudinal study of flortaucipir (18F) in normal ageing, mild cognitive impairment and Alzheimer's disease dementia. Brain 2019;142:1723-1735. **Disclosures:** NMC, APB, RO, RS, OS, ES, NA, and SJ report no relevant disclosures; LC has received research support from GE Healthcare (paid to institution); SP has acquired research support (for the institution) from ki elements / ADDF. In the past 2 years, he has received consultancy/speaker fees from Bioartic, Biogen, Lilly, and Roche. KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a cofounder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. OH has acquired research support (for the institution) from ADx, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE Healthcare, Pfzer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Amylyx, Alzpath, BioArctic, Bio gen, Cerveau, Fujirebio, Genentech, Novartis, Roche, and Siemens. The BioFINDER-2 study 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 Swed ish 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 Forskn ingsstöd (2020–0314) and the Swedish federal government under the ALF agreement (2018-Projekt0279).

OC07- USE OF A BLOOD BIOMARKER TEST IMPROVES ECONOMIC UTILITY IN THE EVALUATION OF PATIENTS WITH SIGNS AND SYMPTOMS OF COGNITIVE IMPAIRMENT . W. Canestaro[1], R. Bateman[2], D. Holtzman[2], M. Monane[3], J. Braunstein[3] *(1. University of Washington School of Pharmacy - Seattle (United States), 2. Washington University School of Medicine - St Louis (United States), 3. C2N Diagnostics - St Louis (United States))*

Background: The availability of anti-amyloid, disease-modifying therapies for Alzheimer's disease (AD) is predicted to dramatically increase demand for confirmation of disease. Accessible and affordable methods to help establish an AD diagnosis are needed. Blood biomarkers (BBMs) offer advantages over positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers in these regards. The PrecivityAD® blood test (C2N Diagnostics, St. Louis, MO) uses high resolution mass spectrometry to measure plasma concentrations of amyloid beta 42 and 40 (Aβ42 and Aβ40) and the presence of apolipoprotein E (ApoE)-specific peptides to establish the APOE proteotype (inferred genotype). The measurements are combined with age into an algorithm to generate the Amyloid Probability Score (APS), which determines the likelihood for presence of brain amyloid plaques with 92% sensitivity and 77% specificity. While the clinical validity for the PrecivityAD test has been demonstrated in multiple studies versus amyloid PET as the reference standard, the economic utility and budget impact of the PrecivityAD test have not been well described in the literature. **Methods:** We compared the use of the PrecivityAD test early in the diagnostic journey versus the first use of amyloid PET and CSF testing in patients with cognitive impairment. Our model, a decision tree that considered a one-million (1MM) US health plan population, compared two scenarios: 1) baseline scenario modeled after current practice, and 2) PrecivityAD test scenario modeled with test adoption in both the primary care setting and as a first evaluation at the neurologist's office. We used estimates of real-world adoption, adherence, and drop-out measures drawn from clinical expert opinion to simulate clinical practice more closely over idealized scenarios. The key model outcomes were the sensitivity and specificity of each diagnostic pathway, difference in costs of the diagnostic work-up, and difference in cost per case identified between the baseline scenario and the PrecivityAD test scenario. **Results:** An approach using the PrecivityAD test early in the evaluation process had comparable sensitivity and specificity to the established approach utilizing PET and CSF biomarker testing. Net savings in the diagnostic

work-up was $4.06MM or $0.34 per member per month (PMPM) in this 1MM lives model, representing a 12.7% reduction in total costs for evaluation. Among diagnosed cases in the model, PrecivityAD testing resulted in cost savings of $611 and $1,832 per case identified at 40% and 100% test penetration, respectively. Savings were driven by reductions in utilization of PET and CSF testing. The model results were dependent on current pricing of CSF and PET biomarker testing as well as percentage adoption of the PrecivityAD test: higher adoption correlated with greater cost savings. **Conclusions:** The use of the PrecivityAD blood test prior to standard methods in patients undergoing evaluation for cognitive impairment may prevent unnecessary test layering, provide cost savings, and thus reduce the predicted burden on both patients and payers. The potential for economic impact is significant: extrapolated to the entire US population, the use of PrecivityAD blood test at a 40% adoption rate would result in greater than $1B in savings based on our modeling. **Key words:** Brain amyloid, blood biomarker, diagnostic evaluation, economic utility. **Disclosures:** William J. Canestaro, PhD, MSc serves as a consultant to C2N Diagnostics. Randall J. Bateman (RJB) is a cofounder of C2N Diagnostics. RJB has an equity ownership interest in C2N Diagnostics and may receive income based on technology licensed by Washington University to C2N Diagnostics. RJB receives income from C2N Diagnostics for serving on the scientific advisory board. RJB receives current grant support from Eli Lilly and Company/Avid Radiopharmaceuticals, Hoffman-La Roche/Genentech, Biogen, Eisai, and Janssen. David M. Holtzman (DMH) is a cofounder of C2N Diagnostics. DMH has an equity ownership interest in C2N Diagnostics and may receive income based on technology licensed by Washington University to C2N Diagnostics. DMH reports serving on the scientific advisory board of C2N Diagnostics, Denali, Genentech, and Cajal Neuroscience and consults for Asteroid. Mark Monane, MD, MBA serves as a consultant to C2N Diagnostics and receives consulting fees and equity compensation from C2N Diagnostics. Joel B. Braunstein, MD, MBA is an officer, co-founder, and board member at C2N Diagnostics and receives salary and equity compensation from C2N Diagnostics.

OC08- A PHASE 2B CLINICAL TRIAL OF NEFLAMAPIMOD IN DEMENTIA WITH LEWY BODIES DESIGNED TO CONFIRM THE EFFICACY RESULTS FROM PHASE 2A.

N.D. Prins[1], A. Gardner[2], H.M. Chu[3], K. Blackburn[2], J.E. Galvin[4], J.J. Alam[2] *(1. Brain Research Center - Amsterdam (Netherlands), 2. EIP Pharma Inc - Boston (United States), 3. Anoixis Corporation - Natick (United States), 4. University of Miami Miller School of Medicine - Boca Raton (United States))*

Background: Neflamapimod targets molecular mechanisms underlying basal forebrain cholinergic degeneration. In a phase 2a 16-week treatment placebo-controlled clinical trial (AscenD-LB) in dementia with Lewy bodies (DLB), patients on neflamapimod significantly improved, vs. those on placebo, on the Clinical Dementia Rating Scale (CDR-SB) and Timed Up and Go (TUG) test. In addition, at the higher of two doses (40mg BID, 40mg TID) evaluated, neflamapimod significantly improved outcomes on a neuropsychological test battery (NTB). To confirm the phase 2a results, a phase 2b clinical study (RewinD-LB) that is similar in design to AscenD-LB has been initiated. The objective of this presentation is to detail the major learnings from AscenD-LB, as well from prior neflamapimod studies in Alzheimer's disease (AD), that were incorporated into RewinD-LB. **Methods:** The RewinD-LB study is a 160-patient (randomized 1:1 to 40mg neflamapimod or placebo) 16-week placebo-controlled study, with a 32-week open label extension for patients who complete the placebo-controlled phase, in patients with early (CDR ≤1.0) DLB (per consensus criteria, including abnormal DaT scan). Patients with abnormal plasma ptau181 (>cut-off for AD co-pathology) will be excluded. Primary endpoint: CDR-SB. Secondary endpoints: TUG, NTB, ADCS-CGIC. Tertiary endpoints: Dementia Cognitive Fluctuations Scale, NPI-12, MDS-UPDRS3 motor examination. In addition, effects of neflamapimod on the volume of the nucleus basalis of Meynert (NbM) within the basal forebrain by MRI will be evaluated. **Results:** Patient Population: In AscenD-LB, in the comparison of placebo with neflamapimod 40mg TID, improvements with neflamapimod treatment were greater in the participants below the plasma ptau cut-off for AD co-pathology compared with that in those above the cut-off; in addition, the Cohen's d effects size vs. placebo treatment was ≥ 0.7 for CDR-SB and TUG (0.56 for NTB). Primary endpoint: in AscenD-LB, compared to the NTB, the CDR-SB and TUG were more sensitive to drug effect (e.g., some evidence of efficacy at 40mg BID evident in these two endpoints) and able to demonstrate more robust effects (i.e., lower p-values). In sample size calculations based on simple t-test at week 16 (with the use of all study visit data in simulations using the MMRM analysis that will be utilized at final analysis, power approaches 100%), assuming the effect size seen in AscenD-LB in patients with normal baseline plasma ptau181, with 80 patients per arm and alpha of 0.05, the statistical power is ~85% with the NTB, 95% with TUG, and >95% with CDR-SB. To evaluate NbM volume by MRI to assess neflamapimod drug effect on the basal forebrain, a retrospective analysis of MRI images obtained in a previously completed phase 2a study in patients with early AD was performed. In that analysis both the NbM volume and its functional dynamic connectivity to deep grey matter was statistically significantly increased from baseline at the end of 12 weeks neflamapimod treatment. **Conclusions:** The RewinD-LB phase 2b clinical study of neflamapimod in DLB has high statistical power to confirm the clinical efficacy results seen in phase 2a and has the po, potential to demonstrate effects on pathologic disease progression in the basal forebrain. **Key words:** neflamapimod, dementia with lewy bodies, basal forebrain, CDR-SB. **Clinical Trial Registry:** NCT05869669; https://clinicaltrials.gov/ct2/show/NCT05869669. **Disclosures:** NDP is CEO and co-owner of Brain Research Center, the Netherlands. Heperformed consultancy work for Aribio, Amylyx, Eli-Lilly and Janssen. He is co-PI of a study with Fuji Film Toyama Chemical. NDP received a speaker fee from Biogen. NDP served on the DSMB of Abbvie's M15-566 trial. AG and HMC are consultants/contractors to, and KB and JJA are employees of EIP Pharma, Inc., the sponsor that is developing neflamapimod as a treatment for DLB. JEG has no competing interests to declare. **References:** 1. Jiang Y et al, Nat Commun 13, 5308 (2022) https://doi.org/10.1038/s41467-022-32944-3

OC09- ACCELERATED B-AMYLOID PLAQUE REDUCTION IN ALZHEIMER'S DISEASE COMBINING ADUCANUMAB INFUSION WITH FOCUSED ULTRASOUND BLOOD-BRAIN BARRIER OPENING.

A.L.I.R. Rezai, P. D'haese, M. Haut, M. Ranjan, J. Carpenter, R. Mehta, K. Wilhelmsen, P. Wang, V. Finomore, S. Hodder *(WVU Rockefeller Neuroscience Institute - Morgantown (United States))*

Background: Anti-β-amyloid monoclonal antibodies are a new treatment option for Alzheimer's disease (AD). However, these therapies require long duration of treatment (>12-18

months), frequent and/or higher dosing, and are associated with side effects including amyloid related imaging abnormality (ARIA). The blood-brain barrier (BBB) is a significant challenge limiting antibody and other therapeutic delivery to the brain. MRI guided focused ultrasound (FUS) has been demonstrated to be a safe and non-invasive technique to transiently open the BBB in AD(1, 2). Our recent work confirmed the long-term safety of FUS-mediated BBB opening (BBBO) of the frontal, parietal, hippocampal, and entorhinal cortex in ten patients with AD(3). We now report a first-in-human proof-of-concept study in AD combining anti-β-amyloid monoclonal antibody infusion with FUS-mediated BBBO to enhance antibody delivery. **Objective:** To assess the safety, feasibility, and effects of combining standard of care aducanumab anti-β-amyloid antibodies with FUS-mediated BBB opening in patients with AD. **Methods:** Patients with mild AD underwent the standard on-label dose escalation monthly infusion of aducanumab. Two hours after each of the first six monthly infusion cycles, low intensity MRI-guided FUS sonication (220 kHz, ExAblate Neuro Type 2 system) was delivered to open the BBB in brain regions with β-amyloid as determined by 18F-Florobetaben β-amyloid PET scan. FUS BBB opening (BBBO) was limited to one hemisphere and compared to the contralateral homologous brain regions with no BBBO. Patients were followed with serial MRI imaging, neurological and cognitive assessments, as well as 18F-Florobetaben PET. **Results:** The first two participants were males (ages 77 and 60 years; baseline MMSE = 25, 28 baseline ADASCog11 = 13 & 7, respectively) who completed 6 cycles of monthly aducanumab infusion, and the third participant was a 64-year-old female (baseline MMSE 27; baseline ADASCog11 = 5) who has completed 5 monthly cycles (to date) of aducanumab infusion with concomitant FUS BBBO. The baseline β-amyloid plaque load, as quantified in Centiloid units across the signature brain regions of the three participants was 203, 139, and 285 units, respectively. The BBB was opened in the frontal, parietal, and temporal lobes, and the hippocampus. All 17 BBBO procedures in multiple brain regions were well tolerated with no procedure related serious adverse events. BBBO was demonstrated in each instance by focal parenchymal gadolinium contrast enhancement followed by BBB closure within 24-48 hours. There were no serious neurological, cognitive, or imaging adverse events and no ARIA were observed to date. PET analysis compared β-amyloid levels in regions of FUS-BBBO as compared to the regions in the contralateral homologous hemisphere with no BBBO. The results revealed a progressive and significant decrease in β-amyloid levels with BBBO. The first and second participants demonstrated a decrease in β-amyloid levels of 108 Centiloid units (48%) and 88 Centiloid units (49%) from baseline to six months, respectively. The third participant had a reduction of 131 Centiloid units (52%) from baseline to five months of treatment. A Wilcoxon signed-rank test across all participants and timepoints indicated a statistically significant difference between the treated and contralateral treatment region ($p < 0.005$). **Conclusion:** The result of this first in human proof-of-concept study demonstrates that FUS-BBBO can be safely combined with aducanumab infusions with accelerated and greater reduction in β-amyloid in a shorter time in the FUS-targeted regions of the brain. This novel targeted therapeutic approach has the potential to advance neurotherapeutics in the treatment of AD and other progressive neurological disorders that are impacted by the BBB. Additional studies with a larger number of patients, larger volume of BBBO, and a long-term follow-up are needed to establish the full potential of this combined approach to rapidly reduce brain β-amyloid and impact cognitive function. **References:** 1. Rezai AR, Ranjan M, D'Haese PF, Haut MW, Carpenter J, Najib U, et al. Noninvasive hippocampal blood-brain barrier opening in Alzheimer's disease with focused ultrasound. Proceedings of the National Academy of Sciences of the United States of America. 2020;117(17):9180-2. 2. Lipsman N, Meng Y, Bethune AJ, Huang Y, Lam B, Masellis M, et al. Blood-brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. Nat Commun. 2018;9(1):2336. 3. Rezai AR, Ranjan M, Haut MW, Carpenter J, D'Haese PF, Mehta RI, et al. Focused ultrasound-mediated blood-brain barrier opening in Alzheimer's disease: long-term safety, imaging, and cognitive outcomes. J Neurosurg. 2022:1-9.

OC10- ALLOPREGNANOLONE REGENERATIVE THERAPEUTIC FOR MILD ALZHEIMER'S DISEASE (REGEN-BRAIN©)

R. Brinton[1], G. Hernandez[1], C. Lopez[1], L. Schneider[2] *(1. University of Arizona - Tucson (United States), 2. University of Southern California - Los Angeles (United States))*

Background: Regenerative medicine to prevent, delay and treat AD holds therapeutic potential by promoting endogenous systems of renewal and repair. Therapeutics that target the regenerative system of the brain while simultaneously targeting mechanisms underlying AD pathology have the potential to delay and, potentially reverse, the course of AD. Allopregnanolone (ALLO) addresses the therapeutic systems biology challenge through pleiotropic mechanisms of action that promote the regenerative system of the brain while simultaneously activating pathways that reduce burden of AD pathology and inflammation. **Objectives:** Based on preclinical and translational data, a double blind randomized-controlled phase 1b/2a multiple ascending dose trial of ALLO in persons with early AD (NCT02221622) was conducted to assess safety, tolerability, and pharmacokinetics. Twenty-four individuals, 12 women and 12 men, participated in the trial (n = 6 placebo; n = 18 ALLO) and underwent brain magnetic resonance imaging (MRI) before and after 12 weeks of treatment. **Results:** Primary outcomes regarding safety and tolerability across all 3 dose cohorts indicated that weekly intravenous administration of ALLO over 12 weeks was safe and well tolerated in all study participants. No differences in the occurrence and severity of adverse events (AE) were observed between treatment arms. No occurrence of ARIA occurred in any of the participants. Pharmacokinetic (PK) analyses indicated a near linear dose dependent Cmax and area under the curve (AUC) total exposure. Little to no sex difference in PK was evident across Allo doses indicating that despite differences in body weight, Cmax at 30 min and AUC were comparable for both sexes. Exploratory MRI analyses included volumetric analyses of hippocampal volume and diffusion tensor imaging of white matter. Hippocampal atrophy rate was determined by volumetric MRI, computed as rate of change, and qualitatively assessed between ALLO and placebo sex, apolipoprotein E (APOE) ε4 allele, and ALLO dose subgroups. White matter microstructural integrity was compared between placebo and ALLO using fractional and quantitative anisotropy (QA). Changes in local, inter-regional, and network-level functional connectivity were also compared between groups using resting-state functional MRI. Rate of decline in hippocampal volume was slowed, and in some cases reversed, in the ALLO group compared to placebo. Gain of hippocampal volume was evident in APOE ε4 carriers (range: 0.6% to 7.8% increased hippocampal volume). Multiple measures of white matter integrity indicated evidence of preserved or improved integrity.

ALLO significantly increased fractional anisotropy (FA) in 690 of 690 and QA in 1416 of 1888 fiber tracts, located primarily in the corpus callosum, bilateral thalamic radiations, and bilateral corticospinal tracts. Consistent with structural changes, ALLO strengthened local, inter-regional, and network level functional connectivity in AD-vulnerable regions, including the precuneus and posterior cingulate, and network connections between the default mode network and limbic system. **Discussion:** ALLO is a first in class regenerative therapeutic with potential for delaying progression and treating AD with a strong foundation of human safety exposure. Based on preclinical discovery, IND-enabling translational research (NIA U01- AG031115), chronic toxicology (NIA U01-AG047222) and outcomes of RCT Phase 1 Multiple Ascending Dose clinical trial (NIA UF1-AG046148 and NIA USC ADRC; IND #113772 (NIA U01-AG031115), we have advanced development of Allo as the first regenerative therapeutic for AD to a NIA (R01AG063826) Phase 2 RCT proof-of-concept clinical trial (REGEN-BRAIN study; NCT04838301; IND:150903). Alzheimer's Drug Discovery Foundation supported ALLO GMP manufacturing and patent development.

OC11- 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], J. Leonard[1], E. Siemers[2], R. Turner[3], W. Bond[4], J. Huffaker[4], and all the SIGNAL AD study investigators, M. Zauderer[1] *(1. Vaccinex, Inc. - Rochester (United States), 2. Siemers Integration LLC - Indianapolis (United States), 3. Re-Cognition Health - Fairfax (United States), 4. 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 progression of Huntington's Disease (HD) and Alzheimer's Disease (AD) and triggers astrocytes that express plexin-B1/B2 cognate receptors 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). The presentation will highlight safety, efficacy, and biomarker data from the completed SIGNAL-HD trial2, describe how neuroimaging and subgroup analysis of the clinical HD results provide further rationale for investigation in AD, as well as 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 in two cohorts of 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 has completed enrollment of 50 subjects with early AD. Study objectives include safety, change in brain metabolism via FDG-PET, and clinical outcomes including CDR-SB and ADAS-Cog. **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 all 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 in EM subjects demonstrated a time-based treatment benefit corresponding to a 36% annualized slowing of the disease. Cognitive treatment benefit was also greater in subjects that were more cognitively impaired at baseline, as evaluated by a Montreal Cognitive Assessment (MoCA) score <26. The ongoing blinded SIGNAL-AD trial has completed enrollment of 50 subjects, and top line data for a full year of randomized, double-blind treatment is anticipated in Q3 2024. Initial blinded safety reviews and review by the Data Monitoring Committee suggest that pepinemab is well tolerated in AD. **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. Top line results from the Phase 1b/2a study in AD (SIGNAL-AD) should be available Q3 2024. **Key words:** pepinemab, VX15/2503, SEMA4D, astrocytes, glial cells, SIGNAL **Disclosures:** T. Fisher, E. Evans, M. Boise, V. Mishra, C. Mallow, J. Leonard, M. Zauderer are all full-time employees of Vaccinex, and own stock and/or options in Vaccinex, Inc. **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

OC12- ASTROCYTE REACTIVITY BIOMARKER FOR THE POPULATIONAL ENRICHMENT OF CLINICAL TRIALS IN PRECLINICAL ALZHEIMER'S DISEASE.

B. Bellaver[1], G. Povala[1], P. C.l. Ferreira[1], J.P. Ferrari-Souzav, D. Teixeira Leffa[1], F. Z. Lussier[1], A. L. Benedet[2], N. J. Ashton[2], E. R. Zimmer[3], H. Zetterberg[2], K. Blennow[2], A. Cohen[1], T. K. Karikari[1], P. Rosa-Neto[4], T. A. Pascoal[1] *(1. University of Pittsburgh - Pittsburgh (United States), 2. University of Gothenburg - Gothenburg (United States), 3. Universidade Federal do Rio Grande do Sul - Porto Alegre (United States), 4. McGill University - Montreal (United States))*

Background: A significant percentage of Aβ-positive cognitively unimpaired (CU) individuals do not develop detectable downstream tau pathology and, consequently, cognitive decline. We recently showed that astrocyte reactivity biomarker abnormality is key to unleashing Aβ effects on tau phosphorylation in preclinical Alzheimer's disease (AD)1. Thissuggests that selecting CU individuals with both Aβ and astrocyte reactivity, without overt p-tau abnormality, could offer a time window very early in the disease process but with an increased risk of developing tau pathology. Here, we tested the utility of astrocyte reactivity biomarker for population enrichment in clinical trials focusing on CU individuals. **Methods:** We assessed 1,016 CU individuals from three cohorts

(TRIAD, Pittsburgh and MYHAT;mean age=69.6±8.9) with Aβ, plasma p-tau and GFAP measures. Individuals were classified as positive (Ast+) or negative (Ast-) for astrocyte reactivity based on plasma GFAP. Lowess and linear regressions accounting for age and sex were used to model the trajectories of plasma p-tau as a function of Aβ. Cohen's d corrected for age and sex was used to estimate effect sizes between groups. The annual rate of progression in tau uptake was measured as follow-up minus baseline uptakes (mean follow-up time=2.3 years) divided by time between scans. To test a strategy of population enrichment in clinical trials using astrocyte positivity in addition to Aβ, we estimated the sample size needed to test a 25% drug effect with 80% of power at a 0.05 level on reducing tau accumulation in CU. **Results:** We observed that plasma p-tau181 increased as a function of Aβ only in CU Ast+ individuals (β=0.34,t=5.37,p<0.0001) with a significant interaction between Aβ and astrocyte reactivity status on plasma p-tau181 (β=0.31,t=4.62,p<0.0001). Similar results were observed for plasma p-tau231and p-tau217. The annual rate of tau-PET accumulation was higher in the CU Ast+ group and predicted by baseline Aβ burden only in CU Ast+. Longitudinal tau-PET accumulation as a function of Aβ/Ast presented initial tau spread over Braak III-IV regions. The presence of Aβ+/Ast+ has a large effect size on longitudinal tau accumulation in early Braak regions, except Braak I (Cohen's d: Braak II=0.61;Braak III=0.40;Braak IV=0.53), whereas Aβ+/Ast-presented a negligible effect size in all Braak regions. Aβ+ alone for population enrichment of a clinical trial focusing on CU individuals would require a sample size of 2130 individuals per study arm to test a 25% drug effect on tau-PET accumulation in Braak II region. Notably, a similar clinical trial using Aβ+/Ast+ would require a sample size of 161 individuals per study arm (a reduction of 92% in relation to using Aβ+ only). Similarly, we observed a decrease of 94% and 42% in sample size to predict tau-PET accumulation in Braak III and IV regions, respectively. **Discussion:** We observed biomarker evidence that astrocyte reactivity plays a key role in the association of Aβ with early tau pathology in preclinical AD. In addition, clinical trials focusing on preclinical AD would benefit from enrolling individuals with both Aβ and astrocyte reactivity to select individuals at the highest risk of fast tau accumulation resulting in more cost-effective trials. **Key words:** preclinical AD; GFAP, reactive astrocytes. **Disclosures:** HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. ERZ serves in the scientific advisory board of Next Innovative Therapeutics (Nintx). PR-N has served on scientific advisory boards and/or as a consultant for Eisai, Novo Nordisk, and Roche. NJA has given lectures in symposia sponsored by Lilly and Quanterix. The other authors declare that they have no conflict of interest.

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OC15- STRESS TESTING THE CL CONCEPT: EVALUATING CENTILOID STABILITY TO TRACER, EFFECTIVE IMAGE RESOLUTION AND QUANTIFICATION METHOD.

M. Shekari[1,2,3], D. Vállez García[4], L.E. Collij[4], D. Altomare[5], F. Heeman[4], H. Pemberton[6,7], N. Roé Vellvé[8], S. Bullich[8], C. Buckley[6], A. Stephens[8], G. Farrar[6], G. Frisoni[5], W.E. Klunk[9], F. Barkhof[4,7], J.D. Gispert[1,2,10]
(1. Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation - Barcelona (Spain), 2. IMIM (Hospital del Mar Medical Research Institute) - Barcelona (Spain), 3. Universitat Pompeu Fabra - Barcelona (Spain), 4. Amsterdam UMC, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 5. Memory Center, University Hospitals and University of Geneva - Geneva (Switzerland), 6. GE Healthcare Pharmaceutical Diagnostics, UK - Amersham (United Kingdom), 7. University College London - London (United Kingdom), 8. Life Molecular Imaging GmbH - Berlin (Germany), 9. University of Pittsburgh - Pittsburgh (United States), 10. Centro de Investigación Biomédica en Red Bioingeniería, Biomateriales y Nanomedicina, (CIBER-BBN) - Barcelona (Spain))

Background: The Centiloid (CL) scale is a well-established standard metric of amyloid load and several cut-off values have been proposed for research and clinical use. However, to confidently apply such reference CL values, it is important to quantify sources of bias and variability in the computation of CL values. The aim of this study is to evaluate the stability of CL values to technical factors such as pipeline design options, tracer, and effective image resolution. **Method:** A total of 533 participants from AMYPAD DPMS and ADNI were included who were cognitively unimpaired (CU) or had subjective memory complaints (SMC), mild cognitive impairment (MCI), or dementia. Amyloid PET scans were acquired with [18F]-Flutemetamol, [18F]-Florbetaben, or [18F]-Florbetapir. T1-weighted MRI, clinical diagnosis, and age were available for all participants. AMYPAD DPMS PET images were harmonized to achieve an effective image resolution of 8mm Full-Width-at-Half-Maximum(FWHM). Using SPM12, 32 Centiloid pipelines were created, calibrated, and validated, based on combinations of four reference regions (Whole Cerebellum[WCB], Cerebellar Gray[CG], Whole Cerebellum+Brainstem[WCB+BSTM], Pons), two target VOI types (standard GAAIN vs subject-based), two reference region types (standard GAAIN vs subject-based) and two analysis spaces (native vs MNI). Generalized Estimating Equations (GEE) were used to evaluate the impact of the different factors on Centiloid. All analyses were stratified into amyloid positives and negatives using a threshold of 24 CL [1]. First, a base model was defined, including Tracer and Diagnosis as between-subject factors and the pipeline design factors as within-subject ones. Then, secondary GEE models were used to additionally evaluate the impact of grey matter atrophy and harmonization status. For all comparisons, changes>3 CL were considered relevant [2] and p-value<0.05 was considered to be statistically significant. **Results:** The tracer effect was not statistically significant for either the amyloid negative or positive groups; the clinical diagnosis was only significant for the amyloid-positive group (CU/SMC: 64.63±4.10CL; MCI:76.29±2.71CL; Dementia:88.04±2.99CL). Reference region(RR) selection and RR type presented the highest impact on CL with Pons rendering the lowest CL compared to WCB for the amyloid-negative group [CL: WCB=4.69±1.43, CG=5.53±1.38, WCB+BSTM=2.36±1.45, Pons=-4.22±1.67]. The amyloid-positive group showed similar behaviors with

smaller effects [CL: WCB=77.84±1.94, CGM=76.25±2.00, WCB+BSTM=76.87±1.93, Pons=74.31±2.20]. When using WCB as RR, comparable CL values were obtained for all tracers across both amyloid-negative and positive groups. Subject-based RR resulted in lower CL values than GAAIN RR VOIs (ΔCL: amyloid-negative= -4.44±0.31 and amyloid-positive=-2.68±0.36]. Using subject-based cortical target CL values were slightly higher (ΔCL: amyloid-negative=3.46±0.45, amyloid-positive=1.13±0.36). Quantification space slightly impacted CL (ΔCL~2.43) for both groups. The subject-based cortical target was insensitive to the degree of gray matter atrophy, unlike the GAAIN VOI (mean difference of 3.99±8.21 CL in participants with dementia). Centiloid was minimally affected by harmonization when using WCB and WCB+BSTM as reference regions, but CG and Pons were sensitive to harmonization status (ΔCL: 5.45 and -5.70 respectively). **Conclusion:** Using the whole cerebellum as reference region yields comparable CL values across different tracers which are robust against differences in image resolution. Subject-based cortical VOI provides more accurate measurements of amyloid load in the presence of atrophy. **Key words:** Amyloid PET, Centiloid, Quantification, Alzheimer's Disease. **Acknowledgements:** On behalf of the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Amyloid Imaging to prevent Alzheimer's dementia, an IMI/EU funded Project (grant agreement No 115952). **Disclosures:** LC has received consultancy fees from GE HealthCare (paid to institution). GF and CB are employees of GE HealthCare. NRV and SB are employees of Life Molecular Imaging GmbH. FB is serving on a steering committee, data and safety monitoring board, or advisory board for Merck, Prothena, Biogen and USC-ATRI. He is a consultant to Combinostics, Roche, IXICO and Celltrion, and is a cofounder and shareholder of Queen Square Analytics Ltd.JDG has received research support from GE Healthcare, Roche Diagnostics and Hoffman – La Roche and consultant or speaker's fees from Biogen, Roche Diagnostics, Philips Nederlands and Life-MI. **References:** 1. R. La Joie et al., «Multisite study of the relationships between antemortem [11C] PIB-PET Centiloid values and postmortem measures of Alzheimer's disease neuropathology,» Alzheimer's & Dementia, vol. 15, no. 2, pp. 205-216, 2019. 2. Ariane Bollack et al,: Stress Testing the Centiloid Concept: Guidance on the Utility of the Measure . CTAD 2023

OC16- END-TO-END AUTOMATED SCORING OF SPEECH-BASED COGNITIVE ASSESSMENTS FOR ALZHEIMER'S DISEASE: A COMPARISON WITH MANUAL SCORING IN THE AMYPRED-US AND AMYPRED-UK STUDIES.

J. Weston[1], U. Meepegama[1], C. Skirrow[1], M. Ropacki[2], E. Fristed[2] *(1. Novoic - London (United Kingdom), 2. Oryzon - Temecula (United States))*

Background: Speech-based cognitive assessments, such as the Wechsler Logical Memory Test (LMT), are commonly used to evaluate cognition in Alzheimer's disease (AD). Standardized instructions and rater training improve administration and scoring consistency but differences in interpretation can lead to discrepancies in manual scores between raters. More objective, automated scoring could improve endpoints for clinical trials through increased accuracy and sensitivity to longitudinal change, as well as reducing the time and cost of using highly trained raters and/or central review. The current study aimed to develop the eRater, an automated scoring system for speech-based cognitive assessments, leveraging natural language processing, and to compare its performance with manual rating. **Methods:** A total of 200 participants (MCI, mild AD, or cognitively unimpaired) were recruited into the AMYPRED-UK (NCT04828122) and AMYPRED-US (NCT04928976) studies. Supervised assessments, including category fluency tests ('animals', 'vegetables' and 'fruit') and the Wechsler LMT immediate and delayed recalls, were administered and responses audio-recorded at the time of testing. Responses were scored manually by one of 15 research staff, and using the eRater. The eRater included (1) a custom transcription model, a multilingual encoder-decoder Transformer, optimized to capture disfluencies and filled pauses, and (2) a language model configured to detect target responses for category fluency and information units for the LMT. A quarter of the participants' LMT Immediate Recall tests were re-scored by one researcher (JW) to evaluate the eRater against a more consistent ground truth. Reliability between manual and automated eRater scores was evaluated with Pearson correlations and 95% confidence intervals using the Fisher transformation method. **Results:** Data was available for between 173 and 191 participants depending on the task (MCI/mild AD in N=89-100, with the remainder of the sample being cognitively unimpaired). eRater showed high convergence with manual scores for LMT immediate and delayed recall components (immediate r=0.94, 95% CI=0.92-0.95; delayed recall r=0.91, 95% CI=0.88-0.93) and category fluency tasks (Animals r=0.95, 95% CI=0.93-0.96; Vegetables r=0.95, 95% CI=0.93-0.96; Fruit r=0.95, 95% CI=0.93-0.96). In a subset of assessments scored by only one rater, the correlation coefficient was similar (r=0.95, 95% CI=0.92-0.97). **Conclusions:** The eRater scoring system demonstrated high convergence with manual scores for speech-based cognitive assessments in Alzheimer's disease research. The eRater's fully automated analysis pipeline reduces the impact of subjectivity in interpretation of scoring criteria. Overall, the results indicate that the automated scoring system produces similar results to manual scores, while having the potential to improve test-retest reliability, and reduce variability and measurement error. In turn, this may help to improve detection of group differences and change over time, and/or reduce sample sizes required for detecting meaningful change in clinical trials. **Key words:** Alzheimer's disease, automated scoring, cognitive assessment, eRater, inter-rater reliability, speech-based tasks. **Disclosures:** All authors are employed by and/or option- or shareholders of Novoic.

OC17- CHARACTERIZATION OF THE SYNAPTIC BLOOD MARKER B-SYNUCLEIN IN DIFFERENT STAGES OF ALZHEIMER´S DISEASE AND OTHER DEMENTIAS.

P. Oeckl[1], G. Bellomo[2], L. Barba[3], D. Alcolea[4], A.L. Wojdala[2], J. Fortea[4], A. Lleó[4], L. Parnetti[2], O. Belbin[4], M. Otto[3] *(1. Ulm University Hospital, Department of Neurology and DZNE Ulm - Ulm (Germany), 2. Section of Neurology, Department of Medicine and Surgery, University of Perugia - Perugia (Italy), 3. Department of Neurology, Martin-Luther-University of Halle-Wittenberg - Halle (saale) (Germany), 4. Memory Unit, Department of Neurology, Institut d'Investigacions Biomèdiques Sant Pau - Hospital de Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain - Barcelona (Spain))*

Background: Synaptic degeneration is the pathological correlate of cognitive impairment in Alzheimer´s disease (AD) and the recent positive studies with anti-amyloid therapy in AD indicated that synaptic biomarkers in cerebrospinal fluid (CSF) might be a promising read-out to track positive effects in AD trials. The presynaptic protein β-synuclein is a synaptic biomarker which now can also be measured in blood of AD patients which is much more easily accessible. However, the

changes of β-synuclein blood levels during the preclinical phase of AD and different symptomatic stages are less well studied but important to evaluate its value for diagnosis and clinical trials. **Methods:** In this cross-sectional study, we investigated patients at different AD stages, other dementias and controls from two memory clinic cohorts from Perugia and Barcelona. Perugia: preclinical AD (preAD, i.e. cognitively unimpaired but positive core AD CSF biomarkers, n=20), prodromal AD (pAD i.e. mild cognitive impairment (MCI) with positive core AD CSF biomarkers, n=20), AD dementia (ADD, n=18), cognitively normal subjects (CN, n=15) and non-AD MCI (n=11); Barcelona: preAD (n=15), pAD (n=45), ADD (n=49), prodromal dementia with Lewy bodies (pDLB, n=35), demented DLB (dDLB, n=38), frontotemporal dementias (FTD, n=61) and CN (n=27). Serum β-synuclein levels were measured by immunoprecipitation mass spectrometry (IP-MS). Amyloid (A) and tau (T) status was defined using CSF Aβ42 or Aβ42/40 ratio and CSF pTau181 validated cut-offs. Cognitive impairment was assessed using the Mini-Mental State Examination (MMSE). Measurement of other blood biomarkers for comparison (pTau181, NfL, GFAP) are ongoing and will also be presented. **Results:** A total of 354 patients were investigated in this study. We observed a gradual increase of serum β-synuclein levels from the preclinical (median: 11.5pg/mL, IQR: 9.4-14.0) to the prodromal (median: 14.9pg/mL, IQR: 12.7-17.3, $p<0.01$) and dementia stages of AD (median: 15.1pg/mL, IQR: 13.7-20.2, $p<0.001$) in the Perugia cohort compared with controls (median: 9.8pg/mL, IQR: 7.7-11.7) and non-AD MCI subjects (median: 9.8pg/mL, IQR: 7.4-11.2). These findings were confirmed in the independent cohort from Barcelona. Serum β-synuclein levels were also slightly higher in pDLB and dDLB but not in FTD patients. When stratified according to the AT status defined by core AD CSF biomarkers, higher serum β-synuclein levels in preAD were present in A+T+ subjects only. In the DLB groups the higher β-synuclein levels were restricted to subjects with amyloid copathology as indicated by CSF biomarkers. Serum β-synuclein strongly correlated with blood pTau181 ($rs=0.79$, $p<0.0001$) and there was a significant negative correlation with measures of cognitive impairment (Perugia $rs=-0.61$, Barcelona $rs=-0.39$). **Conclusions:** We here showed in two independent cohorts that serum β-synuclein levels are already higher in preclinical AD especially in A+T+ subjects indicating that synaptic degeneration in AD starts within the A+T- and A+T+ interphase. In addition, β-synuclein levels were associated with cognitive impairment, both supporting its use as an easily accessible blood biomarker for tracking positive effects on synaptic degeneration in clinical AD trials. **Key words:** β-synuclein, synaptic degeneration, blood biomarker, preclinical Alzheimer´s disease. **Disclosures:** PO and MO are co-inventors of a patent application for using β-synuclein measurement in blood. AL, DA, JF and OB are co-inventors of a patent on markers of synaptopathies.

OC18- REMOTE DETECTION AND CHARACTERIZATION OF COGNITIVE PERFORMANCE TRAJECTORIES IN MILD COGNITIVE IMPAIRMENT AND POPULATIONS AT-RISK FROM THE INTUITION BRAIN HEALTH STUDY.

M. Butler[1], R. Brown[1], A. Becker[1], M. Hobbs[1], P. Saha-Chaudhuri[1], J. Penalver-Andres[1], D. Roggen[1], A. Scotland[1], Y. Zabar[1], R. Hughes[1], H. Lenyoun[2], M. Bianchi[2], A. Gabelle[1], S. Belachew[1], T. Intuition Scientific Study Committee[1] *(1. Biogen - Cambridge (United States), 2. Apple - Cupertino (United States))*

Background: Mild cognitive impairment (MCI) is a clinical syndrome with heterogeneous causes and courses. Deciphering cognitive trajectories with real-world data is important for advancing personalized medicine and clinical trial design. With aging populations increasingly likely to own smart devices and use broadband, new channels are emerging in non-clinical settings to enable development of tools for population-level screening and risk stratification. **Objectives:** Within the framework of the ongoing digital observational study INTUITION (NCT05058950), we examined longitudinal cognitive performance across 6-12 months in individuals with preexisting MCI, newly emergent MCI, and at-risk cognitively normal (CN) cohorts with and without subjective cognitive concerns (SCC). The objectives of the current work were (1) to assess the feasibility of longitudinal cognitive evaluations in unsupervised real-world settings using personal computing and smart devices; (2) to identify patterns within the clinical heterogeneity of MCI by describing cognitive trajectory clusters in relation to biobehavioral risk factors; and (3) to understand earlier stages of MCI by investigating 6-months of pre-diagnosis cognitive data to determine potential detection thresholds using remote assessments. **Methods:** INTUITION1-6 is an ongoing 2-year, observational study in U.S. adults that collects multimodal, longitudinal data via the iPhone and Apple Watch using a custom study application coupled with validated cognitive assessments and surveys about health and habits. The present study focused analyses on MCI and control participants age 50+ years with study-App collected health data and longitudinal cognition from serial performance on a custom 30-minute monthly digital battery by Cambridge Cognition/CANTAB. Over 200 outcomes variables were generated per subject per session, and we derived composite scores to reflect global performance. Adherence and consistency in cognition was assessed by descriptive statistics and intra-class correlations, and Lasso regression techniques were applied for MCI classification. We deployed clustering analyses to decipher longitudinal change patterns. **Results:** 22,149 participants aged 50+ years completed enrollment and study onboarding. 77.7% (N=17,207) completed the baseline cognitive battery with 90.1% offering longitudinal data. Monthly adherence to the battery was 84.9% in those baselined. Longitudinal reliability of cognitive outcomes was moderate-to-strong with intraclass correlation coefficients ranging from r=0.55 to 0.83. Based on demographic, survey, and cognitive composite scores, MCI vs. CN+SCC classification accuracy was 0.92 (95% CI: 0.90, 0.94) from Lasso regression models performed on a pool of N=15,099 (12,643 CN, 2,048 SCC, 408 MCI). Cognitive trajectories across 12 months of cognitive battery composite scores showed consistent and widening separation between MCI and CN subjects. Unsupervised cluster analysis of longitudinal cognition identified MCI subgroups with stable vs. declining performance that were marked by different biobehavioral risk profiles. To date, N=78 participants have reported a new-onset MCI diagnosis and 6-months of pre-diagnosis cognition data show measurable deficits compared to CN participants. Updated longitudinal results will be presented at the conference. **Conclusions:** We provide promising early readouts that support the feasibility of measuring cognition in real-world settings, and for remotely detecting MCI in large-scale demographically diverse populations. Heterogenous cognitive trajectories are emerging in early and new onset MCI populations. Future efforts will further characterize the risk profiles and relationships between biobehavioral mediators of cognitive decline. **Key words:** Brain Health, Mild Cognitive Impairment, Digital Biomarkers, Subjective Cognitive Decline. **Clinical trial registry**: NCT 05058950; https://clinicaltrials.gov. **References:** 1. Butler, P.M., Porsteinsson, A., Kenny, S.,

Lenyoun, H., Hobbs, M., Brown, R., Bianchi, M., Williams, J., Gabelle, A., & Belachew, S. (2022). Intuition: a brain health study using multimodal digital biomarkers to decipher cognitive profiles of individuals at-risk for Alzheimer's and related dementias. Clinical Trials in Alzheimer's Disease Conference (CTAD), Nov 29-Dec 2022, Poster P219. 2. Au, R., Butler, P.M., Lenyoun, H., Kenny, S., Brown, R., Saha-Chaudhuri, P., Bianchi, M., Williams, J., Gabelle, A., & Belachew, S. (2022). Cognitive health in underrepresented populations: early learnings from the Intuition brain health study. Clinical Trials in Alzheimer's Disease Conference (CTAD), Nov 29-Dec 2202, Poster P220. 3. Sha, S.J., Butler, P.M., Gabelle, A., Becker, A., Brown, R., Saha-Chaudhuri, P., Ash, J., Hobbs, M., Kenny, S., Lenyoun, H., Bianchi, M., & Belachew, S. (2023) Remote characterization of individuals with subjective cognitive complaints. Alzheimer's Disease and Parkinson's Disease (ADPD) Conference, Mar 29, 2023, On-demand oral presentation, OD055, P1646. 4. Erkkinnen, M.G., Butler, P.M., Brown, R., Hobbs, M., Gabelle, A., Becker, A., Saha-Chaudhuri, P., Ash, J., Kenny, S., Lenyoun, H., Bianchi, M., & Belachew, S. (2023). Unsupervised digital cognitive assessment reliability from the Intuition brain health study. American Academy of Neurology (AAN) Conference, Apr 23rd, 2023, Scientific Platform Session, S8-009. 5. Ash, J., Salmon, R., Kenny, S., Hobbs, M., Becker, A., Brown, R., Saha-Chaudhuri, P., Lenyoun, H., Bianchi, M., Butler, P.M., & Belachew, S. (2023). Adaptive recruitment strategies for decentralized trials: learnings from Intuition: a brain health study. American Academy of Neurology (AAN) Conference, Apr 24th, 2023, P4/6-001. 6. Hobbs, M., Au, R., Becker, A., Butler, P.M., Lenyoun, H., Kenny, S., Brown, R., Becker, A., Saha-Chaudhuri, P., Bianchi, M., Williams, J., Gabelle, A., & Belachew, S. (2023). Cognitive health in underrepresented populations – early learnings from Intuition: a brain-health study. American Academy of Neurology (AAN) Conference, Apr 27th, 2023, P14/6-009.

OC19- BINDING PROFILES OF LECANEMAB AND DONANEMAB TO DIFFERENT AMYLOID-BETA SPECIES.

L. Lannfelt[1,2], M. Johannesson[1], P. Nygren[1], A. Rachalski[1], E. Button[1], A.S. Svensson[1], E. Gkanatsiou[1], N. Fritz[1], O. Zachrisson[1], L. Söderberg[1], C. Möller[1] *(1. BioArctic AB - Stockholm (Sweden), 2. Department of Public Health/Geriatrics - Uppsala (Sweden))*

Background: Immunotherapy against amyloid β (Aβ) has emerged as a promising treatment for Alzheimer's disease (AD). Both lecanemab and donanemab have shown positive data in phase 3 clinical trials. Patients in the donanemab study were approximately two years later in the disease progression as compared to the AD population investigated with lecanemab. Lecanemab is mainly targeting soluble aggregated Aβ species, while donanemab is reported to target pyroglutamate Aβ (AβpE3) in plaques. There is strong evidence that soluble Aβ aggregates are more toxic than monomers or insoluble fibrils. Immunotherapy with antibodies targeting Aβ is associated with amyloid-related imaging abnormalities with edema (ARIA-E). The incidence of ARIA-E might correlate with antibody binding to Aβ fibrils in the cerebral vasculature, cerebral amyloid angiopathy (CAA). An ARIA-E rate of 24% was reported for donanemab, and a rate of 12.6% was reported for lecanemab. **Objectives:** Here, we have examined, side-by-side, the binding characteristics of lecanemab and donanemab to Aβ isolated from AD brains and different in vitro generated Aβ species. **Methods:** Binding strength of lecanemab and donanemab to different species of Aβ was evaluated by Surface Plasmon Resonance, Immunoprecipitation and Mass spectrometry. Human postmortem brain tissue was extracted and levels of Aβ in different fractions were measured by Aβ specific immunoassays. An analogue of donanemab was produced from sequences published in patents. Lecanemab was achieved from Eisai. **Results:** Insoluble Aβ species were extracted from AD brains and non-demented elderly control brains (NDE). In the AD samples, levels of Aβ42 and AβpE3 were significantly elevated in Braak stage 4, 5 and 6 as compared to NDE with Braak stage 1. Donanemab had stronger binding than lecanemab to Aβ fibrils extracted from vessels in meninges from AD brains. Binding of donanemab to these fibrils correlated with the levels of AβpE3 content in the samples. Lecanemab exhibited low binding to all CAA samples analyzed, independent of AβpE3 content. Binding profiles to synthetic Aβ species showed that donanemab displayed lower binding to fibrils with low content of AβpE3. Lecanemab demonstrated similar binding to fibrils regardless of AβpE3 levels. **Conclusions:** The binding profiles of lecanemab and donanemab to distinctive Aβ species were investigated with three different methods. Lecanemab showed strong binding to Aβ protofibrils in different severity stages and exhibited low binding to all CAA samples analyzed, independent of AβpE3 content. Donanemab had stronger binding than lecanemab to Aβ fibrils isolated from meningeal CAA from AD brains, and the levels of AβpE3 was higher in more severe AD cases. This could have an impact on clinical efficacy and safety of lecanemab and donanemab when treating patients early in the disease.

OC20- ESTIMATING TIME-SAVING TREATMENT EFFECTS IN ALZHEIMER'S CLINICAL TRIALS: EXPLORING ALTERNATIVE APPROACHES.

G. Wang[1], G. Cutter[2], L. Schneider[3], W. Wang[4], B. Mangal[4], Y. Liao[5], Y. Li[1], C. Xiong[1], J.L.L.I.B. Llibre-Guerra[1], E.R.I.C.M. Mcdade[1], R. Bateman[1] *(1. Washington University School of Medicine, St. Louis, MO - St Louis (United States), 2. University of Alabama at Birmingham - Birmingham (United States), 3. Keck School of Medicine, University of Southern California - Los Angeles (United States), 4. Alector, Inc - San Francisco (United States), 5. Asher Biotherapeutics - San Francisco (United States))*

Background: Alzheimer's disease clinical trials commonly employ mixed models for repeated measures (MMRM) to assess efficacy. The primary analysis compares the absolute difference in model-estimated change from baseline between treatment and placebo groups at the end-of-study visit (e.g., 18 months). An alternative method, referred as the backward projection to placebo (BPP), was used by Petersen et al. (2023) to estimate the time-saving treatment effect. This method projects the decline of the treatment arm backward in time until it aligns with the decline observed in the placebo arm. The time difference between these points is purported to be the time-saving effect (e.g., 18-12.7=5.3 months for lecanemab). However, the BPP method does not directly quantify the extent of disease progression delay compared to the placebo arm over the 18-month treatment period. Additionally, BPP method does not directly incorporate the placebo decline from months 15 to 18, nor does it integrate the absolute difference at 18 months. As a result, it has the potential to yield biased estimations. This abstract proposes alternative methods to address these limitations. **Methods:** To directly address how long the treatment delays disease progression compared to the decline in the placebo arm over 18 months, we proposed two alternative methods: the Backward Projection to Treatment

(BPT) method and the additional Time Needed to Reach Placebo decline (TNRP) method. The BPT method projects the absolute treatment difference at 18 months backward in time, aligning it with the decline course of the treatment arm until it matches the observed difference. The TNRP method uses the reciprocal of the percentage reduction at 18 months to estimate the additional time needed for the treatment arm to reach the placebo decline at 18 months. We compare these methods with BPP method using disease progression trajectories adapted from the lecanemab phase 3 trial with various placebo decline trajectories. **Results:** For the lecanemab phase 3 trial, both the proposed BPT and TNRP methods yield larger estimates of the time-saving treatment effect compared to the BPP method: 6.6, 6.7, and 5.3 months, respectively. To compare the performance of these three methods, we hypothetically adjusting the placebo decline from month 15 to month 18 to 1.40 (decelerated placebo decline) and 1.84 (accelerated placebo decline) from the original value of 1.66. For the decelerated decline scenario, the estimated time savings are 3.0, 2.8, and 5.3 months, respectively; for the accelerated decline scenario, the estimated time savings are 9.0, 9.4, and 5.3 months, respectively. The BPP method consistently resulted in an estimate of 5.3 months across all three scenarios, highlighting its inability to capture and utilize the differences in absolute treatment effects that extend beyond the matched time interval of backward projection (i.e., months 15 to 18). All methods can be implemented using a two-step approach with the delta method. **Conclusion:** Estimating time-saving effects enhances the interpretation of absolute treatment effects and helps define «clinically meaningful change.» Alternative methods that integrate the overall placebo decline and absolute difference should be considered to provide more accurate estimates. **Disclosures:** The authors declared no competing interests.

OC21- THE POTENTIAL FOR TIME SAVINGS IN EARLY ALZHEIMER CLINICAL TRIALS. L. Schneider[1], G. Wang[2], R. Kennedy[3], G. Cutter[3] *(1. Keck School of Medicine of USC - Los Angeles (United States), 2. Washington University - Saint Louis (United States), 3. University of Alabama, Birmingham - Birmingham (United States))*

Background: There is considerable controversy over whether the outcomes of anti-amyloid antibodies phase 3 trials are clinically meaningful despite their FDA marketing approval. The statistically significant mean differences on the CDR-SB primary outcome were small and about the same for each antibody. Such small differences imply that the outcome distributions substantially overlap and thus only a very small percent of patients may benefit by any amount from treatment. These estimates, moreover, do not consider the effects of adverse events and dropouts. An ad hoc workgroup surprisingly suggested the clinical outcomes are as large as they are likely to be and "expectations of outcomes from interventions in AD may need to be modified." They argued that any difference on a clinical scale is clinically meaningful; that small effects should be expressed, not as mean between-group differences but as savings in time, or delay in progression; and advocate for estimating "cumulative benefit" by forward projecting the magnitude of the "absolute slowing" of the outcome scale to a future timepoint. Defining clinical meaning in this manner, however, is misleading and serves to exaggerate an outcome making it appear to be substantially effective when it is not. **Objectives:** The time-saving effect used by the workgroup used a hypothetical antibody trial to show a fixed difference between the active and placebo arms of an otherwise clinically not-meaningful, -0.5 difference in CDR-SB. They indicate this fixed difference leads to increasing time savings benefits but ignore the calculation's dependence on disease progression trajectories and the fundamental assumption of noninformative censoring when the time savings are assessed. Time savings are inversely related to the placebo progression when a fixed treatment difference in CDR-SB is maintained as demonstrated. These dependencies can lead to false delay time. Further, a drug that protects for some duration, but then has accelerated declines would show the time savings remain even though the later declines of the treatment arm are steeper and may lead to no differences between the treatment groups. Although the time-saving effect is more easily understood, it is only a mathematical transformation from y axis to x-axis; and does not change the nature of the small absolute difference. Its clinical meaningfulness still depends on the meaningfulness of the difference on the y-axis (e.g., CDR SB), and numerical transformation of this reduction cannot deem it meaningful. This backward projection is not statistically solid in that it assumes the treated and the placebo decline at the same rate during the time-saving period. For example, the time savings of 9 months at month 36 indicates that during this 9-month period the treated group will decline to the placebo's 36-month level. **Methods:** We provide illustrations of these challenges using the donepezil MIS trial, solanezumab Expedition 3 trial, the conflicting projections in aducanumab trials, and with lecanemab. **Results:** For lecanemab, the backward projection indicates a time-saving treatment effect of 5.3 months by projecting the 18-month treatment decline to the 12-month placebo decline. Although the time-saving treatment effect is more appealing, it does not change the difference in CDR SB at month 18. Additionally, from month 12 to month 18, the placebo dropouts were greater, thus, the backward projection essentially matched the timepoints but ignores dropouts in both groups who are likely progressing, creating heterogeneity in the estimated time savings depending on the time of assessment. The second approach advocated by the workgroup to re-define clinical meaningfulness is to project forward the magnitude of the slowing. Figure 2A demonstrates using the donepezil MIS trial that the largest treatment effect (~29% slowing) was observed at the 18-month visit. Projecting this forward the absolute reduction in CDR SB would increase from 0.21 at month 18 to 0.48at month 36. In contrast, the observed benefit lessened and was only 0.04. Forward projection is like a futility analysis, but assumes the observed differences are projected forward rather than assuming the hypothesized benefits. **Conclusions:** The controversy about small effect sizes results in representations that make treatment effects appear larger than they are. Forward and backward projection of clinical trials outcomes to transform clinical outcomes measured as mean differences to an expected time savings or cumulative benefit and an appearance of greater clinical meaningfulness that are unreliable and misleading. As a scientific argument, it violates the analytic rigor built into randomized trials. An argument that a treatment effect at 18 months is equivalent to a 9-month time savings or preservation of function hinges on assumptions such as significant slowing in placebo decline, no missing data, data missing at random, and the same decline rates for both arms during the comparative period. These assumptions have not been observed in real AD clinical trials. Projecting backwards is effectively making comparisons of noncomparable groups. Forward projection imagines the trajectory measured during the trial will continue indefinitely.

OC22- PRECISION MEDICINE ANALYSIS OF HETEROGENEITY IN INDIVIDUAL-LEVEL TREATMENT RESPONSE TO BETA-AMYLOID REMOVAL IN EARLY ALZHEIMER'S DISEASE. M. Pang[1], A. Gabelle[1], P. Saha-Chaudhuri[1], W. Huijbers[1], A. Gafson[1], P. Matthews[2], L. Tian[3], I. Rubino[1], R. Hughes[1], C. De Moor[1], S. Belachew[1], C. Shen[1] *(1. Biogen - Cambridge (United States), 2. Imperial College London - London (United Kingdom), 3. Stanford University School of Medicine - Stanford (United States))*

Background: Alzheimer's disease (AD) is a neurological disorder with variability in pathology and clinical progression. Although recent clinical trials demonstrate that early AD modification using anti-amyloid therapies can slow clinical decline, AD patients may differ in individual-level benefit from these therapies due to intrinsic heterogeneity of the disease. Recently developed statistical methodologies in precision medicine offer opportunities to study individual-level treatment benefit using data from parallel randomized controlled trials. These approaches address limitations of conventional responder analyses and shed light on the nature of heterogeneity of treatment effect (HTE) of anti-amyloid therapies. **Methods:** Random Forest supervised learning models were applied to the EMERGE trial (NCT 02484547) to predict the change from baseline to week 78 on the Clinical Dementia Rating Sum of Boxes (CDR-SB) within the high dose aducanumab and placebo arms, respectively. The predicted values were used to create an individual-level treatment response (ITR) score, which represents the estimated individual-level benefit of high dose aducanumab relative to the placebo. The ITR score was then used to test the existence of HTE through a permutation test. The ITR model's ability to identify patients with different treatment benefit was further validated through analysis of additional clinical endpoints (ADAS-Cog13, MMSE, ADCS-ADL-MCI and NPI-10). Association of baseline characteristics with the ITR score was analyzed through comparison of characteristics between dichotomized ITR groups and separately using a conditional Random Forest approach. **Results:** We found statistical evidence for an association between the ITR score and benefit in slowing CDR-SB worsening (p=0.034), suggesting the existence of HTE. The observed CDR-SB benefit in the group with the top 25% of ITR score and the remaining 75% was 0.97 and 0.18 points, respectively. The difference in CDR-SB benefit of 0.79 points between the two groups was statistically significant (p=0.020). In general, a larger benefit from the high dose aducanumab relative to placebo was observed in the group with the top 25% ITR score as compared with the remaining 75% for other longitudinal clinical endpoints. At baseline, the group with the top 25% ITR score was older, had smaller hippocampal and medial temporal cortex volumes, higher plasma p-tau181, a shorter duration since clinical AD diagnosis, and higher prevalence of microhemorrhages. **Conclusion:** Using an ITR score approach, we demonstrated evidence of heterogeneity in treatment effect of high-dose aducanumab compared with placebo on reducing CDR-SB decline in EMERGE. Several baseline characteristics used as input variables of the ITR score model and routinely collected in typical clinical settings were also shown to be correlated with the ITR score. With the granted accelerated approval by the U.S. Food and Drug Administration (FDA) of aducanumab and lecanemab, recently released positive results of donanemab, and several agents in late-phase clinical development, patient stratification and personalized medicine will become increasingly important for better understanding of how disease trajectory and response to treatment may vary from one individual to another. This ITR analysis provides a proof-of-concept for precision medicine in future AD research and drug development.

OC23- EFFECTS OF AN 18-MONTH MULTIMODAL INTERVENTION ON COGNITIVE FUNCTION (J-MINT PRIME TAMBA): A RANDOMIZED CONTROLLED TRIAL. Y. Oki[1], T. Osaki[2], R. Kumagai[3], S. Murata[4], H. Encho[3], H. Yasuda[1], R. Ono[5], H. Kowa[3] *(1. Department of Public Health, Kobe University Graduate School of Health Sciences - Kobe (Japan), 2. Department of Occupational Therapy, Faculty of Rehabilitation, Kobe Gakuin University - Kobe (Japan), 3. Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences - Kobe (Japan), 4. Department of Preventive Medicine and Epidemiology, National Cerebral and Cardiovascular Center Research Institute - Suita (Japan), 5. Department of Physical Activity Research, National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition - Ibaraki (Japan))*

Background: In recent years, the effectiveness of multimodal intervention in dementia prevention has attracted attention, and several randomized controlled trials (RCTs) have been reported, beginning with the FINGER study [1]. However, there is no consensus on the effectiveness of multidisciplinary interventions, and generalizing strategies to prevent cognitive impairment and dementia is challenging [2]. This study aims to conduct an RCT to examine the efficacy of a multi-domain dementia prevention program, which consists of lifestyle-related disease management, physical exercise, nutrition counseling, and cognitive training on improving or maintaining cognitive function or reducing cognitive decline in older people at risk for dementia. **Methods:** A randomized controlled trial (Japan-Multimodal Intervention Trial for Prevention of Dementia PRIME Tamba; J-MINT PRIME Tamba) was conducted to prevent cognitive decline in community-dwelling older people at risk of dementia [3]. Between Sep 2020, and Oct 2020, we screened 206 individuals and randomly assigned 203 participants (male: 57, mean age: 73.86±4.84, mean MMSE score: 28.65±1.36) were randomly assigned to the intervention group (101 participants) or the control group (102 participants). The intervention group received 90 minutes of group-based physical exercise weekly, cognitive training, nutritional counseling, and vascular risk factor management for 18 months (78 sessions total). The primary endpoint was the change in cognitive function from baseline to 18 months in a global composite score. The composite score was calculated by averaging the Z-scores of each neuropsychological test (i.e., MMSE, FCSRT, logical memory, digit span, DSST, TMT, and letter word fluency test). Statistical analyses were conducted using a linear mixed-effects model with a p-value less than 0.05 was considered statistically significant. **Results:** One hundred participants in the intervention group and 101 in the control group had baseline assessments and were included in the full analysis set. Twenty-six (12.8%) individuals dropped out overall. There was a statistically significant difference in the change in the cognitive composite score from baseline to 18 months, the primary endpoint (intervention group vs. control group; 0.54 ± 0.41 vs. 0.39 ± 0.41, p=0.020). In addition, for each domain of cognitive function, there were significant differences in executive functioning/processing speed (0.41 ± 0.56 vs. 0.21 ± 0.54, p=0.041). **Conclusion:** This study showed that an 18-month non-pharmacological multimodal intervention for community-dwelling older adults at risk of future dementia could improve cognitive composite score total scores, executive functioning, and processing speed.

OC24- ALZHEIMER'S DISEASE IN DOWN SYNDROME: NATURAL HISTORY, BIOMARKERS AND CLINICAL TRIALS. M. Rafii[1], J. Fortea[2], B. Ances[3] *(1. University of Southern California - San Diego (United States), 2. Hospital san Pau - Barcelona (Spain), 3. Washington University - Saint Louis (United States))*

Background: People with Down Syndrome (DS) have a genetic form of Alzheimer's disease (AD) with near full penetrance and AD is now the leading cause of death in this population. **Methods:** Recent data from the Alzheimer's Biomarker Consortium – Down syndrome (ABC-DS) and the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) have demonstrated that the natural history of clinical and biomarker changes in DS are strikingly similar to that of autosomal AD. **Results:** In DS, there are early memory changes in preclinical AD that antedate changes in global cognition. The prevalence of amyloid and tau pathology follows the same sequence as other forms of AD. Importantly, elevated brain amyloid is observed by age 40 while the age of onset for dementia diagnosis is approximately at 54 years and shows a similar predictability to that described in ADAD. Amyloid deposition occurs early in the disease process for ADAD (-20 EYO) and DS (-17 EYO) with the earliest changes seen in striatal and cortical regions. However, subtle differences existed in amyloid deposition for DS vs. ADAD. An inverse relationship was observed between PET and CSF amyloid. Amyloid was elevated in both asymptomatic and symptomatic ADAD and DS compared to healthy controls. Tau deposition was more diffuse for DS compared to ADAD. For any given level of amyloid, tau PET was higher for DSAD compared to ADAD. Neurodegenerative changes occurred earlier and were more diffuse in DS. The combination of changes in amyloid and tau were associated with cognitive changes in both DSAD and ADAD. Furthermore, longitudinal data shows an exponential increase in symptomatic AD incidence with age, emphasizing large statistical power to conduct prevention trials. Mortality data indicates that 70% of deaths in adults with DS are related to AD dementia and that this population appears to have reached a ceiling in life expectancy because of AD. **Conclusions:** The NIH-funded Alzheimer's Clinical Trial Consortium for Down Syndrome (ACTC-DS) launched the Trial Ready-Cohort for Down syndrome (TRC-DS). TRC-DS has enrolled 180 participants with DS ages 25-55 into a longitudinal run-in study in advance of upcoming randomized, placebo-controlled clinical trials. ACTC-DS serves as a platform to bring the latest advances in AD therapeutics to the DS population. Several clinical trials are underway or being planned. **Key words:** Down syndrome, Alzheimer disease, biomarkers, plasma, csf, PET, amyloid, tau. **Disclosures:** MSR- AC Immune, Alzheon, Aptah Bio, Biohaven, Ionis, Keystone Bio; BA- Nothing to disclose. JF- Disclosures: AC Immune, Alzheon, Roche, Lilly, Esteve, Lundbeck. **References:** Videla L, et al. Longitudinal Clinical and Cognitive Changes Along the Alzheimer Disease Continuum in Down Syndrome. JAMA Netw Open. 2022 Aug 1;5(8):e2225573. Iulita MF, et al. Association of Alzheimer Disease With Life Expectancy in People With Down Syndrome. JAMA Netw Open. 2022 May 2;5(5):e2212910. Fortea J, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. Lancet. 2020 Jun 27;395(10242):1988-1997. Boerwinkle AH, Gordon BA, Wisch J, Flores S, Henson RL, Butt OH, McKay N, Chen CD, Benzinger TLS, Fagan AM, Handen BL, Christian BT, Head E, Mapstone M, Rafii MS, O'Bryant S, Lai F, Rosas HD, Lee JH, Silverman W, Brickman AM, Chhatwal JP, Cruchaga C, Perrin RJ, Xiong C, Hassenstab J, McDade E, Bateman RJ, Ances BM; Alzheimer's Biomarker Consortium-Down Syndrome; Dominantly Inherited Alzheimer Network Comparison of amyloid burden in individuals with Down syndrome versus autosomal dominant Alzheimer's disease: a cross-sectional study. Lancet Neurol. 2023 Jan;22(1):55-65. Rafii MS, Ances BM, Schupf N, Krinsky-McHale SJ, Mapstone M, Silverman W, Lott I, Klunk W, Head E, Christian B, Lai F, Rosas HD, Zaman S, Petersen ME, Strydom A, Fortea J, Handen B, O'Bryant S. The AT(N) framework for Alzheimer's disease in adults with Down syndrome. Alzheimers Dement (Amst). 2020 Oct 27;12(1):e12062.

OC25- RISK OF INCIDENT COGNITIVE IMPAIRMENT USING STAGES OF OBJECTIVE MEMORY IMPAIRMENT (SOMI) AND NEUROIMAGING. K. Petersen[1], A. Ezzati[2], B. Nallapu[1], R. Lipton[1], R. Sperling[3], K. Papp[3], D. Rentz[3], E. Grober[1] *(1. Albert Einstein College of Medicine - Bronx (United States), 2. University of California, Irvine - Irvine (United States), 3. Harvard Medical School - Boston (United States))*

Background: The Stages of Objective Memory Impairment (SOMI) system delineates five stages in the decline of episodic memory observed in preclinical and prodromal Alzheimer's disease based on Free and Cued Selective Reminding Test (FCSRT). SOMI assesses both memory retrieval via free recall (FR) and memory storage through total recall (TR). In SOMI-0, FR and TR are normal. In SOMI-1 and -2, retrieval difficulty increases, evidenced by decreasing FR while TR remains intact. In SOMI-3 and -4, cuing fails to recover all items missed on FR, indicating a memory storage deficit. Later SOMI stages are associated with high global amyloid levels and smaller volumes for the hippocampus, entorhinal cortex, and inferior temporal lobes. Using data from the Harvard Aging Brain Study (HABS), we assessed the ability of SOMI to predict incident cognitive impairment and explored the impact of adjusting for PET and MRI biomarkers on these associations. **Methods:** We used data from 231 initially cognitively normal participants with a baseline Clinical Dementia Rating (CDR®) of 0 and longitudinal CDR data as well as baseline neuroimaging biomarker data for volumetric MRI, FDG PET, and PiB PET. Censoring was performed at 5 years (mean follow-up time was 4.06 ± 1.39 years). Cox proportional hazards models were employed to understand the relationship between SOMI stage, neuroimaging biomarkers, and incident cognitive impairment defined by a change in CDR from 0 to CDR≥0.5. **Results:** Participants, at enrollment in the Harvard Aging Brain Study (HABS), were on average 73.6 (SD = 6.0) years old and had 15.9 (3.0) years of education; 60.2% were female, 29.0% were APOE4 positive, and 23.4% progressed to CDR≥0.5. At baseline, 67.1% were SOMI-0, 21.7% were SOMI-1, 4.3% were SOMI-2, and 6.9% were SOMI-3/4 (combined for this analysis). Modeling time to CDR≥0.5 using demographics (age, sex, education), APOE4 status, and SOMI stage (SOMI-0 as reference) as variables, we found hazard ratios (HRs) for SOMI-1 of 2.00 (CI: 1.05-3.79, p=0.035), SOMI-2 of 2.91 (CI: 1.10-7.71, p=0.031), and SOMI-3/4 of 3.52 (CI: 1.45-8.57, p=0.006). Further adjustment of models with one or more biomarker modalities (MRI volumetrics, PiB PET, or FDG PET) did not affect HRs for any of the SOMI stages. In the model including demographics, SOMI stage, and all biomarker measures, HR for SOMI-1 was 2.43 (CI: 1.21-4.89, p=0.012), for SOMI-2 was 3.47 (CI: 1.21-9.96, p=0.021), and for SOMI-3/4 was 5.31 (CI: 2.08-13.54, p<0.001) while entorhinal thickness and entorhinal FDG PET showed significant associations with progression. Results were limited by the small number of participants in SOMI-3/4. **Conclusions:** SOMI

predicts progression from normal cognition (CDR=0) to incident cognitive impairment (CDR≥0.5 and remains a significant predictor when neuroimaging markers of neurodegeneration and amyloid are included. SOMI has the potential to inform the design of clinical trials by identifying cognitive normal participants at higher risk of developing cognitive impairment during the trials. Several ongoing or recently concluded clinical trials, including A4, AHEAD 3-45 study use the FCSRT version on which SOMI is based. Future analyses can determine the extent to which SOMI enhances trial design.

OC26- QUANTITATIVE AMYLOID-PET IN REAL-WORLD PRACTICE: LESSONS FROM THE IMAGING DEMENTIA—EVIDENCE FOR AMYLOID SCANNING (IDEAS) STUDY. R. La Joie[1], E. Zeltzer[1], N. Mundada[1], G. Blazhenets[1], J. Mejia Perez[1], D. Schonhaut[1], L. Iaccarino[2], M. Carrillo[3], L. Hanna[4], C. Gatsonis[4], A. March[5], B. Siegel[6], B. Hillner[7], R. Whitmer[8], G. Rabinovici[1] *(1. University of California, San Francisco - San Francisco, Ca (United States), 2. Avid Radiopharmaceuticals - Philadelphia, Pa (United States), 3. Alzheimer's Association - Chicago, Il (United States), 4. Brown university - Providence, Ri (United States), 5. American College of Radiology - Philadelphia, Pa (United States), 6. Washington University School of Medicine in St. Louis - St Louis, Mo (United States), 7. Virginia Commonwealth University - Richmond, Va (United States), 8. University of California, Davis - Davis, Ca (United States))*

Background: Amyloid-PET quantification has been extensively used in academic research and clinical trials with highly selected samples, harmonized acquisition protocols, and MRI-based preprocessing. Yet, little is known about the feasibility of quantifying real-world amyloid-PET scans, which could be crucial to guide the use of FDA-approved disease-modifying therapies. We aimed to process heterogeneous amyloid-PET scans from IDEAS [1], a large-scale study in patients with cognitive impairment. Major challenges lie in scans being acquired on various scanners without standardization of acquisition or reconstruction protocols, and without MRI to preprocess data. Our goal was twofold: i) quantifying amyloid-PET in Centiloids [2] and ii) assessing the association with visual reads performed at each center. **Methods:** 18,295 Medicare beneficiaries with MCI or dementia underwent PET with one of the FDA-approved radiotracers at 343 facilities. Sites shared 10,700 raw scans with their visual interpretation (positive or negative) by local radiologists or nuclear medicine physicians. Scans were processed using a PET-only pipeline [3], which derives Centiloids based on a cortex-to-cerebellum tissue ratio in template space. Processed scans underwent standardized quality control by 2 raters, and flagged scans were reviewed in a consensus meeting for troubleshooting. Injected dose and time between tracer injection and PET acquisition start were obtained from PET DICOM file headers. **Results:** 9,958 scans (93%) were successfully pre-processed with default parameters and 403 additional scans (4%) were included after minimal manual intervention. 339 scans (3%) were excluded because of technical artifacts or major anatomical lesions. Participants with quantified scans (n=10,361) had a median age of 75 years old and included 51% female and 88% White participants. Participants were at mild clinical stages (63% with MCI, 37% with dementia) and a median MMSE of 26. Participants were scanned with [18F]Florbetapir (n=6,699, 65%), [18F]Florbetaben (n=3,033, 29%) or [18F]Flutemetamol (n=629, 6%). Centiloids showed the expected bimodal distribution and differentiated visually positive (median=74 CL) from negative (median=-2 CL) scans (AUROC=0.913). A threshold of 24.6 CL reached highest concordance with visual reads (kappa=0.715, 86% agreement). Discordant cases (visual positive but CL<24.6 or vice versa, 14% of all scans) were distributed around the threshold (interquartile range=1-41 CL) and were more common when radiologist/nuclear medicine physicians reported lower confidence in their read (discordance rates=10%, 30%, 41% for high, moderate, and low confidence, respectively). PET acquisition generally followed tracer-specific FDA recommendations for injected dose and acquisition time, but major variability was observed. Centiloid values were independent from injected dose ($p>0.30$ for all tracers) but were higher in patients scanned at later time windows for [18F]Flutemetamol ($r=0.14$, $p<0.001$) and, to a lesser extent, for [18F]Florbetaben ($r=0.04$, $p=0.04$), but not for [18F]Florbetapir ($r=-0.001$, $p=0.89$). **Conclusion:** MRI-free, amyloid-PET quantification in a real-world setting was feasible, with results conforming to expected distribution of Centiloids and concordant with visual reads. However, greater standardization of PET acquisition than is currently required by FDA labels will be needed to reliably quantify amyloid PET in clinical practice (e.g., to monitor response to amyloid lowering therapy). The IDEAS dataset will be made available via the Global Alzheimer's Association Interactive Network in 2023. **Key words:** Centiloid, amyloid-PET quantifications, real-world biomarker. **Disclosures:** The IDEAS study was funded by the Alzheimer's Association, the American College of Radiology, Avid Radiopharmaceuticals Inc (a wholly owned subsidiary of Eli Lilly and Company), General Electric Healthcare, and Life Molecular Imaging (formerly Piramal Imaging). Mr March is an employee of the American College of Radiology, and Drs Rabinovici, Siegel, Gatsonis, and Hanna receive research funding from the American College of Radiology. Dr Carrillo is an employee of the Alzheimer's Association and Drs La Joie, Rabinovici, Hillner receive research funding from the Alzheimer's Association. Dr Iaccarino is currently a full-time employee of Eli Lilly and Company / Avid Radiopharmaceuticals and a minor shareholder of Eli Lilly and Company. His contribution to the work presented in this manuscript was performed while he was affiliated with the University of California San Francisco. Dr Siegel reported receiving grants from Blue Earth Diagnostics, and Progenics Pharmaceuticals and receiving personal fees from GE Healthcare, Blue Earth Diagnostics, Avid Radiopharmaceuticals Inc, BTG Management. Dr Rabinovici reported grants from the Rainwater Charitable Foundation, Avid Radiopharmaceuticals Inc, GE Healthcare, Life Molecular Imaging, and Genentech and personal fees from Alector, Eli Lilly, Johnson & Johnson, Genentech, and Roche, and is Associate Editor of JAMA Neurology. **References:** 1. Rabinovici et al. JAMA Neurology 2019. doi:10.1001/jama.2019.2000. 2. Klunk W et al. Alzheimer's & Dementia 2015. doi: 10.1016/j.jalz.2014.07.003. 3. Iaccarino L, et al. Neuroimage 2022. doi: 10.1016/j.neuroimage.2021.118775

OC27- MEASURING MEANINGFUL BENEFIT OF DISEASE MODIFYING TREATMENT ON HEALTH-RELATED RESOURCE USE. C. Zhu[1], M. Sano[1] *(1. Icahn School of Medicine at Mount Sinai - New York (United States))*

Background: Recently several disease modifying treatment (DMT) in early Alzheimer's disease (AD) have shown effectiveness in reducing rate of decline on integrated measures of cognition and function than placebo such as the Clinical Dementia Rating Sum of boxes (CDR-SB). However, questions have been raised about the meaningfulness of this outcome to patients, families, and payers. We aim to examine the

relationship between change in CDR-SB and health-related resource use, which can capture economic impact, a meaningful measure to many of these stakeholders. **Method:** Participants were followed approximately annually in the NACC Unified Data Set (UDS) at the Mount Sinai Alzheimer's Disease Research Center. Health-related resource use was self-reported by the participant and/or study partner using the Resource Use Inventory (RUI). Outcomes included hospitalizations, emergency care, doctors' visits, receipt of unpaid care, home health aides (HHA), and employment/volunteer work. Recall period was 3-months for all items except hospitalizations for which the recall period was 1 year. We modeled each outcome using a two-part or hurdle model, explicitly allowing for estimation of the extensive and intensive margins separately, along with an overall effect. Main independent variables were baseline Clinical Dementia Rating scale Sum of Boxes (CDR-SB) and change in CDR-SB from baseline. Models controlled for participant's baseline demographics (age, sex, race/ethnicity, education, marital status, comorbidities as assessed by the Cumulative Illness Rating Scale, CIRS) and years of follow up. **Results:** Analysis sample included 775 participants who had 1 or more RUI assessments (average follow up=2.4±1.5 years). At baseline, average age=75.3±9.1, 15.0±3.7 years of schooling, 55% female, 51% Non-Hispanic White, 15.6% Non-Hispanic Black, 21.9% Hispanic. 53% were cognitively normal, 21.6% Mild cognitive impairment (MCI), 24.1% dementia. Baseline MMSE=26.6±4.4, CDR-SB=2.2±3.9, CIRS=6.3±3.3. At baseline, unadjusted and adjusted rates of utilization of HHA, informal care, and participation in employment/volunteer work were significantly higher in higher CDR groups (all $p<0.01$). Among those who used a resource item, number of doctors' visits, hours of HHA, and hours of informal care also were significantly higher with higher CDR (all $p<0.01$). Over time, results showed that controlling for participant characteristics and baseline CDR-SB, faster decline in CDR-SB from baseline was independently associated with higher likelihood of using any informal care and HHA and lower likelihood of any employment/volunteer work. Among those who received care, higher baseline CDR-SB and faster decline in CDR-SB from baseline were independent associated with hours of informal care and HHA. Change in CDR-SB was largely unassociated with hospitalizations, ED use, and doctors' visits. **Conclusion:** Change in CDR-SB seen with DMTs may have significant effects on work capacity and the need for informal care, which are indicators of potential economic burden and are meaningful outcomes to patients, families and health systems.

OC28- ESTABLISHING THE VALIDITY OF A NOVEL ELECTRONIC CLINICAL DEMENTIA RATING (ECDR).

R. Nosheny[1], D. Yen[2], T. Howell[1], M. Camacho[3], K. Moulder[2], M. Ashford[3], R. Petersen[4], N. Stricker[4], E. Roberson[5], D. Marson[5], W. Kukull[6], S. Mackin[1], M. Weiner[1], J. Morris[2], Y. Li[2] *(1. UCSF - San Francisco (United States), 2. Washington University - St. Louis (United States), 3. Northern California Institute for Research and Edcuation - San Francisco (United States), 4. Mayo Clinic - Rochester (United States), 5. University of Alabama at Birmingham - Birmingham (United States), 6. University of Washington - Seattle (United States))*

Background: The Clinical Dementia Rating® (CDR®) is well-validated and widely used to detect and stage dementia due to Alzheimer's Disease (AD), and as an AD clinical trial outcome measure. A newly developed, digital, Electronic Clinical Dementia Rating® (eCDR®) can be remotely administered in unsupervised settings to assess cognitive and functional impairment using participant and a study partner questionnaires. It includes an automated scoring algorithm, based on Item Response Theory (IRT) analysis, which generates categorical (box, global) and novel continuous scoring outcomes. The study objective was to evaluate the validity of the eCDR by examining its relationship to the CDR and other in-clinic assessments. **Methods:** Participants (Age 55+, has a study partner, no acute or unstable major medical conditions) were enrolled from three Alzheimer's Disease Research Centers (ADRCs) and the UCSF Brain Health Registry (BHR). Participants completed the Uniform Data Set Version 3 (UDS; including the CDR) in supervised clinical research settings, then completed the eCDR remotely, online and unsupervised using their own device. The main outcome measures were eCDR scores (item; categorical box and global; continuous box and global), CDR scores (item; categorical box and global; sum of boxes (SB)), and UDS assessment scores. eCDR scores were automatically generated using a previously developed scoring algorithm. Percentage concordance (agreement) between eCDR and CDR at the item, box, and global score levels were examined. Accuracy of the eCDR in classifying CDR scores were evaluated using area under receiver operating characteristic curve (AUC) based on logistic regressions. Accuracy of eCDR IRT score to predict CDR-SB were evaluated using linear regressions. Correlation between CDR-SB, eCDR score and UDS neuropsychological assessments were examined using Spearman correlation. **Results:** In 173 participants with item level data (mean age 70.84 ± 7.65, 43.9% female), concordance rate between the eCDR and CDR was ≥90% for 63% of items and 70-89% for 25% of items. Box (domain) level concordance ranged from 80% (Memory) to 99% (Personal care). Global score concordance rate was 81%. Concordance was lowest for items: (1) Requiring comparison of participant and study partner responses to generate an item score; (2) With free text responses; and (3) With response options that differed between eCDR and CDR. In 206 participants with box and global scores (mean age 71.34 ± 7.68, 46.1% female), eCDR IRT global score (continuous) was significantly correlated with CDR-SB (r=0.43, 95% CI =0.31,0.53). eCDR IRT global score predicted CDR global (categorical) score with AUC=0.79 (95% CI=0.70,0.87). Correlations between eCDR scores and in-clinic UDS assessments were highest for functional and global cognition measures, and were similar to those between CDR sum of box scores and the same UDS assessments. **Conclusions:** The strong relationship between the eCDR and CDR supports validity of the eCDR and its potential to screen and assess older adults for cognitive and functional decline related to Alzheimer's disease. The eCDR is highly scalable and can be deployed in clinical research and trials, healthcare settings, and for population-based screening. Instrument optimization and validation in diverse populations is crucial. **Key words:** Alzheimer's Disease, remote assessment, digital assessment, cognitive decline, activities of daily living, Clinical Dementia Rating® (CDR®), electronic Clinical Dementia Rating® (eCDR®). **Disclosures:** RLN reports funding from the following sources in the form of grants to institution: National Institutes of Health, California Department of Public Health, Genentech Inc. DY reports no disclosures. TH reports no disclosures. MC reports no disclosures. KM reports no disclosures. SG reports no disclosures. CB reports no disclosures. JS reports no disclosures. SK reports no disclosures. MTA reports funding from the National Institutes of Health (grant to institution). CM reports no disclosures. RP reports funding from the National Institutes of Health (grants to institution; P30 AG062677, U01 AG006786, U01 AG024904, U24 AG057437, UF1 NS125417 and relationships

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OC29- AI-BASED ENRICHMENT TOOLS SUBSTANTIALLY INCREASE THE EFFICIENCY OF AD CLINICAL TRIALS.

V. Devanarayan[1], Y. Ye[1], H. Hampel[1], L. Kramer[1], M. Irizarry[1], S. Dhadda[1] *(1. Eisai Inc. - Nutley (United States))*

Background: Patient screening data from prior Alzheimer's disease (AD) clinical trials can be used to predict disease trajectories via Artificial Intelligence (AI) algorithms. Such predictions can be used as clinical trial enrichment tools for selecting patients predicted to experience clinical progression. The purpose of this research is to evaluate the impact of AI-based enrichment tools on the efficiency of clinical trials in early AD (mild cognitive impairment or mild AD). **Methods:** Clinical progression was defined as the change from baseline in CDR-SB over the 18-month duration of a clinical trial, and the prediction performance was measured via the Spearman rank correlation between the observed and predicted clinical progression. The treatment effect, defined as the difference in clinical progression between the treatment and placebo groups at month 18, was set at 30%. The impact of AI-based enrichment tools with different levels of prediction performance was assessed via clinical trial simulations on the power and sample size requirements. A reference AI-based enrichment tool was created by constructing via the stochastic gradient boosting algorithm using a clinical trial training cohort of 934 early AD placebo arm patients. Predictions of clinical progression at month-18 for 235 subjects in a validation clinical trial cohort were simulated 500 times from a normal distribution, with the correlations to the observed clinical progression set to range from 0.1 to 0.8, and the mean and variance set based on the predictions from the reference AI model. For each of the 500 sets of simulated predictions corresponding to each correlation scenario, 1000 clinical trials were simulated via the bootstrap procedure. The impact of clinical trial enrichment by selecting only patients with predicted 18-month CDR-SB change of at least 0.5 and 1 was then evaluated for each simulated clinical trial by calculating the power and sample size requirement for each of the scenarios via the analysis of variance. **Results:** Without enrichment, 718 subjects are needed to detect a 30% treatment effect with 80% power and 5% type-I error. Using the enrichment tools with the prediction performance (correlations) of 0.2, 0.4, and 0.6 to select patients with predicted 18-month CDR-SB change of at least 0.5 resulted in the power increase from 80% to 83.8%, 87.8%, and 91.6% respectively, and sample size requirement decreasing by 11.1%, 21%, and 30.1% respectively. Selecting patients with predicted 18-month CDR-SB change of at least 1 increased the power from 80% to 88.1%, 94.2%, and 98.1% respectively, and decreased the sample size requirement by 22%, 38.1%, and 52.4% respectively. The reference AI-based enrichment tool achieved a prediction performance (correlation) of 0.48 in the validation clinical trial cohort. Using this enrichment tool to select patients with predicted 18-month CDR-SB change of at least 0.5 and 1 increased the power from 80% to 89.2% and 97.6% respectively and decreased the sample size requirement by 23.2% and 49.4% respectively. **Conclusion:** AI-based enrichment tools for the identification of appropriate patient populations substantially increase the clinical study power and reduce the sample size requirements. **Key words:** patient screening, machine learning. **Clinical Trial Registry:** NCT02956486; NCT01767311; https://clinicaltrials.gov. **Disclosures:** All authors are employees of Eisai, Inc.

OC30- TIMING OF BIOMARKER CHANGES IN SPORADIC ALZHEIMER DISEASE IN ESTIMATED YEARS FROM SYMPTOM ONSET.

Y. Li[1], D. Yen[1], R. Hendrix[1], B. Gordon[1], S. Dlamini[1], N. Barthelemy[1], A. Aschenbrenner[1], R. Henson[1], E. Mcdade[1], D. Holtzman[1], T. Benzinger[1], J. Morris[1], R. Bateman[1], S. Schindler[1] *(1. Washington University in St. Louis - St. Louis (United States))*

Background: After reaching a threshold value or "tipping point," amyloid accumulates consistently across individuals when measured by amyloid positron emission tomography (PET), allowing formulation of an "amyloid clock" that relates

amyloid burden to time. We applied a previously described amyloid clock model to examine the timing of biomarker changes in sporadic Alzheimer disease (AD) [1]. **Methods:** For each individual, the age at a tipping point in PiB PET accumulation and the age at AD symptom onset were estimated based on previously described models. CSF, imaging, and cognitive measures were aligned by the years from the tipping point and estimated years from symptom onset. Cross-sectional biomarker levels and the longitudinal rate-of-change were modeled as a function of estimated years from symptom onset (EYO) using restricted cubic spline models for the amyloid positive group and the times at which biomarkers in the amyloid PET positive group became significantly abnormal relative to the amyloid negative group were estimated. **Results:** The amyloid PET negative sub-cohort (n=277) included individuals with low levels of amyloid PET signal at all scans (Centiloids ≤7) who were cognitively unimpaired at the time of the scans and had an average age of 63.5 years ± 9.1 years (mean ± standard deviation). The amyloid PET positive sub-cohort (n=118) included individuals with at least one amyloid PET scan in the range (Centiloids 7 to 88) that enabled estimation of their age at the tipping point (Centiloids=7). This sub-cohort had an average age of 70.4 ± 7.4 years and 16% were cognitively impaired. Changes in CSF Aβ42/Aβ40, CSF pT217/T217, and amyloid PET were detected 15-19 years before estimated symptom onset. CSF biomarkers of neuronal injury and synaptic dysfunction (VILIP-1, SNAP-25, and neurogranin) were detected 12-14 years before estimated symptom onset. CSF biomarkers of neuroaxonal injury and inflammation (NfL, YKL-40, and sTREM2) were detected 8-12 years before estimated symptom onset. Changes in CSF pT205/T205, hippocampal volumes, and cognitive measures were detected 8-9 years before estimated symptom onset. **Conclusion:** The amyloid clock enables visualization and analysis of biomarker changes as a function of estimated years from symptom onset on both an individual and a cohort level in sporadic AD. This study demonstrates that estimated years from symptom onset based on an amyloid clock can be used as a continuous staging measure for sporadic AD and aligns with findings in autosomal dominant AD [2, 3]. **Key words:** estimated years from symptom onset. **Disclosures:** D.M. Holtzman and R.J. Bateman cofounded, has equity, and is on the scientific advisory board of C2N Diagnostics. D.M. Holtzman is on the scientific advisory boards of Denali, Genentech, and Cajal Neuroscience and consults for Asteroid. R.J. Bateman has received research funding from Avid Radiopharmaceuticals, Janssen, Roche/Genentech, Eli Lilly, Eisai, Biogen, AbbVie, Bristol Myers Squibb, and Novartis. T.L.S. Benzinger participates as a site investigator in clinical trials sponsored by Avid Radiopharmaceuticals, Eli Lilly, Biogen, Eisai, Jaansen, and Roche. She serves as a consultant to Biogen, Lilly, Eisai, and Siemens. S.E. Schindler has served on a Scientific Advisory Board for Eisai. The other authors declared no competing interests. **References:** 1. Schindler SE, Li Y, Buckles VD, et al. Predicting Symptom Onset in Sporadic Alzheimer Disease With Amyloid PET. Neurology 2021;97:e1823-e1834. 2. Schindler SE, Li Y, Todd KW, et al. Emerging cerebrospinal fluid biomarkers in autosomal dominant Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 2019;15:655-665. 3. Barthelemy NR, Li Y, Joseph-Mathurin N, et al. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat Med 2020;26:398-407.

OC31- RG6289, A NEW γ-SECRETASE MODULATOR FOR THE TREATMENT OF ALZHEIMER'S DISEASE: RESULTS FROM A PHASE I HEALTHY VOLUNTEER STUDY.

S. Sturm[1], A. Portron[1], A. Vogt[2], A. Poirier[1], T. Yang[3], A. Mohamed Abdi[1], G. Kollmorgen[4], C. Simmons[5], K. Mahil[6], L. Lindemann[2], K.H. Baumann[2], T. Mueggler[2], T. Vardar[7], R. Tortelli[2], I. Gerlach[2] *(1. Pharmaceutical Sciences, Roche Pharma Research and Early Development, F. Hoffmann-La Roche Ltd - Basel (Switzerland), 2. Neuroscience and Rare Diseases, Roche Pharma Early Research and Development, F. Hoffmann-La Roche Ltd - Basel (Switzerland), 3. Product Development Safety Risk Management (PDS), F. Hoffmann-La Roche Ltd - Beijing (China), 4. Roche Diagnostics GmbH - Penzberg (Germany), 5. Product Development Data Sciences, F. Hoffmann-La Roche Ltd - Mississauga (Canada), 6. Roche Innovation Center Welwyn, Roche Pharma Research and Early Development, Roche Products Limited - Welwyn (United Kingdom), 7. Product Development Safety Risk Management (PDS), F. Hoffmann-La Roche Ltd - Basel (Switzerland))*

Background: Results from recent clinical studies with anti-amyloid antibodies confirm a causal role of amyloid β (Aβ) in Alzheimer's disease (AD) and validate Aβ as a therapeutic target. Modulators of γ-secretase (GSMs) are an emerging treatment approach for AD. GSMs shift the processing of amyloid precursor protein (APP) by γ-secretase from amyloidogenic long Aβ peptides (Aβ42 and Aβ40) towards an increased production of shorter, non-amyloidogenic Aβ species (Aβ38 and Aβ37). GSMs do not inhibit the enzymatic activity of γ-secretase, do not affect the processing of other γ-secretase substrates such as Notch, and preclinically do not show the typical toxicities that were previously observed with γ-secretase inhibitors. RG6289 is a novel potent and selective, orally bioavailable GSM with good CNS drug-like properties. Data from long-term preclinical toxicology studies support the chronic use of RG6289 in humans. **Methods:** RG6289 was investigated in a Phase I study in healthy volunteers to evaluate its safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD). Single and multiple ascending oral doses of RG70296 or placebo were administered orally. The study had a randomized, double-blind, adaptive design. Plasma and cerebrospinal fluid (CSF) samples were collected after administration of RG6289 to assess its effects on Aβ metabolism (Aβ42, Aβ40, Aβ38, Aβ37). **Results:** A total of n=92 young healthy volunteers (18-64 years of age) and n=8 elderly healthy volunteers (65-77 years of age) were enrolled for single and multiple dose administration, receiving RG6289 (n = 76) or placebo (n=24). In this study, RG6289 demonstrated a favorable safety and tolerability profile at all dose levels after single and multiple doses. No clinically significant changes were observed in vital signs, ECG, laboratory parameters, neurocognitive or neurological examinations. Observed adverse events were of mild intensity or considered not related to the study drug. Plasma concentrations of RG6289 increased in a dose-proportional manner over the dose range with a bi-phasic decline. A dose-dependent reduction of Aβ42 and Aβ40 was observed in CSF and plasma, together with a corresponding increase of Aβ38 and Aβ37 in CSF. PK and PD steady-state appears to be achieved within 7 days following the first administration. Dose escalation was stopped when the PD plateau was reached. Substantial reduction of Aβ42 in plasma was achieved after single and multiple dose administration of RG6289. Changes of Aβ42 in the CSF correlated with changes in plasma after multiple dose administrations at trough levels. Further details will be presented at the conference. **Conclusion:** RG6289 showed a favorable safety and tolerability profile across

all single and multiple doses in young and elderly healthy volunteers in this study. Proof of mechanism was demonstrated based on the observed enzyme modulation increasing levels of Aβ38 and Aβ37, whilst reducing Aβ42 and Aβ40. Results from this study support the further clinical development of RG6289 for the treatment of AD. **Key words:** Alzheimer's Disease, γ-secretase modulator, Amyloid β, healthy volunteers. **Disclosures:** S. Sturm is a full-time employee of F. Hoffmann-La Roche AG and holds F. Hoffmann-La Roche AG stock. A. Portron is a full-time employee of F. Hoffmann-La Roche AG. A. Poirier is a full-time employee of F. Hoffmann-La Roche AG. A. Vogt is a full-time employee of F. Hoffmann-La Roche AG. T. Yang is a full-time employee of F. Hoffmann-La Roche AG. A. Mohamed Abdi is a full-time employee of F. Hoffmann-La Roche AG and holds F. Hoffmann-La Roche AG stock. G. Kollmorgen is a full-time employee of F. Hoffmann-La Roche AG. C. Simmons is a full-time employee of F. Hoffmann-La Roche AG. K. Mahil is a paid consultant for F. Hoffmann-La Roche AG. L. Lindemann is a full-time employee of F. Hoffmann-La Roche A, holds stock or stock options of F. Hoffmann-La Roche AG, and is co-inventor of patents owned by F. Hoffmann-La Roche AG. K. Baumann is a full-time employee of F. Hoffmann-La Roche A, holds stock or stock options of F. Hoffmann-La Roche AG, and is co-inventor of patents owned by F. Hoffmann-La Roche AG. T. Mueggler is a full-time employee of F. Hoffmann-La Roche AG. T. Vardar is a full-time employee of F. Hoffmann-La Roche AG and holds stock or stock options of F. Hoffmann-La Roche. R. Tortelli is a full-time employee of F. Hoffmann-La Roche AG. I. Gerlach is a full-time employee of F. Hoffmann-La Roche AG and holds stock or stock options of F. Hoffmann-La Roche

OC32- A PHASE 1A SINGLE ASCENDING DOSE STUDY OF THE SAFETY, TOLERABILITY, AND BRAIN RECEPTOR OCCUPANCY OF BMS-984923 IN HEALTHY OLDER ADULTS.

A.P. Mecca[1], E. Salardini[1], J.D. Gallezot[1], R.S. O'dell[1], J. Young[1], E. Cooper[1], M.G. Donahue[1], J.L. Waszak[1], J.L. May[1], J. Spurrier[1], T.R. Siegert[2], R.E. Carson[1], S.M. Strittmatter[1,2], C.H. Van Dyck[1] *(1. Yale School of Medicine - New Haven (United States), 2. Allyx Therapeutics, Inc. - New Haven (United States))*

Background: Brain synapse loss in Alzheimer's disease (AD) has been tightly correlated with cognitive symptoms and developing drugs that preserve or restore synapses is an important therapeutic goal. Synaptic toxicity involves soluble Aβ oligomers (Aβo) binding to the cellular prion protein (PRPc) and metabotropic glutamate receptor subtype 5 (mGluR5) receptor complex. Multiple groups have shown that interrupting mGluR5 function rescues preclinical mouse AD phenotypes, making it an attractive drug target. However, mGluR5 has a physiological role as a glutamate receptor and full inhibition impairs function. We have identified a highly potent and orally bioavailable mGluR5 silent allosteric modulator (SAM) , BMS-984923, that does not alter basal or glutamate activity, but does block Aβo/PrPC activation of mGluR5. In studies using multiple preclinical mouse AD models, treatment with BMS-984923 recovers synapse density, restores long term potentiation and returns memory performance to wild-type levels [1,2]. Preclinical animal studies have indicated low toxicity and high tolerability at proposed therapeutic doses, supporting the advancement of BMS-984923 to human studies. **Methods:** Thirty-six participants between the ages of 50 to 80 years old with normal cognition were enrolled in an open-label, single ascending dose study. Six cohorts of 6 participants each were administered a single oral dose of BMS-984923 (10 mg, 40 mg, 70 mg, 100 mg, 150 mg, or 200 mg). Participants in each cohort were monitored for 7 days after receiving the study drug to assess safety and plasma drug exposure. A safety review was conducted at the completion of each cohort prior to escalation to the next dose cohort. For two participants each in the 10 mg, 40 mg, 70 mg, and 100 mg cohorts, three positron emission tomography (PET) scans with the mGluR5 radiotracer [18F]FPEB were conducted off drug, and at approximately 4 and 24 hours post-dose. Distribution volume for each scan was estimated from dynamic scans with a metabolite-corrected input function using a 2-tissue compartment model. Receptor occupancy (RO) was derived from a graphical occupancy plot and related to BMS-984923 plasma concentration. A nonlinear least squares analysis was used to a fit a one parameter model and estimate IC50 with ROmax = 100%. **Results:** All doses of BMS-984923 were well tolerated without serious adverse events. All treatment emergent adverse events (TEAEs) were mild or moderate in intensity and only 8 TEAEs were considered possibly related to treatment. Possibly related TEAEs consisted of 3 reports of brief oral sensations, 1 brief episode of dizziness, 2 reports of transient headache, 1 episode of transient hypertension, and 1 lab measurement of increased triglycerides. Plasma exposure increased linearly with increasing oral doses of BMS-984923. Based on the plasma concentration-RO model, the IC50 (SE) was 33.9 (4.0) ng/mL and IC80 (SE) = 135.7 (16.0) ng/mL. **Conclusion:** BMS-984923 is safe and tolerable at single doses high enough to achieve significant target engagement, supporting continued development for the treatment of AD. Further studies are planned to assess the safety and tolerability of multiple doses of BMS-984923 in healthy older adults and patients with AD. **Key words:** BMS-984923, mGluR5, [18F]FPEB, silent allosteric modulator. **Clinical Trial Registry:** NCT04805983, https://clinicaltrials.gov. **Disclosures:** TRS, SMS and Yale University have financial interest in Allyx Therapeutics, a company developing BMS-984923 for commercial use. Other authors do not have any conflicts of interest related to this study. **References:** 1. Haas LT, et al. Cell Rep 2017; 20(1):76-88. https://doi.org/10.1016/j.celrep.2017.06.023. 2. Spurrier J, et al. Sci Transl Med 2022; 14(647):eabi8593. https://doi.org/10.1126/scitranslmed.abi8593

OC33- A PHASE 1 STUDY DEMONSTRATING SAFETY, CNS TARGET ENGAGEMENT AND PBMC PHARMACODYNAMIC RESPONSE TO ASN51, A NOVEL AND ORALLY ADMINISTERED O-GLCNACASE INHIBITOR.

R. Schubert[1], B. Permanne[1], R. Pokorny[1], P. Fang[1], V. Teachout[1], M. Nény[1], S. Ousson[1], R. Ahmed[1], M. Schneider[1], A. Quattropani[1], D. Beher[1] *(1. Asceneuron - Lausanne (Switzerland))*

Background: Inhibition of the O-linked-β-N-acetylglucosaminidase (OGA) enzyme with orally bioavailable small molecules has demonstrated proof of concept as a disease modifying approach in preclinical in vivo models of both tau and α-synuclein pathology. We previously reported the results of two Phase 1 studies in healthy human volunteers with the novel OGA inhibitor ASN51. The target engagement effects of single doses of up to 50 mg of ASN51 were consistent with essentially complete OGA inhibition in the CNS. Here, we report a third Phase 1 study that evaluated safety, CNS enzyme occupancy, and pharmacodynamic (PD) response in peripheral blood mononuclear cells (PBMC) after both single and repeated doses of ASN51. **Methods:** ASN51-103 was an open label Phase 1 trial with two escalating ASN51 dose (10

mg and 20 mg daily for 14 days) cohorts. In addition to safety, the co-primary endpoints were to assess brain OGA occupancy using [18F]-IMA601 PET and the pharmacodynamic response in PBMC using a protein O-GlcNAcylation immunoassay in healthy subjects. **Results:** An interim analysis conducted after the completion of the 10 mg dose cohort (n = 6 subjects dosed daily for 14 days) showed ASN51 was safe and well tolerated with no clinically relevant laboratory or vital sign changes. Preliminary results showed that the relationship between ASN51 plasma exposure and CNS OGA enzyme occupancy was similar after both single and repeated ASN51 administration. The change from baseline in PBMC O-GlcNAcylation was also similar after single and repeated administration. Results from both 10 mg and 20 mg dose cohorts will be presented at the conference. **Conclusions:** ASN51 has a favorable safety profile after single and repeat dosing for up to 14 days in healthy volunteers. [18F]-IMA601 PET enzyme occupancy and PBMC O-GlcNAcylation PD results demonstrated that ASN51 achieved near-maximal and sustained CNS OGA inhibition in subjects after both single and repeated exposures. Since ASN51 target engagement is maintained following repeated dose exposure, it is suitable for use in longer duration clinical trials. These data demonstrate the safety and target engagement of ASN51 and support its use at doses of 20 mg or less in future efficacy trials in human neurodegenerative diseases characterized by the aggregation of tau or α-synuclein. **Key words:** Tau therapy, O-GlcNAcase inhibitor, target engagement, oral small molecule. **Clinical Trial Registry:** NCT05725005. **Disclosures:** The authors are employees of, consultants of, and/or have an equity interest in Asceneuron.

OC34- E2511, A NOVEL TRKA MODULATOR, ENGAGES ITS CNS CHOLINERGIC TARGET IN A PHASE 1 CLINICAL STUDY. S. Saxena[1], Y. Ye[1], K. Sasaki[1], T. Kamakura[1], G. Ringheim[1], L. Giorgi[1], N. Penner[1], K. Horie[1], V. Devanarayan[1], P. Sachdev[1] *(1. Eisai Inc. - Nutley (United States))*

Background: Progressive decreases in nerve growth factor (NGF)-tropomyosin receptor kinase A (TrkA) induces trophic signaling contributes to cholinergic atrophy and cognitive decline in age-related neurodegenerative diseases, including Alzheimer's disease (AD). E2511 is a novel small-molecule TrkA allosteric modulator that has demonstrated an increase in specific trophic signaling via direct binding to TrkA with a potential to recover and reinnervate damaged cholinergic neurons. **Objectives:** Herein, we used a multi-platform, ultra-deep, global proteomics strategy and brain proteome-driven modules of co-expressing proteins linked to various biological functions to clarify the target engagement of E2511. **Methods:** E2511-A001-005 was a phase 1 randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study in healthy subjects. A total of 32 healthy subjects were randomly assigned to receive either placebo or once-daily E2511 doses of 10, 20, 40, and 80 mg for 14 days. Pre (day -2) and post (day 13) treatment CSF samples from all 4 dose levels were evaluated using global proteomics platforms (including data independent acquisition-mass spectrometry [DIA-MS]), and aptamer-based technology (SOMAscan® assay from Somalogic) to demonstrate target engagement. DIA-MS data was analyzed using Spectronaut (v17) with 1% false-discovery-rate threshold. Protein raw intensities were quantile normalized and log2 transformed. Raw data from SomaScan platform underwent a series of normalization and calibration steps and was log2 transformed. Protein expression changes were identified via analysis of covariance after adjusting for baseline protein expression and clusters identified by PCA analysis. Differentially expressed proteins from each comparison were mapped to the co-expression modules created from published brain proteomes. **Results:** Our multi-platform global proteomics strategy achieved CSF proteome depth of >3000 proteins using the unbiased MS-based platform and evaluated 7630 proteins using the predefined Somalogic panel. Comparison of CSF proteomes from day -2 and day 13 from placebo and E2511-treated subjects across all dose levels demonstrated differential expression of proteins, including those involved in TrkA and cholinergic pathways. Differentially expressed proteins observed in CSF samples from E2511-treated subjects mapped to previously published brain-network modules linked to axonal and synaptic proteins. Other pathway enrichment analyses also supported targeting of axonal and synaptic signaling by E251. **Conclusions:** In a phase1 clinical trial of a novel TrkA modulator (E2511), ultra-deep global proteomics profiling of CSF enabled the identification of proteins potentially linked to E2511 MoA. Pathway enrichment analysis and mapping of unbiased ultra-deep CSF proteomes to groups or "modules" of co-expressed brain proteins that reflect various biological functions corroborated the mechanism of action and target engagement of E2511 in regulating axonal and synaptic biology. Further confirmatory studies using targeted assays are warranted to confirm E2511 proof-of-mechanism and to support dose selection for the pivotal clinical trials. **Disclosures:** All authors are current or former employees of Eisai Co. Ltd. The authors declared no competing interests.

OC35- MODE OF ACTION, CLINICAL PHASE IB DATA IN PATIENTS, AND THE PHASE II DESIGN OF THE ORALLY AVAILABLE ANTI-PRIONIC COMPOUND PRI-002 THAT DISASSEMBLES AB OLIGOMERS INTO AB MONOMERS. D. Willbold[1], N.C. Cosma[2], J. Kutzsche[1], D. Jürgens[3], G. Tischler[3], O. Peters[2] *(1. FZ Jülich - Jülich (Germany), 2. Charité - Berlin (Germany), 3. Prinnovation - Leipzig (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. PRI-002 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. 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 PRI-002 in patients suffering from MCI due to AD and mild AD. Target engagement, safety and efficacy has been evaluated. Based on these results, the design for a phase II proof-of-concept study needed to be developed. **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 PRI-002 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 PRI-002 (72.4±6.9, 27.2±2.9). One patient withdrew informed consent before treatment was started. 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 PRI-002 significantly performed better than those receiving placebo in the CERAD word list at follow up. 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 ($p \leq 0.001$). Oral uptake of PRI-002 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 CSF Aβ oligomers (between day 28 and day 1) and the blood plasma concentrations of PRI-002 in the dosed patients. **Conclusions:** PRI-002 showed an excellent safety profile in MCI and mild AD patients. While no significant biomarker changes were detected after 4 weeks of treatment, a significant improvement of short-term memory function was noted at follow up. Despite the small number of patients, we feel that this phase Ib study results deserve reporting to the scientific community. The design of a phase 2 study, which is scheduled to start later this year, will be reported.

Late Breaking Communications

LB01- BASELINE LEVELS AND LONGITUDINAL CHANGES IN PLASMA AB42/40AMONG SELF-IDENTIFIED BLACK AND WHITE INDIVIDUALS.

C. Xiong[1], J. Luo[1], D. Wolk[2], L. Shaw[2], E. Roberson[3], R. Henson[1], T. Benzinger[1], Q. Bui[1], F. Agboola[1], E. Grant[1], E. Gremminger[1], K. Moulderv, D. Holtzman[1], J. Morris[1], S. Schindler[1] *(1. Washington University - St. Louis (United States), 2. University of Pennsylvania - Philadelphia (United States), 3. University of Alabama - Birmingham (United States))*

Background: Blood-based biomarkers of Alzheimer disease (AD) may facilitate the performance of AD biomarkers in more diverse groups. Multiple studies have demonstrated differences in baseline and longitudinal AD biomarkers between self-identified Black and White individuals. It remains largely unknown, however, whether similar racial differences are present in plasma biomarkers of AD. **Objective:** We evaluated for possible racial differences in baseline and longitudinal plasma Aβ42/40 between self-reported Black and White participants from a multi-center observational study. **Method:** The Study of Race to Understand Alzheimer Biomarkers (SORTOUT-AB) is a multi-center longitudinal study to evaluate for potential differences in AD biomarkers between self-identified Black and White individuals. Longitudinal plasma samples collected at three AD Research Centers (Washington University, University of Pennsylvania, and University of Alabama-Birmingham) from a total of 193 Black and 753 White participants were centrally processed using C2N Diagnostics' PrecivityAD™ blood test for Aβ42, Aβ40, and Aβ42/40. General linear mixed effects models were used to estimate the mean baseline levels of amyloid biomarkers as well as their annual rates of change for each racialized group and to compare these measures between racial groups. Analyses were stratified by baseline age and adjusted for covariates including baseline sex, APOE ε4 carrier status, dementia status, and fasting status. Receiver Operating Characteristic (ROC) curves were used to estimate the optimum cutoffs for these biomarkers to predict baseline dementia status (CDR 0 vs. CDR>0). The plasma Aβ42/40 positivity rate was estimated for each racialized group and compared between the groups by Fisher's exact test. Longitudinal data were fit by linear mixed effects models with race-specific random coefficients were fit. **Results:** Participants were 43 to 91 years at baseline, and longitudinally followed for a mean of 6.38 years. Among 193 Black participants, 160 were CDR 0 and 33 had a CDR>0 at baseline. Among 753 White participants, 629 were CDR 0 and 124 had a CDR>0 at baseline. Regardless of the CDR at baseline, Black participants had a higher level of Aβ42/40, compared to White participants, especially in individuals with baseline ages between 60 and 75 years. Using the cutoff of Aβ42/40 that maximized the Youden index, sum of sensitivity and specificity, to predict CDR>0 at baseline, Black participants had a significantly lower rate of plasma Aβ42/40 positivity at baseline, consistent with brain amyloid. Longitudinally, Black participants had a faster rate of increase in both Aβ42 and Aβ40 than White participants, but no differences were found in the annual rate of change in Aβ42/40. **Conclusion:** Black individuals participating in research studies may have a lower rate of amyloid positivity at baseline, which could decrease the proportion of Black individuals eligible for AD prevention trials and treatment trials for AD dementia. However, there were no significant racial differences in the longitudinal rates of change for plasma Aβ42/40. These findings, if confirmed by larger and more representative studies, may allow future AD prevention trials to target a shared efficacy endpoint.

LB02- PLASMA MTBR-TAU243 IS A SPECIFIC BIOMARKER OF TAU TANGLE PATHOLOGY IN ALZHEIMER'S DISEASE.

K. Horie[1,2,3], R. Koppisetti[1,2], S. Janelidze[4], E. Stomrud[4,5], N. Barthélemy[1,2], C. Sato[1,2], T. Benzinger[6], D. Holtzman[2], J. Morris[2], N. Mattsson-Carlgren[4,5], S. Palmqvist[4,5], S. Schindler[2], O. Hansson[4,5], R. Bateman[1,2] *(1. Tracy Family SILQ Center, Washington University School of Medicine - St. Louis (United States), 2. Department of Neurology, Washington University School of Medicine - St. Louis (United States), 3. Eisai Inc - Nutley (United States), 4. Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University - Lund (Sweden), 5. Memory Clinic, Skåne University Hospital - Malmö (Sweden), 6. Department of Radiology, Washington University School of Medicine - St. Louis (United States))*

Background: Neurofibrillary tangles (NFTs) are a key pathological hallmark of Alzheimer's disease (AD) and are comprised of hyper-phosphorylated tau (p-tau) species including the microtubule binding region of tau (MTBR-tau). While the levels of p-tau181 and p-tau217 in cerebrospinal fluid (CSF) and blood have previously been considered as indicators of AD tau tangles, recent studies indicate that these p-tau species are more strongly associated with amyloid plaques than NFTs. In comparison to CSF p-tau, CSF MTBR-

tau species containing the residue of 243 (MTBR-tau243) are more highly correlated with NFTs as measured by tau positron emission tomography (tau-PET) [1]. In this study, we aimed to translate the CSF MTBR-tau243 findings into plasma and establish the first blood biomarker to specifically quantify NFTs in AD. **Methods:** Plasma MTBR-tau243 was antibody purified, then evaluated via mass spectrometry. Plasma p-tau217 was measured by Meso Scale Discovery [2]. Plasma was collected at the time of the tau-PET scan (18F-flortaucipir or 18F-RO948, respectively). Plasma MTBR-tau243 and p-tau217 were compared as predictors of tau-PET and the Mini-Mental State Examination (MMSE). Spearman correlations adjusted by age, sex and education were used to evaluate the relationships of plasma biomarkers with tau-PET and MMSE. **Results:** MTBR-tau243 was measured in plasma samples from the Knight Alzheimer Disease Research Center (Knight ADRC) (n=35) and the Swedish BioFINDER-2 study (n=108). Approximately half of participants were amyloid positive (57% for Knight ADRC and 47% for BioFINDER-2); 35% of Knight ADRC and 44% of BioFINDER-2 were cognitively impaired. In both Knight ADRC and BioFINDER-2 cohorts, plasma MTBR-tau243 was detected in only tau-PET positive participants. In the Knight ADRC cohort, plasma MTBR-tau243 strongly correlated with CSF MTBR-tau243 (Rho=0.83) and tau-PET (average of entorhinal, amygdala, inferior-temporal, and lateral-occipital) (Rho=0.74), suggesting that plasma MTBR-tau243 is translatable from CSF and predicts tau-PET. In the BioFINDER-2 cohort, plasma MTBR-tau243 was strongly correlated with tau-PET (Braak I-VI regions average) in the entire cohort and amyloid-positive participants (Rho=0.85 and 0.82, respectively) while plasma p-tau217 was less correlated with tau-PET (Rho=0.71 and 0.58, respectively). Interestingly, plasma MTBR-tau243 in amyloid-positive participants exhibited a higher correlation with tau-PET in late Braak regions V-VI (Rho=0.82) vs. than early Braak regions I-II (Rho=0.45), which implies that plasma MTBR-tau243 recapitulates more advanced pathological stages (i.e., neocortical spreading phase) compared to early pathological stages (i.e., subcortical accumulation phase). Plasma MTBR-tau243 was significantly associated with MMSE scores in amyloid-positive participants (Rho=-0.55, p=0.0001) while plasma p-tau217 was not (Rho=-0.26, p=0.091), suggesting the potential clinical applications of plasma MTBR-tau243 in predicting not only NFTs but also cognitive impairment in AD. **Conclusion:** These findings indicate that plasma MTBR-tau243 reflects changes in tau pathology that occur during the clinical symptomatic phase of AD and can be used to stage AD tauopathy, and to determine if cognitive symptoms are likely due to AD pathology. Plasma MTBR-tau243 also holds promise to track the effects of tau-targeting therapies. Plasma p-tau217 and MTBR-tau243 may represent quantitative measures for both amyloid plaques and tau tangles that are simple and accessible for clinical trials and clinical diagnosis. **Key words:** plasma biomarker, tau tangles, MTBR-tau243. **Disclosures:** K.H. is an Eisai-sponsored voluntary research associate professor at Washington University and has received salary from Eisai. Washington University. K.H., N.B., C.S. and R.B. may receive income based on technology (Methods to Detect MTBR-tau Isoforms and use Thereof) licensed by Washington University to C2N Diagnostics. K.H., D.H., and R.B. may receive income based on technology (Anti-tau MTBR Antibodies and Methods to Detect Endogenously Cleaved Fragments of Tau and uses Thereof) licensed by Washington University to C2N Diagnostics. The remaining authors declare no competing interests. **References:** 1. Horie, K. et al. Nat Med 29, 1954–1963 (2023). https://doi.org/10.1038/s41591-023-02443-z. 2. Palmqvist, S. et al. JAMA 324, 772–781 (2020). doi: 10.1001/jama.2020.12134.

LB03- TOPLINE RESULTS FROM THE PHASE 2 PIONEER TRIAL OF ORAL T3D-959 FOR THE TREATMENT OF PATIENTS DIAGNOSED WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE.

J. Stanek[1], S. Chamberlain[1], C. Coutlee[1], W. Strittmatter[1], C. Lineberry[1], B. Swearingen[1], J. Didsbury[1] *(1. T3D Therapeutics, Inc. - Research Triangle Park (United States))*

Background: PIONEER was a Phase 2 randomized, placebo-controlled, multi-center trial evaluating efficacy and safety of the dual PPARδ/γ agonist T3D-959 in patients with mild-to-moderate Alzheimer's disease (AD). We report topline results from PIONEER and a post-hoc subgroup analysis of patients a priori defined, per C2N Diagnostics, LLC. recommendations, by a high baseline plasma pTau-217/Non-pTau-217 ratio. **Methods:** All patients had mild-to-moderate AD per NIA-AA criteria and mild-to-moderate cognitive impairment, without biomarker enrollment criteria. Primary endpoints were ADAS-Cog11 and ADCS-CGIC. Secondary endpoints were plasma Aβ42/40 ratio and Digit Symbol Coding Test. Proteomic biomarkers, including pTau-217, were exploratory endpoints. Efficacy was evaluated as least-squares mean changes from baseline to week 24. A post-hoc subgroup analysis was conducted in patients (N=129) with a baseline plasma pTau-217/Non-pTau-217 ratio ≥0.015 (high pTau-217 ratio). **Results:** 250 patients were randomized to placebo (n=65) or T3D-959 (15-mg, n=63; 30-mg, n=62; or 45-mg, n=60). 100 T3D-959-treated and 29 placebo-treated patients had a high baseline pTau-217 ratio. Primary ADAS-Cog11 and CGIC endpoints were not met in the overall population. ADAS-Cog11 endpoint was met in the high pTau-217 ratio T3D-959 30-mg group (-0.74; n=36) vs placebo group (1.27; n=29; P=0.112), consistent with clinical benefit . Unexpected improvement in ADAS-Cog11 was observed among placebo low pTau-217 ratio patients and expected decline in placebo high pTau-217 ratio placebo-treated patients (-3.17 vs 1.27; P=0.0007), suggesting low pTau-217 ratio subjects may not have AD. The secondary endpoint, plasma Ab42/40 ratio change, was met in the T3D-959 30-mg group (increasing at week 24) vs. placebo decreasing (0.0023 vs -0.0013; P=0.0206).This was a similar magnitude of effect on Ab42/40 as lecanemab at 6-months. In the high pTau-217 ratio patient group the improvement of Ab42/40 ratio was nearly 2-fold greater than the overall group. T3D-959 30-mg treatment in the overall population significantly improved the neurodegeneration biomarker neurogranin (P=0.013) at week 24 vs placebo and numerically improved pTau-217/Non-pTau-217 ratio. Changes in other metabolomic and proteomic markers suggest effects of T3D-959 on inflammation, oxidative stress, and metabolism. A similar proportion of patients experienced ≥1 AE (T3D-959, 37.3%; placebo, 43.1%). Thirteen mild treatment-related AEs (TRAEs) were observed (most commonly diarrhea [2.2%]) vs 4 with placebo. No serious TRAEs were observed. **Conclusions:** A high plasma pTau-217 ratio likely defines an AD population responsive to T3D-959 therapy. ADAS-Cog11 endpoint was met in the high pTau-217 T3D-959 30-mg group. Biomarkers of all three AD diagnostic criteria (Amyloid/Tau/Neurodegeneration) were significantly, numerically, or trending improved, as well as markers of inflammation, insulin resistance and dysfunctional lipid metabolism. T3D-959 30-mg/day demonstrated significant improvement over placebo in the prespecified secondary endpoint of plasma Aβ42/40

ratio change, and in plasma neurogranin at week 24 in the total population. Biomarker results suggest potential disease modification with T3D-959. Along with the strong safety profile of T3D-959, evidence is supportive of a larger study evaluating T3D-959 30-mg/day in patients with mild-to-moderate AD and a baseline plasma p-Tau-217/Non-pTau-217 ratio of ≥0.015. **Key words:** PIONEER, T3D-959, PPAR agonist, pTau-217, plasma biomarkers. **Clinical Trial Registry:** NCT04251182. **Disclosures:** Financial support for PIONEER was provided by the NIA/NIH and the Alzheimer's Association. The authors declared no competing interests.

LB04- SAFETY, IMMUNOGENICITY, CLINICAL EFFICACY AND BIOMARKERS OF ABVAC40, AN ACTIVE VACCINE ANTI-AB40 IN PATIENTS WITH AMNESTIC MILD COGNITIVE IMPAIRMENT OR VERY MILD ALZHEIMER'S DISEASE: FINAL RESULTS OF A PHASE 2 RANDOMIZED STUDY.

J. Terencio[1,2], M. Pascual-Lucas[3], A.M. Lacosta[3], M. Montañés[3], J. Canudas[3], J.A. Allué[3], L. Sarasa[3], N. Fandos[3], J. Romero[3], E. Molina[3], M. Sarasa[3], M. Boada[4] *(1. Grifols - Barcelona (Spain), 2. Araclon Biotech-Grifols - Zaragoza (Spain), 3. Araclon-Biotech - Zaragoza (Spain), 4. Ace Alzheimer Center Barcelona - Universitat Internacional de Catalunya - Barcelona (Spain))*

Background: ABvac40 is an in-development active vaccine targeting Aβ40 for the treatment of Alzheimer's disease (AD). A multicenter, randomized, double-blind, placebo-controlled phase-2 trial (NCT03461276) has been conducted to investigate safety, tolerability and immunogenicity of repeated subcutaneous injections of ABvac40 in patients with a-MCI or vm-AD. Preliminary results demonstrated that ABvac40 was safe and stimulated a strong and specific immune response. Safety findings and final results of secondary efficacy endpoints are presented. **Methods:** The study was conducted between December-2017 and March-2023 at 23 sites and comprised two periods: A and B. In Part-A (18-24 months), patients were randomized to receive five monthly single-dose injections plus a 6-month delayed booster of ABvac40 or placebo. Part-B (18 months) was an extension study with the following cross-over of treatment from Part-A: placebo patients at Part-A received ABvac40, whereas ABvac40-treated patients received placebo and a booster of ABvac40. Primary endpoints were immunogenicity, safety, and tolerability. Safety was assessed as the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs (TESAEs) and TESAEs of special interest (including ARIA-H, ARIA-E and aseptic meningo-encephalo-myelitis). Secondary endpoints, assessed at several time points across Part-A, were neuropsychological tests, AD biomarkers in CSF, cortical fibrillary amyloid deposition, and brain volumetric analysis. Safety analysis used the safety population, and efficacy results used the PP/PP cognition population. **Results:** A total of 124 patients (a-MCI, n=80; vm-AD, n=44) aged 70.4 (SD 5.71), with a MMSE score of 25.8 (SD 1.81) were enrolled, randomized and treated (ABvac40: N=62; placebo: N=62) in study part-A. Overall TEAEs and TESAEs frequency was similar between ABvac40 (87.9% and 23.2%) and placebo groups (82.4% and 16.7%). As previously reported, ARIA-H incidence was equally distributed between groups (9.1% ABvac40; 11.3% placebo) with no cases of ARIA-E or aseptic meningo-encephalo-myelitis. ABvac40 group showed a 38% slowing of disease progression compared to placebo as evidenced by changes in MMSE score starting at month-6, resulting in a statistically significant difference at month-12 (LS-mean difference, 1.44; 95% CI: 0.18, 2.69; P=0.0252). RBANS scores favored the ABvac40 group from month-12, with maximal difference at month-18, although differences were not statistically significant. Shorter time to complete TMT-A was observed in ABvac40 group vs placebo, reaching significancy at month-24 (LS-mean difference –13.65 s, 95% CI: –25.81, –1.48; P=0.0283). There were no relevant differences between groups in CDR-SB, ADCS-ADL-MCI, TMT-B, IGE, and EQ-5D-5L. Rates of amyloid deposition per 18F-flutemetamol PET were minimal for both groups (LS-mean change from baseline of SUVR, 0.008 [0.0067] ABvac40 group, 0.013 [0.0063] placebo group, at month-24). At months 12 and 24, volumetric MRI showed a lesser increase in whole brain atrophy in the ABvac40 group vs placebo, reaching statistical significance at month-24 (LS-mean difference -1.48%; 95% CI: –2.79, –0.16; P=0.0282). No statistically significant differences between groups were found in CSF biomarkers. **Conclusions:** The phase-2 trial of ABvac40 has shown positive results with a favorable safety profile, robust immunogenicity, and potential cognitive benefits for a-MCI and vm-AD patients. While additional research is warranted, these findings present ABvac40 as a promising candidate for early AD treatment. **Key words:** ABvac40, vaccine, Aβ40, clinical trial, Phase 2, immunotherapy, AB1601. **Disclosures:** JT is a full-time employee of Grifols. MPL, AML, JC, MM, JAA, LS, NF, JR and EM are full-time employees of Araclon Biotech-Grifols. MB 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. **Clinical Trial Registry:** NCT03461276

LB05- TAU VACCINE AADVAC1 DEMONSTRATES CLINICAL AND BIOMARKER EFFICACY ON PATIENTS WITH PLASMA P-TAU217 DEFINED ALZHEIMER'S DISEASE IN PHASE II CLINICAL TRIAL: POST HOC ANALYSIS.

B. Kovacech[1], N. Cullen[2], P. Novak[1], J. Hanes[1], E. Kontsekova[1], M. Fresser[3], J. Vanbrabant[4], H. Feldman[5], B. Winblad[6], E. Stoops[4], E. Vanmechelen[4], N. Zilka[1] *(1. Axon Neuroscience R&D Services - Bratislava (Slovakia), 2. Department of Clinical Sciences, Lund University - Lund (Sweden), 3. Axon Neuroscience SE - Larnaca (Cyprus), 4. ADx NeuroSciences NV, Technologiepark 94 – Bio Incubator - Gent (Belgium), 5. Department of Neurosciences, University of California San Diego - La Jolla (United States), 6. Karolinska Institutet, Dept NVS, Center for Alzheimer Research, Division of Neurogeriatrics - Solna (Sweden))*

Background: AADvac1 is the first-in-man, first-in-kind active tau immunotherapy [1], targeting the microtubule-binding region of tau protein, and stimulating the immune system to produce antibodies specific for pathological forms of tau. The vaccine has been shown to be safe and well tolerated [1,2]. A phase II clinical trial demonstrated that the vaccine is associated with benefit on plasma neurofilament light chain (NfL) and CSF tau biomarker concentrations. **Methods:** ADAMANT was a 24-month, Phase II RCT on AADvac1, which enrolled 196 participants at 41 sites across Europe (2016-2019) [2], with 193 participants composing the full analysis set (FAS) under the modified ITT principle due to having at least one post-baseline endpoint assessment. Key inclusion criteria were diagnosis of probable Alzheimer's disease (AD)

(2011 NIA-AA criteria) [3], age of 50 – 85 years, MMSE of ≥20 and ≤26 at screening and medial temporal lobe atrophy (Scheltens score ≥2 on the more atrophied side) and/or positive CSF AD biomarker profile (t-tau, p-tau181, Aβ42). CSF AD biomarker profiles were available only in 46 participants (23.8% of FAS). The trial participants initially received six doses of AADvac1 or placebo at 4-week intervals, followed by five booster doses at 14-week intervals. In this post hoc analysis, we identified a subgroup of the trial participants (n=137, 71% of FAS) with AD biomarkers identified with elevated plasma p-tau217 levels measured by an ADx Homebrew SIMOA assay and undertook an efficacy analysis on clinical and biomarker endpoints. **Results:** In this sub-analysis of those ADAMANT participants with biomarker-confirmed AD diagnosis (plasma p-tau217 positive; AADvac1 n=84, placebo n=53) benefits of AADvac1 are identified on normalization of plasma NfL, MRI volumetry (whole cortex and temporal lobe) and CDR-SB. AADvac1 reduced the mean concentration of plasma NfL by 65% and brain atrophy in the temporal lobe by 27%. The therapeutic effect on plasma NfL, MRI, and CDR-SB was dose-dependent and more pronounced in patients with higher antibody response. There was no effect of AADvac1 treatment on trial participants who were plasma p-tau217 negative (n=56, AADvac1 n=32, placebo n=24). **Conclusions:** Tau-targeted active immunotherapy with AADvac1 showed significant treatment effects in biomarker-confirmed AD patients on cognitive and neurodegeneration-related biomarker endpoints. The response to treatment was directly related to the levels of AADvac1-induced anti-tau antibodies. These findings support a Phase IIb clinical trial on A+T+ biomarker-confirmed patients with early AD. **Key words:** Alzheimer´s disease, dementia, tau vaccine, neurofibrillary lesions, neurofilament. **Trial Registry:** EudraCT 2015-000630-30, NCT02579252. **Data Deposition:** https://www.nature.com/articles/s43587-021-00070-2. **Disclosures:** All authors affiliated with Axon Neuroscience SE and Axon Neuroscience R&D Services SE receive a salary from the company. Howard H. Feldman reports a service agreement through UC San Diego with Axon Neurosciences with funds received by UC San Diego and none personally received. He also has received grant funding to UC San Diego from Biohaven Pharmaceuticals, Annovis (QR Pharma), AC Immune, Vivoryon (Probiodrug), and LuMind Foundation and has service agreements through UC San Diego for consulting with Biosplice, Arrowhead Pharmaceuticals, Novo Nordisk (including travel expenses) DMC and DSMB services for Roche/Genentech Pharmaceuticals and Janssen Research & Development LLC, as well as serving on the Scientific Advisory Board for the Tau Consortium. All related funds are directed to UC San Diego with none personally received. He also reports philanthropic support through the Epstein Family Alzheimer's Disease Collaboration. Bengt Winblad receives honoraria from Axon Neuroscience for Scientific Advisory Board meetings. All authors affiliated with ADx NeuroSciences N.V. receive a salary from the company. Eugeen Vanmechelen is a co-founder of the company. **References:** 1. Novak, P., et al. Lancet Neurol. 2017; 16(2), 123-134. http://doi.org/10.1016/S1474-4422(16)30331-3. 2. Novak, P., et al. Nat Aging. 2021; 1(6), 521-534. http://doi.org/10.1038/s43587-021-00070-2. 3. McKhann, G., et al. Alzheimers Dement. 2011; 7(3), 263-269. http://doi.org/10.1016/j.jalz.2011.03.005

LB06- POOLED ENGAGE/EMERGE INTEGRATED PLACEBO-CONTROLLED PERIOD AND LONG-TERM EXTENSION (LTE) TOPLINE RESULTS: SLOWER CLINICAL PROGRESSION AT WEEK 134 IN ADUCANUMAB-TREATED PATIENTS THAT BECAME AMYLOID PET NEGATIVE AT WEEK 78.

J. O'Gorman[1], J. Murphy[1], P. Montenigro[1], S. Showell[1], G. Dent[1], C. Rubel[1], R.M. Hutchison[1], T. Chen[1], K. Kandadi Muralidharan[1], K. Dawson[1] *(1. Biogen - Cambridge (United States))*

Background: ENGAGE and EMERGE were identically designed, Phase 3 studies that evaluated the efficacy and safety of low and high doses of aducanumab in patients with early Alzheimer's disease from baseline to week-78 [1]. Both studies showed dose- and time-dependent reductions in amyloid PET standardized uptake value ratio (SUVR) – demonstrating effective targeting of disease pathology. In addition to the effects on amyloid PET, EMERGE demonstrated clinical efficacy across all primary and secondary clinical endpoints. To better understand the relationship between amyloid clearance and long-term clinical efficacy we evaluated participants' clinical progression through the long-term extension (LTE) of ENGAGE/EMERGE stratified by amyloid PET status at week-78. **Methods:** Analyses are presented based on amyloid PET substudy data from ENGAGE/EMERGE LTE pooled low and high dose groups with week-78 amyloid PET SUVR data (N=456). The patient population was separated based on an amyloid PET SUVR cutoff at week-78, with amyloid plaque negative defined as PET SUVR ≤ 1.10 (n=130) and amyloid plaque positive defined as PET SUVR > 1.10 (n=326) [2]. All changes in clinical progression were evaluated from baseline through week-134 reported by the mean changes in Clinical Dementia Rating Sum of Boxes (CDR-SB), Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog13), and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for use in Mild Cognitive Impairment (ADCS-ADL-MCI). Results were based on descriptive statistics. **Results:** Over 78 weeks, participants that became amyloid plaque negative had a numerically slower decline as measured by mean changes in CDR-SB, MMSE, ADAS-Cog13, and ADCS-ADL-MCI. At Week 78 the mean change in CDR-SB in amyloid plaque negative participants was 0.89, and 1.39 in amyloid plaque positive participants. In the LTE phase, a similar trend for CDR-SB continued at week-106 (1.23 in amyloid plaque negative group vs. 1.97 in amyloid plaque positive group) and week-134 (1.68 in amyloid plaque negative group vs. 2.65 in amyloid plaque positive group). The magnitude of differences from baseline in favor of amyloid plaque negative participants was consistent across all cognitive endpoints through week-134. **Conclusion:** Pooled data of ENGAGE and EMERGE low and high dose group participants showed slower progression on the CDR-SB, MMSE, ADAS-Cog13, and ADCS-ADL-MCI for aducanumab-treated patients that reached amyloid plaque negative status at week-78 than those that remained amyloid plaque positive. LTE data of this pooled sample show a continued trend through week-134, providing evidence of a clinical benefit of aducanumab particularly for participants who achieve amyloid plaque negative status at week-78. In summary, this observed relationship between amyloid PET SUVR and clinical endpoints provides evidence of slower progression in both studies when amyloid is cleared below the SUVR threshold of 1.10. **Key words:** Aducanumab, Alzheimer's disease, EMERGE, ENGAGE. **Clinical Trial Registry:** NCT02484547, NCT02477800, https://clinicaltrials.gov. **Data**

Deposition: While the data described in this article are not publicly available, the authors and Biogen are supportive of data sharing. Proposals should be submitted through Vivli (https://vivli.org). For general inquiries, please contact datasharing@biogen.com. Biogen's data-sharing policies and processes are detailed on www.biogentrialtransparency.com. **Disclosures:** JO, JM, PM, SS, GD, CR, RMH, TC, KKM, and KD are employees and shareholders of Biogen Inc. **References:** 1. Budd Haeberlein, et al. J Prev Alzheimers Dis. 2022;9(2):197-210. https://doi.org/10.14283/jpad.2022.30; 2. Rajagovindan R, et al. Alzheimer's Dement. 2021;17:e057499. https://doi.org/10.1002/alz.057499

LB07- PRECIVITYAD2 BLOOD TEST: AN ANALYTICALLY AND CLINICALLY VALIDATED TEST COMBINING P-TAU217/NP-TAU217 AND AB42/40 RATIOS TO IDENTIFY BRAIN AMYLOID. K. Kirmess[1], M. Meyer[1], T. Wente-Roth[1], F. Irwin[1], M. Holubasch[1], S. Eastwood[1], V. Venkatesh[1], M. Irizarry[2], D. Verbel[2], P. Sachdev[2], S. Ito[2], K. Yarasheski[1], J. Braunstein[1], P. Verghese[1], T. West[1] *(1. C2N Diagnostics - St. Louis (United States), 2. Eisai Inc. - Nutley (United States))*

Background: In 2020, C2N Diagnostics introduced the PrecivityAD™ blood test as a clinical diagnostic tool under CLIA to aid in the evaluation of cognitive impairment. The test combines Aβ42/40 Ratio in blood, age, and ApoE proteotype to identify presence of amyloid in the brain as measured by amyloid PET. We investigated the benefit to diagnostic accuracy of combining Aβ42/40 Ratio with p-tau217/np-tau Ratio (p-tau217 Ratio), both measured in blood. **Methods:** Based on technology transfer from Washington University School of Medicine, C2N developed a high throughput mass spectrometry assay that measures the concentrations of both phosphorylated and non-phosphorylated tau peptides that contain Threonine-217 (p-tau217 and np-tau217). This assay allows calculation of the p-tau217 Ratio, the percent phosphorylation at this amino acid. Aβ42/40 and p-tau217 ratios were measured in samples from PARIS (a plasma collection IDEAS add-on study, N=224) and MissionAD (a phase 3 clinical trial, N=359). An algorithm (PrecivityAD2) was trained and cross-validated on the two combined cohorts to identify brain amyloidosis as defined by a Centiloid score greater than 25. **Results:** By combining Aβ42/40 and p-tau217 ratios, the APS2 (Amyloid Probability Score 2, the output of the PrecivityAD2 algorithm) was derived and had an AUC-ROC of 0.94 (95%CI: 0.92-0.96) for identifying amyloid positivity. This yielded an overall percent agreement with amyloid imaging of 88% (95%CI: 85-91%) using a binary cutoff value of 47.5. At this cutoff value, the positive percent agreement was 88% (sensitivity, 95%CI: 84-91%), and negative percent agreement was 89% (specificity, 95%CI: 84-92%). In these patients (with a prevalence of amyloid positivity of 53%), the PPV was 90% (95%CI: 86-93%), and NPV was 87% (95%CI: 82-90%). When comparing the diagnostic ability of the p-tau217 Ratio versus the p-tau217 concentration, the ratio had a statistically significant improvement in AUC-ROC over the raw concentration (0.94 for ratio, 0.91 for concentration, $p < 0.001$ by DeLong comparison). Although the AUC-ROC of the APS2 did not differ significantly from that of the p-tau217 Ratio alone to identify amyloid positivity, the APS2 model was found to be significantly more robust (Akaike Information Criteria [AIC] of 412 vs. AIC = 435). **Conclusion:** Combining Aβ42/40 and p-tau217 ratios measured in blood has excellent overall performance for determining amyloid PET status. Comparing p-tau217 concentration to p-tau217 Ratio shows that normalization of the concentration of p-tau217 to the amount of available tau at this epitope improves diagnostic performance. While p-tau217 Ratio and APS2 have similar overall diagnostic performance, combining Aβ42/40 and p-tau217 ratios into one predictor leads to an overall more robust model, which is likely to perform better in real-world clinical care and data sets orthogonal to this training data set.

LB08- EFFICACY OF DONANEMAB BY APOE4 CARRIER STATUS IN TRAILBLAZER-ALZ 2, A PHASE 3 RANDOMIZED CLINICAL TRIAL IN EARLY SYMPTOMATIC ALZHEIMER'S DISEASE. C.D. Evans[1], J.A. Zimmer[1], A.M. Wessels[1], M. Lu[1], J. Sparks[1], M. Mintun[1], D.A. Brooks[1], J.R. Sims[1] *(1. Eli Lilly and Company - Indianapolis (United States)*

Background: In TRAILBLAZER-ALZ 2, treatment with donanemab cleared brain amyloid plaques and significantly slowed disease progression in early symptomatic Alzheimer's disease (AD). Apolipoprotein E ε4 (APOE4) carrier status was identified as a risk factor for incidence of amyloid-related imaging abnormalities1 which could negatively impact treatment response and benefit-risk; therefore, an expanded view of the clinical efficacy benefit for APOE4 carriers is warranted. **Methods:** TRAILBLAZER-ALZ 2 (NCT04437511), a multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial, enrolled participants with early symptomatic AD, with amyloid and tau pathology assessed by positron-emission tomography. Participants (n=1736) were stratified by tau pathology (low-medium tau: n=1182; high tau: n=552) and randomized 1:1 to receive donanemab (n=860) or placebo (n=876) intravenously every 4 weeks (w) for 72w. Donanemab participants meeting amyloid clearance treatment completion criteria at 24w or 52w were switched to placebo infusions in a blinded procedure. The primary outcome was change from baseline in Integrated Alzheimer's Disease Rating Scale (iADRS) score at 76w in the low-medium tau or combined population. Key gated secondary outcomes included the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB), 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog13), Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL), and amyloid and tau PET. **Results:** In the low-medium tau population, APOE4 carriers (n=848, including homozygous n=190, heterozygous n=658) were younger with minimally higher baseline clinical assessments than non-carriers (n=330). Change in iADRS score at 76w was -5.39 with donanemab and -8.36 with placebo in APOE4 carriers (difference, 2.97; 95% CI, 1.37 to 4.57; P<0.001), representing a 36% slowing of disease progression versus -7.62 with donanemab and -11.65 with placebo in APOE4 non-carriers (difference, 4.03; 95% CI, 1.42 to 6.64; P=0.003), representing a 35% slowing of disease progression. Change in CDR-SB score at 76w was 1.09 with donanemab and 1.72 with placebo in APOE4 carriers (difference, -0.63; 95% CI, -0.94 to -0.32; P<0.001), representing a 37% slowing of disease progression versus 1.33 with donanemab and 2.13 with placebo in APOE4 non-carriers (difference, -0.80; 95% CI, -1.31 to -0.30; P=0.002), representing a 38% slowing of disease progression. The corresponding percent slowing for the ADAS-Cog13 and ADCS-iADL was 35% and 39% in APOE4 carriers and 28% and 41% in APOE4 non-carriers. Homozygous APOE4 carriers had numerically lower treatment effects than heterozygous or non-carriers on both the iADRS (% slowing for: homozygous: 30%; heterozygous: 37%; non-carrier: 35%) and CDR-SB (% slowing for: homozygous: 12%; heterozygous: 43%; non-carrier: 38%), but still favored treatment with donanemab. Finally, amyloid clearance was

robust amongst all donanemab-treated participants although numerically smallest in homozygous carriers likely due to ARIA-related dose pauses/discontinuation. **Conclusions:** Similar clinical efficacy of donanemab treatment is observed in both APOE4 carriers and non-carriers. **Key words:** Phase 3, amyloid-targeting therapy, monoclonal antibody, Apolipoprotein E ε4. **Clinical Trial Registry:** NCT04437511 (https://clinicaltrials.gov/) **Disclosures:** Cynthia D. Evans is an employee and minor shareholder at Eli Lilly and Company. **References:** 1. Sims JR, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512–527. doi:10.1001/jama.2023.13239

LB09- EXPLORATORY CLINICAL OUTCOMES FROM BIIB080 (MAPT ASO) PHASE 1B MULTIPLE ASCENDING DOSE AND LONG-TERM EXTENSION STUDY IN MILD ALZHEIMER'S DISEASE. N. Ziogas[1], S. Wu[1], Y. Li[1], L. Lin[1], A. Edwards[1], J. Collins[1], I. Tien[1], C. Mummery[2], R. Lane[3], C. Junge[3], J. Beaver[1], Y. Tian[1], J. Landen[1], D. Gallagher[1], M. Shulman[1] *(1. Biogen - Cambridge (United States), 2. Dementia Research Centre, National Hospital for Neurology and Neurosurgery, University College London - London (United Kingdom), 3. Ionis Pharmaceuticals - Carlsbad (United States))*

Background: BIIB080 is an antisense oligonucleotide (ASO) designed to promote degradation of MAPT pre-mRNA and prevent translation of all forms of tau protein[1]. BIIB080 was evaluated in participants with mild Alzheimer's disease (AD) in a randomized, double-blind, placebo-controlled, multiple ascending dose (MAD), phase 1b trial (13-week treatment period and 23-week posttreatment period) followed by a long-term extension (LTE; 48-week treatment period and up to 23-week posttreatment period)[2]. BIIB080 had substantial impact on tau biomarkers in the MAD and LTE, reducing soluble CSF tau and parenchymal tau pathology as measured by PET[3]. Here, we report exploratory clinical outcomes of the phase 1b study. **Methods:** Forty-six participants were randomized 3:1 across 4 cohorts to receive BIIB080 intrathecal bolus administrations or placebo. Active BIIB080 dose groups in the MAD received 10mg once every 4 weeks (Q4W), 30mg Q4W, 60mg Q4W, or 115mg Q12W. In the LTE, all participants received BIIB080 60mg Q12W or 115mg Q12W. High-dosed groups in the MAD (60mg Q4W and 115mg Q12W) transitioned seamlessly to the LTE; low-dosed groups (10mg Q4W and 30mg Q4W) had variable gaps of 5-19 months. The primary endpoint was safety and tolerability. Exploratory clinical outcomes included MMSE, FAQ, RBANS, and CDR. For the MAD, clinical outcomes were compared between BIIB080-treated groups and pooled placebo; for the LTE, BIIB080-treated groups were compared with external controls selected with propensity score matching. Statistical analyses were based on ANCOVA, adjusting for treatment group, baseline clinical score and baseline CDR-global score. **Results:** Differences in baseline clinical scores were seen between treated groups (low-dosed groups more advanced, high-dosed groups less advanced) vs pooled placebo. At the end of the MAD (Week 37), favorable differences were observed in high-dosed groups on MMSE, FAQ, and RBANS delayed memory scales vs placebo. In low-dosed groups, unfavorable group averages were observed relative to placebo. In the LTE, baseline characteristics were generally similar between BIIB080-treated groups and matched external controls. A favorable trend was seen on CDR-SB, MMSE, and FAQ at the end of the LTE (Week 100) vs matched external controls in participants receiving high doses throughout the study. Mixed results were seen across clinical scales in participants who switched from low dose in MAD to high dose in LTE. In the MAD and LTE, all treatment-emergent adverse events were reported as mild to moderate in severity, except 1 event of severe pain in lower extremity. Eight serious adverse events were reported; none were assessed by the investigator as related to study treatment or study procedure. No deaths were reported. **Conclusions:** BIIB080 phase 1b CSF biomarkers showed target engagement, and tau PET data suggested potential disease-modification[3]. Now we report numerical differences favoring BIIB080 for high-dosed groups on multiple cognitive and functional scales at completion of the MAD and LTE. Caution should be taken during interpretation given the small sample size and use of external controls in the LTE. These data support further investigation of the clinical efficacy and safety of BIIB080 in patients with MCI due to AD/mild AD in the CELIA phase 2 trial. **Key words:** tau, antisense, phase 1b, clinical outcomes. **Clinical Trial Registry:** phase 1b (NCT03186989); phase 2 (NCT05399888) https://clinicaltrials.gov. **Disclosures:** This study was sponsored by Biogen. Editorial support was provided by Meditech Media and funded by Biogen. NZ, SW, YL, LL, AE, JC, IT, JB, YT, JL, DG and MS are employees of Biogen and may hold stock. CM is a BIIB080 trial site Investigator. She is supported by the NIHR Biomedical Research Centre at UCLH and has acted as a consultant to Biogen, Roche, Eli Lilly, Prevail, Alnylam, Alector, Eisai, WAVE, PeerView, and Ionis. RL and CJ are employees of Ionis and may hold stock. **References:** 1. DeVos SL, et al. Sci Transl Med, 2017; 9(374). http://doi:10.1126/scitranslmed.aag0481. 2. Mummery CJ, et al. Nat Med, 2023; 29(6): 1437–1447. http:// doi:10.1038/s41591-023-02326-3. 3. Collins J, et al. Oral presentation at: AD/PD; March 28th- April 1st, 2023; Gothenburg, Sweden. Abstract 2506.

LB10- PHASE 1 SAFETY, TOLERABILITY, AND PHARMACOLOGICAL RESULTS OF ALN-APP, THE FIRST INVESTIGATIONAL RNA INTERFERENCE THERAPEUTIC IN DEVELOPMENT FOR EARLY-ONSET ALZHEIMER'S DISEASE. C. Mummery[1], S. Ducharme[2], J. Brosch[3], E. Vijverberg[4], L. Apostolova[3], A. Sostelly[5], S. Goteti[5], N. Makarova[5], A. Avbersek[6], W. Guo[5], B. Bostwick[5], S. Cohen[7] *(1. University College London - London (United Kingdom), 2. Douglas Mental Health University Institute, Department of Psychiatry and Montreal Neurological Institute, Department of Neurology & Neurosurgery, McGill University - Montreal, Quebec (Canada), 3. Indiana University School of Medicine - Indianapolis, Indiana (United States), 4. Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam UMC - Amsterdam (Netherlands), 5. Alnylam Pharmaceuticals - Cambridge, Massachusetts (United States), 6. Regeneron Pharmaceuticals, Inc. - Tarrytown, New York (United States), 7. Toronto Memory Program - Toronto, Ontario (Canada))*

Background: ALN-APP is a first-in-class, investigational, intrathecally administered RNA interference (RNAi) therapeutic that targets amyloid precursor protein (APP) mRNA to reduce APP production. In doing so, ALN-APP acts upstream of the amyloidogenic process by reducing production of amyloid-β fragments, which are known drivers of Alzheimer's disease, including early-onset Alzheimer's disease (EOAD). By reducing APP levels, ALN-APP may alter the cascade of events that result in neurodegeneration in EOAD, potentially slowing, halting, or reversing disease progression. **Methods:** ALN-APP-001 (NCT05231785) is an ongoing Phase 1 trial assessing safety and tolerability of ALN-APP in patients with EOAD (disease onset <65 years of age, Clinical Dementia Rating global score

of 0.5 or 1.0, Mini-Mental State Examination score >20). Part A is a randomized, double-blind, placebo-controlled, single ascending dose study. Patients are evaluated for 6 months, with additional follow-up of up to 6 months to achieve washout. The primary endpoint is frequency of adverse events (AEs). Secondary endpoints include evaluation of the pharmacological effects of ALN-APP. **Results:** Data describing the safety and pharmacodynamics of ALN-APP at up to 6 months (50mg cohort) and up to 10 months (75mg cohort) and available data on changes in exploratory disease-related biomarkers, including cerebrospinal fluid (CSF) Aβ40 and Aβ42 peptide levels, will be presented at the meeting. As of the June 29, 2023 data cutoff, 20 patients (mean [± standard deviation, SD] age, 61.3 [±5.3] years; 60.0% men; 75.0% white) were randomized to ALN-APP or placebo in 25mg (N=6, 2:1 randomization), 50mg (N=8, 3:1), and 75mg (N=6, 2:1) cohorts. Mean (±SD) duration on study was 8.2 (±2.0), 4.2 (±0.6), and 7.1 (±1.2) months for the 25mg/placebo, 50mg/placebo, and 75mg/placebo cohorts, respectively. At data cutoff, at least one AE was reported for 18/20 patients; all AEs were mild or moderate. No deaths, suspected unexpected serious adverse reactions, or study discontinuations occurred. Many AEs (23/50, 46.0%) were deemed related to the lumbar puncture procedure by the investigator. Mean CSF white blood cell and protein levels remained below the upper limit of normal for healthy individuals in all dose/placebo cohorts at all time points. Peak mean (± standard error of the mean, [SEM]) reduction from baseline in CSF soluble APP (sAPP) α level was 69.4% (±9.6) after a single 75mg dose of ALN-APP, with a maximum individual reduction of 83.7% at Month 2. Peak mean (±SEM) reduction from baseline in sAPPβ after a single 75mg dose was 81.8% (±6.3), with a maximum individual reduction of 89.9% at Month 2. Reductions were observed by Day 15 and sustained over 6 months after the 75mg dose (sAPPα, 55.5% [±7.5]; sAPPβ, 65.1% [±9.2] at Month 6). **Conclusion:** In Part A of this first clinical study of a novel central nervous system-administered RNAi therapeutic, ALN-APP has been well-tolerated and associated with rapid, robust, and durable reductions in CSF sAPPα and sAPPβ levels, reflecting target engagement of APP mRNA. Part A is ongoing and additional, longer-term data may provide more insights into duration of effect and the impact of ALN-APP on biomarkers associated with Alzheimer's disease progression. **Key words:** Phase 1, RNA interference, Alzheimer's disease. **Disclosures:** SG, NM, WG and BB are employees of and shareholders in Alnylam Pharmaceuticals. AA is an employee of Regeneron Pharmaceuticals, Inc. AS is an employee of Alnylam Pharmaceuticals and shareholder in Alnylam Pharmaceuticals and Roche. CM has been a consultant for or received grants honoraria from Biogen, Roche, IONIS Pharmaceuticals, Prevail Therapeutics, Lilly, Alector, Eisai and PeerView. EV has been a principal investigator or consultant for DIAN TU trials, AC immune, Alnylam Pharmaceuticals, CogRX therapeutics, New Amsterdam Pharma, Janssen, UCB, Roche, Vivoryon, ImmunoBrain, Treeway, ReMynd GemVax, Alector, Eli Lilly, Biogen, Fuij Film Toyama, Vigil Neuroscience, and Roche. JB has received research support from Alnylam Pharmaceuticals, Athira, Biogen, Eisai America Inc, Eli Lilly and Company, University of Southern California, Washington University, ABBVIE, Avanir Pharmaceuticals, Axoyant SCI, Green Valley Pharmaceuticals co, F. Hoffman-La Roche Ltd, Takeda Pharmaceuticals, and the University of Southern California. LA has provided consultation to Eli Lilly, Biogen, Genentech, GE Healthcare, Eisai, Roche Diagnostics, Siemens, Alnylam Pharmaceuticals, Corium, Otsuka, Two Labs, FL Dept Health, and the NIH Biobank. LA receives the following research support: NIA U01 AG057195, NIA R01 AG057739, NIA P30 AG010133, Alzheimer Association LEADS GENETICS 19-639372, Alzheimer Association SG-23-1061716, Roche Diagnostics RD005665, AVID Pharmaceuticals and Life Molecular Imaging. LA has received honoraria for participating in independent data safety monitoring boards and providing educational CME lectures and programs. SC has received research support or served as an advisor for AbbVie, AgeneBio, Alector, Alnylam Pharmaceuticals, Alzheon, Davos Alzheimer's Collaborative, Eisai, Eli Lilly, Global Alzheimer's Platform Foundation (GAP), Janssen, Novo Nordisk, RetiSpec, Roche, UCB, Vielight, Alzheimer Society of Toronto, Biogen, Cassava Sciences, Cogstate, Cognivue, INmune Bio, ProMIS Neurosciences, and Voices of Alzheimer's. SD has been a consultant or received research funding or travel support from Alnylam Pharmaceuticals, Biogen, Janssen, Novo Nordisk, and Wave Life Sciences, IntelGenX, AI Therapeutics, Eisai, Prevail Therapeutics/Eli Lilly, and QuRALIS.

LB11- RAPID AMYLOID CLEARANCE AND EFFICACY: RESULTS FROM TRAILBLAZER-ALZ 2, A PHASE 3 STUDY OF DONANEMAB FOR TREATMENT OF EARLY ALZHEIMER'S DISEASE. S. Shcherbinin[1], M. Lu[1], J. Wang[1], H. Wang[1], P. Hauck[1], I. Gueorguieva[1], D. Brooks[1], J. Sims[1], M. Mintun[1], E. Collins[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Background: In TRAILBLAZER-ALZ 2, a randomized, double blind, placebo-controlled phase 3 trial, donanemab significantly slowed clinical progression in participants with early symptomatic Alzheimer's disease (AD) with amyloid and tau pathology. The aim of this analysis was to explore the impact of rapid amyloid clearance (rAC) on downstream biomarkers and clinical efficacy. **Methods:** In TRAILBLAZER-ALZ 2, participants were randomized to receive (1:1) donanemab (n=860) or placebo (n=876) intravenously every 4 weeks (w) for 72w. Donanemab-treated participants were determined as achieving rAC during the trial if the brain amyloid level was below 24.1 Centiloids (CL) at either 24w or 52w as measured by amyloid PET (positron emission tomography). Propensity score matching method was used to select matched placebo-treated participants comparable with donanemab-treated participants with rAC in terms of baseline age, amyloid level, global tau level, and number of E4 alleles (mPlacebo). At 76w, the following biomarker and clinical measurements were compared between the two matched groups: tau PET, plasma P-tau217, plasma glial fibrillary acidic protein (GFAP), integrated AD Rating Scale (iADRS), and Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB). **Results:** The rAC group had significantly less accumulation of tau (AD-signature-weighted neocortical SUVr as determined by PET) at 76w compared to mPlacebo [adjusted mean (SE) change from baseline: 0.0684 (0.006) for mPlacebo, and 0.0461 (0.006) for rAC, difference (SE): -0.0223 (0.008), P=0.007]. The adjusted mean difference (SE) from mPlacebo was -0.0109 (0.006) (P=0.084) in the frontal region, -0.0224 (0.008) (P=0.003) in the parietal region, and -0.0266 (0.008) P=0.002) in the lateral temporal region. The adjusted mean change from baseline of plasma P-tau217 and GFAP were both significantly different from mPlacebo (<0.001). Adjusted mean change in iADRS score (SE) at 76w was -11.5 (0.62) in the mPlacebo group, and -7.6 (0.62) in the rAC group [adjusted mean difference from mPlacebo, 3.86 (0.89) P<0.001], representing a 33.6% slowing of disease progression. The adjusted mean change in CDR-SB score (SE) at 76w was 2.11 (0.11) in the mPlacebo group, and

1.39 (0.11) in the rAC group [adjusted mean difference from mPlacebo, -0.72 (0.16) P<0.001], representing a 34.3% slowing of disease progression. **Conclusion:** Donanemab-treated participants with rAC had significantly less tau accumulation in composite as well as parietal and lateral temporal regions, and greater reduction in P-tau217 and GFAP than mPlacebo. In addition, there was less clinical progression in the rAC group compared to mPlacebo controls. Taken together, these results demonstrate the downstream effect of donanemab-induced rAC on biomarker and clinical efficacy measurements. **Key words:** Donanemab, Alzheimer's disease, Amyloid, Tau. **Clinical Trial Registry:** https://clinicaltrials.gov/:NCT04437511. **Disclosures:** All authors are employees and minor shareholders of Eli Lilly and Company. Eli Lilly and Company are developing patents relevant to this research.

LB12- REDUCED CAREGIVER DISTRESS ASSOCIATED WITH NEUROPSYCHIATRIC SYMPTOMS IN EMERGE, A PHASE 3, DOUBLE-BLIND CLINICAL TRIAL OF ADUCANUMAB IN PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE. J. Cummings[1], S. Cohen[2], J. Murphy[3], P. He[4], C. De Moor[5], F. Forrestal[3], J. Harrison[6,7], J. Jaeger[8,9], C.J. Mummery[10], A.P. Porsteinsson[11], M. Potashman[12], Y. Tian[3], L. Yang[13], J. O'gorman[3], S. Budd Haeberlein[14]
(1. Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, UNLV - Las Vegas (United States), 2. Toronto Memory Program - Toronto (Canada), 3. Biogen Inc. - Cambridge (United States), 4. Takeda Pharmaceutical Company Limited - Boston (United States), 5. Certara - Princeton (United States), 6. Scottish Brain Sciences - Edinburgh (United Kingdom), 7. Alzheimercentrum of the Amsterdam UMC - Amsterdam (Netherlands), 8. CognitionMetrics, LLC - Stamford (United States), 9. Albert Einstein College of Medicine - New York (United States), 10. Dementia Research Centre, Queen Square Institute of Neurology, University College London - London (United Kingdom), 11. University of Rochester School of Medicine and Dentistry - Rochester (United States), 12. Biohaven Pharmaceuticals Inc - New Haven (United States), 13. Alnylam Pharmaceuticals - Cambridge (United States), 14. Enigma Biomedical USA - Nashville (United States))

Background: Psychiatric disturbances are prevalent in patients with early symptomatic Alzheimer's disease (AD) and worsen over time. These disturbances significantly affect the lives of patients and their care partners and are primary contributors to diminished quality of life for both groups of individuals throughout the course of the disease. EMERGE (NCT02484547) was 1 of 2 Phase 3 trials that evaluated the efficacy and safety of aducanumab in participants with early AD. In EMERGE, aducanumab treatment resulted in significantly less progression on all prespecified primary and secondary clinical endpoints [1]. Changes from baseline on the Neuropsychiatric Inventory Questionnaire (NPI-10) was a tertiary endpoint in EMERGE. It is an informant-based assessment that evaluates 10 neuropsychiatric symptoms in patients with AD and measures caregiver distress related to these symptoms. We previously reported that aducanumab treatment was associated with a reduction in AD-related behavioral and psychiatric symptoms, as measured by the NPI-10.2 To further explicate the clinical relevance of this finding, the present study focused on the caregiver distress component of the NPI-10 in EMERGE. **Methods:** Participants with early AD, defined as mild cognitive impairment due to AD or mild AD dementia, and positron emission tomography–confirmed amyloid pathology were included in the study. Participants were stratified by APOE ε4 carrier status and randomized (1:1:1) to receive low-dose aducanumab, high-dose aducanumab, or placebo. Post-hoc item-level analysis of the NPI-10 caregiver distress items at Week 78 was conducted using mixed model for repeated measures. The data from the aducanumab high-dose group (10-mg/kg target dose) and the corresponding placebo group from EMERGE are reported. **Results:** Results are provided as treatment differences (aducanumab adjusted mean−placebo adjusted mean) and change from baseline (Week 78 caregiver distress item score−baseline caregiver distress item score): negative values indicate positive treatment effects and less disease progression. There was a drug-placebo difference on the overall NPI-10 caregiver distress score, with an 84% reduction observed over 78 weeks. An aducanumab treatment effect was evident on several individual NPI-10 caregiver distress items (eg, −0.10+ drug-placebo difference), notably caregiver distress associated with agitation/aggression, apathy/indifference, aberrant motor behavior, and delusion (drug-placebo difference, −0.10 to −0.33). The most notable drug-placebo difference was on agitation/aggression caregiver distress (−0.33 treatment difference). Caregivers in the placebo group had more distress related to agitation (0.26 adjusted mean change from baseline) than caregivers in the aducanumab group, who reported improved distress levels (−0.07 adjusted mean change from baseline). Improved caregiver distress was linked to symptom reduction in participants receiving high-dose aducanumab versus placebo; there was a −0.54 treatment difference in agitation/aggression behaviors and a −0.32 treatment difference in apathy/indifference behaviors, as reported previously [2]. **Conclusion:** Aducanumab 10 mg/kg led to a reduction in caregiver distress and was associated with a reduction in neuropsychiatric symptoms; this supports the clinical meaningfulness of aducanumab treatment. Previous analysis demonstrated an aducanumab effect in reducing agitation/aggression symptoms in patients [2]. Taken together, these findings suggest that aducanumab produces a complementary effect on patients and caregivers that translates into greater preservation of quality of life for both groups of individuals. **Key words:** Aducanumab; NPI-10; Caregiver distress; Alzheimer's disease. **Clinical Trial Registry:** NCT02484547; https://clinicaltrials.gov. **Data Deposition:** While the data described in this article are not publicly available, the authors and Biogen are supportive of data sharing. Proposals should be submitted through Vivli (https://vivli.org). For general inquiries, please contact datasharing@biogen.com. Biogen's data-sharing policies and processes are detailed on www.biogentrialtransparency.com. **Disclosures:** JM, FF, YT, and JO are employees and shareholders of Biogen Inc. PH, CDM, MP, LY, and SBH were employees of Biogen Inc. at the time of this study. JC has provided consultation to AB Science, Acadia, Alkahest, Alpha Cognition, AriBio, Avanir, Axsome, Beren Therapeutics, Biogen Inc., Biohaven, Cassava, Cerecin, Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, Grifols, Janssen, LSP/EQT, Merck, NervGen, Novo Nordisk, Oligomerix, ONO, Otsuka, PRODECO, reMYND, Renew, Resverlogix, Roche, Signant Health, Suven, United Neuroscience, and Unlearn AI pharmaceutical, assessment, and investment companies. SC was an ENGAGE trial site Investigator and an aducanumab Steering Committee Member. She is a consultant to Alnylam, Biogen Inc., Cassava Sciences, Cognivue, Cogstate, Eisai, Eli Lilly, INmune Bio, Lundbeck, ProMIS Neuroscience, RetiSpec, and Roche (no personal fees) and receives research support (paid to institution) from AbbVie, AgeneBio, Alector, Alnylam, Anavex, Biogen

Inc., Cassava Sciences, Eisai, Eli Lilly, Janssen, RetiSpec, Roche, and Vielight. JH is a full-time employee of Scottish Brain Sciences and holds shares in this company. He also reports receipt of personal fees in the past 2 years from Actinogen, Advantage, AlzeCure, AstraZeneca, Athira Therapeutics, Axon Neuroscience, Axovant, BIAL Biotech, Biogen Idec, Boehringer Ingelheim, Brands2life, Cerecin, Cognito, Cognition Therapeutics, COMPASS Pathways, CuraSen, EIP Pharma, Eisai, GFHEU, Heptares, ki:elements, KyNexis, Lundbeck, Lysosomal Therapeutics, Neurotrack, the NHS, Novartis, Novo Nordisk, Nutricia, Prothena, Recognify, Regeneron, reMYND, Roche, Rodin Therapeutics, Sanofi, Signant, Stoke Therapeutics, Syndesi Therapeutics, Takeda, Transposon Therapeutics, Treeway, Virogenics, Vivoryon Therapeutics, and Winterlight Labs. Additionally, he holds stock options in Neurotrack Inc. and is a joint holder of patents with MyCognition Ltd. JJ is the owner and President of CognitionMetrics, LLC, which received fees from Biogen Inc. in consideration of scientific consulting services. CM is a BIIB080 trial site Investigator. She is supported by the NIHR Biomedical Research Centre at UCLH and has acted as a consultant to Biogen, Roche, Eli Lilly, Prevail, Alnylam, Alector, Eisai, WAVE, PeerView, and Ionis. AP reports personal fees from Acadia Pharmaceuticals, Athira, Biogen Inc., Cognitive Research Corp, Eisai, Functional Neuromodulation, IQVIA, Lundbeck, Medscape, Novartis, ONO Pharmaceuticals, and Xenon and grants to his institution from Alector, Athira, Biogen Inc., Cassava, Eisai, Eli Lilly, Genentech/Roche, Vaccinex, the NIA, the NIMH, and the DOD.
References: 1. Budd Haeberlein S, et al. J Prev Alzheimers Dis 2022; 9 (2): 197–210. http://doi.org/10.14283/jpad.2022.30. 2. Poster presented at: Alzheimer's Association International Conference 2021; July 26-30, 2021; Denver, CO. Abstract P57619.

LB13- TIME SAVINGS ESTIMATES FOR DONANEMAB TRAILBLAZER-ALZ PHASE 2 & PHASE 3 STUDIES.

S.P. Dickson[1], S.B. Hendrix[1], L.L. Raket[2], S. Chatterjee[2], J. Christensen[1], B. Haaland[1], J. Sparks[2], J.R. Sims[2], D.A. Brooks[2], M.A. Mintun[2] *(1. Pentara Corporation - Salt Lake City (United States), 2. Eli Lilly and Company - Indianapolis (United States))*

Background: One of the key challenges in any study is determining a meaningful metric by which to judge success. In clinical trials, the outcomes used are often different than those used in clinical practice. It is challenging to know how many points on each scale correspond to a minimal clinically important difference without formal studies, leaving a large interpretability gap in study results. This gap is compounded in complex diseases like Alzheimer's disease, which affects multiple domains, each measured by different outcomes. These challenges are critical in longitudinal studies of progressive diseases and can all be addressed by converting outcomes to a time scale. This conversion is particularly important for disease modifying treatments since it allows multiple outcomes measured on multiple domains to be presented on a unified scale that is immediately interpretable and meaningful to all stakeholders. **Methods:** We use clinical trial results from TRAILBLAZER-ALZ 1 and TRAILBLAZER-ALZ 2, the phase 2 and phase 3 studies, to assess the time savings with 18 months of donanemab treatment. For TRAILBLAZER-ALZ 2, the group with low-medium baseline tau was analyzed. Results are calculated on ADAS-Cog, ADCS-iADL, and CDR-SB then combined across outcomes on the time scale to produce a single comprehensive summary of time savings across all domains of Alzheimer's disease called the global time component test (gTCT). The proportion of subjects experiencing more than a 12-month time savings are calculated using subject-level conversions, which compares active subjects to comparable placebo subjects. **Results:** The gTCT for TRAILBLAZER-ALZ 1 and TRAILBLAZER-ALZ 2 showed consistent results with both falling between 5 and 6 months. The combined time savings across the three key endpoints for TRAILBLAZER-ALZ 1 was 5.22 ($p = 0.04$), while for TRAILBLAZER-ALZ 2 it was 5.27 months ($p < 0.00001$) over 18 months of treatment. On a per person analysis, nearly half of the active patients were estimated to have no clinical progression over one year (Sims et al. JAMA 2023). Looking at the time savings on a per person basis, approximately one quarter of the active subjects (compared to about 10% in the placebo arm) experienced greater than 12 months of time savings over 18 months compared to the expected placebo disease progression. **Conclusions:** We demonstrate that the estimated time savings with donanemab is consistent across domains and between studies of donanemab, with nearly 6 months of delay in disease progression including delay of important milestones (e.g. losing the ability to hold a job or drive). The summary level and subject level estimates are comparable and meaningful. We demonstrated additional flexibility of analysis of the subject-level TCT. The consistency of these results provides further evidence that the effect of donanemab on Alzheimer's disease is real, disease-modifying, and clinically meaningful.

LB14- EVIDENCE THAT LUMIPULSE G PTAU217 PLASMA MEASUREMENTS HAVE THE ABILITY TO QUANTITATIVELY ASSESS TAU STAGE AND BURDEN.

A. Bannon[1], E. Stage[1], M. Vandijck[2], F. Desimone[2], J. Lawson[3], L. Ward[4], V. Doré[5], J. Doecke[6], C. Fowler[4], J. Mejan-Fripp[6], C. Rowe[4] *(1. AbbVie Inc - North Chicago (United States), 2. Fujirebio - Antwerp (Belgium), 3. Fujirebio - Malvern (United States), 4. The Florey Institute of Neuroscience and Mental Health - Melbourne (Australia), 5. CSIRO - Melbourne (Australia), 6. CSIRO - Brisbane (Australia))*

Background: The use of plasma p-tau217 to accurately predict amyloid positivity has been established from previously published and presented data. However, data suggesting plasma p-tau217's utility in predicting tau burden, as measured with tau PET, has been much more limited. **Methods:** In this work, we utilized plasma samples from 387 participants in the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) with both amyloid and tau PET data. Participants were clinically classified as cognitively unimpaired (CU), mild cognitive impairment (MCI) or dementia due to Alzheimer's Disease (AD). Amyloid PET (18F-NAV4694) positivity was defined as Centiloid (CL) values ≥ 25. Tau PET (18F-MK-6240) burden was defined by adopting a Braak staging scheme and the metatemporal region of interest (ROI) as previously published1,2. Regional tau PET positivity was defined as two standard deviations above the mean SUVR of cognitively unimpaired amyloid negative subjects. The fluid analytes measured were plasma p-tau217 and Ab42/Ab40 ratio using reagents generated by Fujirebio and tested on the fully automated immunoassay Lumipulse® platform at Fujirebio (Malvern, PA). **Results:** For plasma p-tau217, concentrations (pg/ml; mean ± SEM) in CU, MCI and AD subjects were 0.18 ± 0.01, 0.36 ± 0.03 and 0.63 ± 0.03, respectively. A receiver operating characteristic (ROC) curve for plasma p-tau217 classifying amyloid PET positivity had an AUC of 0.93 and the correlation with CL was $r = 0.61$, while the AUC for plasma Ab42/Ab40 was 0.84. For tau PET, plasma p-tau217 showed a stepwise increase in concentration (pg/ml; mean ± SEM)

across the Braak stages; Braak stage 0 = 0.15 ± 0.01; Braak I = 0.22 ± 0.05; Braak II = 0.23 ± 0.02 Braak III = 0.30 ± 0.04; Braak IV = 0.49 ± 0.04; Braak V = 0.63 ± 0.04; and Braak VI = 0.88 ± 0.05. ROC curve analysis for classifying tau PET positivity for meta temporal ROI had AUC = 0.93 and the correlation with SUVR was r = 0.79. **Conclusions:** In this cohort, plasma p-tau217 measured on the Lumipulse®, an automated high-throughput immunoassay platform, was not only a strong predictor for both amyloid and tau PET positivity/negativity but also shows promise for quantifying the tau level and stage. **Key words:** plasma p-tau217, amyloid PET, tau PET, Alzheimer's disease, mild cognitive impairment. **Disclosures:** Anthony Bannon, employee of and shareholder in AbbVie Inc; Edwin Stage, employee of AbbVie Inc; Manu Vandijck, employee of Fujirebio; Francesca DeSimone, employee of Fujirebio; John Lawson, employee of Fujirebio; Larry Ward, no disclosures; Vincent Doré, no disclosures; James Doecke, no disclosures; Christopher Fowler, no disclosures; Jurgen Mejan-Fripp, no disclosures; Chrisopher Rowe, Scientific Advisory Board for Enigma Biomedical and Prothena. Research grants to institution from Cerveau Technologies. **References:** Pascoal TA, et al, 18F-MK-6240 PET for early and late detection of neurofibrillary tangles, Brain, 2020 https://doi.org/10.1093/brain/awaa180. Krishnadas N, et al. Rates of regional tau accumulation in ageing and across the Alzheimer's disease continuum: An AIBL 18F-MK6240 PET study. eBioMedicine 2023 doi.org/10.1016/j.ebiom.2023.104450

LB15- AN EXPLORATION OF AMYLOID REMOVAL MEASURES IN RELATION TO CLINICAL BENEFIT: A REVIEW AND META-REGRESSION OF ANTI-AMYLOID TRIALS IN AD. M.A. Scelsi[1], J. Jackson[1], M. Tonietto[2], G. Klein[2], C. Lane[1], J. Smith[1], R. Doody[2], P. Delmar[2] *(1. Roche Products Ltd - Welwyn Garden City (United Kingdom), 2. F. Hoffman-La Roche AG - Basel (Switzerland))*

Background: Recent results of anti-amyloid trials have raised the question how best to characterize the relationship between amyloid PET and clinical endpoints. In particular, it is not clear whether the amount of amyloid reduction over a certain period, or the absolute amyloid level reached at a certain timepoint is most important. This question arises with the results from the CLARITY-AD and GRADUATE trials: despite similar levels of amyloid reduction on PET imaging at their final timepoints, the former, (i.e. CLARITY-AD) met its primary clinical endpoint whereas the latter (i.e. the GRADUATE studies) did not. We attempt to address these questions through statistical modelling of publicly available data from several anti-amyloid trials. **Methods:** We conducted a literature review on clinical trials for aducanumab [1], crenezumab [2], donanemab [3], gantenerumab [4-5], lecanemab [6], and extracted multiple PET and CDR-SB metrics reported for twelve dose arms in nine studies. The Centiloid scale was used to compare results using different tracers; study-level PET summaries were extracted both at an "early" timepoint (approximately 12 months before end-of-study) and at end-of-study. PET summaries included: baseline Centiloid; absolute Centiloid value in treated arm at timepoints specified; change from baseline in Centiloid in treated arm; difference treated-placebo in Centiloid change from baseline; proportion of patients below amyloid positivity threshold at early and late timepoints. We estimated Spearman's correlation between PET and CDR-SB metrics, and fitted linear models relating end-of-study relative reduction (RR) in CDR-SB to either early or late PET metrics. Lastly, we predicted each study result based on all the other studies, and compared predictions with the observed results. **Results:** The RR in CDR-SB at end-of-study showed a moderate correlation with the difference treated-placebo in Centiloid change from baseline (Spearman's rho=-0.55, 95% CI: [-0.85, 0.04], p=0.071). A similar correlation was observed when considering the absolute Centiloid at end-of-study (rho=-0.59, 95% CI: [-0.87, -0.02], p=0.049) or the percentage below threshold at end-of-study (rho=0.56, 95% CI: [-0.02, 0.85], p=0.06). The correlation numerically increased when the early timepoint was considered for all PET metrics, and was highest for early absolute Centiloid (rho=-0.68, 95% CI: [-0.90, -0.17], p=0.019) and early proportion below positivity threshold (rho=0.65, 95% CI: [0.12, 0.89], p=0.023). In a leave-one-out prediction of CDR-SB RR, the lowest difference between the predicted and observed value was achieved using either early Centiloid value or early proportion below positivity threshold as the predictor. Additional expected data will be incorporated into this analysis for the presentation. **Conclusion:** In a meta-regression analysis of amyloid-directed mAb studies, a higher proportion achieving amyloid negativity and a lower amyloid plaque level at an early timepoint displayed numerically higher correlations with CDR-SB RR compared to other amyloid PET metrics. These results are consistent with the hypothesis that early reduction of amyloid to below positivity threshold may be important for clinical benefit. **Disclosures:** M. A. Scelsi and J. Jackson are full-time employees of Roche Products Ltd; C. Lane and J. Smith are full-time employees and shareholders of Roche Products Ltd; M. Tonietto, G. Klein, R. Doody, and P. Delmar are full-time employees and shareholders of F. Hoffmann-La Roche AG. **References:** 1. Budd Haeberlein, Samantha, et al. «Two randomized phase 3 studies of aducanumab in early Alzheimer's disease.» The Journal of Prevention of Alzheimer's Disease 9.2 (2022): 197-210. 2. Ostrowitzki, Susanne, et al. «Evaluating the safety and efficacy of crenezumab vs placebo in adults with early Alzheimer disease: Two Phase 3 randomized placebo-controlled trials.» JAMA neurology 79.11 (2022): 1113-1121. 3. Mintun, Mark A., et al. «Donanemab in early Alzheimer's disease.» New England Journal of Medicine 384.18 (2021): 1691-1704. 4. Ostrowitzki, Susanne, et al. «A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease.» Alzheimer's research & therapy 9.1 (2017): 1-15. 5. Bateman, Randall, et al. "Two phase 3 trials of gantenerumab in early Alzheimer's Disease", submitted for publication. 6. Van Dyck, Christopher H., et al. «Lecanemab in early Alzheimer's disease.» New England Journal of Medicine 388.1 (2023): 9-21.

LB16- PROGRESSION ANALYSIS ON COGNITIVE, FUNCTIONAL, AND BEHAVIORAL ENDPOINTS IN EMERGE, A PHASE 3, DOUBLE-BLIND CLINICAL TRIAL OF ADUCANUMAB IN PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE. S. Cohen[1], J. Cummings[2], J. Murphy[3], P. He[4], M. Levitchi Benea[5], F. Forrestal[3], J. Harrison[6,7], J. Jaeger[8,9], C.J. Mummery[10], A.P. Porsteinsson[11], M. Potashman[12], L. Yang[13], S. Wu[3], Y. Tian[3], S. Budd Haeberlein[14]
(1. Toronto Memory Program - Toronto (Canada), 2. University of Las Vegas - Las Vegas (United States), 3. Biogen Inc. - Cambridge (United States), 4. Takeda Pharmaceutical Company Limited - Boston (United States), 5. Fulcrum Therapeutics - Cambridge (United States), 6. Scottish Brain Sciences - Edinburgh (United Kingdom), 7. Alzheimercentrum of the AUmC - Amsterdam (Netherlands), 8. CognitionMetrics, LLC - Stamford (United States), 9. Albert Einstein College of Medicine - New York (United States), 10. Dementia Research Centre, Queen Square Institute of Neurology, University College London - London (United Kingdom), 11. University of Rochester School of Medicine and Dentistry - Rochester (United States), 12. Biohaven Pharmaceuticals, Inc. - New Haven (United States), 13. Alnylam Pharmaceuticals - Cambridge (United States), 14. Enigma Biomedical USA - Nashville (United States))

Background: EMERGE (NCT02484547) was 1 of 2 Phase 3 trials that evaluated the efficacy and safety of aducanumab, an anti–amyloid-β human monoclonal antibody, in participants with early Alzheimer's disease (AD). Aducanumab treatment resulted in significantly less progression on all prespecified primary (Clinical Dementia Rating-Sum of Boxes [CDR-SB]) and secondary (Mini-Mental State Examination [MMSE], Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 [ADAS-Cog13], and Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment [ADCS-ADL-MCI]) endpoints [1]. No definitive standard exists to determine clinical meaningfulness for treatment effects in early-stage AD. However, the odds of progression at the individual participant level and a decreased risk of progression can be considered indicators of clinical meaningfulness [2,3]. Therefore, a post hoc analysis was conducted in EMERGE to further explore the treatment effect on mitigating the risk of clinical decline, as measured by global and functional endpoints. **Methods:** Participants with mild AD dementia or mild cognitive impairment due to AD and positron emission tomography (PET)-confirmed amyloid pathology were randomized (1:1:1) to receive low-dose aducanumab, high-dose aducanumab, or placebo. To assess aducanumab's effect on delaying clinical progression at the individual participant level, post hoc progression analyses of CDR-SB, MMSE, ADAS-Cog13, and ADCS-ADL-MCI were conducted. To best characterize the population enrolled in EMERGE, the progression analysis employed a data-driven approach to determine the threshold for each measure. The odds ratios for progression for high-dose aducanumab versus placebo were calculated for these threshold cut points. Only the high-dose aducanumab group (and corresponding placebo group data) are reported here, as the high-dose group reached the 10-mg/kg target dose and demonstrated a positive outcome [1]. **Results:** In the EMERGE study, clinical progression was identified as a ≥ 0.5-point increase on the CDR-SB, ≥ 1-point decrease on the MMSE, ≥ 3-point increase on the ADAS-Cog13, and ≥ 3-point decrease on the ADCS-ADL MCI. Based on these thresholds, 58.7%-80.5% and 49.0%-73.9% of participants in the placebo group and high-dose aducanumab group, respectively, were categorized as progressors at Week 78. Participants treated with aducanumab were less likely to experience the same level of disease progression, with an odds ratio of 0.70 on the CDR-SB (95% CI, 0.479-1.010), 0.68 on the MMSE (95% CI, 0.473-0.988), 0.75 on the ADAS-Cog13 (95% CI, 0.542-1.046), and 0.67 on the ADCS-ADL MCI (95% CI, 0.491-0.924), indicating a 25%-33% lower risk of disease progression with high-dose aducanumab compared with placebo over 78 weeks as measured by a variety of cognitive and functional instruments. **Conclusions:** High-dose aducanumab demonstrated broad and consistent treatment effects on slowing clinical progression across multiple clinical endpoints. The current findings indicate a decreased risk of progression with high-dose aducanumab at the individual participant level in an 18-month treatment period. This delay in progression is clinically meaningful, especially in the early symptomatic phase of AD, before disease worsening substantially impacts patient and care partner quality of life. Early intervention enables longer preservation of daily activities and cognition for patients, with both patients and their care partners gaining valuable time. **Key words:** EMERGE, Progression analysis, Alzheimer's disease, Aducanumab. **Clinical Trial Registry:** NCT02484547; https://clinicaltrials.gov. **Data Deposition:** While the data described in this article are not publicly available, the authors and Biogen are supportive of data sharing. Proposals should be submitted through Vivli (https://vivli.org). For general inquiries, please contact datasharing@biogen.com. Biogen's data-sharing policies and processes are detailed on www.biogentrialtransparency.com. **Disclosures:** JM, FF, YT, and SW are employees and shareholders of Biogen Inc. PH, MLB, MP, LY, and SBH were employees of Biogen Inc. at the time of this study. SC was an ENGAGE trial site Investigator and an aducanumab Steering Committee Member. She is a consultant to Alnylam, Biogen Inc., Cassava Sciences, Cognivue, Cogstate, Eisai, Eli Lilly, INmune Bio, Lundbeck, ProMIS Neuroscience, RetiSpec, and Roche (no personal fees) and receives research support (paid to institution) from AbbVie, AgeneBio, Alector, Alnylam, Anavex, Biogen Inc., Cassava Sciences, Eisai, Eli Lilly, Janssen, RetiSpec, Roche, and Vielight. JC has provided consultation to AB Science, Acadia, Alkahest, Alpha Cognition, AriBio, Avanir, Axsome, Beren Therapeutics, Biogen Inc., Biohaven, Cassava, Cerecin, Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, Grifols, Janssen, LSP/EQT, Merck, NervGen, Novo Nordisk, Oligomerix, ONO, Otsuka, PRODEO, reMYND, Renew, Resverlogix, Roche, Signant Health, Suven, United Neuroscience, and Unlearn AI pharmaceutical, assessment, and investment companies. JH is a full-time employee of Scottish Brain Sciences and holds shares in this company. He also reports receipt of personal fees in the past 2 years from Actinogen, Advantage, Alzecure, AstraZeneca, Athira Therapeutics, Axon Neuroscience, Axovant, BIAL Biotech, Biogen Idec, Boehringer Ingelheim, Brands2life, Cerecin, Cognito, Cognition Therapeutics, COMPASS Pathways, CuraSen, EIP Pharma, Eisai, GFHEU, Heptares, ki:elements, KyNexis, Lundbeck, Lysosomal Therapeutics, Neurotrack, the NHS, Novartis, Novo Nordisk, Nutricia, Prothena, Recognify, Regeneron, reMYND, Roche, Rodin Therapeutics, Sanofi, Signant, Stoke Therapeutics, Syndesi Therapeutics, Takeda, Transposon Therapeutics, Treeway, Virogenics, Vivoryon Therapeutics, and Winterlight Labs. Additionally, he holds stock options in Neurotrack Inc. and is a joint holder of patents with MyCognition Ltd. JJ is the owner and President of CognitionMetrics, LLC, which received fees from Biogen Inc. in consideration of scientific consulting services. CJM was an ENGAGE trial site Investigator and an aducanumab Steering Committee Member. She is supported by the NIHR Biomedical

Research Centre at UCLH and has acted as a consultant to Biogen Inc., Roche, Eli Lilly, Prevail, Alnylam, PeerView, and Ionis. AP reports personal fees from Acadia Pharmaceuticals, Athira, Biogen Inc., Cognitive Research Corp, Eisai, Functional Neuromodulation, IQVIA, Lundbeck, Medscape, Novartis, ONO Pharmaceuticals, and Xenon and grants to his institution from Alector, Athira, Biogen Inc., Cassava, Eisai, Eli Lilly, Genentech/Roche, Vaccinex, the NIA, the NIMH, and the DOD. **References:** 1. Budd Haeberlein S, et al. J Prev Alzheimers Dis 2022; 9 (2): 197–210. http://doi.org/10.14283/jpad.2022.30. 2. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH). Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders; 2023. https://www.fda.gov/media/166830/download. 3. Wessels AM, et al. Alzheimers Dement (N Y) 2022; 8 (1): e12312. http://doi.org/10.1002/trc2.12312

LB17- TOPLINE RESULTS OF A PHASE II TRIAL OF EDONERPIC MALEATE IN PATIENTS WITH EARLY STAGE BIOMARKER-PROVEN ALZHEIMER'S DISEASE.

N. Prins[1], C. Teunissen[2], P. Van Bokhoven[3], S. Sikkes[4], W. De Haan[4], T. Okuda[5], P. Scheltens[6] *(1. Brain Research Center - Amsterdam (Netherlands), 2. Neurochemistry Laboratory, Department of Neurochemistry, Amsterdam UMC - Amsterdam (Netherlands), 3. IXA-Neuroscience, Amsterdam Neuroscience, Amsterdam UMC location Vrije Universiteit - Amsterdam (Netherlands), 4. Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location Vumc - Amsterdam (Netherlands), 5. FUJIFILM Toyama Chemical Co., Ltd. - Tokyo (Japan), 6. Amsterdam UMC - Amsterdam (Netherlands))*

Background: Edonerpic maleate (T-817MA) is an orally available small molecule compound which has potent neuroprotective actions. In a past phase 2 study (NCT02079909) significant reduction of tau protein phosphorylated at threonine 181 (p-tau 181) in the cerebrospinal fluid (CSF) at week 52 was observed in a subset of patients who agreed to undergo lumbar punctures (N=17-24) and worsening of ADAS-COG was significantly slower in T-817MA group versus placebo in a subpopulation (<2.6years from diagnosis). Based on these finding a possible disease-modifying effect of T-817MA was suggested. To test its potential as a therapeutic in an earlier stage of Alzheimer's disease (AD), we designed the T817MAEU201 study (NCT04191486). Topline results are presented here. **Methods:** T817MAEU201 is a phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of T-817MA in patients with mild cognitive impairment (MCI) or mild dementia due to AD, as evidenced by abnormal CSF Aβ 1-42 and p-tau 181 at screening. Other key inclusion criteria are 50-80 years of age, MMSE score of 24-30. Randomized patients were treated by either 448 mg of T-817MA or placebo for 78 weeks. To evaluate biomarker levels during the treatment period, CSF and plasma samples were collected at 52 and 78 weeks. The primary endpoint of this study was change of CSF p-tau 181 from baseline to week 78. Key secondary efficacy endpoints were changes in AD-related biomarkers in CSF and/or plasma (amyloid/tau pathology, synaptic degeneration, axonal damage and glial activation), cognition and function assessment by Clinical Dementia Rating Scale Sum of Boxes (CDR-sb) and Cognitive Functional Composite (CFC), magnetic resonance imaging (MRI) and electroencephalography (EEG). Drug concentration in CSF and plasma was also measured to confirm CNS penetration of T-817MA. **Results:** 221 patients were randomized. 188 completed 78 weeks of treatment (14.9% premature discontinuation). Baseline age was 69.7 ± 6.5 years (mean ± SD) and mean MMSE at baseline was 26.6 ± 1.8. Other demographic characteristics will be shown in the presentation. In the mITT population, the change of CSF p-tau 181 from baseline at week 78 were -4.9% in placebo group (n=87) and -4.6% in T-817MA group (n=72). The difference was not statistically significant (p=0.9164). Summary data on CSF and plasma biomarkers, CDR-sb will be presented. In the total population, the most frequently observed adverse effects were COVID-19 (16.8% in placebo; 16.7% in T-817MA) and diarrhoea (7.1% in placebo; 17.6% in T-817MA) which was expected from the previous clinical trials. **Conclusions:** T817MAEU201 was a well-controlled study, well balanced at baseline and excellent retention. Treatment of 448 mg of T-817MA appeared to be safe and tolerable. No changes in CSF p-tau 181 were observed as a result of the intervention vs placebo. **Key words:** Phase 2, edonerpic, p-tau181. **Clinical Trial Registry:** NCT04191486; https://clinicaltrials.gov. **Disclosures:** NP is co-PI of the current trial with Fuji Film Toyama Chemical. NP performed consultancy work for Aribio, Amylyx, Eli-Lilly and Janssen and received a speaker fee from Biogen. NP is CEO and co-owner of Brain Research Center, the Netherlands. CT is employed by Amsterdam UMC. She has grants or contracts for Research of the European Commission (Marie Curie International Training Network, grant agreement No 860197 (MIRIADE), Innovative Medicines Initiatives 3TR (Horizon 2020, grant no 831434) EPND (IMI 2 Joint Undertaking (JU), grant No. 101034344) and JPND (bPRIDE), National MS Society (Progressive MS alliance), Alzheimer Drug Discovery Foundation, Alzheimer Association, Health Holland, the Dutch Research Council (ZonMW), including TAP-dementia, a ZonMw funded project (#10510032120003) in the context of the Dutch National Dementia Strategy, Alzheimer Drug Discovery Foundation, The Selfridges Group Foundation, Alzheimer Netherlands. She is recipient of ABOARD, which is a public-private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). CT is also a contract researcher for ADx Neurosciences, AC-Immune, Aribio, Axon Neurosciences, Beckman-Coulter, BioConnect, Bioorchestra, Brainstorm Therapeutics, Celgene, Cognition Therapeutics, EIP Pharma, Eisai, Eli Lilly Fujirebio, Grifols, Instant Nano Biosensors, Merck, Novo Nordisk, Olink, PeopleBio, Quanterix, Roche, Siemens, Toyama, Vivoryon, and the European Commission. CT has received payment or honoraria from Roche, Novo Nordisk, and Grifols, where all payments were made to her institution. She also serves on editorial boards of Medidact Neurologie/Springer; and in Neurology: Neuroimmunology & Neuroinflammation. CT is editor of Alzheimer Research and Therapy. PVB declares nothing to disclose. SS provided consultancy services for Toyama, Aribio, Biogen, Boehringer, Prothena Biosciences, and she is part of the Scientific Advisory Board of Cogstate. All fees are paid to the institution. SS is the developer of the Amsterdam IADL Questionnaire and the Cognitive Functional Composite. All license fees are paid to the institution. SS receives funding from Health~Holland, Topsector Life Sciences & Health (PPP-allowance; LSHM19051, LSHM20084, LSHM22026-SGF), ZonMW (www.tap-dementia.nl, #10510032120003) in the context of Onderzoeksprogramma Dementie, part of the Dutch National Dementia Strategy, as well

as ZonMW (#7330502051 and #73305095008), and SPREAD+. All funding is paid to the institution. WH heads the Amsterdam UMC EEGlab, which performs centralized EEG analysis for multicenter pharmaceutical trials by Cognition Therapeutics, Vivoryon, Immunobrain, Toyama Fujifilm, Cervomed and Treeway. TO is an employee of FUJIFILM Toyama Chemical Co., Ltd. PS is a full time employee of EQT Life Sciences (formerly LSP) and Professor Emeritus at Amsterdam University Medical Centers. PS has received consultancy fees (paid to the university) from Alzheon, Brainstorm Cell and Green Valley. Within his university affiliation PS was global PI of the phase 1b study of AC Immune, Phase 2b study with FUJI-film/Toyama and phase 2 study of UCB. PS is past chair of the EU steering committee of the phase 2b program of Vivoryon and the phase 2b study of Novartis Cardiology and presently co-chair of the phase 3 study with NOVO-Nordisk.

LB18- CT1812 START STUDY DESIGN: ANTI-AB MONOCLONAL ANTIBODIES AS BACKGROUND THERAPY. C. Van Dyck[1], R. Raman[2], M. Donohue[2], R. Rissman[2], M. Rafii[1], M. Hamby[3], M. Grundman[3], A. Caggiano[3], P. Aisen[2] *(1. Yale School of Medicine - New Haven (United States), 2. Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego - San Diego (United States), 3. Cognition Therapeutics Inc. - Pittsburgh (United States))*

Background: The FDA full approval of lecanemab represents a historic moment for the treatment of Alzheimer's disease (AD). However, it also casts uncertainty about how to conduct clinical trials of other therapeutic agents going forward. For many years clinical trials for AD have incorporated the option of standard-of-care background therapy with cholinesterase inhibitors and memantine. If anti-Aβ monoclonal antibodies (mAbs) are now emerging as the new standard-of-care for early AD, then the conduct of trials in AD cannot ethically or practically exclude them. Trials of some therapies may need to focus on other stages of disease, enroll only individuals who have declined mAbs or have medical exclusions, or be conducted in countries where these drugs are unavailable. All of these options have significant drawbacks. Clinical trials that can be conducted with anti-Aβ mAbs as background therapy should do so. Arguably, treatments that cannot benefit individuals receiving standard-of-care therapy will become less clinically relevant, and the testing of new therapies in conjunction with anti-Aβ mAbs may reveal additive or even synergistic effects. **Objectives:** The newly launched Phase2 CT1812 START study is the first clinical trial in sporadic AD to our knowledge to allow background therapy with anti-Aβ mAbs. This presentation will review the rationale for this decision and present the study design. CT1812 is an investigational small molecule therapeutic agent that is thought to mediate displacement of Aβ oligomers from neuronal synapses thereby reducing synaptotoxicity. **Methods:** The Alzheimer's Clinical Trial Consortium (ACTC) START study, with recruitment initiated in June 2023, will compare treatment with CT1812 to placebo over 18 months in 540 people with mild cognitive impairment or mild dementia due to AD. The primary efficacy endpoint is change from baseline in CDR-SB at 18 months, with planned secondary endpoints including the ADAS-Cog13, ADCS-Activities of Daily Living, volumetric MRI, and CSF/plasma biomarkers. Anti-Aβ mAb treatment is permitted if stable for at least 6 months prior to screening. Participants who meet eligibility criteria will be randomized in a 1:1:1 ratio to 100mg of CT1812, 200mg of CT1812, or placebo. A covariate-adaptive randomization algorithm will be utilized to minimize the imbalance between treatment arms on the following pre-randomization factors: APOE4 carrier status, MMSE score at screening (20-24 versus 25-30), concomitant anti-amyloid treatment (yes, no), and clinical site. For a sample size of 180 participants per group, the study has 80% power to detect a slowing of clinical decline on the primary outcome of CDR-SB of 0.67 points at 18 months assuming a standard deviation of 2.10 and 15% attrition per year. **Results:** This study aims to provide proof-of-concept results for a novel therapeutic agent that targets the displacement of Aβ oligomers from neuronal synapses. **Conclusions:** The START study will provide early experience for the conduct of trials with anti-Aβ mAbs as background therapy. Challenges posed by the allowance of anti-Aβ mAbs include the uncertainty of enrollment rates on these treatments and the potentially increased variability of outcomes. Design considerations and challenges will be discussed.

LB19- PHARMACOKINETIC-PHARMACODYNAMIC (PK-PD) RELATIONSHIP BETWEEN ADUCANUMAB EXPOSURE AND AMYLOID PET OVER LONG-TERM TREATMENT PERIOD INCLUDING DOSING GAP IN THE EMBARK PHASE 3B STUDY. J. Burton[1], K. Ken[2], K. Kandadi Muralidharan[1], R.M. Hutchison[1], P. Montenigro[1], I. Nestorov[1] *(1. Biogen - Cambridge (United States), 2. Kowalski PMetrics Consulting LLC - Naples (United States))*

Background: Aducanumab received accelerated approval for the treatment of Alzheimer's Disease (AD) for patients with mild cognitive impairment or mild dementia. EMBARK is a longitudinal, open-label, multicentre, single-arm, phase 3b study conducted to assess long-term safety, PK, biomarkers, and efficacy of aducanumab in AD participants who were active in prior aducanumab clinical studies. The objective of this work was to characterize the PK-PD relationship between aducanumab exposure and amyloid PET based on pooled data from the phase 3 feeder studies ENGAGE/EMERGE to an interim data cut of EMBARK that includes a treatment gap between studies. **Methods:** Patient-level data for amyloid PET (18F-florbetapir, 18F-flutemetamol, 18F-florbetaben) and dosing history were pooled into a single analysis subset. Standard Uptake Value ratios (SUVr) for amyloid PET measurements were harmonized to the Centiloid scale. A nonlinear mixed effects model was developed using a 2-compartment PK model coupled to an indirect response model for drug effect. Covariates included APOE4 carrier status, baseline age, baseline weight, and baseline Mini-Mental State Examination score. An empirical study effect was used for EMBARK records to account for unobservable factors related to the open-label design. Data preparation was performed in R and model estimation was performed in NONMEM. **Results:** A total of 3036 patients comprising 6309 centiloid records (3067 baseline only) and 75887 dosing records were pooled. Mean baseline was 91.63 centiloids for combined ENGAGE/EMERGE data. The model was stable with good precision of parameter estimates. The drug effect parameters were such that the amyloid plaque clearance rate is increased by 29% at steady-state for 10mg/kg dosing. For ENGAGE/EMERGE, 321 participants had amyloid PET records at conclusion of the placebo-controlled period (week-78) and completion of the long-term extension (130 weeks). Observed (model-predicted) centiloids for these participants at baseline, week-78, and week-130 were 91.1 (91.3), 58.1 (57.8), and 40.8 (38.8), respectively. Model simulations were performed for a typical individual on per protocol dosing of titration to 10mg/kg resulting in 10.4 centiloids at week-130. Of the 321 participants, 128 had an amyloid PET record

at EMBARK baseline. Observed (model predicted) centiloid increase during the median 1.7-year treatment gap for these participants was 4.0 (7.5). Model predicted time to return to baseline centiloids in EMBARK participants is 14.29 years. Of the 128 participants, 28 had EMBARK week-102 amyloid PET records with observed (model predicted) centiloids for these participants of 21.6 (24.7). Observed (model-predicted) percentages of amyloid plaque negative (< 20 centiloids) across all amyloid PET data (using last available participant visit) for week-78, week-130, EMBARK baseline, and EMBARK Week-102 participants were 15.9% (14.4), 29.8% (31.9), 19.7% (18.6), 55.1% (51.3), respectively. **Conclusion:** The developed model accurately characterized PK-PD relationship between aducanumab and amyloid PET across multiple clinical studies, including a treatment gap. The use of the Centiloid scale allows for SUVr data across amyloid PET radiotracers to be utilized improving model precision. The additional longitudinal amyloid PET records from the long-term extension and EMBARK demonstrate maintained/continued plaque reduction related to higher exposure of aducanumab. **Key words:** Alzheimer's, aducanumab, EMBARK. **Clinical Trial Registry:** NCT04241068 https://clinicaltrials.gov. **Data Deposition:** While the data described in this article are not publicly available, the authors and Biogen are supportive of data sharing. Proposals should be submitted through Vivli (https://vivli.org). For general inquiries, please contact datasharing@biogen.com. Biogen's data-sharing policies and processes are detailed on www.biogentrialtransparency.com. **Disclosures:** JB, KKM, PM, RMH, and IN are employees and shareholders of Biogen Inc. Kenneth G. Kowalski is a paid consultant for Biogen.

LB20- A MASS SPECTROMETRIC PANEL OF PHOSPHORYLATED AND NON-PHOSPHORYLATED PLASMA TAU SPECIES REVEALS DIFFERENCES IN THE ASSOCIATIONS WITH EARLY AND INTERMEDIATE TAU PET IN SPORADIC ALZHEIMER'S DISEASE. Laia Montoliu-Gaya[1], Gemma Salvadó[2], Nicholas J Ashton[1], Shorena Janelidze[2], Johanna Nilsson[3], Niklas Mattsson-Carlgren[2], Sophia Weiner[4], Sebastian Palmqvist[2], Juan Lantero-Rodriguez[3], Gunnar Brinkmalm[4], Erik Stomrud[2], Henrik Zetterberg[3], Johan Gobom[3], Kaj Blennow[3], Oskar Hansson[2] *(1. University of Gothenburg - Gothenburg (Sweden), 2. Lund University - Lund (Sweden), 3. University of Gothenburg - Gothenburg (Sweden) - Gothenburg (Sweden), 4. University of Gothenburg - Gothenburg (Sweden) - Gothenburg (Sweden) - Gothenburg (Sweden))*

Background: Recent success in clinical trials for anti-amyloid therapies highlight the need for biomarkers to identify participants at specific stages of Alzheimer´s disease (AD) for an optimal outcome (1). Blood phosphorylated tau (p-tau) at different positions has been shown to accurately detect AD (2). However, there remains an incomplete understanding of the brain pathological information that blood p-tau and non-phosphorylated tau species reflect. A method capable of systematically quantifying multiple phosphorylated and non-phosphorylated plasma tau species in a single-shot analysis, independent of the platform, can provide more accurate insights into the relationships between different tau forms and stage-specific alterations in AD. **Methods:** We used a mass spectrometric targeted method (3) to simultaneously quantify the levels of six different phosphorylated (p-tau 181, 199, 202, 205, 217 and 231), and six non-phosphorylated (0N-specific, 1N-specifc, 195-209, 212-221, PNS 7-14, PNS 151-167) tau peptides in plasma. We analyzed a total of 147 samples from participants in the BioFINDER-2 cohort, including amyloid negative and positive cognitively unimpaired (CU), mild-cognitively impaired (MCI) and AD dementia participants. A subset of participants had available amyloid PET ([18F] flutemetamol, n=104) and/or tau PET ([18F]RO-948, n=125), and cognition (mPACC, n=127). **Results:** The levels of all p-tau peptides were higher in AD dementia compared to amyloid-positive MCI (MCI+) participants, but only p-tau181, p-tau205, p-tau217 and p-tau231 were increased in MCI+ compared to CU+. Plasma p-tau217, p-tau231, p-tau181 and p-tau205 were the site-specific phosphorylations that showed higher correlations with Aβ PET (bp-tau217=0.80; bp-tau231=0.69; bp-tau181=0.57; bp-tau205=0.54; all $p<0.001$) and tau-PET, both at early regions (medial temporal lobe [MTL]: bp-tau217=0.71; bp-tau231=0.55; bp-tau205=0.54; bp-tau181=0.45; all $p<0.001$) or intermediate regions (neotemporal: bp-tau217=0.69; bp-tau205=0.55; bp-tau231=0.50; bp-tau181=0.44; all $p<0.001$) of tau deposition. Interestingly, the associations with tau-PET were significantly higher in amyloid-positive participants in the MTL for p-tau217, p-tau231 and p-tau205 (bp-tau217=0.6; bp-tau231=0.54; bp-tau205=0.56; all $p<0.01$), but only for p-tau217 and p-tau205 in temporal areas (bp-tau217=0.97; bp-tau205=0.62; all $p<0.001$). Longitudinal accumulation of tau (n=33) in the temporal region was significantly associated with baseline p-tau217, p-tau231 and p-tau181 (all $p<0.02$), while tau accumulation in the MTL was only significantly associated with baseline p-tau217 ($p=0.048$), and none of them did with p-tau205. Plasma p-tau217, p-tau231 and p-tau205 at baseline were negatively associated with baseline (bp-tau217=-0.59; bp-tau231=-0.50; bp-tau205=-0.51; all $p<0.001$) and longitudinal (bp-tau217=-0.05; bp-tau231=-0.06; bp-tau205=-0.06; all $p<0.05$) mPACC cognitive measures. Among the non-phosphorylated peptides, 0N-specific consistently showed higher and more significant associations with amyloid- and tau-PET than the other non-p-taus (1N-specific, 195-209 and 212-221). The non-phosphorylated peptides PNS 7-14 and PNS 151-167, specific of the peripheral tau isoform, did not show higher levels with more advanced clinical diagnosis, nor any association with amyloid-PET, tau-PET or cognitive performance. **Conclusion:** Plasma p-tau217, p-tau231, p-tau205, and specific non-phosphorylated tau species have significant although differential associations with amyloid and tau pathologies, which may suggest their relation to distinct stages of the disease. A comprehensive understanding of the pathological information that each plasma tau biomarker reflects is paramount to optimize their use for participant inclusion in clinical trials for disease-modifying treatments. **References:** 1. Pontecorvo MJ, Lu M, Burnham SC, Schade AE, Dage JL, Shcherbinin S, et al. Association of Donanemab Treatment With Exploratory Plasma Biomarkers in Early Symptomatic Alzheimer Disease: A Secondary Analysis of the TRAILBLAZER-ALZ Randomized Clinical Trial. JAMA Neurol. 2022. 2. Karikari TK, Ashton NJ, Brinkmalm G, Brum WS, Benedet AL, Montoliu-Gaya L, et al. Blood phospho-tau in Alzheimer disease: analysis, interpretation, and clinical utility. Nat Rev Neurol. 2022;18(7):400-18. 3. Montoliu-Gaya L, Benedet AL, Tissot C, Vrillon A, Ashton NJ, Brum WS, et al. Mass spectrometric simultaneous quantification of tau species in plasma shows differential associations with amyloid and tau pathologies. Nat Aging. 2023.

LB21- EVALUATING THE EFFICACY OF AR1001 ON PLASMA PTAU 181 LEVELS AND ADAS-COG 13 IN MILD TO MODERATE ALZHEIMER'S DISEASE: RESULTS FROM THE PHASE 2 TRIAL. B.S. Ye[1], D. Greeley[2], F. Kim[2], J.J. Choung[2] *(1. Department of Neurology, Yonsei University College of Medicine - Seoul (Korea, Republic of), 2. AriBio Co., Ltd. - Seongnam (Korea, Republic of))*

Background: AR1001 (mirodenafil), an oral phosphodiesterase (PDE5) inhibitor, is being investigated as a polypharmacological therapeutic agent for Alzheimer's disease (AD) [1]. The phase 2 trial (AR1001-ADP2-US01) aimed to evaluate the safety and efficacy of AR1001 in patients with mild to moderate AD. **Methods:** In this double-blind, randomized, placebo-controlled, parallel-group trial, 210 patients diagnosed with mild to moderate AD were randomized to receive either a placebo, AR1001 10 mg, or AR1001 30 mg. Participants were administered either AR1001 or a placebo daily for 26 weeks. Subsequently, participants from the placebo group could opt to receive 10 mg or 30 mg of AR1001 in an extension phase for an additional 26 weeks. Participants were diagnosed clinically based on the 2011 National Institute of Aging and Alzheimer's Associations criteria, and plasma phosphorylated tau (ptau) 181 levels were measured at baseline, 26 weeks, and 52 weeks using the Single Molecule Array (Simoa®) technology [2]. The primary outcome was the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) 13 measured at baseline, 26 weeks, and 52 weeks. To evaluate the effect of AR1001 group on longitudinal changes of ptau 181 levels or ADAS-cog 13, linear mixed models were performed using time*AR1001 group as a predictor after controlling for age, sex, body mass index, site, and race as covariates. To test the effects of baseline ptau 181 level on longitudinal changes of ADAS-cog 13 by AR1001 group, linear mixed models were performed using time*AR1001 group*baseline ptau 181 level as a predictor after controlling for the same covariates in addition to time*AR1001 group and time*baseline ptau 181 level. **Results:** Sixty-seven, 68, and 69 patients were assigned to the placebo, AR1001 10 mg, and AR1001 30 mg groups, respectively. Age, sex, body mass index, baseline ADAS-cog 13 and baseline ptau 181 level were not different between the three groups. There was a significant time*AR1001 group effect on longitudinal ptau 181 level indicating that the AR1001 30 mg group had a relative decrease in ptau 181 level compared to the placebo group [beta (standard error, SE) = -0.03 (0.01), P = 0.042]. The effect of time*AR1001 group on longitudinal ADAS-cog 13 was not significant (P = 0.644). The three-way interaction effect of time*AR1001 group*baseline ptau 181 level on longitudinal ADAS-cog 13 was significant (P = 0.038). Subgroup analyses showed that higher baseline ptau 181 had a detrimental effect on longitudinal ADAS-cog 13 in the placebo group [beta (SE) = 0.03 (0.01), P = 0.002] and AR1001 10 mg group [beta (SE) = 0.02 (0.01), P = 0.029], but not in the AR1001 30 mg group [beta (SE) = 0.0002 (0.01), P = 0.985]. **Conclusions:** AR1001 30 mg demonstrated significant beneficial effect on longitudinal changes in ptau 181 level, but not on longitudinal changes of ADAS-cog 13. Moreover, the detrimental effects of baseline ptau 181 level on longitudinal ADAS-cog 13 changes were alleviated only in the AR1001 30 mg group. These results suggest a possibility of disease modification by AR1001 with underlying mechanism associated with plasma ptau 181. **Key words:** AR1001, AriBio, Phase 2, ptau 181, biomarker, disease-modifying. **Clinical Trial Registry:** NCT03625622. **Disclosures:** BSY is a consultant for AriBio. DG, FK, JJC are employees of AriBio. The authors declared no competing interests. **References:** Kang BW, Kim F, Cho JY, Kim S, Rhee J, Choung JJ. Phosphodiesterase 5 inhibitor mirodenafil ameliorates Alzheimer-like pathology and symptoms by multimodal actions. Alzheimers Res Ther. 2022;14(1):92. Published 2022 Jul 8. doi:10.1186/s13195-022-01034-3. Wilson DH, Rissin DM, Kan CW, et al. The Simoa HD-1 Analyzer: A Novel Fully Automated Digital Immunoassay Analyzer with Single-Molecule Sensitivity and Multiplexing. J Lab Autom. 2016;21(4):533-547. doi:10.1177/2211068215589580

LB22- ADUCANUMAB PHASE 3B EMBARK STUDY INTERIM ANALYSIS: TOPLINE SAFETY RESULTS. G.G. Curiale[1], P. Montenigro[1], K. Umans[1], T. Sun[1], J. O'gorman[1], K. Smirnakis[1] *(1. Biogen - Cambridge (United States))*

Background: EMBARK is a longitudinal, open-label, multicenter, single-arm, study conducted to assess the long-term safety, pharmacokinetics, biomarkers and efficacy of aducanumab in Alzheimer's disease participants who were active in prior aducanumab clinical studies. Safety data from an interim analysis of participants from EMERGE and ENGAGE are presented here and help to characterize the safety profile of aducanumab in this population. **Methods:** Analyses are presented based on two populations: 1) the EMBARK safety population (n=1618) defined as participants who received at least one dose of study treatment and 2) the EMBARK safety MRI population (n=1578) which is a subset of EMBARK safety population with at least 1 post-baseline MRI, categorized by prior exposure in feeder studies (no aducanumab (n=208), 0 doses of 10 mg/kg (n=784), at least 1 dose of 10 mg/kg (n=586), total (n=1578)). The data are from an interim analysis and the study populations include only participants from the phase 3 studies EMERGE and ENGAGE who comprised greater than 95% of EMBARK participants. Brain MRI was utilized to monitor for ARIA. Symptoms of ARIA were reported as AEs (adverse events). **Results:** The EMBARK safety population had a median exposure of 84 weeks. In the EMBARK safety population, incidences [%(n)] of AEs, serious AEs (SAEs), related SAEs, events leading to treatment discontinuation, and events leading to study withdrawal were 89.2% (1443), 16.5% (267), 1.2% (19), 8.9% (144), and 6.6% (106), respectively. For the safety MRI population, the incidence [%(n)] of any ARIA, ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis by treatment group (no prior aducanumab, 0 doses of 10 mg/kg aducanumab, at least 1 dose of 10 mg/kg aducanumab, and total) were 49.0% (102), 43.4% (340), 22.2% (130), 36.2% (572) for any ARIA; 39.9% (83), 30.9% (242), 11.4% (67), 24.8% (392) for ARIA-E; 30.8% (64), 28.3% (222), 14.7% (86), 23.6% (372) for ARIA-H microhemorrhage; and 22.6% (47), 13.8% (108), 6.0% (35), 12.0% (190) for ARIA-H superficial siderosis. In the safety MRI population by previous exposure group, more than one ARIA-E event was observed in 16.8% (35), 8.4% (66), 2.6% (15), and 7.4% (116) of participants in each exposure group, respectively. Among participants within the safety MRI population with ARIA-E by prior exposure, the maximal radiographic severity was mostly mild or moderate (92.8% (77), 95.5% (231), 100% (67), 95.7% (375)), asymptomatic (78.3% (65), 79.3% (192), 88.1% (59), 80.6% (316)), and rarely serious (2.4% (2), 2.1% (5), 0% (0), 1.8% (7)). **Conclusion:** The EMBARK interim analysis safety dataset provides important insights into the safety of aducanumab. Compared to participants without exposure to aducanumab in a feeder study, participants with exposure to aducanumab in a feeder study had a lower incidence of adverse events of ARIA, ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis. Prior exposure to at least 1 dose of aducanumab 10 mg/kg

was associated with the lowest incidence of ARIA compared to treatment naive participants. The benefit risk profile of aducanumab remains positive. The final data set will continue to inform the long-term safety profile of aducanumab. **Key words:** Aducanumab, ARIA, EMBARK, Alzheimer's disease. **Clinical Trial Registry:** NCT04241068 https://clinicaltrials.gov. **Data Deposition:** While the data described in this article are not publicly available, the authors and Biogen are supportive of data sharing. Proposals should be submitted through Vivli (https://vivli.org). For general inquiries, please contact datasharing@biogen.com. Biogen's data-sharing policies and processes are detailed on www.biogentrialtransparency.com. **Disclosures:** GGC, PM, TS, JO, and KS are employees and shareholders of Biogen Inc. KU is a former employee and current shareholder of Biogen, Inc.

LB23- RESULTS OF A PHASE 2 RANDOMIZED WITHDRAWAL STUDY OF SIMUFILAM IN MILD-TO-MODERATE ALZHEIMER'S DISEASE. I. Cohen[1], S. Malhotra[1], P. Patel[2], S. Hendrix[3], C. Mallinckrodt[3], B. Murray[4], L. Jones[4], A. Hernandez[4], E.C.R.O.W. Crow[4], M. Snyder[4], L. Burns[4], J. Kupiec[4], N. Friedmann[4] *(1. Toronto Memory Program - Toronto (Canada), 2. Brain Matters Research - Delray Beach (United States), 3. Pentara Corporation - Millcreek (United States), 4. Cassava Sciences, Inc. - Austin (United States))*

Background: Simufilam is a novel drug candidate in Phase 3 clinical trials for Alzheimer's Disease (AD) dementia. This oral small molecule targets an altered form of filamin A (FLNA) found in AD. The drug disrupts FLNA's aberrant linkage to the α7 nicotinic acetylcholine receptor (α7nAChR), thereby blocking soluble amyloid beta1-42 (Aβ42)'s signaling via α7nAChR that hyperphosphorylates tau. Simufilam also disrupts aberrant linkages of FLNA with TLR4 and other inflammatory receptors to prevent their activation by Aβ42, suppressing neuroinflammation. We previously showed that 12 months of open-label treatment with simufilam 100 mg b.i.d. improved ADAS-Cog11 scores in 47% of patients (N=216) with mild-to-moderate AD (MMSE $\geq$ 16 and $\leq$ 26). Patients with mild AD (MMSE $\geq$ 21 and $\leq$ 26) in that study improved by -0.73 points over 12 months. Following these encouraging clinical results, we conducted a randomized withdrawal study. **Methods:** All AD patients who completed 12 months of open-label simufilam were eligible to participate in our 6-month, Phase 2, double-blind, placebo-controlled, randomized withdrawal study. 157 patients were randomized (1:1) to continue taking simufilam 100 mg b.i.d or were switched to matching placebo (i.e., withdrawal of active drug). This study had one pre-specified cognitive endpoint: change in ADAS-Cog11. **Results:** Mild-to-moderate AD patients randomized to placebo declined 1.5 points on ADAS-Cog11 over 6 months; patients randomized to simufilam declined 0.9 points, a 38% slowing of decline in favor of drug (95% CI, -2.1 to 1.0). Mild-to-moderate AD patients on simufilam for a full 18 months (i.e., 12 months open-label simufilam plus 6 months of randomized simufilam) declined 1.86 points. Those patients randomized to placebo following 12 months of open-label simufilam declined 2.66 points over the 18-month duration, which is less than the expected 5.5-point yearly decline reported for mild-to-moderate AD [1]. Mild AD patients randomized to placebo (n=36) declined 0.6 points. Mild patients randomized to simufilam (n=40) improved -0.6 points over 6 months, a 205% difference in favor of drug (95% CI, -2.6 to 0.4). Mild AD patients who stayed on simufilam for 18 months (i.e., 12 months open-label simufilam plus 6-months of randomized simufilam) declined only 0.11 $\pm$ 0.72 points on ADAS-Cog11. Mild participants switched to placebo after 12 months open-label simufilam showed only a slight change on ADAS-Cog11 (0.76 $\pm$ 0.80) over the entire 18 months. Conclusions: In this Phase 2, randomized withdrawal study, simufilam 100 mg b.i.d for 6 months slowed cognitive decline by 38% in patients with mild-to-moderate AD versus placebo (difference not significant). Mild AD patients randomized to simufilam improved -0.6 points over 6 months, a 205% difference in favor of drug. Mild AD patients on simufilam for 18 months showed minimal decline in ADAS-Cog scores, indicating stable cognition. Disease-modifying drug effects may underlie the narrow margin between patients who remained on simufilam and patients who switched to placebo during the randomized withdrawal study. Simufilam appeared safe and well-tolerated across 18 months. **Reference:** Ito , K., Ahadieh, S., Corrigan, B., French, J., Fullerton, T., Thomas Tensfeldt, T., Alzheimer's Disease Working Group (2010). Disease progression meta-analysis model in Alzheimer's disease. Alzheimers Dement 6: 39-53.

LB24- PLASMA P-TAU212 IDENTIFIES COGNITIVELY UNIMPAIRED INDIVIDUALS WITH EMERGING AMYLOID-BETA PATHOLOGY. P. Kac[1], A. González-Escalante[2,3,4], M. Milà-Alomà[2,5], N. Ashton[1,6,7,8], M. Shekari[2,3,4,5], P. Ortiz-Romero[2,3], H. Zetterberg[1,6,9,10], J.D. Gispert[2,3,5,11], K. Blennow[1,12], M. Suárez-Calvet[2,3,11,13], T. Karikari[1,14] *(1. Department of Psychiatry and Neurochemistry,Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg - Mölndal (Sweden), 2. Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation - Barcelona (Spain), 3. Hospital del Mar Research Institute - Barcelona (Spain), 4. Universitat Pompeu Fabra - Barcelona (Spain), 5. Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES) - Madrid (Spain), 6. Institute of Psychiatry, Psychology and Neuroscience, Maurice Wohl Clinical Neuroscience Institute, King's College London - London (United Kingdom), 7. NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia at South London and Maudsley NHS Foundation - London (United Kingdom), 8. Centre for Age-Related Medicine, Stavanger University Hospital - Stavanger (Norway), 9. Hong Kong Center for Neurodegenerative Diseases, HKCeND - Hong Kong (China), 10. School of Medicine and Public Health, University of Wisconsin-Madison - Madison (United States), 11. Centro de Investigación Biomédica en Red Bioingeniería, Biomateriales y Nanomedicina - Madrid (Spain), 12. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 13. Servei de Neurologia, Hospital del Mar - Barcelona (Spain), 14. Department of Psychiatry, School of Medicine, University of Pittsburgh - Pittsburgh (United States))*

Background: Plasma phosphorylated-tau (p-tau) biomarkers have found utility in clinical trials for anti-amyloid drug therapies for Alzheimer's Disease (AD) [1 ,2]. Plasma p-tau levels are increased in AD [3–5], and their decrease is observed after drug treatment [1, 2]. Recently published articles suggest that all plasma p-tau biomarkers (i.e., p-tau181, p-tau217 and p-tau231) have shown high accuracies for AD diagnosis6, however some of them appear to be increased earlier in the AD continuum than others [7]. Blood biomarkers that can identify subtle elevations in amyloid-beta pathology among older adults without evidence of cognitive impairment would be ideal candidates for the recruitment and enrichment of participants with preclinical AD in clinical trials. Plasma p-tau212 is a novel, autopsy-confirmed blood biomarker that can discriminate subjective cognitive decline patients from

AD patients in memory clinics. However, we evaluated the capacity of plasma p-tau212 to detect emerging amyloid-beta pathology in cognitively unimpaired individuals with have abnormal levels of CSF Abeta42/40 ratio but remain normal for amyloid-beta PET. **Methods:** In-house developed plasma p-tau212 Single molecule array (Simoa) immunoassay was used to measure p-tau212 levels in the ALFA+ cohort (n=311). N=268 participants had available [18F]flutemetamol (amyloid-beta) PET scans. Participants were classified as Aβ positive (A+) if CSF Aβ42/40 <0.071 and tau positive (T+) if CSF Mid(M)-p-tau181 (measured on the Elecsys platform)>24 pg ml−18. We further classified participants according to their CSF/PET Aβ status. The group with a low burden of Aβ pathology was defined as CSF Aβ42/40 <0.071 and Aβ PET Centiloids <30 and was compared with CSF/PET Aβ negative (CSF Aβ42/40 ≥0.071 and Aβ PET Centiloids <30) and CSF/PET Aβ positive (CSF Aβ42/40 <0.071 and Aβ PET Centiloids ≥30). Centiloid values, CSF and plasma biomarker levels were compared with a one-way analysis of covariance (ANCOVA), adjusted for age and sex. Next, we performed ROC analyses to obtain the AUC for CSF amyloid positivity and Aβ PET. **Results:** Plasma p-tau212 was increased in both A+T- and A+T+ participants compared with A-T- ($p<0.0009$; $p<0.0001$ respectively). Accuracy to discriminate CSF amyloid positivity was 0.694 for p-tau212, 0.702 for p-tau231 and 0.657 for p-tau181. In the low-burden Aβ pathology group, plasma p-tau212 levels were significantly higher, reaching 35.6% mean-fold increase compared with the A- group. P-tau181 and p-tau231 levels were increased 14.7% and 30.5% respectively. Mean-fold increase of p-tau212 in the A+ PET positive group was 58.1% compared with the low burden Aβ pathology group. For p-tau181 and p-tau231 we observe 21.5% and 49.5% respectively. For A+ PET positive group we observe 114% mean-fold increase for p-tau212, 39.4% for p-tau181 and 95.3% for p-tau231 in comparison to A- group. **Conclusions:** Increase of plasma p-tau212 before established Aβ PET positivity makes it a cost-effective and simple-to-implement biomarker for population screening and clinical trial recruitment purposes. Further increase of p-tau212 in Aβ PET positive participants suggests, that this biomarker has utility for clinical monitoring of anti-amyloid therapies. **Key words:** Preclinical Alzheimer's Disease, p-tau biomarkers. **Clinical Trial Registry:** NCT02485730. **Disclosures:** HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche. which is a part of the GU Ventures Incubator Program (outside submitted work). KB has served as a consultant or at advisory boards for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Pharmatrophix, Prothena, Roche Diagnostics, and Siemens Healthineers. HZ and KB are co-founders of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. **References:** 1. Sims, J. R. et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA 330, 512–527 (2023). 2. van Dyck, C. H. et al. Lecanemab in Early Alzheimer's Disease. N. Engl. J. Med. 388, 9–21 (2023). 3. Ashton, N. J. et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. Acta Neuropathol. (Berl.) 141, 709–724 (2021). 4. Karikari, T. K. 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. 19, 422–433 (2020). 5. Palmqvist, S. et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA 324, 772–781 (2020). 6. Suárez-Calvet, M. et al. A head-to-head comparison of plasma phosphorylated tau assays in the real-world memory clinic. Alzheimers Dement. 18, e065391 (2022). 7. Milà-Alomà, M. et al. Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease. Nat. Med. 28, 1797–1801 (2022). 8. Milà-Alomà, M. et al. Amyloid beta, tau, synaptic, neurodegeneration, and glial biomarkers in the preclinical stage of the Alzheimer's continuum. Alzheimers Dement. 16, 1358–1371 (2020).

LB25- ELEVATED AMYLOID AND TAU ARE NOT ASSOCIATED WITH COGNITION IN A DIVERSE CLINICAL TRIAL COHORT. S. Landau[1], T. Harrison[1], T. Ward[1], P. Vemuri[2], S. Lockhart[3], R. Koeppe[4], D. Harvey[5], L. Lovato[3], A. Toga[6], S. Tomaszewski Farias[5], K. Papp[7], H. Snyder[8], C. Decarli[5], W. Jagust[1], L. Baker[3] *(1. UC Berkeley - Berkeley (United States), 2. Mayo Clinic - Rochester (United States), 3. Wake Forest School of Medicine - Winston-Salem (United States), 4. University of Michigan - Ann Arbor (United States), 5. UC Davis - Davis (United States), 6. University of Southern California - Los Angeles (United States), 7. Harvard University - Boston (United States), 8. Alzheimer's Association - Chicago (United States))*

Background: Enrollment of a diverse sample of clinical trial participants is critical for establishing generalizability of trial results, but we have a limited understanding of how sample heterogeneity influences Alzheimer's disease pathophysiology and cognitive outcomes. The U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER) trial developed a novel recruitment strategy to increase cohort heterogeneity across several dimensions including race, ethnicity, and cardiovascular risk. Here, we examined the influence of this increased sample diversity on baseline AD biomarkers by comparing MRI and PET measures in U.S. POINTER imaging substudy participants and a matched Alzheimer's Disease Neuroimaging Initiative (ADNI) participants recruited with less emphasis on diversity. **Methods:** In August 2023, the U.S. POINTER imaging substudy completed enrollment and baseline neuroimaging (MRI, amyloid and tau PET) in 1052 at-risk older adults (age 60-79) without significant cognitive impairment (global CDR<0.5), which comprises 50% of the overall U.S. POINTER trial sample (N=2111). U.S. POINTER imaging participants are representative of older U.S. adults who could benefit from an intervention to reduce dementia risk based on race and ethnicity (32% from under-represented groups), geographical location (5 U.S. sites), and health risk characteristics (sedentary behavior, unhealthy diet, suboptimum cardiovascular health, family history of memory problems). We examined relationships between baseline AD and cerebrovascular biomarkers (cortical summary Aβ and temporal tau PET, hippocampal volume, white matter hyperintensities), cardiovascular risk (Framingham Risk Scores, FRS), and cognition (Preclinical Alzheimer Cognitive Composite, PACC) in the U.S. POINTER imaging sample and an ADNI subsample (N=357) matched to U.S. POINTER imaging participants on age, sex, and CDR. All variables were analyzed using harmonized methods across studies. **Results:** Compared to the matched ADNI sample, U.S. POINTER imaging participants had lower education, higher FRS, a larger

proportion of racial and ethnic minoritized individuals, higher tau, and lower PACC scores. The cohorts did not differ on variables used for matching (age, sex, CDR), or on amyloid positivity (31% in both cohorts), hippocampal volume, or white matter hyperintensities. In regression models predicting tau burden, POINTER participants had comparable amyloid but lower tau than their matched ADNI counterparts (cohort main effect, $p<0.001$) as well as disproportionately lower tau among amyloid+ individuals (cohort X amyloid, $p<0.001$). In regression models predicting PACC performance, FRS was a stronger predictor of cognition in POINTER than ADNI (cohort X FRS, $p=0.03$) whereas tau overall (cohort X tau, $p<0.001$) and tau and amyloid together (cohort X amyloid X tau, $p=0.01$) were stronger predictors of cognition in ADNI than POINTER. In U.S. POINTER alone, amyloid and tau were not associated with PACC scores. **Conclusions:** Comparison of a diverse imaging cohort (U.S. POINTER) to a less diverse cohort (ADNI) matched on key characteristics resulted in similar amyloid burden but elevated cardiovascular risk, lower tau, and poorer cognitive performance in U.S. POINTER participants. AD biomarkers were not predictive of cognition in U.S. POINTER, contrasting with a large body of evidence in more homogeneous cohorts, and suggesting that cohort diversity may affect the influence of amyloid- and tau-modifying therapies on cognition. **Key words:** risk reduction, diversity and recruitment, neuroimaging biomarkers. **Clinical trial registry:** NCT03688126, clinicaltrials.gov. **Data deposition:** Laboratory of NeuroImaging, USC; ida.loni.usc.edu. **Disclosures:** SM Landau, DSMB for KeifeRX and NIH IPAT study, speaking fees from Eisai. TM Harrison, no disclosure. TJ Ward, no disclosure. P Vemuri, no disclosure. SN Lockhart, no disclosure. R Koeppe, no disclosure. DJ Harvey, consultant for NervGen Pharma Corp. L Lovato, no disclosure. AW Toga, no disclosure. ST Farias, no disclosure. KV Papp, no disclosure. HM Snyder, full-time employee of the Alzheimer's Association and spouse is an employee of Abbott Labs. C DeCarli, no disclosure. WJ Jagust, consultant for Lilly, Eisai, Prothena, Bioclinica. LD Baker, no disclosure.

LB26- FEASIBILITY OF REMOTE BLOOD COLLECTION AND PLASMA BIOMARKER ANALYSES TO ASSESS ELIGIBILITY FOR ALZHEIMER'S DISEASE PRECLINICAL CLINICAL TRIALS - THE ALZMATCH STUDY. R. Raman[1], S. Walter[1], G. Jimenez-Maggiora[1], R. Rissman[1], A. Atri[2], D. Goldman[3], J. Grill[4], G.A. Marshall[5], G. Jicha[6], M. Racke[7], R. Turner[8], C. Van Dyck[9], V. Venkatesh[10], R. Sperling[5], P. Aisen[1] *(1. Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego (United States), 2. Banner Sun Health Research Institute and Banner Alzheimer's Institute, Banner Health, Brigham And Women's Hospital - Sun City And Phoenix, Boston (United States), 3. Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California - Los Angeles (United States), 4. Institute for Memory Impairments and Neurological Disorders, University of California Irvine - Irvine (United States), 5. Massachusetts General Hospital, Harvard Medical School - Boston (United States), 6. University of Kentucky - Lexington (United States), 7. Quest Diagnostics - Secaucus (United States), 8. Georgetown University - Washington Dc (United States), 9. Yale College of Medicine - New Haven (United States), 10. C2N Diagnostics - St. Louis (United States))*

Background: Advances in plasma biomarkers allow researchers to improve the efficiency of participant recruitment into preclinical Alzheimer's disease (AD) trials. Plasma biomarkers can be used to identify individuals most likely to qualify for studies ruling out those who have the lowest probability of qualifying based on subsequent amyloid PET or CSF biomarker profiles currently required for AD clinical trial eligibility. Online registries, such as the Alzheimer's Prevention Trials (APT) Webstudy, recruit and follow participants through assessments collected remotely, potentially facilitating the efficient identification and enrollment of large numbers of individuals who may be at higher risk for AD. The AlzMatch Study investigates the feasibility of recruiting APT Webstudy individuals for remote blood sample collection at community-based phlebotomy centers, plasma biomarker quantification at accredited diagnostic laboratories, and centralized statistical prediction algorithms to assess an individual's eligibility for AD preclinical trials. **Methods:** In this study's vanguard phase, APT Webstudy participants were invited to take part in the AlzMatch study if they met the following inclusion/exclusion criteria: 50 years of age and older, residing within 50 miles from both a Quest Diagnostics Patient Services Center (a national diagnostic laboratory with convenient locations for sample collection and processing) and one of six vanguard clinical trial sites, no self-reported dementia diagnosis, ability to communicate in English and being active within the APT registry within the previous 6 months. Primary outcomes were rates of e-consent of invited participants and collection of usable blood samples. Other feasibility outcomes included plasma eligibility status (based on trial inclusion criterion). Analyses was conducted, overall, and by self-reported participant sex, race and ethnicity. **Results:** 300 APT Webstudy participants were referred to the AlzMatch study. The sample included: 62% female sex, 91% college-educated, 67% White race, 9% Black or African American race, 10% Asian race, 12% Hispanic or Latino(a) ethnicity, 59% family history of dementia, with an average age of 64.4±-5.8 years. The AlzMatch e-consent rate was 39% (95% CI of 33.5%-44.5%) overall, and similar across sex (41% Female, 37% Male) and race and ethnicity (37% underrepresented groups [URG], 40% not from URG). Among consented participants, plasma collection rate was 74% (95% CI of 66%-82%), with similar rates across sex (76% Female, 71% Male) and race and ethnicity (75% URG and 75% not from URG). Among participants with blood plasma results, 60% were biomarker eligible to screen for future preclinical AD trials. **Conclusions:** Electronic consent of participants through an online registry, blood sample collections at community-based centers, plasma biomarker quantification and reporting, and biomarker assessments for study eligibility were all feasible with similar engagement rates across demographic groups. The AlzMatch study has expanded to include additional APT Webstudy participants and clinical trial sites. The AlzMatch program has also expanded to provide participants the ability to enroll at community events through participation in the APT Webstudy (AlzMatch Community) or through direct blood collection using on site phlebotomists (AlzMatch CommunityLIVE). **Key words:** Alzheimer's disease, preclinical, recruitment, biomarker eligibility, community. **Disclosures:** No relevant disclosures.

LB27- TWELVE-MONTH RESULTS IN FTD-C9ORF72 PARTICIPANTS FROM INFRONT-2: A PHASE 2 STUDY OF LATOZINEMAB (AL001) IN FTD. L. Carter[1], P. Ljubenkov[2], H. Seelaar[3], O. Kahn[1], L. Long[1], G. Chao[1], J. Okoronkwo[1], M. Smithey[1], J. Huang[1], W. Wangv, G. Romano[1], A. Ludolph[4] *(1. Alector - South San Francisco (United States), 2. University of California San Francisco - San Francisco (United States), 3. Erasmus University Medical Center - Rotterdam (Netherlands), 4. University of Ulm and DZNE - Ulm (Germany))*

Background: Hexanucleotide repeat expansion in the C9orf72 gene is the most common gene variant to cause familial frontotemporal dementia (FTD) and is associated with pathologic TDP-43 accumulation. In nonclinical models of TDP-43 pathology, overexpression of progranulin (PGRN) has been shown to reduce levels of insoluble TDP-43 and protect against axonal damage. These nonclinical findings suggest that elevating CNS PGRN above normal levels may have clinical benefit for individuals with disorders associated with TDP-43 pathology such as FTD-C9orf72. Latozinemab (previously AL001) is a human monoclonal IgG1 antibody being developed by Alector for the treatment of FTD. Latozinemab blocks and downregulates the sortilin receptor, a degradation pathway for PGRN. Interim data from a subset of FTD-C9orf72 participants enrolled in INFRONT-2 was previously shared (N=10 for up to 12 months on-study); here we present clinical outcome assessments and key biomarkers from the full cohort of N=16 FTD-C9orf72 participants for up to 12 months of treatment with latozinemab. **Methods:** INFRONT-2 is an open-label, Phase 2 study investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of latozinemab administered intravenously every four weeks in FTD-C9orf72 and FTD-GRN mutation carriers for 24 months. The primary measure of clinical progression was the CDR® plus NACC FLTD-SB, which was performed every 3 months. A matched control cohort of FTD-C9orf72 participants from the ALLFTD observational cohort was identified via propensity score matching and blinded clinical adjudication. This cohort served as a comparator for an analysis of clinical progression. Fluid biomarkers were analyzed in plasma monthly, and in CSF every 6 months. **Results:** Latozinemab was generally safe and well-tolerated in FTD-C9orf72 participants in INFRONT-2. As previously demonstrated, chronic dosing led to a sustained 2-3-fold increase in PGRN levels in plasma and CSF throughout 12 months of treatment. The rate of clinical progression did not differ between participants receiving latozinemab in INFRONT-2 and untreated matched controls in ALLFTD. The estimate of the treatment effect (ALLFTD-latozinemab) was -0.5 CDR units with a high degree of variability [95% CI -2.96, 2.05] associated with the estimate. GFAP and NfL levels in both plasma and CSF were unchanged over the course of treatment. **Conclusions:** Latozinemab treatment effects were not observed on the rate of clinical disease progression or on plasma biomarkers other than PGRN. The small sample size and a high degree of variability in disease progression in both groups rendered the results uninformative regarding treatment effect in this open-label study. However, there remains a great unmet need for effective therapies in FTD. Latozinemab is being developed for the treatment of FTD-GRN and FTD-C9orf72. A larger placebo-controlled trial is needed to definitively assess the therapeutic potential of latozinemab in treating FTD-C9orf72. **Key words:** FTD-C9orf72, progranulin, AL001, latozinemab. **Clinical Trial Registries:** NCT03987295; https://clinicaltrials.gov and 2019-000138-20 https://www.clinicaltrialsregister.eu. **Disclosures:** LC, OK, LL, GC, JO, MS, JH, WW, and GR are employees of and equity stakeholders in Alector, LLC. PL, HS, and AL are investigators on this trial and declare no competing interests.

LB28- DEVELOPMENT OF ORALLY AVAILABLE, BRAIN PENETRANT COMPOUND REDUCING TAU PATHOLOGY. B. Wolozin[1], P. Ash[1], A. Berson[1], C. Murphy[1], N. Fredette[1], B. Moore[1], J. Vacca[1], R. Schaub[1], G. Larsen[1] *(1. Aquinnah Pharmaceuticals Inc. - Cambridge (United States))*

Background: Increasing data indicates that the pathophysiology of microtubule associated protein tau is mediated by its interactions with RNA and RNA binding proteins via stress granules (SGs) and the translational stress response. Inhibiting the translational stress response with ISRIB or PERK inhibitors reduces tauopathy in animal models, but these compounds exhibit in vivo toxicity. Reducing RNA binding proteins, such as TIA1, also reduces tauopathy and delays disease progression (1, 2). Aquinnah now reports identifying small molecule compounds that inhibit tau/TIA1 SGs in neuronal cell lines and show strong in vivo efficacy in a classic mouse model of tauopathy. **Methods:** Our compound series was identified using high content imaging screening in SH-SY5Y neuroblastoma cells, inducibly over-expressing tau::GFP and TIA1::mKate2, following exposure to stressor. Rat hippocampus (E18) was used to generate primary neurons and 3D human iPSC neuron/astrocyte assembloids were generated as described previously (3). In vivo efficacy studies were conducted in 8 month old P301S tau mice that were treated daily for 1 month, followed by alpha-LISA quantification developed at Aquinnah, using antibodies against misfolded tau (MC-1), pathological phospho-tau, pT18, and phosphor-tau AT8. **Results:** We identified compounds that exhibited a strong ability to reduce tau pathology both in vitro and when administered in vivo by subcutaneous and oral routes. These compounds were characterized for potency, pharmacokinetics, ADME and brain uptake, demonstrating effectiveness at reducing tau pathology in primary rat neurons, and also eliminated tau pathology in 3D human iPSC neuron/astrocyte assembloids. To analyze efficacy in vivo, 8-month P301S tau mice were treated for one month, sacrificed and examined for efficacy. Mice treated subcutaneously showed decreased insoluble tau pathology; levels of MC-1 (misfolded) and pS202/T205 (AT8) tau determined by Alpha-LISAs were 47% ($P<0.001$) and 61% ($P<0.05$) respectively compared to vehicle control. A second compound with improved potency, solubility, and ADME characteristics was used to treat 8-month P301S tau mice QD orally for 28 days. Alpha-LISA analysis again showed greatly decreased pathology in treated mice. Levels compared to vehicle control were: MC-1, 30% ($P=0.0031$); pS202/T205 (AT8), 35%, ($P=0.0018$), and pT181 tau, 40% ($P=0.0005$). Histopathology and a clinical chemistry panel indicated no adverse effects from 28-days of QD treatment. Neuropathological markers for tauopathy are being examined in the brain tissues and will also be presented. **Conclusions:** Aquinnah has identified an orally bioavailable, brain penetrant compound that appears to be safe and is able to strongly reduce tau pathology when administered to animals with mid to late stage tau pathology. These results show strong promise as a potential therapeutic for the treatment of patients with tauopathies, including Alzheimer's disease. **Key words:** Neurofibrillary tangles, therapeutic, mouse model, iPSCs. **Disclosures:** PA, AB, CM, NF, RS, GL are employees of Aquinnah. GL is co-founder and CEO. BW is co-founder and CSO. JV consults with Aquinnah. **Funding:** Alzheimer

Association and Rainwater Foundation (T-PEP-23-974553) and NIH (R44AG060843). **References:** 1. D. J. Apicco et al., Reducing the RNA binding protein TIA1 protects against tau-mediated neurodegeneration in vivo. Nat Neurosci 21, 72-80 (2018). 2. B. Wolozin, P. Ivanov, Stress granules and neurodegeneration. Nat Rev Neurosci 20, 649-666 (2019). 3. H. D. Rickner et al., Single cell transcriptomic profiling of a neuron-astrocyte assembloid tauopathy model. Nat Commun 13, 6275 (2022).

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Posters

CLINICAL TRIALS: METHODOLOGY

P001- VARIATION IN THE MINI-MENTAL STATE EXAMINATION IN SUBJECTS WITH SUSPECTED MILD TO MODERATE ALZHEIMER'S DISEASE: IMPLICATIONS FOR CLINICAL TRIAL DESIGNS.

J. Rock[1], J. Nicodemus-Johnson[2], H. Wood[2], F. Kim[1], J. Kim[3], Y.S. Chun[3], S. Hendrix[2] *(1. AriBio - San Diego (United States), 2. Pentara - Mill Creek (United States), 3AriBNC - Gyeonggi-Do (United States))*

Background: The mini-mental state examination (MMSE) is used globally as both a clinical and research tool to evaluate a person's cognitive function. It includes tests of orientation, concentration, attention, verbal memory, naming, and visuospatial perception. While the examination is not used for diagnosing dementia, it is used to assess cognitive impairment. The simplicity of the test lends itself to widespread use by clinicians. The optimal frequency of administration and repeat reliability of the test has been questioned with respect to individual differences in scores that can occur if the test is administered too often. **Methods:** In a phase 2 study that enrolled 210 subjects from 21 sites in the United States, patients were screened and enrolled (Baseline visit) at two visits over a 2-week period. MMSE was administered at both the Screening and Baseline visits. We analyzed the differences in MMSE scores over this 2-week screening period (Screening MMSE versus Baseline MMSE). Patients were required to have an MMSE score between 16 and 26 at screening to qualify for the study. **Results:** One hundred and nineteen (56.7%) mild and 91 (43.3%) moderate subjects were screened and enrolled. White the overall average (±SD) MMSE for all enrolled subjects increased slightly from Week -2 Screening (21.34 ±3.15) to Baseline (21.62 ± 3.8) visit, this change was not statistically significant (P=0.42). Sixty-six percent (66%) of individuals increased their MMSE score over the 2-week period. Stratification by MMSE score at Screening (≥ 21 [Mild] and ≤20 [Moderate]) demonstrated a trend (fishers P = 0.09) in which individuals with lower Screening MMSE scores (≤20) were more likely to have higher MMSE scores at Baseline compared to the Screening visit. **Conclusions:** This data suggests that changes in MMSE scores may be more prominent in individuals with lower baseline MMSE values. This data is consistent with previous studies that demonstrate small changes are observed in MMSE scores when given in close succession. The implications of this effect have yet to be elucidated, but should be noted when the MMSE scale is administered frequently.

P002- COMMUNICATING TOPLINE TRIAL RESULTS TO PARTICIPANTS AND STUDY PARTNERS IN A PRECLINICAL ALZHEIMER'S DISEASE STUDY.

T. Clanton[1], J. D. Grill[2], J. Karlawish[3], K. Chilcott Holdridge[4], R. Yaari[4], R. Raman[1], S. Walter[1], E. Shaffer[1], P. J. G. Cohen[1], P. S. Aisen[1], R. A. Sperling[5] *(1. Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego (United States), 2. UC Irvine - Irvine (United States), 3. University of Pennsylvania - Philadelphia (United States), 4. Eli Lilly and Company - Indianapolis (United States), 5. Department of Neurology, Harvard Medical School, Brigham and Women's Hospital, Massachusetts General Hospital - Boston (United States))*

Background: Recent efforts emphasize the importance of timely dissemination of topline results to trial participants [1]. Yet, communicating results to participants, especially after the completion of Phase 3 regulatory trials with publicly traded industry partners, has unique challenges and requires compliance with US securities laws as well as Institutional Review Board (IRB) review and approval requirements. The Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) Study was a 240-week, double-blind, placebo-controlled Phase 3 preclinical AD trial funded through a public-private partnership. The A4 Study enrolled 1169 cognitively unimpaired adults (ages 65-85) with elevated amyloid PET and tested solanezumab, a monoclonal antibody targeting soluble amyloid-beta. **Methods:** We developed a communication and dissemination strategy with the goal of providing the topline results for A4 Study participants and study partners immediately upon public release, while complying with research participant protections and confidentiality. Key elements of this strategy included: (a) adhering to financial regulatory requirements, (b) securely disseminating a participant-focused newsletter and video to sites to establish participant expectations on the process and to provide sign-up for notification of study results, (c) using the study website to allow participants, as well as the general public, to sign up in advance for email and/or short message service (SMS) communications, (d) developing a Frequently Asked Questions document to assist sites with participant questions following topline results release, and (e) simultaneous release of topline results press release through study website (in addition to usual sponsor channels), with SMS and email alerts to those who signed up. All participant-facing resources, including the website, email, and SMS content, were provided to sites to submit to their local IRBs as needed. **Results:** The topline study results were posted as a press release on the A4 Study website simultaneously with traditional media release, with 657 emails and 131 SMS pushes sent out to participants, study partners, and other requesters. Compared to the prior day, the A4 'Homepage' views increased from 63 to 352 (458%) and 231 (267%) the day of and the day after the release. The 'Study Results' page views increased from 28 to 1376 (4814%) and 871 (3011%) the day of and the day after the release, respectively. In total, A4 website views increased from 198 on the day prior to the topline results release, to 1994 (907%) and 1315 (564%) the day of and the day after results release, respectively. **Conclusion:** Participants and study partners in the A4 trial had the opportunity to receive the topline results of the A4 Study as soon they were made public. We demonstrated the feasibility of sharing topline study results with participants when careful planning and collaboration among key stakeholders are in place. **Key words:** Alzheimer's, clinical trial, communications,

research participants. **Clinical Trial Registry:** NCT02008357. **Disclosures:** Ms. Clanton has received research funding from the National Institutes on Aging, Alzheimer's Association, Eli Lilly and Eisai. Dr. Grill reports grant funding from the National Institutes of Health (P30 AG066519), Eli Lilly, Eisai, Biogen, Eisai, BrightFocus Foundation, and the Alzheimer's Association. Dr. Karlawish is a site investigator for clinical trials sponsored by Lilly and Biogen. Ms. Chilcott Holdridge is an employee of Eli Lilly and Company, and a minor shareholder of Eli Lilly and Company. Dr. Yaari is an employee of Eli Lilly and Company, and a minor shareholder of Eli Lilly and Company. Dr. Raman has received research funding from the National Institutes of Health, Eli Lilly, Eisai, Alzheimer's Association and American Heart Association. Ms. Walter received salary support from the Alzheimer's Clinical Trials Consortium, National Institutes on Aging, National Institutes of Health (U24AG057437). Ms. Shaffer has received research funding from the National Institutes on Aging, Alzheimer's Association, Eli Lilly and Eisai. Ms. Cohen has received research funding from the National Institutes on Aging, Alzheimer's Association, Eli Lilly and Eisai. Dr. Aisen has research grants from the National Institutes of Health, the Alzheimer's Association, Janssen, Lilly and Eisai, and consults with Merck, Roche, Genentech, Abbvie, Biogen, ImmunoBrain Checkpoint and Arrowhead. Dr. Sperling is a consultant to AC Immune, Acumen, Genentech, Ionis, Janssen, Oligomerix, Prothena, Shionogi, Vaxxinity (Spouse consultant to Merck, Novartis). She also has ACTC Trial Research Funding: Eisai, Alzheimer's Association, GHR Foundation, NIA: U24 AG057437; R01 AG063689; R01 AG054029; R01AG061848. **References:** 1. Largent, E. A., Walter, S., Childs, N., Dacks, P. A., Dodge, S., Florian, H., Jackson, J., Llibre Guerra, J. J., Iturriaga, E., Miller, D. S., Moreno, M., Nosheny, R. L., Obisesan, T. O., Portacolone, E., Siddiqi, B., Silverberg, N., Warren, R. C., Welsh-Bohmer, K. A., Edelmayer, R. M., & Participant FIRST Work Group (2022). Putting participants and study partners FIRST when clinical trials end early. Alzheimer's & dementia : the journal of the Alzheimer's Association, 18(12), 2736–2746. https://doi.org/10.1002/alz.12732

P003- RECRUITMENT AND ELIGIBILITY OF A DIVERSE STUDY POPULATION IN INTERCEPT-AD: A PHASE I TRIAL OF AB OLIGOMER-TARGETING ACU193 IN EARLY ALZHEIMER'S DISEASE.

R. Moxon[1], T. Feaster[1], G. Sethuraman[1], A. Carroll[1], S.T. Gan[1], S. Ziemba[1], K. Price[1], V. Skljarevski[1], K. Sundell[1], J. Hitchcock[1], E. Siemers[1] *(1. Acumen Pharmaceuticals - Charlottesville (United States))*

Background: Enrolling participants from a diverse range of racial and ethnic backgrounds in Alzheimer's disease (AD) clinical trials can pose numerous challenges. Despite efforts to improve diversity, racial and ethnic minorities are still underrepresented in AD research. Some of the obstacles include distrust in medical researchers, barriers presented by cultural and linguistic differences, stigma surrounding the disease, and a lack of awareness of clinical trials among potential participants and caregivers. While there are barriers that contribute to enrolling a diverse group of trial participants, a better understanding of recruitment sources, reasons for screen failure, and differences in clinical presentation could be beneficial to researchers. **Methods:** INTERCEPT-AD is a phase 1 randomized, placebo-controlled, double-blind study of ACU193 in mild cognitive impairment or mild dementia due to AD. Seventeen study sites in the U.S. screened 260 potential participants identified through multiple recruitment tactics and 70 were eligible for participation. Recruitment tactics were grouped post hoc into seven categories: site database, external referral, physician referral, site campaign, and three sponsor-initiated campaigns (A, B, and C). To determine whether there were differences by race or ethnicity in recruitment source, two groups based on participants' race or ethnicity were compared (white [white/non-Hispanic] and ethnically diverse [Hispanic/Latino, Black/African American, American Indian/Alaska Native and Asian]). Screen failure rates and reasons were analyzed with Fisher's exact test between the two groups. **Results:** Potential participants for the INTERCEPT-AD study were recruited from a variety of campaigns. Between white and ethnically diverse participants, the main sources of recruitment varied. White participants were recruited through a relatively balanced combination of sources: site database (29%), campaign A (23%), site campaigns (18%), campaign B (14%), external referrals (8%), campaign C (4%), and physician referrals (3%). In ethnically diverse participants, the majority (54%) were referred from the site's database, followed by campaign A (12%), external referrals (11%), campaign B (9%), physician referrals (8%), site campaign (5%) and campaign C (1%). Of 260 potential participants screened, 52.7% identified as white/non-Hispanic, 31.5% Hispanic/Latino, 14.2% Black/African American, 1.2% American Indian/Alaska Native, .4% Asian. For the 70 eligible participants, 78.6% were white/non-Hispanic, 15.7% Hispanic/Latino, 4.3% Black/African American, 1.4% American Indian/Alaska Native, and 0% Asian. Screen failure rates were significantly different between white potential participants (60%) and ethnically diverse potential participants (88%; $p < 0.001$). The most frequent reason for screen failure in both groups was amyloid-negative PET scan results, which was also significantly different between the two groups ($p < 0.02$), accounting for 54% of screen failures in white potential participants and 68% in ethnically diverse potential participants. **Conclusion:** INTERCEPT-AD screened a racially and ethnically diverse group of candidates. While the recruitment sources varied between white and ethnically/racially diverse study candidates, a representative group completed the screening process. However, diversity was reduced with screen failures, especially due to amyloid-negative imaging. These factors highlight the importance of considering the intersection of race, ethnicity, culture, and healthcare in clinical trial recruitment of diverse patient populations. **Key words:** Ethnicity, racial and ethnic minorities, dementia, amyloid PET. **Disclsoures:** Authors RM, TF, GS, AC, STG, SZ, KP, KS, JH and ES are employees of Acumen Pharmaceuticals and VS is a consultant of Acumen Pharmaceuticals

P004- INVESTIGATING TREATMENT EFFECT HETEROGENEITY IN DATA-DRIVEN SUBGROUPS OF TOMMORROW.

C. Shand[1], N.P. Oxtoby[1] *(1. University College London - London (United Kingdom))*

Background: Undetected heterogeneity can confound clinical trials unless accounted for in trial design, e.g., via stratification, covarying, or screening. We aim to discover subgroup heterogeneity using unsupervised machine learning, then perform post hoc subgroup analyses in completed trials. Here we report analysis of TOMMORROW data (NCT01931566), accessed via the Vivli platform. **Methods:** Data is from ADNI (training; N=701; 60 CN; 518 MCI; 183 AD) and TOMMORROW (testing; N=3391). ADNI is an observational study. TOMMORROW was a phase 3 trial of both a biomarker risk algorithm for developing MCI due to AD (MCI-AD)

and the efficacy of the Type 2 Diabetes drug pioglitazone for delaying this onset in cognitively normal individuals1. TOMMORROW was terminated by futility analysis. Inclusion criterion: individuals having complete feature and covariate data. Our machine learning model discovered clusters of MCI-AD cognitive decline in ADNI data (baseline visit) using the Subtype and Stage Inference (SuStaIn) algorithm. Model input features were the six cognitive test scores available in both ADNI and TOMMORROW, i.e., CDRSB, MMSE, category fluency (CATFLU), neuropsychiatric inventory (NPI), Trails A (TRAA), and Trails B (TRAB). Cognitive test score data (in both cohorts) was adjusted for age, biological sex, and years of education relative to controls (cognitively unimpaired, amyloid negative, APOE-e4 non-carriers in ADNI). The cross-validation information criterion was used to determine the number of subtypes in the trained model, which was used to assign baseline subtype and stage to the N=3391 individuals with complete data in TOMORROW trial. Following the TOMMORROW trial protocol, a Cox proportional hazards model assessed differences in the time to event (MCI-AD) across subtypes and stages. Subtypes were also compared statistically by demographics using ANOVA/chi-squared tests. **Results:** SuStaIn identified five subtypes of cognitive decline due to MCI-AD (ADNI data): 1) preserved executive (32%); 2) preserved fluency (29%); 3) fluency-led (25%); 4) psychiatric-led (11%); and 5) executive-led (2%). Deploying this model on TOMMORROW, N=1601 (47.2%) individuals were assigned to stage zero (effectively a null subtype, or subtype zero), indicating no cognitive impairment. The remaining were split N=829/279/377/250/55 to subtype 1, 2, 3, 4, and 5 respectively. There were statistically significant, but small magnitude, differences between subtypes in age, sex, years of education, and baseline MMSE, Global CDR, Trails A, and Trails B. Hazard ratios for the primary outcome varied across subtypes, with subtype zero showing the greatest difference (HR 1.11; 0.37-3.35 99% CI; p=.81). Individuals assigned to stage zero were significantly less likely to convert to MCI (HR 0.34; 0.18-0.64 99% CI; P<.0001). **Conclusion:** A computational model trained using Subtype and Stage Inference identified subtle cognitive heterogeneity (subtypes) at baseline in the Phase 3 TOMMORROW trial. Post hoc analysis revealed subgroup differences in a primary outcome — time to onset of MCI due to AD, namely the data-driven subgroup having minimal cognitive impairment (model stage zero) showed significantly lower rates of conversion to MCI-AD. This may have confounded the trial's futility analysis Our results support the use of computational modelling in the design of clinical trials in AD. **Disclosures:** This abstract is based on research using data from data contributors Takeda Pharmaceuticals that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

P005- HOW SHOULD THE NEXT GENERATION OF ALZHEIMER'S DISEASE CLINICAL TRIALS BE ANALYZED IN THE ESTIMANDS FRAMEWORK? THE GRADUATE I & II EXPERIENCE. R. Abbas[1], N. Voyle[2], G. Palermo[1], G. Kerchner[1], C. Lane[2], A. Thanasopoulou[1], J. Smith[2], R. Doody[1,3], P. Delmar[1] *(1. F. Hoffmann-La Roche Ltd - Basel (Switzerland), 2. Roche Products Ltd - Welwyn Garden City (United Kingdom), 3. Genentech, Inc. - South San Francisco (United States))*

Background: GRADUATE I(NCT03444870) and GRADUATE II (NCT03443973) were two 27-month, global, Phase III, randomized, placebo-controlled trials assessing the efficacy and safety of gantenerumab in early Alzheimer's disease (AD). The ICH E9R1 estimand guidance [1] has formalized a framework for the design and reporting of clinical trials, with an emphasis on aligning the scientific question of interest with the analytical methods, including the handling of post-randomization intercurrent events. This provides grounds for improvement and innovation to the design, conduct and analysis of clinical studies in the highly regulated environment of PhaseIII trials. The GRADUATE studies were among the first pivotal trials in Alzheimer Disease to fully adopt this approach. **Methods:** The primary clinical question as stated in the protocol was to assess the effect of gantenerumab on disease progression at week 116, irrespective of use or initiation of symptomatic AD treatments, and in the absence of a substantial impact of the COVID-19 pandemic. The four estimand attributes (target population, variable, treatment, population level summary) and additional intercurrent events were defined in accordance to this aim. Intercurrent events (ICEs) were prespecified and classified in two categories: Study drug or condition related (SDCR) or non-study drug or condition related (NSDCR). SDCR ICEs were handled with a Treatment Policy strategy (treatment effect "regardless of whether or not the ICE occurred"); NDSCR ICEs, including impact of the COVID-19 pandemic, were treated with a Hypothetical strategy (treatment effect "as if ICE had not occurred"). The missing data analysis was pre-specified to be in line with the estimand, ICE handling strategy and plausible based on the mode of action of gantenerumab. Missing data following SDCR ICEs were imputed based on the placebo group trajectory irrespective of treatment arm, following a copy increments from reference (CIR) assumption. All data following NSDCR ICEs were imputed from the randomized treatment arm using the Missing at Random assumption (MAR). The estimand approach was also utilized to plan sensitivity analyses, define supplementary estimands and applied to secondary efficacy and pharmacodynamic endpoints. **Results:** Defining, characterizing and classifying ICEs was challenging in some cases. An internal independent adjudication committee was formed to classify ambiguous ICEs. We developed a new approach allowing differential handling of missing data in line with the primary estimand while the usual MMRM approach relies only on the MAR assumption. This was implemented in a novel R package named "RBMI" [2, 3]. Overall in both studies, 546 ICEs were reported. More ICEs were reported in the active treatment arms. The majority of ICEs were SDCR. The most frequently reported ICE category was a "withdrawal from study treatment due to safety or tolerability reasons". At one year, the ICE-free rate was 85% in the treatment arms and 88% in placebo arms [4]. **Conclusions:** The GRADUATE studies showed the feasibility and the benefits of applying an estimand framework in large pivotal studies, and constitute an important point of reference for future and ongoing trials. **Key words:** gantenerumab, estimand, missing data, intercurrent events. **Disclosures:** Rachid Abbas is an employee of F. Hoffmann-La Roche, Ltd. and is a shareholder in F. Hoffmann-La Roche Ltd. Nicola Voyle is an employee of Roche Products Ltd. and owns stock or stock options in F. Hoffmann-La Roche Ltd. Giuseppe Palermo is an employee of F. Hoffmann-La Roche, Ltd. and is a shareholder in F. Hoffmann-La Roche Ltd. Geoffrey Kerchner is an employee of F. Hoffmann-La Roche Ltd. and is a shareholder in F. Hoffmann-La Roche Ltd. Christopher Lane is a full-time employee of Roche Products Ltd and owns stock/stock options/shares in F. Hoffmann-La Roche Ltd. Angeliki Thanasopoulou is an employee of F. Hoffmann-La Roche, Ltd. and is a shareholder in F. Hoffmann-La Roche Ltd. Janice

Smith is an employee of Roche Products Ltd. and owns stock or stock options in F. Hoffmann-La Roche Ltd. Rachelle S Doody is an employee of F. Hoffmann-La Roche Ltd and Genentech Inc., part of F. Hoffmann-La Roche Ltd. Rachelle S Doody is a shareholder in F. Hoffmann-La Roche Ltd. Paul Delmar is an employee of F. Hoffmann-La Roche, Ltd. and is a shareholder in F. Hoffmann-La Roche Ltd. **References:** 1. ICH E9 (R1) addendum on estimands and Sensitivity Analysis in Clinical Trials to the guideline on statistical principles for clinical trials. 2. Gower-Page, C., Noci, A., & Wolbers, M. (2022). rbmi: A R package for standard and reference-based multiple imputation methods. Journal of Open Source Software, 7(74), 4251. 3. Wolbers, M., Noci, A., Delmar, P., Gower-Page, C., Yiu, S., & Bartlett, J. W. (2022). Standard and reference-based conditional mean imputation. Pharmaceutical statistics, 21(6), 1246-1257. 4. Abstract: 15th Conference Clinical Trials Alzheimer's Disease, November 29- December 2, 2022, San Francisco , USA: Symposia - Oral Communications - Late Breaking News. J Prev Alzheimers Dis. 2022;9(S1):S8-S50.

P006-FACTORS INFLUENCING OLDER ADULTS' INTENTION TO PARTICIPATE IN A SECONDARY PREVENTION TRIAL IN ALZHEIMER'S DISEASE.

E. Largent[1], J. Grill[2], J. Karlawish[1], A. Bleakley[3] *(1. University of Pennsylvania - Philadelphia (United States), 2. University of California, Irvine - Irvine (United States), 3. University of Delaware - Newark (United States))*

Background: The failure to recruit sufficient numbers of representative Alzheimer's disease (AD) research participants at an acceptable rate delays scientific progress. Thus, there is an urgent need to identify ways to increase recruitment of research participants, particularly representative participants. The Reasoned Action Approach (RAA) provides a conceptual framework to understand why individuals do or do not intend to participate in AD research. According to the RAA, "intention" to perform a target behavior is a function of one's feelings about personally performing the behavior ("attitudes"), perceptions about what others think ("injunctive norms") and do ("descriptive norms"), and beliefs about one's ability to perform ("capacity") and control over ("autonomy") the behavior. **Methods:** A national opt-in RAA survey of 603 US adults aged 65+ not diagnosed, per self-report, with Mild Cognitive Impairment (MCI), dementia, or AD. The survey instrument, designed by the authors, was informed by a literature review and the results of elicitation interviews with cognitively normal older adults. Survey respondents were given a description of the HEALTHY MIND Study, a hypothetical secondary prevention trial in which participants would undergo biomarker testing and be randomized to receive an investigational IV drug or placebo, and asked about their intention to enroll in the next three months. Results were weighted to be nationally representative. We examined the correlation of underlying beliefs with intention and performed regression analyses to identity the salient RAA determinants of intention to enroll in the HEALTHY MIND Study. **Results:** Of the 603 participants, 407 self-identified as White, 148 as Non-Hispanic Black, and 35 as Hispanic. Results showed that 24% of respondents reported intending to participate in the HEALTHY MIND Study. In the full sample, analyses showed that intention was significantly driven by attitudes (b = 0.45, SE(.10) p=<.01), as well as by descriptive norms (b= 0.26, SE(.09), p<.01), injunctive norms (b = 0.22, SE(.08), p<0.01), and capacity (b = 0.24, SE(.05), p<0.01); autonomy was not related to intention. Various attitudinal beliefs were correlated with intention, including that enrollment in the HEALTHY MIND Study would "allow me to track my brain health over time," "allow me gain access to a treatment that may lower my risk of dementia," and "help to advance science" or "help others in the future." Though differences between Black and White respondents were not statistically significant, attitudes were more important for Black (b = 0.75, SE(.10), p<0.01) than White (b= 0.29, SE(.13), p<.05) respondents; by comparison, descriptive norms were less important for Black (b = 0.06, SE(.12), ns) than White (b = 0.42, SE(.10), p<.01) respondents. **Conclusions:** A key premise of the RAA is that underlying beliefs differ between those who do and do not intend to perform the target behavior and that interventions can be tailored to address salient underlying beliefs, thereby changing intention and, ultimately, behavior. Such tailoring can improve recruitment for AD research. Our data suggest that messages focused on attitudinal beliefs such as tracking brain health, accessing novel therapies, and helping others may be particularly successful in promoting enrollment in secondary prevention trials. **Key words:** Secondary prevention; recruitment; representation; research design. **Disclosures:** This research was supported by the National Institute on Aging (K01-AG064123). The authors report no conflicts of interest.

P007- EVALUATION OF MACHINE LEARNING MODELS THAT PREDICT ALZHEIMER'S DISEASE PROGRESSION IN OBSERVATIONAL STUDIES AND RANDOMIZED CLINICAL TRIALS.

S. Broomé[1], S. Belachew[2], B. Caba[2], E. Cavedo[1], J. Dubois[2], A. Gabelle[2], R. Gabr[2], A. Gafson[2], D. Ioannidou[1], X. Jiang[2], Y. Jin[2], N. Oxtoby[3], M. Pang[2], N. Paragios[1], W. Huijbers[2] *(1. TheraPanacea - Paris (France), 2. Biogen - Cambridge (United States), 3. Toybox Science - Mildenhall (United Kingdom))*

Background: Machine learning (ML) models that predict rates of clinical progression can help enrich clinical trials in Alzheimer's disease (AD). Until now, prediction models have been developed using observational data. Here, we share an evaluation of ML models for predicting AD progression in observational versus randomized controlled trial (RCT) data sets and using various input data modalities. **Methods:** We compared performance for prediction of AD progression in observational data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) used in The Alzheimer's Disease Prediction Of Longitudinal Evolution (TADPOLE) Challenge (N =1737) and the pooled placebo arms of ENGAGE (NCT02477800) and EMERGE (NCT02484547) RCTs (N=1093). For observational data, we used the ADNI LB4 (Leaderboard) dataset of the TADPOLE Challenge with an average follow-up of 35 months. For the RCT data the average follow-up was 18 months. The primary prediction target was the ADAS-Cog-13 score at the last visit. As a secondary prediction target, we evaluated ventricle volume as a percentage of intracranial volume (ICV) from MRI. From a single input visit with multiple data modalities (demographics, cognitive scores, genetic status, imaging features), the ML task was to predict the target outcome at that last visit. During training, we used all longitudinal visits, to generate all possible pairs between any reference and target visit. For the results, we only used baseline as an input versus the target visit. This paired training enabled use of various ML methods, without explicitly modeling the disease trajectories. Using 5-fold cross validation, we evaluated several ML models (support vector machine, random forests including XGboost, ridge regression), the ensemble of these base models, and the influence of various input feature sets. **Results:** We report only ensemble model results because they

consistently outperformed individual models in all experiments. First, in observational data, we benchmarked our model against the TADPOLE Challenge. Our prediction of ADAS-Cog-13 showed a mean absolute error (MAE) of 4.18 ([3.70, 4.66], 95% CI) -- on-par with the best TADPOLE Challenge results (MAE = 4.23) [1]. On ventricle volume prediction, we outperformed the best TADPOLE Challenge results (MAE = 0.30 ([0.26, 0.34], 95% CI) vs 0.38). Next, we trained the models on the RCT data. The best model achieved a MAE = 4.82 for the prediction of ADAS-Cog-13, and a MAE = 0.18 for ventricle volume prediction and included the following input features: age, sex, diagnosis, APOE4 status, ADAS-13, and volumes of the hippocampus, ventricles, and default-mode network brain regions of interest. **Conclusions:** On ADAS-Cog-13, we observed slightly higher errors with models trained and tested with RCT vs observational data. Nevertheless, in the RCT setting the MAE = 4.82 on predicting ADAS- Cog-13 was numerically better than state-of-the-art disease progression models developed by Maheux et al (MAE = 5.98) [2]. Our ML models performed well on prediction of ventricle volume in both settings. Future ML experiments using combined, larger datasets, and more advanced ML methods may further improve these predictions. **Registry:** NCT024778001 (ENGAGE); NCT02484547 (EMERGE); https://clinicaltrials.gov. **Disclosures:** This research was funded by TheraPanacea and Biogen. Sofia B, EC, DI, NP are TheraPanacea employees. Shibeshih B, YJ, BC, JD, RG, Audrey G, Arie G, XJ, MP, WH are Biogen employees. NO is a paid consultant for TheraPanacea. **References:** 1. Marinescu, R. V., et al., «The Alzheimer's Disease Prediction Of Longitudinal Evolution (TADPOLE) Challenge: Results after 1 Year Follow-up», Journal of Machine Learning for Biomedical Imaging, 2021. 2. Maheux et al., «Forecasting individual progression trajectories in Alzheimer's disease», Nature Communications, 2023.

P008- STUDY DESIGN OF POLARIS-AD, AR1001 PHASE 3 STUDY IN EARLY ALZHEIMER'S DISEASE. S. Sha[1], S. Kim[2,3], J. Cumming[4], C. Teunissen[5], D. Greeley[6], M. Kim[6], J. Rock[6], F. Kim[6], J.J. Choung[6] *(1. Stanford University - Palo Alto (United States), 2. Seoul National University College of Medicine - Seoul (Korea, Republic of), 3. Seoul National University Bundang Hospital - Seoul (Korea, Republic of), 4. University of Nevada, Las Vega - Las Vegas (United States), 5. Amsterdam University Medical Centers - Amsterdam (Netherlands), 6. AriBio Co., Ltd - Seongnam (Korea, Republic of))*

Background: Despite the growing armamentarium of treatments for Alzheimer's disease (AD), the recognition that AD is multifactorial in its etiology necessitates additional searches for treatments that are multi-factorial in mechanism. AR1001 (mirodenafil), an oral phosphodiesterase (PDE5) inhibitor, attenuates pathology of Alzheimer's Disease in preclinical models by four mechanisms: 1) enhancing neurogenesis and inhibiting neuronal apoptosis by activating the cAMP-response element binding protein (CREB) signaling and inhibition of Caspase pathway, 2) improving synaptic plasticity by stimulating the Wnt pathway, 3) increasing autophagy and thereby reducing beta-amyloid (Aβ) and phosphorylated tau burden, and 4) attenuating neuroinflammation in microglia by reducing pro-inflammatory cytokines. Thus, studying AR1001 for the treatment of AD is warranted. A successful phase 2 study of AR1001 assessed the safety and efficacy in people with mild to moderate Alzheimer's dementia, aged 55 to 80 years. Safety and tolerability supported oral AR1001 at 10 mg and 30 mg once daily for 52 weeks. The other primary endpoint, the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog-13) was not met at week 26, but post-hoc analysis of the mild AD group showed improvement for the 30 mg group at 52 weeks (4.019 points, $p = 0.039$). The exploratory endpoint of plasma pTau-181 was met in both 10 mg and 30 mg groups with reduction from baseline at 52 weeks (-1.214 pg/ml, $p < 0.0001$; -1.355 pg/ml, $p < 0.0001$, respectfully). Given the safety profile, potential efficacy in the mild AD group with the 30mg dose, and improvement in the plasma pTau-181 biomarker, a phase 3 trial evaluating AR1001 in people with early AD is justified. **Method:** To evaluate the efficacy and safety of AR1001 in participants with early Alzheimer's disease (MCI due to AD and mild Alzheimer's dementia), we designed a phase 3 global, double-blind, randomized, placebo-controlled, multi-center trial, POLARIS-AD. A total of 1,150 participants, ages 55-90 years will be enrolled with confirmed brain amyloid. Eligible participants in the treatment group will receive 30 mg of oral AR1001 once daily for 52 weeks and open label extension phase for an additional 104 weeks. **Results:** To analyze the primary endpoint of efficacy, the Clinical Dementia Rating – Sum of Boxes will be used to compare AR1001 to placebo from baseline to Week 52. The other primary endpoint of safety will be evaluated by comparing frequency of treatment emergent adverse events and Columbia Suicide Severity Rating Scale of AR1001 with placebo from baseline to Week 52. Secondary endpoints include ADAS-Cog13, Amsterdam-Instrumental Activities of Daily Living Questionnaire-Short Version, Geriatric Depression Scale, and Mini-Mental Status Examination change from baseline to Week 52. Biomarker endpoints in plasma and CSF include pTau (181, 217, and/or 231), total tau, Aβ 42/40 ratio, NfL, and GFAP from baseline to Week 52. Exploratory endpoints include Quality of Life in Alzheimer's Disease, pharmacokinetics analyses, and all aforementioned endpoints through the extension phase. **Conclusion:** POLARIS-AD will address whether treatment with 30mg of oral AR1001 is efficacious and safe in people with early AD. **Clinical Trial Registry:** NCT05531526; https://clinicaltrials.gov. **Disclosures:** SS is a primary investigator for Polaris-AD. SK, JC, and CT are consultants for AriBio. DG, MK, JR, FK, JJC are employees of AriBio. The authors declared no competing interests. **References:** Kang BW, et al. Alzheimer's Research & Therapy 2022; 14:92. https://doi.org/10.1186/s13195-022-01034-3. AR1001 Phase 3 Clinical Study Protocol. Version 0.1: AR1001-ADP3-US01. AriBio Co., Ltd. Nov 2022. Clinical Study Report. Version 4 AR1001-ADP2-US01. AriBio Co., Ltd. Jan 2023. CTAD. Journal of Prevention of Alzheimer's Disease, Volume 8, November 2021, oral communication. https://www.ctadalzheimer.com/files/files/CTAD21%20Oral%20communications.pdf

P009- ENRICHMENT FOR CLINICAL TRIAL OF EARLY AD USING COMBINATION OF PHS AND PLASMA P-TAU181 AS SCREENING INSTRUMENTS. X. Wang[1], X. Wang[1], S. Edland[1], I. Broce[1], S. Banks[1] *(1. University of California, San Diego - La Jolla (United States))*

Background: Enrolling non-demented participants with genetic risk factors for and/or biomarker evidence of high risk of Alzheimer's disease (AD) may improve clinical trial efficiency, reducing trial cost and study participant burden. It's important to identify a low-cost, less-invasive screening instrument for trials enrichment. Here we aim to evaluate the combination of genetic risk (G) and baseline plasma p-tau biomarkers (T) for AD clinical trials enrichment. **Methods:** We included 686 non-demented participants (cognitively normal:

n = 271, age: 74.86 ± 6.56 years; mild cognitively impaired: n = 415, age: 72.47 ± 7.80 years) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study who self-identified as non-Hispanic White and had available polygenic hazardous score (PHS), baseline plasma p-tau181 and longitudinal cognitive data. Cognitive outcomes were: MMSE, CDRSOB, ADAS11, mPACCdigit and mPACCtrailsB. Participants were grouped by the previously published cutoffs of PHS (PHS < 0.074: G-; PHS ≥ 0.074: G+) [1]and baseline plasma p-tau181 (p-tau181 < 19.8pg/ml: T-; p-tau181 ≥ 19.8pg/ml: T+) [2]. We performed power analyses in the combined CN and MCI group to estimate the required sample size for two-arm clinical trials designed to detect a 25% difference in cognitive decline using different cognitive outcome measures and trial lengths of 1 or 2 years. Power calculations assumed Mixed Model Repeated Measures (MMRM) analysis adjusting for baseline age, sex, education, and baseline diagnosis. Three sample sizes were calculated and compared, one estimating the sample size required for trials restricting enrollment to both high plasma p-tau181 and high PHS participants (G+T+), the other two for trials using only high plasma p-tau181 (T+) or high PHS as the inclusion criterion (G+). **Results:** At each time point, for five cognitive measures, clinical trials enrolling G+T+ participants significantly reduced the sample size than trials using only high plasma p-tau181 or PHS as inclusion criterion, especially at two years. At two years, using multiple biomarkers (G+T+) required roughly 70%-80% fewer participants for enrollment compared to using only G+ and 25%- 40% fewer participants compared to using T+ only. **Conclusions:** The combination of PHS and baseline plasma p-tau181 outperform single model in clinical trial enrichment, which would be a promising screening instrument for enrollment. Additional tau species may show more sensitivity and should be assessed in future models. **Key words:** Alzheimer's disease, polygenic hazardous score, plasma p-tau181, clinical trials enrichment. **Disclosure:** All authors have nothing to disclose. **References:** 1. Wang X, Broce I, Qiu Y, Deters KD, Fan CC, Dale AM, et al. A simple genetic stratification method for lower cost, more expedient clinical trials in early Alzheimer's disease: A preliminary study of tau PET and cognitive outcomes. Alzheimers Dement. 2023. 2. Hansson O, Cullen N, Zetterberg H, Alzheimer's Disease Neuroimaging I, Blennow K, Mattsson-Carlgren N. Plasma phosphorylated tau181 and neurodegeneration in Alzheimer's disease. Ann Clin Transl Neurol. 2021;8:259-65.

P010- VALIDATING AN AUTOMATIC PHONE-BASED SPEECH BIOMARKER MEASURING COGNITION SB-C AGAINST PACC5 AND MOCA IN THE SWEDISH H70 EPIDEMIOLOGICAL COHORT.

J. Tröger[1], F. Öhman[2], E. Mallick[1], A. König[1], J. Skoog[2], A. Zettergren[2], S. Kern[2], S. Sacuiu[2], M. Schöll[2], N. Linz[1], I. Skoog[2] *(1. ki elements GmbH - Saarbrücken (Germany), 2. Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg - Gothenburg (Sweden))*

Introduction: A speech biomarker measuring cognition in an automated, remote and low-burden fashion can be a powerful tool to screen for Alzheimer's (AD) and other neurodegenerative diseases. This has applications both in clinical trial research as well as for case finding in healthcare once newly approved AD drugs enter the market. As new tools and methods have to be validated against the current standard, the aim of this research is to investigate validity by comparing an automatic remote speech biomarker measuring cognition against established AD cognitive assessments such as the PACC-5 or MoCA. **Methods:** The ki:e Speech Biomarker for cognition (ki:e SB-C; Tröger et al., 2022) was collected from 206 (107 F) participants of the H70 epidemiological cohort (Rydberg Sterner et al., 2019) with 29 (20 F) of them presenting with mild cognitive impairment. Spearman rank correlations were computed between ki:e SB-C Cognition Score, an adaptation of PACC5 (Öhman et al., 2022) and the MoCA score. Furthermore, to benchmark the performance of ki:e SB-C to screen for MCI, we trained 3 Machine Learning classifiers (SVM with class weights and GridSearch), once with SB-C and once MoCA score. Models were evaluated using Leave One Out cross-validation. Balanced accuracy, ROC AUC score as well as sensitivity and specificity were reported as classification performance. **Results:** ki:e SB-C Cognition Score was significantly correlated with both PACC5 score ($r = 0.80$, $p < 0.001$, Cohen's $d = 2.67$) and MoCA score ($r = 0.51$, $p < 0.001$, Cohen's $d = 1.17$). The classification experiment results show that ki:e SB-C Cognition Score is comparable to your MoCA score in diagnostic performance while showing a higher sensitivity to detect MCI. **Conclusion:** Overall we present evidence that the automated remote speech biomarker for cognition SB-C relates well to established AD cognitive assessments in MCI patients from the H70 epidemiological birth cohort. Results are encouraging and point towards potential application in both pharmaceutical research and future healthcare scenarios in AD. **Disclosure:** JT, EM, AK, and NL are employed by the digital biomarker company ki:elements. NL, AK and JT own shares of the company. SK has served at SK scientific advisory boards and / or as consultant for Geras Solutions and Biogen. AZ, IS, JS, MS, SS, FÖ have no conflict of interest to report. **References:** Tröger, J., Baykara, E., Zhao, J., Ter Huurne, D., Possemis, N., Mallick, E., ... & Ritchie, C. (2022). Validation of the remote automated ki: e speech biomarker for cognition in mild cognitive impairment: Verification and validation following DiME V3 Framework. Digital biomarkers, 6(3), 107-116. Rydberg Sterner, T., Ahlner, F., Blennow, K., Dahlin-Ivanoff, S., Falk, H., Havstam Johansson, L., Hoff, M., Holm, M., Hörder, H., Jacobsson, T., Johansson, B., Johansson, L., Kern, J., Kern, S., Machado, A., Mellqvist Fässberg, M., Nilsson, J., Ribbe, M., Rothenberg, E., … Skoog, I. (2019). The Gothenburg H70 Birth cohort study 2014–16: Design, methods and study population. European Journal of Epidemiology, 34(2), 191–209. https://doi.org/10.1007/s10654-018-0459-8. Öhman, F., Berron, D., Skoog, J., Bodin, T. H., Kern, S., Zettergren, A., ... & Schöll, M. (2022). Smartphone-based long-term delayed memory performance is associated with the Preclinical Alzheimer's Cognitive Composite and CSF levels of β-amyloid. Alzheimer's & Dementia, 18, e067920..

P011- A SYSTEMATIC REVIEW AND META-ANALYSIS OF AGITATION TRIALS IN INDIVIDUALS WITH DEMENTIA: ARE COGNITIVE MEASURES NEEDED?

H. Belanger[1], K. Gohil[1], J. Finman[1], G. Kay[1] *(1. Cognitive Research Corporation (CRC), University of South Florida - St Petersburg (United States))*

Background: Randomized controlled trials have investigated the potential of various medications to treat agitation in dementia. Many such trials include measures of cognitive performance. It is unclear whether cognition is significantly impacted in these trials. The purpose of this review and meta-analysis was to determine the extent to which various agents used to treat agitation may impact cognitive performance in these trials. **Method:** Electronic databases, including PubMed, EMBASE, International Pharmaceutical Abstracts (IPA), clinicaltrials.gov, and the Cochrane Central

Register of Controlled Trials (CENTRAL), were systematically searched from inception to April 22, 2023, using a combination of keywords and Medical Subject Headings (MeSH) terms including dementia, agitation/aggression, and trials. We also conducted a manual search by screening the reference lists of the included studies and recent reviews. We included placebo-controlled trials of pharmaceuticals that recruited individuals with dementia specifically for agitation/aggression issues and that included standardized cognitive assessment. Trials testing medications specifically designed to treat cognition (e.g., acetylcholinesterase inhibitors) were excluded. Effect sizes were calculated using standardized mean differences (SMD) using R software, Version 4.0.3. Publication bias was assessed using funnel plots and Egger's test of funnel plot asymmetry. Heterogeneity among studies were assessed with the I^2 statistic. Interpretation of the I^2 was made by assigning attributes of low, moderate, and high to the values of 0 to 25%, 50 to 75%, and more than 75%, respectively.1 Fixed effect meta-analysis was to be used if there was no substantial heterogeneity and random effects models were to be used if heterogeneity was present. The random effects model utilized the DerSimonian-Laird method for evaluation of within-study variance. Study methodology was pre-registered with Prospero (CRD42023414140). **Results:** The analysis was based on 16 studies involving 1,394 cases treated for agitation and 1,487 control cases. Due to significant heterogeneity (I2 = 88%, p<.01), a random effects model was used. The overall effect of treatment on cognitive performance (SMD = 0.06) was small and not statistically significant (95% Confidence Interval: -0.16 to 0.28). Eggers' test did not indicate the presence of funnel plot asymmetry. Findings were not moderated by cognitive test, as effect sizes (n = 3) based on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-COG) and the Mini-Mental State Exam (MMSE) (n = 15) were similarly not statistically significant. **Conclusion:** There is no significant effect on cognition in clinical trials testing various agitation medications. Including measures of cognition in agitation trials may therefore unnecessarily burden participants and increase costs. **Key words:** agitation, dementia, cognition, clinical trials. **Disclosures:** All authors are employees of CRC, a contract research organization. GK is co-founder, owner of CRC. **Reference:** Higgins JP, Thompson SG, Deeks JJ, Altman DG. doi: 10.1136/bmj.327.7414.557

P012- EFFECTS OF INFORMANT REPLACEMENT IN ALZHEIMER'S DISEASE CLINICAL TRIALS.
M. Nishida[1], M. Nuno[2], J. Grill[1], D. Gillen[3] *(1. University of California, Irvine - Irvine (United States), 2. University of Southern California - Los Angeles (United States))*

Background: Alzheimer's disease (AD) clinical trials require participants to enroll with a study partner, or "informant." Informants attend study visits and complete validated assessments of participants' cognitive and functional performance. A change in the person filling this role, or informant replacement (IR), can occur anytime during the study, but IR impacts on AD trial outcomes are unknown. **Methods:** Using retrospective analyses of 4 randomized trials conducted by the Alzheimer's Disease Cooperative Study (ADCS), we assessed relationships between IR and ADCS Activities of Daily Living (ADCS-ADL) scores. We used generalized estimating equations (GEE) to estimate the association between IR and mean change in ADCS-ADL between successive visits. These models were repeated for the outcome of absolute successive difference to assess variability in ADCS-ADL. We adjusted for a priori specified potential confounding variables including participant sex, age, informant type, trial, time, and previous ADCS-ADL measurement. We examined whether the trajectories of ADCS-ADL were different before and after IR using GEE. Along with time and an indicator of IR, this model adjusted for confounders participant sex, age, informant type at baseline, and trial. Finally, we used an ANCOVA model to analyze the association between IR and difference in 18-month change from baseline, and an F-test to compare the variance of this change. The ANCOVA model also adjusted for participant sex, age, informant type, trial, and baseline ADCS-ADL measurement. **Results:** Out of N=1338 participants across all trials, 67 (5%) experienced IR at least once. For visits standardized to be three months apart, we estimated that the mean between-visit change in ADCS-ADL was approximately -3.44 points (95% CI: -5.32, -1.65, P-value <0.001), indicating greater functional worsening, for participants who experienced IR compared to participants with stable informants and adjusting for covariates. Similarly, we estimated that participants who experienced IR demonstrated 3.27 points (95% CI: 1.68, 4.85; P-value <0.001) greater mean absolute change between consecutive visits. We estimated that the average change in ADCS-ADL was approximately -0.69 points (95% CI: -0.73, -0.64; P-value <0.001) per month for all participants before IR and -0.71 points (95% CI: -1.04, -0.39; P-value <0.001) per month after IR. This difference was not significant (P-value = 0.874). IR was, however, associated with a -5.33 point (95% CI: -8.05, -2.61; P-value <0.001) difference in ADCS-ADL at the time of IR compared to participants with stable informants. IR was not associated with a significant difference in 18-month change from baseline (Est.=-2.79 95% CI: -6.89, 1.32; P-value = 0.183). We estimated that the ratio of variances in change from baseline for participants with IR compared to those with stable informants was 1.69 (95% CI: 1.15, 2.71; P-value = 0.007). **Conclusions:** Our results suggest that IR is associated with systematic bias and increased variability between successive visits and increased variance overall for 18-month ADCS-ADL reporting. These results emphasize the need to consider informant replacement when planning trials, retaining participants and their informants, and addressing replacement when performing trial analyses. **Key words:** informant replacement, study partner change. **Disclosures:** This project was based upon work funded by the National Institute of Aging RF1 AG059407 and Diversity Supplement to the UCI ADRC Grant No. P30-AG066519-03.

P013- HARNESSING THE POWER OF CONTINUOUS TIME: LEARNINGS FROM RECENT LARGE CLINICAL TRIAL DATA.
P. Delmar[1], L. Lau Raket[2], J. O'gorman[3], G. Wang[4], M. Donohue[5] *(1. F.Hoffmann-La Roche Ltd. - Basel (Switzerland), 2. Eli Lilly and Company, Indianapolis, USA - Indianapolis (United States), 3. Biogen - Cambridge (United States), 4. Washington University School of Medicine, - Saint Louis (United States), 5. University of Southern California - San Diego (United States))*

Background: Longitudinal assessment scales, e.g. CDR-SB over time, are the usual main endpoints of clinical trials in AD. Typically, the data is analyzed and reported on the basis of discrete visits rather than using time on a continuous scale. However, there is a growing interest in leveraging continuous time models. Recently, we saw the first instance of using natural cubic spline-based analysis of continuous time variable for the primary endpoint analysis in a pivotal Phase 3 study. This represents an important milestone in this area. Recent methodological developments and large dataset from recent clinical trials provide a unique opportunity to develop empirical

evidence and recommendations about these methods. **Methods:** The project was conducted under the umbrella of The AD Estimand Scientific Working Group. The AD Estimand SWG is a collaboration of industry and academic statisticians involved in AD Clinical Research. Using harmonized scripts, the group analyzed data from several recent large and well controlled clinical trials. Clinical and biomarker endpoints from these trials were analyzed by modeling the time effect with natural splines or other linear and non-linear functions and compared to usual MMRM with categorical visit approach. The results were collated across trials and endpoints. Interpretation was done qualitatively and quantitatively using goodness of fit and other metrics. Furthermore, the results were compared to recently published results based on studies not included in the analysis. **Results:** In the context of large, well powered phase 3 clinical trials, the main strengths of continuous time models are to allow more flexible trial design and visit windows, enable interpolation between observed timepoints, extrapolation and simulations. These models take advantage of using the exact date of assessment instead of discretized visit windows and can more systematically use early termination visit information. On the other hand, continuous time functions could over-smooth and obscure interesting features of time course trajectory. This needs to be carefully considered when planning and conducting analysis. In the context of hypothesis generating study, typical phase 2 settings, continuous time model can also provide benefit in terms of power and precision. Moving forward, it will be important to establish operational characteristics of these methods combined with different strategies for handling missing data in the context of the Estimand framework. **Conclusion:** The utility of recently proposed continuous time model approaches was evaluated based on a large amount of data from several recent clinical trials. These methods efficiently utilize all available data across time and provide greater flexibility in study design and result interpolation. They may result in more precise treatment effect estimates but their smoothing effect need to be well understood by analysts in order to avoid pitfalls in their interpretation. **References:** Donohue, Michael C., et al. «Natural cubic splines for the analysis of Alzheimer's clinical trials.» Pharmaceutical Statistics (2022). Dhadda, Shobha, et al. «Consistency of efficacy results across various clinical measures and statistical methods in the lecanemab phase 2 trial of early Alzheimer's disease.» Alzheimer's Research & Therapy 14.1 (2022): 182.

P014- INTERNET-BASED INSOMNIA INTERVENTION TO PREVENT COGNITIVE DECLINE: USE OF INTERNET-BASED RECRUITMENT, INTERVENTION, AND ASSESSMENT METHODS. M. Mattos[1], C. Manning[1], W. You[1], K. Macdonnell[1], L. Ritterband[1] *(1. University of Virginia - Charlottesville (United States))*

Background: Individuals with cognitive impairment experience insomnia symptoms at greater rates than those without cognitive concerns. Although the exact mechanisms underlying this relationship are not yet known, one promising approach to maintaining and improving cognitive health is to reduce or eliminate insomnia. The current trial uses Internet-based recruitment, intervention, and assessment methods to evaluate the impact of an Internet-delivered cognitive behavioral therapy for insomnia (CBT-I) intervention and the extent to which it contributes to cognitive health in individuals with mild cognitive impairment (MCI). This presentation will discuss challenges and successes using Internet-based recruitment and assessment methods. **Methods:** Using a randomized controlled trial design, 144 participants with insomnia who meet study criteria for MCI are being recruited to compare the effects of an Internet-based CBT-I Intervention (SHUTi OASIS) versus a patient education (PE) control condition. Only Internet-based recruitment methods, including targeted advertisements on population-specific and social networking sites, are being used. Inclusion criteria include ≥ 65 years of age, sleep-onset insomnia and/or sleep maintenance insomnia symptoms (>30 minutes for at least 3 nights/week for past three months); sleep disturbance (or associated daytime fatigue) that causes significant distress or impairment; cognitive impairment through study assessment; and stable medication regimen. Exclusion criteria include current treatments for insomnia or medical conditions that would preclude study involvement (e.g., severe depression, untreated obstructive sleep apnea, Parkinson's disease). The primary outcome is the intensity of insomnia as measured by the Insomnia Severity Index and wake after sleep onset; daytime variables include levels of fatigue and quality of life. The trajectory of cognition in older adults is measured across three neuropsychological domains (memory, attention/psychomotor, and executive functioning) using Cambridge Cognition CANTAB online tasks at 12- and 24-month assessments. Assessments occur at baseline, post-intervention (est. 13 weeks), and 6-, 12- ,18- , and 24- months. All assessments are administered online and include two weeks of daily sleep diaries, a Qualtrics-delivered questionnaire, and CANTAB tasks. **Results:** Institutional review board approval has been received. Recruitment began in 2023 and is expected to be completed in 2025. In the first few months of study recruitment, recruitment approaches continue to be refined to efficiently and effectively target the study population. This has included using community-engaged studios to create advertisements, modifications to advertisement placement and online sites, and clinical trial match services. The coordination of Internet-based assessments across three different platforms will be discussed. Data collection is expected to be completed in 2027. **Conclusions:** Findings from this trial will determine the efficacy of Internet-delivered CBT-I to improve sleep and daytime functioning in older adults with MCI. Online recruitment and assessment approaches from this trial will inform future Internet-based studies to increase reach and participation in Alzheimer's disease and related dementia clinical trials. **Key words:** insomnia, mild cognitive impairment, cognitive behavioral therapy, Internet. **Clinical Trial Registry:** NCT05565833; https://clinicaltrials.gov. **Disclosures:** Research reported in this publication was supported by the National Institute On Aging of the National Institutes of Health under Award Number K76AG074942. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors declare no competing interests.

P015- EXPLORING THE IMPACT OF BASELINE DISCORDANCE BETWEEN FUNCTIONAL SCALES IN EARLY AD CLINICAL TRIALS. A. Kott[1], X. Wang[2], D. Miller[2] *(1. Signant Health - Prague (Czech Republic), 2Signant Health - Blue Bell (United States))*

Background: The deterioration in patient's functional abilities is one of the hallmarks of Alzheimer's Disease. Measures such as the ADCS-ADL, FAQ and A-IADL-Q have been used in AD clinical trials to assess study participants' level of functioning. Significant discordance between instruments that measure similar concepts could indicate different discriminative ability of each instrument or could

indicate caregiver and/or rater unreliability among other reasons. In the current analysis we assess the relationship between 2 instruments, the ADCS-iADL and the FAQ and explore the impact of possible between scale discordances on Baseline MMSE and CDR-SB scores and their Screening to Baseline changes. **Methods:** Screening and Baseline data for MMSE, CDR-SB, FAQ and ADCS-iADL were retrieved from our database of Early AD subjects. The relationship between Baseline FAQ and ADCS-iADL was assessed using linear regression with the iADL scores entering the equation in a quadratic form. Outliers more than 1.96 SD from the predicted score were identified and categorized as positive or negative outliers if the FAQ score was either higher or lower than the iADL score would indicate. Differences in MMSE and CDR-SB Baseline scores and their change between Screening and Baseline were explored with ANOVA and Bonferroni corrected post-hoc comparison tests. **Results:** Data were available for 2,027 subjects. As expected, a significant relationship between the FAQ and ADCS-iADL was identified, with the shared variance of 41.1%. Of the 96(4.7%) identified outliers, 65 were positive outliers, i.e., FAQ indicated more functional impairment than the iADL. All ANOVA analyses identified significant differences between the groups in all 4 assessed variables, with post-hoc tests indicating significant impact of the positive outliers only. Subjects identified as positive outliers had scores higher by 1.72 points in CDR-SB and by 1.97 points lower in MMSE and deteriorated significantly more between screening and baseline (by 0.52 CDR-SB points and 1.10 MMSE points, respectively) compared to the remaining subjects. **Conclusions:** To our knowledge this is the first exploration of the impact of discordances between functional scales on cognitive measures. While our data indicate a significant overall effect, this effect is observed only in those instances where the FAQ scores indicate significantly poorer functioning compared to iADL. We currently do not have a definitive explanation for this effect. While it is possible that caregiver or rater unreliability may contribute to this picture, the impact on MMSE and CDR does not seem to support this hypothesis. A plausible explanation could be that the higher than predicted FAQ scores identify a subset of subjects with lower cognitive performance. This would be in agreement with the observed differences in the MMSE and CDR-SB scores. We hypothesize that the FAQ-iADL positive discordance could be used as a marker of possible baseline inflation. Additional research to answer this question is needed. **Disclosures:** All authors are employees of Signant Health

P016- A PRAGMATIC, INVESTIGATOR-DRIVEN PROCESS FOR DISCLOSURE OF AMYLOID PET SCAN RESULTS TO ADNI4 RESEARCH PARTICIPANTS.

C. Erickson[1], J. Karlawish[1], J. Grill[2], K. Harkins[1], S. Landau[3], R. Petersen[4], P. Aisen[5], M. Weiner[6], E. Largent[1]
(1. University of Pennsylvania - Philadelphia (United States), 2. University of California Irvine - Irvine (United States), 3. University of California Berkley - Berkley (United States), 4. Mayo Clinic - Rochester (United States), 5. University of Southern California - San Diego (United States), 6. University of California San Francisco - San Francisco (United States))

Background: Substantial evidence from prior AD biomarker disclosure studies demonstrates that participants understand their results with adequate education and that disclosure does not result in anxiety, depression, or suicidality1–3. These studies, while important, have notable limitations. Disclosure processes have been highly structured, measures have largely focused on assessing psychological impact, and participants are not representative of the population of persons with AD. Increasing accessibility to biomarker testing and availability of disease-modifying therapies mean more people may learn AD biomarker information, so pragmatic disclosure practices are necessary before adoption in larger scale settings. **Methods:** The Alzheimer's Disease Neuroimaging Initiative (ADNI) is formally incorporating amyloid PET disclosure into their most recent protocol (ADNI-4): participants across the cognitive spectrum (unimpaired, MCI, and dementia) who wish to know their results may learn them. ADNI assembled a "disclosure team" with experience in the design, implementation, and study of AD biomarker disclosure in longitudinal cohort studies and clinical trials. The disclosure team developed an evidence-based disclosure framework and supporting materials (e.g., participant education sheet and investigator training manual) in collaboration with ADNI leadership and key stakeholders, including members of the Clinical Core, PET Core, Engagement Core, and the Coordination Center. The process sought to minimize burden and emphasize investigator choice and discretion while also seeking to promote participants' understanding of their results and well-being. If participants choose to learn their results, they will participate in two visits in addition to the standard ADNI visits. One visit is for disclosure: an ADNI investigator will return the participant's amyloid PET result and answers questions. The other visit is a telephone check-in one-week post-disclosure. ADNI-4 participants will undergo multiple amyloid PET scans and can learn the results of each. Additionally, ADNI-4 participants may be on anti-amyloid therapies that affect their PET scan results. Participant measures include perceived risk of dementia (unimpaired and MCI only), purpose in life, post-disclosure distress, disclosure satisfaction, value of learning result, and post-disclosure behavior changes, among others. Investigator reflections on the disclosure visit (e.g., challenges encountered, topics discussed, etc.) will also be collected. **Results:** Data collection is ongoing. Results will characterize the impact of learning amyloid PET information on diverse individuals and investigators' perspectives. **Conclusion**: ADNI is one of the largest studies to date to incorporate biomarker disclosure. It is a unique opportunity to deepen knowledge of the participant and investigator experience as well as to test a more flexible approach to disclosure that could be implemented in real-world settings. Due to several factors—the scale of disclosure in terms of number of participants and number of disclosures per participant, the greater diversity of research participants, the number of disclosing investigators across a variety of sites, and the possibility that participants will be on anti-amyloid therapy—ADNI-4 offers a closer approximation of real-world settings than any prior studies of disclosure. Collection of novel participant and investigator data will provide information to usher in a new phase of the science of disclosure and is crucial to the implementation of disclosure processes in real-world settings. **Key words:** Biomarker disclosure, Pragmatic, ADNI. Clinical Trials Registry: NCT05617014; https://clinicaltrials.gov/ct2/show/NCT05617014. **Disclosures:** SML is on advisory boards for KeifeRX advisory board and the IPAT study. She has received speaker fees from Eisai. JDG reports grant funding from the National Institutes of Health, Eli Lilly, Eisai, Biogen, Eisai, BrightFocus Foundation, and the Alzheimer's Association. **References:** 1. de Wilde A, van Buchem MM, Otten RHJ, et al. Disclosure of amyloid positron emission tomography results to individuals without dementia: a systematic review. Alzheimers Res Ther. 2018;10:72. doi:10.1186/s13195-018-0398-3. 2. Bemelmans SASA, Tromp K, Bunnik EM, et al. Psychological, behavioral and social effects of disclosing Alzheimer's disease

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P017- RG6289, A NEW γ-SECRETASE MODULATOR FOR THE TREATMENT OF ALZHEIMER'S DISEASE: DOSE SELECTION FOR A PHASE II TRIAL BASED ON POPULATION PK/PD MODELING. D. Lott[1], A. Portron[1], M. Alam[1], C. Cantrill[1], R. Croney[2], F. Alcaraz[3], R.M. Rodríguez Sarmiento[4], L. Lindemann[1], L. Mueller[1], T. Mueggler[3], T. Vardar[5], R. Tortelli[3], S. Sturm[1], I. Gerlach[3] *(1. Pharmaceutical Sciences, Roche Pharma Research and Early Development, F. Hoffmann-La Roche Ltd - Basel (Switzerland), 2. Roche Innovation Center Welwyn, Roche Pharma Research and Early Development, Roche Products Limited - Welwyn (United Kingdom), 3. Neuroscience and Rare Diseases, Roche Pharma Early Research and Development, F. Hoffmann-La Roche Ltd - Basel (Switzerland), 4. Medicinal Chemistry, Roche Pharma Early Research and Development, F. Hoffmann-La Roche Ltd - Basel (Switzerland), 5. Product Development Safety Risk Management (PDS), F. Hoffmann-La Roche Ltd - Basel (Switzerland))*

Background: Recent clinical data from antibodies targeting amyloid β (Aβ) provide supporting evidence that Aβ is a valid therapeutic target to impact the course of Alzheimer's disease (AD). There is a high unmet need for effective, safe, and easy to use disease modifying treatments. RG6289 is a novel, potent and selective, orally bioavailable γ-secretase modulator (GSM) with good CNS drug-like properties. Data from long-term preclinical toxicology studies support the chronic use of RG6289 in humans. Single and multiple ascending doses were assessed in a first-in-human Phase I study in healthy volunteers to evaluate the safety and tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of RG6289 under fasted and fed conditions. Since there is no data available on the degree of therapeutic Aβ42 lowering that is required to impact the course of AD, the upcoming trial with RG6289 in individuals with very early stages of AD will explore a broader range of amyloid reduction. **Methods:** Data from the Phase I study after single and multiple dose administration were used to develop a population PK/PD model in order to characterize the relationship between RG6289 concentrations and Aβ42 lowering in plasma. It was aimed to identify covariates that may influence the effect of RG6289 on Aβ42 levels. Model-based simulations were performed to investigate and compare plasma Aβ42 reduction for different multiple doses to support dose selection for Phase II in people with AD. In addition, the relationship between Aβ42 lowering in plasma and CSF was explored. **Results:** The PK model which was found to best describe the concentration-time course of RG6289 included food intake, body weight and age as significant covariates. While PK was linear with dose, concomitant food intake delayed absorption, resulting in lower maximum concentrations without affecting overall exposure (AUC). There was an inverse relationship between body weight and RG6289 concentrations and, in addition, RG6289 exposure increased with age. In contrast, none of the tested covariates had a relevant impact on the PD parameters of the model. The relationship between RG6289 PK and plasma Aβ42 reduction was described with an indirect-response model. Aβ42 reduction in CSF and plasma showed a good correlation at the observed trough values after multiple doses such that plasma Aβ42 reduction was considered as a proxy for the changes in CSF. Based on the final population PK/PD model, three doses of RG6289 were selected that produce different steady-state PD effects on Aβ42 within the target range of 30-70% Aβ42 reduction. **Conclusion:** Based on the final population PK/PD model, food did not have any relevant effect on the PD of RG6289. Age effects on PK were taken into account when selecting the final doses for the upcoming Phase IIa study. The three selected doses are covering a broad range of Aβ42 lowering expected to be therapeutically relevant in the very early stages of AD. **Key words:** Alzheimer's Disease, γ-secretase modulator, Amyloid β, Dose selection. **Disclosures:** D. Lott is a full-time employee of F. Hoffmann-La Roche AG and holds stock or stock options of F. Hoffmann-La Roche AG. A.Portron is a full-time employee of F. Hoffmann-La Roche AG. M. Alam is a full-time employee of F. Hoffmann-La Roche AG. C. Cantrill is a full-time employee of F. Hoffmann-La Roche AG. R. Croney is a full-time employee of F. Hoffmann-La Roche AG and holds stock or stock options of F. Hoffmann-La Roche. F. Alcaraz is a full-time employee of F. Hoffmann-La Roche AG. R. M. Rodríguez Sarmiento is a full-time employee of F. Hoffmann-La Roche AG. L. Lindemann is a full-time employee of F. Hoffmann-La Roche AG, holds stock or stock options of F. Hoffmann-La Roche AG, and is co-inventor of patents owned by F. Hoffmann-La Roche AG. L. Mueller is a full-time employee of F. Hoffmann-La Roche AG. T. Mueggler is a full-time employee of F. Hoffmann-La Roche AG. T. Vardar is a full-time employee of F. Hoffmann-La Roche AG. R. Tortelli is a full-time employee of F. Hoffmann-La Roche AG. S. Sturm is a full-time employee of F. Hoffmann-La Roche AG and holds F. Hoffmann-La Roche AG stock. I. Gerlach is a full-time employee of F. Hoffmann-La Roche AG and holds stock or stock options of F. Hoffmann-La Roche AG.

P018- RECRUITMENT SOURCE, ELIGIBILITY, AND REASON FOR PRESCREEN-FAIL ACROSS SEX, RACE & ETHNICITY: A PRELIMINARY ANALYSIS OF PRESCREENING DATA FROM THE AHEAD STUDY. D. Kirn[1,2], S. Wang[3], J.D. Grill[4], K. Ernstrom[3], A. Ikoba[2], E. Sprague[1], G. Jimenez-Maggiora[3], E. Shaffer[3], R. Sperling[1,5], R. Raman[3] *(1. Department of Neurology, Brigham and Women's Hospital, Harvard Medical School - Boston (United States), 2. Department of Neurology, Massachusetts General Hospital, Harvard Medical School - Charlestown (United States), 3. Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego (United States), 4. Institute for Memory Impairments and Neurological Disorders, University of California Irvine - Irvine (United States), 5. Department of Neurology, Massachusetts General Hospital, Harvard Medical School - Boston (United States))*

Background: Recruiting diverse and demographically representative samples into multi-site clinical trials is critically important and challenging. Though screening data can be informative to evaluate selection bias into a trial, additional emphasis should be placed on participant interactions at the prescreening phase (prior to consent), when preliminary eligibility is commonly assessed by study sites. The Alzheimer's Clinical Trials Consortium (ACTC) launched the Data-Driven Approach to Recruitment (DART), a study to centrally collect prescreening data from US-based sites in the AHEAD study, consisting of two sister trials in the preclinical Alzheimer's disease population [1]. **Methods:** The AHEAD study is an ongoing study that aims to evaluate the safety and efficacy of lecanemab (BAN2401, Eisai Inc.) in cognitively

unimpaired adults who have evidence of amyloid on PET imaging. Prescreening data, including sex, race, ethnicity, recruitment source, eligibility, and reason for prescreen-fail (if applicable), were collected from participating study sites under the DART protocol. For these preliminary analyses, we evaluated the impact of recruitment source, eligibility reasons, and reason for prescreen-fail by sex, race, and ethnicity. We combined self-reported race and ethnicity into mutually exclusive categories (Hispanic White, Hispanic Black or African American, non-Hispanic (NH) White, NH Black or African American, NH Asian, Others). Fisher-Freeman-Halton Exact Tests were used for comparisons and an unadjusted p-value of 0.05 was considered statistically significant. **Results:** The analyses included prescreening data for 2824 participants from 29 active US-based AHEAD study sites (median screens per site was 57; range 9, 617). The sample was primarily female (66.7%), NH White (67.4%), and the mean age was 66.4±7.4 years. Compared to men, women were more likely to be identified through the study website and less likely to be identified through registries and national campaigns. NH Asian participants were more likely to be identified through social media (15.9%), and NH Black or African American participants were more likely to be identified through local campaigns (55.4%), as compared to the other racial and ethnic groups. While overall prescreen eligibility rates were similar across sex and race/ethnicity, there were some observed differences in the reasons for pre-screen failure. Men and Hispanic White participants were more likely to prescreen fail due to medical exclusion criteria, while women and NH Asian participants were more likely to screen fail due to non-medical inclusion criteria. NH Black or African American participants were more likely to be lost to follow-up when compared to the other racial and ethnic groups. **Conclusion:** These preliminary analyses suggest that effective recruitment methods may differ by sex and race/ethnicity, suggesting that multiple strategies are essential to recruit a demographically representative cohort. Though no significant difference in eligibility status across sex or racial/ethnic groups was observed, the reasons prescreen-fail show that some underrepresented groups were more likely to be lost to follow-up during the prescreening stage. These analyses confirm the utility of collecting prescreening data in multi-center clinical trials. **Key words:** Clinical trial, recruitment, prescreening, diversity. **References:** 1. Rafi M, et al. Alzheimer's & Dementia 2023; 19(4): 1227-1233. https://doi.org/10.1002/alz.12748

P019- IMPACT OF RECRUITMENT METHODS ON RACIAL AND ETHNIC DIVERSITY: RESULTS FROM THE DAVIS MEMORY AND AGING COHORT AT MASS GENERAL BRIGHAM. S. Moreno[1], A. Ikoba[1], C. Christiano[1], J.A. Ussui Anzai[1], A. Roman[1], D. Kirn[2], L. Jackson-Pope[1], M.C. Muniz[1], J.P. Chhatwal[3], S.A. Gale[4], G.A. Marshall[4], R.A. Sperling[4], H.S. Yang[5], D.J. Selkoe[4], D.M. Rentz[6] *(1. Center for Alzheimer Research and Treatment, Brigham and Women's Hospital - Boston (United States), 2. Department of Neurology, Brigham and Women's Hospital - Boston (United States), 3. Department of Neurology, Mass General Hospital - Boston (United States), 4. Department of Neurology, Brigham and Women's Hospital, Harvard Medical School - Boston (United States), 5. Department of Neurology, Brigham and Women's Hospital - Boston (United States), 6. Center for Alzheimer Research and Treatment, Brigham and Women's Hospital - Boston (United States) - Boston (United States))*

Background: Recruiting participants from diverse backgrounds is a prerequisite for generalizable clinical research. However, it remains unclear which recruitment methods effectively include underrepresented groups (URGs) in clinical research. We investigated the impact of different recruitment methods on the participation of URGs in Alzheimer's disease (AD) clinical studies. **Methods:** The Davis Memory and Aging Cohort (MAC) is a brief cross-sectional AD study recruiting participants ranging from no cognitive impairment to mild dementia. We summarized recruitment sources into four categories: (1) referrals (from clinicians or researchers), (2) advertisements, (3) clinic walk-ins (Brigham and Women's Hospital neurology clinic patients), and (4) community visits (from a community center with higher proportions of URG residents). Interested MAC participants are screened for additional observational studies or clinical trials. With data collected from June 2021 to May 2023 from participants 55 years or older, we used logistic regression models to determine the impact of recruitment methods (categorical predictor, reference: referral group) on the proportion of URGs (binary outcome, defined as race/ethnicity other than Non-Hispanic White) in MAC. For URG participants, we used Fisher's exact test to assess the impact of recruitment sources on their participation in additional studies. **Results:** N=510 MAC participants with available data were included in our analyses. Most participants are female (N=329, 65%) and Non-Hispanic White (N=420, 82%) with a mean age of 68.6 ± 7.2 years. 18% identified as URGs (N=90, mean age = 68.1 ± 9.2 years, female 78%, education = 13.9 ± 4.0 years): N=49 Black or African American, N=27 White Hispanic, N=6 Asian, and N=8 Other. MAC participants from different recruitment sources showed variable demographic characteristics: referral (N=287, mean age = 67.4 ± 7.0 years, female 64%, education = 16.2 ± 2.7 years, URGs N=29 [10%]); advertisement (N=164, mean age = 69.0 ± 7.7, female 66%, education = 16.5 ± 2.9 years, URGs N=32 [20%]); clinic (N=30, mean age = 71.3 ± 8.4 years, female 50%, education = 16.0 ± 3.5 years, URGs N=4 [13%]); and community (N=29, mean age = 73.2 ± 8.5 years, female 76%, education = 12.2 ± 3.7 years, URGs N=25 [86%]). Adjusting for age, sex, and education, the advertisement (OR = 2.6, 95% CI 1.5 to 4.8, p=9.8×10-4) and community (OR = 55.2, 95% CI 18.0 to 215.3, p=1.1×10-10) groups had higher proportions of URGs than the referral group; the clinic group was not significantly different from the referral group. Among N=90 URG participants, 59 expressed interest in other studies, 13 screened for longitudinal observational studies, and 3 screened for clinical trials. Fisher's exact test did not show significant differences in longitudinal study participation of URGs by recruitment source (p=0.48). **Conclusion:** Compared to the clinician/researcher referral, the advertisement and community recruitment methods improved URG participation in a brief cross-sectional AD research study. The sample sizes for community/clinic groups are limited, and thus our findings should be interpreted cautiously. We plan to further enroll MAC participants from the community and the clinic to determine the optimal recruitment approaches for longitudinal AD studies. **Key words:** Alzheimer's disease, recruitment, diversity, community visits. **Disclosures:** No relevant conflict of interest.

P020- IMPROVING DIVERSE RECRUITMENT IN AN EARLY PHASE THERAPEUTIC AD TRIAL THROUGH A PRE-SCREENING STUDY, APHELEIA-001. D. Batchuluun[1], K. Smith[1], T. Magee-Rodgers[1], L. Zisko[1], J. Dwyer[1], J. Bork[1], R. Mohs[1], J. Schwartzbard[2], A. Bannon[3], S.Y. Lynch[3], C. Lee[3], D. Mcgeeney[3] *(1. Global Alzheimer's Platform Foundation - Washington (United States), 2. Aventura Hospital and Medical Center - Aventura (United States), 3. AbbVie, Inc. - North Chicago (United States))*

Background: Franzen et al. (2022) reported of the 101 AD trials included in their systematic review, 94.7% of study participants were Caucasian. Representation of diverse groups is low in dementia treatment trials (Vrays et al., 2018) resulting in the need for more work to be done to address this inequality. Apheleia-001, launched April 2022, is a novel prescreening study designed by the Global Alzheimer's Platform Foundation (GAP) in collaboration with AbbVie, Inc., to efficiently identify trial-eligible participants. This trial was designed to recruit participants who are at risk for AD in the US population, including those from under-represented communities. Apheleia-001 identifies appropriate participants using paper and digital cognitive tests, demographic and medical information, and blood-based biomarkers. Data will be used to evaluate which demographic, clinical assessments, and blood and digital biomarkers are useful in identifying participants with the appropriate clinical phenotype and amyloid pathology; racial and ethnic differences in sensitivity and specificity of biomarkers will also be assessed. Participants eligible through Apheleia-001 are referred to an early phase therapeutic AD trial. **Objectives:** To determine whether the racial/ethnic makeup of participant referrals from Apheleia-001 to an early AD phase 1 trial is proportionate to the general early AD population in the US, and to assess for potential racial and ethnic differences in AD biomarker results. **Methods:** GAP's Inclusive Research Initiative (IRI) supports clinical research centers in engaging and building relationships within underrepresented communities. IRI methods implemented to enhance diverse representation in the Apheleia-001 study were: -Site selection based on proximity to underrepresented populations; -DEI (Diversity Equity and Inclusion) webinars to support sites in fostering an inclusive research setting; -Creation of marketing materials intentionally focused on diverse communities; -Deployment of GAP's team of diverse Community Connectors; -Collection and monitoring of demographic information for all study participants. Only participants who consent to Apheleia 001, meet all Apheleia-001 eligibility criteria, and are considered at intermediate to high risk for amyloid positivity will be referred to an early phase therapeutic AD trial. **Results:** As of April 25, 2023, 472 participants have been prescreened in the Apheleia-001 study with over 95 participants being referred to an early phase trial. 159 (34%) participants were from underrepresented populations (URPs). Of these, 25 met all study criteria and were referred to an early phase therapeutic trial. **Conclusions:** Apheleia-001 successfully enrolled 34% of participants from URPs. Furthermore, Apheleia-001 referred 25 URP participants to an early phase AD trial. This represents >25% of the total referral population for this study, far exceeding Franzen's systematic review results of 94.7% inclusion of predominantly white study participants in 101 ADRD clinical trials (2022). Data collection is ongoing, and results will help understand potential racial and ethnic differences in biomarker results and screen failure rates for clinical trials. **References:** Franzen, S., Smith, J. E., van den Berg, E., Rivera Mindt, M., van Bruchem-Visser, R. L., Abner, E. L., ... & Papma, J. M. (2022). Diversity in Alzheimer's disease drug trials: The importance of eligibility criteria. Alzheimer's & Dementia, 18(4), 810-823. Vyas, M. V., Raval, P. K., Watt, J. A., & Tang-Wai, D. F. (2018). Representation of ethnic groups in dementia trials: systematic review and meta-analysis. Journal of the neurological sciences, 394, 107-111.

P021- ON ADAPTIVE RANDOMIZATION IN TIME-TO-EVENT ALZHEIMER'S DISEASE CLINICAL TRIALS. N. Hakhu[1], J. Grill[1], D. Gillen[1] *(1. University of California, Irvine - Irvine (United States))*

Background: Randomized controlled clinical trials (RCTs) assign patients to a treatment with a specified probability. One approach to accelerate drug development and trial efficiency aligning with the National Plan to Address Alzheimer's Disease is adaptive randomization: changing the treatment allocation probabilities during a trial's enrollment period. Two types of adaptive randomization are covariate-adaptive randomization and response-adaptive randomization that use the trial's comparative data at baseline (e.g., demographic characteristics or biomarker status) and post-baseline (e.g., clinical outcome or surrogate endpoint assessments), respectively, to change treatment allocation probabilities. BAN2401-G000-201 (NCT01767311) [1] is an example of an early Alzheimer's disease clinical trial with a continuous primary endpoint that used response-adaptive randomization to assign patients to one of five doses of lecanemab or placebo. To our knowledge, adaptive randomization has yet to be used in Alzheimer's disease clinical trials with a time-to-event primary endpoint (e.g., time to impairment of daily function or time to dementia). Because adaptive randomization includes the possibility of accelerating recruitment and providing participants a greater chance of receiving the treatment that appears more promising based on the trial's comparative data [2], adoption in time-to-event Alzheimer's disease clinical trials may be near. Currently, there is a gap in understanding the impact of adaptive randomization on estimation of treatment effects in RCTs with a censored time-to-event primary endpoint in the presence of time-varying treatment effects. In this presentation, we quantify the impact of adaptive randomization where the target of inference is a marginal hazard ratio that does not depend on censoring patterns during the trial. **Methods:** We analytically showed that adaptive randomization induces covariate-dependent censoring and that this change modifies the trial estimand. We then illustrated the impact through simulation studies examining statistical operating characteristics (bias and confidence interval coverage) of the Cox proportional hazards estimator [3] and our proposed reweighting of the Cox proportional hazards estimator by extending Boyd, Kittelson, and Gillen's censoring-robust estimation approach [4] to account for adaptive randomization. We considered scenarios with time-varying treatment effects (ranging from early to late benefit) with fixed and adaptive randomization (treatment arm allocation probabilities ranging from 0.5 to 0.8) of 800 subjects. We generated true event times from piecewise exponential distributions for treatment and control arms, right-censoring observed event times at the maximum study duration of 4 years. **Results:** We showed via Monte Carlo simulations across a range of time-varying treatment effects settings that: (i) adaptive randomization can yield under- or over-estimates when using the Cox proportional hazards model; (ii) adaptive randomization alters the treatment-arm specific censoring distributions; and (iii) the censoring-robust estimation procedure by Boyd, Kittelson, and Gillen yielded approximately

unbiased estimates and nominal confidence interval coverage. **Conclusions:** We found that adaptive randomization in time-to-event RCTs can yield biased treatment effect estimates when using the Cox proportional hazards model, while estimation by Boyd, Kittelson, and Gillen yielded valid inference in the settings we investigated. Removing the dependence of trial-specific censoring patterns from the target of inference can allow for a more appropriate comparison of treatment efficacy across Alzheimer's disease clinical trials. **Key words:** adaptive randomization, time-to-event endpoint, time-varying treatment effects, bias. **Disclosures:** The authors declared no competing interests. **References:** 1. Swanson CJ, et al. Alzheimer's Res. Ther. 2021; 13:80. https://doi.org/10.1186/s13195-021-00813-8. 2. FDA. Adaptive Designs for Clinical Trials of Drugs and Biologics: Guidance for Industry.; 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry. 3. Cox D. J R Stat Soc Series B Stat Methodol 1972; 34: 187-202. https://doi.org/10.1111/j.2517-6161.1972.tb00899.x. 4. Boyd, Kittelson, and Gillen. Stat Med 2012; 31: 3504-2515. https://doi.org/10.1002/sim.5440.

P022- VIEWS AND PERCEPTIONS OF AMYLOID IMAGING AMONG RACIAL AND ETHNIC GROUPS IN A PRECLINICAL ALZHEIMER'S DISEASE TRIAL.

C.M. Magana-Ramirez[1], G. Irizarry[2], D.L. Gillen[1,3], J.D. Grill[2,3,4]
(1. Department of Statistics, University of California, Irvine, California - Irvine (United States), 2. Department of Neurobiology and Behavior, University of California, Irvine, California - Irvine (United States), 3. Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, California - Irvine (United States), 4. Department of Psychiatry and Human Behavior, University of California, Irvine, California - Irvine (United States))

Background: To ensure the generalizability of results, trials of new Alzheimer's disease (AD) interventions must be representative of the broader disease-suffering population [1]. Minority race and ethnicity groups, however, remain underrepresented in AD research. To increase the participation of underserved communities, researchers need to better understand community attitudes toward enrolling in clinical trials [1, 2]. **Methods:** We used data from the Anti-Amyloid treatment in Asymptomatic AD (A4) Study to examine whether willingness to participate in amyloid imaging in the setting of a preclinical AD trial varied by ethnicity and race. Participants completed the Views and Perceptions of Amyloid Imaging (VPAI) questionnaire before undergoing amyloid PET and after disclosure of imaging results (described as "elevated" or "not elevated" amyloid). VPAI items assess the strength of participants' motivations to undergo amyloid imaging in the setting of a preclinical AD trial [2]. We assigned participants to 5 mutually exclusive groups based on self-reported information on race and ethnicity: Hispanic/Latino, non-Hispanic/Latino (NH) Asian, NH Black, NH White, and NH Other. Due to small sample sizes of individuals who identified as American Indian, Alaskan Native, Native Hawaiian or other Pacific Islander, multirace, or did not report a race, these participants were placed into the Other group. We used linear regression to quantify differences in mean VPAI scores across mutually exclusive racial and ethnic groups with adjustment for a priori specified potential confounding factors including sex, family history of AD, study partner type, education, and age. We also considered differences in domain-specific constructs including perceived risk, altruism, planning, and curiosity[2]. Finally, we considered the within-subject change in VPAI scores after disclosure of amyloid imaging results, with stratification by amyloid status. **Results:** Racial and ethnic groups differed in their baseline VPAI scores ($p < 0.001$). Hispanic/Latino, NH Asian, and NH Black participants scored higher, on average, relative to NH White participants. Relative to NH White participants the estimates for mean differences in VPAI score pre-disclosure were: Hispanic/Latino: 3.5 points, 95% CI: [2.6, 4.4]; NH Asian: 3.0 points, 95% CI: [1.7, 4.2]; NH Black: 2.8 points, 95% CI: [2.0, 3.6]. In domain-specific areas, Hispanic/Latino, NH Asian, and NH Black participants tended to score higher for perceived risk, plan/prepare, and curiosity domains, but not altruism, relative to NH White participants. In "not elevated" amyloid subpopulations, statistically significant differences in the mean pre-post disclosure changes in VPAI score were observed across mutually exclusive race and ethnicity groups ("not elevated": $p = 0.005$; "elevated": $p = 0.71$). In "not elevated" amyloid subpopulations, NH Asian and NH Black participants tended to score higher in their mean pre-post disclosure changes in VPAI score, relative to NH White participants. The interaction of mutually exclusive race and ethnicity groups and amyloid status on pre-post disclosure changes in VPAI score was not significant ($p = 0.81$). **Conclusion:** Our findings suggest differences across ethnic and racial groups in motivations to enroll and undergo amyloid imaging in preclinical AD trials. These observations may be informative to tailored recruitment strategies in future preclinical AD trials. **Key words:** (diversity, recruitment, preclinical, disclosure). **Clinical Trial Registry:** NCT02008357; https://clinicaltrials.gov. **Data Deposition:** The A4 study data are publicly available through the LONI database (https://ida.loni.usc.edu/collaboration/access/appLicense.jsp;jsessionid=928492AAEB34B6B2D0BAB5F973C7113C). **Disclosures:** The authors declared no competing interests. **References:** 1. Raman R, et al. JAMA Netw Open; 4(7) doi:10.1001/jamanetworkopen.2021.14364. 2. Ryan M, et al. Ann Clin Transl Neurol 2021; 8(8): 1646–1655. doi:10.1002/acn3.51414

P023- APPLICATION OF THE PERSONALIZED MEDICINE APPROACH TO A BEHAVIORAL INTERVENTION STUDY: THE INTERNET-BASED CONVERSATIONAL ENGAGEMENT CLINICAL TRIAL (I-CONECT).

C.Y. Wu[1], K. Yu[2], S.E. Arnold[1], S. Das[1], H.H. Dodge[1]
(1. Neurology, Massachusetts General Hospital, Harvard Medical School - Charlestown (United States), 2. Neurology, Oregon Health & Science University - Portland (United States))

Background: One of the challenges in dementia clinical trials is large inter-individual variability in treatment responses. Identifying the characteristics of a promising population for specific treatment is critical, but traditional responder analysis, which simply characterizes those who responded well, is insufficient because it does not consider individual-level response given that the participant would be placed in the control arm. A two-step approach was proposed by Zhao et al. (2013) to address this issue. It first builds prediction models for an outcome of interest separately for the treatment and placebo groups using baseline participant characteristics as predictors. Then, an individual-level treatment response (ITR) score is estimated at the participant level, representing the difference between the predicted outcomes under the treatment and placebo arms. Response heterogeneity is assessed, and the characteristics of those with high ITR score is identified. We applied this ITR-based personalized medicine approach to the Internet-based conversational engagement clinical trial (I-CONECT, NCT02871921) results. **Methods:** I-CONECT is a

multi-site, single-blind, randomized controlled trial. It aimed to examine the effects of frequent social interactions, specifically conversational interactions, on cognitive functions and emotional well-being among socially isolated non-demented subjects (MCI or normal cognition (NC), 1:1 ratio) aged 75 and older. 156 participants were randomized either into the control or experimental group. The experimental group engaged in video chats with study staff 4 times per week for 6 months, while the control groups received only weekly 10-minute phone calls. The current analysis focused on cognitive outcomes that showed significant treatment effects: the Montreal Cognitive Assessment (MoCA) (primary outcome) and semantic fluency tests (Category Fluency Animals (CFA)) (secondary outcome) at the 6-month follow-up. We first estimated individual-level treatment response (ITR) scores using 300 iterations of 3-fold cross-validated Random Forest regression models for the experimental and control groups separately. Next, we calculated the observed difference in MoCA change scores within the 10th to 95th quantiles of ITR scores. This enabled us to construct an area between the curves (ABC) plot, providing an estimation of the heterogeneity of treatment effects. We evaluated feature importance using two approaches: SHapley Additive exPlanations (SHAP) scores and Mean Decrease in Impurity (MDI) scores. We included variables encompassing self-reported frequency of social interactions, personality, and clinical and demographic variables of our interests as predictors in the models. **Results:** Treatment heterogeneity was observed from the ABC plot, indicating significant variations in response to the intervention across participants. For the MoCA (n=140), high responders were more likely to be older, have fewer years of education, report poorer self-perceived health, spend less time out-of-home, and have less social time with family and friends. For CFA (n=140), high responders were more likely to be younger, have more years of education, exhibit normal cognitive function (as opposed to MCI), have lower levels of depression, and spend more social time with family and friends. **Conclusions:** The response to the I-CONECT intervention varied depending on the participant's characteristics. The ITR-based responder's analyses applied here are useful in developing personalized interventions and treatments. **Key words:** Social isolation, loneliness, tele-health, Alzheimer's disease; dementia. **Clinical Trial Registry:** NCT02871921. **Disclosures:** None. **References:** 1. Zhao, L., et al. J Am Stat Assoc 2013; 108(502): 527-539. http://doi.org/10.1080/01621459.2013.770705

P024- UNDERSTANDING NON-PROGRESSORS IN ALZHEIMER'S DISEASE CLINICAL TRIALS. S. Wu[1], J. Murphy[1], W. Feng[2], P. Montenigro[1], Y. Tian[1] *(1. Biogen - Cambridge (United States), 2. Keros Therapeutics - Lexington (United States))*

Background: Alzheimer's disease (AD) is known to be heterogenous in symptom type, co-morbidities, and speed of progression. Current disease modifying therapies (DMTs) aim to slow symptom progression in the early stages of the disease. Designing randomized clinical trials (RCTs) for this early-staged population is challenging, as this population progresses slowly, and requires large and long trials to demonstrate clinical efficacy. Selecting the appropriate study population is especially important, to ensure the proper stage of the disease continuum and to enroll patients with sufficient and measurable deficits that will progress over the course of the trial. Data from recent AD trials suggest that some patients in the placebo arm did not show any clinical progression as measured by one or more clinical assessments. As an example, in the aducanumab ENGAGE and EMERGE studies [NCT02477800, NCT02484547], approximately 25% of participants in the placebo arms did not progress on the Clinical Dementia Rating Sum of Boxes (CDR-SB) at the end of the 78-week placebo-controlled period. Inclusion of such non-progressing patients in a clinical trial may dilute the estimated effect size of the treatment, as there is little room to slow the disease progression if the participants do not progress. The ENGAGE and EMERGE studies provide a rich data source to evaluate the characteristics of non-progressors. Observations from these investigations could help identify screening criteria to limit the proportion of non-progressing participants in future RCTs. **Methods:** Using the pooled placebo data from ENGAGE and EMERGE studies, we evaluated the prognostic factors for clinical progression measured by CDR-SB. In this work, we focused on the neuropsychological prognostic factors and compared the baseline values of these factors between the non-progressing and progressing patients. Analyses were repeated using the ADNI dataset (pre-selected to have similar population characteristics as ENGAGE and EMERGE) to evaluate consistency of findings. **Results:** Among multiple prognostic factors, baseline ADAS-Cog 13 had the highest correlation with change from baseline CDR-SB. A subtest-level analysis of the ADAS-Cog 13 identified the baseline Word Recall and Delayed Word Recall tests had lower baseline scores in the non-progressors than the progressors, in both the pooled placebo data of ENGAGE and EMERGE and the ADNI data. Excluding participants in ENGAGE and EMERGE whose baseline Word Recall and Delayed Word Recall were within 1 standard deviation of the age-adjusted mean of cognitive normal population resulted in a decrease of the non-progressor proportion from 25% to approximately 20%. **Conclusion:** Through evaluation of the baseline characteristics of non-progressors in multiple datasets, we observed that patients with lower baseline scores for the Word Recall and Delayed Word Recall subtests of the ADAS-Cog 13 are likely to not progress in an 18 to 24-month follow-up. This is supported by clinical evidence that early symptoms of AD tend to be related to memory and patients who have smaller deficit in the memory domain are less likely to progress. Excluding patients with low baseline scores of Word Recall and Delayed Word Recall may help reduce the proportion of non-progressors. More work is needed to understand if other baseline characteristics and/or biomarkers, in combination with baseline ADAS-Cog 13, could further refine the population for a clinical trial. **Key words:** Alzheimer's disease, clinical trials, non-progressors, CDR-SB, ADAS-Cog 13. **Reference:** Budd Haeberlein, S., Aisen, P., Barkhof, F. et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis 9, 197–210 (2022).

P025- A PHASE 2 CLINICAL PROTOCOL: PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL-GROUP TO CONFIRM SAFETY AND EFFICACY OF NA-831 IN COMBINATION WITH ADUCANUMAB IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE. L. Tran[1], F. Vu[1], M. Kurkinen[1] *(1. Biomed Industries, Inc. - San Jose))*

Background: Aducanumab is a monoclonal antibody that targets aggregated forms (plaque) of amyloid beta (Aβ) found in the brains of people with Alzheimer's disease. Aducanumab (brand name Aduhelm) has been approved by the FDA for patients with early Alzheimer's disease (AD). NA-831 is an experimental drug that has showed a proof of safety and efficacy in Phase 2 clinical trial for patients with early

Alzheimer's disease. AD patients are treated with a number of comedications not only to address cognitive impairment (standard-of-care) but also other comorbidities. It is clear that amyloid reduction at best leads to modest changes in clinical deterioration and that there is room for additional therapeutics to improve patient quality of life. In addition, amyloid-related imaging abnormalities side-effects need to be taken into account opening the possibilities of dose-sparing with new combinations. **Aims:** The phase 2 study consists of a Core and Open Label Extension (OLE) Phase will be conducted to evaluate the efficacy and safety of combination therapy of NA- 831 and aducanumab with patients with Early Alzheimer's Disease (EAD). The Core is a 12-month treatment, multi-centers, double blind, placebo controlled parallel group study. The Extension Phase is up to approximately 18 months (including 3 months follow up). **Methods:** Core Study: Participants will be divided in 3 groups, randomly assigned in a 1:1 ratio to receive a drug or a combination of two drugs or placebo. Group 1: will receive one 30 mg of NA-831 capsule orally once a day or placebo, Group 2: will receive and intravenous aducanumab following the following schedule: Infusions 1-2: 1 mg/kg IV q4Weeks or placebo. Infusions 3-4: 3 mg/kg IV q4Weeks or placebo. Infusions 5-6: 6 mg/kg IV q4Weeks or placebo. Infusion 7 and beyond: 10 mg/kg IV q4Weeks or placebo. Group 3: will receive one 30 mg of NA-831 capsule orally once a day, and intravenous aducanumab following the following schedule: Infusions 1-2: 1 mg/kg IV q4Weeks or placebo. Infusions 3-4: 3 mg/kg IV q4Weeks or placebo. Infusions 5-6: 6 mg/kg IV q4Weeks or placebo. Infusion 7 and beyond: 10 mg/kg IV q4Weeks or placebo. The core study will be double blinded. Open Label Extension Phase: Participants completing the core study will receive one 30 milligram (mg) NA-31capsule orally once a day, and intravenous aducanumab (6 mg per kilogram of body weight every 4 weeks). The Extension Phase is up to approximately 18 months (including 3 months follow up). **Enrolment:** 240 participants. Ages: 50 to 90 Years. All sexes are eligible for study. Key Inclusion Criteria: **Diagnosis:** Mild Cognitive Impairment (MCI) due to Alzheimer's disease - intermediate likelihood: Meet the National Institute of Aging - Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to Alzheimer's disease - intermediate likelihood. Have a global Clinical Dementia Rating (CDR) score of 0.5 and CDR Memory Box score of 0.5 or greater at Screening and Baseline. Report a history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; must be corroborated by an informant. **Mild Alzheimer's disease dementia:** Meet the NIA-AA core clinical criteria for probable Alzheimer's disease dementia. Have a global CDR score of 0.5 to 1.0 and a CDR Memory Box score of 0.5 or greater at Screening and Baseline. **Key Exclusion Criteria:** Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's Alzheimer's disease. History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of Screening. Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures in the participant. **Results to be presented:** I. Key Outcome Measures: Core Study: Change from Baseline in the CDR-SB at 12 Months [Time Frame: Baseline, 12 months]. Extension Phase: Number of Participants Reporting One or More Treatment-emergent Adverse Events (TEAEs) [Time Frame: From first dose of study drug up to approximately 18 months (including 3 months follow up) for the extension phase]. II. Secondary Outcome Measures:. Core Study: Change from Baseline in Alzheimer Disease Assessment Scale - Cognitive Subscale 14 (ADAS-cog14) at 12 Months [Time Frame: Baseline, 12 months]. Core Phase: Change from Baseline in Alzheimer's Disease Composite Score (ADCOMS) at 12 Months [Time Frame: Baseline, 12 months]. Core Study: Change from Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) at 12 Months [Time Frame: Baseline, 12 months]. Additional study will include (a) complex PK-PK interaction studies, or (c) providing evidence that the combination has a synergistic effect. **Conclusions:** The Phase 2 clinical trial will be conducted more than 20 sites in the US and several countries. The details of the Phase 2 methodology and protocol will be presented and discussed.

P025B- A PHASE 3 CLINICAL PROTOCOL: PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL-GROUP TO CONFIRM SAFETY AND EFFICACY OF NA-831 IN COMBINATION WITH LECANEMAB IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE. L. Tran[1], F. Vu[1], M. Kurkinen[1] *(1. Biomed Industries, Inc. - San Jose (United States))*

Background: Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, which has been approved by the FDA for patients with early Alzheimer's disease (AD). NA-831 is an experimental drug that has showed a proof of safety and efficacy in Phase 2 clinical trial for patients with early Alzheimer's disease. AD patients are treated with a number of comedications not only to address cognitive impairment (standard-of-care) but also other comorbidities. It is clear that amyloid reduction at best leads to modest changes in clinical deterioration and that there is room for additional therapeutics to improve patient quality of life. In addition, amyloid-related imaging abnormalities side-effects need to be taken into account opening the possibilities of dose-sparing with new combinations. **Aims:** The phase 3 study consists of a Core and Open Label Extension (OLE) Phase will be conducted to evaluate the efficacy and safety of combination therapy of NA- 831 and lecanemab with patients with Early Alzheimer's Disease (EAD). The Core is an 18-month treatment, multi-centers, double blind, placebo controlled parallel group study. **Methods:** Core Study: Participants will be divided in 3 groups, randomly assigned in a 1:1 ratio to receive a drug or a combination of two drugs or placebo. Group 1: will receive one 30 mg of NA-831 capsule orally once a day or placebo. Group 2: will receive and intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. Group 3: will receive one 30 mg of NA-831 capsule orally once a day and intravenous lecanemab (5 mg per kilogram of body weight every 2 weeks) or placebo. The core study will be double blinded. Open Label Extension Phase: Participants completing the core study will receive one 30 milligram (mg) NA-31capsule orally once a day, and intravenous lecanemab (5 mg per kilogram of body weight every 2 weeks). **Enrolment:** 630 participants. Ages: 50 to 90 Years. All sexes are eligible for study. **Key Inclusion Criteria:** Diagnosis: Mild Cognitive Impairment (MCI) due to Alzheimer's disease - intermediate likelihood: Meet the National Institute of Aging - Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to Alzheimer's disease - intermediate likelihood. Have a global Clinical Dementia Rating (CDR) score of 0.5 and CDR Memory Box score of 0.5 or greater at Screening and Baseline. Report a history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; must be corroborated by an informant. **Mild Alzheimer's disease dementia:** Meet the NIA-AA core clinical criteria for probable Alzheimer's

disease dementia. Have a global CDR score of 0.5 to 1.0 and a CDR Memory Box score of 0.5 or greater at Screening and Baseline. **Key Exclusion Criteria:** Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's Alzheimer's disease. History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of Screening. Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures in the participant. **Results to be presented:** I. Key Outcome Measures: Core Study: Change from Baseline in the CDR-SB at 18 Months [Time Frame: Baseline, 18 months]. Extension Phase: Number of Participants Reporting One or More Treatment-emergent Adverse Events (TEAEs) [Time Frame: From first dose of study drug up to approximately 24 months (including 3 months follow up) for the extension phase]. II. Secondary Outcome Measures: Core Study: Change from Baseline in Alzheimer Disease Assessment Scale - Cognitive Subscale 14 (ADAS-cog14) at 18 Months [Time Frame: Baseline, 18 months]. Core Phase: Change from Baseline in Alzheimer's Disease Composite Score (ADCOMS) at 18 Months [Time Frame: Baseline, 18 months]. Core Study: Change from Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) at 18 Months [Time Frame: Baseline, 18 months]. Additional study will include (a) complex PK-PK interaction studies, or (c) providing evidence that the combination has a synergistic effect. **Conclusion:** The Phase 3 clinical trial will be conducted more than 30 sites in the US and several countries. The details of the Phase 3 methodology and protocol will be presented and discussed.

P026- SIMULATING COVARIATE-ADAPTIVE RANDOMIZATION STRATEGIES IN ALZHEIMER'S DISEASE CLINICAL TRIALS.

C. Flournoy[1], R. Raman[1], P. Aisen[1], M. Donohue[1] *(1. USC Alzheimer's Therapeutic Research Institute - San Diego (United States))*

Background: Randomization methods that reduce the chance of imbalance across treatment arms for select prognostic factors are commonly used in clinical trials. The availability of anti-amyloid treatments introduces potential influence on cognitive or biomarker outcomes in Alzheimer's Disease (AD) trials. To mitigate these potential effects, it is important to ensure that the proportion of participants receiving concomitant anti-amyloid treatment is balanced across treatment arms. Known prognostic risk factors in Alzheimer's clinical trials include APOE4 genotype, some cognitive measure, and study site. Stratified randomization with permuted blocks is a popular balancing approach; however, the addition of concomitant anti-amyloid treatment doubles the number of strata. A covariate-adaptive randomization method is an approach that allows for adjustment of prognostic factors with many factors. We conduct a simulation study to compare the performance of a permuted block randomization approach and a covariate-adaptive randomization approach using a ranked G-score imbalance measure. **Methods:** Clinical trial populations were simulated with prognostic factors distributed according to characteristics seen in past AD trials. The simulations explored the impact on randomization imbalance of study size (N=400, 700, or 1000) with respective number of sites (20, 50, and 70), and number of arms (2 or 3) using either permuted block or covariate-adaptive randomization. One thousand clinical trials were simulated for each study design. For each simulated trial, Fisher's exact test was used to evaluate balance across treatment arms for the prognostic factors APOE genotype, MMSE (two groups), and concomitant anti-amyloid therapy status. A chi-squared test was used to evaluate balance with respect to study site. Performance of randomization methods was assessed by comparing the proportion of simulated randomized data iterations with significant imbalances across each prognostic factor individually and in the aggregate. **Results:** We found that the chance of significant ($p<0.05$) imbalance with permuted block approach for any given variable was low across all scenarios (no more than 7 trials out of 1,000), but across all scenarios, the covariate-adaptive randomization approach did not produce any significant imbalance. Plotting the distribution of p-values across all simulated trials suggests that as study size increases, covariate-adaptive randomization becomes more effective across all covariates. Study site was more balanced using stratified randomization compared to covariate-adaptive randomization, however this balance comes at the expense of the other prognostic factors. **Conclusion:** Both stratified randomization and covariate-adaptive randomization methods are effective mechanisms for balancing prognostic factors across the treatment arms. However, covariate-adaptive randomization produced more consistently balanced results in every study scenario and should be considered as the number of known prognostic risk factors to be adjusted in a randomization strategy increases. **Key words:** Randomization, Stratified, Covariate-adaptive. **Disclosures:** I have no potential conflict of interest in relation to this simulation study or analysis. **References:** Pocock, S. J., & Simon, R. (1975). Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics, 31(1), 103–115. https://doi.org/10.2307/2529712

P027- PERSISTENCE PAYS - THE RELATIONSHIP BETWEEN REPEATED RESCHEDULE ATTEMPTS AND EVENTUAL ATTENDANCE AND SCREENING RATES.

S. Starling[1] , G. Munoz[1] , P. Sablone[1] , M. Evans[1] , S. Rutrick[1] *(1. Adams Clinical - Watertown (United States))*

Background: Screening for Alzheimer Disease (AD) clinical trials can be challenging in regard to participant recruitment and retention. With high no-show and cancellation rates for prescreening visits, identifying strategies to improve attendance is critical for speeding up enrollment in AD trials1. Some participants habitually no-show or cancel their prescreening visits and it is unclear at what point rescheduling attempts are no longer beneficial. We examined whether the number of rescheduling attempts impacted the eventual likelihood of a participant attending a prescreening visit, and likelihood to eventually screen for an industry trial. **Methods:** Our sample includes prospective AD trial participants scheduled for prescreening visits in 2022. They were primarily recruited by advertising with Facebook and Google. After potential participants submitted contact information online, a recruiter called them to conduct a remote interview. Potentially eligible participants were scheduled for an in-person prescreening visit with a clinician. If the participant cancelled or no showed their prescreening visit they were recontacted by text and/or phone call to attempt a reschedule. This analysis examined how the number of rescheduling attempts related to two outcome measures: prescreening visit show rates, and likelihood of eventually screening for an industry trial. **Results:** From January to December 2022, 917 individuals were scheduled for an initial prescreening visit with a clinician. Of those, 332 (36%) attended that initial visit. 224 of the participants who did not attend their first visit were scheduled for a second prescreening visit (2nd attempt), of which 103 (46%) attended.

51 of the participants who did not attend the 2nd attempt were rescheduled (3rd attempt), and of those, 21 (41%) attended. Of the remaining participants, 20 were scheduled for subsequent visits and 6 (30%) eventually attended. Prescreening visit attempt number was not a predictor of eventual prescreening visit attendance (β=-.112, p=.177). Of the participants who attended their first scheduled prescreening visit 53% eventually screened for an industry trial. The screening rate was 55%, 62%, and 67% respectively for participants who attended their 2nd, 3rd, or 4th (or later) attempted prescreening visit. Prescreening visit attempt number was not a predictor of eventual screening for an industry trial (β=-.086, p=.520). **Conclusions:** These findings suggest that it remains beneficial to continue rescheduling participants until they can attend a prescreening visit. Later attempts are just as likely as earlier attempts to yield an attended prescreening visit, as well as an eventual industry screening. As not all potential participants who missed prescreening visits were rescheduled, future work should focus on strategies to reach and reschedule those individuals. **Disclosures:** The authors have no conflicts of interest to report. **References:** 1. Puffer, S., & Torgerson, D. (2003). Recruitment difficulties in randomized controlled trials. Controlled Clinical Trials, 24, 214-215

P028- METHODOLOGIES THAT SUPPORT THE IDENTIFICATION OF DISEASE MODIFYING THERAPIES WHICH ARE A RADICAL SHIFT FROM SHORT ACTING SYMPTOMATIC TREATMENTS: OWNING INSTEAD OF RENTING OUR TREATMENT EFFECTS.

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

Background: For many years, the only approved treatments for Alzheimer's disease were fast acting, primarily symptomatic treatments. Over the past 2 decades, many clinical trials have targeted investigational disease-modifying (DM) treatments for Alzheimer's disease. Although many of these studies failed, new methodologies were developed and used to improve the chances of success for these treatments and to distinguish DM treatments from primarily symptomatic ones. Now that we have approved DM treatments, it is time to revisit the methodologies that contributed to these successes and can contribute to a healthy environment for future DM treatments. **Objectives:** To review the past two decades of Alzheimer's disease clinical development and to identify and describe important contributors to success of DM treatments. **Methods:** Symptomatic effects are often large, but transient, and may only impact a single domain of disease, while DM effects consistently accumulate by slowing disease progression, impacting all aspects of disease with no expected improvements over baseline (only slowing progression). Symptomatic effects are like renting a home since effects are lost when treatment stops. DM effects are like buying a home since the treatment effect accumulates as treatment is given, and benefit is retained even when treatment stops. Treatments can be both symptomatic and DM, but we discuss the concepts separately for simplicity. Based on these definitions, we identify and describe methodologies from the Alzheimer's disease literature and research practices related to better measuring DM effects or separating DM effects from symptomatic effects. We also assess the impact that these approaches have had on the field as a whole, and specifically in setting the stage for achieving successful clinical trials for DM therapies. **Results:** The Staggered Start and Randomized Withdrawal study designs assess whether a treatment effect is permanent by either treating both groups or removing treatment after a randomized, double blind period. The groups are then compared to see whether the group receiving treatment in the first phase maintains a permanent benefit over the group who originally received placebo. These methods and even discussions of DM effects were mostly abandoned when Teva was unable to get a disease modification claim on the label for rasagiline in Parkinson's, but understanding how a treatment works is critical whether or not a label reflects a specific mechanism of effect. The Natural History Staggered Start analysis was proposed as a way of separating out the DM component of a slope separation over time, but has often been replaced by the simpler, but sometimes inaccurate, conclusion that any slope separation represents a DM effect. This conclusion leads to an important way of measuring an effect size: as a Percent Slowing or the percentage of the placebo decline that was prevented. This is often interpreted as the same percentage effect on time, and as a DM effect. This may be the case, but it requires linear progression over time and lack of an increasing symptomatic effect with more disease severity. Some have proposed Projecting Effects Forward as a way of demonstrating clinical meaningfulness, but extrapolation is not a reliable form of prediction and should be avoided. In 2009, the early work that led to ADCOMS, APCC and API-LOAD Composite Scales was initiated. These scales were optimized for progression over time and were designed to measure disease modification by identifying the most progressive aspects of disease in a specific stage. This work was presented publicly and spawned multiple other composite scores, many of which were not focused on disease modification. Interestingly, both lecanemab and donanemab used composite scores (ADCOMS and iADRS) in their proof of concept studies, enabling the highly successful phase 3 studies. Time to Event Analyses seem to be related to disease modification, but it is challenging to identify events that are clearly disease-related and unaffected by symptom amelioration. PK/PD Modeling and Correlational Analyses relating changes in biomarkers and clinical outcomes are promising, but with disease modification, these outcomes often move together and show the same relationships in the active and placebo groups since the active group looks like the slower progressing placebo patients. Global Statistical Tests allow assessment of treatment effects across multiple trial endpoints simultaneously by standardizing them. This aligns with the important requirement that a DM therapy should impact all aspects of disease. Time Component Tests have been recently developed as a method of converting treatment effects on any outcome measure into "time savings" estimates which can then be combined across outcomes to get a more stable estimate. Monoclonal antibodies have resulted in time savings of 4-6 months with 18 months of treatment. **Conclusions:** In the past several decades, in parallel to developing amyloid targeted agents, substantial efforts have been spent laying the groundwork for clinical study methodologies that are favorable to DM therapies. Acknowledging these efforts and continuing to use them will enable further development of DM therapies.

P029- THE TIME MACHINE: HOW CONVERTING TREATMENT EFFECTS TO TIME SAVINGS WILL CHANGE THE WORLDS.

S.P. Dickson[1], B.A. Haaland[1], J. Christensen[1], M. Morgan[1], C.H. Mallinckrodt[1], S.B. Hendrix[1] *(1. Pentara Corporation - Salt Lake City (United States))*

Background: No single outcome captures all aspects of Alzheimer's disease progression and all are plagued by variability, both imprecision inherent in the instruments and their measurements and true intra-subject variability caused

by the day-to-day ebb and flow of symptoms. Even from screening to baseline, 95% prediction intervals for ADAS-Cog extend 10 points in either direction (spanning 25% of the scale) and MMSE varies by +/- 5 points (33% of the scale). Yet from these imperfect and highly-variable outcomes, sponsors are expected to select one outcome that will best represent how their treatment affects this complex disease. This may make sense with a symptomatic treatment that could have dramatic effects on only a single domain of the disease without altering disease progression. Disease-modifying effects are broad, permanent, and accumulate over time, and should therefore be evaluated by a different standard. First, if a treatment does slow disease progression, then modest or even small but permanent annual effects may eventually grow larger than the acute effects of symptomatic treatments. Second, disease-modifying treatments will permanently impact all aspects of disease, so if a single outcome is used it must be comprehensive enough to capture these broad effects, which build up over time, allowing it to mark disease progression, but momentum around identifying minimal clinically important difference for each outcome has worked against our ability to discover disease-modifying effects. Our outsized focus on clinical meaningfulness has incentivized standards that can only be met by symptomatic treatments, stranding the field on an island of non-permanent effects, when the only way to make truly meaningful progress is to force a paradigm shift that reveals the permanent and aggregating effects of disease-modifying treatments. Composite scores, which combine items across domains to create single broad outcomes with smaller variability, have the potential to create a path for more disease-modifying treatments to achieve approval and general availability; however, confusion around the interpretation of multi-domain composites has obstructed acceptance by both regulators and clinicians. The true paradigm shift that will allow disease-modifying treatments to be evaluated fairly in a way that is easily understood by all is the ability to convert all outcomes to the gold standard of meaningfulness in progressive diseases: time. Recent work has shown how this can be done on the summary level to demonstrate the time saving effects of treatments ranging from monoclonal antibodies like donanemab to nutritional interventions like Souvenaid, but implementation of the method on the subject level provides an analytical solution that may allow outcomes that span multiple domains to be combined naturally in a way that will permit their use as a primary outcome in clinical trials while providing an important per-person metric. **Objectives:** We demonstrate the properties of a subject-level time component test (TCT), which converts outcomes to time to be able to measure the time saving effects of a treatment. The time component for each outcome can then be combined naturally into a global TCT (gTCT) that incorporates all outcomes. **Methods:** A subject-level TCT requires careful characterization of the placebo arm of a clinical trial, including modeling within and across visits. Any nuisance covariates are first modeled using a mixed model with repeated measures (MMRM) which includes all covariates but time and visit. The covariate-adjusted residuals from this model are used for the remainder of the analysis. Percentile scores on the outcome variable are transformed into percentile scores on the time scale for both the placebo and active treatment arms. This allows a comparison of the distributions of the time outcome that parallels the usual primary MMRM on the outcome level. With all the outcomes on the same time scale, they can be averaged by subject and visit to create a single global time component to be used in a gTCT which is similarly analyzed using MMRM. **Results:** The type I error of the subject-level TCTs and the gTCT is well-controlled. Statistical significance of the TCT is similar to and sometimes greater than the significance of the MMRM on the original scale. When there is consistency of effect across outcomes, the gTCT has lower variability and greater significance than the individual outcomes. All treatment differences are reported as time savings with confidence intervals and p-values, which makes results easily understandable and interpretable. **Conclusion:** With a well-defined subject-level test on the scale of time, disease-modifying treatments can be measured with a single, inherently-meaningful, easily-interpretable, comprehensive outcome with low enough variability to reveal significant disease-modifying effects in effective treatments. This paradigm shift has the potential to allow even small and mid-sized sponsors to demonstrate the efficacy of their disease-modifying treatment.

P030- WHY YOUR AD CLINICAL TRIAL MIGHT SUCCEED (THE RIGHT REASONS AND THE WRONG ONES).

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

Background: After nearly two decades of study failures in Alzheimer's disease (AD), the field has finally seen multiple successes with the monoclonal antibodies aducanumab, lecanemab, and donanemab. While these three successes do indicate that amyloid reduction can play a part in modifying disease progression, having an effective candidate is not the only ingredient needed to achieve success. We can't know all the ways a study might fail, but by investigating what the successful trials did right and what the others could have improved we can increase our chances of building on recent victories. **Objectives:** Use the lessons learned from the recent AD clinical trial successes along with the dozens of failures to explain what researchers and sponsors can do to improve their chances of success in AD clinical trials. **Methods:** We've compared our analyses of publicly available trial results for aducanumab, lecanemab, and donanemab to other promising treatments that do not appear to have a clear path to regulatory approval and highlighted some of the key learnings from both sets that can be implemented to improve study design. We also estimate the power improvements that these decisions can bring. **Results:** We've divided the reasons an AD clinical trial might succeed into positives and negatives. Some of the right reasons a study might succeed include the following: 1) a composite outcome is used in phase 2 to gain more information with fewer subjects to decide whether to proceed to phase 3, 2) the sample size is appropriately large to detect an effect size down to the smaller effect sizes that are appropriate for disease-modifying treatments that might not be appropriate for symptomatic treatments, 3) the population is appropriate to discover treatment effects, by both making sure they are sufficiently but not overly progressive in order to be able to see slowing of progression and by making sure that the population is appropriate to the mechanism, 4) serial phase 3 studies are planned rather than parallel studies, and 5) avoiding co-primary endpoints. Some of the wrong reasons for study success include 1) an imbalance of rapid progressors, which can have an outsized impact on perceived efficacy for better or worse, 2) planning for so many subjects that you can detect an effect size that is too small to be meaningful, 3) an overdependence on subgroup analyses, and 4) an outcome that is overly discreet, which, may seem like it could decrease the chance of getting a positive result for small effect sizes, but in many instances can increase the probability of a false positive result. **Conclusion:** We don't know how many study failures from the past two

decades could have been avoided, but each one has left segments of the population without a feasible treatment for AD. At a very basic level, one of the main reasons for failures is that researchers and sponsors have been discouraged from using all the information available to them in order to make decisions about proceeding to the next stage of drug development. No single outcome captures all aspects of disease progression, and undue emphasis is given to the one domain captured by the primary endpoint, resulting in decisions that are less reliable than if they were based on multiple outcomes. Eisai and Lilly circumvented this in phase 2 by using a composite outcome in their primary endpoint, but hesitancy to embrace composite outcomes stems from confusion around interpretation of these outcomes. Going forward we hope that as people begin to understand and embrace the concept of converting outcomes to their time savings component it will make it easy to see how different outcomes work together to describe disease progression and its slowing. This creates the ability to combine outcomes naturally on the time scale, which everyone readily understands, and effective treatments will have an easier path to approval and greater availability to those who need these treatments most.

LP001- PHASE 3 POLARIS-AD: AR1001 STUDY DESIGN IN EARLY ALZHEIMER'S DISEASE. S. Sha[1], S. Kim[2], J. Cummings[3], C. Teunissen[4], D. Greeley[5], J. Rock[5], M. Choung[5]
(1. Stanford University - Palo Alto (United States), 2. Seoul National University College of Medicine - Seoul (Korea, Republic of), 3. University of Las Vegas - Las Vegas (United States), 4. Amsterdam UMC - Amsterdam (Netherlands), 5. AriBio Co LTD - San Diego (United States))

Background: Despite the growing armamentarium of treatments for Alzheimer's disease (AD), the recognition that AD is multifactorial in its etiology necessitates additional treatments options that are multi-factorial in mechanism. AR1001 (mirodenafil), an oral phosphodiesterase (PDE5) inhibitor, attenuates pathology of Alzheimer's Disease in preclinical models by four mechanisms: 1) enhancing neurogenesis and inhibiting neuronal apoptosis, 2) improving synaptic plasticity, 3) increasing autophagy, and 4) attenuating neuroinflammation in microglia. Thus, studying AR1001 for the treatment of AD is warranted. A Phase 2 study of AR1001 assessed the safety and efficacy in study participants with mild to moderate Alzheimer's dementia, aged 55 to 80 years. After 52 weeks of once daily oral dosing of 10 mg and 30 mg, AR1001 demonstrated safety and tolerability. A total of 39 Treatment Emergent Adverse Events (TEAEs) related to the study drug were reported in 24 (11.4%) participants compared to 23 events in 13 (18.6%) participants treated with placebo. The most common TEAEs were dizziness and headache which were mild and moderate in severity. The primary endpoint, Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog-13) was not met at week 26, but post-hoc analysis of the mild AD group showed improvement for the 30 mg group at 52 weeks (4.019 points, $p = 0.039$). The exploratory analysis of plasma phosphorylated tau (p-Tau)181 for both 10 mg and 30 mg groups showed decreased levels from baseline at 52 weeks (-1.214 pg/ml, $p < 0.0001$; -1.355 pg/ml, $p < 0.0001$, respectfully). Given the safety profile and efficacy in the mild AD group with the 30mg dose, coupled with an improvement in the plasma p-Tau181 levels, a phase 3 trial evaluating AR1001 in people with early AD was justified. **Methods:** We designed a global, Phase 3 double-blind, randomized, placebo-controlled study, POLARIS-AD to evaluate the efficacy and safety of AR1001 in participants with early Alzheimer's disease (MCI due to AD and mild Alzheimer's dementia) which was initiated in December 2022. A total of 1,300 participants, aged 55-90 years with early AD will be enrolled with confirmed brain amyloid. Eligible participants will be randomized 1:1 ratio to receive 30 mg of AR1001 once daily for 52 weeks followed by a two-year extension phase. **Result:** The primary efficacy endpoint, Clinical Dementia Rating – Sum of Boxes, and primary safety endpoint, frequency of TEAEs, will compare the AR1001 cohort to placebo cohort from baseline to Week 52. Secondary endpoints include ADAS-Cog-13, Amsterdam-Instrumental Activities of Daily Living Questionnaire-Short Version, Geriatric Depression Scale, and Mini-Mental Status Examination change from baseline to Week 52. Biomarker endpoints in plasma and CSF include ptau (181, 217, MTBR-tau243), total tau, Aβ 42/40 ratio, NfL, and GFAP from baseline to Week 52. **Conclusion:** POLARIS-AD will evaluate whether AR1001 is efficacious and safe in early AD population in a Phase 3 global clinical trial. The Phase 2 study of AR1001 demonstrated safety, tolerability, reduction of plasma p-Tau181 levels, and improvement in performance ADAS-Cog-13 in mild AD subgroup, supporting evaluation in this cohort for a Phase 3 study. **Clinical Trial Registry:** NCT05531526; https://clinicaltrials.gov. **Disclosures:** SS is a primary investigator for Polaris-AD. SK, JC, and CT are consultants for AriBio. DG, MK, JR, FK, JJC are employees of AriBio. The authors declared no competing interests. **References:** Kang BW, et al. Alzheimer's Research & Therapy 2022; 14:92. https://doi.org/10.1186/s13195-022-01034-3. AR1001 Phase 3 Clinical Study Protocol. Version 0.1: AR1001-ADP3-US01. AriBio Co., Ltd. Nov 2022. Clinical Study Report. Version 4 AR1001-ADP2-US01. AriBio Co., Ltd. Jan 2023. CTAD. Journal of Prevention of Alzheimer's Disease, Volume 8, November 2021, oral communication. https://www.ctadalzheimer.com/files/files/CTAD21%20Oral%20communications.pdf

LP002- NEGATIVE AMYLOID BIOMARKERS FOLLOWING TREATMENT (NAFT): A CALL FOR HARMONIZATION AND FUTURE INVESTIGATIONS. C. Sexton[1], J. Cummings[1], D. Galasko[3], M. Ikonomovic[4], S. Landau[5], J. Llibre-Guerra[6], C. Mummery[7], R. Ossenkoppele[8,9], J. Price[10], S. Risacher[11], R. Smith[9], C. Van Dyck[12], M. Carrillo[1] R. La Joie[13,14]
(1. Alzheimer's Association - Chicago (United States), 2. University of Nevada Las Vegas - Las Vegas (United States), 3. University of California, San Diego - San Diego (United States), 4. VA Pittsburgh Healthcare System - Pittsburgh (United States), 5. University of California, Berkeley - Berkeley (United States), 6. Washington University School of Medicine in St Louis - St Louis (United States), 7. University College London - London (United Kingdom), 8. Amsterdam University Medical Center - Amsterdam (Netherlands), 9. Lund University - Lund (Sweden), 10. Massachusetts General Hospital - Boston (United States), 11. Indiana University School of Medicine - Indianapolis (United States), 12. Yale School of Medicine - New Haven (United States), 13. University of California, San Francisco - San Francisco (United States), 14. University of Pittsburgh School of Medicine - Pittsburgh (United States))

Background: Clinical trials have shown that amyloid-targeting monoclonal antibody-based therapies can significantly reduce amyloid plaque burden as measured with PET imaging. In some cases, amyloid-PET signal drops below a pre-determined positivity threshold: the amyloid-PET is "negative". With the recent FDA approval of anti-amyloid therapies, there is a need to better characterize this group of patients with Negative Amyloid biomarkers Following Treatment (NAFT) to improve patient care, management and prognosis. **Methods:**

In August 2023, the Alzheimer's Association gathered a group of clinicians and scientists with expertise in clinical trials and biomarkers of Alzheimer's disease and related dementias. This group aims to summarize the current knowledge on patients with NAFT, identify gaps in knowledge, and make recommendations on the naming and operationalization of this entity, and its implementation in the clinic. **Results:** A review of available results from the 3 FDA-approved drugs showed that up to 80% of treated patients were considered to be NAFT by the end of the trial. The workgroup identified several gaps in knowledge and avenues for clarification. First, with regard to characterization/current knowledge of these individuals, a lack of autopsy studies on individuals with NAFT was noted, which limits our understanding of the underlying neuropathological features: are all amyloid deposits depleted from the brain parenchyma or is amyloid PET-detectable fibrillar beta amyloid plaque burden simply below positivity thresholds for PET? To what extent is vascular amyloid cleared? Or plaque-associated inflammatory response altered? Second, with regard to possible operationalization of a definition of NAFT, it was noted that while several trials of monoclonal antibodies identified patients with NAFT based on a quantitative analysis of amyloid-PET scans, the methods and threshold employed vary between studies. In addition, the operational definition of NAFT is not directly applicable to clinical practice, as amyloid-PET scans are currently only interpreted visually, per FDA approved guidelines. Further, the group discussed the possibility to use CSF or emerging plasma markers to identify patients with NAFT. While fluid biomarkers (such as Ab42/40 and Ptau-species) are impacted by anti-amyloid treatments, it is as yet unclear whether fluid biomarker levels revert to the normal (or "negative") range in patients with a "negative" amyloid-PET following treatment. Further studies are needed to better characterize the timecourses of fluid and imaging biomarker changes and their relationships, both during treatment and after, including the extent and rate at which different biomarkers may become abnormal again following treatment termination. Finally, the group discussed the range of possible applications for a definition, including role in future disease-modifying trials and potential for use for diagnosis vs prognosis, tracking disease progression, re-starting treatment and therapies targeting other elements of Alzheimer's pathology. Implications for sporadic vs dominantly-inherited Alzheimer's vs Down syndrome, and groups underrepresented in research, were also discussed. **Conclusion:** This group will propose a harmonized definition of patients with NAFT for the operationalization of this definition in research, clinical practice and trials. Feedback from the broader community on these efforts will be solicited during the presentation and through a formal feedback process launched at CTAD 2023. **Key words:** Anti-amyloid treatment, Amyloid-PET, real-world biomarker, operationalization. **Disclosures:** Claire Sexton, full time employee of the Alzheimer's Association. Jeffrey L Cummings, consultation to Acadia, Actinogen, Acumen, AlphaCognition, Aprinoia, AriBio, Artery, Biogen, BioVie, Cassava, Cerecin, Diadem, EIP Pharma, Eisai, GemVax, Genentech, GAP Innovations, Janssen, Jocasta, Karuna, Lilly, Lundbeck, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Optoceutics, Ono, Otsuka, PRODEO, Prothena, ReMYND, Roche, Sage Therapeutics, Signant Health, Simcere, Suven, SynapseBio, TrueBinding, Vaxxinity, and Wren pharmaceutical, assessment, and investment companies. He is supported by NIGMS grant P20GM109025; NINDS grant U01NS093334; NIA grant R01AG053798; NIA grant P20AG068053; NIA grant P30AG072959; NIA grant R35AG71476; Alzheimer's Disease Drug Discovery Foundation (ADDF); Ted and Maria Quirk Endowment; and the Joy Chambers-Grundy Endowment. Douglas Galasko, consultant for Eisai, GE Healthcare, Eli Lilly, DSMB for Artery Therapeutics. Milos D Ikonomovic, no disclosures. Susan M Landau, DSMB for KeifeRX and NIH IPAT study, speaking fees from Eisai.Jorge Llibre-Guerra, nothing to disclose. Catherine Mummery, advisory board/ consultancy Biogen, Roche, WAVE, IONIS, Prevail, Lilly; received grant from Biogen; speaker for sponsored events for Biogen, Roche, EISAI, IONIS, Lilly. Rik Ossenkoppele, research support from Avid Radiopharmaceuticals, Janssen Research & Development, Roche, Quanterix and Optina Diagnostics. He has given lectures in symposia sponsored by GE Healthcare, and is a consultant for Asceneuron. Julie Price, Supported by NAI R01AG062559; P01AG036694;T32AG066592; R01AG076153; U19AG068054; R01AG079142. Shannon Risacher, nothing to disclose. Ruben Smith, has given a lecture in a symposium sponsored by Roche. Christopher H. van Dyck has provided consultation to Eisai, Roche, Ono, and Cerevel and receives grant support for clinical trials from Lilly, Biogen, Eisai, Roche, Genentech, UCB, and Cerevel. Maria Carrillo, full-time employee of the Alzheimer's Association and has a daughter in the neuroscience program at USC. She has no financial conflicts to disclose. Renaud La Joie, no disclosures.

LP003- IMPLICATIONS OF MISSING DATA AND DROPOUTS IN RANDOMIZED CLINICAL TRIALS IN EARLY ALZHEIMER'S DISEASE. D. Berry[1] *(1. Berry Consultants - Austin (United States))*

Background: Randomized controlled trials (RCTs) in Alzheimer's disease can have high dropout rates. Patient discontinuations in clinical trials are due to a variety of factors, including adverse events, lack of efficacy, and progression of disease. High dropout rates and other types of data missingness introduce biases that affect the trial's internal validity, external validity, and generalizability of results. Inappropriately handling dropouts may lead to very poor estimates of treatment effect. Ignoring missing data is wrong. Missingness is itself an outcome that can be highly informative. Data missingness is an issue in all clinical trials but it has aspects that are specific to Alzheimer's disease. **Objective:** To evaluate the implications of missingness in RCTs in early Alzheimer's disease. **Methods:** We evaluate commonly-used models for handling missing data in clinical trials. We address sources of bias resulting in missingness and assess the implications of high dropout rates. In particular, we describe and give examples of the use of Bayesian multiple imputation in clinical trials for early Alzheimer's disease. This approach has been proposed as a solution for the missingness dilemma (Little RJ et al. N Engl J Med 2012; 367:1355-1360). **Results:** Linear mixed models are sometimes used to handle missingness when a series of outcomes are measured repeatedly over time (mixed-effect models for repeated measures (MMRM)). Likelihood-based methods such as MMRM are applicable assuming missing completely at random (MCAR) and missing at random (MAR). In clinical trials of early Alzheimer's disease, outcome data are unlikely to be MAR. Assuming otherwise may greatly overestimate or underestimate the effect of an experimental treatment. It is wrong to assume that missing data are MAR and therefore wrong to advertise such models as an acceptable solution to the missing data problem. Discontinuation or attrition rates greater than 20-25% may pose serious threats to the validity and generalizability of trial results (Fewtrell et al. Arch Dis Child. 2008; 93:458-461). Without appropriately

modeling eventual outcomes, different discontinuation rates in control and treatment arms loses the benefit of randomization. A recent systematic review and network meta-analysis investigating cognitive enhancers for Alzheimer's dementia concluded that approximately two-thirds of published RCTs exhibit a high risk of bias concerning incomplete outcome data due to attrition (Veroniki AA et al. BMJ Open. 2022 Apr 26;12(4):e053012). **Conclusion:** Discontinuations or missing data greater than 20-25% can have a significant impact on interpreting results. Conventional methods for managing missing data may not be suitable for RCTs in early Alzheimer's disease. An appropriately modeled Bayesian multiple imputation can at least partially correct the maleffects of missingness. **Conflict of Interest Statement:** Donald Berry is co-owner of Berry Consultants, LLC, a company that designs adaptive Bayesian clinical trials for pharmaceutical companies, including Eisai, medical device companies, NIH cooperative groups, patient advocacy groups, and international consortia.

LP004- DETERMINANTS OF INDIVIDUAL DIFFERENCES IN THE EFFICACY OF AEROBIC EXERCISE TO IMPROVE BRAIN HEALTH AND REDUCE ALZHEIMER'S DISEASE RISK IN OLDER AFRICAN AMERICANS. B. Fausto[1], S. Malin[2], P. Duberstein[3], K. Erickson[4], L. Hu[5], M. Gluck[1] *(1. Center for Molecular and Behavioral Neuroscience, Rutgers, The State University of New Jersey–Newark - Newark, New Jersey (United States), 2. Department of Kinesiology and Health, Rutgers University - New Brunswick, New Jersey (United States), 3. Department of Health Behavior, Society and Policy, Rutgers School of Public Health - Piscataway, New Jersey (United States), 4. AdventHealth Research Institute - Orlando, Florida (United States), 5. Department of Biostatistics and Epidemiology, Rutgers School of Public Health - Piscataway, New Jersey (United States))*

Background: Older African Americans—especially those with lower income and those living in urban neighborhoods—have a greater risk of Alzheimer's disease (AD) compared to the general population. This health disparity is attributable, in part, to modifiable factors including insufficient levels of aerobic exercise. However, not everyone gains the same degree of neuroprotection from exercise. Here we describe the protocol for a phase II randomized clinical trial to address whether exercise influences brain health in cognitively unimpaired older African Americans. The primary goals are to test the efficacy of aerobic exercise in the form of a cardio-dance fitness intervention to improve cognitive and neural markers of AD risk in older African Americans and examine whether ABCA7 genotypic variations moderate the efficacy of this intervention. We will also explore whether aerobic exercise modifies AD neuropathology or merely helps compensate for age-related changes in brain health. **Methods/design:** This study uses a randomized, controlled experimental design with blinded assessors and investigators. We are recruiting 280 sedentary older African Americans, ages 60 and above, to be randomized to one of two equally engaging six-month interventions: (1) a moderate-to-vigorous intensity cardio-dance aerobic fitness condition (n = 140) or (2) a low-intensity strength, flexibility, and balance condition (n = 140). All participants will undergo—at enrollment and post-intervention—health assessments; cognitive tests; saliva sample collection for ABCA7 genotyping; structural and functional magnetic resonance imaging; and a blood draw to assess key AD neuropathological markers: amyloid (Aβ 42/40) and tau (p-tau231, p-tau181). **Discussion:** This work lays the foundation for future larger clinical trials to develop personalized exercise prescriptions for older African Americans with varying health, genetic, and social determinant risk profiles so as to optimize low-cost non-pharmacological interventions for improving their brain health.

LP005- INVESTIGATING PARTIALLY DISCORDANT RESULTS IN ADUCANUMAB ENGAGE AND EMERGE TRIALS USING SUBTYPE AND STAGE INFERENCE MACHINE LEARNING. N. Oxtoby[1], C. Shand[1], F. Barkhof[1,2,3] *(1. UCL Centre for Medical Image Computing, Department of Computer Science, University College London - London (United Kingdom), 2. UCL Queen Square Institute of Neurology, University College London - London (United Kingdom), 3. Department of Radiology & Nuclear Medicine, Amsterdam University Medical Center - Amsterdam (Netherlands))*

Background: Undetected heterogeneity within and between treatment arms can confound clinical trials unless accounted for in trial design, implementation, and analysis (e.g., stratification, covarying, screening). We used Subtype and Stage Inference (SuStaIn) — an unsupervised machine learning method — to perform a data-driven investigation into the partially discordant results (presence/absence of statistically significant treatment effect) between two Phase 3 clinical trials of aducanumab (EMERGE: NCT02484547; ENGAGE: NCT02477800) in early AD patients. **Methods:** Experimental design: SuStaIn was deployed on ADNI data to learn a computational model of AD atrophy subtypes. The trained model was used to stratify baseline data from enrolled EMERGE and ENGAGE participants into atrophy subtypes, followed by post hoc subgroup statistical analyses to compare the trials at baseline (longitudinal data was not available to the authors). Inclusion criteria: amyloid positive; no missing data in covariates (age, sex, education, intracranial volume) nor brain volumes estimated from automatic processing of T1w MRI. Outliers on intracranial volume were excluded (IQR method). Training data (ADNI): N=364 (70 CN, 207 MCI, 87 AD). Testing data: 1532 (EMERGE) and 1563 (ENGAGE). Model inputs: we used FreeSurfer v7.1.1 to process raw T1w MRI into brain volumes adjusted for covariates and z-scored relative to controls (ADNI: N=144 cognitively normal, amyloid-negative). Model events included subtle atrophy (z = 0.5, 1) and prominent atrophy (z = 3). We were blinded to treatment assignment. **Statistical analyses:** a $\chi 2$ contingency test compared subgroup breakdown in EMERGE vs ENGAGE. Within subgroups, Mann-Whitney U tests compared EMERGE vs ENGAGE by demographics (age, sex, APOE4, education), clinical outcomes (ADAS-Cog13; CDRSB; ADL-MCI) and SuStaIn stage (atrophy severity). **Results:** SuStaIn estimated four atrophy subtypes: 1) "Typical" (early hippocampus/amygdala/temporal lobe; 34.4% prevalence); 2) "Cortical" (early temporal/frontal/parietal; 25.2%); 3) "Subcortical" (early striatal; 14.3%); and 4) "Aggressive" (early z=3 events in hippocampus/amygdala; 5.4%), plus a no-atrophy group labelled 0) "Stage Zero" (20.8%). Deploying the model stratified EMERGE/ENGAGE as: Stage Zero 10.7/7.3%; Typical 43.5/47.3%; Cortical 31.7/32.7%; Subcortical 7.2/6.7%; Aggressive 6.9/6.1%. EMERGE had a more subtle atrophy profile ($\chi 2$ = 13.7, dof = 4, p = 0.008), i.e., more Stage Zero (11% vs 7%) and fewer Typical Subtype (44% vs 47%). There were within-subgroup significant differences between EMERGE and ENGAGE. The «Typical" subgroup in EMERGE was older (72 vs 71, p=0.001) and had received slightly fewer years of education (15 vs 16; p=0.07). The Cortical subgroup in EMERGE was slightly less impaired (ADAS-Cog-13: 22.2 vs 22.8, p=0.09). The Subcortical subgroup in EMERGE had more males (70% vs 57%, p=0.05). There was nonsignificant (p=0.17) imbalance

in APOE4 carriage, with EMERGE having more noncarriers and fewer carriers. **Conclusion:** A computational model of spatiotemporal atrophy subtypes in AD, that was trained on ADNI data using the Subtype and Stage Inference algorithm, detected baseline imbalances between the Phase 3 EMERGE and ENGAGE trials of aducanumab. Our comparisons of baseline data suggest that ENGAGE may have had higher resilience to treatment than EMERGE: younger (possibly earlier onset, more aggressive AD), higher APOE4 carriage, more females, and more advanced atrophy stages. This undetected biological heterogeneity between EMERGE and ENGAGE may have contributed to the partially discordant results. An open question for future work — in any trial — is whether treatment response varies by data-driven subgroup. Such a result would support using data-driven disease progression modelling in trial design and treatment assignment.

LP006- CONFIRMATORY BUT NOT INDEPENDENT? IMPLICATIONS OF USING EARLY PHASE RESULTS AS CONFIRMATORY EVIDENCE IN AD REGISTRATION TRIALS. D. Gillen[1], J. Grill[1], S. Schlund[1], S. Emerson[2]
(1. University of California, Irvine - Irvine (United States), 2. University of Washington - Seattle (United States))

Background: Food and Drug Administration (FDA) guidance provides multiple approaches to demonstrating substantial evidence of effectiveness (SEE). In general FDA requires two adequate and well-controlled (AWC) trials, each convincing on its own, to establish efficacy [1]. In some cases, however, data from one AWC trial and confirmatory evidence may be sufficient to establish efficacy. Recently sponsors have proposed that, in addition to one AWC trial, data from early phase studies in the same developmental program may provide confirmatory evidence to establish SEE. One example is the new drug application of aducanumab for the treatment of Alzheimer's disease. Beyond concerns with discrepant phase III study results, the sponsor cited data from Study 103, a phase Ib study, as providing supportive evidence of effectiveness [2]. Use of earlier phase data does not, however, provide independent confirmatory evidence since the initiation of a phase III study is almost certainly dependent upon positive findings in earlier phase trials. In addition, type I error rates are generally not controlled in early phase trials. We illustrate the impact of utilizing early phase trial data as confirmatory evidence on the probability of approving effective therapies and propose the use of group sequential stopping rules as an alternative to maintain statistical criteria. **Methods:** In the context of drug development the positive predictive value (PPV) represents the probability that an approved therapy is truly effective. PPV is determined by type I error, power, and the prevalence of effective therapies investigated. In phase III registration trials, type I error rates are commonly bounded at 0.05, while power is chosen to be 80-90% for a defined alternative. Further, the prevalence of effective therapies being studied may be 10% or less [3]. We used FDA's standard policy of requiring two convincing AWC trials as a benchmark and compare PPV under varying early phase type I error rates and degrees of dependence. We propose group sequential stopping rules [4] to maintain PPV when data from early phase trials are meant to provide confirmatory evidence. **Results:** We show PPV can drop from 98% to under 78% when early phase data are used. Decreases in PPV primarily stem from increased type I error rates in early phase trials and the dependence of phase III trial initiation on successful early phase results. Finally, we show that our proposed phase II-III stopping rule maintains PPV. Our illustrations are informed by data from the aducanumab development trials. **Conclusion:** Using dependent early phase trial results in place of independent confirmatory evidence can result in substantially lower PPV for AD trials. Group sequential stopping boundaries can maintain PPV but require pre-specification during phase II development. **Key words:** evidence of effectiveness, FDA approval, confirmatory data, aducanumab. **Disclosures:** Dr. Grill reports grant funding from the National Institutes of Health, Eli Lilly, Eisai, Genentech, Biogen, BrightFocus Foundation, and the Alzheimer's Association. He reports consulting for SiteRx, Cogniciti, and Flint Rehab. The other authors declared no competing interests. **References:** 1. US FDA. Demonstrating substantial evidence of effectiveness for human drug and biological products: Guidance for industry. Department of Health and Human Services (2019). https://www. fda. gov/media/13366 0/download. 2. Haeberlein B, et al. J Prev Alz Dis. 2022; 9(2):197-210.https://doi.org/10.14283/jpad.2022.30. 3. Mullard, A. Nat Rev Drug Discov 2016; 15: 447.https://doi.org/10.1038/nrd.2016.136. 4. Emerson S, et al. Stat Med 2007; 10;26(28):5047-80.https://doi.org/10.1002/sim.2901.

LP007- OPTIMIZING ALZHEIMER'S DISEASE CLINICAL TRIAL DATA FOR FACILITATING SCIENTIFIC DISCOVERY. K.A. Welsh-Bohmer[1], S. Haneline[2], R. Wilgus[1], J. Shostak[1], H. Zou[3], S. Luo[1], M. Lutz[4], B.L. Plassman[4], D.K. Burns[2], R. Li[5], F. Rockhold[1], M. Clement[6], T. Maruyama[6]
(1. Duke Clinical Research Institute (DCRI) - Durham (United States), 2. Zinfandel - Chapel Hill (United States), 3. UNC-Chapel Hill - Chapel Hill (United States), 4. Duke University - Durham (United States), 5. Vivli - Cambridge (United States), 6. Alzheimer's Disease Data Initiative (ADDI) - Kirkland (United States))

Background: Data sharing across research groups is critically important for understanding differences in results across studies and for driving new medical insights. Data from pharmaceutical trials are of particular interest for understanding mechanisms of disease and treatment response. However, accessing and using clinical trial data can be challenging. The National Philanthropic Trust recently funded a study through the Alzheimer's Disease Data Initiative (ADDI) aimed at optimizing the use of data from the recently completed TOMMORROW trial (clinicaltrials.gov: NCT01931566), a clinical trial designed to test low dose pioglitazone to delay the onset of Mild Cognitive Impairment due to Alzheimer's disease (MCI-AD) in healthy older adults at high genetic risk for developing MCI-AD. **Objectives:** The goals of the project were to (1) evaluate the clinical trial dataset from the perspectives of researchers of varying experience with pharmaceutical trials; (2) determine ease of use; (3) develop procedures, work products, and recommendations to facilitate use of the TOMMORROW trial data, and (4) provide guidance on data sharing for other concluding AD clinical trials. **Methods:** The two year project had 2 phases. Phase 1: clinical-trial analysts (n=6) examined the TOMMORROW analysis ready (ADaM) and standard data model (SDTM) datasets, the accompanying documentation, and ran analyses to determine ease of use. Feedback in bi-weekly work sessions led to tools and a User Guide to assist future users of the dataset. Phase II: a group of data scientists (n=11) were given access to the TOMMORROW data and User Guide on ADDI's AD Workbench within the Duke protected environment. They completed surveys querying: (1) ease of navigating the TOMMORROW datasets; 2) usefulness of the documentation for understanding the study design, data structure, data variables, and derived/calculated measures; 3)

ease of analysis within the AD Workbench; 4) comparability of data outcomes across the ADDI and Duke platforms for basic data validation; 5) suggested improvements. **Results:** Phase I users found navigating the TOMMORROW clinical trial data not as easy as using datasets like Alzheimer's Disease Neuroimaging Initiative (ADNI) designed specifically for data sharing. The users identified areas where additional documentation would be helpful, particularly around the calculated composite measures and other derived measures. Phase II users uniformly reported the additional tools useful. Analyses completed on the ADDI Workbench were analogous to those done in the Duke environment. Functionality was good and the ADDI Workbench's responsiveness was rated as very good. Improvements suggested included offering quick guides, infographics, a FAQ section, and more orientation on the ADDI TOMMORROW landing page. **Conclusions:** Clinical trial datasets are complex and not as straightforward to navigate as observational datasets designed specifically for data sharing. The development of tools and centralizing access to these data products on a common platform, such as the ADDI Workbench, can help facilitate use of clinical trial datasets. The TOMMORROW datasets are available through the Vivli data sharing platform (www.vivli.org) and are discoverable through the Global Alzheimer's Association Interactive Network (www. GAAIN.org). The TOMMORROW User Guide, FAQs, Infographics and other useful work products can be found on the ADDI Workbench (www.alzheimersdata.org). **Disclosures:** The authors declare no competing interests. This project was funded by a grant from the National Philanthropic Trust to Duke University (Dr. Kathleen Welsh-Bohmer, PI). The original TOMMORROW clinical trial was sponsored by Takeda Pharmaceutical Company in alliance with Zinfandel Pharmaceutical Company.

LP008- INCORPORATING THE STUDY PARTICIPANT'S VOICE INTO EARLY DEVELOPMENT OF ACU193 FOR EARLY ALZHEIMER'S DISEASE: A QUALITATIVE INTERVIEW STUDY FOLLOWING PARTICIPATION IN THE INTERCEPT-AD STUDY. K. Johnston[1], V. Brown[1], C. Presnall[1], E. Merikle[1], S. Cline[2], T. Feaster[2] *(1. Fortrea, Inc. - Durham (United States), 2. Acumen Pharmaceuticals - Charlottesville (United States))*

Background: The collection of patient experience data has gained increasing recognition as a crucial component of clinical trials, to the extent that incorporation of the patient voice into drug development has been codified in recent legislation [1]. Qualitative patient interviews conducted within the trial setting are among the most common means of ascertaining the patient experience; topics are expansive but often include assessment of meaningful change, interpretation of clinical outcome assessment scores, and treatment experience [2,3]. Although less commonly reported, interviews conducted earlier in development can be used to inform subsequent phases, particularly regarding participant recruitment and trial procedures. As part of a phase 1 study of ACU193, a monoclonal antibody selective for soluble amyloid β oligomers, we conducted semi-structured qualitative exit interviews among a subset of participants with early Alzheimer's disease (AD; mild cognitive impairment or mild dementia due to AD) and their study partners to obtain feedback on disease experience, treatment expectations, trial experience, and the decision-making process preceding trial enrollment. Results pertaining to decision-making regarding trial participation and trial experience are presented. **Methods:** A subset of trial participants was interviewed as part of the phase 1 INTERCEPT-AD study evaluating the safety and tolerability of the monoclonal antibody ACU193. Interviews occurred within 7 days of the end-of-study visit, were 90 minutes long, and included both participants and study partners, the latter of whom were interviewed separately. Trial participation topics included referral source, motivations for participating, individuals involved in decision-making, and concerns regarding study medication and procedures. Questions regarding trial experience assessed the positive and negative aspects of participation. The semi-structured interview guide was developed in accordance with FDA Patient Focused Drug Development guidance [3, 4]. Coding and analysis of the transcripts followed principles of qualitative thematic analysis, with additional features drawn from grounded theory, conforming to best practices in the field [5]. **Results:** Twenty-eight patients and their study partners from 9 clinical sites were interviewed. Participants first heard about the INTERCEPT-AD study primarily from social media (46.4%) or their physicians (36.0%). When deciding whether to enroll in the study, many participants (39.3%) sought help from family members while others (25.0%) decided independently. Participants were motivated to enroll primarily to help improve their symptoms of AD or benefit themselves (71.4%) and, secondarily, to potentially benefit others (42.9%). Of the 12 (42.9%) participants who expressed concerns about enrolling, their apprehensions revolved mostly around potential side effects (25.0%). Burdens of trial participation were largely related to four challenges: 1) distance to clinics (60.7%), 2) time commitment required to participate (28.6%-53.6%), 3) issues with study procedures (including the cognitive tests: 42.9%, blood draws/needles: 32.1%, and lumbar punctures: 25.0%), and 4) a desire for more information about the study medication, including scan results and treatment group assignment (42.9%). **Conclusions:** Participants and their study partners reported a broad array of factors related to participation in the INTERCEPT-AD study, including referral sources, decision-making resources and factors, and burdens experienced during the study. These findings will be used to inform study procedures in subsequent trials of ACU193. **Key words:** Phase 1, Patient experience, Exit interviews, Patient-focused drug development. **Disclosures:** Johnston, Brown, Presnall, Merikle: Employed by Fortrea, Inc. which received funds from Acumen Pharmaceuticals to conduct this study. Cline: Consultant to Acumen Pharmaceuticals. Feaster: Employee and shareholder at Acumen Pharmaceuticals. References: 1) Eastern Research Group, Inc. Assessment of the Use of Patient Experience Data in Regulatory Decision-Making; 2021:1-3. https://www.fda.gov/media/150405/download?attachment. 2) FDA CDER. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders; 2020. https://www.fda.gov/media/139088/download. 3) FDA CDER. Patient-Focused Drug Development: Methods to Identify What is Important to Patients; 2022. https://www.fda.gov/media/131230/download. 4) FDA CDER: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making; 2023. https://www.fda.gov/media/166830/download. 5) Patrick DL. Burke LB, Gwaltney CJ, et al. Content validity – establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1 – eliciting concepts for a new PRO instrument. Value in Health 2018; 14(8): 967-77. doi:10.1016/j.jval.2011.06.014

LP009- REDUCING SCREEN FAILURE RATES DUE TO BIOMARKER CUT-OFFS IN EARLY ALZHEIMER'S DISEASE TRIALS USING A PROGNOSTIC MODEL.

A. Tam[1], C. Laurent[1], C. Dansereau[1] *(1. Perceiv AI - Montreal (Canada))*

Background: Disease-modifying trials in early Alzheimer's disease (AD) have high screen failure rates (above 70%), which are associated with long enrollment periods and high patient-screening costs. Trials need enrichment strategies to select the most appropriate participants (i.e. likely decliners) while simultaneously minimizing screen failures. Some recent trials have enriched for individuals at particular disease stages based on tau pathology. However, universal cut-offs for AD biomarkers still need to be established and the application of a tau cut-off can exacerbate screen failures. Here, we explored how to enrich for likely decliners while minimizing screen failures and avoiding the binarization of tau pathology through the use of a multimodal prognostic model that forecasts clinical progression, Foresight ADTM. **Methods:** In amyloid positive early AD participants from ADNI, we quantified the screen failure rate due to tau enrichment with cerebrospinal fluid (CSF) phosphorylated tau 181 (p-tau181) measured by the Roche Elecsys assay at a cut-off of 26.9 pg/mL, which we found best separated cognitively normal individuals and patients with AD dementia. We performed a power analysis to estimate sample sizes for detecting a 30% treatment effect at 80% power required by a two-arm trial that would enroll participants based on this cut-off. Then, while maintaining the same power and sample size as the p-tau181 cut-off, we estimated the screen failure rate associated with enriching the population with likely decliners predicted by Foresight ADTM, a machine learning model that uses APOE4 genotype, demographics, clinical assessments, and CSF concentrations of amyloid beta 42, p-tau181, and total tau to predict individual risks of cognitive and functional decline over 2 years. **Results:** Using the 26.9 pg/mL p-tau181 cut-off, 36.3% of the sample failed this screening criterion, and 452 total participants would be required to properly power the study. To enroll a trial with the same power as this cut-off, selecting predicted decliners by Foresight ADTM would screen out only 19.5% of participants, leading to a 46.3% reduction in screen failure. Foresight ADTM can therefore be used to screen fewer participants than when using a p-tau181 cut-off, while preserving statistical power. Similar results were found at different p-tau181 cut-offs. Lastly, at a matched screen failure rate of 36.3%, a sample selected by Foresight ADTM would require only 384 participants, which represents a 15.0% reduction in sample size compared to the 452 participants needed when using the 26.9 pg/mL p-tau181 cut-off, demonstrating that Foresight ADTM can also offer a more powerful enrichment strategy than a p-tau181 cut-off. **Conclusions:** A prognostic model that combines clinical information and biomarkers can enrich trials with lower screen failure rates compared to enrichment with CSF p-tau181 cut-offs only, while maintaining equivalent statistical power. Enrichment with reduced screen failures can minimize trial durations and reduce patient-screening costs by accelerating enrollment.

LP010- RATIONALE AND DESIGN OF A PHASE 2B TRIAL TO EVALUATE THE EFFICACY OF A SPECIFIC INHIBITOR OF 11B-HSD1, XANAMEM®, IN MILD AND MODERATE AD.

D. Hilt[1], J. Taylor[1], T. Miller[1], J. Harrison[2,3,4], C. Chen[5], C. Ritchie[2] *(1. Actinogen Medical - Sydney (Australia), 2. Scottish Brain Sciences - Edinburgh (United Kingdom), 3. King's College - London (United Kingdom), 4. Alzheimercentrum, AUmc - Amsterdam (Netherlands), 5. Memory Aging and Cognition Centre, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore - Singapore (Singapore))*

Background: Xanamem® is a brain-penetrant inhibitor of 11β-HSD1, which converts intracellular cortisone to cortisol and is highly expressed in brain regions such as the hippocampus. Elevated plasma and CSF cortisol is strongly associated with cognitive dysfunction, neurotoxicity, and Alzheimer's Disease (AD). Thus, reducing cortisol levels in the brain is considered an important therapeutic goal in the treatment of AD. Effects of Xanamem on cognition have been assessed in 3 independent placebo-controlled, double-blind trials. The XanaHES (n=42, 20 mg) and XanaMIA (n=105, 5 & 10 mg) Phase 1b trials used the computerised Cogstate system to assess cognition in normal, older volunteers. A pattern of clinically significant improvements was observed in attention and working memory compared to placebo in the Xanamem groups, with Cohen's d up to 1.27. The XanADu-X biomarker extension study (n=72, 10 mg) explored clinical and cognitive outcomes in subgroups (n=34 each) of the XanADu Phase 2a AD trial with higher (H) or lower (L) plasma p-tau181 in a new prospective analysis. Xanamem largely prevented clinical progression over 12 weeks, displaying a clinically significant benefit (Cohen's d of 0.41) on the CDR-SB compared to placebo in the H group but not in the L group. In both L and H groups improvements were seen favouring Xanamem in tests of executive function (Cohen's d=0.34 and 0.26, respectively) and the MMSE (Cohen's d=0.32 and 0.16, respectively). Together, these data suggest Xanamem may be both a procognitive and disease-course modifying agent. These cognitive and clinical benefits will be examined in the XanaMIA Phase 2b trial. **Methods:** XanaMIA is a phase 2b, double blind, randomized, placebo-controlled, parallel-groups, 36-week, 3-arm trial to assess the safety, tolerability, and efficacy of Xanamem 5 mg and 10 mg daily in patients with mild or moderate dementia due to Alzheimer's Disease. This multi-centre trial will randomise (1:1:1) 330 participants over 50 years old meeting the diagnostic criteria for AD with a CDR global score of 0.5-1, a MMSE of 18-26, and elevated plasma p-tau181. Participants will also be required to have a 0.5 SD cognitive deficit compared to normative data as measured by a symbol coding test. The primary efficacy endpoint is change from baseline to week 36 on a computerized, global cognitive composite including measures of attention, working memory, executive function, and episodic memory. The key secondary outcome, the CDR-SB, will assess integrated cognition and function. Other measures of cognition, function, and behavior will also be examined. The study design includes a 6-week pre-screening period (to assess AD plasma biomarker positivity), 4-week screening period, a 36-week treatment period, and a 4-week follow-up period. **Results:** The results of the XanaMIA Phase 2B trial are expected in 2025. **Conclusions:** Xanamem displays activity in multiple domains of cognition including attention, working memory, and executive function with clinically meaningful effects in normal subjects and in patients with p-tau181-elevated mild AD. The XanaMIA Phase 2B trial is a robustly designed study using contemporary, treatment-sensitive endpoints, and patient enrichment

strategies to demonstrate the procognitive and disease-course modifying benefits of Xanamem. **Key words:** Cortisol, cognitive enhancement, ptau181, randomised controlled trial. **Disclosures:** DH, JT, and TM are employees of Actinogen Medical; JH is an employee of Scottish Brain Sciences. He reports receipt of personal fees in the past 2 years from AbbVie, Actinogen, Alto Pharma, AlzeCure, ADvantage, Astra Zeneca, Athira Therapeutics, Bial Biotech, Biogen Idec, Boehringer Ingelheim, Brands2life, Cerecin, Cognition Therapeutics, Compass Pathways, Corlieve, Curasen, EIP Pharma, EQT Life, GfHEU, Heptares, ImPACT, Lundbeck, Lysosome Therapeutics, Neurotrack, the NHS, Novartis, Novo Nordisk, Nutricia, Prothena, Recognify, reMYND, Roche, Shionogi, Signant, Stoke Therapeutics, Syndesi Therapeutics, Takeda, Vivoryon Therapeutics and Winterlight Labs. Additionally, he holds stock options in Neurotrack Inc. and is a joint holder of patents with My Cognition Ltd.; CC has received consultancy fees from Actinogen Medical, Eisai, and Cerecin, and research funding from the National Medical Research Council of Singapore; CR Dr Ritchie reported receiving personal fees from Actinogen, Biogen, Cogstate, Eisai, Eli Lilly, Janssen Cilag, Merck, Novo Nordisk, Roche Diagnostics, and Signant and being founder of and majority shareholder in Scottish Brain Sciences.

LP011 IMPACT OF A SITE SUPPLEMENTAL FUNDING PROGRAM TO ALLEVIATE RECRUITMENT BURDEN: EXPERIENCES IN THE PRECLINICAL ALZHEIMER'S DISEASE AHEAD STUDY.

L.K. Shum[1], R. Raman[1], O. Langford[1], V. Salcedo[1], A. Liu[1], R. Sperling[2,3], J.D. Grill[4], C.M. Glover[5,6,7], P. Aisen[1], K. Johnson[2,3], S. Dhadda[8], M. Irizarry[8], D. Molina-Henry[1] *(1. Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego, Ca (United States), 2. Brigham and Women's Hospital, Harvard Medical School - Boston, Ma (United States), 3. Massachusetts General Hospital, Harvard Medical School - Boston, Ma (United States), 4. University of California, Irvine - Irvine, Ca (United States), 5. Department of Neurological Sciences, Rush Medical College - Chicago, Il (United States), 6. Department of Psychiatry and Behavioral Sciences, Rush Medical College - Chicago, Il (United States), 7. Rush Alzheimer's Disease Center - Chicago, Il (United States), 8. Eisai Inc. - Nutley, Nj (United States))*

Background: The AHEAD Study is a multi-center trial that tests whether lecanemab can slow cognitive decline in a preclinical Alzheimer's disease (AD) population. The planned enrollment in the AHEAD Study is 1,400 global randomized participants, including 75 North American (NA) sites. Study screening assessments include blood and PET biomarker tests, as well as clinical and cognitive assessments, resulting in substantial study staff burden. To facilitate site recruitment, the central study team launched a Site Supplemental Funding Program (SSFP) to appropriately compensate study sites that incurred additional burden associated with high volumes of participant screening. **Methods:** The SSFP pilot was implemented from March to May 2023. The SSFP provided NA study sites with an additional monthly stipend to cover the time and effort associated with achieving 15 or more eligible participants screened in a calendar month. Qualified participant screens for the SSFP were defined as including signed informed consent, blood plasma collection, and not being excluded for criteria that should be identified prior to in-person screening (e.g., ineligible age, lack of study partner, contraindications to MRI, prohibited medications, planned surgery requiring general anesthesia). The announcement of the SSFP was widely disseminated to all NA sites through electronic written communication and at study operations and recruitment focused webinars. The impact of this program on the overall NA screening rate in the AHEAD Study was evaluated. **Results:** Overall, the number of screens per calendar month increased from a 3-month average of 366 prior to launching the program (Dec 2022 to Feb 2023) to 608 in the first 3-months of the initiative (March to May 2023). Of the 75 NA sites, 22 (29%) unique sites qualified for supplemental funding at least once during the three-month pilot. Six sites qualified for supplemental funding each month of the pilot program. Prior to the implementation of the SSFP, an average of 5 sites had a screening rate ≥15 participants per month. After implementation, an average of 13 sites had a screening rate ≥15 participants per month. **Conclusion:** Implementation of the SSFP resulted in increased monthly screens in the AHEAD Study. With this success, the SSFP was extended for the duration of the AHEAD Study enrollment period. Careful assessment of site burden and supplemental funding to overcome infrastructure limitations to site capacity may accelerate trial accrual. **Key words:** recruitment, site engagement, clinical trials, preclinical AD. **Clinical Trial Registry:** NCT04468659. **Disclosures:** Ms. Shum is involved in the AHEAD 3-45 Study which is a public-private partnership with funding from the National Institute on Aging (National Institutes of Health), Eisai, GHR Foundation, Alzheimer's Association, and philanthropic organizations. Dr. Raman has received research funding from the National Institutes of Health, Eli Lilly, Eisai, Alzheimer's Association and American Heart Association. Mr. Langford is involved in the AHEAD 3-45 Study which is a public-private partnership with funding from the National Institute on Aging (National Institutes of Health), Eisai, GHR Foundation, Alzheimer's Association, and philanthropic organizations. Ms. Salcedo is involved in the AHEAD 3-45 Study which is a public-private partnership with funding from the National Institute on Aging (National Institutes of Health), Eisai, GHR Foundation, Alzheimer's Association, and philanthropic organizations. Mr. Liu is involved in the AHEAD 3-45 Study which is a public-private partnership with funding from the National Institute on Aging (National Institutes of Health), Eisai, GHR Foundation, Alzheimer's Association, and philanthropic organizations. Dr. Sperling has served as a paid consultant for AC Immune, Alector, Acumen, Alnylam, Bristol Myers Squibb, Cytox, Genentech, Janssen, Neuraly, NervGen, Neurocentria, Oligomerix, Prothena, Renew, Vigil Neuroscience, Ionis and Vaxxinity. She receives research support from Eisai and Eli Lilly as part of public-private partnership clinical trials, and also receives research support from the following grants: P01 AG036694, U24 AG057437, R01 AG063689, R01 AG054029, R01 AG053798, GHR Foundation, National Institute on Aging, Fidelity Biosciences, and the Alzheimer's Association. (Spouse consultant to Merck, Janssen). Dr. Grill reports grant funding from the National Institutes of Health), Eli Lilly, Eisai, Biogen, BrightFocus Foundation, and the Alzheimer's Association. He reports consulting for SiteRx, Cogniciti, and Flint Rehab. Dr. Glover has no competing interests. Dr. Aisen has research grants from the National Institutes of Health, the Alzheimer's Association, Janssen, Lilly and Eisai, and consults with Merck, Roche, Genentech, Abbvie, Biogen, ImmunoBrain Checkpoint and Arrowhead. Dr. Johnson has served as a paid consultant for Bayer, GE Healthcare, Janssen Alzheimer's Immunotherapy, Siemens Medical Solutions, Genzyme, Novartis, Biogen, Roche, ISIS Pharma, AZTherapy, GEHC, Lundberg, and Abbvie. He is a site coinvestigator for Eli Lilly/Avid, Pfizer, Janssen Immunotherapy, and Navidea. He has spoken at symposia

sponsored by Janssen Alzheimer's Immunotherapy and Pfizer. He also receives research support from Eisai as part of public-private partnership clinical trials and receives research support from the following grants P01 AG036694, R01 AG063689, R01 AG054029, GHR Foundation, National Institute on Aging, and the Alzheimer's Association. Dr. Dhadda is an employee of Eisai Inc. Dr. Irizzary is an employee of Eisai Inc. Dr. Molina-Henry is involved in the AHEAD 3-45 Study which is a public-private partnership with funding from the National Institute on Aging (National Institutes of Health), Eisai, GHR Foundation, Alzheimer's Association, and philanthropic organizations.

LP012- ESTABLISHING AN EVIDENCE-BASED PATIENT RECRUITMENT STRATEGY THROUGH A SITE RECRUITMENT NEEDS ASSESSMENT FOR A HOSPICE-ELIGIBLE POPULATION WITH DEMENTIA. K. López Aguiñiga[1], A. Zokas Fritts[2], J. Mintzer[2], B. Reynolds[3], M. Chadwick[3], O. Brawman-Mintzer[4], G. Jicha[5], M. Kindy[6], B. Huisa-Garate[7], J. Keller[8], T. Clanton[1], B. Smith[1], J.D. Grill[9], P. Aisen[1], R. Raman[1] *(1. Alzheimer's Therapeutic Research Institute (ATRI) - San Diego (United States), 2. Medical University of South Carolina - Charleston (United States), 3. Georgetown University - District Of Columbia (United States), 4. Ralph H. Johnson Veteran Affairs Medical Center - Charleston (United States), 5. University of Kentucky - Lexington (United States), 6. University of South Florida - Tampa (United States), 7. The Neuron Clinic - San Marcos (United States), 8. Pennington Biomedical Research Center - Baton Rouge (United States), 9. University of California, Irvine - San Diego (United States))*

Background: A significant challenge in the conduct of clinical trials among hospice-eligible individuals living with dementia is the lack of evidence-based strategies for the successful recruitment of a diverse study sample into these trials. The Alzheimer's Clinical Trials Consortium's (ACTC) Life's end Benefits of cannaBidiol and tetrahYdrocannabinol (LiBBY) study is a 12-week, double-blind, placebo-controlled, Phase 2 trial with 150 participants evaluating the possible benefits of Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as a treatment option for agitation in hospice-eligible people 40 years or older with Alzheimer's disease (AD) or other dementias. **Methods:** To further understand and fill information gaps pertaining to recruitment for the LiBBY trial, we performed a participant recruitment needs assessments via video conference call as part of the study site start-up activities. The primary goals of the call were to develop a site-specific representative participant recruitment strategy through understanding each site's recruitment capacity, access, goals, and needs to enroll participants in the study. The call included the following key elements: (a) participation of the site Principal Investigator, recruitment contact, and study coordinator, (b) a standardized questionnaire of discussion topics provided to sites when scheduling the call and utilized as a guide when conducting the call, (c) recording of calls to support call summary and data collection, and (d) standardized data collection. Questionnaire topics included anticipated participant screen and access, anticipated approach to the recruitment of underrepresented groups (URGs), existing referral sources and partnerships, anticipated residence of participants and caregivers, helpful recruitment materials, and any other anticipated challenges. **Results:** Needs assessment calls were completed with the six selected study sites that were in the start-up phase at the time. Call duration ranged from 37 to 65 minutes. The anticipated number of screens per site per quarter range from 3-10 participants, with all sites anticipating a screen ineligibility rate below 20%. All sites report having a thorough pre-screening process and a commitment to enrolling a diverse sample with at least 30% of screened participants from URGs. Primary referral sources identified are hospice care service partners and established internal referral processes with medical providers (e.g., neurologists). Most sites anticipate that a majority of participants will reside at home and receive support from an informal caregiver (4/6 sites), defined as someone the participant knows and provides unpaid care (e.g., family). The identified key URGs are individuals from underrepresented racial and ethnic groups, those living in rural or disadvantaged neighborhoods, and are Veterans. Foreseeable challenges to URG recruitment reported by sites include hospice care inaccessibility, stigma toward the investigational product (IP), and availability of the IP at the facility. **Conclusion:** The recruitment needs assessment calls demonstrated the perceived feasibility of successful recruitment for the LiBBY Study. The impact of early site engagement and establishment of recruitment expectations will be quantified as the LiBBY trial progresses. A site engagement plan is suggested to monitor site reported recruitment projections and plans. Data collected from these calls will be used to develop, implement, and evaluate site-specific recruitment strategies and inform central recruitment activities. **Key words:** Alzheimer's, recruitment, hospice, agitation. **Clinical Trial Registry:** NCT05644262. **Disclosures:** No relevant disclosures declared. All co-authors listed are involved in the LiBBY Study. The LiBBY Study is funded by the National Institute on Aging (NIA) of the National Institutes of Health (NIH).

LP013- INVITING DIVERSE COMMUNITIES TO CLINICAL RESEARCH PARTICIPATION THROUGH MEDICAL RECORD RETRIEVAL AND REVIEW. K. King[1], E. Beck[2] *(1. Biogen - Wilmington (United States minor outlying islands), 2. SiteRx - New York (United States minor outlying islands))*

Background: The imperative for increased diversity in clinical research is gaining heightened recognition, driven by evolving regulatory standards and the overarching goal of advancing healthcare for all. In Alzheimer's disease specifically, there has been growing awareness and effort to ensure clinical trial participants are representative of the persons impacted by the disease. Advocacy events, treating physicians referrals and other trusted community-based resources are critical levers in increasing awareness of research opportunities for patients. To help bridge from conversations in the community to engagement at research sites, strategies are needed to assist minority populations in initiating "what's next?" **Objective:** Medical record retrieval and review to pre-qualify the potential eligibility of candidates at the point of expressed interest in the community can be a useful tool for inviting historically under-represented participants into the research process. This research will evaluate the impact of offering medical record retrieval and pre-qualification review on candidate perceptions of research, traceability from community events to trial sites, and impact on velocity and conversion into the research screening process. **Methods:** SiteRx, a technology platform specializing in neurology-focused research recruitment services, provides a unique SiteRx Middleware™ solution designed to assist patients in navigating the pathway to research participation. This solution consists of health record retrieval and pre-eligibility review, followed by facilitation of health record transmittal to applicable research sites for screening. In partnership with a sponsor, local research sites and community organizations, SiteRx Middleware will be deployed at a community event

focused on Alzheimer's Disease research. The event is aimed at reaching and engaging 100 community patients and their caregivers/families, with the primary objectives of raising awareness, providing education, and facilitating access to research as a care option. Data will be collected on patient opt-in to SiteRx Middleware and subsequent progress through the recruitment funnel. **Results:** Early results indicate availability of a service to retrieve and review medical records is well-received by non-Caucasian research candidates. Among candidates identified through a social media campaign for an early AD trial, SiteRx Middleware opt-in candidates were 11.6% Black, 7% Latinx, 2.3% American Indian, and 2% Asian. Data from an upcoming in-person community-based event will include demographic information on attendees and engagement with SiteRx Middleware including percent opt-in, percent medical records retrieved, percent medical records reviewed, and percent pre-qualified based on health record review, and conversion through screening activities at sites. Additional results will be available related to general traceability of participants at community events, time saved at sites, clinical insights based on health record comparison to inclusion/exclusion criteria, and conversion through screening activities. **Conclusion:** Raising awareness of clinical trials in the community is important for increasing participation of under-represented minorities in AD research. Medical record retrieval and review of interested candidates can be a valuable tool for translating patient interest in the community setting into actionable next steps. SiteRx and a sponsor will pilot the use of SiteRx Middleware at a community event to understand the adoption by attendees and value to sites, sponsors, patients and community stakeholders.

LP014- ADDRESSING REPRESENTATIVE ALZHEIMER'S DISEASE ENROLLMENT IN CLINICAL RESEARCH VIA REAL-WORLD CONVERSION ANALYSIS ACROSS THE RECRUITMENT FUNNEL. M. Stalder[1] *(1. SiteRx - New York (United States))*

Background: Enhancing recruitment of a diverse pool of candidates for Alzheimer's disease research requires effective collaboration among various stakeholders within the community, healthcare sector, and clinical trial realm. With less than 5% of doctors being clinical trialists, few patients have treating physicians who are providing direct access to research opportunities. While it is widely acknowledged that underrepresented minority groups encounter obstacles related to trust in clinical research and other barriers that hinder their ability to engage with the research process, a comprehensive approach to addressing diversity requires a deeper understanding of the inherent characteristics of patients, their physicians, and the research sites that either facilitate or impede this critical process. **Objectives:** This study aims to assess the multifaceted challenges faced by Alzheimer's Disease research candidates, focusing on diverse representation and access to research opportunities. Our objectives are to explore the underlying characteristics of diverse patient populations, their relationship to converting research candidates across the research funnel and to develop strategies for enhancing diverse representation and equitable access in Alzheimer's Disease clinical research. **Methods:** SiteRx will conduct a post-hoc analysis on its comprehensive real-world patient database, focusing on individuals eligible for Alzheimer's Disease clinical trials. The variables under investigation will include: - Sources of information about clinical research for patients; - Entities responsible for inviting patients to participate in research; - Geographic locale (urban vs. rural) and its influence on access to healthcare facilities and research sites; - Patient demographics, such as age, sex, and cultural background; - Race and ethnicity of each stakeholder involved in the patient journey (patient, caregiver, HCP, site staff). By analyzing these variables, we aim to understand conversion across the key steps of Initial Clinical Fitness for Research, Interest in Research, Scheduling at Research Sites and Visiting Research Sites for screening. **Results:** Early data supports that the patient's distance to a research site has considerable impact on the likelihood to consent to release of information and scheduling their first visit with a research site, with particular sensitivity of distance to site for diverse populations. Patients within 50 miles of a research site are 1.8x more likely to Consent and Screen than patients 50-75 miles; further, patients within 50 miles are 4.3x more likely to convert from to Consent and Screen than patients >75 miles away from a research site. Continued exploration of the relationship of diverse characteristics and their individual impact will uncover the unique hindrances faced by patients of diverse backgrounds. **Conclusion:** Developing a comprehensive approach that provides individuals with the opportunity to learn about research from medical experts who share similar backgrounds, facilitating navigation through the intricate steps of the recruitment funnel, and providing support and guidance at every stage of the process can help effectively break down barriers that unique populations face and, in turn, promote more comprehensive access to research opportunities. Continuing to develop the science of research recruitment using real word data is critical to developing more impactful strategies for diversifying Alzheimer's research participation.

LP015- EXAMINING THE ROLE OF COMMUNITY ENGAGEMENT IN ENHANCING THE PARTICIPATION OF MINORITIZED COMMUNITIES IN ALZHEIMER'S DISEASE CLINICAL TRIALS; A RAPID REVIEW. S. Dabiri[1], D. Molina-Henry[1] *(1. Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego (United States))*

Background: Despite evidence of higher prevalence and incidence of Alzheimer's disease (AD) in minoritized communities, including African American/Black, Hispanic/Latinx, and Asian, these minoritized groups are underrepresented in AD clinical trials. Minoritized racial and ethnic communities broadly face unique barriers preventing their participation in research; however, community-based strategies have been thought to hold promise in other fields including cancer and cardiovascular clinical trials (Greiner et al., 2014; Brewer et al., 2022). In this systematic rapid review, we synthesized the available evidence on community-engaged recruitment strategies utilized to foster participation of minoritized communities in ADRD research, and available evidence on participants' attitudes and perceptions toward ADRD research. **Methods:** We searched and identified studies describing community-based recruitment approach in the recruitment of minoritized communities across 7 electronic databases (Pubmed, OVID MEDLINE, Cochrane Central Register of Controlled Trials, CINAHL, PsychINFO, Web of Science, and EMBASE). Screening and data extraction were conducted by a single reviewer. **Results:** A total of 1915 studies were screened and 50 met the inclusion criteria. Most studies reported the use of multiple community-based recruitment approaches to meet their recruitment goals. Of the 50 studies, 44% reported educational presentations as a main approach to raise awareness and recruit participants. Collaborations with community-based faith organizations, community advisory

board, and local clinics or health professionals were also among the most frequently reported strategies for gaining access to potential participants. 50% did not specify whether they evaluated their recruitment approaches. In studies that included a form of evaluation, the reported methods were heterogeneous including comparing the outcomes of different recruitment strategies, tracking before and after implementing community-based strategy, or meeting recruitment targets. 52% of studies targeted more than one minoritized population, with African Americans being the most frequently targeted ethnic and racial group, followed by Latinx. 38% of the studies collected information about participants' attitudes and perceptions toward AD. In general, there were gaps in knowledge about AD and its increased risk among minoritized populations. Distrust and stigma were also commonly reported as barriers to research participation. **Conclusion:** The available evidence on the use of a community-based recruitment approach to include minoritized populations in AD clinical trials is limited. Consequently, there exists a significant need for a systematic assessment of recruitment strategies so that effective evidence-based community-based recruitment approaches can become widely available for other investigators. This would enable the achievement of a representative sample in AD clinical trials, contributing to improved inclusivity and integrity in treatment outcomes. This work was supported by an award from the American Heart Association Grant #946223/ SFRN Center Science of Diversity in Clinical Trials/2022. **Key words:** AD clinical trial, recruitment, minorities, disparities, community-based. **Disclosures:** The authors declare no competing interests. **References:** Brewer, L. C., Jenkins, S., Hayes, S. N., Kumbamu, A., Jones, C., Burke, L. E., Cooper, L. A., & Patten, C. A. (2022). Community-based, cluster-randomized pilot trial of a cardiovascular mHealth intervention: Rationale, design, and baseline findings of the FAITH! Trial. American heart journal, 247, 1–14. https://doi.org/10.1016/j.ahj.2022.01.009. Greiner, K. A., Friedman, D. B., Adams, S. A., Gwede, C. K., Cupertino, P., Engelman, K. K., Meade, C. D., & Hébert, J. R. (2014). Effective recruitment strategies and community-based participatory research: community networks program centers' recruitment in cancer prevention studies. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 23(3), 416–423. https://doi.org/10.1158/1055-9965.EPI-13-0760

LP016- DEVELOPING A SCREENING PLATFORM FOR EARLY-PHASE CLINICAL TRIALS TO PREVENT AD (THE EPIICH PLATFORM). G. Bowman[1], H. Shrestha[1], H. Dodge[2], J.L. Lupo[3], J. Momper[4], J. Silverman[3], C. Revta[3], K. Rynearson[5], S. Edland[5], J. Rosand[6], S. Arnold[2], H. Feldman[7], R. Tanzi[1] *(1. McCance Center for Brain Health, Clinical Trials Unit and Genetics and Aging Research Unit, Department of Neurology, Massachusetts General Brigham and Harvard Medical School - Boston (United States), 2. Interdisciplinary Brain Center, Department of Neurology, Massachusetts General Brigham and Harvard Medical School - Boston (United States), 3. Alzheimer's Disease Cooperative Study, University of California San Diego - San Diego (United States), 4. Department of Pharmacology, University of California San Diego - San Diego (United States), 5. Department of Neurosciences, University of California San Diego - San Diego (United States), 6. McCance Center for Brain Health, Clinical Trials Unit, Department of Neurology, Massachusetts General Brigham and Harvard Medical School - San Diego (United States), 7. Alzheimer's Disease Cooperative Study and Department of Neurosciences, University of California San Diego - San Diego (United States))*

Background: Recent breakthroughs in the Alzheimer's disease (AD) field include: 1) high-throughput, systematic in vitro screening of approved drugs, natural products (many of which are generally recognized as safe), and their combinations using 3D cell culture models of AD ("AD-in-a-dish"); 2) the emergence of responsive peripheral biomarkers for AD pathology; and 3) the clinical validation and regulatory approval of amyloid-b immunotherapies in AD. These events provide rationale and feasibility for developing and validating a human screening clinical trial platform that can effectively screen promising therapeutics for safety and tolerability as well as early indication of target engagement based on modes of action of the intervention in mind. The Early-Phase Intra-individual Interventions for Cerebral Health (EPIICH) platform trial incorporates both peripheral canonical biomarkers for identification of people with AD pathology for clinical trials and the broader range of biomarkers for outcome measures to qualify biological effects. Therefore, go-no-go qualification is determined though biomarker classification guided by our understanding of the modes of action intersecting the biology of the disease and the compounds combined chemical properties. This trial platform will adapt single-case experimental design with frequent biomarker sampling to the AD field while simultaneously permitting the sponsor the opportunity to demonstrate disease modification effects over 6 months by including parallel and placebo controlled arms with amyloid PET outcomes. This study will test the hypothesis the top lead (ACTA010) raises plasma abeta42/40 ratio, reduces plasma p-tau217/181 and reduces plasma GFAP over 6 months of treatment, and that active experimental agent is safe and well tolerated in high risk individuals. **Objective:** EPIICH trial ACTA010 compares a novel combination of repurposed known drugs/natural products, at both the intraindividual and group level to ascertain safety and tolerability and beneficial effects on biomarkers of AD pathology. The trial will also collect critical preliminary data to inform the development of the EPIICH screening platform for AD prevention. **Methods:** Randomized-controlled "trident" hybrid clinical trial testing ACTA010 (i.e., single-case and parallel group trial components) in people aged 60 and above with and without cognitive impairment (SCI, MCI , mild dementia, MoCA > 20) and plasma indication of AD pathology confirmed by amyloid PET. Participants undergo a 7.5-month intervention, 1-month observational lead in period to characterize the intraindividual control condition defined by

the pre-treatment dynamic range of AD pathology biomarkers followed by equal, random and blinded allocation to one of three treatment arms for 6-months and a 2-week post treatment washout visit. Primary outcomes are plasma AD biomarkers and secondary outcomes include other biomarkers of interest and amyloid PET. Plasma and CSF PK parameters are tested to ascertain bioavailability and to evaluate PK PD relationships. The outcomes are normalized based on the intraindividual variability observed during the pre-treatment period and analyzed by generalized mixed effects models to examine the differences in trajectories across trial arms. **Results:** Sixty subjects are planned for enrollment (20 per group) across 5-10 sites requesting up to six pre-treatment blood draws over two months (i.e., 1-month screening, baseline, weeks 1, 2, 3, and 4 pre-treatment), amyloid PET (screening amyloidosis confirmation and one post treatment follow-up), and nine post-randomization blood draws (weeks 5, 6, 7, 8, 12, 16, 20, 24, 28). **Conclusion:** This trial will test a promising agent with in vitro support for disease modification and permit knowledge building through the collection of novel data to inform a larger trial platform to enable rigorous testing expeditiously to confirm or refute promising pre-clinical findings and public-private investment priorities under the primary and secondary AD prevention paradigm.

CLINICAL TRIALS: RESULTS

P031- COMBINED EXERCISE AND COGNITIVE INTERVENTIONS FOR ADULTS WITH MILD COGNITIVE IMPAIRMENT AND DEMENTIA: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS.

D.D. Xue[1], P.W.C. Li[1], D.S.F. Yu[1], R.S.Y. Lin[2], Y.W. Lao[3] *(1. School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong - Hong Kong (Hong Kong), 2. University of Rochester School of Nursing, New York, USA - New York (United States), 3. Sir Run Run Shaw Hospital, Zhejiang University School of Medicine - Hangzhou (China))*

Background: Exercise and cognitive interventions are beneficial for adults with preclinical and clinical dementia, but it is unclear whether "the more the better" phenomenon applies in this group population by combining exercise and cognitive interventions, and what intervention designs would optimize the effects. This review aimed to compare the effects of combined exercise and cognitive interventions with the corresponding single approach and control groups in adults with mild cognitive impairment and dementia. It also aimed to identify the optimal intervention design and factors affecting treatment effects. **Methods:** A comprehensive search was conducted in ten electronic databases from inception to 23rd November 2022. The search strategy used a combination of medical subject headings and free-text terms related to mild cognitive impairment, dementia, exercise, cognitive intervention, combined interventions, and randomized controlled trials. Two authors independently performed the literature search, screening, and appraised the methodological quality of studies using Cochrane's risk of bias tool. Pairwise meta-analyses were performed to assess the effects of combined interventions relative to the single type of intervention and control groups, with further subgroup analysis to explore the factors affecting the treatment effects from combined interventions. Network meta-analyses were used to identify the optimal intervention components. **Results:** Twenty-nine randomized controlled trials involving 2,910 participants were included. Most studies (90%) had a high risk of bias and only three had an unclear risk of bias. Pairwise meta-analyses indicated that combined interventions were superior to exercise alone to improve response inhibition, working memory, and delayed recall, but not superior to cognitive interventions on all outcomes. Combined interventions outweighed active/passive control in improving global cognition, response inhibition, immediate recall, delayed recall, category fluency, processing speed, and visuospatial ability. No subgroup differences were found for the severity of dementia (mild cognitive impairment vs dementia), combination format (sequential vs simultaneous combination), mode of delivery (group-based vs individual-based vs mixed), training duration (short: ≤ 12 weeks vs medium: 13–24 weeks vs long: > 24 weeks), and types of control (active vs passive control). The network meta-analysis indicated that the optimal intervention components varied across different outcomes. Multimodal exercise had the highest probability in improving global cognition and visuospatial ability when combined with cognitive training, while ranked the best in improving letter fluency when combined with cognitive stimulation. Aerobic exercise ranked the best in improving working memory and activities of daily living when combined with cognitive stimulation, while aerobic exercise alone ranked the best for efficacy on processing speed. Cognitive training was ranked as the most effective approach for delayed recall. **Conclusion:** This review suggests the advantage of combined interventions over exercise alone and comparable effects as cognitive interventions in the population with mild cognitive impairment and dementia. **Key words:** Combined interventions, exercise, cognitive intervention, mild cognitive impairment, dementia, network meta-analysis. **Registry:** CRD 42021241485 (https://www.crd.york.ac.uk/prospero/). **Disclosures:** This study did not receive any grants. The authors declared no competing interests.

P032- 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], 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 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. The natural next step in the evolution of these quantitative tools requires the consideration of additional baseline and longitudinal biomarkers in earlier disease stages from recently acquired contemporary clinical trials. **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. The fitted statistical models will subsequently be applied to 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, 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 69 studies with 97,527 individual patient records. Analysis subsets generated from 8 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). Mixed-effects modelling approaches have been applied to predict longitudinal CDR-SB and ADAS-cog scores separately using baseline covariates (demography, ApoE4 status, fluid and imaging biomarkers). 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. **Disclosures:** Michael Irizarry is an employee of Eisai.

P033- CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) CONSORTIUM: DATA-DRIVEN SOLUTIONS FOR CLINICAL TRIAL DESIGN AND INFORMED DECISION MAKING. S. Sivakumaran[1], N. Cullen[1], C. Lau[1], E. Priest[1], H. White[1], M. Irizarry[2], G. Klein[3], K. Romero[1], A. Leuzy[1,4,5], Y. Karten[1] *(1. Critical Path Institute - Tucson (United States), 2. Eisai Inc. - Nutley (United States), 3. F. Hoffmann-La Roche Ltd - Basel (Switzerland), 4. Lund University - Malmo (Sweden), 5. Enigma Biomedical USA - Knoxville (United States))*

Background: The Critical Path for Alzheimer's Disease (CPAD) Consortium at the Critical Path Institute (C-Path) provides the drug development industry, regulatory agencies, academia, and patient advocacy organizations the opportunity to collaborate, to improve noncompetitive aspects of the Alzheimer's disease (AD) therapeutics research and development process. The structure of CPAD as a neutral convener, combined with CPAD's extensive track record of developing regulatory-grade quantitative drug development tools, motivates sponsors to share patient-level data and neuroimages from Phase II and Phase III AD clinical trials. CPAD leverages these data and uses C-Path's core competencies in data management and standardization, quantitative modeling, and regulatory science to develop tools and solutions that help de-risk decision making in AD drug development. **Method:** Clinical data are curated, standardized, and aggregated into analysis subsets. These subsets are used to develop disease progression models that form the basis for clinical trial simulation (CTS) tools, which help optimize patient and endpoint selection, and the design of efficacy studies. In addition, CPAD collaborates with the USC Laboratory of Neuro Imaging (LONI) and Global Alzheimer's Association Interactive Network (GAAIN) to demonstrate clinical and technical validity of the image analysis pipeline developed by LONI, with the aim of providing a standardized pipeline for processing and analysis of PET and MRI images in the context of drug development and regulatory decision making. Finally, CPAD is leading a precompetitive effort with leading academic and industry experts to 1) test and validate a tau-PET quantification method that harmonizes derived measures across tracers and cohorts, and 2) explore and evaluate the readiness of tau-PET as a surrogate marker in AD drug development to support accelerated drug approval. **Results:** As of April 2023, CPAD's clinical trial repository contains 69 studies with 97,527 individual de-identified patient records, with a rich source of key AD biomarkers (biofluids and imaging). Different linear and non-linear mixed effects models have been fit based on relevant biomarker combinations, characterizing the time course of clinically relevant measures (ADAS-Cog, CDR-SB, other clinical assessment scales and biomarkers). The models are accessible via a CPAD developed web-based platform that facilitates the sharing of statistical modeling codes and results, while ensuring data and model privacy. Work is ongoing to demonstrate the clinical validity and technical feasibility of the LONI standardized imaging pipeline to address a specified drug development need. To harmonize tau-PET quantification, two different methods (a Centiloid-like approach and a Joint Propagation model) were tested and validated across multiple tracers, cohorts and studies. A data and research plan has been drafted to explore and evaluate the readiness of tau-PET as a surrogate marker in AD. **Conclusion:** The precompetitive collaboration, data acquisition and analysis pioneered by CPAD is fundamental to the generation of actionable quantitative drug development tools for accelerating and advancing AD drug development and building consensus among stakeholders that provide confidence to sponsors for the adoption of the tools. **Disclosures:** Michael Irizarry is an employee of Eisai. Gregory Klein is an employee of F. Hoffmann-La Roche Ltd.

P034- COMBINATION TREATMENT OF A NOVEL B2 ADRENOCEPTOR AGONIST, CST-2032, AND NADOLOL IMPROVES COGNITIVE MEASURES IN PATIENTS WITH ALZHEIMER'S DISEASE. J. Harrison[1], R. Martin[2], P. Butera[2], J. Reynolds[2], A. Ford[2], G. Vargas[2] *(1. Institute of Psychiatry, Psychology & Neuroscience King's College London - London (United Kingdom), 2. CuraSen Therapeutics - San Carlos (United States))*

Background: The locus coeruleus (LC), the primary source of forebrain noradrenaline, is among the earliest sites of neuronal loss and pathology in AD and PD. Deteriorating LC signaling could be therapeutically replaced using exogenous selective adrenoceptor (AR) agonists to reactivate the adrenergic stimulus to cortical and limbic structures. Prior studies established that β2-ARs agonists increase regional cerebral blood flow in hippocampus, thalamus and amygdala, areas associated with cognition, attention, alertness and emotional salience, and may offer benefit for treatment of cognitive and emotional impairment in AD or PD [1, 2, 3]. This abstract describes the safety and efficacy of the novel selective β2-AR agonist, CST-2032, when administered with low-dose nadolol, in patients with AD. **Methods:** Blinded oral CST-2032 (3mg) + nadolol (3mg), or placebo was administered for 2 weeks in a 2-period crossover design to patients with MCI or mild dementia due to probable AD, and Montreal Cognitive Assessment (MoCA) score between 14-26, across 16 sites in the USA and New Zealand. Multiple measures of cognition

were evaluated, including the digit symbol substitution test (DSST) and the facial expression recognition test (FERT) at baseline and during each treatment period. Nadolol is a β2-AR preferring antagonist with negligible CNS absorption and was administered with CST-2032 to inhibit known peripheral effects of β2-AR agonists. **Results:** 36 patients with AD were enrolled, 58% male, average 67 years old, with mean MoCA score of 20.9 and MoCA Memory Index of 7.8. An additional 18 participants were enrolled with PD who are included in the evaluation of safety. In DSST, greater increases in the total number of correct symbols were observed over the 14 days of dosing with CST-2032+nadolol compared with placebo (LSMean difference between active and placebo: 1.73 [p=0.045], 0.69 [p=0.43] and 1.88 [p=0.033], on Days 1, 7 and 14, respectively). In addition, CST-2032+nadolol was consistently associated with reduced reaction times, reduced misclassification, and improved accuracy to detect facial expressions, consistent with a general improvement in cognition. Based on an interim evaluation of safety, combination therapy was well tolerated; most reported AEs were mild/moderate, 2 SAEs were reported which were deemed to be unrelated to drug. Typical peripheral adverse events of β2-AR agonists were reported infrequently in the overall population (no reports of tachycardia or hypokalemia, and 1 subject with adverse events of tremor or palpitations), and only modest effects were observed on heart rate (mean change from baseline -3.0 bpm on active vs -1.3 bpm on placebo on Day 14) and potassium (mean concentrations of 4.3 mmol/L on active and placebo on Day 14). **Conclusion:** AD subjects had impaired cognition at enrollment. Short-term treatment with the β2-AR agonist, CST-2032, when administered with the peripherally restricted antagonist nadolol, significantly improved performance in the DSST, a cognitive test involving attention, processing speed and executive function, as well as in measures of social cognition. Combination therapy with CST-2032+nadolol was well-tolerated. The effects of 14-day treatment with CST-2032+nadolol support further studies to explore whether broader clinical benefit is achieved in patients with cognitive impairment following longer duration of treatment. **Key words:** Clinical Trial in Phase 2, β2-adrenoceptor, Alzheimer's disease, cognition. **Clinical Trial Registry:** NCT05104463. **Disclosures:** this study was funded by CuraSen Therapeutics, Inc.; JH is a paid consultant to CuraSen; RM, PB, JR, AF and GV are employees of CuraSen. Data in this abstract have never been presented elsewhere. **References:** 1. Lodeweyckx T et al. AD/PD 2023. 2. Lodeweyckx T J Prevention of Alzheimer's Disease 2021, 8(4): S87. 3. Vargas G et al. AD/PD 2023

P035- SAFETY AND FEASIBILITY TRIAL OF DAPAGLIFLOZIN IN EARLY ALZHEIMER'S DISEASE. J. Burns[1], J. Morris[1], E. Vidoni[1], H. Wilkins[1], I.Y. Choi[1], P. Lee[1], S. Hunt[1], J. Mahnken[1], W. Brooks[1], R. Lepping[1], P. Adany[1], A. Gupta[1], R. Swerdlow[1] *(1. University Of Kansas Alzheimer's Disease Center - Kansas City (United States))*

Background: There is growing interest in targeting the metabolic manifestations of Alzheimer's Disease (AD) as a therapeutic strategy. Dapagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i) used to treat type 2 diabetes mellitus (T2DM), has systemic metabolic effects (i.e., insulin sensitivity and weight loss) and metabolomic data suggest potential mitochondrial effects. Additionally, epidemiological studies suggest SGLT2i may reduce the long-term risk of dementia in T2DM patients. **Methods:** We conducted a 12-week exploratory study investigating safety, tolerability, and metabolic effects of dapagliflozin on the brain and systemically in individuals with an AD clinical syndrome or MCI due to AD. We randomized 48 participants to dapagliflozin (10 mg) vs. placebo (2:1 ratio) and performed brain magnetic resonance spectroscopy (MRS), oral glucose tolerance testing, brain fluorodeoxyglucose (FDG) PET, dual X-ray absorptiometry (body composition), and cognitive testing at baseline and 12 weeks. **Results:** Sample: Data are presented on n=46 participants with follow-up data. The participants had a mean age of 71.2 years (8.0SD), BMI 28.3 kg/m2 (4.4SD), mean MMSE of 20.2 (5.5SD), were predominantly male (65%, n=30), and largely without T2DM (91.3%; n=42). Safety and Tolerability: Dapagliflozin was safe and well-tolerated. Participants took 99% of their doses with no treatment-related withdrawals. The dapagliflozin group had more total adverse events (AEs; n=41) vs the placebo group (n=18) but only 4 AEs (2 in each group) were considered possibly or probably related to study drug (dysuria and frequency with dapagliflozin; dysuria and diarrhea with placebo) and these were mild and resolved. MRS Measures: There was no change in the pre-specified primary outcome of MRS-determined N-acetylaspartate-to-creatine ratio (NAA/Cr; p=0.60), considered a proxy measure of mitochondrial mass. We observed a trend to increased NAA concentrations (p=0.06) that correlated with changes in urinary NAA (r=0.32, p=0.04). We also observed an increase in brain glutathione (GSH), a major brain antioxidant that represents cerebral antioxidant defences and is lower in AD (p<0.05). FDG-PET: There were no differences across treatment and placebo groups in FDG PET globally and regionally (hippocampal, anterior cingulate, precuneus, and posterior cingulate regions). Cognition: The treatment group improved in executive function (Stroop Interference) compared to the placebo group (mean difference +4.1 points, p=0.03) with no change in ADAS-Cog, Trailmaking A, Trailmaking B, delayed Logical Memory, and MMSE. Systemic Metabolic Measures: We observed treatment-related reductions in hemoglobin A1c (adjusted mean difference -0.18, p=0.02), 2-hr Glucose Area Under the Curve (-2109.0 mg min/dL, p=0.03), and body composition (total mass –1.73kg, p=0.012; fat mass -0.95kg, p=0.05; and lean mass -0.85kg, p=0.01). There were no treatment-related effects on fasting levels of beta-hydroxybutyrate, glucose, insulin, and cholesterol (total, LDL, and HDL). **Conclusions:** Dapagliflozin was safe and well-tolerated in a largely non-diabetic population with early AD and MCI but did not increase brain NAA/Cr, the pilot study's pre-specified primary outcome. Dapagliflozin therapy was associated with systemic metabolic effects (glucose disposal, body weight), improvement in executive function, and increases in MRS measures of brain GSH and NAA concentrations. These exploratory findings suggest dapagliflozin may influence cognition and cerebral metabolism, as suggested by epidemiological studies. **Disclosures:** Astra Zeneca funded the study.

P036- PHASE 3 CLINICAL STUDIES IN ALZHEIMER'S AND PARKINSON'S DISEASE; INTERIM ANALYSIS AND FDA GUIDANCE FOR BOTH INDICATIONS. C. Fang[1], E. Damiano[1], M. Gaines[1], M. Shaffer[2], A.M. Nagy[3], L. Sanders[4], M. Maccecchini[1] *(1. Annovis Bio - Berwyn (United States), 2. Wuxi - Austin (United States), 3. TFS - Lund (Sweden), 4. DCRI - Durham (United States))*

Background: Overexpression of neurotoxic proteins drives downstream events that dysregulate axonal transport, lead to inflammation, nerve cell death, and loss of function. By inhibiting the translation of neurotoxic aggregating proteins

- amyloid precursor protein, tau, alpha-synuclein etc., buntanetap restores axonal transport, lowers inflammation, and protects nerve cells from dying. In two double-blind, placebo controlled phase2a studies, buntanetap showed efficacy in both AD patients as measured by ADAScog11 and PD patients as measured by MDS-UPDRS. These encouraging data supported our further development of buntanetap into phase 3 as a potential treatment for both AD and PD. **Methods:** Therefore, we started two double-blind, placebo controlled phase3 studies to further test buntanetap's efficacy and safety in AD and PD patients. **Results:** For the AD study, a total of 320 moderate AD patients are being recruited for a 3-month treatment; they are administered three doses of buntanetap as well as control (placebo, 7.5, 15 and 30 mg QD); the primary endpoints are ADAS-Cog11 and ADCS-CGIC. The interim analysis will read out in fall, when 30% of the patients have been treated for 2 months. For the PD study, patients are dosed with either 10mg or 20mg buntanetap or placebo QD. A total of 520 early PD patients were recruited and are being treated for a 6-month treatment. The primary endpoint is MDS-UPDRS 2 and 3. We conducted an interim analysis, when 30% of the patients had been treated for 2 months and the outcome was positive. We went to FDA to seek their guidance on buntanetap's development plan in treating AD and PD for symptomatic, disease-modifying in early, moderate and advanced patients. We will report the outcome of the interim analysis in our AD study and the response from the FDA as to the best way to develop buntanetap for AD and PD at CTAD. **Conclusions:** Buntanetap is being developed to treat both AD and PD and Annovis will receive FDA guidance on the development plans in treating both diseases both as symptomatic and disease modifying treatment. **Key words:** Buntanetap, Alzheimer's disease, Parkinson's disease, interim analysis, FDA guidance. **Disclosures:** Maria Maccecchini, Cheng Fang, Melissa Gains, and Eve Damiano are employees of Annovis Bio. Anne-Mari Nagy is an employee of TFS, which contracts with Annovis for the AD and PD clinical trials. Michelle Schaffer is an employee of Wuxi/Pharmapace, which contracts with Annovis for statistical support of the AD and PD studies, Laurie Sanders is an employee of Duke university and part of DCRI, which contracts with Annovis for the AD study.

P037- SAFETY, TOLERABILITY, AND PHARMACOKINETICS FINDINGS IN A PHASE 1 SINGLE DOSE STUDY OF DONANEMAB IN HEALTHY CHINESE PARTICIPANTS. Y. Cui[1], R. Wu[2], I. Gueorguieva[3], C. Qian[2], J. Xu[1] *(1. Peking University First Hospital - Beijing (China), 2. Eli Lilly and Company - Shanghai (China), 3. Eli Lilly and Company - Bracknell (United Kingdom))*

Background: Donanemab is being developed to slow cognitive and functional decline in early symptomatic Alzheimer's disease (AD) based on its ability to reduce brain Aβ plaques. This placebo-controlled, parallel-group treatment, participant- and investigator-blind, randomized, phase 1 study (Study AACK) investigated the safety, tolerability, and pharmacokinetics (PK) of a single dose donanemab in healthy Chinese participants. **Objectives:** The primary objective of Study AACK is to investigate the safety and tolerability of donanemab compared to placebo following single dose intravenous (IV) administration in healthy Chinese participants. The PK profile of donanemab is also evaluated as the secondary objective. **Methods:** The study included 3 cohorts, each with 12 participants randomized 5:1 to donanemab (single dose IV, dose level 350 mg, 700 mg, and 1400 mg, respectively) or placebo. Eligible participants were healthy native Chinese participants, 18 to 40 years-old with BMI 18.0 to 28.0 kg/m2 (inclusive). Adverse events and PK samplings were collected for 12 weeks after a single dose. **Results:** All 36 participants who enrolled in the study were dosed and completed the study. Among these participants, all were male, aged between 18 and 38 years, with weight ranging from 54.5 to 89.1 kg and BMI ranging from 19.6 to 27.2kg/m2 across 3 cohorts. Overall, 21 participants (58.3%) reported a total of 32 treatment-emergent adverse events (TEAEs), and 3 participants reported 4 TEAEs related to study treatment. No TEAEs with severity categorized as severe or serious adverse events were observed. No participant discontinued the study due to adverse events. There were no dose- or treatment-related trends in the incidence of all TEAEs reported during the study between the treatment groups (placebo: 5 participants [83.3%] reported 8 TEAEs, with 1 participant reported 1 TEAE related to study treatment; donanemab 350 mg: 6 participants [60%] reported 11 TEAEs, with 2 participant reported 3 TEAEs related to study treatment; donanemab 700 mg: 4 participants [40%] reported 7 TEAEs, and donanemab 1400 mg: 6 participants [60%] reported 6 TEAEs). Among participants who received donanemab, the most commonly reported TEAEs were asymptomatic COVID-19 in 6 participants, blood creatine phosphokinase increased in 3 participants, and COVID-19 in 3 participants. There were no clinically meaningful findings in the clinical laboratory evaluations, vital sign measurements, electrocardiograms, neurological findings, or other observations related to safety in this study. Individual Tmax ranges overlapped between doses, with Tmax ranging from 0.85 to 3.00 hours across doses. Elimination half-life was approximately 103, 150 and 162 hours following a single 350, 700 and 1400 mg dose, respectively. Individual t1/2 ranged from 70.0 to 292 hours across doses. Over the dose range of 350 mg, 700 mg, and 1400 mg, geometric mean AUC(0-tlast) and AUC(0-∞) increased with dose increase; for a 2-fold increase in dose there was between an approximately 2.3 to 2.5-fold increase in geometric mean AUC(0-tlast) and AUC(0-∞). Clearance values were 0.04, 0.03 and 0.03 L/h following a 350, 700 and 1400 mg dose of donanemab, respectively. Geometric mean Cmax increased 2-fold between the 350 mg and 700 mg doses and there was an approximately 2.3-fold increase between the 700 mg and 1400 mg doses. The between-participant variability for AUC(0-tlast), AUC(0-∞), and Cmax for the 350 mg and 700 mg doses was low, ranging from 9% to 23%. The between-participant variability was slightly higher for the AUC(0-tlast), AUC(0-∞), and Cmax for the 1400 mg dose, ranging from 27% to 30%. **Conclusion:** Donanemab was safe and well tolerated in healthy Chinese participants following single IV doses of 350 mg, 700 mg, and 1400 mg. Donanemab AUC(0-∞) and Cmax increased with dose increase. Clearance values were generally comparable across the dose levels. These PK results are generally comparable to those disclosed in PK study of donanemab in US and Japanese patients with AD [1]. **Key words:** donanemab; safety; pharmacokinetics; healthy Chinese participants. **Conflicts of interest:** RW, IG, and CQ are full-time employees of Eli Lilly and Company and may hold stock or stock options. **Reference:**
1. Lowe S, et al. Donanemab (LY3002813) Phase 1b Study in Alzheimer's Disease: Rapid and Sustained Reduction of Brain Amyloid Measured by Florbetapir F18 Imaging. J Prev Alzheimers Dis. 2021;8(4):414-424. doi: 10.14283/jpad.2021.56.

P038- SAFETY OF HIGHER DOSES OF GANTENERUMAB IN THE OPEN-LABEL EXTENSION OF THE DOMINANTLY INHERITED ALZHEIMER'S NETWORK TRIALS UNIT (DIAN–TU-001 TRIAL). J. Llibre-Guerra[1], N. Joseph-Mathurin[1], Y. Li[1], G. Wang[1], A. Aschenbrenner[1], X. Chengjie[1], B. Gordon[1], J. Hitchcock[2], R. Perrin[1], C. Hofmann[3], J. Wojtowicz[4], A. Alireza[5], E. Mcdade[1], R. Bateman[1], D. Clifford[1] *(1. Washington University School Of Medicine In St.louis - St. Louis (United States), 2. Hitchcock Regulatory Consulting, Inc - St. Louis (United States), 3. Roche Innovation Center Basel - Basel (Switzerland), 4. F. Hoffmann-La Roche Ltd - Basel (Switzerland), 5. Banner Sun Health Research Institute - Sun, Arizona (United States))*

Background: The double-blind period of the DIAN–TU-001 phase 3 trial with gantenerumab provided evidence of significant but incomplete reduction of amyloid plaques, cerebrospinal fluid total tau, and phospho-tau181 in dominantly inherited Alzheimer's disease (DIAD).[1] Drug effect on cognition was not conclusive in this population plausibly due to 1) no evidence of cognitive decline in the asymptomatic subgroup, 2) late dose escalation during the trial (from 225 mg to 1200 mg SC every 4 weeks [q4w]), and 3) incomplete amyloid plaque reduction. The trial transitioned to an open-label extension (OLE) period using higher doses of gantenerumab (1500 mg SC q2w). Here we describe safety data of higher doses of gantenerumab based on safety monitoring in the ongoing trial. Treatment assignment from the double-blind period remains blinded. **Method:** 74 DIAD participants entered the OLE period. All participants initiated at a gantenerumab dose of 120 mg SC q4w and received at least 3 doses at each titration step (120 mg, 255 mg, 510 mg, and 1020 mg). After three doses at 1020 mg q4w, participants continued to escalate to 1020 mg q2w for 6 doses and then to the maximum target dose of 1500 mg q2w. The average time to reach the target dose is ~15 months. The advancement into the next titration step was guided by the safety monitoring amyloid-related imaging abnormalities (ARIA) algorithm. **Result:** As of April 12, 2023, 62/74 (83.7%) participants completed titration to the higher doses (1020-1500 mg q2w); 24.1% (n=15/62) of the participants at higher doses experienced ARIA-Edema, and most episodes were asymptomatic (11/15). Radiologically, 8/15 (53.3%) ARIA-E episodes were multifocal and with a predominant occipital distribution. The largest cross-sectional diameter of ARIA-E at initial findings ranged from 3 to 81 mm. The mean time for ARIA-E resolution was 59.5 days. Most ARIA-E episodes occurred after titration to doses of 1020-1500 mg q2w and within the initial 3-4 months of receiving the higher doses. ApoE-4 status remained the main ARIA-E predictor. Overall, the incidence and severity of ARIA-E events remained comparable to DIAN-TU 001 double-blind treatment period (24.1% vs 19.2%) [1, 2]. **Conclusion:** Safety data from the DIAN–TU-001 OLE study demonstrates that gantenerumab at doses 1020-1500 mg administered SC q2w (three times higher than during phase 3) is well tolerated in the DIAD population, with no new or unexpected safety findings relative to the double-blind period. All ARIA-E cases were detected on routine safety MRI scans, allowing early intervention and risk management reduction to prevent permanent injury. **Key words:** Dominantly Inherited Alzheimer's disease, Open-label Extension, Safety, Amyloid-Related Imaging Abnormalities. **References:** 1. Salloway, Stephen, Martin Farlow, Eric McDade, et al. «A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease.» Nature medicine 27, no. 7 (2021): 1187-1196. 2. Joseph-Mathurin, Nelly, Jorge J. Llibre-Guerra, Yan Li, et al. «Amyloid-Related Imaging Abnormalities in the DIAN-TU-001 Trial of Gantenerumab and Solanezumab: Lessons from a Trial in Dominantly Inherited Alzheimer Disease.» Annals of neurology 92, no. 5 (2022): 729-744.

P039- A SINGLE ASCENDING DOSE STUDY OF ABBV-916, AN ANTI-AMYLOID ANTIBODY, IN HEALTHY VOLUNTEERS. S. Bachhav[1], H. Florian[2], J. Boiser[3], Y. Wang[4], D.D. Shiller[1], S.Y. Lynch[2], O. Graff[2], H. Xiong[1] *(1. Clinical Pharmacology, AbbVie Inc - North Chicago (United States), 2. Neuroscience Clinical Development, AbbVie Inc - North Chicago (United States), 3. Pharmacovigilance and Patient Safety, AbbVie Inc - North Chicago (United States), 4. Statistics, AbbVie Inc - North Chicago (United States))*

Background: Alzheimer's disease (AD), a progressive and ultimately fatal neurodegenerative disease, is the most common cause of dementia in the elderly. The clearance of amyloid-beta (Aβ) plaque in the brain is one of the promising disease-modifying treatment approaches to slow down cognitive decline in AD. ABBV-916, an anti-amyloid antibody, selectively targets AβpE3 (N-terminal truncated amyloid beta with pyroglutamate-modification at amino acid position 3) and is being developed as a disease-modifying treatment for early AD. This Phase 1, randomized, double-blind, single ascending dose study investigated the safety, tolerability, pharmacokinetics (PK), and immunogenicity of ABBV-916 in healthy adults. **Methods:** Seventy-two healthy volunteers (HVs), aged between 18 – 45 years, were enrolled and randomized to receive ABBV-916 or placebo. This age range was selected to minimize the risk of amyloid related imaging abnormalities (ARIAs), an on-target toxicity from Aβ engagement [1]. After dosing, HVs were followed for 20 weeks for PK, immunogenicity, and safety assessments. Cerebrospinal fluid (CSF) samples were collected after dosing in one of the cohorts for determination of ABBV-916 levels in the brain. **Results:** A single dose of ABBV-916 was generally well tolerated in HVs. No clinically significant laboratory or ECG findings, ARIAs, deaths, or serious adverse events were reported. Three HVs experienced infusion reactions, one Grade 2 requiring infusion discontinuation, and two Grade 1 which did not. The PK profile of ABBV-916 was approximately linear with low inter subject variability. Quantifiable levels of ABBV-916 in CSF were detected with a CSF:Serum penetration ratio of 0.13% (0.1% - 0.21%). About 9% (5 out of 55) HVs administered with ABBV-916 had positive anti-drug antibody titer post-dose. All titers were low (<24 titer units) and did not change ABBV-916 PK. **Conclusion:** Single doses of ABBV-916 were safe and well tolerated in HVs. The data supported further evaluation of ABBV-916 in AD patients. **Key words:** amyloid beta, safety, pharmacokinetics, Phase 1, healthy volunteers. **Disclosures:** The study was funded by AbbVie. AbbVie contributed to the research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options. **Reference:** 1. Caballero MÁ A, Song Z, Rubinski A, et al. Age-dependent amyloid deposition is associated with white matter alterations in cognitively normal adults during the adult life span. Alzheimers Dement. 2020;16(4):651-61.

P040- EFFICACY OF ANTI-AMYLOID-β MONOCLONAL ANTIBODY THERAPY IN PRODROMAL VERSUS MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS. J. Dantas[1], P. Romeiro[2], C. Dagostin[3], N. Felix[4], D. Navalha[5], A. Mutarelli[6], P. Caramelli[7], S. Batista[8], L. Teixeira[9] *(1. Federal University of Rio Grande do Norte - Natal (Brazil), 2. University Center Tiradentes - Maceió (Brazil), 3. University of the Extreme South of Santa Catarina - Criciúma (Brazil), 4. Federal University of Campina Grande - Campina Grande (Brazil), 5. Eduardo Mondlane University - Maputo (Mozambique), 6. Federal University of Minas Gerais - Belo Horizonte (Brazil), 7. Behavioral and Cognitive Neurology Unit, Federal University of Minas Gerais - Belo Horizonte (Brazil), 8. Universidade Federal do Rio de Janeiro, - Rio de Janeiro (Brazil), 9. Universidade Federal de Campina Grande - Campina Grande (Brazil))*

Background: Studies targeting amyloid-ß in patients with Alzheimer's disease (AD) have reported conflicting results. Early initiation of therapy might yield better outcomes. We performed a meta-analysis to compare the efficacy of monoclonal antibodies against amyloid-ß versus placebo in patients with mild cognitive impairment (MCI) and mild AD dementia. **Methods:** We systematically searched PubMed, Embase, Cochrane Library, and Clinicaltrials.gov from inception to August 2023 for randomized controlled trials comparing monoclonal antibodies with placebo in MCI or mild dementia due to AD. **Results:** Nineteen studies comprising 15,275 patients were included. In patients with early AD, monoclonal antibodies reduced the rate of decline compared with placebo, in both the Clinical Dementia Rating Scale, sum of boxes (CDR-SB; MD -0.30; 95% CI -0.42 to -0.19; p<0.01) and the Alzheimer's Disease Assessment Scale, cognitive subscore (ADAS-cog; SMD -0.80; 95% CI -10.25 to -0.35; p<0.01). The results were similar between clinical stages for CDR-SB (MCI: MD -0.19; 95% CI -0.35 to -0.03; p=0.02; mild dementia: MD -0.45; 95% CI -0.65 to -0.25; p<0.01; test for subgroup differences: p=0.13), as well as for ADAS-Cog (MCI: SMD -0.83; 95% CI -1.49 to -0.17; p=0.01; mild dementia: SMD -0.69; 95% CI -1.32 to -0.05; p=0.03; test for subgroup differences: p=0.47). These results are consistent with the subanalysis on high-clearance antibodies only, both for CDR-SB (MD -0.32; 95% CI -0.50 to -0.15; p<0.01) and for ADAS-Cog (SMD -1.21; 95% CI -1.73 to -0.68; p<0.01). **Interpretation:** Anti-amyloid-ß monoclonal antibodies reduce cognitive and functional decline compared with placebo in early AD. Starting immunotherapy in patients with MCI was not significantly different than starting in the mild dementia stage. **PROSPERO registry:** CRD42023430698. **Disclosures:** Dr. Caramelli declares participation as principal investigator in clinical trials for Novo Nordisk, and participation in an advisory board for Roche. Dr. Caramelli has also developed material for continuous medical education and participation as a speaker in symposia sponsored by Aché, Knight Therapeutics, Roche, and Torrent laboratories.

P041- HIGH ADHERENCE AND TOLERABILITY OF A SENSORY STIMULATION SYSTEM IN A 6-MONTH SHAM-CONTROLLED CLINICAL TRIAL IN ALZHEIMER'S DISEASE. C.V. Seshagiri[1], Z. Malchano[1], A. Boasso[1], M. Hajós[1], E. Hempel[1], K.G. Saikali[1], B. Vaughan[1], R. Kern[1] *(1. Cognito Therapeutics - Cambridge (United States))*

Background: Sensory stimulation is an emerging therapeutic approach for the treatment of Alzheimer's disease (AD). In a recent sham-controlled study (NCT03556280 , OVERTURE), we evaluated the feasibility and safety of Cognito Therapeutics' auditory and visual sensory stimulation system in participants with mild- to moderate AD after 6 months of 1-hour, daily stimulation. We present here results on the adherence to the therapy which demonstrate that the sensory stimulation therapy was well-tolerated by trial participants. **Methods:** 76 participants were randomized 2:1 (active vs sham). Of the 76 participants randomized, 70 received treatment. Analyses and summaries were performed on the 70 participants who received treatment. Participants in the active arm (n = 43) received sensory stimulation that produced gamma frequency activation as confirmed via EEG, while participants in the sham arm (n = 27) received sensory stimulation that was ineffective in evoking the gamma frequency EEG response seen in the active arm. Participants in both arms used the sensory stimulation device at home for one hour daily over 6-months. Device usage was logged on the stimulation device, and device logs were retrieved from the devices upon completion or termination. The device logs were post-processed to correct observed device clock drift and the total minutes of therapy for each day in the study was recovered. Adherence rates per participant were calculated as the percentage of days in the period of observations when the device was used for 45 minutes or more. Adherence rates were computed for the entire study duration as well as for weeks 1-4 and weeks 21-24 to compare changes in adherence from the beginning to the end of the study. **Results:** The trial was completed by 33 (76.7%) participants in the active arm and 20 (74.1%) participants in the sham arm. Device use logs were unavailable or incomplete for 3 participants who received sensory stimulation (1 completer, 2 early terminators). Completers had a higher mean adherence rate compared with those that terminated early (completers: 84.9% vs early terminators: 75.1%, p = 0.025, Wilcoxon Rank Sum Test). Among completers, adherence declined from weeks 1-4 as compared with weeks 21-24 (week 1-4: 89.7% vs week 21-24: 82.1%, p = 0.013, Wilcoxon Signed Rank Test). However, even at week 24, adherence to daily therapy remained relatively high. **Conclusions:** This clinical trial demonstrates that Cognito's sensory stimulation was well tolerated by mild- to moderate-AD patients. The higher mean adherence rate among completers as compared with early terminators suggests that participants that completed the 6-month course of therapy more fully incorporated daily sensory stimulation into a regular routine. Further, high adherence rates even after 6 months of daily use among completers suggests that participants who tolerate and incorporate daily therapy early, remain adherent to the daily sensory stimulation therapy. **Key words:** Sensory Stimulation System, Adherence, Gamma Oscillations. **Disclosure:** This clinical trial was sponsored by Cognito Therapeutics. All authors are employees of and have equity in Cognito Therapeutics.

P043- EFFECT OF ALZ-801 (VALILTRAMIPROSATE), AN ORAL INHIBITOR OF AMYLOID OLIGOMER FORMATION, ON PLASMA BIOMARKERS, VOLUMETRIC BRAIN IMAGING BIOMARKERS, AND CLINICAL OUTCOMES OF ALZHEIMER'S DISEASE: 12-MONTH RESULTS OF PHASE 2 BIOMARKER STUDY IN EARLY AD APOE4 CARRIER SUBJECTS. J. Hey[1], S. Abushakra[1], P. Scheltens[2], J. Hort[3], K. Sheardova[4,5], L. Pazdera[6], N. Prins[7], S. Rutgers[7], P. Dautzenberg[7], J. Yu[1], P. Kesslak[1], L. Bracoud[8], A. Power[1], J. Suhy[8], M. Tolar[1] *(1. Alzheon - Framingham (United States), 2. Amsterdam University Medical Centers, Alzheimer Center - Amsterdam (Netherlands), 3. Charles University Department of Neurology - Brno (Czech Republic), 4. Memory Center, St. Anne University Hospital - Brno (Czech Republic), 5. International Clinical Research Center - Brno (Czech Republic), 6. Vestra Research Clinics - Rychnov And Kněžnou (Czech Republic), 7. Brain Research Center - Den Bosch (Netherlands), 8Clario, Inc. - San Mateo (United States))*

Background: ALZ-801 (valiltramiprosate) is an oral, brain-penetrant, small molecule inhibitor of amyloid oligomer formation in development for Alzheimer's disease (AD). ALZ-801 is being evaluated as a disease-modifying treatment in two Early AD trials: a Phase 2 study in APOE4 carriers and APOLLOE4 Phase 3 study in APOE4 homozygotes. The fully enrolled Phase 2 study evaluates effects on plasma biomarkers, volumetric MRI (v-MRI), clinical outcomes and correlations between vMRI and cognition. The ongoing 78-week APOLLOE4 Phase 3 trial is fully enrolled in Early AD patients with APOE4/4 genotype. **Methods:** Phase 2 study enrolled subjects with MMSE ≥ 22 and CDR-G 0.5/1, and amyloid positive by CSF or PET scans who received ALZ-801 265 mg BID over 2 years (7 European sites). Fluid biomarker analyses were performed at the Laboratory of Dr. Blennow (Molndal, Sweden), Volumetric v-MRI measures are performed by Clario. Cognitive tests include the Rey Auditory Verbal Learning Test (RAVLT) and Digit Symbol Substitution Tests (DSST), and MMSE. Change from baseline (CBL) analyses performed on the modified intent-to-treat population (mITT) population using paired t-tests and 2-sided p-values. A PK sub-study was conducted at 65 weeks (n=23) with bioanalysis and PK analyzed by WinNonlin. Pearson correlations of MMSE changes to changes of hippocampal volume (HV) and lateral ventricle volume (LVV) were conducted. **Results:** mITT population included 84 subjects with 75 completing 52 weeks of treatment. Mean age was 69 years, 51% female, MMSE 26.0, 70/30% MCI/Mild AD. Significant plasma p-tau181 reduction started at 13 weeks and was sustained reaching -41% at 52 weeks (p=0.016), with significant reduction in plasma Aβ42 and Aβ40 at 52 weeks (-5%, p=0.002 & p=0.005). HV was reduced by 25% compared to matched external ADNI controls. Composite cognitive Z-score improved significantly at 13 and 26 weeks and remained above baseline at 52 weeks, 65 and 78 weeks compared to matched ADNI group. At 52 and 65 weeks, changes of MMSE from baseline showed significant correlations to HV (r=0.32 and 0.34; p<0.01, n=66) and LVV changes (r=0.42 and 0.44; p<0.001, n=65). PK/PD analysis in 23 subjects showed trends (r=0.21-0.16, ns) between decrease of HV atrophy and LVV expansion and plasma AUC24h of tramiprosate + 3-SPA (active and metabolite). Mild nausea was the most common treatment-related adverse event, with no ARIA-E to date. Results of the final analysis at 104 weeks will be reported. **Conclusions:** At the 12-month timepoint, ALZ-801 produced a sustained significant reduction of plasma p-tau181, a marker of amyloid-induced neuronal injury in AD, as well as slowing of hippocampal atrophy and cognitive stabilization, suggesting a disease modifying effect in AD. Early AD subjects treated with ALZ-801 265 mg BID through 65 weeks in the Phase 2 biomarker study also showed strong positive correlations between MMSE stability, HV reduction and decreased ventricular enlargement in Early AD APOE4 carriers supporting the impact on the underlying AD pathology. The clinical and biomarker effects are being confirmed in the pivotal APOLLOE4 Phase 3 trial in Early AD

P044- SAFETY AND PHARMACOKINETICS OF MULTIPLE ASCENDING DOSES OF E2511, A NOVEL TRKA ALLOSTERIC MODULATOR, IN HEALTHY VOLUNTEERS. N. Penner[1], N. Hall[1], C. Cai[2], M. Mikamoto[2], J. Aluri[1], T. Yagi[1], J. Chang[1], A. Ardati[1], S. Hersch[1], L. Giorgi[3], L. Reyderman[1] *(1. Eisai - Nutley (United States), 2. Eisai - Tsukuba (Japan), 3. Eisai - Hatfield (United Kingdom))*

Background: Loss of cholinergic neurons is known to be a consistent feature of AD that contributes to memory and attention deficits and other higher brain function impairments. E2511 is a novel tropomyosin receptor kinase A (TrkA)-biased positive allosteric modulator that was designed to restore cholinergic neurons in neurodegenerative disorders involved in cognitive impairment, including Alzheimer's disease [1]. **Methods:** E2511-A001-005 was a Phase 1 randomized, double-blind, placebo-controlled, multiple ascending dose study in healthy adult subjects ≤55 year old. The study consisted of 4 non-Japanese cohorts (n=8 each, 6:2 E2511:placebo), receiving oral once daily doses of 10, 20, 40 and 80 mg E2511 for 14 days, and 3 Japanese cohorts (n=5 each, 4:1 E2511:placebo), receiving oral once daily doses of 20, 40 and 80 mg E2511 for 14 days. Safety was evaluated before dose escalation and included review of adverse events (AE), laboratory tests, physical, neurological and psychiatric examinations, vital signs, ECGs and EEGs. Serial blood samples for determination of plasma concentrations of E2511 were collected. CSF for PK assessment was collected on Day 13 in non-Japanese cohorts only. Plasma and CSF concentrations of E2511 were quantified using validated liquid chromatography with tandem mass spectrometry methods. **Results:** 32 healthy non-Japanese subjects and 15 healthy Japanese subjects were randomly assigned to receive either E2511 or placebo; 24 non-Japanese and 12 Japanese subjects received E2511 with the rest receiving placebo. E2511 was generally well tolerated with no changes of clinical concern for any laboratory parameters. There were no clinically significant changes in vital signs or ECGs. There were no E2511 dose-related trends in the incidence of treatment emergent AEs (TEAEs). Most of the TEAEs were mild in severity. In non-Japanese subjects TEAEs included post lumbar puncture syndrome (7 [29.2%]), back pain (5 [20.8%]), headache (4 [16.7%]), nausea (3 [12.5%]), constipation (2 [8.3%]), dermatitis contact (2 [8.3%]), and dizziness (2 [8.3%]). In Japanese subjects TEAEs included dermatitis contact (3 [25.0%]) and neck pain (2 [16.7%]). Majority of TEAEs were due to study procedures and not related to the study drug. One subject in the E2511 80 mg non-Japanese cohort experienced a serious and severe TEAE of mania, which led to withdrawal of study drug. There were no deaths during the study. Pharmacokinetics of E2511 appeared to be linear with dose-proportional increase in plasma exposure. After oral administration, E2511 was rapidly absorbed with tmax reached at approximately 1 hour post-dose. E2511 half-life was approximately 4 hours with little or no accumulation after multiple doses. PK of E2511 was similar between Japanese and non-Japanese subjects. The CSF-to-plasma ratios for non-Japanese subjects on Day 13 ranged from 14.9% to 32.3%, confirming brain penetration of E2511. **Conclusions:** Safety and PK profile of E2511 after

multiple doses was favorable supporting further progression of E2511 into clinical development. **Key words:** Alzheimer's disease, Pharmacokinetics (PK), Tropomyosin Receptor Kinase A (TrkA). **Clinical Trial Registry:** NCT05147337; https://clinicaltrials.gov. **Disclosures:** All authors are current or former employees of Eisai Co. Ltd. The authors declared no competing interests. **Reference:** 1. Tomioka T et al, Alzheimer's Dement. 2021;17(Suppl. 9):e051985. https://doi.org/10.1002/alz.051985

P045- ARIA BY CLINICAL SUBGROUP AND BASELINE AMYLOID PET CENTILOID LEVELS FROM THE LECANEMAB CLARITY AD STUDY. M. Sabbagh[1], D. Li[2], S. Dhadda[2], M. Irizarry[2], S. Hersch[2], L. Giorgi[2], A. Matta[3], L. Kramer[2] *(1. Barrow Neurological Institute - Phoenix (United States), 2. Eisai Inc - Nutley (United States), 3. Eisai Co., Inc - Hatfield (United Kingdom))*

Background: Amyloid-related imaging abnormalities due to edema (ARIA-E) or hemosiderin deposition (ARIA-H) have been observed on brain imaging after treatment with placebo and anti-amyloid immunotherapies, although incidence and timing of ARIA vary among treatments and the number of APOE alleles. Lecanemab is an amyloid beta-directed antibody selectively targeting protofibrils and has been FDA-approved for the treatment of early AD. In multiple clinical trials, lecanemab has been shown to be well tolerated, with an increase in ARIA-E and ARIA-H relative to placebo. The frequency of ARIA in the overall early Alzheimer's disease population of the lecanemab phase 3 Clarity AD study have been published (van Dyck 2023), and this presentation reports the occurrence of ARIA in key clinical and biomarker subgroups. **Objective:** To evaluate the frequency of ARIA-E and ARIA-H in key subgroups of the Clarity AD trial, including by baseline amyloid PET centiloid levels and by clinical subgroup (mild cognitive impairment [MCI] and mild Alzheimer's disease [mAD]). **Methods:** Clarity AD was a phase 3, 18-month treatment (Core study), multicenter, double-blind, placebo-controlled, parallel-group study with an open-label extension (OLE) in patients with early AD. Eligible patients are randomized 1:1 across 2 treatment groups (placebo and lecanemab 10 mg/kg biweekly). ARIA occurrence was monitored throughout the study by central reading of magnetic resonance imaging. ARIA occurrence was evaluated descriptively in the following subgroups: by baseline centiloid tertiles (low:≤68.185, middle:>68.185-101.245, and highest:>101.245) and clinical subgroup (MCI and mAD). Results were also evaluated by ApoE4 status within the subgroups. **Results:** Overall, 1107 patients were MCI (lecanemab:552; placebo:555) and 688 patients were mAD (lecanemab:346; placebo:342). Baseline centiloid tertiles were defined as low:≤68.185 (n=479), middle:>68.185-101.245 (n=492), and highest:>101.245 (n=478). When evaluating ARIA-E in subgroups based on baseline centiloid tertiles, the event rates were 8.5% and 3.3% for the low tertile, 15.3% and 1.6% in the middle tertile, and 13.4% and 0.9% in the highest tertile for the lecanemab and placebo groups, respectively. No trends were observed for ARIA-H (low:11.1% for lecanemab, 9.4% for placebo; middle:20.3% for lecanemab, 11.7% for placebo; highest:17.5% for lecanemab, 6.5% for placebo) or isolated ARIA-H (ie, ARIA-H that occurs in the absence of ARIA-E; (low:4.3% for lecanemab, 7.4% for placebo; middle:10.6% for lecanemab, 10.2% for placebo; highest:8.9% for lecanemab, 6.0% for placebo)). The event rates of ARIA-E, ARIA-H, and isolated ARIA-H were similar within each ApoE4 group regardless of baseline centiloids. In the clinical subgroup analysis, ARIA-E rates were 12.7% and 1.4% for MCI patients and 12.4% and 2.1% for mild AD patients in the placebo and lecanemab groups, respectively. The event rates of ARIA-H were (MCI:16.7% for lecanemab, 8.3% for placebo; mild AD:18.2% for lecanemab, 10.2% for placebo) and isolated ARIA-H (MCI:16.7% for lecanemab, 8.3% for placebo; mild AD:18.2% for lecanemab, 10.2% for placebo) were similar between patients with MCI and mild AD. **Conclusion:** The frequency of ARIA-E in the Clarity AD trial was similar when evaluated by baseline amyloid PET tertile centiloid levels and by clinical subgroup. No trends were observed for ARIA-H or isolated ARIA-H. ApoE4 zygosity did not impact results across the baseline amyloid or clinical subgroups. **Conflicts of interest statement:** Marwan Noel Sabbagh MD. **Ownership interest (Stock or stock options):** NeuroTau, uMethod Health, Versanum, Athira, TransDermix, Seq BioMarque, NeuroReserve, Cortexyme/Quince Therapeutics, Lighthouse Therapeutics. **Consulting:** Alzheon, Biogen, Roche-Genentech, Eisai, KeifeRx, Lilly, Synaptogenix, NeuroTherapia, T3D, Signant Health, Novo Nordisk. **Royalties:** Humanix. **Board of Director:** EIP Pharma, David Li, Shobha Dhadda, Michael Irizarry, Steve Hersch, Luigi Giorgi, Andre Matta, Lynn D Kramer are all employees of Eisai.

LP017- A PHASE 1B DOUBLE BLIND MULTIPLE ASCENDING DOSE STUDY OF THE SAFETY AND PHARMACOKINETICS OF NTRX-07 IN NORMAL VOLUNTEERS AND PATIENTS WITH MILD COGNITIVE IMPAIRMENT OR EARLY ALZHEIMER'S DISEASE. J. Foss[1], T. Giordano[1], M. Kiraly[1] *(1. NeuroTherapia, Inc. - Cleveland (United States))*

Background: NTRX-07 is an orally administered, brain-permeable, selective cannabinoid receptor type 2 (CBR2) agonist under development for treating neuroinflammatory-related diseases, including Alzheimer's Disease (AD). Preclinical studies of NTRX-07 in AD models have demonstrated decreased inflammatory changes in the brain, improved clearance of A-beta proteins, improved long-term potentiation, and improved learning and memory in rodent models [1]. A previous Phase 1a study of NTRX-07 demonstrated no significant adverse effects with single doses up to 2 mg/kg in healthy volunteers [2]. The objectives of the present study were to study the safety and pharmacokinetics (PK) of repeat dosing in older volunteers and a cohort of subjects with AD. Exploratory endpoints included a food effect cohort and plasma biomarkers of inflammation. **Methods:** The IRB approved study procedures, and informed consent was obtained. Three cohorts of volunteers 45-80 years of age with well-controlled comorbidities and one cohort of AD patients diagnosed with cognitive impairment consistent with prodromal AD per International Working Group criteria or mild AD per National Institute on Aging - Alzheimer's Association criteria (n=6 active, 2 placebo per cohort) were enrolled. Participants were admitted to the site for the dosing duration and returned 7-12 days after the last dose for a safety visit. Participants received NTRX-07 (10, 30, or 90 mg) or a placebo in a double-blinded randomization orally once daily for seven days. Subjects were assessed for changes in vital signs, including maneuvers to induce lightheadedness, electrocardiograms, electroencephalograms (EEG), and laboratory studies. The second cohort returned and received a single repeat dose after a standard high-fat meal. The AD cohort also underwent cognitive testing and had blood samples for biomarkers drawn. Subjects had PK sampling done after the first and final dose of the study drug. **Results:** There were no dose-limiting or serious

adverse events during the trial. One subject withdrew from the trial due to social reasons. Five participants had orthostatic changes in blood pressure, three of which were asymptomatic, and none required treatment. No participants had changes in the timed get-up and go, Nystagmus test, or Romberg test. No participants had abnormalities on the EEG. No clinically meaningful changes in ECG or safety labs were observed. PK at the high dose was similar between Non-AD and AD participants with an average of AUC0-24h (h•ng/mL) of 1291 and 1556, and Cmax (ng/ml) of 439 and 477, respectively. A decrease in levels on Day 7 suggested a change in clearance. The high-fat meal decreased Cmax, but AUC was comparable. No significant changes in cognitive scores were observed, though there was an interesting trend toward improvement in the AD participants. No significant changes in biomarkers were observed. **Conclusions:** NTRX-07 was safely administered for 7 days at doses up to 90 mg/day. The primary side effect observed was mild transient orthostatic changes in blood pressure, usually with early doses. Plasma levels were within the target ranges based on the allometric scaling of preclinical data. Future studies of NTRX-07 in the AD population are planned to determine the effect on biomarkers and cognitive effects. **Disclosures:** Drs. Foss, Kiraly, and Giordano are employees of NeuroTherapia, Inc. and hold stock options in the company. This study was supported in part by the Alzheimer's Drug Discovery Foundation. **References:** 1. Wu J, Hocevar M, Foss JF, Bie B, Naguib M. 2017. Eur J Pharmacol. 811:12–20 doi: 10.1016/j.ejphar.2017.05.044. 2. Foss J, Naguib M, Giordano T. 2020. Alzheimer's Dementia. doi: 10.1002/alz.039150

LP018- BASELINE CHARACTERISTICS FROM EVOKE AND EVOKE+: TWO PHASE 3 RANDOMIZED PLACEBO-CONTROLLED TRIALS OF ORAL SEMAGLUTIDE IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE.

P. Scheltens[1], A. Atri[2,3,4], H.H. Feldman[5], O. Hansson[6,7], F.K. Knop[8,9,10,11], M. Sano[12,13], C. Dethlefsen[14], P. Johannsen[14], T. León Colombo[15], C.T. Hansen[14], J. Cummings[16] *(1. Alzheimer Centre, VU University Medical Center Amsterdam - Amsterdam (Netherlands), 2. Banner Sun Health Research Institute - Sun City, Az (United States), 3. Banner Alzheimer's Institute - Phoenix, Az (United States), 4. Brigham and Women's Hospital, Harvard Medical School - Boston, Ma (United States), 5. Alzheimer's Disease Cooperative Study, Department of Neurosciences University of California San Diego - La Jolla, Ca (United States), 6. Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University - Lund (Sweden), 7. Memory Clinic, Skåne University Hospital - Malmö (Sweden), 8. Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen - Hellerup (Denmark), 9. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen - Copenhagen (Denmark), 10. Steno Diabetes Center Copenhagen - Herlev (Denmark), 11. Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen - Copenhagen (Denmark), 12. Icahn School of Medicine at Mount Sinai - New York, Ny (United States), 13. James J Peters VAMC - Bronx Ny (United States), 14. Novo Nordisk A/S - Søborg (Denmark), 15. Novo Nordisk A/S - Madrid (Spain), 16. University of Nevada - Las Vegas, Nv (United States))*

Background: Disease-modifying treatment options for early Alzheimer's disease (AD) are limited. Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), is approved for use in type 2 diabetes (T2D) or obesity. We report the preliminary baseline characteristics in the ongoing phase 3 evoke and evoke+ trials investigating the safety and efficacy of oral semaglutide for early AD. **Methods:** evoke (NCT04777396) and evoke+ (NCT04777409) are multicenter, randomized, double-blind, placebo-controlled trials. Eligible individuals were 55–85 years, amyloid-positive, with mild cognitive impairment (MCI) due to AD (Clinical Dementia Rating [CDR] global score of 0.5 plus CDR of ≥0.5 in ≥1 of three instrumental activities of daily living categories) or mild AD dementia (CDR global score of 1.0). Participants had a Repeatable Battery for the Assessment of Neuropsychological Status delayed memory index score ≤85 and a Mini-Mental State Examination (MMSE) score ≥22. Participants were randomized 1:1 to once-daily oral semaglutide 14 mg (titrated from 3 mg for the initial 4 weeks and 7 mg for the following 4 weeks) or placebo plus standard of care for 156 weeks (104 weeks + 52-week extension). The primary endpoint is change in the CDR – Sum of Boxes (CDR-SB) from baseline to week 104. Secondary confirmatory endpoints are change in the AD Cooperative Study Activities of Daily Living Scale for MCI (ADCS-ADL-MCI) score and the time to progression to CDR global ≥1.0 among participants with CDR global = 0.5 at baseline in the combined evoke and evoke+ populations. Exploratory endpoints include plasma biomarkers of neuroinflammation and a cerebrospinal fluid substudy. Baseline characteristics of enrolled patients were compiled after completion of enrollment on September 8th 2023 and without knowledge of the randomization assignment. As the trials are ongoing, data may be subject to minor changes until database lock. **Results:** evoke and evoke+ enrolled 1,855 and 1,835 participants each; data from 118 randomized participants from evoke+ are not included here. In evoke and evoke+, mean (SD) age was 71.8 (7.1) and 72.6 (7.1) years; 53.0% and 51.8% of participants were female; most participants (76.6%) were White; 59.7% and 54.5% were in receipt of AD medication; 11.8% and 15.4% were diagnosed with T2D; mean (SD) BMI was 25.7 kg/m2; 46.0% and 42.6% were heterozygous apolipoprotein ε4 carriers, and 12.2% and 11.8% were homozygotes. In evoke+, 2.8% of participants had significant small vessel pathology. In evoke and evoke+, mean (SD) CDR-SB score was 3.7 (1.5) and 3.7 (1.6); ADCS-ADL-MCI score was 39.4 (7.3) and 38.9 (7.5); 72.5% and 68.7% of participants had a CDR global score of 0.5; AD Assessment Scale–Cognitive Subscale-13 score was 26.8 (7.3) and 26.7 (7.6); Montreal Cognitive Assessment score was 18.8 (3.6) and 18.8 (3.7); AD Composite Score was 0.5 (0.2) and 0.5 (0.2); MMSE score was 24.1 (3.0) and 24.1 (3.1); and Neuropsychiatric Inventory score was 4.6 (7.1) and 4.6 (6.9). **Conclusions:** evoke and evoke+ are the first large-scale phase 3 trials to investigate the disease-modifying potential of semaglutide in early AD. Both studies recruited a very similar population. The trials' primary read-out is expected in the second half of 2025. **Key words:** phase 3; early Alzheimer's disease; baseline characteristics; semaglutide. **Disclosures:** Philip Scheltens is a full-time employee of EQT Life Sciences (formerly LSP) and Professor Emeritus at Amsterdam University Medical Centers. He is co-chair of the Steering Committee for the phase 3 studies evoke and evoke+ with Novo Nordisk. Alireza Atri has received honoraria for consulting; participating in independent data safety monitoring boards; providing educational lectures, programs, and materials; or serving on advisory boards for AbbVie, Acadia, Allergan, the Alzheimer's Association, Axovant, AZ Therapies, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, JOMDD, Lundbeck, Merck, Prothena, Roche/Genentech, Novo Nordisk, Qynapse, Sunovion, Suven, and Synexus. He receives royalties from Oxford University Press for a medical book on dementia. His institution receives institutional grant/contract funding for his work from AZ

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LP019- THE BRAIN AMYLOID AND VASCULAR EFFECTS OF EICOSAPENTAENOIC ACID (BRAVE) STUDY.

C. Van Hulle[1], H. Zylstra[1], K. Cronin[1], A. Cole[1], E. Beckman[1], A. Eierman[2], M. Blazel[3], K. Lazar[1], K. Johnson[1], L. Rivera[1], C. Gleason[1], H. Zetterberg[4], S. Johnson[1], C. Carlsson[1] *(1. University of Wisconsin-Madison - Madison (United States), 2. Medical College of Wisconsin-Green Bay - Green By (United States), 3. Case Western Reserve University School of Medicine - Cleveland Ohio (United States), 4. Sahlgrenska Academy - Moldal (Sweden))*

Background: Alzheimer's disease (AD) pathology is characterized by amyloid plaques, neurofibrillary tangles, and reduced regional cerebral blood flow (rCBF) in brain regions related to memory and learning. The omega-3 fatty acid eicosapentaenoic acid (EPA) has beneficial cardioprotective properties, reducing inflammation and enhancing endothelial function. Icosapent ethyl (IPE), a purified form of EPA, improves cardiovascular outcomes and strokes in at-risk patients (NCT01492361). EPA lowers triglycerides without raising LDL, unlike docosahexaenoic acid (DHA)-based omega-3 formulations. Veterans report higher rates of some cardiovascular diseases (CVD) than non-veterans. Given Veterans higher risk for vascular dysfunction, and the high co-occurrence of cerebrovascular dysfunction with AD pathology, improved vascular health may be a key modifiable risk factor for delaying the onset of AD among Veterans. Yet, Veterans remain an understudied population in AD related clinical research. We conducted a proof-of-concept investigation into the efficacy of an FDA approved high dose EPA in improving cerebrovascular function in healthy, cognitively unimpaired Veterans. **Methods:** Veterans Affairs (VA) eligible Veterans were invited to enroll into an 18-month randomized, placebo-controlled, double-blind, parallel-group clinical trial assessing the efficacy of Vascepa® IPE. The primary outcome is change over baseline in 18-month rCBF on treatment compared to placebo. Secondary outcomes are change over baseline in 18-month CSF biomarkers for AD pathology (Aβ42, pTau181, total tau). An exploratory aim is to investigate change in global cognition. At baseline, 9 and 18 months, participants had an MRI scan, LP procedure, and completed the Alzheimer's Disease Cooperative Study Preclinical Alzheimer's Cognitive Composite (ADCS-PACC) battery to measure global cognition. To characterize the vascular health of study enrollees, we measured baseline cardiovascular risk factors (atherosclerotic cardiovascular disease [ASCVD] risk score, body mass index, waist-hip ratio, blood pressure, and heart rate). Participants reported on their medication use, health conditions, dietary intake of fish oil, physical and mental activities. We also captured experiences unique to Veterans including military experience, TBI exposure, and PTSD symptoms. **Results:** We screened 206 individuals for exclusion criteria (memory disorder, inability to complete study protocols); 179 were consented and 131 were randomly assigned in a 1:1 ratio to either placebo or 4mg/day IPE. We have previously presented baseline demographics including military experience, self-reported health, and the baseline associations between cognitive performance and hippocampal volume, cardiovascular risk, and neighborhood disadvantage. Trial outcomes will be completed in Sept 2023. Here we report on mean baseline values for the pre-specified outcomes. At baseline, N=127, 119, and 129 participants had an MRI scan, LP procedure, and complete cognitive battery, respectively (N=111 participants had both successful baseline MRI and LP); to date, 110 participants completed all study visits. Mean global rCBF = 50.2 mL/100g

tissue/min (SD=16.2); mean CSF values for Ab42 = 1296 pg/mL (SD=581), phospho-tau181 = 19.7 pg/mL (SD=6.67), total tau=223 pg/mL (SD=71.8); mean global cognition as measured by the ADCS-PACC = -0.0001 (SD=0.64), suggesting normal amyloid and tau levels and cognitive performance at study entry. **Conclusion:** The impact of IPE on cerebrovascular health in cognitively unimpaired Veterans will be presented at the conference. **Key words:** Veterans, omega-3-fatty acid, cerebral blood flow, cerebrospinal fluid. **Clinical Trial Registry:** NCT02719327; https://clinicaltrials.gov. **Disclosures:** The authors have nothing to disclose.

LP020- NEUROGENESIS HYPOTHESIS AND CLINICAL TRIALS OF NA-831 FOR THE TREATMENT OF ALZHEIMER'S DISEASE AND MAJOR DEPRESSIVE DISORDER. L. Tran[1], Z. Tran[1] *(1. Biomed Industries, Inc. - San Jose (United States))*

Background: The hippocampus is critical for learning and memory contains neural progenitor cells. The hippocampus continues to generate new neurons throughout life, a process is known as adult hippocampal neurogenesis (AHN). Hippocampal neurogenesis is persistent through the tenth decade of human life, and is detectable in patients with Alzheimer's disease (AD). There was a marked and progressive decline of DCX+ cell numbers in AD patients as compared with neurologically healthy individuals. AHN impairment compromises hippocampal function in AD and MCI. This indicates that reduced AHN causes memory impairments and cognitive deterioration in the disease. In addition, AHN is crucial for the regulation of mood. If disturbed, it can have severe consequences for mental health. AHN has been shown to be involved in Major Depressive Disorder (MDD) and Alzheimer's disease pathology. The clinical trials of a new drug, NA-831 presented here provide some evidence that AHN is involved in both AD and MDD. **Results:** Phase 2A Clinical Trials of NA-831 for the treatment of Alzheimer's Disease. NA-831 is a small drug molecule, easily crosses the blood brain barrier with excellent bioavailability. The drug exhibits neuroprotection, neurogenesis and memory enhancing properties. A randomized clinical trial of NA-831 was performed in 112 participants with mild and moderate Alzheimer's disease, half received the drugs and half received placebo. The patients with MCI received 10 mg of NA-831 or placebo orally per day. The patients with mild and moderate Alzheimer's disease received 30 mg of NA-831 or placebo orally per day. Subjects with MCI to meet the NIA-AA core clinical criteria for mild cognitive impairment due to Alzheimer's disease. CDR score of 0.5 and a Memory Box score of 0.5 or greater at Screening and Baseline. MMSE score ≥22. Subjects with mild & moderate Alzheimer's disease to meet the NIA-AA core clinical criteria for probable Alzheimer's disease dementia. MMSE: 17-21. NA-831 showed a significant improvement for patients with mild and moderate AD with the ADAS-Cog-13 score change of an average of 4.1 as compared to the placebo after 24 weeks of treatment (p = 0.001; ITT). CIBIC-Plus showed 78 % patients improved (p = 0.01; ITT). mNA-831 was well-tolerated at 30 mg/day. There were no serious adverse events observed. Phase 1B Clinical Trials of NA-831 for Major Depressive Disorder (MDD). We completed a Phase 1B pilot study, which was a randomized, double-blind, fixed-dose, placebo-controlled, active reference study to investigate the efficacy, safety, and tolerability of two fixed doses (20 and 40 mg/d) of NA-831 vs. that of placebo after 6-week treatment in 32 adult patients with major depressive disorder (MDD). Venlafaxine XR was used as the active reference. The most common adverse effects reported in the active NA-831 treatment groups were mild headache and dry mouth. Both doses of NA-831 resulted in a significant improvement compared to placebo on the primary efficacy analysis. The difference between active treatment and placebo of ~7 points on the MADRS translates into a clinically relevant difference in response rates of 32.5 % units, compared to an average of 16% units for antidepressants approved by the USA and European health authorities. Treatment with NA-831 for 6-week was well tolerated and efficacious in reducing depressive and anxious symptoms in patients with MDD. **Conclusion:** The Neurogenesis Hypothesis has been shown to be a viable approach for further research for Alzheimer's disease (AD) and Major Depressive Disorder (MDD). Biomed is in the process of conducting a Phase 2B and Phase 3 trials of NA-831 for the treatment of AD and MDD.

LP022- RETISPEC'S AI-BASED RETINAL TEST: RESULTS OF A MULTI-SITE, PROSPECTIVE, VALIDATION STUDY TO PREDICT BRAIN AB PATHOLOGY IN A DIVERSE POPULATION OF ADULTS WITH PRECLINICAL, MCI, AND PROBABLE ALZHEIMER'S DISEASE. A. Hazan[1], C. Bornbaum[1], E. Shaked[1], J. Giordano[1], Y. Edlitz[2,3], D. He[4], D. Kerwin[5] *(1. RetiSpec - Toronto (Canada), 2. Weizmann Institute of Science - Rehovot (Israel), 3. MLAIA Data Science - Tel Aviv (Israel), 4. Analytical Solutions Group, Inc. - North Pontomac (United States), 5. Kerwin Medical Center - Dallas (United States))*

Background: With recently approved disease-modifying therapies, scalable Alzheimer's disease (AD) diagnostics are urgently needed. The retina shares developmental and biological similarities with the brain, which can be measured using non-invasive hyperspectral retinal imaging. By combining hyperspectral imaging with artificial intelligence (AI), RetiSpec's technology may enable easy and efficient identification of AD markers across various AD stages. **Methods:** The Global Alzheimer's Platform Foundation® led a prospective, randomized, cohort study (Bio-Hermes) evaluating relationships between brain amyloid (Aβ) PET scans and AD diagnostics, including retinal, digital, and blood tests. This parent study enrolled 1000 participants between ages 60-85 and included a diversity target of 20% (Black/African American and Latino). A retinal imaging substudy evaluated the performance of RetiSpec's AI-based eye test to predict Aβ-PET status. RetiSpec's AI is an ensemble model based on a 3-dimensional spectral-spatial architecture that scrutinizes retinal regions of the optic disc including the superior and inferior regions as compared to the spectral response from the fovea region. A portion of Aβ labels were unblinded for algorithm training while the remainder of data were blinded as a hold-out set for validation. Predictive performance on Aβ-PET status was assessed through receiver-operating characteristic (ROC) curve analysis. An Area Under the Curve (AUC) value of ≥0.7 was predefined as the threshold for overall success. ROC curves are reported for each sample group (blinded, unblinded, and total evaluable) using a predefined cut-off for predicting Aβ-PET status. Exploratory analysis included: a logistic regression to obtain an APOE- and age-adjusted RetiSpec model, and comparison of performance between the RetiSpec model and blood plasma tests collected in the parent study (Aβ40/Aβ42 ratio, pTau181, pTau217). Test performance was evaluated by AUC with Aβ-PET status as comparator. **Results:** N=271 participants (60.5% females) with a mean age of 71.9 (60-86) from 6 sites were imaged and analyzed. Cohort distribution

included: Healthy: N=135, MCI: N=74, Probable AD: N=62. Mean MMSE score was 27.1 (17-30). The substudy sample was generally representative of the Bio-Hermes parent study. Modest differences in ethnicity and MMSE were attributable to a healthier substudy population and a slightly lower proportion of Hispanic/Latino participants; nevertheless, the substudy obtained 20% of participants from underrepresented minority populations. N=176 participants were unblinded and N=95 remained blinded with a total of N=86 Aβ positive and N=185 Aβ negative. RetiSpec's model obtained an AUC of 0.77 (95%CI=0.70-0.83) on the total evaluable sample (sensitivity 80%; specificity 64%). The unblinded and blinded samples showed similar performance to the total sample: AUC=0.78 (95%CI=0.70-0.86) and AUC=0.73 (95%CI=0.62-0.83), respectively. The APOE/Age-adjusted RetiSpec model on N=264 demonstrated an AUC of 0.80. When compared with N=187 substudy participants who were commonly evaluable with plasma biomarkers, all tests performed within 0.1 AUC: RetiSpec AUC=0.76; pTau181 AUC=0.79; Aβ40/Aβ42 AUC=0.80; pTau217 AUC=0.86. **Conclusions:** In this prospective validation study, RetiSpec's AI-based retinal test demonstrated strong performance for prediction of Aβ-PET status across healthy, MCI and probable AD cohorts. This accessible technology may hold potential to aid in the evaluation of AD by providing decision support at the point-of-care and enabling more timely access to disease-modifying therapies.

LP023- DOPAMINERGIC THERAPY FOR FRONTOTEMPORAL DEMENTIA PATIENTS: PRELIMINARY RESULTS FROM A PHASE 2 MULTI-SITE, RANDOMIZED CLINICAL TRIAL. AM. Assogna[1,2], F. Di Lorenzo[1], S. Bonnì[1], A. Benussi[3], I. Borghi[1], E. Cerulli Irelli[4], E. Premi[3], V. Cantoni[3], V. Pezzopane[1], L. Mencarelli[1], C. Motta[2], C. Ferrari[5], M. Alessandro[2], G. Koch[1,6] *(1. Department of Clinical and Behavioural Neurology,Santa Lucia Foundation - Rome (Italy), 2. Memory Clinic, Department of Systems Medicine, University of Tor Vergata, - Rome (Italy), 3. Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, - Brescia (Italy), 4. Department of Human Neurosciences, Sapienza, University of Rome - Rome (Italy), 5. Office of Research and Clinical Trials, Fondazione Poliambulanza Istituto Ospedaliero, - Brescia (Italy), 6. Department of Neuroscience and Rehabilitation, University of Ferrara, and Center for Translational Neurophysiology of Speech and Communication (CTNSC), Italian Institute of Technology (IIT), - Ferrara (Italy))*

Background: Frontotemporal dementia (FTD) is a common form of dementia with no approved pharmacological treatment. Clinical and experimental evidence show that dopamine transmission is impaired in FTD. The aim of the current study was to provide the first-time evidence of the clinical impact, at cognitive and behavioral level, of a dopamine-based treatment in newly diagnosed behavioral-variant Frontotemporal Dementia (bvFTD) patients. **Methods:** This was a phase IIa 24-week randomized, double-blind, placebo-controlled study. The study is designed to evaluate the efficacy and safety of Rotigotine (RTG) transdermal administration at the dosage of 4 mg or 6 mg per day versus Placebo (PLC) in newly diagnosed behavioural Frontotemporal Dementia (bvFTD) patients. The trial was conducted at Santa Lucia Foundation in Rome, Italy and at Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Italy, from June 2021 to April 2023. Patients were enrolled if they had an established diagnosis of probable Frontotemporal dementia behavioural variant (bvFTD) based on the International consensus clinical diagnostic criteria and were aged from 40 to 80 years. 75 bvFTD patients were randomly allocated to the three treatment arms (RTG 4 mg/day, RTG 6 mg/day or placebo). The primary efficacy outcome measure was the change at 24-weeks from baseline in the Frontal Assessment Battery (FAB), a battery to evaluate executive functions. Secondary outcome measures included the Neuropsychiatric Inventory scale (NPI), the Frontal Behavioural Inventory (FBI), CDR Dementia Staging Instrument from the National Alzheimer's Coordinating Center and Frontotemporal lobar degeneration modules - sum of boxes (CDR plus NACC FTLD - SOB), Screening for Aphasia in Neurodegeneration (SAND), Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL), Mini Mental State Examination (MMSE) and Addenbrooke's Cognitive Examination Revised (ACE-R). **Results:** A total of 128 patients were screened of which 75 were randomized (25 to RTG 4 mg/day, 26 to RTG 6 mg/day, 24 to placebo). 68 patients (90.6%) completed the treatment. Mean age was 66.6 years in the RTG 4 mg/day group, 65.3 in the RTG 6 mg/day group and 67.6 years in the placebo group. Patients in the RTG 4 mg/day group and in the RTG 6 mg/day group did not show improvement for the primary outcome measure (FAB) as compared to patients treated with placebo. The estimated mean rates change (W0-W24) in FAB score was 0.184 for RTG 4 mg group [95% confidence interval (CI) (-0.669 to 1.037)], 0.6273 for RTG 6 mg group and [95% CI (- 0.225 to 1.037)] and 1.08 for placebo group [95% CI (0.249 to 1.918)]. No significant effect of RTG 4 mg/day and RTG 6 mg/day treatment was found on other secondary outcome measures. **Conclusions:** Our preliminary results shows that Rotigotine administration did not improve clinical outcomes in bvFTD patients. However, the findings of this trial provide data in a large sample on progression of bvFTD that might be useful for the design of other clinical trials. **Trial Registration:** NCT04937452.
Keywords: FTD, Rotigotine, dopamine, executive functions.
Disclosures: The authors declared no competing interests.
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LP024- RESULTS FROM: A PILOT ELECTROENCEPHALOGRAPHY (EEG) STUDY TO EVALUATE THE EFFECT OF CT1812 TREATMENT ON SYNAPTIC ACTIVITY IN SUBJECTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE. W. De Haan[1,2], A.O. Caggiano[3], P. Scheltens[4], M. Grundman[5], E.P. Scheijbeler[1,2], M.E. Hamby[3], E.G.B. Vijverberg[1] *(1. Department of Clinical Neurophysiology and MEG Center, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 2. Alzheimer Center, Department of Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC - Amsterdam (Netherlands), 3. Cognition Therapeutics - Purchase (United States), 4. EQT Group - Amsterdam (Netherlands), 5. Global R&D Partners and Department of Neurosciences, University of California - San Diego (United States))*

Background: CT1812 is an orally delivered small molecule in development for Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). CT1812 is a ligand for the sigma-2 receptor and evidence from in vitro, in vivo and clinical trials indicates that it can modulate the binding of toxic amyloid beta oligomers to their targets on neurons. Recent clinical trials with anti-amyloid antibodies have confirmed that amyloid removal can slow progression of Alzheimer's disease [1, 2]. The objective of this trial was to determine if acute displacement of amyloid oligomers with CT1812 alters synaptic activity as measured by quantitative electroencephalography (EEG). **Methods:** A pilot phase 2, single site, double-blind, placebo controlled, crossover design study was conducted in 16 participants with mild to moderate AD (NCT04735536). Participants were randomized to receive four weeks of either CT1812 (300 mg, PO, qD) or placebo during the first treatment period. Following a two-week washout, participants then switched treatment for another four-week period. Quantitative, resting-state EEG was performed before and after each four-week treatment period. Change from baseline in relative spectral power for theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30 Hz) frequency bands, and functional connectivity (corrected amplitude envelope correlation, AECc) were ranked outcomes comparing the CT1812 to the placebo treatment periods using a linear mixed model with fixed effects for treatment group (CT1812 or placebo), sequence, and period, and a random effect for subject within sequence. Cerebrospinal fluid and plasma were also collected for canonical AD biomarker and unbiased proteomic analyses. Safety and tolerability were assessed with reported adverse events (AEs), physical exams and laboratory testing. **Results:** Safety findings were similar to previous clinical studies with CT1812. In this study there were no deaths, no serious adverse events (SAEs), no severe AEs and no discontinuations due to AEs. There was one participant with mild elevation of liver transaminase which returned to normal with study drug discontinuation. The most common AEs reported while on CT1812 treatment were nausea and headache. All prespecified EEG parameters showed consistent trends of improvement during the CT1812 treatment period, with significant decreases in central relative theta power and increases in global alpha AECc. Changes in biomarkers will also be reported. **Conclusions:** CT1812 was generally safe and well tolerated in this small pilot study and consistent with previous clinical experience. CT1812 treatment showed improvement of EEG parameters that are consistent in magnitude and effect size with previously reported trials [3, 4]. Given the limited size and the duration of this study, these data are promising evidence of the ability of CT1812 to enhance synaptic activity. CT1812 is an experimental therapeutic that may offer an alternative approach to modulate amyloid oligomer toxicity and is currently in proof-of-concept studies in mild to moderate AD (NCT03507790), early AD (NCT05531656) and DLB (NCT05225415). This study was supported by a grant from the National Institute on Aging (AG058710). **References:** 1. van Dyck et al., (2023) Lecanemab in Early Alzheimer's Disease. NEJM 388: 9-21; 2. Sims et al., (2023) Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Tria. JAMA 330:512-527; 3. Scheltens et al., (2018) Safety, tolerability and efficacy of the glutaminyl cyclase inhibitor PQ912 in Alzheimer's disease: results of a randomized, double-blind, placebo-controlled phase 2a study. Alzheimer's research & therapy, 10: 1-14; 4. Briels et al., (2019) In pursuit of a sensitive EEG functional connectivity outcome measure for clinical trials in Alzheimer's disease. Clin Neurophysiol. 131:88-95. **Key words:** sigma-2 receptor, dementia, Alzheimer's disease, electrophysiology. **Disclosures:** MH and AC are employees and shareholders of Cognition Therapeutics; MG is an employee of Global R&D Partners and a consultant to Cognition Therapeutics. WH and ES are employees of the Amsterdam UMC EEG lab, which performs centralized EEG analysis for multicenter pharmaceutical trials by Cognition Therapeutics, Vivoryon, Immunobrain, Toyama Fujifilm, Cervomed and Treeway. EV is or has been PI for PI for DIAN TU trials, AC immune, Alnylam, CogRX therapeutics, New Amsterdam Pharma, Janssen, UCB, Roche, Vivoryon, ImmunoBrain, GemVax and Alector, Eli Lilly, Biogen and Fuij Film Toyama. Consultant for New Amsterdam Pharma, Treeway, ReMynd, Vivoryon, Biogen, Vigil Neuroscience, and Roche. PS is a full-time employee of EQT Life Sciences (formerly LSP) and Professor Emeritus at Amsterdam University Medical Centers. He has received consultancy fees (paid to the university) from Alzheon, Brainstorm Cell and Green Valley. Within his university affiliation he was global PI of the phase 1b study of AC Immune, Phase 2b study with FUJI-film/Toyama and phase 2 study of UCB. He is past chair of the EU steering committee of the phase 2b program of Vivoryon and the phase 2b study of Novartis Cardiology and presently co-chair of the phase 3 study with NOVO-Nordisk.

LP025- PALMITOYLETHANOLAMIDE COMBINED WITH LUTEOLINE IN FRONTOTEMPORAL DEMENTIA PATIENTS (PEA-FTD): A PHASE 2 RANDOMIZED CLINICAL TRIAL. M. Assogna[1], F. Di Lorenzo[1], S. Bonnì[1], I. Borghi[1], E. Cerulli Irelli[2], L. Mencarelli[1], M. Maiella[1], E.P. Casula[1], V. Pezzopane[1], C. Motta[3], C. Ferrari[4], C. Caltagirone[1], M. Alessandro[5], G. Koch[1,6] *(1. Department of Clinical and Behavioural Neurology, Santa Lucia Foundation - Rome (Italy), 2. Department of Human Neurosciences, Sapienza, University of Rome - Rome (Italy), 3. Memory Clinic,University of Tor Vergata, - Rome (Italy), 4. Office of Research and Clinical Trials, Fondazione Poliambulanza Istituto Ospedaliero, - Brescia (Italy), 5. Memory Clinic, Department of Systems Medicine, University of Tor Vergata - Rome (Italy), 6. Department of Neuroscience and Rehabilitation, University of Ferrara, and Center for Translational Neurophysiology of Speech and Communication (CTNSC), Italian Institute of Technology (IIT), - Ferrara (Italy))*

Background: Frontotemporal dementia (FTD) is a devastating neurodegenerative disorder with no approved pharmacological treatment. Neuroinflammation is a key contributor to the pathogenetic process in FTD. The aim of this study was to determine whether treatment with co-ultramicronized Palmitoylethanolamide combined with Luteoline (co-ultraPEAlut) may have a clinical impact in FTD patients. **Methods:** This was a phase 2, monocentric,

randomized, double-blind, placebo-controlled trial, conducted at Santa Lucia Foundation in Rome, Italy, from June 2019 to December 2022. Patients were enrolled if they had an established diagnosis of probable FTD according to current diagnostic criteria and were aged from 40 to 85 years. Co-ultramicronized Palmythoilethanolamide combined with Lutheoline oral suspension at the dosage of 700 mg+ 70 mg twice every day or placebo were administered for 24 weeks. The primary efficacy outcome measure was the change at 24-weeks from baseline in the CDR Dementia Staging Instrument from the National Alzheimer's Coordinating Center and Frontotemporal lobar degeneration modules - sum of boxes (CDR plus NACC FTLD - SOB). Secondary outcome measure included the Frontal Assessment Battery (FAB), Screening for Aphasia in Neurodegeneration (SAND), Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL), Neuropsychiatric Inventory scale (NPI), Mini Mental State Examination (MMSE) and Addenbrooke's Cognitive Examination Revised (ACE-R). **Results:** A total of 93 patients were screened of which 48 were randomized (25 to co-ultraPEAlut and 23 to placebo). Mean age of patients was 63.2±8.4 and 23 (47.9%) were female. 45 patients (93%) completed the treatment. Patients in the co-ultraPEAlut group showed less decline for the primary outcome measure (CDR plus NACC FTLD) as compared to patients treated with placebo. The estimated mean rates change (W0-W24) in CDR plus NACC FTLD score was 0.6 for co- ultraPEAlut [95% confidence interval (CI) (0.2 to 1)] and 1.4783 for placebo group [95% CI (1.062 to 1.895)]. Estimated mean change in ADCS-ADL score was -1.8 for the co-ultraPEAlut (95% CI, - 3.664 to 0.0641) and -7.39 for the placebo group (95% CI -9.335 to -5.4478). Estimated mean change in SAND scores was -3.987 for the co-ultraPEAlut (95% CI, -7.75 to -0.223) and -10.349 for the placebo group (95% CI, -14.33 to -6.367). No significant effect of co-ultraPEAlut treatment was found on other secondary outcome measures. **Conclusion:** Co-ultramicronized Palmythoilethanolamide combined with Lutheoline exhibits encouraging efficacy in slowing down the progression of cognitive and functional symptoms in FTD patients. These findings warrant further investigation and hold promise for the development of effective therapeutic interventions for FTD. **Trial Registration:** NCT04489017. **Key words:** FTD, PEA-LUT, neuroinflammation. **Disclosures:** The authors declared no competing interests. **References:** 1. Boxer AL, Gold M, Feldman H, Boeve BF, Dickinson SL, Fillit H, Ho C, Paul R, Pearlman R, Sutherland M, Verma A, Arneric SP, Alexander BM, Dickerson BC, Dorsey ER, Grossman M, Huey ED, Irizarry MC, Marks WJ, Masellis M, McFarland F, Niehoff D, Onyike CU, Paganoni S, Panzara MA, Rockwood K, Rohrer JD, Rosen H, Schuck RN, Soares HD, Tatton N. New directions in clinical trials for frontotemporal lobar degeneration: Methods and outcome measures. Alzheimers Dement. 2020 Jan;16(1):131-143. doi: 10.1016/j.jalz.2019.06.4956. Epub 2020 Jan 6. PMID: 31668596; PMCID: PMC6949386. 2. Bevan-Jones WR, Cope TE, Jones PS, Kaalund SS, Passamonti L, Allinson K, Green O, Hong YT, Fryer TD, Arnold R, Coles JP, Aigbirhio FI, Larner AJ, Patterson K, O'Brien JT, Rowe JB. Neuroinflammation and protein aggregation co-localize across the frontotemporal dementia spectrum. Brain. 2020 Mar 1;143(3):1010- 1026. doi: 10.1093/brain/awaa033. PMID: 32179883; PMCID: PMC7089669. 3. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EG, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011 Sep;134(Pt 9):2456-77. doi: 10.1093/brain/awr179. Epub 2011 Aug 2. PMID: 21810890; PMCID: PMC3170532. 4. Assogna M, Casula EP, Borghi I, Bonnì S, Samà D, Motta C, Di Lorenzo F, D'Acunto A, Porrazzini F, Minei M, Caltagirone C, Martorana A, Koch G. Effects of Palmitoylethanolamide Combined with Luteoline on Frontal Lobe Functions, High Frequency Oscillations, and GABAergic Transmission in Patients with Frontotemporal Dementia. J Alzheimers Dis. 2020;76(4):1297-1308. doi: 10.3233/JAD-200426. PMID: 32623398.

LP026- OVERTURE OPEN-LABEL EXTENSION DATA CONFIRMS SAFETY, ADHERENCE AND DURABILITY OF TREATMENT BENEFITS OVER 18 MONTHS. R. Kern[1], C. Kuang[1], M. Hajos[1], A. Konisky[1], A. Boasso[1], E. Hempel[1], B. Vaughan[1], C. Seshagiri[1], Z. Malchano[1], S. Hendrix[2], K. Saikali[1] *(1. Cognito Therapeutics - Cambridge (United States), 2. Pentara Corporation - Salt Lake City (United States))*

Background: The OVERTURE (NCT03556280) randomized controlled trial (RCT) evaluated Cognito's proprietary gamma sensory stimulation device in mild-moderate Alzheimer's disease and included a 12-month open label extension (OLE). We report results from the OLE to evaluate the 18-month safety, adherence and durability of treatment benefits. **Methods:** Participants who completed the 6-month RCT were eligible to receive 1-hour daily treatment for additional 12 months in the OLE. An 'as treated' population was evaluated for safety, adherence, and efficacy (ADCS-ADL and MRI measures). Limited OLE MMSE data was obtained during the COVID pandemic. Mild-moderate AD ADNI1 MRI historical controls (n=380) were used for whole brain volume (WBV) comparisons. Regression modeling controlled for age and MMSE, time-to event analysis and a disease-modification (DM) analysis was performed using the off-treatment period between the RCT and OLE. **Results:** In the RCT, 135 participants were screened, 74 randomized and 53 completed confirming safety, tolerability and adherence, with no observed ARIA or treatment-limiting SAEs. Active vs. sham showed less reduction in MMSE (76%), ADCS-ADL (77%) and WBV loss (69%). 44/53 (83%) RCT completers entered the OLE and 22 completed 18 months. Continued active treatment showed comparable ADCS-ADL and WBV outcomes in RCT and OLE: ADCS-ADL -0.49/month OLE and -0.46/month RCT; WBV -0.09%/month OLE and -0.06%/month RCT. Sham participants who switched to active treatment showed 18-month estimated ADCS-ADL decline comparable to continued active treatment and superior to continued sham (-8.62 active and -24.18 continued sham, p=0.0070; -8.50 sham switch to active and -24.18 continued sham, p=0.0035). WBV showed similar findings (-1.30% sham switch to active, -1.50% continued active, -2.62% ADNI, and -4.84% continued sham; active vs. continued sham p=0.0459, active vs. ADNI p=0.0307; sham switch to active vs. ADNI p=0.1472; sham switch to active vs. continued sham p=0.0379). Continued active was superior to sham in observed ADCS-ADL and WBV at 18 months, despite the benefits of switching to active treatment. Active treatment showed a longer time to ≥15% decline in ADCS-ADL total score vs. sham (mean days (SE); 422.27 (32.73) vs. 150.96 (13.95)). The DM analysis showed significant separation at the end of the RCT (p=0.0006). This

separation was maintained after 12 months of OLE treatment (p=0.0045), with non-converging slopes during the OLE period. Device level adherence was 80% in the OLE and RCT. No new safety signals emerged, and ARIA was not observed. **Conclusions:** Continued active treatment in the OVERTURE OLE demonstrated durability and concordance2 of clinical and MRI benefits, safety and device adherence over 18 months. Sham participants switched to active treatment demonstrated a rate of ADCS-ADL and WBV decline comparable to continued active treatment but did not "catch up" to the earlier treated group. These treatment outcomes are consistent with disease modification, and support early treatment. **Key words:** Sensory Stimulation System, Gamma Oscillation, Alzheimer's Disease, Open-Label Extension. **Clinical Trial Registry:** OVERTURE: NCT03556280. **Disclosures:** RK, CK, MH, AK, AB, EH, BV, CS, ZM, KS are employees of, or own equities in Cognito Therapeutics. SH is an employee of Pentara Corporation. **References:** 1. https://adni.loni.usc.edu. 2. M. ten Kate J Prev Alz Dis 2023

LP027- BASELINE RISK FACTORS FOR ARIA-E IN THE GRADUATE I AND II STUDIES OF GANTENERUMAB. P. Delmar[1], N. Voyle[2], M. Grundman[3], S. Salloway[4], J. Wojtowicz[1], M. Lyons[2], C. Lane[2], A. Thanasopoulou[1], S. Rossomanno[1], S. Bullain[1], G. Klein[1], T. Bittner[5], A. Schneider[1], J. Smith[2], R. Doody[5] *(1. F. Hoffmann-La Roche Ltd - Basel (Switzerland), 2. Roche Products Ltd - Welwyn Garden City (United Kingdom), 3. Global R&D Partners, LLC and Dept. of Neurosciences, University of California - San Diego (United States), 4. Butler Hospital and Warren Alpert Medical School of Brown University - Providence (United States), 5. F. Hoffmann-La Roche Ltd and Genentech, Inc. - Basel (Switzerland))*

Background: Amyloid-related imaging abnormalities (ARIA) have been reported in individuals with Alzheimer's disease treated with gantenerumab and other antibodies that target aggregated forms of amyloid. ARIA include MRI signal abnormalities suggestive of vasogenic edema and sulcal effusions (ARIA-E) as well as microhemorrhages and leptomeningeal hemosiderin deposits (ARIA-H). Our objective was to evaluate baseline risk factors associated with the incidence of ARIA-E in participants treated with gantenerumab in the Phase 3 GRADUATE studies. **Methods:** Brain MRI scans were used to monitor for ARIA-E in the GRADUATE studies. Participants were included in the pooled GRADUATE 1 and 2 MRI safety population if they received at least one dose of study drug and had at least one post-baseline MRI scan. Further, only participants who received gantenerumab were included in this analysis. A comprehensive list of potential risk factors was identified using a literature search and expert advice. All biomarker values were log10 transformed. Univariate cox regression models with a Bonferroni correction for multiple testing were used to assess risk factors associated with ARIA-E. **Results:** 993 participants were included in the analyses. Incident ARIA-E occurred in 247 (24.9%) participants. Risk of ARIA-E increased with the number of APOE ε4 alleles (HR [95% CI]: 1.98 [1.40; 2.80] and 4.65 [3.23; 6.70] for 1e4 and 2e4 respectively, $p < 0.0001$), Fazekas Score >0 at baseline (HR [95% CI]: 1.65 [1.32; 2.05]; $p<0.0001$), and number of focal areas of leptomeningeal hemosiderosis at baseline (HR [95% CI]: 1.86 [1.30; 2.64]; p=0.0006). Risk of ARIA-E decreased with increasing baseline CSF Aβ42 concentration (HR [95% CI]: 0.05 [0.01; 0.24], 95% CI; p=0.0003). Other factors associated with increased risk of ARIA-E ($p < 0.05$) that did not meet the Bonferroni corrected threshold for multiple testing included: total number of ARIA-H lesions and number of microbleeds at baseline, cardiovascular risk factors (including higher systolic blood pressure and dyslipidemia), female sex, higher baseline CSF pTau181, and higher baseline amyloid PET burden. **Conclusions:** In addition to well-established risk factors for ARIA-E, e.g. APOE genotype and evidence of baseline ARIA-H, higher Fazekas score and lower CSF Aβ42 concentration at baseline were significant risk factors for ARIA-E in the gantenerumab phase 3 studies. These findings, along with other factors found to be associated with increased risk of ARIA-E (e.g. higher amyloid PET burden, higher CSF pTau181, higher systolic blood pressure, and history of dyslipidemia) suggest that the severity of AD neuropathology and comorbid cerebrovascular pathology may also contribute to ARIA-E risk. **Key words:** Amyloid related imaging abnormalities, ARIA-E, ARIA-H, risk factors, gantenerumab. **Disclosures:** Nicola Voyle, Marco Lyons, Christopher Lane and Janice Smith are employees of Roche Products Ltd and own stocks or stock options in F. Hoffmann-La Roche Ltd. Michael Grundman is an employee of Global R&D Partners, LLC and a consultant to Roche/Genentech. Stephen Salloway was the co-chair of the Investigator Steering Committee for the Aducanumab Phase III programme; he served as a site PI for the aducanumab and lecanemab Phase III studies and the donanemab Phase II trial, and he was the Project Arm Leader for gantenerumab in DIAN-TU. He has received consulting income from Biogen, Lilly, Roche, Genentech, Bolden, Amylyx, Prothena, and Eisai. He has no stock or royalties related to any medication in development. Dr. Salloway serves on the planning committee for the National Disease Modifying Treatment and Diagnostic Registry Work Group and he is a member of the ADRD Therapeutics Work Group. He is the first author for the report of ARIA in aducanumab Phase III (Salloway, JAMA Neurology, 2022), the report of gantenerumab and solanezumab in DIAN-TU (Salloway, Nature Medicine, 2021). He is a co-author on the report of the donanemab phase 2 trial (Mintun, NEJM, 2021) and the Aducanumab Appropriate Use Recommendations (Cummings, Journal of the Prevention of Alzheimer's Disease, 2021). Jakub Wojtowicz, Paul Delmar, Angeliki Thanasopoulou, Szofia Bullain, Gregory Klein, Tobias Bittner and Andres Schneider are employees of, and own stocks or stock options in, F. Hoffmann-La Roche Ltd. Tobias Bittner is also an employee of Genentech, Inc., part of F. Hoffmann-La Roche Ltd. Simona Rossomanno is an employee of F. Hoffmann-La Roche Ltd. Rachelle S Doody is an employee of F. Hoffmann-La Roche Ltd and Genentech, Inc., part of F. Hoffmann-La Roche Ltd; and is a shareholder in F. Hoffmann-La Roche Ltd.

LP028- DONANEMAB: CHARACTERIZATION OF IMMUNOGENICITY FROM THE TRAILBLAZER-ALZ & TRAILBLAZER-ALZ 2 TRIALS. G. Mullins[1], P. Ardayfio[1], I. Gueorguieva[1], G. Anglin[1], J. Bailey[1], L. Chua[1], J. Zimmer[1], C. Evans[1], E. Nery[1], H. Wang[1], R. Khanna[1], D. Brooks[1], J. Sims[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Background: Donanemab is an immunoglobulin G1 antibody targeting existing amyloid plaques in adults with Alzheimer's disease. We evaluated treatment-emergent (TE) anti-drug antibodies (ADA) in donanemab-treated participants from two pivotal clinical trials and their potential effect on pharmacokinetics, efficacy, and safety. **Methods:** Data were integrated from two multicenter, randomized, double-blind, placebo-controlled, phase 2 & 3 studies of donanemab in participants with early symptomatic Alzheimer's disease (TRAILBLAZER-ALZ/NCT03367403 & TRAILBLAZER-ALZ

2/NCT04437511). In both, participants were randomized 1:1 to donanemab (700mg for first three doses, 1400mg thereafter) or placebo intravenously Q4W up to 72 weeks. A multi-tiered immunogenicity testing strategy was used to detect and characterize ADA, consisting of screening, confirmation, titration, and detection of neutralizing antibodies. ADA were assessed at baseline, Weeks 4, 8, 12, 16, 24, 36, 52, 76, and during follow-up. Impact of ADA on amyloid plaque reduction and clinical efficacy was assessed by covariate analysis of population pharmacokinetics/pharmacodynamics and a separate repeated measures model. **Results:** Of 922 TE ADA-evaluable donanemab-treated participants, 812 (88.1%) were TE ADA-positive, and 758 (85.1%) were neutralizing antibody-positive. Maximum post-baseline titers ranged from 1:10–1:5242880 (median 1:5120). In pharmacokinetic analysis, donanemab clearance increased linearly with logarithm of ADA titer. This resulted in a 17% decrease in area under the concentration versus time curve during one dosing interval at steady state and a 31% decrease in drug concentration before the next dose comparing low (<1:5120) to high (>1:20480) titer groups. In exposure-response analysis, plaque reduction was associated with maintaining serum donanemab concentrations above a median threshold of 15.2 μg/mL (95% confidence interval: 8.5–18.0). While clearance increased with increasing titer, the majority of participants maintained concentrations above this threshold; both pharmacokinetics/pharmacodynamics and repeated measured models demonstrated significant plaque reduction irrespective of titer. Both models demonstrated that, irrespective of titer, no association was observed between ADA presence or titer and donanemab's clinical efficacy. Of participants reporting infusion-related reactions (IRRs), nearly all (97%) were ADA-positive; approximately half (56%) had maximum titer in the upper titer group (>1:20480). Although a greater proportion of participants with higher maximum titer reported IRRs, the majority (92%) of TE ADA-positive participants and the majority (67%) of participants in the upper titer group (>1:20480) did not report an IRR. In the donanemab arm, 84 (8.5%) participants experienced IRRs; 4 (0.4%) participants in the placebo arm had an IRR. There was no clear relationship between titer group and proportion of participants reporting a serious/severe event. All 3 participants with reported anaphylaxis were TE ADA-positive; 2 had titers in the upper group, and 1 had titer in the middle group. No significant impact of immunogenicity was observed on ARIA-E risk. **Conclusions:** In the phase 2 & 3 TRAILBLAZER-ALZ studies, presence or titer of ADA was not associated with clinically meaningful impact on donanemab pharmacokinetics, plaque reduction, or clinical efficacy. The majority of TE ADA-positive participants and the majority of participants in the upper titer group did not report an IRR. The high incidence of TE ADA does not appear to substantially impact donanemab's overall positive benefit-risk balance.

LP029- DONANEMAB: CHARACTERIZING INFUSION-RELATED REACTIONS FROM TRAILBLAZER-ALZ & TRAILBLAZER-ALZ 2. P. Ardayfio[1], G. Mullins[1], J. Zimmer[1], C. Evans[1], G. Anglin[1], I. Gueorguieva[1], E. Nery[1], H. Wang[1], R. Khanna[1], D. Brooks[1], J. Sims[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Background: Donanemab (LY3002813) is an immunoglobulin G1 antibody developed to facilitate removal of existing brain amyloid plaques in individuals with Alzheimer's disease. The current analysis characterizes infusion-related reactions (IRRs) across two pivotal clinical trials of donanemab. **Methods:** Data were collected from two multicenter, randomized, double-blind, placebo-controlled Phase 2 & 3 studies of donanemab in participants with early symptomatic Alzheimer's disease (TRAILBLAZER-ALZ, NCT03367403 & TRAILBLAZER-ALZ 2, NCT04437511). Participants received donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo infusions intravenously Q4W for up to 72 weeks. Data were summarized by treatment arm using descriptive statistics. **Results:** A total of 984 participants received donanemab, and 999 participants received placebo. In the donanemab arms, 84 (8.5%) participants experienced IRRs while on treatment; 4 (0.4%) participants in the placebo arm had an IRR. Most IRRs occurring on the day of infusion in the donanemab arm were mild. Six (0.6%) serious hypersensitivity events (including IRRs) were reported in the donanemab arm. The majority (92.1%) of events occurred during or within 30 minutes of the infusion and >70% of first IRRs occurred by the fourth infusion; the majority of immediate hypersensitivity events (including IRRs) resolved within 24 hours. The most common IRR symptoms reported in donanemab-treated participants on the day of infusion were erythema (4.7%), chills (4.0%), nausea/vomiting (4.0%), sweating (2.3%), and difficulty breathing/dyspnea (2.1%). The frequency of non-immediate hypersensitivity was similar in the donanemab (5.2%) and placebo (5.2%) arms. The frequency of IRRs on first rechallenge was similar among participants who received prophylaxis medication versus those who did not. Of 922 evaluable donanemab-treated participants, 812 (88.1%) were treatment-emergent (TE) anti-drug antibody (ADA)-positive. Nearly all (97.6%) donanemab-treated participants reporting IRRs were TE ADA-positive. Of the 82 participants reporting IRRs on the day of infusion, 46 (56.1%) had maximum ADA titers in the upper titer group, 25 (30.5%) were in the middle titer group, and 11 (13.4%) were in the lower titer group. However, 67% of participants in the upper titer group did not report an IRR. All 3 participants with reported anaphylaxis were TE ADA-positive; 2 had titers in the upper group, and 1 had titer in the middle group. **Conclusions:** In the Phase 2 & 3 placebo-controlled TRAILBLAZER-ALZ trials, the majority of IRRs among donanemab-treated participants were mild in severity, although serious IRRs and anaphylaxis have been reported. The majority of IRRs occurred during or within 30 minutes of infusion, and while prophylactic medication was commonly used to reduce the risk of an IRR on rechallenge, the frequency of IRRs with and without this intervention was similar. Nearly all participants reporting IRRs were TE ADA positive. However, the majority of both TE ADA-positive participants and participants in the upper ADA titer group did not experience IRRs.

LP030- CEREBRAL AMYLOID ANGIOPATHY AND COMORBID CARDIOVASCULAR RISK FACTORS IN APOE4/4 HOMOZYGOTES WITH EARLY ALZHEIMER'S DISEASE: BASELINE RESULTS FROM APOLLOE4 PHASE 3 TRIAL OF ORAL ANTI-AMYLOID AGENT ALZ-801. R. Mclaine[1], E. Liang[1], S. Abushakra[1], D. Watson[2], M. Boada[3], S. Cohen[4], M. Sabbagh[5], A. Power[1], S. Flint[1], W. Pak[1], J. Hey[1], M. Tolar[1] *(1. Alzheon, Inc. - Framingham (United States), 2. Alzheimer's Research and Treatment Center - Wellington (United States), 3. Ace Alzheimer's Center - Barcelona (Spain), 4. Toronto Memory Program - Toronto (Canada), 5. Barrow Neurolgical Institute - Phoenix (United States))*

Background: The APOE4 genotype is a major risk factor for Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA) with a gene-dose effect. High vascular amyloid burden

in APOE4 carriers increases the risk of amyloid related imaging abnormalities (ARIA) with amyloid antibodies, likely due to microglia-induced vascular inflammation leading to edema, microhemorrhages, lobar macrohemorrhages, and cortical superficial siderosis, with APOE4/4 patients exhibiting highest risk. APOE4 carriers are also at increased risk of hyperlipidemia, atherosclerosis, and cardiovascular disease (CVD). The prevalence of CVD or CV risk factors in APOE4/4 AD patients, who are at highest risk of ARIA, has not been reported. We analyzed the prevalence of hypertension, hyperlipidemia, obesity, and type 2 diabetes in APOE4/4 homozygotes enrolled in an ongoing Phase 3 clinical trial of ALZ-801, an oral brain-penetrant inhibitor of amyloid oligomer formation (Abushakra 2017, Kocis 2017, Hey 2018). **Methods:** The Phase 3 trial (APOLLOE4, NCT04770220) enrolled 325 APOE4/4 homozygotes, ages 50-80 years with Early AD (MMSE ≥22). A total of 313 subjects underwent baseline MRIs with 1.5/3T scanners with central CAA and white matter disease (WMD) evaluations. Subjects with any number of lobar microhemorrhages (MH) were enrolled, but subjects with ARIA-E and using anti-coagulants were excluded. Subjects with or without CAA lesions (>4 MH, any siderosis, any macrohemorrhage) were compared for presence of CV risk factors and use of anti-hypertensives, statins, and acetylsalicylic acid (ASA) or other anti-platelet agents. **Results:** The overall study population was 51% female, with mean age 69 years, MMSE 26, 65% with MCI and 82% were white subjects. The CAA and non-CAA groups included 47 subjects (15%) and 266 subjects (85%) respectively. The CAA group, compared to non-CAA group, was mostly male (70% vs 45%), older (mean age 71 vs. 68 years, p=0.004), had lower MMSE (25 vs 26, p=0.018), higher CDR-G =1 (26% vs. 14%, p=0.051), higher ADAS-cog (27 vs. 23, p=0.002), and more severe deep and periventricular WMD (p=0.015; p=0.054). The two groups had similar hypertension (38% vs. 39%), diabetes (11% vs. 8%) and obesity (9% vs. 5%) prevalence. However, the CAA group had higher prevalence of coronary artery disease (CAD, 17% vs. 8%, p=0.049) and ASA or anti-platelet agents use (38% vs 22%, p= 0.026). Hyperlipidemia prevalence was numerically higher (53% vs. 41%, p= 0.15), while statin use was similar (43% vs. 41%). Anticoagulants were not allowed. **Conclusion:** ALZ-801, an oral anti-oligomer agent in late-stage development has not shown increased ARIA in prior studies, allowing inclusion rates of APOE4/4 patients with higher CAA burden in its Phase 3 pivotal trial (APOLLOE4). In this trial, APOE4/4 subjects with CAA lesions were mostly males who were slightly older with more advanced AD than non-CAA subjects. They also show higher rates of hyperlipidemia, CAD and use of ASA/antiplatelets. The higher prevalence of CV disease and antiplatelets agent use may further increase the risk of hemorrhagic ARIA complications in patients treated with anti-amyloid antibodies in clinical practice settings. Therefore, APOE4/4 homozygotes, and possibly heterozygotes with CAA require heightened vigilance when considering anti-amyloid antibody treatment. **Key words:** Cerebral amyloid angiopathy, ARIA, Cardiovascular risk factors, APOE4, homozygotes, microhemorrhage, siderosis, ALZ-801, amyloid oligomers. **Clinical Trial Registry:** NCT04770220; https://clinicaltrials.gov. **Data Deposition:** N/A. **Disclosures:** RM/EL/SA/AP/SF/WP/JH/MT are employees of Alzheon Inc. DW/MB/SC are investigators in the Phase 3 trial, MS is a consultant and advisor for Alzheon, Inc.

LP031- ACI-35.030 ANTI-PHOSPHO-TAU ACTIVE IMMUNOTHERAPY FOR THE TREATMENT OF EARLY ALZHEIMER'S DISEASE (AD): UPDATE FROM THE PHASE 1B/2A STUDY DATA AND PERSPECTIVES.

O. Sol[1], J. Streffer[2], J. Mermoud[1], M. Vukicevic[1], E. Gollwitzer[1], D. Hickman[1], V. Hliva[1], J. Gray[1], L. Steukers[3], L. Li[4], A. Pfeifer[1], M. Kosco-Vilbois[1], P. Scheltens[5] *(1. AC Immune SA - Lausanne (Switzerland), 2. University of Antwerp - Antwerp (Belgium), 3. Janssen - Beerse (Belgium), 4. Janssen - New Jersey (United States), 5. Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, VUmc - Amsterdam (Netherlands))*

Background: Two active immunotherapies, ACI-35.030 (liposomal formulation) and JACI-35.054 (conjugated formulation), targeting phosphorylated-Tau (pTau) are currently being tested in a Phase 1b/2a clinical trial (NCT04445831) to evaluate the safety, tolerability and immunogenicity of different doses of these clinical candidates. Following data presented at CTAD in 2022, confirming the excellent antibody response profile of ACI-35.030, including maturation of the patient's antibodies towards pathological Tau, this candidate was selected for further development in collaboration with Janssen Pharmaceuticals, Inc. (Janssen). The latest interim data from the blinded study will be presented. **Methods:** This multicenter, double-blind, randomized, placebo-controlled study is being conducted in Europe and has successfully completed the treatment phase. The primary and secondary objectives are safety, tolerability, and immunogenicity of different doses of the two active immunotherapies in 50-75-year-old participants with early AD (MCI due to AD or mild AD dementia). The active and placebo are randomized as 3:1 ratio in each cohort and administered at weeks 0, 8, 24 and 48. Participants are then followed for a further 26-week post-injection period. **Results:** A total of 57 participants were randomized in the study: 41 participants received any one of the three doses of ACI-35.030 or placebo, and 16 participants received either one of the two doses of JACI-35.054 or placebo. Up to the time of submission, the retention rate in the study was >90%. Both active immunotherapies were generally safe and well tolerated at all tested doses. Most adverse events were of mild intensity and none of the withdrawals was related to safety events. Previous interim data for ACI-35.030 demonstrated an early and high responder rate and a strong, boostable and durable IgG antibody response specific for pathological forms of Tau such as pTau and enriched paired helical filaments (ePHF). Furthermore, based on epitope mapping, the antibodies demonstrated a broad coverage of the immunogenic peptide. Compared to ACI-35.030, JACI-35.054 showed good, although lower, responder rates with a kinetic profile showing a delayed onset of antibody response. The antibody titers exhibited generally a higher variability, a lower specificity for pathological Tau species and a preference for only the C-terminal of the immunogenic peptide. Additional updated study-related data will be presented during the conference. **Conclusion:** In general, the liposome-based active immunotherapy ACI-35.030 showed a better antibody profile in terms of rapid response, higher responder rate, homogeneity of the antibody response across study participants, epitope coverage and evidence of antibody maturation towards pathologic forms of Tau. ACI-35.030 has been selected to move into the next stage of clinical development in preclinical AD.

LP033- ACU193-SABO COMPLEX MEASUREMENT IN CSF: ADDITIONAL ANALYSES USING A SENSITIVE ASSAY OF TARGET ENGAGEMENT FOR THE SABO-SELECTIVE ANTIBODY ACU193 IN INTERCEPT-AD. E. Cline[1], J. Moore[1], H. Zhang[1], G. Sethuraman[1], E. Siemers[1], R. Dean[1], J. Jerecic[1] *(1. Acumen Pharmaceuticals - Charlottesville (United States))*

Background: ACU193 is a humanized monoclonal antibody selective for soluble amyloid β oligomers (sAβOs), which have been shown in numerous cellular and animal models, as well as human tissues, to accumulate early in the pathogenesis of Alzheimer's disease (AD) and trigger many facets of AD neuropathology and cognitive decline [1]. The ability of ACU193 to engage its intended sAβO target in the central nervous system was recently tested in the INTERCEPT-AD phase 1 study in mild cognitive impairment or mild dementia due to AD (NCT04931459). Initial analysis revealed a dose-dependent target engagement for ACU193 that approached maximal engagement at the highest doses administered [2]. Here, we will present additional analyses of the target engagement data from the INTERCEPT-AD study. **Methods:** INTERCEPT-AD was a phase 1, randomized, placebo-controlled study with two parts. Part A was a single ascending dose study of four cohorts randomized in a 6:2 ratio to ACU193 (2, 10, 25, 60 mg/kg) or placebo. Part B was a multiple ascending dose study including three administrations of ACU193 to three cohorts randomized in an 8:2 ratio to ACU193 (10 or 60 mg/kg Q4W, 25 mg/kg Q2W) or placebo. To assess target engagement, the complex of ACU193 and sAβOs was measured in cerebrospinal fluid (CSF) on the MSD S-PLEX immunoassay platform from two CSF samples per participant, collected at baseline and 5-37 days after the last dose. ACU193-sAβO complex levels were assessed for correlation to dose and various demographic, pharmacokinetic, and pharmacodynamic parameters. **Results:** Measurement of the ACU193-sAβO complex in CSF was found to be dependent on the administration of ACU193, i.e., the target engagement assay did not yield a measurable signal at baseline or in the CSF of placebo-treated participants. Comparing post-dose CSF samples over the entire trial population, ACU193-sAβO complex levels were observed to decrease over time from the last dose, with the highest complex levels measured within 11 days of dosing. In addition, ACU193-sAβO complex levels were observed to increase with increased reduction in amyloid plaque. No correlation was observed with complex measured after dosing and baseline plaque. Neither APOE4 genotype, ARIA incidence, nor gender impacted ACU193-AβO complex levels with statistical significance. **Conclusions:** Measurement of ACU193-AβO complex in CSF provided a practical approach for measuring central target engagement of the sAβO-selective antibody ACU193. This is evidenced by the dose-dependence of the complex levels, indicating clearance of the complex from the brain into the CSF. The correlation between complex levels and CSF sampling time demonstrates that CSF samples within 11 days of dosing provide optimal target engagement signal in this study design; however, this will need to be reassessed for longer studies. Increased target engagement with increased plaque reduction suggests a relationship between ACU193 removal of AβO from the brain and plaque reduction. However, comparison of ACU193-AβO complex levels and magnitude of plaque reduction show that the former is a more sensitive measure of target engagement for ACU193. **Key words:** soluble amyloid β oligomers, dose-dependent target engagement, Alzheimer's disease. **Clinical Trial Registry:** NCT04931459; https://www.clinicaltrials.gov. **Disclosures:** ENC, HZ, SG, ES, & JJ are employees and shareholders in Acumen Pharmaceuticals, Inc. JM & RAD are consultants and shareholders in Acumen Pharmaceuticals, Inc. **References:** 1. Cline EN, Bicca MA, Viola KL, Klein WL. The Amyloid-beta Oligomer Hypothesis: Beginning of the Third Decade. J Alzheimers Dis. 2018;64(s1):S567-S61. 2. Siemers ER, Feaster HT, Skljarevski V, Sundell K, Sethuraman G et al. (2023, July 16-20). A Phase I Trial of Oligomer Targeting ACU193 in Early Alzheimer's Disease. Developing Topics platform presentation at Alzheimer's Association International Conference, Amsterdam, Netherlands.

LP034- INTERCEPT-AD: ACU193 CSF PHARMACOKINETICS IN EARLY ALZHEIMER'S DISEASE. H. Zhang[1], J. Moore[1,2], E. Cline[1], M. Rafizadeh[1], E. Siemers[1], R. Dean[1,3], J. Jerecic[1] *(1. Acumen Pharmaceuticals - Charlottesville (United States), 2. Pacific BioDevelopment - Davis (United States), 3. Department of Pathology & Laboratory Medicine, Indiana University School of Medicine - Indianapolis (United States))*

Background: Amyloid beta (Aβ) accumulation in the brain plays a major role in Alzheimer's disease (AD) pathogenesis. Five dominant pools of Aβ species exist in AD brain: soluble Aβ monomers, soluble oligomers (sAβOs) and protofibrils, as wells as insoluble fibrils and amyloid plaques.1 Numerous studies suggest that sAβOs are the most toxic Aβ species, contributing to initiation and progression of AD.2 ACU193 is a humanized, affinity matured, IgG2 subclass monoclonal antibody with high selectivity for sAβOs. A multi-center, randomized, placebo-controlled, double-blind, single- and multiple-dose phase 1 study INTERCEPT-AD (NCT04931459) investigated the safety, tolerability, and pharmacokinetics (PK) of intravenous ACU193 in individuals with early AD (mild cognitive impairment or mild dementia due to AD). We report here the ACU193 PK in cerebrospinal fluid (CSF) and its correlation with serum PK and amyloid plaque reduction. **Methods:** Sixty-two participants with early AD were enrolled into one of seven cohorts: either single ascending dose (SAD; 2, 10, 25, or 60 mg/kg) or multiple ascending dose (MAD; 10 or 60 mg/kg every four weeks [Q4W] or 25 mg/kg every two weeks [Q2W] for a total of three infusions). CSF samples were collected at baseline and 5 to 37 days post the last dose. CSF ACU193 concentrations were measured by the Meso Scale Diagnostics (MSD) laboratory using an S-PLEX immunoassay that measures both bound and unbound (free) ACU193 (i.e., total drug). Serum ACU193 concentrations were determined by an electrochemiluminescence (ECL) immunoassay that measures only the unbound form of ACU193 (i.e., free drug) with Aβ-derived diffusible ligands (ADDLs; i.e., synthetic sAβOs) as capture. CSF ACU193 concentrations were correlated with serum ACU193 concentrations for matched visits for each participant. Correlation of ACU193 CSF PK with dose regimen, CSF sampling time, and change in amyloid plaque load in the brain was also assessed. **Results:** Measurable exposures of ACU193 were detected in CSF and increased in a dose-related manner following single and multiple dose administration. There was a modest correlation between 'total' CSF ACU193 concentrations and 'free' serum ACU193 concentrations for both SAD and MAD regimens. A negative correlation was shown between CSF ACU193 concentration and CSF sampling time post last dose. Amyloid plaque burden (Δ centiloids) decreased with increasing CSF ACU193 concentrations in multiple dose groups. **Conclusions:** An ultra-sensitive CSF-PK assay was utilized to analyze ACU193 drug concentrations in the central nervous system of participants in the INTERCEPT-AD trial.

ACU193 penetrated the blood brain barrier and was measured in the CSF. Results of the analysis indicate that ACU193 CSF PK is characterized by dose-proportional exposure in both SAD and MAD cohorts. A decrease in CSF ACU193 concentration over time demonstrated the clearance of ACU193 from the central nervous system. A trend towards correlation between CSF drug exposure level and change in amyloid plaque burden was observed in this small study. Further investigation of this finding will be explored in future studies. **Key words:** phase 1, amyloid β oligomers, dose-proportional drug exposure. **Clinical Trial Registry:** NCT04931459. **Disclosures:** HZ, ENC, MR, ES, & JJ are employees and shareholders at Acumen Pharmaceuticals, Inc. JAM and RAD are consultants for and shareholders at Acumen Pharmaceuticals, Inc. **References:** 1. Siemers, E., Hitchcock, J., Sundell, K. et al. ACU193, a Monoclonal Antibody that Selectively Binds Soluble Aβ Oligomers: Development Rationale, Phase 1 Trial Design, and Clinical Development Plan. J Prev Alzheimer's Dis (2022). 2. Viola, K.L., Klein, W.L. Amyloid β oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis. Acta Neuropathol 129, 183–206 (2015).

CLINICAL TRIALS: IMAGING

P046- BRAIN STRUCTURE-ALLELIC ASSOCIATIONS AND NETWORKS IN ALZHEIMER'S DISEASE.

S.M. Moon[1] *(1 Konkuk University Chungju Hospital- Chungju (Korea, Republic of))*

Background: Alzheimer's disease (AD), the most prevalent form of dementia, affects 6.5 million Americans and over 50 million people globally. Clinical, genetic, and phenotypic studies of dementia provide some insights of the observed progressive neurodegenerative processes, however, the mechanisms underlying AD onset remain enigmatic. This paper examines late-onset dementia-related cognitive impairment utilizing neuroimaging-genetics biomarker associations. **Methods:** The participants, ages 65 to 85, included 266 healthy controls (HC), 572 volunteers with mild cognitive impairment (MCI), and 188 AD dementia patients. All the ADNI participants included in this study were those with a baseline MMSE score of 20-30, and available genetic and imaging data. The 1,026 ADNI participants included: 266 HC's (CDR=0, Male:138, Female:128), 572 MCI's (CDR=0.5, Male:227, Female:245), and 188 AD dementia patients (CDR=0.5/1, Male:102, Female:86). Subjects with AD dementia were probable AD dementia according to the NIA-AA diagnostic criteria for AD. Genotype dosage data for AD-associated single nucleotide polymorphisms (SNPs) were extracted from the imputed ADNI genetics archive using sample-major additive coding. Such 29 SNPs were selected, representing a subset of independent SNPs reported to be highly associated with AD in a recent AD meta-GWAS study by Jansen and colleagues. Using multinominal linear modeling of diagnosis, we studied the associations between the three individual cohorts (HC, MCI and AD dementia). The differences of the 200 NIMs and 29 SNPs between HC, MCI, and AD dementia cohorts. The results of a 3-way ANOVA (ROI, Dx, SNP) may be less interpretable compared to a multinomial linear modeling (Outcome = Dx). We computed the odd ratios (ORs) and relative risks (RRs) for AD and MCI, relative to HC. The MCI and AD effects quantified the metrics «relative to HC». These represent extensions the binary outcome in logistic regression, but reflect 3 categorical outcomes (HC, MCI, AD), which may also be analyzed via more general multi-nominal linear modeling. **Results:** We identified the significant correlations between the 29 genomic markers (GMs) and the 200 neuroimaging markers (NIMs). The ORs and RRs for AD and MCI (relative to HC) were predicted using multinomial linear models. **Conclusions:** In the HC and MCI cohorts, mainly cortical thickness measures were associated with GMs, whereas the AD cohort exhibited different GM-NIM relations. Network patterns within the HC and AD groups were distinct in cortical thickness, volume, and proportion of White to Gray Matter (pct), but not in the MCI cohort. **Key words:** ADNI, Alzheimer's disease, mild cognitive impairment, neuroimaging, networking, genetics. **References:** 1. Moon S, Dinov ID, Hobel S, et al. Structural brain changes in earlyonset Alzheimer's disease subjects using the LONI pipeline environment. J Neuroimaging. 2015;25(5):728-737. 2. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide metaanalysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat Genet. 2019;51(3):404-413. 3; Misra A, Chakrabarti SS, Gambhir IS. New genetic players in lateonset Alzheimer's disease: findings of genome-wide association studies. Indian J Med Res. 2018;148(2):135-144. 4. Shi G, Shen Z, Liu Y, Yin W. Identifying biomarkers to predict the progression and prognosis of breast cancer by weighted gene coexpression network analysis. Front Genet. 2020;11:597888.

P047- IMPACT OF ANODAL TRANSCRANIAL DIRECT CURRENT STIMULATION ON WHITE MATTER MICROSTRUCTURE INTEGRITY IN MILD COGNITIVE IMPAIRMENT PATIENTS ACCORDING TO EFFECT MODIFIERS AS RISK FACTORS FOR ALZHEIMER'S DISEASE.

D.W. Kang[1] *(1. Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of))*

Background: Little research exists on how individual risk factors for Alzheimer's disease (AD) affect the intermediate phenotype after transcranial direct current stimulation (tDCS), despite the importance of precision medicine-based therapeutic approaches. **Objective:** To determine how an application of sequential anodal tDCS (2 mA/day, left dorsolateral prefrontal cortex, 10 sessions) affects changes in white matter (WM) microstructure integrity in 63 mild cognitive impairment (MCI) patients with effect modifiers such as Aβ deposition, APOE ε4 carrier status, BDNF Val66Met polymorphism status, and sex. **Methods:** We examined individual effect modifier-by-tDCS interactions and multiple effect modifiers-by-tDCS interactions for diffusion metrics. We also evaluated the association between baseline Aβ deposition and changes in WM microstructure integrity following anodal tDCS. **Results:** We found that APOE ε4 carrier status and sex had a significant interaction with anodal tDCS, resulting in increased fractional anisotropy (FA) in the right uncinate fasciculus (UF) after stimulation. Additionally, we observed multiple effect modifiers-by-tDCS interactions on WM integrity of the right UF, leading to a more pronounced increase in FA values in APOE ε4 carriers and females with Val66 homozygotes. Finally, baseline Aβ deposition was positively associated with a difference in FA of the left cingulum in the hippocampal area, which showed a positive association with the changes in the score for delayed memory. **Conclusion:** Our study shows the differential impact of individual AD risk factors on changes in the early intermediate phenotype after sequential anodal tDCS in MCI patients. This research emphasizes the importance of precision medicine approaches in tDCS for the prodromal stages of AD.

P048- MEASURING CHANGES IN LONGITUDINAL TAU-PET WITH [18F]MK-6240: GROUP-LEVEL VS INDIVIDUALIZED ROIS DEFINITION. N. Sidorenko[1], M. Tonietto[1], A. Leuzy[2], G. Klein[1] *(1. Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd - Basel (Switzerland), 2. Clinical Memory Research Unit, Department of Clinical Sciences, Lund University - Malmö (Sweden))*

Background: Tau-PET is being increasingly used as a biomarker in Alzheimer disease (AD) clinical trials. Longitudinal changes in tau burden are commonly assessed using the same group-level regions of interest (ROIs) for each participant in the trial, which provides a useful and yet suboptimal method to assess disease progression. Alternatively, defining the ROIs separately for each patient accounts for individual differences and may result in a more sensitive estimation of longitudinal changes in tau [1]. The latter approach has been recently validated for two tracers: [18F]RO948 and [18F]flortaucipir [2]. Here, we tested this method using [18F]MK-6240. **Methods:** First, we used of the data from 883 participants from five research sites of the Cerveau MK-6240 User Group dataset, who had a valid baseline PET scan. The [18F]MK-6240 standardized uptake value ratio (SUVR) was calculated at 90-110 min after tracer injection. The calculation was performed in all cortical ROIs (averaged across hemispheres and subsequently grouped into six Braak ROIs) delineated by FreeSurfer v.6 with the inferior cerebellar cortex as reference region [3,4]. We ran a series of Gaussian-mixture models on SUVRs from each ROI to establish a threshold discriminating between individual probabilities of having normal/abnormal tau-PET. For further analyses, we focused on a subset of participants with a follow-up Tau-PET scan acquired at least 6 months after the first visit. The set comprised 53 amyloid-β (Aβ)+ cognitively unimpaired (CU) individuals and 25 Aβ+ cognitively impaired (CI) individuals with MCI or AD dementia. Group-level ROI definition relied on the conventionally defined Braak ROIs. The individualized approach consisted in using identified thresholds to determine which Braak ROI was the latest affected (i.e., exceeded the threshold) for each participant. This ROI was used for estimating longitudinal tau changes for that participant. Accordingly, we calculated individual annual changes in SUVR [(SUVRFollow-up – SUVRBaseline)/Time] in both group-level and individualized ROIs, which we then converted into Cohen's d for further between-group comparison. **Results:** Cohen's d calculated for individually defined best performing ROIsm were numerically higher than those for Braak ROIs in both Aβ+CU and Aβ+CI: Aβ+ CU: Individually defined high-tau stage: Cohen's d = 0.49, 95%CI = [0.26, 0.75]. Group-level Braak stage with highest effect size (Braak I): Cohen's d = 0.4, 95%CI = [0.13, 0.49]. Sample size reduction assuming a 30% intervention effect = 35%. Aβ+ CI: Individually defined high-tau stage: Cohen's d = 0.76, 95%CI = [0.32, 1.19]. Group-level Braak stage with highest effect size (Braak VI): Cohen's d = 0.63, 95%CI = [0.21, 0.91]. Sample size reduction assuming a 30% intervention effect = 33%. **Conclusion:** Our results dovetail previous reports that the use of individualized ROIs enhances analytical sensitivity to longitudinal changes in tau, which allows for a better detection of putative treatment effects and thereby represents an asset for future clinical trials involving [18F]MK-6240. **Key words:** tau-PET, Alzheimer disease, biomarkers, precision medicine. **Clinical Trial Registry:** NA. Data. **Deposition:** NA. **Author disclosures:** Nick Sidorenko is an employee of F. Hoffmann-La Roche Ltd. Matteo Tonietto is an employee of F. Hoffmann-La Roche Ltd. Antoine Leuzy is a consultant for Enigma Biomedical USA. Gregory Klein is an employee of F. Hoffmann-La Roche Ltd. **Conflict of interests:** The authors declared no competing interests. **Acknowledgements:** we would like to kindly thank University of Wisconsin-Madison, Massachusetts General Hospital, Biogen Inc, Austin Health and the AIBL Study of Aging, and Columbia University Irving Medical Center for providing the data for this study. **References:** 1. Ossenkoppele R, van der Kant R, Hansson O. The Lancet Neurology. doi:/10.1016/S1474-4422(22)00168-5. 2. Leuzy A, Binette AP, Vogel JW, et al. JAMA Neurol. doi:10.1001/jamaneurol.2023.1067. 3. Cho H, Choi JY, Hwang MS, Kim YJ, Lee HM, Lee HS, Lee JH, Ryu YH, Lee MS, Lyoo CH. Annals of neurology. 2016 Aug;80(2):247-58. doi:/10.1002/ana.24711. 4. Diedrichsen J. Neuroimage. 2006 Oct 15;33(1):127-38. doi:/10.1016/j.neuroimage.2006.05.056

P049- REGIONAL AB-TAU INTERACTIONS CAN PREDICT INDIVIDUAL-LEVEL TIME PERIODS OF THE OPTIMAL THERAPEUTIC WINDOW FOR AMYLOID-LOWERING TREATMENTS. G. Lim[1], H. Cho[2], C.H. Lyoo[2], J.K. Seong[1,3,4,5], W.J. Lee[1], A.D.N.I. Alzheimer's Disease Neuroimaging Initiative[6] *(1. NeuroXT - Seoul (Korea, Republic of), 2. Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine - Seoul (Korea, Republic of), 3. School of Biomedical Engineering, Korea University - Seoul (Korea, Republic of), 4. Department of Artificial Intelligence, Korea University - Seoul (Korea, Republic of), 5. Interdisciplinary Program in Precision Public Health, Korea University - Seoul (Korea, Republic of), 6. Alzheimer's Disease Neuroimaging Initiative - Los Angeles (United States))*

Background: The intricate relationship between amyloid-beta (Aβ) and tau has fueled extensive efforts to understand Alzheimer's disease (AD) pathogenesis and increase efficacy of disease-modifying treatments. We have previously shown1 that Aβ and tau interact via two key mechanisms to promote tau spreading and suggested stratifying subjects into the following groups: (1) "latent tau," for subjects yet to undergo remote Aβ-tau interaction in the entorhinal cortex, (2) "spreading tau," for subjects who have undergone remote interaction but not local Aβ-tau interaction in the inferior temporal gyrus, and (3) "propagating tau," for subjects who have undergone accelerated tau propagation. An outstanding question is determining how long the optimal therapeutic window is at an individual level by predicting their disease progression speed. **Methods:** We used longitudinal data to investigate differences in temporal sequences2 of disease progression among subjects with different Aβ-tau interaction scores. Our study includes 257 subjects from the Gangnam Severance Hospital (GS / CN: 74, MCI: 41, AD: 30) and the Alzheimer's Disease Neuroimaging Initiative (ADNI / CN: 72, MCI: 32, AD: 8) with longitudinal Aβ (GS: 18F-florbetaben, ADNI: 18F-florbetapir) and tau (18F-flortaucipir) PET data. We first converted regional SUVR data to W-scores with reference to baseline data from healthy subjects and with age, sex, and education as covariates. After classifying subjects into aforementioned groups, we fitted restricted cubic spline models to find annual rates of tau accumulation and cognitive decline as functions of baseline levels. We then integrated model equations using modified Euler's method, with initial conditions at time 0 anchored to the average of values corresponding to the lower quartile, to obtain predicted trajectories as functions of time. **Results:** Predicted tau trajectories suggest that baseline Aβ-tau interaction can indicate future tau accumulation speed. Specifically, global cortical tau level of subjects in latent and spreading groups

do not exceed a W-score of 2.5 ("tau-positive"), while subjects in the propagating group take 2.5 years upon crossing into the propagating group to become tau-positive. This trend is consistent with predicted cognition: regardless of initial scores, subjects with greater Aβ-tau interaction experience faster cognitive decline. Critically, subjects in the spreading group take about 2.9 years on average to cross into the propagating group, which implicates that the efficacy of amyloid-lowering treatments may drop drastically after 2.9 years, even for those within the therapeutic window. Interestingly, for subjects in the spreading group, regions corresponding to Braak's stages III-IV become tau-positive in 4.4 years, but neither the global cortex nor regions corresponding to stages V-VI become tau-positive. Meanwhile, for subjects in the propagating group, regions corresponding to Braak's stages III-IV and V-VI become tau-positive in 0.6 and 2.8 years, respectively. **Conclusions:** Our findings demonstrate that subject stratification based on current Aβ-tau interaction can differentiate the speed of future tau spreading and cognitive decline. These temporal trajectories help identify the time it takes for an individual to reach the next stage in the AD progression model, thereby confirming the possibilities of using cross-sectional PET scans to predict an individual's disease progression speed and the critical period for efficacious amyloid-lowering treatments. **Key words:** Alzheimer's disease, amyloid-beta, tau, therapeutic window. **Disclosures:** The authors declare no conflicts of interests. **References:** 1. Lee WJ, Brown JA, Kim HR, et al. Regional Aβ-tau interactions promote onset and acceleration of Alzheimer's disease tau spreading. Neuron 2022; 110: 1932–1943.e1–e5. https://doi.org/10.1016/j.neuron.2022.03.034. 2. Baek MS, Cho H, Lee HS, et al. Temporal trajectories of in vivo tau and amyloid-β accumulation in Alzheimer's disease. Eur J Nucl Med Mol Imaging 2020; 47: 2879–2886. https://doi.org/10.1007/s00259-020-04773-3

P050- UTILITY OF [18F]PI-2620 PET IN CLINICAL TRIALS: INSIGHTS INTO TAU PATHOLOGY DEPOSITION IN DOWN SYNDROME. I. Barroeta[1], J. Pegueroles[1], V. Montal[1], M. Rozalem[1], A. Morcillo[1], S. Zsadanyi[1], L. Vaque[1], B. Benejam[1], L. Videla[1], M. Carmona-Iraqui[1], A. Bejanin[1], V. Camacho[2], A. Flotats[2], A. Lleo[1], J. Fortea[1] *(1. Unidad de Memoria, Servicio de Neurología, Institut d'Investigacions Biomèdiques Sant Pau, Hospital de la Santa Creu i Sant Pau. Universitat Autònoma de Barcelona, Barcelona - Barcelona (Spain), 2. Nuclear Medicine Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain - Barcelona (Spain))*

Background: People with Down syndrome (DS), a form of genetically determined AD, are a unique population for clinical trials. This study aimed to evaluate the utility of the second-generation PET Tau tracer [18F]PI-2620 to assess the neurofibrillary tau burden in adults with DS and its relationship with amyloid PET. **Methods:** A total of 48 subjects, including cognitively unimpaired euploid individuals (n=18), asymptomatic DS (n=18), DS with prodromal AD (n=4), and DS with AD dementia (n=8), were enrolled in the study. All subjects underwent dynamic [18F]PI-2620 PET/CT, [18F] Flutemetamol PET/CT, and 3T brain MRI scans. PET scans were co-registered with T1 MR images and intensity normalized. Tau deposition was quantified in specific regions corresponding to Braak stages I-II, III-IV, and V-VI. Differences between clinical diagnoses were assessed using ANOVA, and the relationship between amyloid and tau burden was analyzed through vertex-wise analysis. **Results:** The observed pattern of tau deposition in symptomatic individuals with DS demonstrated the typical AD distribution, including the temporal lobe and precuneus. Significant differences in [18F]PI-2620 uptake were detected along the DS continuum, particularly between the asymptomatic group and those with AD dementia. Vertex-wise regression analysis revealed a direct relationship between tau burden and global amyloid deposition, with specific involvement in typical AD regions. The progressive increase in tau PET deposition following Braak staging, as measured by [18F]PI-2620, in the DS AD continuum was only evident in subjects with high amyloid burden. **Conclusion:** [18F]PI-2620 PET exhibited high affinity for tau aggregates in symptomatic individuals with DS, mirroring the deposition patterns observed in sporadic AD. The use of this tracer can potentially contribute to monitoring of treatment efficacy in DS (and AD) populations. **Disclosures:** No conflict of interest

P051- AUTOMATED BRAIN MRI SEGMENTATION USING A NOVEL AI-BASED METHOD. T. Cajgfinger[1], J. Schaerer[1], P.H. Chen[2], C. Conklin[3], M. Ingalhalikar[3], D. Scott[4], J. Suhy[4], L. Bracoud[1] *(1. Clario - Lyon (France), 2. Clario - Estenfeld (Germany), 3. Clario - Philadelphia (United States), 4. Clario - San Mateo (United States))*

Background: Brain segmentation is a cornerstone of most quantitative brain MRI analyses, as it not only offers a means to measure the volume of various brain structures, but also enables regional quantification of other imaging techniques such as PET, DTI, or fMRI. Numerous automated methods were developed in the past decades, based on classic approaches combining MRI signal itself, a-priori knowledge, and atlases. Lately, AI-based methods have gained popularity and exceeded performance of classic techniques, for various image processing tasks. We developed a novel method, trained using FreeSurfer [1, 2 segmentation results, to segment the same structures from T1-weighted MRI images. **Methods:** The method consists of several pre-processing steps, including bias field correction, registration to MNI space and skull stripping [3]. A 3D U-shape Nested transformer-based segmentation model is then employed to perform the actual segmentation. The model was implemented using MONAI [4, 5] (Medical Open Network for Artificial Intelligence), including data augmentation, and trained on random 3D patches (96×96×96). For training/validation, 4315/1445 scans were selected from ADNI, from 1413/354 individual subjects including 336/92 normal controls (CN), 160/42 subjective memory complaints (SMC), 254/68 early MCI (EMCI), 424/101 late MCI (LMCI), and 239/51 AD. Performance was assessed via visual assessment, numerical comparison to FreeSurfer, test/re-test, using 396 datasets from ADNI-2, ROC analysis to separate CN, LMCI and AD subjects, cross-sectional comparison across visits fitting linear regression models, and assessing impact on atrophy using Tensor-Based Morphometry [6]. Results: The proposed method succeeded in all scans selected. Average run-time was 2 minutes (compared to 8 hours for FreeSurfer, with a 3.9% failure rate). We visually inspected 50 cases including all cases with >5% difference in brain volume between methods. Overall, segmentations appear smoother than those from FreeSurfer. The new method also appeared more reliable, as all outliers were cases where FreeSurfer missed significant portions of the brain. When comparing results with FreeSurfer numerically, an average Dice coefficient of 85% was found for all brain structures, with a strong correlation between volumes (r>0.94). The new method showed much improved test/re-test performance compared to FreeSurfer. In particular, for the whole brain, the mean absolute difference decreased from 8893

mm3 (SD=13038 mm3) to 4511 (SD=4442 mm3). Frequency of outliers, defined as cases with an absolute difference in whole brain volume >20000 mm3, strongly reduced from 6.6% to 0.5%. Separation between groups, as assessed by ROC analysis, was equivalent to FreeSurfer (for whole brain, AUC = 0.461 vs. 0.456 for CN vs. LMCI, and 0.659 vs. 0.650 for CN vs. AD). When comparing cross-sectional results across visits, the new method showed much smoother results (residuals 35% lower). Impact of segmentation method on registration-based atrophy assessment was minimal (mean difference <1%, r>0.99). **Conclusions:** We developed a novel, rapid and robust segmentation method, with results comparable to the well-established FreeSurfer algorithm, improved success rate and lower test-retest variability. Impact of segmentation masks from the new method on atrophy assessment is minimal. This supports the use of this method in future clinical trials, where FreeSurfer was traditionally employed before. **Key words:** MRI, brain segmentation, artificial intelligence. **Disclosures:** All authors are full-time employees of Clario. **References:** 1. Fischl et al., Whole Brain Segmentation: Automated Labeling of Neuroanatomical Structures in the Human Brain, Neuron. 2002; doi:10.1016/s0896-6273(02)00569-x. 2. Fischl et al., Automatically Parcellating the Human Cerebral Cortex, Cereb. Cortex. 2004; doi:10.1093/cercor/bhg087. 3. Isensee F et al., Automated brain extraction of multisequence MRI using artificial neural networks. Hum Brain Mapp. 2019;40(17):4952-4964. doi:10.1002/hbm.24750. 4. MONAI Consortium. (2022). MONAI: Medical Open Network for AI (1.1.0). Zenodo. https://doi.org/10.5281/zenodo.7459814. 5. Shapey J et al., Segmentation of vestibular schwannoma from MRI, an open annotated dataset and baseline algorithm. Sci Data. 2021;8(1):286. Published 2021 Oct 28. doi:10.1038/s41597-021-01064-w. 6. Calmon G et al., Automatic measurement of changes in brain volume on consecutive 3D MR images by segmentation propagation. Magn Reson Imaging. 2000;18(4):439-453. doi:10.1016/s0730-725x(99)00118-6

P052- ASSESSING THE RELATIONSHIP BETWEEN CENTRAL CHOLINERGIC INTEGRITY AND AMYLOID ACCUMULATION IN INDIVIDUALS WITH DOWN SYNDROME USING [18F]-FEOBV AND [11C]-PIB PET: PRELIMINARY DATA. J.K. Russell[1], A.C. Conley[1], B.D. Boyd[1], R. Schlossberg[1], A.J. Rosenberg[2], L.M.Y. Acosta[1], M.S. Rafii[3], S. Shokouhi[1], P.A. Newhouse[1] *(1. Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center - Nashville (United States), 2. Vanderbilt University Institute of Imaging Science, Vanderbilt University Medical Center - Nashville (United States), 3. Alzheimer's Therapeutic Research Institute and Department of Neurology, Keck School of Medicine, University of Southern California - San Diego (United States), 4. Geriatric Research, Education, and Clinical Center, Veterans Affairs Tennessee Valley Health System - Nashville (United States))*

Background: Individuals with Down Syndrome (DS) are at high risk of developing Alzheimer's disease (AD) as they age. This is partly due to the increased risk conferred by the extra copy of the amyloid precursor protein (APP) gene, found on the triplicate chromosome 21. In AD, cholinergic basal forebrain projections degenerate and play a significant role in the observed cognitive deficits. In the present study, we assess the relationship between cholinergic integrity, as measured directly by [18F]-FEOBV uptake, and amyloid accumulation, as measured by [11C]-PiB uptake. **Methods:** Seven non-demented individuals with DS (18-50 years old) completed a FEOBV PET scan (6.5mCi dose with a 30-minute static scan following a 3-hour uptake), and an MRI, with six of these individuals also completing a PiB PET scan (15mCi with a 30-minute static scan following a 30-minute uptake). Participants over 25 years old were recruited from the TRC-DS study, where individuals undergo multimodal imaging and plasma biomarker assessment. A Brodmann area (BA) atlas from MRIcron and Freesurfer cortical and subcortical parcellations were registered to participants' MRI scans and transformed to native PET space. For FEOBV, regional uptake was normalized to supraventricular white matter, and for PiB, regional uptake was normalized to cerebellum generating standard uptake value ratios (SUVRs). Initial analysis assessed uncorrected associations between PiB SUVR, FEOBV SUVR, and age. **Results:** Individuals with DS displayed regional FEOBV SUVRs comparable to normal non-DS individuals from work published by others. FEOBV SUVR in the posterior cingulate cortex displayed a trend towards a negative association with age (r=-0.73, p=0.063). When assessing the relationship between FEOBV SUVR and PiB uptake, negative associations in BA26, 35, 36, 37, 41, and the hippocampus were seen (all p<0.05, r<-0.8). Additionally, trends toward negative associations between FEOBV and PiB uptake were observed in BA20, 21, 28, 29, and the thalamus (p<0.01, r<-0.7). Previous groups demonstrated age-related increases in amyloid deposition, similarly in this cohort, we observed age-related increases in PiB uptake; all regions assessed, r>0.55, with significance (p<0.05) in numerous cortical and subcortical regions. **Conclusion:** These data show FEOBV uptake is highest in striatal regions, with moderate levels seen in the hippocampus and decreasing throughout cortical regions. This similar pattern to published work in normal non-DS individuals, suggests FEOBV PET imaging is a valid modality for assessing cholinergic integrity in DS individuals. While a trend toward a negative association between age and FEOBV SUVR is observed in the parietal cortex, more robust negative associations between regional FEOBV SUVR and regional PiB SUVR are observed. This is consistent with previous studies in individuals with DS, which demonstrated plasma amyloid biomarkers associated with decreasing cholinergic basal forebrain volume, suggesting an important link between amyloid deposition and cholinergic integrity in this population. Interestingly, no association between striatal PiB uptake and FEOBV uptake was observed. Although the striatum displays early amyloid deposition in individuals with DS, the lack of striatal FEOBV uptake association with amyloid suggests the intrinsic striatal cholinergic interneurons are relatively preserved despite amyloid accumulation in these non-demented individuals with DS. **Key words:** Down Syndrome, Amyloid, Cholinergic, PET. **Clinical Trial Registry:** NCT05231798, NCT04165109. **Disclosures:** This work was supported by the following grants: Alzheimer's Association AARG-21-850839 and NIA 1R21AG075643-01.

P053- MINIMIZING SAMPLE SIZES FOR TRIALS USING MK-6240: IMPACT OF REFERENCE AND TARGET TISSUES. J.A. Becker[1], C. Lois[1], E. Thibault[1], G. Del Carmen Montenegro[1], J.S. Sanchez[2], B. Healy[3], F.L. Fu[1], J.C. Price[1], G. El Fakhri[1], K.A. Johnson[1] *(1. Massachusetts General Hospital - Boston (United States), 2. Washington University School of Medicine - St. Louis (United States), 3. Harvard T.H. Chan School of Public Health - Boston (United States))*

Background: Choice of target and reference tissues impacts parameter-estimates and variances when modeling longitudinal

PET data for clinical trial design. We investigated effects of these choices on estimated sample-sizes required to detect tau change-rate differences using longitudinal MK-6240 data in a cohort of amyloid positive (aβ+) subjects. **Methods:** Baseline MR-T1, dynamic PiB and longitudinal dynamic MK-6240 PET (1-4 time points; mean follow-up 1.42±1.1 yrs, range 0 to 3.03 yrs) were acquired for N=43 aβ+ (PiB FLR>1.12 DVR, where FLR is a large amyloid susceptible cortical aggregate region) cognitively normal or mildly impaired (MMSE 27±4) subjects. All PET data were acquired on the Discovery GE-DMI tomograph at MGH. Baseline PiB for each subject was acquired from 0 to 60 minutes post-injection (PI) and quantified by distribution volume ratio (40-60 min DVR; Logan graphical method, cerebellar-grey reference). All MK-6240 PET data were acquired from 0 to 120 minutes PI and were reconstructed into 54 frames using vendor OSEM-reconstruction. Late-time MK-6240 frames (90-110 min) were motion corrected using the SPM12 realignment tool, averaged and rigidly registered to Freesurfer-processed MR-T1 using the SPM12 coreg tool, and then quantified by SUVR in Desikan atlas target regions. Three reference tissues were considered: cerebellar-cortex, cerebellar-white-matter, and cerebral-white-matter. Longitudinal mixed-effects models (random intercept and slope) were fit to log-transformed tau SUVR data in each target region. Sample-sizes assuming α=0.05 and 80% power in a hypothetical trial of 3 PET time-points (0, 1 and 2 years) were analytically computed based on model-estimated tau change-rates and variance-components for each target region; confidence intervals (CI) were computed via parametric bootstrapping. The minimum detectable difference in change-rate between treatment- and placebo-groups was taken to be a fraction of each target region's estimated mean change-rate. Sample size estimates and CIs were computed for a range of fractional differences. **Results:** Medial temporal structures including rhinal cortex (RC; Sanchez et al Sci-Trans-Med 2021) and amygdala quantified by SUVR using cerebellar-white-matter reference yielded the smallest estimated sample sizes, with a smaller bootstrapped 95% CI found for amygdala compared to RC. It was estimated that detecting a 30% treatment-effect using RC as the MK target region required approximately 58 subjects per arm (95% CI: 24 to 401), whereas amygdala required 83 subjects/arm (95% CI: 39 to 175). Smaller sample sizes for the best performing target regions were driven by a sum of two ratios: (change-rate random effect variance/change-rate^2) and (residual-variance/change-rate^2). The former ratio was smaller in the best performing regions yielding smaller sample size estimates. RC and amygdala change-rates were similar at ~0.08 SUVR/yr (cerebellar-grey reference). Poorer results were obtained using alternative reference tissues; e.g., amygdala size/arm 452 (95% CI: 142 to 3908) with cerebral-white-matter reference. **Conclusion:** Optimizing processing and analysis of PET data can reduce sample sizes, thereby reducing subject burden, trial cost and duration. **Key words:** PET imaging, clinical trial sample size. **Disclosures:** JCP is supported by NAI RO1AG062559, PO1AG036694;T32AG066592, R01AG076153, U19AG068054 and R01AG079142. Other authors declare no competing interests.

P054- CEREBRAL AMYLOID ANGIOPATHY IN APOE4/4 HOMOZYGOTES WITH ALZHEIMER'S DISEASE: BASELINE CHARACTERISTICS OF SUBJECTS ENROLLED IN APOLLOE4 PHASE 3 TRIAL OF ORAL ALZ-801 IN EARLY AD.

R. Mclaine[1], S. Abushakra[1], E. Liang[1], J. Barakos[2], A. Power[1], D. Watson[3], E. Macsweeney[4], A. Porsteinsson[5], J. Suhy[6], J. Hey[1], M. Tolar[3] *(1. Alzheon, Inc. - Framingham (United States), 2. California Pacific Medical Center & Clario - San Francisco (United States), 3. Alzheimer's Research and Treatment Center - Wellington (United States), 4. Re:Cognition Health - London (United Kingdom), 5. University of Rochester School of Medicine and Dentistry - Rochester (United States), 6. Clario - San Mateo (United States))*

Background: Amyloid-targeting immunotherapies including the two antibodies approved for the treatment of Alzheimer's disease (AD) are associated with an increased risk of amyloid-related imaging abnormalities with edema and/or hemorrhages (ARIA-E, ARIA-H). ARIA is related to presence of amyloid plaque in brain microvessels (cerebral amyloid angiopathy, CAA), and indicates inflammation in or around the vascular media. APOE4 is a risk factor for both AD and CAA. ARIA incidence increases with the number of APOE4 alleles, with APOE4/4 homozygotes showing the highest incidence and risk of clinically severe cases. Amyloid antibody trials exclude subjects with MRI evidence of moderate to severe CAA, namely >4 lobar microhemorrhages (MHs) or >1 cortical superficial siderosis (SS). ALZ-801 (valiltramiprosate) is an oral drug that inhibits formation of neurotoxic Aβ oligomers and has shown promising efficacy and biomarker effects in a Phase 2 study of APOE4 carriers, with no increased risk of ARIA (Abushakra 2016 & 2022). A Phase 3 Early AD trial of this oral anti-amyloid oligomer agent ALZ-801 in APOE4/4 homozygotes (APOLLOE4, NCT04770220) is fully enrolled, and has allowed subjects with a larger burden of CAA lesions including >10 MH and/or >2 SS lesions. **Methods:** The Phase 3 trial enrolled 325 APOE4/4 homozygotes with Early AD with age 50-80 years, MMSE ≥22, CDR-G scores of 0.5 or 1. Baseline 1.5T/3T MRI scans were centrally evaluated by Clario for eligibility including detection of MH and SS. We analyzed the subjects with >4 lobar MH or >1 SS on baseline MRIs. The clinical characteristics of these moderate or severe CAA subjects were compared to the rest of study population. **Results:** In the overall study population mean age was 69 years, 51% were female, MMSE 26, 82% non-Hispanic white, 65% with MCI. Of 325 subjects, 313 had baseline MRIs and showed 32% with any MH, 9% with any SS, and 90% with white matter disease. A total of 34 subjects (11%) had >4 MHs and/or >1 SS lesion, including 7 subjects (2%) with both MH and SS. The CAA subgroup characteristics compared to rest of population were: mean/median age 71 vs. 68 years, females 24% vs. 55%, Mild AD 50% vs. 34%, MMSE score 25 vs. 26, RBANS-Memory score 55 vs. 59, and cholinesterase inhibitor use in 53% vs. 27%. **Conclusions:** This unique Early AD Phase 3 trial in APOE4/4 homozygotes shows high prevalence of CAA lesions at baseline, with 11% showing at least moderate CAA which is defined as >4 lobar microhemorrhages or >1 siderosis lesions. The group with radiographically moderate/severe CAA when compared to the rest of trial population, tended to be older and predominantly male with more advanced cognitive deficits. For APOE4/4 AD patients, who are at highest risk of ARIA with amyloid antibodies, consideration of these risk factors is important in decision making and treatment choices. Unlike anti-amyloid antibody treatments, ongoing studies of ALZ-801 have not shown increased ARIA risk in APOE4 carriers

or homozygotes. Oral ALZ-801 may offer potential safety advantages over amyloid immunotherapies especially for the APOE4/4 homozygous AD population. **Key words:** ARIA, APOE4, homozygote, ALZ-801, cerebral amyloid angiopathy, microhemorrhage, siderosis. **Clinical Trial Registry:** NCT04770220; https://clinicaltrials.gov. **Data Deposition:** Not available. **Disclosures:** SA/RM/EL/AP/JH/MT are employees of Alzheon Inc. JB/JS are employees or consultant for Clario, DW and EM are investigators in the Phase 3 trial, AP is a consultant and advisor for Alzheon, Inc.

P055- CHANGES IN CORTICAL MICROSTRUCTURE IN BRAIN REGIONS ASSOCIATED WITH COGNITIVE STATUS AND DISEASE DURATION AFTER SHORT-TERM TREATMENT WITH XPRO1595 FOR ALZHEIMER'S DISEASE. P. Pope[1], C.J. Barnum[1], R.J. Tesi[1], T. Soedere[2] *(1. INmune Bio, Inc., Boca Raton, FL, USA; 2. Allucent, Cary, NC, USA)*

Background: XPro1595 is a dominant-negative protein variant of human tumor necrosis factor (TNF) that selectively neutralizes only soluble TNF. XPro1595 crosses the blood-brain barrier in pharmacologically active concentrations and was shown to decrease CSF levels of inflammatory cytokines in a recent, 12-week, phase-1b safety and dose-finding study in patients with Alzheimer's disease (AD). CSF samples were also analyzed post-hoc using a panel of 92 protein biomarkers more specific to neurological diseases [1]. Here we report results of the first analysis of CSF neurology- related proteomics affected by short-term treatment with XPro1595 in AD. **Methods:** CSF samples from patients (N=9) who completed 12-weeks of treatment with XPro1595 0.3 mg/kg/wk (n=3) or 1.0 mg/kg/wk (n=6) were selected for analysis. Concentrations of neurology-related proteins (NRPs) were determined by the proximity extension assay (PEA) method and reported as Normalized Protein eXpression (NPX) units on a Log2 scale. AD biomarkers were quantified using the Roche Elecsys NeuroToolKit (NTK) and reported as pg/mL. Correlations and treatment effects were analyzed using linear regression and two-sided t-tests, respectively. Due to the small sample size and exploratory nature of the study, the threshold for determination of informative values was set at $P<0.05$ (nominal), with no correction for multiple comparisons. **Results:** At baseline, NPX values for the NRP representing isoforms of tau (MAPT) correlated with NTK concentrations of pTau ($r=0.889$, $P=0.001$) and tTau ($r=0.926$, $P<0.001$), thus indicating strong concordance between assays. NPX values for 36 NRPs detected within limits of quantification correlated negatively with NTK Aβ42/40 (n=30) or positively with NTK pTau (n=16), or both (n=10), and were designated as AD- NRPs in this cohort. Thirty-five (97%) of the designated AD-NRPs also correlated with NTK α-synuclein (all $r>0.690$, $P<0.05$). Week-12 results showed dose-related changes in NPX values for all (100%) AD-NRPs, with a trend toward significant down-regulation in the high-dose group. Statistical analysis identified dose-dependent (high-dose vs. low-dose) changes from baseline (CFB) in NPX values for 14 AD-NRPs (PRTG, GZMA, CPA2, MANF, PVR, PLXNB3, DDR1, PDGF-R-alpha, GFR-alpha-1, GCP5, GAL-8, CPM, MSR1, GDF-8), all $P<0.05$ (unadjusted). Of these, DDR1 (epithelial discoidin domain-containing receptor 1) and GDF-8 (growth/differentiation factor 8; myostatin) were the differentially affected AD-NRPs most strongly associated with Aβ42/40 and pTau, respectively. At baseline, DDR1 NPX values correlated with Aβ42/40 ($R2=0.711$, $P=0.01$), but not pTau ($R2=0.610$, $P=0.081$), whereas GDF-8 correlated with Aβ42/40 ($R2=0.613$, $P=0.02$) and pTau ($R2=0.499$, $P=0.034$). Finally, DDRI and PRTG (protogenin) showed the strongest trends toward significant, dose-related, down-regulation, decreasing in all patients (n=6) in the high-dose group: DDR1 NPX, high- dose (mean CFB = -0.27, $P=0.082$); PRTG NPX, high-dose (mean CFB = -0.25, $P=0.078$). **Conclusions:** In this study, short-term treatment with XPro1595 in patients with AD was associated with changes in NPX values for multiple neurology-related proteins detected in CSF. Pathogenic processes specific to AD and associated with these proteins in the current literature include Aβ and cerebrovascular pathologies, blood- brain barrier permeability, myelination, neuroinflammation, neurodegeneration, and synaptic functions, among others. Additional research into the molecular pathways affected by treatment with XPro1595 is warranted. **Clinical Trial Registry:** NCT03943264; https://clinicaltrials.gov. **Disclosures:** PP's employer received a grant from the Alzheimer's Association. PP, CJB and RJT are employees of and own stock or stock options in INmune Bio. **References:** 1. Olink® Target 96 Neurology. Accessible: https://olink.com/products- services/target/neurology-panel/

P056- ASSOCIATION OF CHOLINERGIC INTEGRITY TO AGE, AMYLOID, CORTICAL VOLUME AND COGNITIVE PERFORMANCE IN HEALTHY POSTMENOPAUSAL WOMEN USING [18F]-FEOBV PET. A. Conley[1], J. Russell[1], B. Boyd[1], T. Castellano[1], A. Rosenberg[2], B. Bosko[1], J. Dumas[3], P. Newhouse[1] *(1. Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center - Nashville (United States), 2. Department of Radiology, Vanderbilt University Medical Center - Nashbille (United States), 3. Clinical Neuroscience Research Unit, Department of Psychiatry, University of Vermont Larner College of Medicine - Burlington (United States), 4. Geriatric Research, Education, and Clinical Center, Veterans Affairs Tennessee Valley Health System - Nashville (United States))*

Background: Women are at a greater risk of developing Alzheimer's disease (AD) in later life, and a potential reason for this heightened risk may be the change in hormone levels following menopause. Estrogen is involved in the regulation of the cholinergic system, and the decline of estrogen levels post-menopause is thought to accelerate cholinergic and cognitive decline in some women. The examination of cholinergic decline can be explored using the investigational radiotracer [18F]-fluoroethoxybenzovesamicol radiotracer (FEOBV), as the tracer binds to the presynaptic vesicular cholinergic transporter. Previous results have shown that [18F]-FEOBV can characterize cholinergic system decline in AD patients compared to cognitively unimpaired older adults. The present study is an investigation into whether [18F]-FEOBV can be used as a prospective marker of cholinergic system integrity in a sample of cognitively unimpaired postmenopausal women, who were part of a larger study examining cholinergic compensation following the menopause transition. To explore the effectiveness of using [18F]-FEOBV to assess in vivo cholinergic activity, we assessed whether higher [18F]-FEOBV standardized uptake value ratios (SUVR) would be associated with age, amyloid SUVR, basal forebrain volumes, and cognitive performance. **Methods:** Eighteen healthy postmenopausal women aged 50-70 years completed an [18F]-FEOBV PET scan (6.5 mCi dose), in addition to an amyloid PET scan, structural MRI, and cognitive assessments. The supraventricular white matter was used as reference region to calculate [18F]-FEOBV SUVR. This region was used as a reference to avoid any partial volume effects from the ventricular tissue. The cerebellar gray matter was used as a

reference to compute amyloid SUVR. Both amyloid and FEOBV SUVRs were extracted from several regions of interest across the cortex using the Brodmann area (BA) atlas and FreeSurfer cortical and subcortical parcellations. Analyses focused on associations between [18F]-FEOBV SUVR and the key outcome variables. **Results:** Analyses showed a positive relationship between [18F]-FEOBV SUVR in the nucleus accumbens and BA 38, and the gray-matter volume of the basal forebrain of both hemispheres. Amyloid SUVR was positively associated with [18F]-FEOBV SUVR in BA 1, 27, and 30. A negative relationship was found between age and [18F]-FEOBV SUVR in the caudate, hippocampus, and putamen. Switching speed on the Trail-making task was negatively associated with [18F]-FEOBV SUVR in the nucleus accumbens, caudate, hippocampus and putamen; with higher[18F]- FEOBV SUVR associated with faster performance. **Conclusions:** In this sample of cognitively unimpaired postmenopausal women, [18F]-FEOBV uptake decreased with increasing age. [18F]-FEOBV uptake was also associated with basal forebrain volume and Trails switching speed, a measure of cognitive flexibility. Interestingly amyloid uptake was positively related to [18F]-FEOBV uptake in some areas of the cortex, which may reflect cholinergic compensation in response to increased accumulation of amyloid in the cortex. Overall, these results indicate the relationship between cholinergic integrity, amyloid aggregation, cortical volumes and cognitive processes in postmenopausal women. They also highlight the potential of [18F]-FEOBV PET both to identify women who are at a greater risk of future cognitive decline, and as an indicator of which participants may benefit from inclusion in trials of future cholinergic therapeutics.

P057- REAL-WORLD IMPLEMENTATION OF PATIENT STRATIFICATION WITH FASTER COGNITIVE DECLINE USING MRI-BASED PREDICTION OF REGIONAL TAU POSITIVITY. Y.H. Song[1], W.J. Lee[2], J.K. Seong[1] *(1. Korea University - Seoul (Korea, Republic of), 2. NeuroXT - Seoul (Korea, Republic of))*

Background: Recent research has identified the involvement of the inferior temporal gyrus (ITG) in the acceleration of tau propagation in Alzheimer's disease after initial accumulation of tau in the lateral entorhinal cortex (EC) [1], and further in faster cognitive decline [2]. Accurate assessment of tau accumulation in these regions therefore is crucial for predicting disease progression and cognitive decline. However, the use of positron emission tomography (PET) is limited due to its high cost and radiation exposure burden. The objective of this study was to develop an accurate and robust deep learning-based algorithm for classification of regional tau positivity in the EC, ITG, and middle temporal gyrus (MTG) by using only cortical thickness and some demographic factors including age, sex, education, and mini-mental state examination (MMSE) score. **Methods:** The study utilized subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort: two training sets and one validation set. The validation set included 353 subjects, all of whom underwent T1-weighted magnetic resonance imaging (MRI) and [18F]flortaucipir-PET imaging. These subjects also had MMSE scores and follow-up data within 18-30 months. The training sets for regional tau positivity classification consisted of 402 ADNI subjects, who underwent T1-weighted MRI and [18F]flortaucipir-PET imaging but no follow-up data within 18-30 months. Additionally, the training set for feature encoding included 563 amyloid-negative subjects from the ADNI cohort who underwent only T1-weighted MRI. Pre-processing of the T1-weighted MRI images involved using FreeSurfer v7.2 to extract cortical thickness measurements. The tau PET images were co-registered with the corresponding T1-weighted MRI images, underwent partial volume correction, and were mapped onto the cortical surface. Regional tau positivity was determined using a cutoff at z-score 2.0, based on amyloid-negative subjects in the training set as reference. We then employed one-ring convolution operations on an icosahedron cortical mesh structure to operate on the cortical surface. Subsequently, we trained a one-ring convolutional autoencoder (CAE) with the feature encoding training set, enabling the feature extraction of cortical thinning patterns associated with Alzheimer's disease by its residual and encoded vector. Furthermore, we trained one-ring convolutional neural network-based classifiers using the extracted cortical thinning features, encoded vectors, and demographic factors to classify EC and ITG+MTG tau positivity separately. **Results:** The validation set subjects were classified into three classes based on their regional tau positivity: class 1 (EC and ITG+MTG tau-negative), class 2 (EC tau-positive and ITG+MTG tau-negative), and class 3 (ITG+MTG tau-positive). All reported results are measured using the validation set. The accuracy of EC tau positivity classification was 84.99%, while ITG+MTG tau positivity classification had the accuracy of 87.25%. Furthermore, the accuracy of subject stratification based on the predicted regional positivity was 83.29% compared to those using tau PET scans. In the longitudinal analysis, the average annualized MMSE score changes were -0.06, -0.34, and -1.57 for classes 1, 2, and 3, respectively, which shows significantly faster cognitive decline in the ITG+MTG tau-positive group. Note that this subject stratification was done based on only structural MRI analysis, and the prediction of longitudinal cognitive decline shows almost the same pattern compared to that of using tau PET-based subject stratification. **Conclusion:** During the progression of Alzheimer's disease, tau positivity seems initiated at the lateral EC, while its propagation is accelerated through ITG to neocortical areas. The current study tried to capture those two pivotal moments only using structural MRI and some demographic and clinical factors, which should have wider applicability compared to tau PET scans. One possible future work could be utilizing a deep generative model to improve the performance of our classifiers, and also diffusion-weighted MRI for more sensitive detection of regional tau positivity. **References:** 1. Lee, W. J., Brown, J. A., Kim, H. R., La Joie, R., Cho, H., Lyoo, C. H., ... & Seeley, W. W. (2022). Regional Aβ-tau interactions promote onset and acceleration of Alzheimer's disease tau spreading. Neuron, 110(12), 1932-1943. 2. Ossenkoppele, R., Pichet Binette, A., Groot, C., Smith, R., Strandberg, O., Palmqvist, S., ... & Hansson, O. (2022). Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. Nature Medicine, 1-7.

P058- ASSOCIATION OF AMYLOID PET BURDEN WITH LONGITUDINAL COGNITIVE DECLINE IN A HETEROGENEOUS ALZHEIMER'S DISEASE RESEARCH COHORT. E. Johns[1], K. Younes[1], S. Mukherjee[2], C.B. Young[1], J. Mez[3], T.J. Hohman[4], D. Tosun[5], S. Biber[6], W.A. Kukull[6], P. Crane[2], E.C. Mormino[1] *(1. Department of Neurology and Neurological Sciences, Stanford University - Palo Alto (United States), 2. Department of Medicine, The University of Washington - Seattle (United States), 3. Department of Neurology, Boston University - Boston (United States), 4. Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center - Nashville (United States), 5. Department of Radiology and Biomedical Imaging, University of California, San Francisco - San Francisco (United States), 6. Department of Epidemiology, National Alzheimer's Coordinating Center, University of Washington - Seattle (United States))*

Background: Background: Amyloid positivity is a reliable indicator of cognitive decline in both aging and Alzheimer's disease (AD). However, previous studies have often overlooked individuals with common, coexisting conditions and have instead concentrated on specific amnestic clinical manifestations, which restricts the applicability of their findings. We aimed to examine the predictive significance of amyloid PET in a large diverse cohort of Clinically Unimpaired (CU) and Clinically Impaired (CI) participants (Mild Cognitive Impairment and Dementia) with a broad demographic background from multiple centers in the national Alzheimer's Disease Research Center program. **Methods:** We analyzed 918 amyloid PET scans collected from multiple sites using an MRI-Free pipeline. The PET frame data were motion corrected, summed to the optimal window for each ligand, and processed through an MRI-Free pipeline [1]. To create standardized uptake value ratios (SUVRs), we utilized a global cortical target region and whole cerebellum reference region from the Global Alzheimer's Association Interactive Network (GAAIN) atlas. Gaussian Mixture Modeling was performed SUVRs within each amyloid dataset to determine the probability of amyloid positivity, which served as a measure of amyloid PET burden. We used linear mixed models to test the association between cognitive performance and amyloid burden, both in a cross-sectional and prospective longitudinal manner. These models were conducted separately for CU and CI individuals, controlling for age, sex, ethnicity/race, and years of education. The cognitive outcome measures consisted of harmonized composite memory, executive, and language scores [2]. **Results:** We identified a total of 249 subjects in the CI group and 669 subjects in the CU group. The CI group consisted of individuals with diverse primary etiologies, including Alzheimer's disease (AD), alpha-synucleinopathy, vascular issues, psychiatric conditions, and genetic factors. Among the CI group, a higher probability of amyloid positivity was associated with poorer cross-sectional performance in memory (β (SE) = -0.03 (0.04), 95% CI = [-0.39, -0.21], $p<0.001$) and language (-0.08 (0.04) [-0.17, -0.00], $p=0.04$), as well as prospective decline in memory (-0.09 (0.02) [-0.12, -0.04], $p<0.001$), executive function (-0.14 (0.07) [0.03, 0.32], $p<0.001$), and language (-0.05 (0.02) [-0.08, -0.01], $p=0.003$). In the CU group, an increased likelihood of amyloid positivity was associated with poorer cross-sectional performance in memory (-0.04 (0.02) [0.08, -0.00], $p=0.048$), as well as prospective decline in memory (-0.04 (0.01) [-0.06, -0.01], $p=0.002$) and language (-0.02 (0.009) [-0.04, -0.00], $p=0.035$). **Conclusion:** In both CU and CI groups, amyloid PET burden is significantly associated with both cross-sectional and longitudinal cognitive decline. Amyloid burden is a significant prognostic marker of cognitive functioning within a diverse clinical cohort. **Key words:** Amyloid PET, Clinicial Impairment, Prognostic markers. **Disclosures:** ECM consults for Neurotrack, Eli Lilly, and Roche. **References/** 1. Landau SM, Ward TJ, Murphy A, et al. Quantification of amyloid beta and tau PET without a structural MRI. Alzheimers Dement. 2023;19(2):444-455. doi:10.1002/alz.12668. 2. Mukherjee S, Choi S-E, Lee ML, et al. (2022). Cognitive domain harmonization and cocalibration in studies of older adults. Neuropsychology. Advance online publication. https://doi.org/10.1037/neu0000835

P059- STRESS-TESTING THE CENTILOID CONCEPT: VALIDATION OF THE BETWEEN-TRACER ACCURACY OF THE CENTILOID METHOD IN AN INDEPENDENT COHORT. J.D. Gispert[1,2,3], D. Vállez García[4], L.E. Collijv[4], M. Shekari[1,2,5], L. Presotto[6,7], R. Manber[7], R. Wolz[7,8], H. Zetterberg[9,10,11,12], K. Blennow[13,14], A. Stephens[15], G. Farrar[16], P.J. Visser[17,18,19], C. Ritchie[20], F. Barkhof[4,21] *(1. Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation. Barcelona, Spain - Barcelona (Spain), 2. IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain - Barcelona (Spain), 3. Centro de Investigación Biomédica en Red Bioingeniería, Biomateriales y Nanomedicina, (CIBER-BBN), Barcelona, Spain - Barcelona (Spain), 4. Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Radiology and Nuclear Medicine, De Boelelaan 1117, Amsterdam, Netherlands & - Amsterdam (Netherlands), 5. Universitat Pompeu Fabra, Barcelona, Spain - Barcelona (Spain), 6. University of Milano-Bicocca - Milan (Italy), 7. IXICO, London, UK - London (United Kingdom), 8. Imperial College, London, UK - London (United Kingdom), 9. Dementia Research Institute, University College London, London, UK. - London (United Kingdom), 10. Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK. - London (United Kingdom), 11. Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China. - Hong Kong (China), 12. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden. - Gothenburg (Sweden), 13. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Mölndal, Sweden. - Gothenburg (Sweden), 14. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden. - Mölndal (Sweden), 15. Life Molecular Imaging GmbH, Berlin, Germany - Berlin (Germany), 16. GE Healthcare Pharmaceutical Diagnostics, UK - Amersham (United Kingdom), 17. Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, Netherlands. - Maastricht (Netherlands), 18. Alzheimer Center, Department of Neurology, Neuroscience Campus Amsterdam, Amsterdam University Medical Center, VU Medical Center, Amsterdam, Netherlands. - Amsterdam (Netherlands), 19. Department of Neurobiology, Care Sciences and Society, Division of Neurogeriatrics, Karolinska Institute, Stockholm, Sweden. - Stockholm (Sweden), 20. Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK. - Edinburgh (United Kingdom), 21. Institute of Neurology and Centre for Medical Image Computing, University College London, UK - London (United Kingdom))*

Background: The Centiloid (CL) scale has been proposed to enable quantitative comparison of amyloid load irrespective of the tracer used. In order to calibrate CL values, reference datasets are publicly available on the GAAIN website with head-to-head PET scans acquired with 11C-PIB and 18F-labelled amyloid tracers. However, the accuracy of the CL calibration in a large cohort has not yet been validated in independent and

large datasets. On the other hand, CSF AD biomarkers have also been developed out of which the ratio p-tau181/Aβ42 is the one showing the highest agreement with amyloid PET. **Methods:** This study included 158 participants of the EPAD Longitudinal Cohort Study (LCS) and the AMYPAD Prognostic and Natural History Study (PNHS) who underwent amyloid PET scanning with either 18F-florbetaben or 18F-flutemetamol and cerebrospinal fluid (CSF) sampling less than one year apart. Concentrations of Aβ42 and p-tau181 in CSF were determined using the fully automatized Roche Elecsys System in a single laboratory (University of Gothenburg) according to the manufacturer's instructions. Amyloid PETs were visually read and quantified in CL units with IXICO's validated pipeline using the whole cerebellum as the reference region. In order to assess the accuracy of the CL transformation across tracers a linear model was set with log-transformed CL values as the outcome and log-transformed CSF p-tau181/Aβ42 and tracer as predictors. After undoing the log-transform, the marginal mean difference between the two tracers was considered to be the bias of the between-tracer CL calibration. The linearity between logCL and log CSF p-tau181/Aβ42 was assessed with scatterplots and linear regression analysis. **Results:** The mean±SD difference between the time of amyloid PET scan and the CSF sampling was 62±94 days. The sample's mean [range] CL value was 26.78 [-12.66, 145.67] CL. After log-transformation, the association between CL and CSF p-tau181/Aβ42 became linear with r = 0.79. In the linear model, log CSF p-tau181/Aβ42 was significantly associated with log CL ($p<0.001$) and tracer was not ($p=0.153$). The marginal mean of the between-tracer difference [95% Confidence Interval] in the CL values predicted by CSF p-tau181/Aβ42 was 1.09 [0.84, 1.42] CL. **Conclusions:** We have set up a statistical model capable of estimating the bias associated with the use of two different 18F-labelled amyloid PET tracers by using CSF p-tau181/Aβ42 as a predictor of CL values. The CL transform provides a between-tracer calibration that is accurate below 1.5 CL which is approximately half of the test-retest variability of amyloid PET imaging (~3 CL). **Key words:** Quantitative, PET, Amyloid, CSF biomarkers, Agreement. **Disclosures:** JDG has received research support from GE Healthcare, Roche Diagnostics and Hoffman – La Roche and consultant or speaker's fees from Biogen, Roche Diagnostics, Philips Nederlands and Life-MI.

P060- ESTIMATING THE TIME BETWEEN AMYLOID- AND TAU-PET POSITIVITY: IMPLICATIONS FOR ALZHEIMER'S DISEASE PREVENTION TRIALS. A. Moscoso[1], F. Heeman[1], T. Dunås[1], M. Schöll[1] *(1. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg - Gothenburg (Sweden))*

Background: Alzheimer's disease (AD) is characterized by a preclinical stage in which abnormal accumulation of amyloid-β (Aβ) leads to phosphorylated tau aggregation. This sequence of events represents the transition between the "AD pathologic change" stage (A+T-) to the much riskier full AD neuropathology stage (A+T+, Jack et al. Alzheimers Dement. 2018). Thus, to understand the clinical relevance of the A+T- stage in the long term, it is important to understand the temporal course of Aβ and aggregated tau in AD. In this study, we used longitudinal Aβ- and tau-positron emission tomography (PET) to estimate the expected time gap between Aβ- and tau-PET positivity, and explored factors that influenced this gap. **Methods:** We estimated the natural history of amyloid accumulation in AD using longitudinal Aβ-PET data from 1690 AD-continuum subjects from the ADNI. Specifically, we fitted a non-linear mixed effects model (3-knot spline) and modeled the subject-specific "age of Aβ positivity" as random effects. An interval-censored time-to-event analysis using "time to amyloid positivity" as the time variable was performed on 318 Aβ+ ADNI participants who had available tau-PET ([18F]flortaucipir) visual reads using an FDA-approved visual interpretation method. Cox proportional hazards regression was used to assess whether age of onset of amyloid positivity, sex, APOE status, and cognitive impairment at follow-up influenced the onset of tau-PET positivity relative to the onset of Aβ-positivity. **Results:** After ~11 years from Aβ positivity, 50% of the cognitively unimpaired (CU) individuals progressed to tau-PET positivity, while only ~17% remained tau-PET negative after 20 years. Among the studied factors, only the presence of cognitive impairment accelerated the onset of visual tau-PET positivity (HR=2.52, $p<0.001$, median tau-free survival difference ~6 years). Both female sex (HR=1.44, $p=0.16$, median tau-free survival difference~2.5 years) and the APOE-ε4 allele (HR=1.44, $p=0.15$, median tau-free survival difference~2.5 years) were trend-level associated to faster onset of tau-PET positivity. **Conclusions:** The time gap between Aβ- and tau-PET positivity typically spans a decade and is highly variable across individuals. This long gap implies that a significant fraction of the A+T- CU older individuals will never develop tau-PET positivity and subsequent clinical decline in their lifespan, which suggests that these subjects may not benefit from current anti-amyloid therapies for AD. Future project steps include the identification of the subset of A+T- CU individuals that can benefit from anti-amyloid therapies and the cost-effectiveness analysis of using anti-amyloid therapies in the CU population. **Key words:** Amyloid, Tau, Prevention, Trial, Unimpaired, PET. **Disclosures:** Nothing to disclose.

P061- A NOVEL TAU STAGING SCHEME USING [18F] MK-6240 PET VISUAL READ EXTENT SCORES. E. Stage[1], D. Wooten[1], J. Seibyl[2], N. Seneca[1], A. Bannon[1], H. Florian[1], R. Comley[1], Q. Guo[1] *(1. AbbVie - North Chicago (United States), 2. Institute for Neurodegenerative Disorders - New Haven (United States))*

Background: Current tau PET visual read methods focus on identifying an Alzheimer's (AD)-like pattern of tau deposition. In the context of clinical trials, however, simply identifying the subjects who present with AD tauopathy misses a key element in subject selection. That element is selecting subjects on the basis of tau load, or by how advanced a subject's tauopathy is. Depending on the target population of a therapeutic, it may be best to select subjects with a specific tau load to maximize a treatment effect. Here, we report the application of a new method for visually determining tau load using the recently developed [18F]MK-6240 visual read algorithm [1]. **Objectives:** The purpose of this study is to explore the utility of a visual read staging scheme that can determine an AD subject's tau load. In doing so, we hope to facilitate the use of tau load for patient selection in clinical trials. **Methods:** This work includes data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) and from the phase 2 study evaluating the efficacy and safety of tilavonemab in patients with early AD (NCT02880956). Information on the study protocols and subjects involved can be found in the publication by Florian et al. in 2023 [2] and online for AIBL at https://aibl.csiro.au/about/. For this study we used 510 longitudinal [18F]MK-6240 tau PET scans from 274 subjects (214 from the tilavonemab study and 60 from AIBL) with corresponding

T1-weighted MRI scans. All subjects from the tilavonemab study were considered to have early AD (CDRgl=0.5 and RBANS >85) with a previously acquired positive amyloid PET scan. AIBL subjects included 13 cognitively normal amyloid-negative (CN-), 16 CN+, 13 mild cognitive impairment amyloid-positive (MCI+) and 18 AD+ subjects. [18F]MK-6240 scans were read according to the method developed by Seibyl et al. in 2023 [1]. Briefly, scans were assessed by up to three readers for presence of tau in three brain region clusters: 1) temporal lobes (left and right hippocampus, mesial temporal, inferior temporal and lateral temporal), 2) extra-temporal (left and right occipital, frontal, parietal and posterior cingulate) and 3) subcortical (globus pallidus, thalamus, pons, midbrain, deep cerebellar/dentate) relative to cerebellar gray matter. Scans were then read as presenting with a Negative, Positive not AD, Positive Atypical AD or Positive AD pattern. In addition to the read category, subjects were evaluated for the extent of tau present within the temporal and extra-temporal regions with readers rating as None, <25%, 25 to 75% or >75% of a region (respectively, an extent score of 0, 1, 2 or 3). Finally, regional gray matter SUVR values were calculated using MRI segmentation from Freesurfer 6.0 and the inferior cerebellar gray matter cortex as a reference region. Subjects were then assigned to an in vivo Braak stage using regional cutoff values for corresponding Braak regions defined as 2.5 standard deviations (SD) above the mean SUVR for young (age <65) amyloid-negative cognitively normal subjects. **Results:** The numbers of scans by read category within all visits (unique subjects) were as follows; 90 (41) Negative, 5 (2) Positive not AD, 5 (1) Positive atypical AD and 410 (230) Positive AD pattern. There was 87% agreement between readers on category and 76% for extent across all brain regions. For staging, we focused solely on the first available scan for the Positive AD subjects (n = 230). All Positive AD pattern subjects were amyloid-positive and 95% had cognitive impairment. As measured by SUVR, 7% had no or low tau load (Braak 0, I and II), 24% had moderate tau load (Braak III and IV), 67% had high tau load (Braak V and VI) and 2% had a NonBraak pattern. Using the regional extent scores (0, 1, 2 or 3) we defined a set of rules to assign subjects into a low, moderate or high tau group. The rules were: 1. Low tau - the extent score must be below 1 for at least one temporal region in both hemispheres. 2. Moderate tau – the extent score must be greater than or equal to 1 for each temporal region in at least one hemisphere. 3. High tau – the extent score must be greater than or equal to 1 for every region in at least one hemisphere. Considering the SUVR-defined tau load as the "ground truth", our read extent staging allowed us to detect low, moderate or high tau subjects with an accuracy of 93%, 86% and 87%, respectively. **Conclusion:** This study shows the potential advantages of the current visual read algorithm for patient selection by tau load. Future analyses will focus on the relationship between visual extent scores and plasma biomarkers. **References:** 1. Seibyl JP, et al. J Nucl Med. 2023;64(3):444-451. 2. Florian H, et al. Tilavonemab in early Alzheimer's disease: results from a phase 2, randomized, double-blind study. Brain. 2023

P062- CORTICAL MICROSTRUCTURAL CHANGES ASSOCIATED WITH RBANS SCORES IN COGNITIVELY UNIMPAIRED AND MCI IN THE EUROPEAN PREVENTION OF ALZHEIMER'S DEMENTIA (EPAD) STUDY.

M. Torso[1], G. Ridgway[1], M. Valotti[1], I. Hardingham[1], S. Chance[1,2] *(1. Oxford Brain Diagnostics - Oxford (United Kingdom), 2. for the European Prevention of Alzheimer's Dementia (EPAD) Consortium)*

Background: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [1] can provide valuable information about an individual's cognitive profile and can track cognitive changes over time. Diffusion MRI has shown the potential to detect early cortical microstructural changes in neurodegenerative diseases [2]. The main aim of this study was to investigate the association between cognitive performance, as measured by RBANS, and cortical microstructure in participants who were either cognitively unimpaired or had mild cognitive impairment. **Methods:** Data of 348 individuals (CDR 0=305, CDR 0.5=43) aged 50 or older with T1-weighted, diffusion MRI and RBANS scores, were obtained from the European Prevention of Alzheimer's Dementia (EPAD). Structural T1-weighted and diffusion MRI (dMRI) were used to calculate three minicolumn-related 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, 3]. The RBANS total scale score and the index scores (Immediate Memory, Delayed Memory, Visuospatial/Constructional, Language and Attention) at baseline were used to investigate the association between cortical microstructural changes and cognitive status. Associations were evaluated with linear models, adjusting for age, sex and site ID. Only results surviving False Discovery Rate (FDR) correction were reported. **Results:** Regional analysis showed a significant bilateral negative correlation between total scale score values and PerpPD+ values at baseline, more prominent in inferior temporo-occipital (fusiform left: pFDR<0.005, $\eta2$=0.222; fusiform right: pFDR<0.01, $\eta2$=0.180; lingual left: pFDR<0.01, $\eta2$=0.178; lingual right: pFDR<0.05, $\eta2$=0.132), limbic (isthmus cingulate left: pFDR<0.01, $\eta2$=0.178; isthmus cingulate right: pFDR<0.05, $\eta2$=0.146) and medial orbito-frontal areas (left: pFDR<0.05, $\eta2$=0.117; right: pFDR<0.01, $\eta2$=0.173), reminiscent of Braak limbic stages. AngleR showed only a significant association in left entorhinal cortex (pFDR<0.01, $\eta2$=0.197). Concerning the Delayed Memory score, PerpPD+ showed a significant bilateral fronto-temporo-parieto-occipital pattern, involving mainly fusiform (left: pFDR<0.005, $\eta2$=0.221; right: pFDR<0.005, $\eta2$=0.179), superior temporal (left: pFDR<0.01, $\eta2$=0.163; right: pFDR<0.005, $\eta2$=0.194) and entorhinal cortex (left: pFDR<0.005, $\eta2$=0.176; right: pFDR<0.05, $\eta2$=0.148). Further significant associations were found with AngleR values mainly in entorhinal (left: pFDR<0.005, $\eta2$=0.224), superior temporal (left: pFDR<0.01, $\eta2$=0.194; right: pFDR<0.05, $\eta2$=0.156) and fusiform cortex (left: pFDR<0.01, $\eta2$=0.185; right: pFDR<0.05, $\eta2$=0.174). The Immediate Memory score associations revealed a predominantly left fronto-temporal pattern with PerpPD+ including mainly medial orbito-frontal (left: pFDR<0.005, $\eta2$=0.221), fusiform (left: pFDR<0.01, $\eta2$=0.192), rostral middle frontal (left: pFDR<0.01, $\eta2$=0.179) and inferior temporal (left: pFDR<0.01, $\eta2$=0.178; right: pFDR<0.05, $\eta2$=0.178). The Language score demonstrated significant associations with PerpPD+ values mainly in inferior temporal (left: pFDR<0.005, $\eta2$=0.207; right:

pFDR<0.005, η2=0.208), fusiform (left: pFDR<0.005, η2=0.193; right: pFDR<0.005, η2=0.197) and superior temporal (left: pFDR<0.05, η2=0.148; right: pFDR<0.05, η2=0.168). No other associations were detected. **Conclusion:** The analysis revealed specific patterns of association between cortical diffusivity measures and RBANS cognitive scores, particularly ventral temporal (including inferior frontal and limbic) with total scale score and Delayed Memory score, left fronto-temporal regions with Immediate Memory score, and lateral temporal regions with Language score suggesting that cortical diffusivity measures have the potential to detect microstructural alterations underlying cognitive changes in the early stages of the Alzheimer's continuum. **Key words:** cortical microstructure, cortical diffusivity, RBANS. **Disclosures:** SAC has a patent (WO2016162682A1) related to the diffusion MRI analysis used in the present study. SAC is a co-founder of a company, Oxford Brain Diagnostics, from which he has received funding for the research and preparation of this abstract. MT and GR are currently employed at Oxford Brain Diagnostics. **References:**
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P063- AMYLOID PET SCAN READS IN IDEAS – COMPARISON OF LOCAL CLINICIAN AND EXPERT READS.
C. Windon[1], B. Siegel[2], M. Carrillo[3], C. Gatsonis[4], L. Hanna[5], B. Hillner[6], A. March[7], R. Whitmer[8], A. Arora[9], S. Bullich[10], C. Buckley[11], P. Sherwin[11], G. Rabinovici[1]
(1. Memory and Aging Center, UCSF Weill Institute for Neurosciences, University of California, San Francisco - San Francisco (United States), 2. Mallinckrodt Institute of Radiology, Washington University in St Louis - St. Louis (United States), 3. Alzheimer's Association - Chicago (United States), 4. Department of Epidemiology and Biostatistics, Brown University School of Public Health - Providence (United States), 5. Center for Statistical Sciences, Brown University School of Public Health - Providence (United States), 6. Department of Medicine, Virginia Commonwealth University - Richmond (United States), 7. American College of Radiology - Reston (United States), 8. Department of Public Health Sciences, University of California, Davis - Davis (United States), 9. Avid Radiopharmaceuticals - Philadelphia (United States), 10. Life Molecular Imaging GmbH - Berlin (Germany), 11. GEHC - Massachusetts (United States))

Background: With the approval of anti-amyloid therapies, it is anticipated that amyloid PET will be used much more extensively in clinical practice. However, little is known about the accuracy of visual reads by community radiologists and nuclear medicine physicians in a clinical environment, where variability of image interpretation is subject to greater impact by image noise, resolution, and uniformity. The IDEAS (Imaging Dementia – Evidence for Amyloid Scanning) study captured over 17,000 amyloid PET scan interpretations from local radiologists and nuclear medicine physicians. We sought to establish the reliability of clinical interpretations by local readers in IDEAS by comparing them with retrospective visual reads performed by highly experienced experts in amyloid PET interpretations. **Methods:** Randomly selected amyloid PET/CT scans performed using one of three FDA-approved agents [18F-Florbetaben (FBB), 18F-Florbetapir (FBP), 18F-Flutemetamol (FMM)] and previously interpreted by local readers from the IDEAS study were assigned to vendor-selected panels of 3 expert readers for interpretation; 500 scans per agent and 1 panel per agent. Scans were stratified to match frequencies observed in the overall study by 1) participant age; 2) impairment level (mild cognitive impairment (MCI) vs dementia); 3) positive/negative interpretation; and 4) type of PET facility (independent vs. hospital-based). Visual interpretations (positive or negative for Aβ cortical deposition) were performed according to agent-specific, FDA-approved interpretation criteria. Expert panel readers were blinded to clinical and demographic data. Cohen's kappa statistic with two-sided 95% confidence interval estimates examined agreement between local reader and majority expert panel visual interpretation as well as individual expert readers. **Results:** A total of 4489 visual interpretations were provided by expert panel readers across the 3 tracers. Median age for scanned participants was 75 (range 65-96), 51.4% were female, 60.5% had MCI, and 84.6% of scans were obtained outside of a hospital-based facility. Local readers interpreted 60.9% of scans as positive and 39.1% as negative. Across all radiotracers, agreement between the majority expert read and local readers was excellent (k coefficient 0.76; 95% CI 0.73 – 0.80, p<.0001) with 86.6% (791/913) agreement for positive scans and 90.9% (532/585) agreement for negative scans. Agreement by individual radiopharmaceuticals was excellent for FBB (k coefficient 0.78 (95% CI 0.72 – 0.83, p<.001)), good for FBP (k coefficient 0.72 (95% CI 0.66 – 0.78, p<.001)), and excellent for FMM (k coefficient 0.78 (95% CI 0.73 – 0.84)). Agreement levels between local readers and individual experts by tracer showed more variation: FBB Reader 1 (FBB1) k coefficient 0.78 (95% CI 0.72 – 0.83), FBB2 0.77 (0.72 – 0.83), FBB3 0.72 (0.66 – 0.78), FBP1 0.73 (0.68 – 0.79), FBP2 0.68 (0.61 – 0.74), FBP3 0.71 (0.65 – 0.77), FMM1 0.77 (0.71 – 0.82), FMM2 0.61 (0.53 – 0.68), FMM3 0.78 (0.72 – 0.84). All p<.0001. **Conclusion:** We found good to excellent agreement between local readers and majority assessment of three-member expert panels for all combined scans and scans by individual radiotracers. Visual interpretation of amyloid PET can be performed in a clinical setting with high reliability. **Key words:** Amyloid, PET, IDEAS, Visual Interpretation. **Clinical Trial Registry:** NCT02420756; https://clinicaltrials.gov. **Disclosures:** Dr Windon reported grants from the Alzheimer's Association and the National Institutes of Health and has received honorariums from the American Academy of Neurology and LCN. Ms Hanna, Mr March, and Dr Gatsonis reported funding from the American College of Radiology. Dr Carrillo is employed by the Alzheimer's Association. Dr Hillner reported receiving grants and clinical trial support from the American College of Radiology and the Alzheimer's Association. Dr Siegel reported grants from the American College of Radiology and nonfinancial support from the Alzheimer's Association during the conduct of the study and personal fees from the American College of Radiology (self and spouse), Avid Radiopharmaceuticals, Curium Pharma, Progenics Pharmaceuticals, American Medical Foundation for Peer Review & Education, Siemens Healthineers (spouse), Capella Imaging, GE Healthcare, Lantheus Medical Imaging, Radiological Society of North America (self and spouse), ECOG-ARIN (spouse), Evicore Healthcare (spouse), and grants

from Curium Pharma, Progenics Pharmaceuticals, ImaginAb, and Blue Earth Diagnostics outside the submitted work. Dr. Arora is a full-time employee of Avid Radiopharmaceuticals. Dr Bullich is a full-time employee of Life Molecular Imaging GmbH. Dr Buckley and Dr Sherwin are full-time employees of GE Healthcare (GEHC). Dr Rabinovici reported grants from the National Institutes of Health, American College of Radiology, Alzheimer's Association, Rainwater Charitable Foundation, Avid Radiopharmaceuticals Inc, GE Healthcare, Life Molecular Imaging, and Genentech and personal fees from Alector, Eli Lilly, Johnson & Johnson, Genentech, and Roche, and is Associate Editor of JAMA Neurology. **References:** Minoshima S, Drzezga AE, Barthel H, Bohnen N, Djekidel M, Lewis DH, et al. SNMMI procedure standard/EANM practice guideline for amyloid PET imaging of the brain 1.0. J Nucl Med. 2016;57:1316–22. https://doi.org/10.2967/jnumed.116.174615. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. JAMA. 2019;321(13):1286-1294. doi:10.1001/jama.2019.2000

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

V. Kotari[1], M. Case[1], K. Holdridge[1], R. Yaari[1], A. Schultz[2], K. Johnson[3], P. Aisen[4], R. Sperling[2], J. Sims[1], S. Shcherbinin[1]
(1. Eli Lilly and Company - Indianapolis (United States), 2. Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School - Boston (United States), 3. Departments of Neurology and Radiology, Massachusetts General Hospital, Harvard Medical School - Boston (United States), 4. Alzheimer's Therapeutic Research Institute, Keck School of Medicine, University of Southern California - San Diego (United States))

Background: The A4 Study (NCT02008357) was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial, which assessed the safety and efficacy of solanezumab in preclinical Alzheimer's Disease (AD). It included cognitively unimpaired participants with brain amyloid pathology on florbetapir. Tau pathology was measured in a sub-study using flortaucipir (FTP). **Methods:** N=383 baseline FTP scans were analyzed using established image processing pipeline to evaluate global tau burden and regional tau patterns in a standard brain atlas space. Global burden was measured using AD-signature weighted neocortical standardized uptake value ratio (tauSUVR) [1] relative to PERS I[2]. Previously established tauSUVR cut points of >1.11 [3] and >1.46 [4] were utilized to quantitatively define positive FTP scan and high tau level, respectively. Regional tau uptake was measured in 35 cortical and sub-cortical regions extracted from FreeSurfer-GTM atlas with cerebellar gray reference region [5], which were used to pre-specify 5 composite regions and order them into a hypothetical pathologic spreading: 1) "early" (amygdala, entorhinal cortex, parahippocampal gyrus), 2) "early extension" (amygdala, entorhinal cortex, parahippocampal, fusiform, inferior and middle temporal, and inferior parietal gyri), 3) "middle" (fusiform, inferior and middle temporal, and inferior parietal gyri), 4) "middle extension" (fusiform, inferior and middle temporal, inferior parietal, lateral occipital, posterior cingulate, superior parietal, and supramarginal gyri), 5) "late" (lateral occipital, posterior cingulate, superior parietal, and supramarginal gyri). We evaluated cross-sectional associations between global amyloid burden and regional tau SUVRs and performed subgroup analysis by sex and APOE ε4 status. **Results:** The majority (94.5%) of participants were classified as "tau negative" (tauSUVR <1.11) using the global measure, while only a single participant (0.3%) had high tau level (tauSUVR >1.46). Regional classifications suggested that lower tau signal was on average observed in regions identified later in pathologic sequences. In more detail, the baseline tau (mean±SD) SUVR in the composite regions was 1.20±0.14(early), 1.18±0.12(early extension), 1.18±0.12(middle), 1.12±0.11(middle extension), and 1.03±0.11(late). When all 35 regions were sorted based on mean baseline tau SUVR, hypothesized earlier tau spreading regions demonstrated higher SUVRs. The larger correlation with amyloid level was observed in regions positioned earlier in the hypothesized tau spread sequence: fusiform and entorhinal cortex (rho=0.34), parahippocampal gyrus (rho=0.32), amygdala and inferior temporal gyrus (rho=0.29). The subgroup analysis revealed female participants had significantly lower age (71.3±4.6vs73.2±5.0, p<0.01), higher MMSE (28.8±1.2vs28.4±1.4, p<0.05) and middle temporal (1.20±0.13vs1.16±0.11, p<0.05) and inferior parietal tau (1.14±0.14vs1.10±0.12, p<0.01) SUVR. APOE ε4 carriers were younger (71.6±4.7vs72.9±5.0, p<0.05) with higher amyloid level (70.6±31.2vs53.4±30.1,p<0.01). **Conclusions:** Cross-sectional baseline A4 tau PET data confirmed that cognitively unimpaired participants with evidence of brain amyloid pathology are primarily global «tau negative» and such global flortaucipir assessments are not adequate to characterize preclinical AD. As previously reported[6], majority of the tau uptake was restricted to the temporal regions. However, the average baseline tau signal appeared to follow the hypothesized tau spread. The subgroup analysis confirmed that female sex and APOE ε4 carrier status are likely risk factors for higher tau burden. The influence of age, sex, amyloid level, and APOE ε4 status on regional tau will be presented during the meeting. **References:** 1. Devous MD, Joshi AD, Navitsky M, Southekal S, Pontecorvo MJ, Shen H, et al. Test–Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F 18. J Nucl Med 2018;59:937–43. https://doi.org/10.2967/jnumed.117.200691. 2. Southekal S, Devous MD, Kennedy I, Navitsky M, Lu M, Joshi AD, et al. Flortaucipir F 18 Quantitation Using Parametric Estimation of Reference Signal Intensity. J Nucl Med Off Publ Soc Nucl Med 2018;59:944–51. https://doi.org/10.2967/jnumed.117.200006. 3. Fleisher AS, Pontecorvo MJ, Devous MD, Lu M, Arora AK, Truocchio SP, et al. 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Disclosures/ Conflicts of Interest: Vikas Kotari, Michael Case, Karen Chilcott Holdridge, Roy Yaari, John R. Sims, and Sergey Shcherbinin are employees of Eli Lilly and Company and stock holders.

LP036- INTERIM MRI SAFETY ANALYSIS FROM A 76-WEEK PHASE 3 CLINICAL TRIAL OF SIMUFILAM IN ALZHEIMER'S DISEASE. J. Kupiec[1], L. Bracoud[2], J. Suhy[3], L. Rodriguez[1], L. Burns[1] *(1. Cassava Sciences - Austin (United States), 2. Clario - Lyon (France), 3. Clario - San Mateo (United States))*

Background: Simufilam is a novel drug candidate in Phase 3 clinical trials for Alzheimer's Disease (AD) dementia. This oral small molecule targets an altered form of filamin A (FLNA) found in AD. The drug disrupts FLNA's aberrant linkage to the α7 nicotinic acetylcholine receptor (α7nAChR), thereby blocking soluble amyloid beta1-42 (Aβ42)'s signaling via α7nAChR that hyperphosphorylates tau. Simufilam also disrupts aberrant linkages of FLNA with TLR4 and other inflammatory receptors to prevent their activation by Aβ42, suppressing neuroinflammation. A global, 76-week Phase 3 clinical study (REFOCUS-ALZ) is evaluating twice-daily simufilam 50 mg and 100 mg vs. placebo (1:1:1) in over 1,000 Alzheimer's patients with mild-to-moderate disease (MMSE $\geq$ 16 and $\leq$ 27). All patients undergo a screening MRI to rule out severe vascular pathology and potentially confounding findings. An optional volumetric MRI sub-study is part of this Phase 3 study, with scans at screening, Weeks 40 and 76. **Methods:** A total of 222 patients opted to participate in the volumetric MRI sub-study. The MRI protocol was conducted on 1.5T and 3T scanners and consisted of 3DT1, FLAIR, T2*, T2 and DWI sequences. Neuroradiologists continuously assess follow-up MRI scans to monitor for new imaging abnormalities, including ARIA-E and ARIA-H. Quantitative changes in brain volume (whole brain, ventricles and hippocampus) will be determined at the conclusion of the study. Study participants, clinical research staff and scientists at Cassava Sciences, Clario and Premier Research all remain blinded to treatment assignments. **Results:** As of September 1, 2023, Week-40 safety reports were issued on 181 patients. ARIA-E was not observed in any patients. No clinically significant findings were identified in 160 subjects (88%) at screening or Week 40. Thirteen patients (7%) had clinically significant findings at screening that persisted at Week 40, including infarcts, uni- and multi-focal cortical superficial siderosis (CSS), and other infrequent abnormalities. Seven patients (4%) had findings at Week 40 not apparent at screening, including: cortical or lacunar infarcts (n=3); CSS in patients who had either pre-existing CSS in other areas and/or $\geq$4 microhemorrhages (MCHs) at baseline (n=3); and one case of unifocal CSS in a patient with an e4/e4 apolipoprotein E (ApoE) genotype. At screening, 71% of patients did not exhibit ARIA-H (i.e., MCHs); 19% had 1-4 MCHs, 6% had 5-9 MCHs and 4% had $\geq$10 MCHs. Of those without MCHs at screening, 95% did not develop any new MCHs, while 5% had 1 or 2 (these patients did not have a predominant ApoE genotype). Overall, 85% of patients did not develop new MCHs. Twenty patients with MCHs at screening exhibited new MCHs at Week 40 (14 had 1-4, and 6 had $\geq$ 5). **Conclusions:** This interim neuroradiologic evaluation of Week 40 MRIs from 181 patients enrolled in the REFOCUS-ALZ Phase 3 clinical study suggests simufilam is not associated with ARIA-E emergence. ARIA-H was a common baseline finding, occurring in 29% of patients. In this blinded dataset, new MCHs occurred predominantly in patients with pre-existing MCHs: 39% of patients with pre-existing MCHs vs. 5% of patients without pre-existing MCHs. **Key words:** simufilam, Alzheimer's disease, MRI, ARIA, siderosis. **ClinicalTrials.gov ID:** NCT05026177. **Disclosures:** LB and JS are full-time employees of Clario and have no conflicts of interest. LR, LHB and JWK are full-time employees of Cassava Sciences.

LP037- ADVANCING PRACTICALITY FOR THE REAL-WORLD ANTI-AMYLOID TREATMENT: APPLICATION OF SOLITAIRE T2-FLUID-ATTENUATED INVERSION RECOVERY-BASED BRAIN VOLUMETRIC ANALYSIS MODEL. H.W. Kim[1], Z. Rieu[1], H. Lee[1], M.W. Lee[1], J. Kang[2], W.J. Moon[3] *(1. Research Institute, Neurophet Inc. - Seoul (Korea, Republic of), 2. Research Institute of Medical Science, Konkuk University of Medicine - Seoul (Korea, Republic of), 3. Department of Radiology, Konkuk University Medical Center - Seoul (Korea, Republic of))*

Objectives: Throughout the anti-amyloid disease-modifying treatment cycle, multiple magnetic resonance imaging (MRI) scans are recommended for regular monitoring. Due to time and cost burden, only T2-FLAIR scans might be feasible for follow-up. This study aimed to develop and validate an innovative model for accurate segmentation of brain volumetric analysis using only T2-fluid-attenuated inversion recovery (FLAIR) MRI scans. We compared the model's performance by comparing it with software necessarily requiring T1 MRI. **Methods:** Utilizing MRIs from Alzheimer's Disease Neuroimaging Initiative (ADNI) and UK Biobank (UKB) sites, 3D T1 and 3D T2-FLAIR images were obtained for cognitive normal (CN), mild cognitive impairment (MCI), and Alzheimer's Disease (AD) cases. Volumetric analysis was conducted using FreeSurfer 7.1.0 and AQUA® 3.0.2 (Neurophet Inc.) for T1 images, while a novel in-house semi-supervised method was employed for solitaire T2-FLAIR volumetric analysis. Regions of interest (ROIs) of AD spectrum was included, covering 20 distinct regions in both hemispheres. Comparisons were made among FreeSurfer T1, AQUA T1, and in-house T2-FLAIR approaches employing dice similarity coefficient (DSC) and volume similarity (VS) utilizing Jaccard coefficient. **Results:** The validation included 30 individuals in each CN, MCI, and AD sets. Their mean ages were 76.06$\pm$6.80, 75.92$\pm$6.73, and 75.85$\pm$6.85 years, respectively. Sex distribution was balanced with 50% of female in each group. For the segmentation algorithm comparison, we categorized the groups as follows: group_1 (AQUA T1 vs in-house T2-FLAIR), group_2 (FreeSurfer T1 vs in-house T2-FLAIR), and group_3 (FreeSurfer T1 vs AQUA T1). In the total set of 90 subjects, DSC values were as follows: group_1 (0.88$\pm$0.02), group_2 (0.82$\pm$0.03), and group_3 (0.86$\pm$0.03). The VS values for this group were: group_1 (0.79$\pm$0.02), group_2 (0.70$\pm$0.04), and group_3 (0.75$\pm$0.04). For the CN set, DSC values were as follows: group_1 (0.88$\pm$0.01), group_2 (0.83$\pm$0.02), and group_3 (0.87$\pm$0.02). The VS values for this group showed similar patterns: group_1 (0.79$\pm$0.02), group_2 (0.71$\pm$0.03), and group_3 (0.77$\pm$0.03). Within the MCI set, DSC values were observed: group_1 (0.88$\pm$0.02), group_2 (0.82$\pm$0.03), and group_3 (0.86$\pm$0.03). Correspondingly, the VS values for this set displayed group_1 (0.79$\pm$0.02), group_2 (0.70$\pm$0.03), and group_3 (0.76$\pm$0.03). For the AD set, DSC values were noted as follows: group_1 (0.87$\pm$0.03), group_2 (0.81$\pm$0.04), and group_3 (0.84$\pm$0.04). The VS values for this set followed a similar pattern: group_1 (0.78$\pm$0.05), group_2 (0.69$\pm$0.05), and group_3 (0.74$\pm$0.05). **Conclusions:** Our innovative solitaire T2-FLAIR-based volumetric analysis model demonstrates its practical utility in real-world Alzheimer's disease modifying treatments, particularly in situations where T1 scans are not feasible.

LP038- LONGITUDINAL TAU PET ANALYSIS PIPELINE WITH CONSISTENT PROGRESSION MEASURES ACROSS TRACERS AND DIAGNOSES IN COMMONLY USED AS WELL AS SUBJECT-SPECIFIC AD REGIONS OF INTEREST. Z. Saad[1], D. Henley[2,3], R. Datta[1], C. Rowe[4], H. Kolb[1] *(1. Neuroscience Biomarkers and Global Imaging, Janssen R&D, Johnson & Johsnon - San Diego (United States), 2. Neuroscience Clinical Development, Janssen R&D, Johnson & Johsnon - San Diego (United States), 3. Indiana University School of Medicine, 4. Austin Health and University of Melbourne - San Diego (United States))*

Background: Tau PET is the gold standard for in-vivo quantification of tau Neuro Fibrillary Tangles (NFT) and is strongly associated with cognitive decline. Since NFT presence and accumulation is heterogenous across patients and brain regions, individualized assessments are important for tracking pathology progression. **Objectives:** Implement and test performance of a pipeline for analyzing longitudinal tau PET from multiple tracers and across disease stages in anatomical and subject specific ROIs. **Methods:** This pipeline requires a T1 weighted MRI in addition to tau PET scans. For minimizing smoothing bias, longitudinal tau PET scans are aligned to a spatial midpoint and their average is used a reference for aligning MRI scans and derived regions of interest. The pipeline produces output using multiple cost functions and a QC process is used to select the best alignment or modify parameters when needed. The pipeline utilizes FreeSurfer [1], AFNI [2, 3], and ANTS [4] software for segmentation, registration, and quantification. Tau PET SUVR was estimated using cerebellar gray as a reference region with the option of uniformizing the smoothness across longitudinal PET scans. SUVR estimates were obtained over anatomically defined regions, over individualized ROIs based on functional connectedness defined by quartiles 1-4 (Q1-Q4) from more proximal to distal to the NFT epicenter at baseline [5], and over subject-specific tau-naïve composite ROIs which consisted of brain regions within +/- 1 SD of the SUVR in a tracer-matched control cohort of CN amyloid negative (A-) participants. The tau-naïve composite ROI allows for the assessment of treatment impact in regions where NFT have yet to form. In total, data was analyzed from 765 ADNI[6] participants (298 with follow up), and 794 subjects from the AIBL study and the Cerveau consortium (194 with follow up). **Results:** For brevity, we report here on results from cortex, Q1-Q4, and tau-naïve composite ROI in the following 4 groups: CN_A-, CN_A+, MCI_A+, AD_A+. For each of Flortaucipir and MK6240, Tau PET signal was progressively and significantly ($p<0.05$) higher across the 4 groups in cortex and Q1 ROIs. Similar numerical trends were observed for Q2, Q3, and Q4 with monotonic decrease from Q1 to Q4. For cortex, Q1, and notably the tau naïve ROIs, annualized change measures showed a monotonic increase ($p<0.05$) across the first three groups but no significant increase between MCI and AD cohorts. The tau naïve ROI results suggest that treatment effects can be detected in regions without NFT evidence at BL. This ROI may be optimal when assessing the effects of treatment that aim to halt the spread of tangles to unaffected brain areas. **Conclusions:** We have implemented and tested a tau PET processing pipeline optimized for deriving SUVR with minimal longitudinal bias from traditional anatomy-based ROIs to patient-centered approaches based on connectomic or tau-naïve regions at BL. Results were consistent despite differences in tracers and scanning parameters between cohorts. This consistency lends support to efforts for deriving a universal scale and for the feasibility of pooling data for establishing reasonably likely surrogacy for clinical outcomes. Efforts are ongoing to package the pipeline for portability. **References & Acknowledgements:** 1. Fischl et al., Neuron. 2002;[2. Cox RW, Comput Biomed Res. 1996; 3. Saad & Reynolds, Neuroimage 2012; 4. gNMI/ITK-SNAP – Yushkevich et al. NeuroImage 2006; 5. Franzmeier et al. Sci. Adv. 2020; 6. ADNI – Peterson et al. Neurology. 2010. 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, DH, 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.

LP039- THE UTILITY OF [18F]FDG BRAIN UPTAKE TO PREDICT DISEASE PROGRESSION AND ESTIMATIONS OF SAMPLE AND EFFECT SIZE COMPARED TO CLINICAL SCALES TO HELP GUIDE CLINICAL TRIAL DEVELOPMENT PLANS. N. Seneca[1], E. Stage[1], S. Finnema[1], S. Gladstein[1] *(1. Abbvie - North Chicago (United States))*

Background: Brain hypometabolism measured using [18F] FDG PET is an established functional brain imaging biomarker of Alzheimer's disease (AD). Hypometabolism has recently been shown to have strong relationships with brain atrophy and tau pathology, but not amyloid pathology [1]. Thus, future AD clinical trials may consider more widely utilizing [18F] FDG PET as a functional brain imaging measure. Further estimation of sample and effect size is needed to help guide clinical trial design and to refine previously published estimates [2]. **Methods:** Data was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). [18F]FDG metaROI imaging data were processed and normalized by ADNI and the UC Berkeley group. A total of 622 subjects were used for the prognostic analysis and 631 subjects (n = 201 CN, n = 353 MCI, and n = 77 AD) for the longitudinal/sample size analysis, although exact number varies depending on data available for each measure (e.g., imaging (i.e., [18F]FDG) and clinical scales (e.g., ADAS-COG, MMSE and CDR-SB)) at each time-point. For prognostic analysis, disease progression is defined as 24-month CDR-SB change >= 1. Sample size calculations used a two-group t-test at 80% power with a 0.05 one-sided significance level. **Results:** When analyzing the entire dataset regardless of diagnosis, we obtained the changes from baseline to 6-, 12- and 24-months. The changes of [18F]FDG PET and CDR-SB at the 12- and 24-month follow-up showed more sensitive signal change (Cohen's D; 12m change > 0.35, 24m change > 0.46) compared to ADAS-Cog and MMSE(Cohen's D; 12m change < 0.29, 24m change < 0.38). We compared the ability to predict 6-, 12- and 24-month clinical progression of MCI subjects using [18F]FDG PET and clinical scales. We found that both [18F]FDG PET and ADAS Cog resulted in larger effect sizes and AUCs (AUCs greater than 0.700) compared to CDR-SB and MMSE (AUCs less than 0.700) as prognostic markers to predict disease progression over a 24-month period. Finally, assuming a positive modulation of 10% to 20% of [18F]FDG hypometabolism by therapeutic intervention, we estimated that < 20 subjects per group would be needed to detect the drug effect. **Conclusion:** These results indicate that [18F]FDG hypometabolism is a better pharmacodynamic and prognostic marker compared to some clinical scales for monitoring and predicting disease

progression. Identification of subjects during screening who have a higher likelihood to progress during the timeframe of a clinical trial may help to select subjects who will show clinical benefit earlier and increase the likelihood of a positive response to novel therapeutics. Further analysis is on-going to include AD pathological PET measures as well as various MRI outcome measures to compare the interrelationships between pathological and functional changes in the brain. **References:** 1. Strom A, et al. Brain 2022; 145: 713-728–160. DOI: 10.1093/brain/awab294. 2. Herholz K, et al. The Journal of Nuclear Medicine 2011; 52: 1218–1226. DOI: 10.2967/jnumed.111.090902

LP040- STRESS TESTING THE CL CONCEPT: VALIDATION OF GENERALIZABLE CENTILOID CUT-OFF VALUES IN TWO LARGE, INDEPENDENT AND REPRESENTATIVE CLINICAL ALZHEIMER COHORTS.

J.D. Gispert[1,2,3], C. Buckley[4], S. Bullich[5], D. Altomare[6], M. Shekari[2,3,7], L. Collij[8,9], D. Vállez-García[8], A. Stephens[5], G. Farrar[4], A. March[10], R. La Joie[11], G. Rabinovici[11], G. Frisoni[6], F. Barkhof[8] *(1. Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation. Barcelona, Spain - Barcelona (Spain), 2. IMIM (Hospital del Mar Medical Research Institute) - Barcelona (Spain), 3. Universitat Pompeu Fabra - Barcelona (Spain), 4. GE Healthcare Pharmaceutical Diagnostics - Amersham (United Kingdom), 5. Life Molecular Imaging GmbH - Berlin (Germany), 6. Memory Center, Department of Rehabilitation and Geriatrics, University Hospitals and University of Geneva - Geneva (Switzerland), 7. Memory Center, Department of Rehabilitation and Geriatrics, University Hospitals and University of Geneva - Barcelona (Spain), 8. Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Radiology and Nuclear Medicine, Amsterdam (Netherlands), 9. Clinical Memory Research, Lund University - Lund (Sweden), 10. American College of Radiology - Washington (United States), 11. Department of Neurology, Weill Institute for Neurosciences, Memory and Aging Center, University of California, San Francisco - San Francisco (United States))*

Background: The Centiloid method has been proposed as a quantitative metric of amyloid load, irrespective of the PET tracer and quantification method. Several cut-off values have been proposed for various clinical and research purposes. However, few of such proposed cut-offs have been validated in large, independent, and representative cohorts. Here, we aimed to validate Centiloid cut-off values for 95% specificity in two large cohorts (IDEAS and AMYPAD-DPMS) that represent the typical clinical population where amyloid PET is considered for the diagnostic workup. **Methods:** This work included 984 amyloid PET scans from the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) project (Rabinovici et al. 2019) and 729 scans from the AMYPAD-Diagnostic and Patient Management Study (DPMS) (Altomare et al. 2023). IDEAS recruited Medicare beneficiaries with Mild Cognitive Impairment (MCI) or dementia, amyloid PET scans were acquired using 18F-florbetaben, 18F-florbetapir or 18F-flutemetamol, and Centiloid (CL) values were calculated with the rPOP PET-only method (Iaccarino et al. 2022). The AMYPAD DPMS included participants from memory clinics with Subjective Cognitive Decline plus (SCD+), MCI, or dementia who were scanned with either 18F-florbetaben or 18F-flutemetamol, and CL quantification was performed using the PET-only method AMYPYPE (Buckley et al. 2019). CL cut-off values for 95% specificity in a binary classification between amyloid-positive and negative were calculated using Gaussian Mixture Modeling (GMM) with two Gaussians. The cut-off for 95% specificity was calculated as the mean+1.6449*SD of the 'negative' Gaussian, as P(Z<1.6449)=0.95. To obtain 95% confidence intervals (95%CI), the GMM was repeated 10,000 times in random subsamples of the two cohorts. The point estimate of the CL cut-off was defined as the median of the distribution of CL cut-offs and the 95%CI as the interval between the 5th and 95th percentiles. The CL cut-offs obtained in IDEAS and AMYPAD DPMS were replicated if the respective point estimates were included in the 95%CI of the other cohort. **Results:** The proportion of amyloid-positive cases was 66% in IDEAS and 52% in AMYPAD-DPMS. The mean[95%CI] of the Gaussian representing amyloid-negative patients was -1.56[-3.31,1.11]CL for IDEAS and 0.46[-0.91,1.88]CL for AMYPAD-DPMS, and that referring to the amyloid-positive ones was 70.11[63.00,81.10]CL for IDEAS and 84.05[79.11,87.57]CL for AMYPAD-DPMS. The SD [95%CI] of the negative Gaussian was 12.90[10.23,17.96]CL for IDEAS and 13.05[11.52,14.44]CL for AMYPAD-DPMS. The CL cut-off value [95%CI] for 95% specificity was 21.69[18.49,24.65] CL for AMYPAD-DPMS and 24.42[18.15,29.25] CL for IDEAS. **Conclusions:** Centiloid cut-off values in the 22-24 CL range provide 95% specificity in a binary classification based on quantitative amyloid PET. These values are well-aligned with those predicting intermediate-to-high AD neuropathology and with positivity by visual reads (La Joie et al. 2019; Amadoru et al. 2020). Our results confirm that comparable CL values can be obtained using different quantification methods (Bullich et al. 2023). The obtained cut-off values are robust for this context of use, as they have been replicated in two independent cohorts representing the typical memory clinic population, using a different mix of the three clinically approved amyloid PET tracers and CL was quantified with different PET-only methods. **Key words:** Amyloid PET, quantitative PET, clinical population, diagnostic, PET-only quantification

LP041- IMPROVED DIFFERENTIAL DIAGNOSIS OF HYDROCEPHALUS EX VACUO AND IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS BY INTEGRATING RADSCALE AND DILATATION OF PERIHIPPOCAMPAL FISSURE.

J.I. Lim[1], S.Y. Lee[1], M.K. Kim[2], S.W. Park[3], J.Y. Lee[1], J.H. Rhim[2], J.Y. Lee[4], Y.K. Kim[5], S.H. Lee[6] *(1. Department of Psychiatry, SMG-SNU Boramae Medical Center - Seoul (Korea, Republic of), 2. Seoul National University College of Medicine - Seoul (Korea, Republic of), 3. Department of Radiology, SMG-SNU Boramae Medical Center - Seoul (Korea, Republic of), 4. Department of Neurology, SMG-SNU Boramae Medical Center - Seoul (Korea, Republic of), 5. Department of Nuclear Medicine, SMG-SNU Boramae Medical Center - Seoul (Korea, Republic of), 6. Department of Neurosurgery, SMG-SNU Boramae Medical Center - Seoul (Korea, Republic of))*

Background: Alzheimer's disease (AD) and idiopathic normal pressure hydrocephalus (iNPH) are characterized by moderate to severe ventriculomegaly, making it difficult to distinguish between two diseases. iNPH Radscale is a combined scoring of seven different structural imaging markers to differentiate iNPH from healthy controls, but may be insufficient to distinguish iNPH and hydrocephalus ex vacuo caused by AD. Another key feature of AD is significant hippocampal atrophy, which can be identified as dilatation of the perihippocampal fissure (PHF). This study aims to investigate single radiological scales and composite indexes as clinically useful tools to distinguish hydrocephalus ex vacuo and iNPH. **Methods:** A total of 54 patients with ventriculomegaly (iNPH, 25; hydrocephalus ex vacuo, 29) were recruited in this study. Two radiologists rated nine

parameters using magnetic resonance imaging (Evan's index, height of Sylvian fissures, width of temporal horns, degree of callosal angle, superior parietal sulci narrowing, focally enlarged cerebral sulci, periventricular hypodensities, Radscale, and PHF scale). **Results:** The height of Sylvian fissure ($p < 0.01$), the degree of callosal angle ($p < 0.05$), the narrowing of superior parietal sulci ($p < 0.05$), Radscale ($p < 0.001$), and PHF scale ($p < 0.05$) significantly discriminated the iNPH group from the hydrocephalus ex vacuo group after controlling for age and global clinical dementia rating. The final binary logistic regression model included Radscale and PHF scale, and the composite score made from these two indicators was statistically different between iNPH and hydrocephalus ex vacuo. Receiver operating characteristic analysis showed an area under the curve, a sensitivity, and a specificity of 0.89, 0.72, and 0.86, respectively. **Conclusion:** The integrated index including both Radscale and PHF scale may be used as a noninvasive tool for improved differential diagnosis of between iNPH and hydrocephalus ex vacuo. **Key words:** Hydrocephalus ex vacuo, Normal pressure hydrocephalus, Alzheimer's disease, Magnetic resonance imaging, Radscale, Perihippocampal fissure. **Disclosures:** This study was supported by grant no. 26-2014-42 from the SK Telecom Research Fund. The authors have no potential conflicts of interest to disclose. **References:** 1. Kockum, K., Lilja-Lund, O., Larsson, E. M., Rosell, M., Söderström, L., Virhammar, J., & Laurell, K. (2018). The idiopathic normal-pressure hydrocephalus Radscale: A radiological scale for structured evaluation. European Journal of Neurology, 25(3), 569-576. https://doi.org/10.1111/ene.13555. 2. Kim, M., Park, S. W., Lee, J. Y., Kim, H., Rhim, J. H., Park, S., ... & Lee, S. H. (2021). Differences in brain morphology between hydrocephalus ex vacuo and idiopathic normal pressure hydrocephalus. Psychiatry Investigation, 18(7), 628-635. https://doi.org/10.30773/pi.2020.0352

LP042- CHARACTERIZATION OF DISTORTION CORRECTION ON DTI MEASUREMENTS IN A LARGE MULTI-CENTER CLINICAL TRIAL.

C. Conklin[1], S. Radonjic[1], L. Bracoud[1], M. Ingalhalikar[1], S. Rathore[2], D. Otero Svaldi[2], A. Fleisher[2], D. Scott[1] *(1. Clario - Philadelphia (United States), 2. Eli Lilly and Company - Indianapolis (United States))*

Background: Diffusion Tensor Imaging (DTI) is a sensitive imaging biomarker to assess white matter and cortical microstructure in clinical trials for neurodegenerative diseases, including Alzheimer's Disease (AD). Understanding how Alzheimer's therapies affect the trajectory of microstructural changes in the brain is becoming increasingly important in the field. To adequately assess this in a clinical trial setting, minimizing scanner variability and ensuring quality of regional measures across scanners is essential for deriving accurate DTI endpoints, given the number and variety of MRI scanners involved in a global multi-center trial. **Methods:** Screening DTI data for 229 subjects across 38 unique scanners (4 GE 1.5T, 13 GE 3T, 3 Philips 1.5T, 3 Philips 3T, 1 Siemens 1.5T and 14 Siemens 3T) participating in the Eli Lilly 19X-MC-MTAE trial in early symptomatic AD were analyzed. DTI imaging parameters included 2mm3 voxels,30 directions, with b-values of 0 and 1000. Additionally, separate b0 reverse phase encode sequence with identical parameters was acquired for distortion correction. Parallel imaging was only used on 3T scanners. All DTI data were motion corrected, co-registered to native b0, distortion corrected (DC) [1-3] and skull stripped for registration to template space prior to tensor estimation. Data was analyzed following the same pipeline with and without distortion correction. DTI measures of fractional anisotropy (FA), mean diffusivity (MD), and free water fraction were derived. The effects of distortion correction on the variability and magnitude of regional DTI measures were assessed using pair-wise comparisons of the derived DTI measures. Subject 3DT1 sequences with 1.25x1.25x1.2 mm3 voxels were parcellated through FreeSurfer [4] to generate the cortical/sub-cortical parcellations needed for regional statistics. White matter regions of interest were obtained through the JHU atlas [5]. **Results:** Statistically significant differences in whole brain DTI metrics were observed between vendors and field strengths prior to and following distortion correction. Large effects (Cohen's d, marginal significance $p < 0.05$) were seen in mean FA between DC data and non-DC data in the whole brain (0.89), whole WM (0.73), whole GM (0.81) aggregates, and regionally in orbital frontal cortex (0.86), temporal cortex (0.85), and sagittal stratum tract (0.77). The distortion correction step was associated with a 70% reduction in mean free water corrected MD standard deviation for whole brain, whole GM, and temporal regions. The magnitude of free water estimates within the sagittal stratum, internal capsule, and pontine crossing tract were lower following distortion correction (effect size > 0.7, marginal significance $p < 0.05$). **Conclusion:** We describe standardized MRI acquisition and processing toward reducing variability and improving accuracy of DTI measurements in a large multi-site clinical trial. Application of distortion correction significantly affected DTI measures across several brain regions. Distortion correction reduced variability in MD measures across scanners. Additionally, distortion correction led to decreased freewater magnitude in the white matter, suggestive of improved segmentation of true white matter voxels. As local availability of DTI licenses on clinical scanners participating in clinical trials is becoming more common, the assessment and control of variability across sites becomes an integral part of deriving reliable endpoints. **Key words:** Diffusion Tensor Imaging, Distortion Correction, Alzheimer's Disease. **Disclosures:** Chris Conklin, Stefan Radonjic, Luc Bracoud, Madhura Ingalhalikar are full-time employees or consultants of either Clario and have nothing to disclose. Saima Rathore, Diana Svaldi, and Adam Fleischer are full-time employees of Eli Lilly and Company. **References:** 1. C. Pierpaoli, L. Walker, M. O. Irfanoglu, A. Barnett, P. Basser, L-C. Chang, C. Koay, S. Pajevic, G. Rohde, J. Sarlls, and M. Wu, 2010, TORTOISE: an integrated software package for processing of diffusion MRI data, ISMRM 18th annual meeting, Stockholm, Sweden, abstract #1597. 2. Mustafa Okan Irfanoglu, Amritha Nayak, Jeffrey Jenkins, and Carlo Pierpaoli ,TORTOISEv3:Improvements and New Features of the NIH Diffusion MRI Processing Pipeline, ISMRM 25th annual meeting, Honolulu, HI, abstract #3540. 3. Irfanoglu MO, Modi P, Nayak A, Hutchinson EB, Sarlls J, Pierpaoli C.DR-BUDDI (Diffeomorphic Registration for Blip-Up blip-Down Diffusion Imaging) method for correcting echo planar imaging distortions, Neuroimage. 2015 Feb 1;106:284-99. doi: 10.1016/j.neuroimage.2014.11.042. Epub 2014 Nov 26. 4. Fischl, et al. Whole Brain Segmentation: Automated Labeling of Neuroanatomical Structures in the Human Brain, Neuron. 2002; doi: 10.1016/s0896-6273(02)00569-x. 5. Mori et al. MRI Atlas of Human White Matter, Elsevier 2005.

CLINICAL TRIALS: BIOMARKERS INCLUDING PLASMA

P064- THE VIEWMIND AI SOLUTION (VIMAS) DETECTS AND CHARACTERISES NEUROCOGNITIVE DECLINE ALONG THE ALZHEIMER'S DISEASE CONTINUUM.

M.A. Parra[1], F. Lopera Restrepo[2], G. Fernandez[3], D. Verge[4]
(1. University of Strathclyde - Glasgow (United Kingdom), 2. Grupo de Neurociencias - Antioquia (Colombia), 3. ViewMind - Bahia Blanca (Argentina), 4. ViewMind - West Chester (United States))

Background: Dementia prevention entails both early detection and effective treatments. Recent advances in drug developments have started to address the latter need. However, the former need remains largely unmet. Clinical trials for Alzheimer's disease (AD) still rely on costly biomarkers for screening purposes (Aβ-PET) which fail to meet recruitment targets albeit their prohibitive costs (Insel et al., 2020). Pre-screening with reliable and low-cost neurocognitive biomarkers can address this challenge. We present a series of studies carried out to support the validity of a novel digital neurocognitive biomarkers to tackle such unmet needs. The novel ViewMind AI Solution combines state of the art cognitive markers, high precision eye-tracking metrics (ET), and AI to address four outstanding needs in AD diagnosis and care: (1) preclinical detection, (2) risk profiling and prediction, (3) differential diagnosis and (4) culture-free assessments. **Methods:** The ViewMind AI Solution records ET variables during memory binding (Parra et al., 2011). The task assesses low-level integrative memory abilities, and it has been proposed as a novel memory marker for AD (Costa et al., 2017; Rentz et al., 2013). Here we report on a series of studies involving 246 participants recruited from different cohorts, countries, and demographics. They underwent standard clinical, functional, and neuropsychological assessments. Study 1 investigated ViewMind AI Solution's sensitivity to normal ageing in a sample of healthy young (n=25) and older adults (n=25) collected in Scotland. Study 2 and 3 aimed to confirm its sensitivity to AD dementia. Samples of healthy controls (n = 13 and 18) and AD patients (n = 13 and 18) collected at the Axis Neuroscience Centre of Bahia Blanca Argentina entered study 2 and 3, respectively. Study 4 and 5 focused on early detection including cases in the prodromal and pre-symptomatic stages of AD. Study 4 followed up longitudinally 65 patients with Mild Cognitive Impairment (MCI) and 42 controls all recruited at Axis Neuroscience Centre. Study 5 involved a sample of carriers of the mutation E280A-PSEN1 (16 asymptomatic and 11 symptomatic) who will inevitably develop familial AD (Lopera et al., 1997). Each group had a respective control group (n = 56 and 28, respectively). **Results:** Study 1 confirmed that the ViewMind AI Solution, including its behavioural and ET measures (i.e., gaze duration and pupil behaviours), is not affected by normal ageing (in preparation). Gaze duration significantly differentiated AD patients from controls in Study 2 and in Study 3, with pupil behaviours achieving values of sensitivity and specificity of 100% (Fernández & Parra, 2021). Baseline data from study 4 prospectively predicted AD dementia achieving, at year three, a PPV of 94% and a NPV of 100% (Parra et al., 2022). A Random Forest Model involved a 5-fold cross-validation approach with 80% of the data randomly selected for training and 20% for testing. This model separated symptomatic carriers from controls with 100% accuracy (False Negative Rate = 0%, NPV and PPV = 100%). In the case of asymptomatic carriers, the model achieved 96% accuracy (False Negative Rate = 0%, NPV = 100%, and PPV = 93%) (in preparation). **Conclusion:** The ViewMind AI Solution holds sensitivity for AD across its continuum. It can detect who is likely to develop cognitive impairment when still in the healthy aging group and who will eventually progress to dementia when in the early or advanced prodromal stages. ViewMind AI Solution can aid AD pharmacological trials by pre-screening candidates who will likely meet Aβ+ criterion thus increasing recruitment accuracy and significantly reducing trials cost. **Key words:** Alzheimer's disease, Eye-Tracking, Cognitive Markers, AI, Biomarkers, Preclinical Detection. **Disclosures:** MAP and FL are consultants for ViewMind serving as Neuroscientific Officer and Clinical Advisor, respectively. GF is ViewMind Chief Scientific Officer. **References:** Costa, A., Bak, T., Caffarra, P., Caltagirone, C., Ceccaldi, M., Collette, F., Crutch, S., Della Sala, S., Demonet, J. F., Dubois, B., Duzel, E., Nestor, P., Papageorgiou, S. G., Salmon, E., Sikkes, S., Tiraboschi, P., van der Flier, W. M., Visser, P. J., & Cappa, S. F. (2017). 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P065- PREDICTING COGNITIVE STAGE TRANSITION USING P-TAU181, CENTILOID, AND OTHER MEASURES.

S.H. Koh[1], H.S. Kwon[1], Y. Lee[1], H.J. Yu[2], S.H. Choi[2], H. Kim[1]
(1. Hanyang University Guri Hospital - Guri (Korea, Republic of), 2. Bundang Jesaeng Hospital - Seongnam (Korea, Republic of))

Background: A combination of plasma phospho-tau (p-tau), amyloid beta (Aβ)-positron emission tomography (PET), brain magnetic resonance imaging, cognitive function tests, and other biomarkers might predict future cognitive decline. This study aimed to investigate the efficacy of combining these biomarkers in predicting future cognitive stage transitions within 3 years.

Methods: Among the participants in the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE-V) study, 49 mild cognitive impairment (MCI) and 113 cognitively unimpaired (CU) participants with Aβ-PET and brain imaging data were analyzed. **Results:** Older age, increased plasma p-tau181, Aβ-PET positivity, and decreased semantic fluency were independently associated with cognitive stage transitions. Combining age, p-tau181, the Centiloid scale, semantic fluency, and hippocampal volume produced high predictive value in predicting future cognitive stage transition (area under the curve = 0.879). **Conclusions:** Plasma p-tau181 and Centiloid scale alone or in combination with other biomarkers, might predict future cognitive stage transition in non-dementia patients. **Highlights:** Plasma p-tau181 and Centiloid scale might predict future cognitive stage transition. -Combining them or adding other biomarkers increased the predictive value. -Factors that independently associated with cognitive stage transition were demonstrated. **Key words:** dementia, Alzheimer's disease, centiloid, p-tau181. **Disclosures:** The authors report no conflict of interest

P066- RELATIONSHIP BETWEEN BRAIN AMYLOID DEPOSITION AND REGIONAL ELECTROENCEPHALOGRAM ABNORMALITIES IN OLDER ADULTS. W.J. Kim[1], J. Park[2] *(1. Yonsei University College of Medicine - Yongin-Si, Gyeonggi-Do (Korea, Republic of), 2. National Health Insurance Service Ilsan Hospital - Goyang-Si, Gyeonggi-Do (Korea, Republic of))*

Background: Amyloid PET has been widely used for research and clinical practice; however, determining other markers is still important owing to its problems with radiation exposure. In an animal study, changes in theta wave were reported in the hippocampus even very early in the disease, when histologically negligible accumulation of amyloid beta was observed. In a magnetoencephalography study, patients with amyloid-positive MCI had higher theta power in both hippocampi compared to those with amyloid-negative SCD. Although quantitative EEG can be expected to serve as a marker for amyloid deposition, it possesses problems of low spatial resolution and detection abnormality of basal portion of brain. We aimed to determine EEG markers related to amyloid deposition through amyloid PET and EEG analysis using a three-dimensional source localization method. **Methods:** Amyloid deposition was measured using amyloid PET, and the SUVR for each region of interest was obtained through analysis using a partial volume effect correlation technique. EEG was measured in a resting state with eyes closed, and source localization of EEG was calculated by applying it to an individual brain model constructed using the participants' MRI. Relative power was calculated for each band of alpha, beta, theta, and delta for each region of interest used for PET. The correlation between regional relative EEG power and SUVR was analyzed. Imaging data were processed using statistical parametric mapping and the PETPVE12 toolbox implemented in Matlab R2021. From September 2020 to April 2021, 165 older adults including NL, SCD, and MCI were recruited through community advertisements. **Results:** A total of 165 participants were enrolled and 147 completed assessments; 110 participants with more than 240 seconds of effective EEG data were included in the final analysis. Participants had a mean age of 73.12 (±4.21) years and 70% were female; The mean MMSE, CDR, and GDS scores were 26.69 (±2.5), 0.2 (±0.25), and 1.40 (±0.62), respectively. No significant difference was observed in the clinical characteristics between the included and excluded groups in the analysis. Hippocampal relative theta power and SUVR demonstrated a significant positive correlation (r=0.253, p=0.008); no significant correlation was observed in other regions. The same correlation was observed in the analysis of only the amyloid-negative NL and amyloid-negative SCD groups with (R=0.265, p=0.014). An increase in relative theta power in the hippocampus correlated with a decrease in the delayed recall function as measured by verbal learning tests (r=-0.224, p=0.019). The subgroup analysis also demonstrated the same significant correlation (r=-0.243, p=0.024). **Conclusion:** This study found that an increase in the relative theta power in the hippocampus was related to an increase in the amyloid deposition, consistent with previous studies. Hippocampal hyperactivity is one of the major mechanisms of brain toxicity in animal models of AD. Amyloid deposition itself influences hippocampal hyperactivity, the results of this study suggest that this mechanism also works in humans. Since this relationship was observed in the amyloid-negative NL and SCD groups, whether it can be used as a very early indicator of amyloid deposition needs to be confirmed through follow-up studies.

P067- RELATIONSHIP BETWEEN TELOMERE SHORTENING AND EARLY SUBJECTIVE DEPRESSIVE SYMPTOMS AND COGNITIVE COMPLAINTS IN OLDER ADULTS. S.H. Koh[1], H.J. Yu[2], K.H. Park[3], S.H. Choi[4] *(1. Department of Neurology, College of Medicine, Hanyang University - Guri (Korea, Republic of), 2. Bundang Jesaeng Hospital - Seongnam (Korea, Republic of), 3. Department of Neurology, College of Medicine, Gachon University Gil Medical Center - Incheon (Korea, Republic of), 4. Department of Neurology, College of Medicine, Inha University Medical Center - 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. **Key words:** Telomere length, Cognitive impairment, Depression. **Disclosures:** There is no conflict of interest.

P068- DIRECT COMPARISON OF FOUR BLOOD PLASMA-BASED BIOMARKERS IN PRECLINICAL ALZHEIMER'S DISEASE. P. Snyder[1], J. Alber[1], A. Jeromin[2], L. Chaby[2], S. Portbury[2], L. Thompson[3], J. Strenger[4], P.J.S.N.Y. Price[1] *(1. The University of Rhode Island - Kingston (United States), 2. ALZpath, Inc. - Carlsbad (United States), 3. Alpert Medical School of Brown University - Providence (United States), 4. Butler Hospital - Providence (United States))*

Background: Although tremendous recent progress has been made in developing blood plasma-based biomarkers for the detection of Alzheimer's disease (AD), more work is required to understand the sensitivities of these markers at the preclinical disease stage, as well as their specificities for identifying high-risk for AD vs. healthy normal aging in individuals without clinical symptoms. We compared three different blood plasma biomarkers for AD (Aβ 40/42 ratio, pTau181, and pTau217) and one marker of general axonal damage and neurodegeneration (neurofilament light chain; NfL) in Low-Risk (LR) versus High-Risk (HR) cognitively healthy adults, all enrolled in a larger study aimed at developing retinal imaging screening markers for AD. **Methods:** All participants were recruited via community advertisements within the Providence, Rhode Island greater metropolitan area. All subjects were between 55-80 years of age and presented with no cognitive impairments. LR subjects (N = 43; mean age = 65 years; 30 females) did not carry any APOE ε4 allele, had no family histories for AD, nor any cognitive complaints. HR subjects (N = 55; mean age = 66 years; 34 females) carried one or two copies of the APOE ε4 allele, all had a biological parent who had succumbed to AD and reported subjective memory concerns. Both groups had mean MoCA general cognition scores of 27, nearly identical SDs of ~1.7 points. NfL, Aβ 40/42 ratio, and pTau181 assays were all performed by single molecule array (SIMOA) platform technology by Quanterix (Lexington, MA) in the laboratory of Dr. Sid O'Bryant (Univ. of North Texas Health Sciences Center). Plasma pTau217 was measured with a novel validated SIMOA assay, developed by one of us (A.J.) for ALZPath, Inc. **Results:** A difference between high and low risk for AD was observed only with the pTau217 assay (between-groups difference, HR > LR, p = 0.03). Both the plasma NfL and pTau181 concentrations (pg/ml) showed main effects for age (NfL: slope = 0.52, p < .0001, R2 = 0.41; pTau181: slope = 0.11, p < .0024, R2 = 0.27), and no between-group differences. Neither the plasma Aβ 40/42 ratio, nor the pTau217 assay showed main effects for age. For a subset of 25 subjects for whom Florbetapen amyloid PET imaging was available, group differences (elevated vs. non-elevated neocortical amyloidosis) were found for both the plasma Aβ 40/42 ratio (HR < LR, t = 1.98, df = 21, p = 0.03) and for the pTau217 assay (HR > LR, t = -3.89, df = 19, p = 0.00005), but this between-groups difference was considerably more robust for the pTau217 assay (AUC = 0.850). **Conclusions:** In this sample of cognitively healthy adults (mean age = 65 years), an assay for pTau217 was superior for both separating those with familial and genetic risk for AD from a comparator group of low-risk individuals, as well as reliably identifing those with elevated neocortical amyloidosis. The plasma beta-amyloid, NfL and pTau181 assays all showed main effects for aging, and neurofilament light chain concentrations had no specific relationship to disease risk. **Key words:** Blood Plasma, Biomarkers, Early Detection, Phospho-tau, pTau217, Alzheimer's DIsease. **Disclosures:** Corresponding Author: Dr. Peter J. Snyder (pjsnyder@uriedu). This study was supported by a grant to P.J.S. by the MPM Health Foundation (Clearwater, FL). A.J. serves as the Chief Science Officer, and P.J.S. serves as a Scientific Advisory Board member to ALZPath, Inc. Neither A.J. nor any staff member of ALZPath were involved in any portion of the study conduct, data analyses or interpretation of results. All other authors report no relevant disclosures.

P069- BLOOD RNAS AS FLUID BIOMARKERS FOR THE DIFFERENTIATION BETWEEN ALZHEIMER'S DISEASE AND DEMENTIA WITH LEWY BODIES. K. Beyer[1], J. Mena[1], D. Adamuz[1], D. Vilas[2], I. Lourdes[2], Á. Ramiro[2], P. Pau[2] *(1. Research Institute Germans Trias i Pujol - Badalona (Spain), 2. Hospital Germans Trias i Pujol - Badalona (Spain))*

Background: Dementia with Lewy bodies (DLB), the second most frequent degenerative dementia after Alzheimer's disease (AD), is still heavily underdiagnosed. When misdiagnosed, it is mostly classified as AD increasing the risk of inadequate treatments. Another major problem associated with DLB misdiagnosis is the suboptimal selection of patients to be included in AD clinical trials, and a very slow inclusion rate of patients for DLB clinical trials. Over the past years there has been significant advance in differential diagnosis of DLB, as by the development of seeding assays, permitting the detection of oligomeric alpha-synuclein (AS) species in cerebrospinal fluid (CSF). However, CSF obtaining is highly invasive, thus there is an urgent need of easily obtainable and cost-effective biomarkers to facilitate an accurate DLB diagnosis. We have been developing blood-based biomarkers, matching these characteristics. Here, we present the results of an on-going validation study of combining platelet-derived miRNAs and blood SNCA mRNAs, which includes individuals at prodromal disease stages. **Methods:** The participants were 99 individuals recruited from three Barcelona hospitals, divided into three main cohorts: 38 DLB patients, 21 of them fulfilling criteria for probable DLB and 17 for prodromal DLB, 37 AD patients, 21 fulfilling criteria for probable AD including 15 patients with early onset AD (EOAD), and 16 for MCI-AD, and 24 disease-free participants without familial history of dementia as controls (CTRLs). Whole blood, platelet-depleted blood, and platelets were obtained. After RNA purification and retrotranscription, 12 miRNAs are quantified using miRCURY LNA miRNA Custom PCR Panels and five SNCA isoforms by quantitative real-time PCR. Statistical analysis uses the following tests: the ddCt method, Wilcoxon-Mann-Whitney test, two-tailed unpaired T-test, stepwise multiple regression; for multiple comparisons Kruskal-Wallis non-parametric test and multiple corrections Dunn's test; ROC curve calculation. **Results:** Expression of hsa-miR-N°4 was decreased in DLB, including pDLB, compared to CTRLs (p=0.013), AD (p=0.021), MCI-AD (p=0.008), overexpressed in MCI-AD compared to controls (p=0.032) and markedly diminished pDLB vs MCI-AD (p<0.005). Expression of hsa-miR-N°7 was also decreased in DLB, including pDLB, compared to CTRLs (p=0.035), AD (p=0.048), MCI-AD (p=0.042), but remained unchanged in AD and MCI-AD compared to CTRLs. Hsa-miR-N°11 was increased in DLB compared to all other groups (p<0.05). SNCA isoform expression is ongoing and shows that the main SNCA isoforms are inversely expressed in DLB and AD. In whole blood, SNCA mRNA is increased by 20% in AD and decreased by 25% in DLB (p=0.009), in platelets it is decreased by 40% in AD and unchanged in DLB (p=0.019). The most important difference in SNCA isoform expression was observed in platelet-depleted blood. An increase between 50-120% was observed in AD (p<0.001) and a decrease of 19% in DLB (p=0.037) resulting in robust differences between AD and DLB (p>0.001). **Conclusion:**

We present a combined non-invasive and cost-effective biomarker suitable for: (1) a reliable clinical diagnosis assuring adequate disease management, and (2) patient stratification previous inclusion in clinical trials for AD or DLB. The combination of platelet-derived miRNAs and SNCA-isoforms from whole and platelet-depleted blood increase substantially the diagnostic potential for DLB and its differentiation from AD throughout different disease stages. **Key words:** whole blood, platelets, RNA biomarkers, Alzheimer disease, dementia with Lewy bodies. **Disclosures:** The authors declared no competing interests.

P070- SYSTEMATIC LITERATURE REVIEW OF THE CLINICAL AND NON-CLINICAL VALUE OF IMAGING AND FLUID BIOMARKER TESTING TO DIAGNOSE, IDENTIFY AND MONITOR PATIENTS WITH ALZHEIMER'S DISEASE. S. Masud[1], H. Hu[2], S. Menon[1], M. Strait[1], C. Siegfried[1], E. Somers[2], C. Plaideau[1] *(1. Veranex - Boston (United States), 2. Eisai Inc. - Nutley (United States))*

Background: Understanding the validity and utility of tests used to diagnose and monitor patients with early Alzheimer's Disease (AD) is essential for informed care management decisions, including treatment with recently approved amyloid-targeting monoclonal antibody therapies. While amyloid positron emission tomography (PET) is the current gold standard in the US, there has been a rapid increase in the number of studies evaluating the use of biomarkers such as β-amyloid (Aβ), and Tau detected in cerebrospinal fluid (CSF) and plasma as alternative testing modalities. The purpose of this study was to characterize the clinical evidence of established and emerging AD tests, while also summarizing information related to the non-clinical value of the test such as costs or patient wait times. **Methods:** Medline/PubMed was searched to identify full-text articles published between 1/2018 -12/2022 examining clinical and non-clinical value of AD biomarker tests. We included studies that evaluated Aβ, Tau, glial fibrillary acidic protein (GFAP) and apolipoprotein E (APOE) biomarkers across different modalities and sample types (PET, CSF, and blood-based biomarker [BBB] tests). The target population was limited to adults with mild cognitive impairment or mild dementia due to AD. In addition, studies were required to address diagnostic precision (analytical validity [AV]), test performance compared to a reference standard (clinical validity [CV]), the test's impact on diagnostic thinking, therapeutic decision-making, patient outcomes (clinical utility [CU]), or related non-clinical utility (NCU) parameters. We analyzed the quality of evidence, evidence gaps, and temporal trends of included studies by test type. **Results:** Out of a total of 2,299 studies identified, we included 136 articles that met the inclusion criteria in our systematic literature review. Across all biomarkers and modalities, we observed that 116/136 studies (85%) focused on the CV of testing. Our analysis further indicated that CU studies were limited and only available for Aβ and Tau CSF testing and Aβ and Tau PET. NCU studies were found for Aβ and Tau CSF and BBB tests. We found that between 2018 and 2022, there was an 8-fold increase in the number of articles supporting the clinical and non-clinical value of Aβ and Tau BBB tests compared to little or no increase for CSF, PET, and APOE tests. **Conclusion:** Our review of the literature from the past 5 years shows that most studies demonstrate the diagnostic performance of AD testing (CV). A smaller number of high-quality studies demonstrate the CU of PET and CSF testing for Aβ and Tau. Although there are no CU studies to date for BBB, there are several studies demonstrating its NCU. Due to the potential impact of CSF and BBB testing on healthcare costs and AD patient journey, it will be critical to track future studies of the value of these emerging test modalities. **Key words:** precision medicine, Alzheimer's Disease, biomarkers, diagnostics. **Disclosures:** This project was funded by Eisai Inc.

P071- SERUM TAU-A AND TAU-C LEVELS AND THEIR ASSOCIATION WITH COGNITIVE IMPAIRMENT AND DEMENTIA PROGRESSION IN A MEMORY CLINIC DERIVED COHORT. T.M.A. Axelsen[1,2,3], P.H. Høgh[4,5], A.B. Bihlet[6], M.K. Karsdal[2], K.H. Henriksen[2], S.G. Hasselbalch[7], A.H. Simonsen[5,7] *(1. Department of Biomedical Sciences, University of Copenhagen - Copenhagen (Denmark), 2. Nordic Bioscience - Herlev (Denmark), 3. Sanos Clinic, Herlev, Denmark - Herlev (Denmark), 4. Regional Dementia Research Centre, Department of Neurology, Zealand University Hospital - Roskilde (Denmark), 5. Department of Clinical Medicine, University of Copenhagen - Copenhagen (Denmark), 6. NBCD - Søborg (Denmark), 7. Danish Dementia Research Centre (DDRC), Department of Neurology, Rigshospitalet - Copenhagen (Denmark))*

Background: Low levels of serum-measured fragments of Tau cleaved by ADAM-10 (Tau-A) and Caspase-3 (Tau-C) have been found linked to Alzheimer's disease related single nucleotide polymorphisms, change in cognitive function, and risk of dementia. **Methods:** In a cross-sectional study design, competitive enzyme-linked immunosorbent assay (ELISA)-measured levels of Tau-A and Tau-C were compared between groups in a memory-clinic-derived cohort of cognitively unimpaired (CU) subjects (n=49), patients with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) (n=45), and in a group with Alzheimer's dementia (n=52) using ANOVA for crude comparison and ANCOVA tests for adjusted values. Serum levels of Tau-A and Tau-C were correlated to established cerebrospinal fluid (CSF)-markers of AD – β-Amyloid1-42 (AB42), Phosphorylated-tau-181 (p-tau), and total-tau using Pearson correlation. The MCI due to AD group were followed up retrospectively and levels of Tau-fragments were correlated to the time from MCI-diagnosis to progression to dementia using cox-regression. **Results:** The ratio between Tau-A and Tau-C differed between the three groups (p=0.015) CU mean 1.07 (95% confidence interval (CI) 0.95 to 1.21), MCI group mean 1.03 (95%CI 0.89 to 1.21) and AD dementia group 0.83 (95% CI 0.74 to 1.07). Age- and sex-adjusted Tau-A levels differed between groups (p=0.023) with estimated marginal mean values of 34.52 (95% CI 29.36 to 40.57) ng/ml for CU, 27.91 (95%CI 23.76 to 32.79) ng/ml for MCI and 24.97 (95%CI 21.44 to 29.07) ng/ml for AD dementia. Tau-C was trending towards significant correlation to CSF-levels of AB42 (Pearson correlation coefficient 0.164, p=0.051). No other significant correlation between the fragments and the CSF-amyloid1-42, CSF-P-tau-181, or total tau were found. Those with Tau-C-levels in the 2nd quartile had a hazard ratio (HR) of 2.91 (95% CI 1.01 to 8.44, p=0.04) of progression compared to those in the 1st quartile. Those in the 3rd quartile was found to have a borderline significant (p=0.055) HR of 2.63 (95% CI 0.98 to 7.05) when compared to those in the lowest quartile. **Conclusions:** Lower levels of serum Tau-A and a lower ratio between Tau-A and Tau-C were associated with AD with a trend towards lower levels being associated with more advanced disease. Tau-C levels were found associated with CSF AB42 suggesting low levels of the fragments to be associated with AD and possibly dynamic throughout the disease course. Tau-C values in the middle range were associated with faster progression

from MCI to dementia, which may be due to subgroups in the population having different aspects of pathology driving the disease. **Key words:** Serum biomarkers, Alzheimer's Disease, Progression rate, Tau-A, Tau-C, Tau-fragments. **Disclosures:** Nordic Bioscience holds a patent on the assays for measuring serum Tau-A and Tau-C. The principal investigator's PhD-study is funded by the Danish Research Fund which has close economic ties to Nordic Bioscience A/S. Kim Henriksen and Morten A. Karsdal are employees of Nordic Bioscience and hold shares in the company.

P072- BIOMARKER RESPONSES TO GAMMA SENSORY STIMULATION IN ALZHEIMER'S DISEASE PATIENTS ASSESSED IN HOPE CLINICAL TRIAL. M. Hajos[1], M. Shpokayte[1], C. Houser[1], E. Hempel[1], C. Seshagiri[1], A. Galley[1], Z. Malchano[1], R. Kern[1] *(1. Cognito Therapeutics - Cambridge (United States))*

Background: Several clinical trials (Overture NCT03556280, Etude NCT03661034, Flicker NCT03543878) have demonstrated the safety and feasibility of Cognito Therapeutics Sensory Stimulation System in participants with Alzheimer's disease (AD). Overture, a randomized, controlled, 6-month trial also revealed clinical benefits, including significantly reduced decline in cognitive and functional abilities, as assessed by MMSE and ADCS-ADL. MRI biomarker measurements in this trial demonstrated significantly reduced brain volume loss, and no observable change in amyloid plaque burden as measured by PET SUVR (Hajós et al., 2023). Flicker, a delayed-start 8-week clinical trial showed no observed changes in CSF amyloid and tau biomarkers, however a reduction in immune factors, including a significant decrease in CSF TWEAK (He at al., 2021). Further, proteomic analysis of CSF samples from the Flicker study revealed differential expression profiles across multiple domains related to AD pathological changes (unpublished data, Emtherapro Inc./Emory University). The Flicker trial also reported improvement in brain connectivity by functional MRI (He at al., 2021). Results of these clinical trials provided guidance for design and initiation of the phase 3 HOPE trial, which includes biomarker measurements in all trial participants, as well as additional advanced biomarker assessments in a biomarker substudy. **Methods:** HOPE is a controlled, randomized (1:1), US-based multicenter trial, actively enrolling participants with AD based on clinical presentation and plasma p-tau181 positivity as a proxy for amyloid pathology. Inclusion criteria include age over 50 years and MMSE scores of 15-26. Participants in both active and sham (placebo) arm self-administer home therapy via Cognito Therapeutics Sensory Stimulation System for 60 minutes daily for 12 months. Biomarker measurements, including fluid, neuroimaging and neurophysiological signals are carried out at baseline, at 3, 6 and 12 months of treatment. **Results:** All HOPE trial participants contribute to plasma biomarkers measurements, carried out at baseline, 6 and 12 months of treatment. Plasma biomarkers include traditional AD markers, such as Aβ42, Aβ40, p-tau-181, p-tau-217, and markers of neurodegeneration and neuroinflammation (e.g., NfL, GFAP, MIP1α, IGFBP2). Brain volumetric changes will also be assessed in all participants by 3T MRI at baseline, 6 and 12 months of therapy. Prespecified brain volumes include whole brain, whole cerebral cortex, lateral ventricle, hippocampus, white matter, occipital and temporal lobe, and occipital and temporal cortical thickness. Neurophysiological measurements (resting EEG and sensory evoked steady-state oscillation) are done at baseline, and at 6 and 12 months of therapy. Additional biomarker measurements will be carried out in a HOPE biomarker substudy, including CSF amyloid and tau, neuronal and synaptic injury (VILIP-1, neurogranin, SNAP-25), and neuroinflammation, (YKL-40, TWEAK, sTREM2, HMGB1). CSF proteomic analysis will be done in collaboration with Emtherapro Inc./Emory University (Johnson et al., 2020) CSF biomarkers will be measured at baseline, 3 and 12 months of therapy. Advanced neuroimaging will be obtained (DTI, MTR) at baseline, 6 and 12 months of therapy. **Conclusions:** The planned HOPE biomarker evaluation, including advanced CSF and MRI biomarker measurements are designed to identify early efficacy biomarkers and provide insight to mode of action of gamma sensory stimulation in AD patients. **Key words:** Sensory Stimulation System, Gamma oscillation, Alzheimer's Disease. **Clinical Trial Registry:** Hope: NCT05637801. **Disclosures:** Authors are employees of, or own equities in Cognito Therapeutics. **References:** He et al., PMID: 34027028; PMCID: PMC8118113. Hajós et al., doi: https://doi.org/10.1101/2023.03.23.23287637. Johnson et al., PMID: 35115731; PMCID: PMC8825285

P073- A ROBUST AND SPECIFIC ELISA FOR N-ACETYLATED VAMP-2, A NOVEL SYNAPTIC BIOMARKER FOR ALZHEIMER'S DISEASE IN CSF. C. De Rocker[1], J. Goossens[1], A. Cervantes Gonzalez[2], A. Lleo[2], O. Belbin[2], E. Vanmechelen[1] *(1. ADx NeuroSciences - Gent (-Zwijnaarde) (Belgium), 2. CIBERNED - Madrid (Spain))*

Background: Synaptic proteins are a new target of biomarkers in Alzheimer's disease (AD) since synaptic integrity is a strong predictor of early cognitive decline in dementia. VAMP-2 (a.k.a synaptobrevin 2) is a particularly promising biomarker for AD that is associated with core AD biomarkers [1] and episodic memory [2]. While VAMP-2 was first described as a potential new synaptic biomarker using mass spectrometry, verification of VAMP-2 in immunoassay formats require an approach based on highly sensitive immunoassay platforms such as Simoa from Quanterix. **Results:** We recently reported an ELISA assay of VAMP-2 based on a newly characterized rabbit monoclonal antibody, but both the new antibody RD078 and the detector antibody showed some cross-reactivity towards VAMP-2 [3]. Because high specificity of antibodies in assays is crucial for its clinical performance, we screened a rabbit antibody library for new highly specific VAMP-2 monoclonals. Rabbits were immunized with a synthetic N-terminal acetylated peptide to generate specific antibodies to the VAMP-2 N-terminus. Two new monoclonal antibodies were characterized on Western blot on human brain extracts and recombinant (non-acetylated) VAMP proteins. In contrast to other VAMP-2 monoclonal antibodies, the new monoclonals were only reactive on brain-derived VAMP-2, illustrating their specificity for the acetylated protein. Furthermore, these new monoclonal antibodies were able to quantify VAMP-2 in CSF using sandwich ELISAs and can differentiate Alzheimer patients from controls in this matrix. **Conclusion:** In contrast to the previously established ELISA based on RD078, these newly generated monoclonals seem to be more robust, but more analytical work is needed to support this aspect. Furthermore, while the clinical performance of the VAMP-2 ELISA is comparable, the performance of the immunoassay in clinical studies on serum/plasma to differentiate AD from controls is still work in progress.

P074- ALZHEIMER'S DISEASE AND MICROBIOTA: THE MICMALZ COHORT. G.U. Busto[1,2], L.N. Mekki[3], S. Artero[3], Y. Dauvilliers[2,4], A. Gabelle[1], K. Bennys[1,2], S. Claeysen[1] *(1. Resource and Research Memory Center (CMRR), Department of Neurology, Montpellier University Hospital - Montpellier (France), 2. University of Montpellier, INSERM Institute Neuroscience Montpellier (INM), - Montpellier (France), 3. The Institute of Functional Genomics (IGF), University of Montpellier, CNRS, INSERM, Montpellier, France - Montpellier (France), 4. Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital - Montpellier (France))*

Background: Gut microbiota plays a critical role in human health and influences brain functioning (mood and cognition). Microbiota is modulated by normal aging, but also by Alzheimer's disease (AD) risk factors as poor diet or alteration of sleep patterns. Patients with AD exhibit a dysbiosis characterized by changes in the relative proportions of specific bacterial phyla [1]. Eventually, fecal microbiota transplants (FMT) can improve cognitive deficits and reduce amyloid-ß deposition, at least in mouse models of AD [2]. **Methods:** We generated a cohort of AD patients, with control participants matching on age, sex, body mass index, Mini Nutritional Assessment® and education, to sample and compare microbiota composition in the stool and blood compartments. This metagenomic study will be completed by targeted and non-targeted metabolomic analysis to inform about microbiota impact on the host. We precisely evaluated cognition, sleep parameters and dietary habits of the subjects. Moreover, stool samples from 19 patients were pooled by 4, with similar age and sex, from each group, and were transplanted in a mouse model of AD (5XFAD, n = 94) or their control littermates (n = 113) to evaluate the consequences on gut microbiota composition, memory-related behaviors and molecular and cellular biomarkers of AD physiopathology. **Results:** We generated a cohort of well characterized patients using Albert MS, 2011 diagnosis criteria at different stages of the disease and representative of mild to moderate AD patients with 45 AD patients [age 75 (SD 0.9), 51% women, mini-mental state examination (MMSE) 22 (interquartile range, IQR, 17-25)] and 37 controls [age 72 (SD 1.5), 62% women, MMSE 29 (IQR 27-30)]. Our preliminary results indicate i) a potential dysbiosis in AD patients that translates to mouse microbiota composition following FMT. A specific bacterial genus is increased both in 5XFAD and control mice potentially indicating over-representation in AD patients relative to the controls; ii) an impact of microbiota transplanted from AD patients to mouse model on memory and behavior, with an alteration of novel object recognition but also on biomarkers of AD pathology including an increase in mouse Aß1-42 expression level. **Conclusions:** Our results suggest that gut microbiota dysbiosis is associated with AD status and point to a specific bacterial genus. Moreover, FMT from AD patients in an AD mouse model recapitulates important features of the disease, with memory impairment and Aß1-42 accumulations. **Key words:** Alzheimer's disease, gut microbiota, sleep, dietary habits, mouse model. **Clinical Trial Registry:** NCT04841135. **Disclosures:** none related to this study. #The MICMALZ group. IGF: Curel T., Deri G., Ismeurt C., La Thuy, Maillou J.. CMRR: Ban D., Bruchet L.-M., Flores M., Gouirand J., Grasselli-Monboisse C., Huby S., Léger C., Manzano-Gonzalez G., Turpinat C.. Sleep: Pesenti C., Thobois O. CREFRE: Bernal T., Collet X., Waget A. Vaiomer: Fourtanier J., Lelouvier B., Servant F. **References:** 1. N. M. Vogt et al., "Gut microbiome alterations in Alzheimer's disease," Sci Rep, vol. 7, no. 1, p. 13537, Oct. 2017, doi: 10.1038/s41598-017-13601-y. 2. J. Sun et al., "Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice," Transl Psychiatry, vol. 9, no. 1, p. 189, Aug. 2019, doi: 10.1038/s41398-019-0525-3.

P075- PROTEOMIC ANALYSIS OF PLASMA IN A PHASE 2 CLINICAL TRIAL IN ALZHEIMER'S PATIENTS TO IDENTIFY PHARMACODYNAMIC BIOMARKERS OF THE S2R MODULATOR CT1812. B. Lizama[1], E. Cho[1], D. Duong[2], K. Pandey[3], C. Williams[1], A. Caggiano[1], N. Seyfried[2], V. Di Caro[1], M. Hamby[1] *(1. Cognition Therapeutics, Inc - Pittsburgh (United States), 2. Emory University School of Medicine - Atlanta (United States), 3. Emtherapro, Inc. - Atlanta (United States))*

Background: A Phase 2 randomized, double-blind, placebo-controlled 6-month trial, SHINE (NCT03507790), to study the effects the sigma-2 receptor (S2R) modulator CT1812 in patients with Alzheimer's disease (AD) is currently ongoing. An unbiased assessment of plasma proteomes from the first 24 patients of SHINE (SHINE-A) was performed to identify plasma pharmacodynamic biomarkers of CT1812, and for comparative analyses with a previous biomarker analysis identifying CSF pharmacodynamic biomarkers of CT1812. **Methods:** Tandem-mass tag mass spectrometry (TMT-MS) proteomics was performed on baseline, 1 mo, and end of study (6 mo) plasma biofluids taken from the first 24 participants that completed the SHINE 6 mo trial (SHINE-A) to test the effects of two doses (100 mg, 300 mg; given orally, once daily) of CT1812 compared to placebo in mild to moderate AD patients. Treatment effects were assessed through differential abundance analyses using two statistical levels ($p<0.1$, $p<0.05$) followed by pathway analyses (MetaCore, STRING). Plasma proteomes were compared across timepoints and to a previous CSF proteomics analysis of SHINE-A to determine whether any plasma and CSF biomarkers were commonly altered by CT1812 within cohort. **Results:** Across all samples, 1,968 proteins were detected. Hierarchical clustering and MSD analyses ($p<0.05$) demonstrated stratification of patients by treatment. At 1 mo, 94 ($p<0.1$) and 40 ($p<0.05$) proteins were found to be differentially abundant in CT1812 treated patients vs placebo; whereas at 6 mo, 103 ($p<0.1$) and 37 ($p<0.05$) proteins were found to be differentially abundant. At 1 mo, inflammatory, amyloid-beta, and beta-catenin related pathways were identified as significantly ($p<0.05$) altered. Similar pathways were affected at 6 mo (CT1812 vs placebo; $p<0.05$), but also highlighted a role of CT1812 in impacting endosomal trafficking; consistent with CT1812's mechanism elaborated in neurons in vitro. Ten proteins were commonly altered in a similar direction at both 1 and 6 mo plasma (CT1812 vs placebo; $p<0.1$). Notably, ten proteins were identified as significantly ($p<0.1$) regulated in CT1812 treated patients across plasma and CSF. **Conclusions:** Plasma biomarker findings extend beyond that previously identified in CSF, and shed light on potential biological proteins and/or pathways affected by CT1812. Comparative analyses of plasma biomarkers to that found in CSF help to home in on identification of plasma biomarkers that may reflect changes occurring in the brain versus the periphery. Future investigation is warranted to determine if plasma and CSF biomarker findings replicate in independent cohorts of AD patients. **Key words:** Amyloid-beta oligomers, TMEM97, S2R. Clinical Trial Registry: NCT03507790; https://clinicaltrials.gov/show/NCT03507790. **Disclosures:** MH, AC, CW, BL, EC, VD are employees of Cognition Therapeutics. The authors declare no competing interests. This work was supported by NIH grant AG058660.

P076- ASSOCIATIONS BETWEEN THE NIH TOOLBOX EMOTION BATTERY AND TAU PATHOLOGY IN PRECLINICAL ALZHEIMER'S DISEASE: ANALYSIS OF DATA FROM THE MULTI-SITE ARMADA STUDY. K. Yu[1], J.R. Gatchel[2], E.H. Ho[3], S. Arnold[4], H.H. Dodge[4] *(1. Layton Aging and Alzheimer's Disease Center, Department of Neurology, Oregon Health & Science University - Portland (United States), 2. Department of Psychiatry, Massachusetts General Hospital/McLean Hospital, Harvard Medical School - Boston (United States), 3. Department of Medical Social Sciences, Northwestern University - Evanston (United States), 4. Department of Neurology, Massachusetts General Hospital, Harvard Medical School - Boston (United States))*

Background: Depression has been recognized as a risk factor or prodromal condition of Alzheimer's Disease (AD), and has been shown to be associated with cerebrospinal fluid (CSF) tau, tau PET, and amyloid accumulation among older adults with normal cognition [1–10]. However, associations among broader domains of socioemotional function (e.g., psychological well-being, social satisfaction, and negative affect) and AD pathology have not been examined. This study explored the associations between socioemotional constructs measured by the NIH Toolbox Emotion Battery (NIHTB-EB) and CSF AD biomarkers in older adults with normal cognition and those with MCI/AD dementia. **Methods:** We used baseline data from the Advancing Reliable Measurement in Alzheimer's Disease and Cognitive Aging (ARMADA) study. ARMADA is a multisite study with protocols for CSF assessment at each site [11]. We selected sites that had the largest sample with CSF biomarkers for each cognitive group: (n=31 participants with normal cognition from University of Wisconsin-Madison(UW-M); n=28 with MCI or AD dementia from Emory University (EU) and Northwestern University (NU) with both sites using the comparable CSF assay protocols (labs run by ATHENA). Five CSF-derived AD biomarkers were available from the UW-M site, including P-tau, T-tau, AB42, AB42/40 ratio, and AB42/P-tau ratio. The EU and NU site has all these biomarkers except for the AB42/40 ratio. Socioemotional domains (negative affect, psychological well-being, and social satisfaction) were measured with self-reported NIH Toolbox Emotion Battery (NIHTB-EB). We ran linear regression models with participants with NC (UW-M site) and MCI/AD (EU and NU) separately and each of the CSF predictors above as separate outcomes. The model with EU and NU data controlled for site and disease stage (MCI vs. AD). Additionally, all models controlled for age, sex, and education. **Results:** The UW-M site NC sample (N=31) had a mean age of 72.6 (SD=6.1), 64.5% female, 83.9% had a bachelor's degree, and one African American. The EU and NU sample with MCI or AD (combined N=28) had a mean age of 72.2 (SD=5.6), 35.71% female, 82.1% had a bachelor's degree, and one African American. The model results with participants with NC showed that higher T-tau was associated with lower social satisfaction (B=-3.84, SE=1.35, p=.008) and higher negative affect (B=3.68, SE=1.63, p=.033). Higher P-tau was associated with lower social satisfaction (B=-0.37, SE=0.14, p=.013). None of the CSF AD biomarkers were associated with the NIHTB-EB outcomes among those with MCI or AD. **Conclusions:** Findings from this exploratory study suggest that T-tau and P-tau were associated with worse socioemotional function among older adults with normal cognition. Markers for amyloid were not related to emotional well-being regardless of disease stages. These findings support existing literature suggesting that emotional functioning may be associated with tau pathology at the preclinical stage of AD. This study contributes to the literature by examining these associations with recently developed NIHTB-EB and data from multiple research sites. Findings needed to be replicated in future studies with larger, more diverse samples and harmonized CSF assay protocols to exclude possible confounding effects. **Key words:** Neuropsychiatric symptoms; mild behavioral impairment; Tau pathology; Early detection. **Disclosures:** None. **References**: 1. d'Oleire Uquillas F, Jacobs HIL, Biddle KD, et al. Regional tau pathology and loneliness in cognitively normal older adults. Transl Psychiatry. 2018;8(1):282. doi:10.1038/s41398-018-0345-x. 2. Donovan NJ, Okereke OI, Vannini P, et al. 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P077- PLASMA PROTEIN MARKERS TO SCREEN FOR BLOOD-BRAIN BARRIER DYSFUNCTION IN ALZHEIMER'S DISEASE. B.M. Tijms[1] *(1. Amsterdam UMC - Amsterdam (Netherlands))*

Background: Between 13% and 37% of individuals with Alzheimer's disease (AD) that participated in amyloid clearing antibody trials suffered from ARIA in response to treatment (Haeberlein et al., 2022; van Dyck et al., 2022; Sims et al., 2023). It is pivotal to have markers that can be used to exclude individuals with AD who may be at increased risk for ARIA. We have discovered and validated an AD subtype that was

characterized by blood-brain barrier (BBB) dysfunction, based on cerebrospinal fluid proteomics (Tijms et al, 2020; Tijms et al., 2023). Here we aimed to determine the prevalence of AD with BBB dysfunction in 6 independent CSF proteomic cohorts, and we studied if AD with BBB dysfunction can be detected in blood. **Objectives:** 1. To study the prevalence of AD with BBB in 6 independent cohorts with CSF proteomics. 2. To detect AD with BBB dysfunction with plasma proteomics. **Methods:** We first trained a classifier to detect AD with BBB dysfunction in our discovery cohort, which included 419 AD individuals from Alzheimer center Amsterdam with available CSF proteomics (Tijms et al., 2023), of whom 56 (13.4%) had BBB dysfunction. With this classifier we predicted which individuals with AD had BBB dysfunction in 5 independent cohorts that had at least 50 individuals with AD: Modeste et al., 2023 (76 controls; 127 AD), Tijms et al., 2020 (77 controls; 235 AD), Dayon et al., 2018 (55 controls; 52 AD); Johnson et al., 2020 (cohort 1: 44 controls; 52 AD; cohort 2: 140 controls; 147 AD), and determined the prevalence of BBB dysfunction. Next, we studied to what extent AD with BBB dysfunction could be detected with plasma proteomics, in AD individuals from EMIF-AD MBD who also had plasma proteomics available (n=207). In this subset, we used machine learning to predict CSF based BBB dysfunction based on 3687 proteins from plasma as measured with somascan (3k panel). Finally, we estimated the prevalence of BBB in the remaining individuals with AD in the plasma cohort (n=353). **Results:** The prevalence of AD with BBB dysfunction was on average 18.1% (Modeste cohort: 22.8%; Tijms 2020 cohort: 23%; Dayon cohort: 16.1%; Johnson cohort 1: 3.8%; cohort 2: 14.3%). We then tested if CSF defined BBB dysfunction could be detected with blood proteomics. Using all available plasma proteins, it was possible to predict BBB dysfunction with a high accuracy of 83%. After applying the classifier to the remaining 353 AD individuals with plasma proteomics, we observed that 58(16%) had BBB dysfunction. **Conclusion:** Our results suggest that AD with BBB dysfunction can be detected in plasma with high accuracy, which may have use to screen individuals at risk for ARIA. Future studies aim to develop optimal plasma panels for AD with BBB dysfunction detection. **References:** Dayon, L. et al. Alzheimer disease pathology and the cerebrospinal fluid proteome. Alzheimer's Res Ther 10, 66 (2018). Dyck, C. H. van et al. Lecanemab in Early Alzheimer's Disease. New Engl J Med (2022) doi:10.1056/nejmoa2212948. Haeberlein, S. B. et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimer's Dis 1–14 (2022) doi:10.14283/jpad.2022.30. Johnson, E. C. B. et al. Large-scale proteomic analysis of Alzheimer's disease brain and cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation. Nature Medicine 1–31 (2020) doi:10.1038/s41591-020-0815-6. Modeste, E. S. et al. Quantitative proteomics of cerebrospinal fluid from African Americans and Caucasians reveals shared and divergent changes in Alzheimer's disease. Mol. Neurodegener. 18, 48 (2023). Sims, J. R. et al. Donanemab in Early Symptomatic Alzheimer Disease. JAMA 330, (2023). Tijms, B. M. et al. Pathophysiological subtypes of Alzheimer's disease based on cerebrospinal fluid proteomics. Brain 143, 3776–3792 (2020). Tijms, B. M. et al. Large-scale cerebrospinal fluid proteomic analysis in Alzheimer's disease patients reveals five molecular subtypes with distinct genetic risk profiles. medRxiv (2023) doi:10.1101/2023.05.10.23289793.

P078- A NOVEL PLASMA CNS-DERIVED TTAU ASSAY FOR DETECTION OF AMYLOID POSITIVITY IN ALZHEIMER'S DISEASE. G. Triana-Baltzer[1], A. Scaglione[1], S. Moughadam[1], K. Van Kolen[2], V. Raymont[3], M. Woolrich[3], J. Rowe[4], H. Kolb[1] *(1. Janssen R&D - San Diego (United States), 2. Janssen R&D - Beerse (Belgium), 3. University of Oxford - Oxford (United Kingdom), 4. University of Cambridge - Cambridge (United Kingdom))*

Background: Assays for measurement of specific phosphorylated Tau (pTau) species in plasma are now available, greatly improving the ability to detect Amyloid (A) and Tau (T) positivity in a minimally invasive manner. Some have also been used as pharmacodynamic readouts to reveal perturbation of Alzheimer's Disease (AD) pathology or target engagement. However unique therapeutic candidate mechanisms of action might impact levels of distinct phosphorylated species differentially, thus a measure of total tau might better reflect the full impact of a therapeutic intervention on soluble tau. In addition, reporting a ratio of pTau to total Tau (tTau) may provide improved diagnostic power via accounting for inter-subject comorbidity-driven tau clearance differences. Despite this need, historical measures of total tau in serum or plasma appear to be plagued by matrix interference and/or contaminated via detection of peripheral nervous system (PNS)-derived tau. It has been hypothesized that targeting the Exon4/5 junction of tau could allow for central nervous system (CNS)-origin specificity (as exon4A is only found in PNS tau), and recent experience with Simoa pTau assay development has afforded other techniques for minimizing background effects. **Methods:** A novel Simoa assay designed to recognize CNS-derived plasma tTau (Janssen CD tTau) was evaluated in technical validation experiments (linear range, sensitivity, dilution linearity, precision, spike recovery) using custom calibrant material and human plasma. Capture antibody specificity for the tau peptides of CNS-origin were confirmed via Biacore SPR. Plasma from three clinical cohorts (NTAD1, NTAD2, ACI35-1802) was probed with the CD tTau assay to evaluate concordance with established A and T assays (Aβ42/40 and p217+Tau), relative signal in Cognitively Normal (CN)/A- vs Cognitively Impaired (CI)/A+ subjects, and precision with real world samples. **Results:** Janssen plasma CD tTau assay revealed LLOD = 28 fg/ml and LLOQ = 123 fg/ml, dilution linearity from 1:4 to 1:32, and good spike recovery. SPR experiments revealed low nanomolar affinity to peptide containing the exon 4/5 junction (pT82 KD = 2.13e-09 M, hT36 KD = 5.81e-09 M), but no appreciable binding to peptides containing the exon4/4A or 4A/5 junction. Measurement of CD tTau in plasma from the NTAD 1, NTAD 2, and ACI35-1802 cohorts revealed 194/199 samples in linear range with mean CV% = 13.0+/-21.2). CD tTau concentrations correlated moderately with plasma NFL (r2 = 0.3586 and 0.4005 in NTAD cohort 1 and 2, respectively) and more strongly with plasma p217+tau (r2 = 0.7589 and 0.6153 in NTAD cohort 1 and 2, respectively). Importantly the CD tTau assay differentiated CI/A+ from CN/A- subjects (NTAD1: CN/A- mean+/-SD = 2.754+/-0.793 pg/ml, CI/A+ mean concentration = 4.233+/-1.284 pg/ml, p<0.0001. NTAD 2: CN/A- mean = 1.333+/-0.692 pg/ml, CI/A+ mean concentration = 3.238+/-2.105 pg/ml, p=0.0013). **Conclusion:** Here we report on a novel highly sensitive, accurate, and precise assay for measuring CNS-Derived tTau in plasma. The CD tTau assay only recognizes tau lacking exon4A, correlates moderately with established A-T-N markers, appear to detect more tau species than pTau assays, and differentiates subjects by amyloid status.

Additional work will focus on the assay's predictive power (and corresponding cutoffs) for amyloid and tau PET status, and for rate of change on cognitive assessments and clinical stage (MCI/AD). In addition, the assay will be evaluated for its utility as a pharmacodynamic biomarker of anti-tau treatment effects. **Key words:** Tau, Alzheimer's Disease, Biomarker, Brain. **Disclosures:** GTB, AS, SM, KVK, and HCK are employees of Janssen R&D.

P079- PHARMACODYNAMIC EFFECTS OF SEMORINEMAB ON BIOMARKERS OF TAU, SYNAPTIC FUNCTION, AND GLIOSIS IN A PHASE 2 TRIAL OF MILD-TO-MODERATE ALZHEIMER'S DISEASE (LAURIET).
S. Schauer[1], B. Toth[1], J. Lee[1], V. Anania[1], L. Honigberg[1], K. Wildsmith[1], V. Ramakrishnan[1], F. Yeh[1], M. Dolton[1], S. Sanabria Bohorquez[1], E. Teng[1], C. Monteiro[1] *(1. Genentech - South San Francisco (United States))*

Background: Semorinemab is a humanized anti-tau IgG4 monoclonal antibody under investigation as a disease-modifying treatment for Alzheimer's disease (AD). In a Phase 2 trial for mild-to-moderate AD (Lauriet, NCT03828747), patients that received semorinemab demonstrated significant reductions in cognitive decline (ADAS-Cog11) relative to placebo. However, no changes to the co-primary functional endpoint (ADCS-ADL), the secondary endpoints (CDR-SB, MMSE), or the exploratory Tau PET endpoint were observed. Longitudinal plasma and cerebrospinal fluid (CSF) samples were collected from a subset of participants for fluid biomarker assessments. **Methods:** Lauriet was a multicenter, double-blind, placebo-controlled study that enrolled 272 participants with AD aged 50-85 years, MMSE scores of 16-21, and global CDR scores of 1 or 2. Participants were randomized to receive monthly IV doses of 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. Total tau, phospho-tau181 (ptau181), phospho-tau217 (ptau217), Neurogranin (Ng), SNAP-25, Neuropentraxin-2 (NPTX2), YKL-40, and GFAP were measured with qualified ELISAs. N-terminal tau was measured using a targeted mass spectrometry method. **Results:** Semorinemab induced a >20-fold increase in plasma total tau and plasma phospho-tauT217 levels over baseline, changes indicative of peripheral target engagement. Plasma total tau plateaued by Week 5, and plasma phospho-tau217 peaked by Week 24. CSF samples were available from a subset of participants at baseline and either Week 49 or 61 post-treatment (n=53). Relative to baseline, significant annualized reductions in CSF total tau (placebo 1%, semorinemab -12%), ptau181 (placebo -1%, semorinemab -14%), and ptau217 (placebo 19%, semorinemab -27%) were observed with semorinemab but not placebo. There were no differences in N-terminal tau levels between treatment groups. Changes to a subset of synaptic and gliosis biomarkers were observed. Annualized reductions in Neurogranin and SNAP-25 were greater with semorinemab treatment (Ng: placebo -1%, semorinemab -8%; SNAP-25: placebo -2%, semorinemab -7%), but NPTX2 trended downward relative to baseline in both treatment groups over the course of the study (placebo -10%, semorinemab -10%). Concentrations of CSF YKL-40 increased with semorinemab, but not placebo (YKL-40 annualized change from baseline: placebo 1%, semorinemab 46%); plasma YKL-40 levels did not differ between treatments over the course of the study. There was no substantial difference in CSF GFAP levels between treatment groups (annualized change from baseline: placebo 5%, semorinemab 3%), but semorinemab prevented the accumulation of plasma GFAP when compared to placebo (change from baseline at Week 49: placebo 13%, semorinemab 1%, Week 61: placebo 30%, semorinemab 2%). **Conclusion:** In participants with mild-to-moderate AD, administration of semorinemab was associated with changes to plasma and CSF species of tau linked to AD pathology. These data provide evidence that semorinemab engages tau in the CNS and periphery in a manner consistent with data previously reported in prodromal-to-mild AD patients (Tauriel, NCT03289143), and that modulation of extracellular tau levels may impact synaptic biology and moderate reactive astrogliosis.

P080- CSF PROTEOMIC INSIGHTS INTO THE MECHANISM OF ACTION OF GAMMA SENSORY STIMULATION IN ALZHEIMER'S DISEASE.
K. Pandey[1], A. Singer[2], D. Duong[3], J. Lah[3], A. Levey[3], N. Seyfriend[3], M. Spokayte[4], Z. Malchano[4], M. Hajos[4] *(1. Emtherapro. Inc. - Atlanta (United States), 2. Georgia Tech - Atlanta (United States), 3. Emory University - Atlanta (United States), 4. Cognito Therapeutics - Cambridge (United States))*

Background: Preclinical transgenic mouse models of Alzheimer's disease (AD) have shown that non-invasive, visual and auditory gamma sensory stimulation diminishes AD-related pathologies. The Sensory Stimulation System is a home-use gamma sensory stimulation device developed by Cognito Therapeutics, Inc. (Cambridge, MA) to evoke steady state, EEG-confirmed, gamma oscillations in humans for the treatment of AD. In the FLICKER study (NCT03543878) ten participants with MCI due to AD were recruited from the Emory Goizueta Alzheimer's Disease Research Center (ADRC) and received 4 or 8 weeks of daily gamma sensory stimulation. Cerebrospinal fluid (CSF) was collected at baseline, 4- and 8-week follow-up time points. Unbiased proteomic analysis of CSF samples was conducted to characterize underlying mechanism of action and assess effects of treatment using sensory stimulation. **Methods:** Unbiased proteomic quantification and analysis was conducted (Emtherapro, Atlanta, GA) using tandem-mass tag spectrometry (TMT-MS) of CSF collected from FLICKER participants at baseline, 4 and 8 weeks after daily gamma sensory stimulation. CSF proteome of FLICKER participants were compared to within-study pooled AD and control CSF reference standards from the Goizueta ADRC to benchmark baseline protein levels of patients and, to assess treatment effects, via differential expression analysis (one-way ANOVA; $p<0.05$). Previous studies of 516 samples from control, asymptomatic AD and AD brains revealed 44 distinct modules related to AD (Johnson et. al., 2022). CSF proteome of FLICKER participants were mapped to the brain-derived co-expression modules to characterize underlying mechanism of action at a molecular level and, to assess effect of treatment on participants. **Results:** A total of 2,785 CSF proteins were detected across all CSF samples. Differential expression analysis of proteins from baseline (N=5) vs. FLICKER treatment (N=5, 8 weeks), normalized for baseline CSF proteomes, revealed 110 proteins that met the significance threshold of $p<.05$ with 60 proteins upregulated and 50 proteins downregulated as result of treatment. Fifty-two of the significant ($p<.05$) proteins were classified into 12 brain-derived AD modules. Treatment had a significant impact on CSF proteins linked to AD biologies represented by brain modules related to Complement/acute phase (M26), Synapse/neuron (M1), Oligo/myelination (M3), Post synaptic density (M5), and Neurotransmitter regulation (M36). Further,

GO-elite pathway analysis of the CSF proteins with altered abundance (p<0.05, no FDR correction) showed significant changes in lipoprotein regulation, metabolic processes and cholesterol activity due to gamma sensory stimulation. **Conclusions:** CSF proteomic analysis following 8 weeks of daily sensory stimulation in the FLICKER study demonstrated treatment driven upregulation and downregulation of proteins associated with AD biology. These results provide human biomarker support for previous pre-clinical findings (citation) that demonstrated a broad mechanism of gamma sensory stimulation on synaptic regulation, glial function and immunological responses. These data provide support for the evaluation of CSF proteomic biomarkers in Cognito's HOPE phase 3 trial, as a promising therapy for AD. **Key words:** Gamma Stimulation, Proteomics, Alzheimer's Disease. **Clinical Trial Registry:** NCT03543878. **Disclosures:** KP is an employee and owns shares in Emtherapro, AS owns shares in Cognito Therapeutics, NS, DD and AL are consultants to and own shares in Emtherapro, AL consultant and scientific adviser to Cognito, MS, ZM, MH are employees of and own shares in Cognito Therapeutics. **References:** Johnson et al., PMID: 35115731; PMCID: PMC8825285.

P081. CHANGES IN THE NEUROLOGY RELATED CSF PROTEOME AFTER SHORT-TERM TREATMENT WITH XPRO1595 FOR ALZHEIMER'S DISEASE. P. Pope[1], C. Barnum[1], R. Tesi[1] *(1. INmune Bio, Inc. - Boca Raton (United States))*

Background: XPro1595 is a dominant-negative protein variant of human tumor necrosis factor (TNF) that selectively neutralizes only soluble TNF. XPro1595 crosses the blood-brain barrier in pharmacologically active concentrations and was shown to decrease CSF levels of inflammatory cytokines in a recent, 12-week, phase-1b safety and dose-finding study in patients with Alzheimer's disease (AD). CSF samples were also analyzed post-hoc using a panel of 92 protein biomarkers more specific to neurological diseases [1]. Here we report results of the first analysis of CSF neurology-related proteomics affected by short-term treatment with XPro1595 in AD. **Methods:** CSF samples from patients (N=9) who completed 12-weeks of treatment with XPro1595 0.3 mg/kg/wk (n=3) or 1.0 mg/kg/wk (n=6) were selected for analysis. Concentrations of neurology-related proteins were determined by the proximity extension assay (PEA) method and reported as Normalized Protein eXpression (NPX) units on a Log2 scale. AD biomarkers were quantified using the Roche Elecsys NeuroToolKit (NTK) and reported as pg/mL. Correlations were analyzed using linear regression with a P≤0.05 threshold for identification of informative values. Treatment effects were determined by two-sided t-tests, with P-values adjusted for multiple comparisons using the Benjamini-Hochberg method and a 10% false discovery rate (FDR). **Results:** At baseline, NPX values for the neurology-related protein (NRP) representing isoforms of tau (MAPT) correlated with NTK concentrations of pTau-181 (r=0.889, P=0.001) and tTau (r=0.926, P<0.001) in CSF, thus indicating strong concordance between assays. NPX values for 33 NRPs detected within limits of quantification correlated negatively with NTK Aβ42/40 (n=27) or positively with NTK pTau-181 (n=17), or both (n=12), and were designated as AD-NRPs in this cohort. Thirty-two (97%) of the designated AD-NRPs also correlated with NTK α-synuclein (all r>0.690, P<0.05). Week-12 results showed dose-related changes in NPX values for 31 (94%) AD-NRPs, with a trend toward significant down-regulation in the high-dose group (mean NPX change from baseline = -0.26, nominal P<0.001). Correction for FDR identified dose-dependent changes from baseline in NPX values for 12 AD-NRPs (PRTG, GZMA, GFR-α-1, MSR1, MANF, JAM-B, PVR, PLXNB3, DDR1, PDGFRα, GCP5, and Gal-8); least squares mean change 0.20 vs. -0.29, low-dose vs. high-dose, respectively (all pFDR≤0.05). Statistical analysis revealed one AD-NRP (epithelial discoidin domain-containing receptor 1; DDR1) significantly downregulated after treatment with the 1.0 mg/kg/wk dose of XPro1595. DDR1 NPX decreased in all patients (n=6) in the high-dose group at week-12 (LS mean change =-0.27; 95% CI, 0.218 to 0.311; P=0.041). DDR1 was also identified through linear regression as the AD-NRP most strongly associated with Aβ42/40 at baseline (β=-0.052, R2 = 0.711, F(1,6)=14.76, P=0.009). Conversely, baseline DDR1 predicted α-synuclein (β=0.002, R2=0.646, F(1,7)=12.77, P=0.009), but not tau (pTau-181; R2=0.372, P=0.081). **Conclusions:** In this study, short-term treatment with XPro1595 in patients with AD was associated with changes in NPX values for multiple neurology-related proteins detected in CSF. Pathogenic processes specific to AD and associated with these proteins in the current literature include Aβ and cerebrovascular pathologies, blood-brain barrier permeability, myelination, neuroinflammation, neurodegeneration, and synaptic functions, among others. Additional research into the molecular pathways affected by treatment with XPro1595 is warranted. **Clinical Trial Registry:** NCT03943264; https://clinicaltrials.gov. **Disclosures:** PP's employer received a grant from the Alzheimer's Association. PP, CJB and RJT are employees of and own stock or stock options in INmune Bio. **Reference:** 1. Olink® Target 96 Neurology. Accessible: https://olink.com/products-services/target/neurology-panel/

P082- A BIOMARKER TO AID ALZHEIMER'S DISEASE STAGING: STREM2 IS DECREASED IN AMYLOID POSITIVE/TAU NEGATIVE, YET INCREASED ONCE TAU AGGREGATES LEADING TO INCREASED COGNITIVE DECLINE. R. Canovas[1], C.J. Fowler[2], S. Rainey-Smith[3,4,5,6], M. Carboni[7], I. Suridjan[7], G. Kollmorgen[8], C. Logan[9], V. Dore[1,10], J. Fripp[11], C.L. Masters[2], Q. Li[2], S.J. Collins[12], P. Maruff[13], J.D. Doecke[11] *(1. Australian E-Health Research Centre, CSIRO, Parkville - Melbourne, Vic (Australia), 2. The University of Melbourne, The Florey Institute - Melbourne, Vic (Australia), 3. Centre for Healthy Ageing, Murdoch University - Murdoch, Wa (Australia), 4. Australian Alzheimer's Research Foundation, - Perth, Wa (Australia), 5. University of Western Australia - Perth, Wa (Australia), 6. Edith Cowan University, School of Medical and Health Sciences, Centre of Excellence for Alzheimer's Disease Research & Care - Joondalup, Wa (Australia), 7. Roche Diagnostics International Ltd - Rotkreuz (Switzerland), 8. Roche Diagnostics GmbH - Penzberg (Germany), 9. Centralised & Point of Care Solutions, Roche Diagnostics GmbH - Penzberg (Germany), 10. Department of Molecular Imaging & Therapy Austin Health - Melbourne, Vic (Australia), 11. Australian E-Health Research Centre, CSIRO - Brisbane, Qld (Australia), 12. Department of Medicine & The Florey Institute, The University of Melbourne, Parkville - Melbourne, Vic (Australia), 13. Cogstate Ltd - Melbourne, Vic (Australia))*

Background: The development of high accuracy biofluid assays now allows the use of fluid-based biomarkers into Alzheimer's disease (AD) clinical pathological models. Integration of amyloid and tau biomarkers into AD models has confirmed the centrality of amyloid and tau biology in AD related neurodegeneration, and to the expression of AD symptoms, such as cognitive decline, and clinical disease progression. AD disease models are now seeking to exploit

and use validated fluid biomarkers of other neurodegenerative processes, such as neuroinflammation, to increase understanding of AD beyond amyloid and tau. The triggering receptor expressed on myeloid cells 2 (sTREM2) can be measured in the CSF, providing an opportunity to determine the extent to which measurement of neuroinflammation can add information to amyloid, tau and neurodegeneration based (ATN) models of AD related cognitive decline. **Methods:** CSF, pre-clinical Alzheimer's Cognitive Composite (PACC) scores and the Clinical Dementia Rating Sum of Boxes (CDR-SB) were collected among 237 participants from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing. CSF was assessed amongst four ATN groups at baseline; 1) A-/T-/N- (reference group), 2) A+/T±/N± (amyloid+), 3) A-/T±/N± (amyloid-), and 4) A+/T+/N+. sTREM2 was measured using the NeuroToolKit (NTK) panel of exploratory prototype assays (Roche Diagnostics International Ltd). Longitudinal change in Ab (via the Centiloid) and cognition given low/high levels of sTREM2 within ATN groups was investigated using linear mixed models. **Results:** At baseline, 176 (74%) were Cognitively Unimpaired (CU), 33 (14%) had MCI and 28 (12%) had AD. ATN groups consisted of 71 (30%) A-T-N-, 64 (27%) amyloid-, 38 (16%) amyloid+ and 64 (27%) A+T+N+. Compared with the A-T-N- group, mean levels of sTREM2 were decreased for the amyloid+ group (A-T-N-: 6.85 [SD:1.65]; amyloid+: 6.05 [SD:2.13], p=0.048), were increased substantially in the amyloid- group (8.86 [SD:2.51],p=<0.001) and then increased moderately in the A+T+N+ group (7.57 [SD:2.11], p=0.029) demonstrating increased sTREM2 associated with T/N+, but decreased in A+ prior to A/T becoming positive. Rates of Aβ accumulation were not different for participants with low/high levels of sTREM2 (p>0.05). In participants who were Aβ+, high levels of baseline sTREM2 was associated with faster cognitive decline when compared to those with low levels of sTREM2 (high β: -0.219 [SE: 0.059], low β: -0.028 [SE: 0.028], p=0.011). Similar relationships were seen for CDR-SB, albeit these were not statistically significant (p=0.168). **Conclusions:** High levels of sTREM2 aligned with T/N+ participants, whilst low levels of sTREM2 aligned with Aβ+ participants prior to accumulating Tau or exhibiting signs of neurodegeneration. As sTREM2 increases in Aβ+ patients, levels align with cognitive decline at similar rates observed in A+T+N+ participants. Thus, sTREM2 may be useful in disease staging as an early marker of Aβ positivity, prior to Tau aggregation and neurodegeneration.

P083- SEX DIFFERENCES IN AMYLOID PET: A SECONDARY ANALYSIS OF THE IMAGING DEMENTIA–EVIDENCE FOR AMYLOID SCANNING (IDEAS) STUDY. M. Abu Raya[1], E. Zeltzer[1], I.E. Allen[1], M. Carrillo[2], C. Gatsonis[3], L. Hanna[4], B.E. Hillner[5], L. Iaccarino[1], A. March[6], N. Mundada[1], J.M. Perez[1], B.A. Siegel[7], R.A. Whitmer[8], R. La Joie[1], G. Rabinovici[1] *(1. University of California San Francisco - San Francisco (United States), 2. Alzheimer Association - Usa (United States), 3. Brown University - Providence, Rhode Island (United States), 4. Brown University - Providence, Rhode Island (United States), 5. VCU Health - Virginia (United States), 6. American College of Radiology - Philadelphia (United States), 7. Washington University in St. Louis - St. Louis (United States), 8. UCDAVIS - Davis (United States))*

Background: Alzheimer's Disease is more common in females, but previous studies on sex differences in amyloid burden included small samples and yielded inconsistent results [1, 2, 3]. **Methods:** IDEAS was a single-arm longitudinal study evaluating the clinical utility of amyloid PET in Medicare beneficiaries age ≥ 65 years with MCI or dementia meeting Appropriate Use Criteria [4]. Of 18,295 acquired scans, Centiloids were successfully measured for 10,361 using a customized PET-only pipeline [5]. An autopsy-derived threshold of 24 [4] Centiloids was used to define amyloid positivity [6]. We used multivariate logistic regression to calculate odds ratios (OR) of quantitative amyloid PET positivity for males and females, after adjusting for age, education, race, ethnicity, cerebrovascular risk factors, kidney function, family history of AD, MMSE and impairment levels. We used linear regression to assess the association between sex and Centiloids after adjusting for the same variables. **Results:** Of 10,361 included individuals, 51% were females, 62.7% had MCI, and 37.3% dementia. Median (IQR) age was 75 (70-80) years for females and 76 (71-80) years for males. Rates of risk factors (traumatic brain injury; congestive heart failure; ischemic heart disease, hypertension; diabetes mellitus; dyslipidemia; stroke/TIA; tobacco use) were significantly higher in males than females, whereas females had significantly higher rates of history of depression (20% in females vs. 13% in males, p<0.001) and family history of AD (13% in females vs. 11% in males, p<0.001). Females (39.3%; 95% CI: 37.9-40.3) had higher rates of dementia than males (35.2%; CI 95%: 33.9-36.5), p<0.001). The frequency of amyloid PET positivity was higher in females (62.9%; 95% 61.6-64.2) than in males (55.3%, 95% 53.9-56.7), p<.001. Median [IQR] Centiloids was also higher in females (49 [2, 85]) than males (37 [-1, 83], p<.001). In the adjusted logistic regression, female sex was a risk factor for amyloid positivity (OR=1.359; 95% CI: 1.240, 1.490; p<.001). In the adjusted linear regression, Centiloids positively associated with female sex. The adjusted standardized coefficient is 3.6 and the R-squared contribution to the model is 5.1%. These findings remained consistent when applying the models to the MCI and dementia groups separately. **Conclusion:** Female sex is associated with higher frequency of amyloid-PET positivity and higher amyloid burden after adjusting for other demographic factors, level of impairment, and comorbidities. Sex differences in amyloid burden may have implications for eligibility and clinical response to anti-amyloid treatments. **Key words:** Dementia; MCI (Mild Cognitive Impairment); Imaging Dementia–Evidence for Amyloid Scanning Study (IDEAS); Positron emission tomography; Centiloid. **Disclosures:** The IDEAS study was funded by the Alzheimer's Association, the American College of Radiology, Avid Radiopharmaceuticals Inc (a wholly owned subsidiary of Eli Lilly and Company), General Electric Healthcare, and Life Molecular Imaging (formerly Piramal Imaging). Mr March is an employee of the American College of Radiology, and Drs Rabinovici, Siegel, Gatsonis, and Hanna receive research funding from the American College of Radiology. Dr Carrillo is an employee of the Alzheimer's Association and Drs La Joie, Rabinovici, Hillner receive research funding from the Alzheimer's Association. Dr Iaccarino is currently a full-time employee of Eli Lilly and Company / Avid Radiopharmaceuticals and a minor shareholder of Eli Lilly and Company. His contribution to the work presented in this manuscript was performed while he was affiliated with the University of California San Francisco. Dr Siegel reported receiving grants from Blue Earth Diagnostics, and Progenics Pharmaceuticals and receiving personal fees from GE Healthcare, Blue Earth Diagnostics, Avid Radiopharmaceuticals Inc, BTG Management. Dr Rabinovici reported grants from the Rainwater Charitable Foundation, Avid Radiopharmaceuticals Inc, GE Healthcare, Life Molecular Imaging, and Genentech and personal fees from Alector, Eli Lilly, Johnson & Johnson, Genentech, and Roche, and is Associate Editor of JAMA

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P084- THE MASTERMIND OF THE ALZHEIMER'S BLOOD-BASED BIOMARKERS: DEVELOPMENT OF CUTOFFS AND A VISUALIZATION TOOL FOR USE IN CLINICAL DEMENTIA PRACTICE. C. Teunissen[1], I.M.W. Verberk[1], J. Jutte[1,2], M.Y. Kingma[1,2], A.C. Van Harten[1,3], A. Den Braber[1,3], S. Vigneswaran[1,4], M. Gouda[3], M.P. Van Engelen[1,3], A.W. Lemstra[3], Y.A.L. Pijnenburg[3], W.M. Van Der Flier[3,5], M. Schut[2], D. Wilson[6] *(1. Neurochemistry Laboratory, Department of Clinical Chemistry, Amsterdam UMC, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 2. Translational Artificial Intelligence laboratory, Department of Clinical Chemistry, Amsterdam UMC, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 3. Alzheimer Center, Department of Neurology, Amsterdam UMC, Vrije Universiteit Amsterdam, - Amsterdam (Netherlands), 4. Alzheimer Center, Department of Neurology, Amsterdam UMC, Vrije Universiteit Amsterdam, - Amsterdam (Pays-Bas) - Asmterdam (Netherlands), 5. Amsterdam Public Health, Methodology & Digital Health - Amsterdam (Netherlands), 6. Quanterix - Billerica (United States))*

Background: Studies consistently show that the blood-based biomarkers phosphorylated tau (P-tau), glial fibrillary acidic protein (GFAP), amyloid-beta (Aβ)42/40 and neurofilament light (NfL) are useful to support the diagnosis of Alzheimer's disease (AD). Interpretation of results of four blood-based biomarkers simultaneously is however complex. A decision algorithm with a corresponding visualization tool will aid in the interpretation of the Alzheimer blood test results. We aim to develop a clinical decision making tool for AD plasma biomarkers. **Methods:** From the Amsterdam Dementia Cohort, we included 1199 individuals with subjective cognitive decline (SCD; n=259 amyloid negative, n=64 amyloid positive), mild cognitive impairment (MCI; n=116 amyloid negative, n=167 amyloid positive), AD-dementia (n=320), frontotemporal dementia (FTD; n=162) and dementia with Lewy bodies (DLB; n=111). Plasma biomarkers were measured with SIMOA. We guided our analyses by clinically relevant questions: identify amyloid positivity across the clinical continuum (1) and in preclinical/prodromal stages (2), discriminate AD from FTD (3) and AD from DLB (4). We applied LASSO regression with 10-fold cross validation and 1,000 interactions for panel selection. For the selected biomarkers, we established individual cutoffs at Youden's indices, and performed logistic regression analysis to calculate individualized risk scores of having AD, FTD or DLB. We developed an interpretation tool in interactive UpSet plots and histograms, combining the individual biomarker results according to their cutoffs and individualized risk scores. **Results:** LASSO regression showed that P-tau181, GFAP and NfL were robustly selected for the pre-defined clinically relevant questions, where, depending on the clinical question, P-tau181 was selected in 99-100% of the iterations, GFAP was selected in 99-100% of the iterations, and NfL was selected in 29-100% of the iterations. Aβ42/40 was never selected. UpSet plots were constructed based on Youden's cutoffs for P-tau181, GFAP and NfL, and we visualized the frequencies of patients per combination of abnormal and normal biomarker results. These plots are useful to infer the likelihood of new patients to have AD, FTD or DLB. For example, when the aim is to differentiate AD-dementia from FTD, the UpSet plots show that in our cohort 100% of the cases who scored abnormal on NfL and normal on P-tau181 and GFAP had FTD (n=29). Next, when P-tau181 is abnormal while NfL and GFAP are normal, in our cohort 89% of those cases had AD (n=89). 10-fold cross-validated logistic regression models including P-tau181, GFAP and NfL gave AUCs of AUC=0.85±0.04 to define a positive amyloid status across the Alzheimer's continuum, or AUC=0.83±0.04 when investigating the SCD and MCI stages only, of AUC=0.87±0.07 to differentiate AD-dementia and FTD, and of AUC=0.74±0.09 to differentiate AD-dementia and DLB. Results for new patients can be compared to the results obtained in histograms of this reference cohort, where we marked the Youden's index, as well as 90% sensitivity and 90% specificity lines. **Conclusions:** The UpSet plots and histograms are incorporated in one interactive Alzheimer blood test results interpretation tool. The tool will next be validated in external cohorts and in real-world clinical testing. **Disclosures:** Research of CET is supported by the European Commission (Marie Curie International Training Network, grant agreement No 860197 (MIRIADE), Innovative Medicines Initiatives 3TR (Horizon 2020, grant no 831434) EPND (IMI 2 Joint Undertaking (JU), grant No. 101034344) and JPND (bPRIDE), National MS Society (Progressive MS alliance), Alzheimer Association, Health Holland, the Dutch Research Council (ZonMW), Alzheimer Drug Discovery Foundation, The Selfridges Group Foundation, Alzheimer Netherlands. CT is recipient of ABOARD, which is a public-private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). CT is recipient of TAP-dementia, a ZonMw funded project (#10510032120003) in the context of the Dutch National Dementia Strategy. CET has a collaboration contract with ADx Neurosciences, Quanterix and Eli Lilly, performed contract research or received grants from AC-Immune, Axon Neurosciences, BioConnect, Bioorchestra, Brainstorm Therapeutics, Celgene, EIP Pharma, Eisai, Fujirebio, Grifols, Instant Nano Biosensors, Merck, Novo Nordisk, PeopleBio, Roche, Siemens, Toyama, Vivoryon. She is editor of Alzheimer Research and Therapy, and serves on editorial boards of Medidact Neurologie/Springer, and Neurology: Neuroimmunology & Neuroinflammation.

P085- AD RISK GENES FOR BLOOD-BRAIN BARRIER DYSFUNCTION. P.J. Visser[1,2,3], S. Van Der Lee[1], C. Teunissen[1], W. Vander Flier[1], F. Berven[4], B. Tijms[1] *(1. Amsterdam UMC - Amsterdam (Netherlands), 2. Maastricht University - Maastricht (Netherlands), 3. Karolinska Institute - Stockholm (Sweden), 4. University of Bergen (Norway)*

Background: Dysfunction of the blood brain barrier (BBB) is a major feature of Alzheimer's disease [1]. It may have an impact on efficacy and side effects of AD antibody-based treatments. Aim of this study is to investigate the pathophysiology of BBB in AD. To this end we tested which AD risk genes [2] were associated with BBB impairment. We tested this association both in individuals with amyloid pathology and in cognitively normal individuals with normal AD biomarkers as we previously showed that AD related BBB dysfunction may be present before amyloid pathology can be detected [3]. **Methods:** We performed untargeted mass spec

proteomics in cerebrospinal fluid (CSF) from 187 controls with normal cognition and normal CSF abeta and 419 individuals with abnormal CSF abeta from the Amsterdam Dementia Cohort. We operationalised BBB dysfunction in two ways: 1) as a continous measure of 80 proteins previously associated with increased BBB permeability (BBB-P) [2, 4] as a continous measure of 125 immunoglobulines (Ig). We first tested which genes were enriched for BBB dysfunction related proteins with a Fisher's exact test. Next we tested continous correlations of the number of risk alleles of those variants with protein levels with linear models adjusting for age and sex. Finally, we tested if genes associated with BBB dysfunction were also related to 14 proteins that are known to play a role in BBB vascular cell integrity (PDGFRB, CDH2, MFGE8 (medin), HTRA1, LAMB1, EDN1, LRP1, JAM3, CDH5, ANXA3, ICAM1, AMBP, VWF and PTPRB). **Results:** Ten genes were associated with markers of BBB dysfunction: APOE, ABI3, TSPAN14, COX7, TMEM106B, LILRB2, MYO15, MME (neprilysin) PLCG and KLF16. APOE risk alleles had the strongest effect and increasing numbers of APOE risk alleles were associated with higher levels of BBB-P and Ig in both cognitively normal individuals and AD individuals. In controls, increasing number of ABI3 and TSPAN14 risk alleles were associated with higher BBB-P and IG levels. Cox7 and TMEM106B alleles were only associated with BBB-P levels and LILRB2 alleles only with Ig levels. In AD individuals, MYO15A was associated with increasing BBB-P and Ig levels, MME (neprilysin) was only associated with BBB-P levels, and PLCG and KLF16 were only associated with Ig levels. The risk alleles of all genes, except COX7C, correlated with at least 1 BBB vascular cell damage marker. APOE, TSPAN14, and MYO15 correlated with more than 5 BBB vascular cell damage markers. **Conclusion:** About 12% of the AD GWAS genes are associated with BBB dysfunction. BBB may be a very early feature of AD, as this was already observed in older individuals with normal AD markers. AD genes associated with specific aspects of BBB dysfunction suggesting that the BBB pathophysiology is heterogeneous and that BBB dysfunction may require personal medicine approaches. **Key words:** Blood Brain barrier, proteomics. **Disclosures:** The authors declared no competing interests. **References:** 1. Tijms et al. Brain 2020, PMID: 33439986. 2. Tijms et al. Proteomes 2021, PMID: 34449748. 3. Bellenguez et al. Nat Genet. 2022, PMID: 35379992. 4. Dayon et al. Proteome Res 2019, PMID: 30702894

P086- MIP-1A SERUM LEVELS CORRELATE ALONGSIDE POSITIVE OUTCOME OF CLINICAL ENDPOINTS IN ALZHEIMER'S DISEASE PATIENTS RECEIVING PLASMA EXCHANGE WITH ALBUMIN REPLACEMENT.

C. Minguet[1], R. Gonzalo[1], A. Ortiz[1], I. Bravo[1], L. Núñez[1], A. Ruiz[2,3], O. López[4], M. Boada[2,3], A. Páez[1], M. Costa[1] *(1. Grifols - Barcelona (Spain), 2. Universitat Internacional de Catalunya, Ace Alzheimer Centre Barcelona - Barcelona (Spain), 3. Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED) - Madrid (Spain), 4. University of Pittsburgh School of Medicine - Pittsburg (United States))*

Background: Evidence suggests that pathogenesis of Alzheimer's disease (AD) goes beyond the neuronal compartment and encompasses peripheral inflammatory mechanisms that contribute to cognitive impairment. Previous studies have demonstrated that peripheral intervention performed on AD patients, such as plasma exchange with albumin replacement (PE-Alb) procedures used in the AMBAR clinical trial (NCT01561053)1, could induce both peripheral and central beneficial effects on inflammation by significantly reducing a number of proinflammatory cytokines, chemokines and vascular injury indicators2. This study assessed whether inflammatory mediators and clinical effects of the AMBAR PE-Alb treatment were associated. **Methods:** Relationship between serum levels of IFN-γ, IL-6, IL-8, IL-10, IL-13, TNF-α, Eotaxin, Eotaxin-3, IP-10, MCP-1, MCP-4, MDC, MIP1α, MIP-1β, TARC, SAA, CRP, ICAM-1, and VCAM-1, and the four AMBAR clinical efficacy endpoints of cognitive and functional measures (ADCS-ADL, ADAS-Cog, CDR-sb, and ADCS-CGIC) was assessed over time through a repeated measures correlation analysis, and a parsimonious and extended mixed models for repeated measures (MMRM) approaches. Parsimonious MMRM model comprises the change from baseline (CFB) of the clinical endpoints values as a response variable and the triple interaction term as a fix effect factor, which comprises the 19 inflammatory mediator levels, study group with control group as a reference, and study visit. Extended model also comprises adjustment for age, baseline Mini Mental State Examination (MMSE) and baseline level of clinical outcomes. The variable "Patient" was included in both models as a repeated factor. A mediation analysis was performed to ensure that statistical correlation found between inflammatory mediators and the clinical endpoints values were not derived or influenced by other variables. Predicted clinical endpoints trajectories according to levels of MIP-1α (macrophage inflammatory protein 1-alpha) from the parsimonious MMRM were assessed. MIP-1α is a granulocyte activator that causes acute neutrophilic inflammation and can induce the synthesis and release of pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α). **Results:** Results from repeated measures correlations showed that MIP-1α levels had a positive correlation with CFB of ADAS-Cog, CDR-sb, and ADCS-CGIC in control patients (r value between 0.33 and 0.22; statistically significant in ADAS-Cog and CDR-sb). Conversely, the positive correlation between Mip1α and clinical endpoints was not observed in PE-Alb treated patients. When analyzing MMRM triple interaction estimates in the parsimonious model, MIP-1α was significantly correlated with ADAS-Cog (beta: −0.73; p-value<0.05), CDR-sb (beta: −0.24; p<0.05) and ADCS-CGIC (beta: −0.16; p<0.05). Six other potential biomarkers (IFN-γ, ICAM-1, IL-8, CRP, MCP-1, and MCP-4) showed a statistically significant correlation with one of the clinical endpoints. This correlation significance was still observed when analyzing the extended model. The mediation analysis did not report any variable affecting the relationship between the triple interaction term and clinical endpoints. Predicted trajectories of clinical endpoints would support a positive effect of PE-Alb treatment, especially in those patients with high MIP-1α levels. **Conclusions:** Serum level of the inflammatory mediator MIP-1α was a sensitive and reliable biomarker for measuring efficacy of PE-Alb treatment in AD patients. Based on these findings, targeting early stages of the disease is warranted, including further investigation on MIP-1α potential. **Key words:** Alzheimer's disease, inflammation, MIP-1α, clinical endpoints. **Disclosures:** CM, RG, IB, MC, AP and LN are full time employees at Grifols. **References:** Boada, M., et al. (2019). Plasma exchange for Alzheimer's disease Management by Albumin Replacement (AMBAR) trial: Study design and progress. Alzheimers Dement (N Y), 5, 61-69. Ortiz, A. M., et al. (2021). Inflammatory biomarkers in patients undergoing therapeutic plasma exchange with albumin replacement as a treatment for Alzheimer's disease. Alzheimers Dement, 17, e057735.

P087- PROTEOMIC ANALYSES IN THE 24-WEEK PEGASUS TRIAL USING THE OLINK PLATFORM: PROVIDING INSIGHT INTO THE BIOLOGIC ACTIVITY OF SODIUM PHENYLBUTYRATE AND TAURURSODIOL IN ALZHEIMER'S DISEASE. N. Cullen[1], R. Miller[2], M. Gutierrez[2], R.E. Tanzi[3], L. Mehta[2] *(1. BioFINDER Group, Department of Clinical Sciences, Lund University - Lund (Sweden), 2. Amylyx Pharmaceuticals, Inc. - Cambridge (United States), 3. Department of Neurology, Genetics and Aging Research Unit, McCance Center for Brain Health, Massachusetts General Hospital, Harvard University - Boston (United States))*

Background: Current disease-modifying therapies for Alzheimer's disease (AD) are exclusively based on amyloid reduction; however, amyloid deposition is an upstream event in AD pathogenesis, warranting exploration of other potential disease-modifying therapeutic targets in AD. AMX0035, an oral, fixed-dose sodium phenylbutyrate and taurursodiol combination (PB&TURSO), significantly improved cerebrospinal fluid (CSF) levels of biomarkers of core AD pathology (amyloid beta [Aβ]42/Aβ40 ratio, total tau, and phosphorylated tau 181 [p-tau181]), synaptic and neuronal degeneration (neurogranin and fatty acid binding protein-3 [FABP3]), and gliosis (YKL-40, also known as chitinase 3–like protein 1) in a phase 2, randomized, placebo-controlled trial in AD (PEGASUS; NCT03533257) [Arnold SE, et al. J Prev Alzheimers Dis. 2022;9(suppl 1):S47-S48]. PB&TURSO also significantly slowed functional decline and prolonged survival in a phase 2 trial in amyotrophic lateral sclerosis [Paganoni S, et al. N Engl J Med. 2020;383(10):919-930; Paganoni S, et al. Muscle Nerve. 2022;66(2):136-141]. **Objective:** To elucidate the potential neuroprotective mechanisms of PB&TURSO in AD via analysis of broad proteomic changes in participants from PEGASUS and correlations with CSF and plasma biomarker changes. **Methods:** PEGASUS enrolled adults aged 55 to 89 years with mild cognitive impairment or mild to moderate dementia (baseline Montreal Cognitive Assessment score ≥8) with supporting biomarkers of AD pathology. Participants were randomized to receive PB&TURSO or matching placebo for 24 weeks and were permitted to continue stable dosing regimens of standard-of-care AD medications. CSF and plasma samples were prospectively collected at baseline and week 24. Participants included in this analysis received ≥1 dose of study medication and completed the study with both CSF and plasma samples having been successfully collected at baseline and week 24. A total of 288 proteins were quantified in CSF and plasma using 3 Olink protein biomarker assay panels: Target 96 Neurology, Target 96 Inflammation, and Target 96 Cardiometabolic. First, the associations between corresponding Olink proteins in CSF vs plasma were analyzed using Spearman correlation, both at baseline in the pooled treatment groups and longitudinally over 24 weeks in the placebo group. Next, changes in each CSF and plasma protein level were compared between treatment groups by fitting separate analysis of covariance models with change in protein level as the outcome and age, sex, treatment group, and baseline protein level as covariates. A standardized treatment effect for each protein was calculated. Finally, we examined the association between the 24-week changes in significantly altered proteins in the PB&TURSO group and 24-week changes in CSF levels of the following prespecified biomarkers: core AD pathology biomarkers Aβ42/Aβ40 ratio, total tau, and p-tau181; synaptic and neuronal degeneration biomarkers neurogranin, FABP3, and neurofilament light chain; gliosis biomarkers YKL-40 and glial fibrillary acidic protein; inflammation-related biomarkers interleukin (IL)-6, IL-8, IL-15, monocyte chemoattractant protein 1, macrophage inflammatory protein 1β, and matrix metalloproteinase-10; and metabolic biomarkers 8-hydroxy-2′-deoxyguanosine, soluble insulin receptor, and 24S-hydroxycholesterol (24-OHC). These associations were analyzed using linear regression, with change in the Olink protein as the outcome and change in the CSF biomarker, age, and sex as covariates. **Results:** Of 95 randomized participants in PEGASUS (PB&TURSO, n=51; placebo, n=44), 66 (PB&TURSO, n=32; placebo, n=34) had available samples for the Olink protein assays and were included in this analysis. Baseline CSF and plasma levels of corresponding Olink proteins were significantly associated for 44 proteins (15.9%) in the pooled treatment groups (correlation coefficients, 0.331-0.782). Longitudinal analysis in the placebo group showed no significant association between 24-week changes in the CSF and plasma levels for any Olink protein after adjustment for multiple comparisons; associations were nominally significant for 12 proteins, with half showing a negative correlation between CSF and plasma changes. Regarding the effect of treatment on Olink proteins, significant changes (all decreased) were observed in the PB&TURSO vs placebo group for 17 CSF proteins (MAPT, UNC5C, CLM-6, ROBO2, CNTN5, ADAM 23, LAYN, CD200, NTRK2, SKR3, CDH6, CLM-1, SPOCK1, Dkk-4, NTRK3, LAIR-2, and TWEAK). No significant between-group differences were found in the 24-week change in any plasma Olink protein. On analysis of the correlation between the changes in the 17 significantly altered proteins and changes in CSF biomarker levels in the PB&TURSO group, 15 proteins were found to be associated with CSF neurogranin; 14, with CSF p-tau181; 13 and 12, with CSF total tau from 2 different assays, respectively; 10, with CSF YKL-40; and 9, with CSF 24-OHC. Specifically, in all cases, decreases in the Olink panel protein were associated with decreases in the CSF biomarker concentration. **Conclusion:** In the 24-week PEGASUS trial, our analyses of Olink proteins showed treatment effects of PB&TURSO across a variety of biological pathways, with the largest effect in CSF related to tau and neurodegeneration. Though exploratory, these analyses provide unique insights into the biological activity of PB&TURSO in AD beyond amyloid reduction and build upon the initial biomarker findings in PEGASUS. **Disclosures:** Conflicts of interest will be listed in the presentation at CTAD.

P088- STATISTICAL CONSIDERATIONS FOR ASSESSING THE RELATIONSHIP BETWEEN DISEASE PROGRESSION BIOMARKERS AND CLINICAL ENDPOINTS IN ALZHEIMER'S DISEASE. T. Chen[1], R.M. Hutchison[1], C. Rubel[1], J. Murphy[1], J. Xie[1], P. Montenigro[1], W. Cheng[1], K. Fraser[1], G. Dent[1], J. O'gorman[1], S. Hendrix[2], O. Hansson[3], P. Aisen[4], Y. Tian[1] *(1. Biogen - Cambridge, Ma (United States), 2. Pentara Corporation - Millcreek, Ut (United States), 3. Lund University - Malmö (Sweden), 4. University of Southern California - San Diego, Ca (United States))*

Background: Changes in disease progression biomarkers of Alzheimer's disease reflect underlying pathophysiologcal changes in the brain. They provide evidence of downstream disease-modification effects and early changes may predict later clinical changes. It is important to assess the relationship between biomarkers and clinical endpoints using the appropriate statistical approaches and understand the different purpose of each approach. **Methods:** We examined amyloid-PET, tau-PET and various plasma-pTau measures (including ptau181 and ptau217, as measured by immunoassay or LC/MS) from clinical trials on Alzheimer's disease (AD) to elucidate

the different features of disease progression biomarkers at different stages of AD. We provided statistical considerations on assessing the biomarker relationship to clinical endpoints at both subject-level and group-level. **Results:** Amyloid accumulation starts at the pre-symptomatic stage and plateaus during the symptomatic stage. Tau accumulation aligns with clinical symptoms onset. Plasma pTau progression lies between amyloid and tau. In clinical trials, subject-level correlation assesses the biological relationship between biomarkers and clinical endpoints in the placebo arm, and this relationship may be altered in the treated arm, with different patterns in each case that requires unique considerations. In contrast, group-level correlation directly assesses the relationship between the placebo-adjusted group-level drug benefits and can be applied to measures from all 3 biomarkers. **Conclusions:** Subject-level and group-level correlations between biomarker and clinical endpoints answer different research questions and should be carefully considered in analysis plans. Group-level correlation leverages the fundamental aspects of randomized placebo-controlled trials and assesses the biomarker predictivity of a drug's benefit on clinical endpoints. **Key words:** Alzheimer's disease, biomarker, correlation, statistical considerations. **Disclosures:** TC, RMH, CR, JM, JX, PH, WC, KF, GD, JO and YT are employees of Biogen and may be stockholders. SH is CEO of Pentara Corporation and has received consultancy/speaker fees from Biogen and consults with many companies in the Alzheimer's field. OH has acquired research support (for the institution) from AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Alzpath, Biogen, Cerveau and Roche. PSA is Chair of the Steering Committee of Aducanumab program, has received research support from Lilly, Janssen, Eisai, the Alzheimer Association, NIH and FNIH, and has consulted for Merck, Roche and ImmunoBrain Checkpoint.

P089- VALIDATION OF CLINICAL CUTOFFS FOR THE BETA-AMYLOID (ABETA42), P-TAU181 AND P-TAU181/ABETA42 ROCHE ELECSYS GENERATION 2 ASSAYS.

J. Bornhorst[1], R. Deters[1], J. Theobald[1], A. Algeciras-Schimnich[1] *(1. Mayo Clinic - Rochester (United States))*

Background: Measurement of beta-amyloid (1-42) (Abeta42) and phosphorylated-Tau (p-Tau181) in cerebrospinal fluid (CSF) is useful in the evaluation of Alzheimer Disease (AD). The p-Tau181/Abeta42 ratio provides the best concordance (>90%) with amyloid positron emission tomography (PET). We previously established cutoffs for concordance with amyloid-PET for first generation (Gen1) Roche Elecsys assays for these markers, using a community-based sample cohort (Mayo Clinic Study of Aging; MCSA), as follows: p-Tau181/Abeta42: </= 0.023; Abeta42: >1026 pg/mL; and p-Tau181: </=21.7 pg/mL. Recently, a re-standardized Roche Elecsys p-Tau181/Abeta42 FDA approved second generation ratio (Gen2) with additional updated preanalytical protocols became available with a manufacturer's provided ratio cutoff of </= 0.023 being consistent with normal amyloid-PET. This study compares the performance of the Gen1 versus Gen2 assays and evaluates the transferability of various clinical cutoffs. **Methods:** CSF samples (n=100) submitted for clinical testing, spanning the analytical measurement range of each assay, were tested using Gen1 and Gen2 assays. CSF samples were collected in polypropylene low bind tubes under our current preanalytical protocol (at least 80% of the tube total volume, frozen and vortexed prior to testing). Passing-Bablok regression analysis equation was used to transformed previously established Gen1 cutoffs into Gen2 cutoffs. To evaluate the clinical performance of the in-house established Gen2 cutoffs versus the manufacturer's Gen2 cutoffs, two sets of data were evaluated. First, using the dataset from the MCSA study, pre-existing Gen1 Abeta42, pTau181, and p-Tau181/Abeta42 values were converted to expected Gen2 assays values using the regression equations obtained from the method comparison study. These were then evaluated against amyloid-PET for positive and negative percent agreement (PPA and NPA) using the current Gen1 cutoff, the newly derived Gen2 cutoff, and the manufacturer's Gen2 cutoff. A second data set of 136 sequentially submitted CSF samples were tested with both the Gen1 and Gen2 assays to assess their classification based on the current Gen1 cutoff, the newly derived Gen2 cutoff, and the manufacturer's Gen2 cutoff. **Results:** Regression equations (all r2=0.998) were Abeta42(Gen2)=0.79(Gen1) + 24.3, p-Tau(Gen2)=0.90(Gen1) + 2.0, and p-Tau181/Abeta42(Gen2)=1.11(Gen1)+0.0028. Calculated clinical cutoffs were: p-Tau181/Abeta42: </= 0.028; Abeta42: >834 pg/mL; and p-Tau181: </=21.6 pg/mL. Using the MCSA dataset, PPA and NPA with amyloid-PET were as follow: 92%/93% for Gen1 results with a cutoff of </= 0.023, 97%/84% for the calculated Gen2 results using a </= 0.023 cutoff, and 92%/92% for the calculated Gen2 results using a </= 0.028 cutoff. In the second data set, the number of p-Tau181/Abeta42 ratio positive samples was 76 for Gen1 results with a cutoff of </= 0.023, 82 for the Gen2 reagents using a </= 0.023 cutoff, and 77 for the Gen2 reagent using a </= 0.028 cutoff. **Conclusions:** We demonstrated that the Gen2 p-Tau181/Abeta42 ratio manufacturer's recommended cutoff of </= 0.023 resulted in a larger number of samples with normal amyloid-PET that would be considered abnormal for p-Tau181/Abeta42 when using our current preanalytical protocol. Accordingly, a Gen2 reagent p-Tau181/Abeta42 ratio cutoff of </= 0.028 best preserved previously established optimal clinical concordance to amyloid-PET measurement in the assessed clinical populations.

P090- STRUCTURAL AND FUNCTIONAL DMN PRESERVATION AFTER 24 WEEKS OF RTMS IN ALZHEIMER'S DISEASE PATIENTS.

G. Koch[1], L.L. Mencarelli[1], M. Torso[2], M. Assogna[1], F. Giove[1], E. Santarnecchi[3], E. Santarnecchi[3] *(1. Santa Lucia Foundation IRCCS - Rome (Italy), 2. Oxford Diagnostics - Oxford (United Kingdom), 3. MGH - Boston (United States))*

We recently showed that repetitive Transcranial Magnetic Stimulation (rTMS) over Precuneus (PC) slow down disease progression in mild to moderate AD patients (Koch et al.,Brain 2022), suggesting the PC is the ideal target for stimulation to slow down cognitive decline in AD. The PC is a key node of the Default Mode Network (DMN) and it is the earliest region to be affected by amyloid deposition as well as by gray matter loss, and functional connectivity disconnection between regions and organizations within networks. To detect any neurobiological modulation reflected in structural and functional changes in mild-to-moderate AD patients after 24 weeks of PC-rTMS, here we performed a randomized sham-controlled study including 16 patients evaluated through MRI before and after the rTMS treatment. We used voxel-based morphometry (VBM), and functional connectivity (FC) analyses to identify treatment-related neuronal reorganization in AD patients. Furthermore, to investigate the effect of PC-rTMS on cortical microstructure, whole brain grey matter. Over 24 weeks, high-frequency rTMS treatment reveals its efficacy in slowing down the gray matter

degeneration in the Real Group. Significantly smaller voxel-wise gray matter volumes were observed in the Sham Group after the 24 weeks of PC-rTMS over the Precuneus (p-uncorr < 0.01), as expected in the absence of treatment. On the other hand, in the Real Group, a preserved GM integrity in the PC was shown after the treatment (p-uncorr > 0.05). No areas of increased GM volume were found in patients with AD, regardless of the treatment. Considering the location of MRI changes good spatial specificity is observed in our data, thus with a slowdown of gray matter deterioration primarily over the Precuneus. However, the effects of rTMS may spread also to other areas, not directly targeted by the stimulation (Beynel et al., 2020). The seed-based functional connectivity analysis reveals significantly higher regional connectivity strengths in the Real compared to the Sham Group (x/y/z = 06, -68, 30; size = 766 mm3; F(1,11) = 6.20, p-FDR = 0.039). The network mapping ran on a database of 1000 healthy participants reveals the belonging to the DMN. Besides significant spatial-specific effects on the stimulated region (PC) shown by both VBM and seed-to-voxel analysis, we observed that rTMS modulates the connectivity between PC and superior parietal lobule (SPL) in the Real Group compared to the Sham Group (x/y/z = 08, -52, 56; size = 1040 mm3; F(1,11) = 6.20, p = 0.013). At the microstructural level, we found a significantly greater increase (associated with neurodegenerative decline) in sham than real rTMS group in PC AngleR Δ (F3,10 = 18.457, p = 0.002, ηp2 = 0.649) and whole brain AngleR Δ (F3,10 = 10.585, p = 0.009, ηp2 = 0.514). Overall, the present findings promote a framework for the investigation of rTMS-based interventions over PC to slow down gray matter degeneration in AD patients, together with a modulation in the functional connectivity of the targeted area. These findings also suggest that PC rTMS can slow neurodegenerative changes in the microstructure of cortical grey matter, indicating cortical microstructural preservation and potential slowing AD.

P092- ASSOCIATIONS BETWEEN BLOOD-BASED BIOMARKERS AND AMYLOID PET MEASUREMENTS IN COGNITIVELY UNIMPAIRED PRESENILIN 1 E280A MUTATION AND NON-MUTATION CARRIERS FROM THE API AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE COLOMBIA PREVENTION TRIAL. V. Bhargava[1], M. Malek-Ahmadi[1,2,3], F. Lopera[4], S. Rios-Romenets[4], N. Londono[4], C. Aponte[4], Y.T. Quiroz-Gaviria[5], J. Langabaum[2], P. Tariot[2], Y. Su[1,2,3], K. Chen[1,2], D. Clayton[6], R. Doody[6], E. Reiman[1,2,3,7] *(1. University of Arizona College of Medicine Phoenix - Phoenix (United States), 2. Banner Alzheimer's Institute - Phoenix (United States), 3. Arizona Alzheimer's Consortium - Phoenix (United States), 4. Neurosciences Group of Antioquia, Universidad de Antioquia - Medellin (Colombia), 5. Massachusetts General Hospital and Harvard Medical School - Boston (United States), 6. Genentech - San Francisco (United States), 7. Translational Genomics Research Institute - Phoenix (United States))*

Background: Blood-based biomarkers have promise in the detection, tracking, and study of preclinical Alzheimer's disease (AD) and the evaluation of putative prevention therapies. Presenilin 1 (PSEN1) E280A mutation carriers from the world's largest autosomal dominant AD (ADAD) kindred are virtually certain to develop early-onset dementia in their 40s. Here, we sought to characterize the extent to which baseline plasma pTau181 and pTau217 (indicators of amyloid-mediated tau pathophysiology and tau tangles), glial fibrillary acidic protein (GFAP, an indicator of astrogliosis), and neurofilament light (NfL, an indicator of neurodegeneration) are related to PET measurements of amyloid plaque burden in cognitively unimpaired PSEN1 E280A mutation carriers from the recently completed Alzheimer's Prevention Initiative Autosomal Dominant AD (API ADAD) Colombia Trial (NCT01998841). **Methods:** Baseline data from 249 cognitively unimpaired kindred members (166 PSEN1 mutation carriers average age 37 ± 5.8 years old and 83 noncarriers average age 43 ± 7.5 years old) were included in this analysis. Plasma pTau181, pTau217, GFAP and NfL plasma measurements were characterized on the Elecsys platform using Roche NeuroToolKit immunoassays. Mean cortical-to-cerebellar florbetapir PET standardized uptake value ratios (SUVRs) were used to characterize amyloid plaque burden. Relationships between log-transformed plasma biomarker measurements and PET measurements were characterized using Spearman correlation with and without adjustment for age, sex, and presence or absence of the APOE4 allele. Mediation analysis was further performed for those who remained significant after covarying out age, sex, and APOE4 allele presence, to test if the relationships between neuroimaging and a plasma biomarker were mediated by other plasma biomarkers. **Results:** Log-transformed plasma pTau181, pTau217, GFAP, and NfL measurements were correlated with PET measurements of amyloid plaque burden (r=0.48, p<0.001; r = 0.17, p = 0.03; r=0.45, p<0.001, and r=0.24, p=0.002; respectively) in cognitively unimpaired PSEN1 mutation carriers. None of the associations was significant in the non-carriers. Correlations remained significant for plasma pTau181 and GFAP after adjustment for age, sex, and APOE4 (p<0.001) in PSEN1 mutation carriers. Mediation analysis revealed that the relationship between amyloid PET SUVR and GFAP was mediated by pTau181 (p<0.001). **Conclusion:** Plasma pTau181, an indicator of amyloid plaques and amyloid-mediated tau pathophysiology and plasma GFAP, an indicator of astrogliosis, are correlated with PET measurements of amyloid plaque burden in cognitively unimpaired PSEN1 E280A mutation carriers. The relationship between PET amyloid SUVR and plasma GFAP is at least partially mediated by plasma pTau81, suggesting a possible role of phosphorylated tau in the pathway between amyloid deposition and neuroinflammation in cognitively unimpaired ADAD mutation carriers. **Key words:** PSEN1 mutation carriers, Autosomal Dominant Alzheimer's Disease, Blood Based Biomarkers, Neuroimaging. **Disclosures:** VB: None; MA: Biomedical Research Alliance of New York; FL: grants from NIA, NIA, Roche, MSD, Biogen and Tau Consortium; SR: None; NL: None; CA: None; YQ: Serves as a consultant for Biogen; JL: Serves as a consultant to Biogen, Denovo Biopharma. She reports receiving grants from the NIA unrelated to this project; PT: Consulting Fees: Acadia, Lundbeck, Merck, Otsuka+Astek, T3D therapeutics; Advisory Board: Abbvie, AC Immune, Acadia, Atria, Corium, Cortexyme, Eisai, Genentech, ImmunoBrain, Merck, Novo Nordisk; Research Support: Abbvie, Biogen, Cortexyme, Eli Lily, Genentech, Merck, NIA, Novartis, Roche; Grants: National Institute on Aging (RF1 AG041705, 1UF1AG046150, R01 AGO31581, R01 AG05544, P30 AG19610); YS: None; KC: None; DC: Serves as a a full-time employee of Genentech, Inc, a member of the Roche Group, and owns stock in F. Hoffmann-La Roche Ltd.; RD: Works for Genentech and F Hoffman-LaRoche and own stock and stock options in F Hoffman-LaRoche; ER: Compensated scientific advisor to Alzheon, Aural Analytics, Denali, Retromer Therapeutics, and Vaxxinity and co-founder/advisor to ALZPath (none of which are directly related to this project); Patents: US Patent $11/632, 747, "Biomarkers of Neurodegenerative disease." Contributor to a patent owned by the University of Rocheste. **Funding:** This work was supported in part through grants from NIA (R01 AG055444

and P30 AG072980), Banner Alzheimer's Foundation, NOMIS Foundation, and the Arizona Alzheimer's Consortium. **Clinical Trial Registry:** NCT01998841; http://clinicaltrials.gov

P093- PLASMA P-TAU217 AS A COST-EFFECTIVE SURROGATE BIOMARKER FOR CLINICAL TRIALS ACROSS THE AD CONTINUUM. P.C.L. Ferreira[1], B. Bellaver[1], G. Povala[1], J.P. Ferrari-Souza[1], F.Z. Lussier[1], D.T. Leffa[1], H. Karim[1], C.H. Hong[2], H.W. Rho[2], D.L. Tudorascu[1], T.K. Karikari[1], B.E. Snitz[3], S.J. Son[2], T.A. Pascoal[1] *(1. Department of Psychiatry, School of medicine, University of Pittsburgh - Pittsburgh (United States), 2. Department of Psychiatry, Ajou University School of Medicine - Sowon (Korea, Republic of), 3. Department of Neurology, School of Medicine, University of Pittsburgh - Pittsburgh (United States))*

Background: Brain amyloid-beta(Aβ) and tau pathologies can be reliably captured using Positron Emission Tomography(PET) and Cerebrospinal Fluid biomarkers. However, due to their high costs, limited accessibility, and invasiveness, blood-based biomarkers have emerged as a simple and cost-effective alternative to be used in clinical practice and trials. In this context, recent clinical trials have used changes in plasma biomarkers as secondary outcomes to monitor disease modification, demonstrating the utility of blood biomarkers as surrogate markers in such trials [1, 2]. Notably, plasma phosphorylated tau at threonine 217(p-tau217) shows promise as a biomarker associated with brain Aβ, neurofibrillary tangles, and cognitive impairment. **Objective:** Evaluate the potential utility of plasma p-tau217 as a surrogate biomarker in clinical trials for preclinical Alzheimer's Disease(AD) and symptomatic individuals. **Methods:** We measured longitudinal plasma p-tau217 in two time points (24 months follow-up) in a total of 188 individuals across two cohorts. 63 Cognitive unimpaired(CU) individuals from the MYHAT cohort[population-based; mean age=75.5(5.7)] and 125 Cognitive Impaired(CI) individuals with initially suspected AD from the BICWALZS cohort[memory clinic-based; mean age=72.1(7.6)]. All individuals had Aβ-PET at baseline. Aβ-PET positivity(Aβ+) was determined using Positron Emission Tomography(PET) using previously validated cutoffs. Plasma p-tau217 was quantified using the ALZpath assay. Effect size was calculated as the mean change in biomarker divided by the standard deviation. 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 a 0.05 level on reducing changes in plasma markers. Using data from a previous study [2, 3], we estimated changes in tau-PET(18F-flortaucipir uptake) as a neuroimaging biomarker and plasma p-tau181 as a fluid biomarker for surrogacy. **Results:** Longitudinal rate of change in plasma p-tau217 presented a high effect size in both groups: CU Aβ+ [rate of change=0.149(0.21)pg/ml/year, effect size=0.71] and CI Aβ+ [rate of change=0.203(0.24)pg/ml/year, effect size=0.84]. We showed that therapeutic clinical trials conducted over 24 months would require 1,178 individuals per study arm for the unenriched CU group and 956 individuals per study arm for the CI group. The use of CU Aβ+ as an enrichment strategy reduced the sample size by 62%(n = 455), and the use of CI Aβ+ positivity reduced it by 58%(n = 396). We compared the total estimated trial cost [plasma biomarker($200), PET($3,000), and cognitive assessment($1,000)] [2, 3] for an Aβ+ population, using plasma p-tau217 with the cost of using plasma p-tau181 and tau-PET for surrogacy. Our results demonstrated that the total cost of a clinical trial, including CU Aβ+ individuals using plasma p-tau217 was 6-fold lower($5.2M) than using plasma p-tau181($29.1M) and 5-fold lower than using tau-PET($24.9M). Similarly, the total cost for a clinical trial, including CI Aβ+ individuals, showed a 1.6-fold lower cost($4.5M) when using plasma p-tau217 as a surrogate compared to tau-PET($7.2M). **Conclusion:** Our results suggest that plasma p-tau217 could potentially be used to monitor population interventions targeting CU and CI Aβ+ individuals. Additionally, we demonstrated that the cost of using plasma p-tau217 in clinical trials across the AD spectrum would be significantly lower than using tau-PET or plasma p-tau181 as surrogate biomarkers. **Key words:** surrogate biomarkers, plasma p-tau217, cost-effective, clinical trial monitoring. **References:** 1. Pontecorvo MJ, et al. JAMA Neurology 2022. DOI: 10.1001/jamaneurol.2022.3392. 2. Ferreira PCL, et al. Neurology 2023. DOI: 10.1212/WNL.0000000000207115. 3. Jack CR Jr, et al. Brain 2018. DOI: 10.1093/brain/awy059.

P094- PLASMA BIOMARKERS AND LONGITUDINAL COGNITIVE DECLINE IN NON-DEMENTED ALZHEIMER'S DISEASE. K. Cody[1], R. Langhough[1], L. Du[1], E. Jonaitis[1], N. Chin[1], B. Jeffers[1], M. Vandenlangenberg[1], S. Asthana[1], K. Kirmess[2], M. Meyer[2], K. Yarasheski[2], T. West[2], T. Betthauser[1], S. Johnson[1] *(1. Wisconsin Alzheimer's Disease Research Center, University of Wisconsin - Madison (United States), 2. C2N Diagnostics - St. Louis (United States))*

Background: Blood biomarkers sensitive to early Alzheimer's disease (AD) proteinopathy and cognitive decline have significant implications for clinical trials and research. In late-middle-aged non-demented individuals, we investigated the clinical performance of C2N plasma biomarkers against PET measures of brain amyloid and tau and their associations with longitudinal cognitive trajectories. **Methods:** Individuals who were non-demented at plasma assessment with available plasma biomarker concentrations, amyloid and tau PET imaging within one year of plasma assessment, and longitudinal cognitive assessments were selected from the Wisconsin Registry for Alzheimer's Prevention and Wisconsin AD Research Center cohorts (N=304; Cognitively unimpaired, n=281(92.4%); MCI, n=23(7.6%); Age, M(SD): 67.7(7.0) years; 68% Female; 41% APOEe4 carriers; 91% non-Hispanic white). Plasma biomarker concentrations were quantified using high-resolution mass spectrometry-based assays (C2N Diagnostics) and were expressed as ratios: amyloid ratio (Aβ42:Aβ40), p-tau217 ratio (% phosphorylated-tau217:non-phosphorylated-tau217), p-tau181 ratio (% phosphorylated-tau181:non-phosphorylated-tau181). Two amyloid probability scores (APS) were also tested: APS (score of 0-100 based on amyloid ratio, age, APOE genotype) and APS2 (score of 0-100 based on amyloid and p-tau217 ratios). To understand plasma markers' potential to screen for amyloid and tau PET positivity, receiver operating characteristic analyses identified optimal thresholds (Youden's J); thresholds were used to estimate sensitivity, specificity, and related values for amyloid PET positivity (Global [11-C]PiB DVR >1.19; Equivalent Centiloid >22) and tau PET positivity (Temporal meta-ROI [18-F] MK-6240 SUVR >1.30). Associations of plasma biomarkers and longitudinal retrospective decline on a Preclinical Alzheimer's Cognitive Composite were investigated using linear mixed effects (LME) models. **Results:** All plasma biomarkers were significantly associated with concurrent global brain amyloid (n=304) and temporal tau PET burden (n=286) with AUC's ranging from .76 (p-tau181 ratio) to .96 (APS2). The p-tau217 ratio alone and when combined with the amyloid ratio (e.g.

APS2) demonstrated high screening potential for amyloid and tau PET positivity. For APS2, positive predictive values (PPV's) were .76 and .38 for amyloid and tau PET; for p-tau217 ratio, PPV's were .71 and .44, respectively. Negative predictive values were ≥.96 indicating minimal risk of false negatives. Significant savings in time and resources could be achieved by screening with APS2 or p-tau217 ratio: for example, instead of ~2,100 PET scans to find ~500 PET amyloid+ individuals, ~2,300 plasma assays would be needed to identify ~650-700 plasma p-tau217+ for amyloid PET scans. Each plasma biomarker*age2 interaction was significant in parallel LME models indicating faster retrospective decline with worse biomarker status (Years from cognitive baseline to plasma, M(SD): 8.2(2.5)). The APS2 model of cognitive decline showed the best fit (AICc=2544.5) followed by the p-tau217 ratio model (AICcΔ=9.1; AICcΔ>50 for amyloid ratio and p-tau181 ratio models). Effect size (ES) estimates at age 70 comparing decline of those above vs below the optimal threshold yielded ESAPS2=.16, ESp-tau217=.16, ESAβ42/40=.11, and ESp-tau181=.11. **Conclusions:** In a predominantly unimpaired sample, C2N mass spectrometry-based plasma biomarkers correlated well with concurrent AD brain pathophysiology and with retrospective cognitive decline. Results indicate that these plasma biomarkers can accurately detect both amyloid and tau PET positivity and highlight the potential utility of plasma biomarkers to identify non-demented candidates for AD clinical trials.

P095- CEREBROSPINAL FLUID CELLULAR TRANSCRIPTOMICS AS BIOMARKERS OF CENTRAL NERVOUS SYSTEM DRUG-TARGET ENGAGEMENT OF A PERIPHERALLY ADMINISTERED VACCINE IN OLDER ADULTS WITH AND WITHOUT COGNITIVE IMPAIRMENT (BCG-AD). M. Weinberg[1,2], M. Kodali[1,2], R. Jayakumar[1], D.L. Faustman[1], S. Das[1,2], S. Arnold[1,2] *(1. Mass General Hospital - Boston, MA (United States), 2. Harvard Medical School - Cambridge, MA (United States))*

Background: The immune system, intimately involved in all phases of Alzheimer's disease (AD), may prove an ideal drug target for mono- or multi-pronged therapy against AD. Vaccines, if effective, present an ideal cost-effective and globally equitable means of preventing and/or treating neurodegenerative disease. Multiple cohort studies, including ours [1], observe a beneficial association of Bacillus Calmette-Guérin (BCG) vaccine treatment of bladder cancer and the incidence of Alzheimer's Disease (AD) and related dementias. Preclinical studies with the BCG vaccine observe improved cognition, increased hippocampal dendritic complexity, and decreased disease-related biomarkers in AD-transgenic mice. We recently completed a small Phase-IIb open-label trial of the BCG vaccine in healthy older adults and those with AD pathology. Here we present basal and functional transcriptomics analyses from blood and cerebrospinal fluid (CSF) cells collected from individuals pre- and post-BCG vaccination, in a proof-of-concept demonstration of central nervous system drug-target engagement from a peripherally administered vaccine. **Methods:** Plasma, CSF, peripheral blood mononuclear cells (PBMCs), and CSF immune cells were derived from donor samples immediately before, and 3mo and 12mo after receiving two doses of intradermal live attenuated BCG vaccine (Japan). Plasma and CSF were studied for immune and AD-related fluid biomarkers. Cells were cultured and treated with heat-killed (hk)BCG (vaccine-matching stimulus), lipopolysaccharide (LPS, a non-specific pathogenic stimulus), or control. Cytokine release in PBMC media measured vaccine responsivity (hkBCG) and extent of trained immunity effect (LPS). Trained immunity is a recently characterized phenomenon wherein particular exposures such as BCG vaccination can lead to epigenetic changes in innate immune cells, resulting in immunometabolic shifts in these cells, and stably more robust responses to non-specific pathogenic stimuli. We next examined the evidence for CSF cell drug target engagement. A subset of CSF cells derived from donors before and after vaccine treatment were exposed to hkBCG, LPS, or control in-vitro, and single-cell and bulk RNA sequencing was performed. **Results:** Both basal and functional changes in CSF cells are readily appreciated after BCG vaccination in older adults. We will provide an overview of basal and functional differences in CSF cell transcriptomics, emphasizing cellular phenotype-specific contributions to these effects. We relate our findings to time from BCG vaccine treatment, AD disease status, basal cytokine levels, and PBMC-based evidence of vaccine responsiveness. **Conclusions:** Our preliminary results from CSF transcriptomics in response to the BCG vaccine demonstrate overlapping and compartment-specific (central nervous system versus peripheral blood) effects of peripherally administered BCG vaccine on the older adult immune system, providing proof-of-concept of central nervous system drug-target engagement of BCG. This study demonstrates how immune cells confer rich biomarker data of disease state and drug responsivity. **Disclosures:** This study was supported by NIH Grants: R25MH094612, T32-MH112485, U13AG067696, UL1-TR002541, NIA-P30AG062421, Alzheimer's Association grants AACSF-22-970716 and PTC REG-20- 653582, the Massachusetts Life Sciences Center, and the Cure Alzheimer's Fund. **References:** 1. Weinberg MS, Zafar A, Magdamo C, et al. Association of BCG Vaccine Treatment With Death and Dementia in Patients With Non–Muscle-Invasive Bladder Cancer. JAMA Netw Open. 2023;6(5):e2314336. doi:10.1001/jamanetworkopen.2023.14336

P096- BIO-HERMES STUDY TOPLINE RESULTS: Aβ42/40 AND P-TAU 181/217 BLOOD-BASED BIOMARKERS COMPARED TO AMYLOID PET AND CSF IN A DIVERSE, COMMUNITY-BASED POPULATION. D. Beauregard[1], R. Mohs[1], J. Dwyer[1], S. Hollingshead[1], J. Gaudioso[1], J. Bork[1], D. Kerwin[2] *(1. Global Alzheimer's Platform Foundation - Washington, Dc (United States), 2. Kerwin Medical Center - Dallas (United States))*

Background: Accurate and expeditious detection of Alzheimer's disease (AD) pathology in affected patients continues to be a major hurdle in advancing AD modifying clinical research [1, 2]. A robust screening process that can identify patients with a high probability to randomize into AD therapeutic research trials would greatly enhance the ability to conduct and reduce the time needed to complete clinical trials. To more accurately reflect clinical trial populations and to increase diversity, the Bio-Hermes study used 17 sites and monitored recruitment to achieve 17%, 22%, and 31% underrepresented minorities (URM) in each of the 3 clinical trial cohorts of Cognitively Normal (CN), Mild Cognitive Impairment (MCI), and Mild AD, respectively. In addition to blood-based biomarkers and the presence of amyloid plaques identified through brain amyloid PET and CSF, numerous digital tests and genetic assays were performed resulting in a robust Bio-Hermes database. **Methods:** Within 18 months, 17 sites enrolled 1,001 participants (60-85 y/o) in clinically defined cohorts of: CN (n=417), MCI (n=312), and Mild AD (n=272). Traditional and digital cognitive testing, amyloid

PET imaging, biospecimen collection, and speech analytics were performed. A subset of participants received a retinal exam. Blood biomarkers included Aß 42/40, p-Tau181/217/231, NfL, GFAP, full genome sequencing, including APOE status, and proteomics. Digital biomarkers included memory recall, executive functions, and drawing-based and speech-elicitation tasks. Blood biomarkers' relationship to amyloid PET was measured using Spearman's rank correlation. A ROC curve analysis assessed the sensitivity and specificity of each biomarker and combination of biomarkers compared with amyloid positivity from PET and CSF. **Results:** Brain amyloid positivity results were 21%, 35%, and 60% for the CN, MCI, and Mild AD cohorts, respectively. Initial data analysis by Global Alzheimer's Platform Foundation® (GAP) compared results of blood Aß 42/40, t-Tau, p-Tau 181 and p-Tau 217 tests with brain amyloid positivity. ROC analysis showed more favorable AUC for Aß 42/40 and p-Tau 217 (0.8881) combination, p-Tau 217 (0.8855), Aß 42/40 and p-Tau 181 (0.8190) combination, Aß 42/40 and t-Tau (0.7922) combination. For Black or African Americans, brain amyloid positivity was 24%, 23%, and 36% for the CN, MCI, and Mild AD cohorts, respectively, and for Hispanics or Latinos results were 4%, 35%, and 55%, respectively. Additional correlation and URM data will be available July 2023. **Conclusion:** Initial topline results show blood-based AD biomarkers are associated with brain amyloid positivity warranting further analysis of the Bio-Hermes community-derived database of blood-based and digital biomarkers. **Key words:** biomarkers, validation, PET. **Clinical Trial Registry:** NCT04733989; https://clinicaltrials.gov. **Disclosures:** No disclosures to report. **References:** 1. Malzbender K, Lavin-Mena L, Hughes L, Bose N, Goldman D, Patel D. Key Barriers to Clinical Trials for Alzheimer's Disease 2020. 2. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535–62. https://doi.org/10.1016/j.jalz.2018.02.018.

LP043- NOVEL DIAGNOSTIC PLATFORM ENABLING PROTEIN SPECIFIC BIOMARKER SIGNATURE FOR THE DIAGNOSIS OF AD. M. San Nicolo[1], O. Peters[2], H. Wunderlich[1], T. Grimmer[3], L. Frölich[4], A. Schaepe[1], R. Metzler[1], S. Mertzig[1], K. Hallermayer[5], H. Waltenberger[6], T. Heydler[1], M. Haack[1] *(1. Noselab GmbH - Munich (Germany), 2. Charite - Berlin (Germany), 3. TUM - Munich (Germany), 4. ZI Mannheim - Mannheim (Germany), 5. GMX - Munich (Germany), 6. Microcoat - Munich (Germany))*

Background: Clinical evidence shows a significant drainage of cerebrospinal fluid (CSF) and its metabolites along the olfactory route into the nose. We developed a proprietary, nasal secretion-based diagnostic platform which allows a detailed quantification of the key Alzheimer' disease (AD) biomarkers in size and relative amount: pTau181 (pTau), total Tau (tTau), Amyloid-β1-40 (Aβ40), Amyloid-β1-42 (Aβ42) and Pan-amyloid Beta (PanAβ). Thus, enabling a minimally invasive assessment of AD biomarkers in patients with cognitive impairment in daily clinical routine. **Methods:** Multicenter, prospective, single blinded cohort study including patients with cognitive impairment and availability of CSF measurements for the core AD-specific proteins. The presence (A+) or absence (A-) of amyloid pathology was determined by the amyloid ratio Aβ42/Aβ40 in CSF as reference test and compared to nasal secretion-based classification of AD biomarkers. Nasal secretion was collected from the vicinity of the olfactory cleft using a proprietary collection device [nosecollect] and the relative protein amount as well as protein specific quaternary substructures (monomeric and oligomeric species) were quantified for Aβ42, Aβ40, PanAβ, pTau181 and tTau using an automated, capillary-based protein separation and immunodetection system [NosetestAD]. **Results:** For this analysis, 39 patients with cognitive impairment were included at 3 university memory clinics in Germany. The sampling procedure using [nosecollect] is painless and yields a high sample volume (mean 450 µl). Different monomeric, oligomeric, and higher n-meric protein species of AD biomarkers pTau181, total Tau, Aβ40, Aβ42 and pan-Aβ were detected, and quantified for each protein and each quaternary subspecies alone and in relation to the specific relative protein amount. Patients with CSF-confirmed amyloid pathology (A+) show a significantly different protein-specific biomarker signature in nasal secretion as compared to patients without amyloid pathology (A-). This finding was evident for multiple quaternary bands. Our protein-specific biomarker signature, revealing monomeric, oligomeric, and higher n-meric protein subspecies allows for a highly significant discrimination (p-value <0.001) of A+ vs. A- with an AUC of >0.90 in a prospective setting in clinical routine. **Conclusion:** Detection of AD specific proteins along the brain-nose-interface constitutes a safe, minimally invasive, easy to obtain diagnostic procedure in close proximity to the brain and thus to the origin of the pathology. It is highly suitable for simultaneous detection and monitoring of multiple AD relevant biomarkers. Within a cohort of patients with cognitive impairment A+ patients can be significantly distinguished from A- patients using our protein-specific biomarker signature displaying different levels of monomeric, oligomeric, and higher n-meric species of AD relevant proteins. Our diagnostic platform has the potential to use in screening, diagnosis, patient stratification, intraindividual disease and treatment monitoring in AD and other neurodegenerative diseases. **Clinical Trial Registry:** NCT05791552; https://clinicaltrials.gov. **Disclosures:** MSN, HW, AS, RM, SM, TH and MH are employees at Noselab GmbH, OP, TG, LF and KH are consultants for Noselab GmbH.

LP044- A CROSS-SECTIONAL STUDY OF PLASMA AB42/40 RATIO, P-TAU217, P-TAU181, GFAP AND NF-L IN A CLINICAL COHORT CHARACTERIZED BY CNS AMYLOID PET IMAGING. A. Chenna[1], Y. Badal[1], M. Lo[1], B. Yee[1], B. Lim[1], C. Fowler[2], R. Martone[3], C. Petropoulos[1], J. Winslow[1] *(1. Labcorp-Monogram Biosciences - South San Francisco, Ca (United States), 2. The Florey Institute of Neuroscience and Mental Health - Parkville, VIC (Australia), 3. Labcorp Drug Development - Indianapolis, IN (United States))*

Background: Recent advances in automated immunoassays have enabled sensitive detection of Aβ42/40, p-Tau181, and p-Tau217 in plasma, leading to increased accuracy in the identification of CNS amyloid PET positivity in pre- and symptomatic Alzheimer's disease subjects. The FNIH round robin comparison of plasma Aβ42/40 ratio assays identifying amyloid PET+ status recently reported a ROC-AUC = 0.83 for the Fujirebio Lumipulse plasma Aβ42/40 assay, comparable to mass spectrometry assay performance. Similarly, the plasma p-Tau217 Quanterix Simoa assay developed by ALZpath exhibited concordance with amyloid PET in separate clinical cohorts with ROC-AUC = 0.92-0.96. Further characterization is needed to determine applicability to therapeutic clinical trials and diagnostic testing. In this report we detail a cross-sectional, multi-plasma biomarker characterization of AIBL cohort samples using Lumipulse and Simoa plasma Aβ42/40

ratio assays, and the Simoa p-Tau217, p-Tau181, GFAP, and Nf-L assays. **Methods:** Two hundred participants of the AIBL cohort were selected representing a cross-sectional population of four clinical diagnostic and amyloid PET subgroups: cognitive normal (CN) Aβ- (n= 75), CN Aβ+ (n= 50), mild cognitive impairment (MCI) Aβ+ (n=25), and AD Aβ+ (n= 50), which were balanced for age, gender and sample storage. EDTA-plasma samples were analyzed with the Lumipulse Aβ42/40 assay, the Simoa Neuro-4-plex E assay (Aβ42, Aβ40, GFAP, Nf-L), the ALZpath Simoa p-Tau217 assay, and the Simoa p-Tau181 v2 assay. Univariate analyses of biomarker levels were performed to evaluate differences between Aβ- vs Aβ+ groups overall, within diagnostic subgroups, and for associations with amyloid PET status. **Results:** Lumipulse and Simoa Aβ42/40 ratios were lower in Aβ+ vs Aβ- groups (Mann-Whitney p<0.0001). Differences were also observed across CN Aβ-, CN Aβ+, MCI Aβ+ and AD Aβ+ subgroups (Kruskal-Wallis p <0.0001). ROC-AUC vs amyloid PET status was 0.88 and 0.85, respectively, for Lumipulse and Simoa Aβ42/40 ratios. Moderate Spearman correlations between Lumipulse and Simoa Aβ42/40 ratios and amyloid PET centiloids were R = -0.53 and -0.49, respectively (p<0.0001). Simoa p-Tau217 and p-Tau181 levels were elevated in Aβ+ vs Aβ- groups (p<0.0001), respectively. Each p-Tau increased in median levels with disease severity, with a maximum median fold increase relative to CN Aβ- of 4.0 and 1.9 for p-Tau217 and p-Tau181, respectively. ROC-AUC vs amyloid PET status was 0.95 and 0.81, respectively, for Simoa p-Tau217 and p-Tau181. Simoa GFAP and Nf-L levels were elevated in Aβ+ vs Aβ- clinical groups, respectively (p <0.0001; p=0.0002), however, association with amyloid PET status was less discriminating than amyloid and tau biomarkers, with ROC-AUC= 0.72 and 0.65, respectively. **Conclusion:** A cross-sectional plasma biomarker study of a clinically well-characterized cohort revealed an improved association of Aβ42/40 ratios and p-Tau217 levels with CNS amyloid PET status across the AD continuum, as measured by recently developed immunoassays. These results support further clinical and analytical validation of plasma biomarkers in support of their application in AD drug development and patient management. **Acknowledgements:** We would like to thank Dr. Andreas Jeromin of ALZpath, Inc. for access and assistance with the p-Tau217 assay. **Key words:** Alzheimer's disease, neurodegeneration, amyloid beta, p-Tau, biomarker. **Disclosures:** AC, YB, ML, BY, BL, RM, CJP, JWW are employees of Labcorp. AC, YB, BY, RM, CJP, JWW are Labcorp shareholders.

LP046- ANALYTICAL VALIDATION AND INITIAL CLINICAL EVALUATION OF A NEW BLOOD-BASED DIAGNOSTIC TEST FOR ALZHEIMER'S DISEASE.

A. Schade[1], A. Abel[1], A. Chambers[1], J. Fil[1], H. Reiske[1], M. Lu[1], A. Morris[1], M. Pontecorvo[1], E. Collins[1], M. Mintun[1], M. Hodsdon[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Background: Blood-based biomarkers have been gaining interest in the diagnostic work-up of neurodegenerative diseases, including Alzheimer's disease (AD). Among the most interesting for AD is a post-translationally modified fragment of tau protein, P-tau217. Herein we report a robust analytical validation and initial clinical performance of a P-tau217 immunoassay test on a Quanterix SP-X platform for identifying amyloid-PET positive patients. **Methods:** We developed a P-tau217 chemiluminescent immunoassay that is read on the Quanterix SP-X imager. A formal analytical validation consisting of three manufactured P-tau217 kit lots, nine different operators, and six SP-X imagers was performed in our CAP-accredited CLIA lab, assessing: precision, sample stability, analytical specificity, interfering substances, parallelism and dilutional linearity, curve fitting, quality controls, analytical sensitivity (LoB, LoD, LLoQ), and analytical measurement range. Additionally, [328] plasma samples from participants being screened in the TRAILBLAZER-ALZ 2 clinical trial were analyzed to determine positive and negative agreement to florbetapir PET with a SUVR 1.1 threshold as a preliminary assessment of clinical performance in providing evidence of brain β-amyloid plaque pathology. **Results:** Analytical validation demonstrated [robust] performance across multiple lots, operators, and instruments. [Summarize test analytical performance.] Initial clinical assessment of this P-tau217 test demonstrates [high] positive and negative agreement with PET. [summarize PPA/NPA, ROC AUC, PPV and NPV at this particular prevalence level]. **Conclusions:** This novel plasma P-tau217 immunoassay using the Quanterix SP-X platform has undergone systematic analytical validation and could prove to be a useful diagnostic test to identify the presence or absence of amyloid pathology. Additional clinical evaluation data may be available at time of presentation. **Key words:** blood-based biomarkers; Alzheimer's disease diagnostic; plasma P-tau217; amyloid pathology. **Disclosures:** All authors are employees and minor shareholders of Eli Lilly and Company.

LP047- ANALYTICAL AND CLINICAL VALIDATION OF B-AMYLOID 1-40, 1-42, AND THE 1-42/1-40 RATIO USING A CLINICAL AUTOANALYZER.

A. Harris[1], T. Le[1], B. Collier[1], M. Chappell[1], D. Boles[1], R. Grant[1] *(1. Labcorp - Burlington (United States))*

Background: Alzheimer's Disease (AD) is the predominant form of dementia in aging populations, with an estimated patient population of 6.7 million in the US, and an annual death rate in 2018 recorded at 122,000 [1]. One of the diagnostic hallmarks of AD is extracellular deposits of β-amyloid plaques in the cortex and limbic brain region where the major molecular components of β-amyloid plaques is β-amyloid 1-42 (Aβ42) [2-3]. Reduced concentrations of Aβ42 in cerebrospinal fluid (CSF) and plasma are associated with increased retention of Aβ tracers in the brain β-amyloid plaques observed with positron emission tomography (PET). Correlation to PET results is further improved by using the ratio of Aβ42 to β-amyloid 1-40 (Aβ40) to account for variation in total β-amyloid from person-to-person [4-6]. Although PET imaging and measurements in CSF have been traditionally used to investigate the presence of β-amyloid plaques, these techniques are financially burdensome and invasive to the patient. As an alternative, blood and plasma-based measurements are currently being investigated to broaden testing accessibility. **Methods:** The Sysmex HISCL®-5000 Immunoassay System was used to validate chemiluminescence enzyme immunoassays for the measurement of Aβ40 and Aβ42 in EDTA plasma samples as a laboratory developed test (LDT) to determine the Aβ42/40 ratio. Validation of these measurements included investigation of assay imprecision, analytical measurement range (AMR), common interferences as well as measurements of sample stability. In addition, clinically defined specimens [7] as well as specimens from healthy volunteers were acquired and measured to verify an appropriate reference interval with respect to β-amyloid PET results. The Aβ42/40 ratio of the clinically defined samples was also determined using assays from two other manufacturers. **Results:** Measuring plasma and

QC materials produced within-laboratory CVs ≤ 6.5% for both Aβ40, Aβ42, as well as the Aβ42/40 ratio. The AMR of each assay was found to be suitable for measurements of anticipated plasma concentrations and acceptable levels of common assay interferents were identified. Sample stability was demonstrated to allow appropriate shipping and handling of specimens. Clinically defined specimens were analyzed by generating a receiver operator characteristic (ROC) curve of the Aβ42/40 results. ROC analysis produced an area under the curve (AUC) of 0.94 with an efficiency of 92.4% and a proposed cutoff of 0.102 for the Aβ42/40 ratio. This cutoff produced a sensitivity and specificity of 96.0 and 86.7%, respectively. This cutoff is consistent with the cutoff proposed by the manufacturer [5] and was further verified by results from healthy volunteers. Furthermore, the observed ROC AUC observed (0.94) for other existing commercial assays (using the same clinically defined specimens) was ≤ 0.89 with efficiencies ≤ 87.4%. **Conclusion:** Measurement of Aβ42/40 in patient plasma samples using a high efficiency platform is now available as an LDT to assist physicians with identifying patients with β-amyloid plaques and potentially the presence of Alzheimer's disease. **Key words:** Alzheimer's disease, neurodegeneration, amyloid beta. **Disclosures:** ABH, TL, BBC, MRC, DB, and RPG are all employees of Labcorp and participate in the employee stock purchase program. **References:** Alzheimer's Association, 2023 Alzheimer's disease facts and figures. Alzheimer's Dement., 19: 1598-1695. Perl DP. Neuropathology of Alzheimer's disease. Mt Sinai J Med. 2010;77(1):32-42. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. J Intern Med. 2018;284(6):643-663. Lewczuk P, Matzen A, Blennow K, et al. Cerebrospinal Fluid Aβ42/40 Corresponds Better than Aβ42 to Amyloid PET in Alzheimer's Disease. J Alzheimers Dis. 2017;55(2):813-822. Yamashita K, Miura M, Watanabe S, et al. Fully automated and highly specific plasma β-amyloid immunoassays predict β-amyloid status defined by amyloid positron emission tomography with high accuracy. Alzheimers Res Ther. 2022 Jun 23;14(1):86. Yamashita K, Watanabe S, et al. Fully automated chemiluminescence enzyme immunoassays showing high correlation with immunoprecipitation mass spectrometry assays for β-amyloid (1-40) and (1-42) in plasma samples. Biochem Biophys Res Commun. 2021 Oct 22;576:22-26. The Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing. https://aibl.csiro.au/research/biomarkers/ Accessed July 31, 2023.

LP048- THE ALZHEIMER'S ASSOCIATION GLOBAL BIOMARKER STANDARDISATION CONSORTIUM (GBSC) PLASMA PHOSPHO-TAU ROUND ROBIN STUDY.

N. Ashton[1], A. Keshavan[2], L. Grötschel[1], L. Shaw[3], K. Blennow[4], J. Schott[5], H. Zetterberg[6] *(1. University of Gothenburg - Göteborg (Sweden) - Göteborg (Sweden), 2. University College London - London (United Kingdom) - London (United Kingdom), 3. University of Pennsylvania - Philadelphia (United States) - Philadelphia (United States), 4. University of Pennsylvania - Philadelphia (United States), 5. University College London - London (United Kingdom), 6. University of Gothenburg - Göteborg (Sweden))*

Background: Blood biomarkers for Alzheimer's disease (AD) pathology are poised to enter clinical practice for the evaluation of individuals with cognitive decline and are likely to play a key part in determining eligibility for emerging anti-amyloid therapies. Several plasma assays quantifying phosphorylated tau (pTau) have been shown to predict AD pathology with varying degrees of accuracy. In this study we engaged leading assay vendors and performed a head-to-head, blinded comparison and commutability study of 28 different pTau assays. **Methods:** Paired EDTA plasma and cerebrospinal fluid (CSF) samples from 40 individuals evaluated at University College London, were sent to 11 participant centres. In total, 28 p-tau biomarkers (pTau181 [n=10], pTau205 [n=1], pTau212 [n=1], pTau217 [n=11], p-tau231 [n=5]) were measured blinded and in duplicate on multiple platforms. Pilot candidate reference materials (n=12) were also supplied to each vendor. The reference standard for AD pathology was determined by CSF Aβ42/40 <0.065 and CSF p-tau181 >57 pg/mL on the LUMIPULSE G1200 platform. **Results:** Of the evaluated participants, 25/40 had CSF profile of AD. All plasma pTau217 assays had areas under the curve (AUC) >0.9 for identifying AD pathology (range: 0.93–1.00); assays targeting pTau181 and pTau231 were more variable and generally had lower diagnostic performance, with a few exceptions (Lilly pTau181, UGOT IPMS pTau231, ADx pTau181). High correlations were observed between all p-tau217 assays (r = 0.89–0.97). However, relationships between plasma and CSF pTau were substantially weaker (r = 0.46–0.67) and non-significant in the AD pathology group. All pTau assays in CSF were highly correlated amongst themselves regardless of phosphorylation site or platform (r > 0.98). No commutable candidate reference material was found. **Conclusion:** Our results suggest that plasma pTau assays – and particularly those targeting pTau217 – have high diagnostic accuracy for detecting AD pathology using CSF as the gold standard. This ranges from mass spectrometry techniques, immunoassay methods and fully automated instrumentation. While there were generally good associations between the various pTau217 assays, offering optimism in translatability between pTau217 plasma assays, this was not observed when comparing plasma and CSF biomarkers. While further studies are required to understand this discrepancy, our results suggest that several pTau217 assays are sufficiently robust to be considered for clinical use.

LP049- GENE EXPRESSION PROFILE OF SYNCHRONIZED CELLS IDENTIFIES ALZHEIMER'S DISEASE IN AUTOPSY VALIDATED SKIN AND BLOOD SAMPLES.

F. Chirila[1,2], W. William[1], J. Jack[1], G. Guang[1], D. Daniel[1] *(1. Synaps Dx - Rockville (United States), 2. Spot Dx - Morgantown (United States))*

A gene expression profile has never been identified for late-onset (sporadic) Alzheimer's Disease (AD), >95% cases, although genes with high penetrance are known for early onset (familial) AD. Further, the genetic bridges linking early with late-onset AD have yet to be identified despite the common neuropathology. Here, novel genetic analyses of living, synchronized skin fibroblasts, and immortalized blood B-lymphocytes revealed an AD-specific gene expression profile for a core of five genes, FAM149B (P<0.0370 in training-set, and P<0.0150 in validation-set in the skin; P<0.0386 in the blood), NHLH1 (P<0.0319 in training-set, and P<0.0119 in validation-set in the skin; and P<0.0012 in the blood), SHISA5 (P<0.0188 in training-set, and P<0.0169 in validation-set in the skin; P<0.0121 in the blood), URB2 (P<0.0051 in training-set, and P<0.0219 in validation-set in the skin; P<0.0138 in blood), and WASF2 (P<0.0027 in training-set, and P<0.0476 in validation-set in the skin; P<0.0056 in blood), in autopsy-confirmed, blinded samples for two Cohorts: AD and non-AD dementia. Additionally, eighteen families of dysregulated genes in the skin fibroblasts of autopsy-confirmed AD patients are further validated in the immortalized blood B-lymphocytes (P<0.05). Three well-represented families of late-onset dysregulated genes in skin

fibroblasts and blood B-lymphocytes from autopsy-confirmed AD patients, ADAM (P<0.0321 in training-set, and P<0.0082 in validation-set in the skin; P<0.0016 in blood-one gene), IL (P<0.0298 in training-set, and P<0.0399 in validation-set in the skin; P<0.0484 in blood-nine genes), and RAB (P<0.0137 in training-set, and P<0.0186 in validation-set in the skin; P<0.0357 in blood-seven genes), are also in the gene network of PSEN1, 2, and APP, suggesting functional bridging of late with early-onset AD. The family of genes, ribosomal protein, RPL5(P<0.0220 in training-set, and P<0.00422 in validation-set in the skin; P<0.0073 in blood-one gene), found to be dysregulated in samples from both skin and blood from autopsy-confirmed AD, has been linked to various human congenital disorders termed ribosomopathies and is in the interaction network of the PRKCE gene, which encodes protein kinase C epsilon. This study has three validation layers— the validation set in the skin samples, the validation with blood B-Cells, and most importantly, the gold-standard autopsy validation for the ADs/Non-ADDs. In prior autopsy-validated clinical trials, we have developed three different but highly correlated diagnostic assays for AD using skin fibroblasts: Morphometric Imaging [1-3], PKC epsilon [4], and AD index [5, 6] with extremely high sensitivity (86-100%) and specificity (83-100%). These trials included 145 cases, of which > 80% were hyper-validated, i.e., autopsy or genetically confirmed AD or non-Alzheimer's Disease dementia patients (non-ADD) and non-demented healthy controls (HC). The top four functional groups of dysregulated genes included vascular, cell dynamics, neurological, and inflammation. The AD-dysregulated genes found in this study were associated with growth, size, and protein level differences in skin and blood cells, nine AD risk factors, and molecular pathways. Cell synchronization could offer a gateway for precision AD diagnostics and therapeutics, as it locks the oscillatory gene expression (7) in the same resting phase, G0, of the cell cycle, reducing the «genetic noise» and improving the signal-to-noise ratio. **References:** 1. Chirila F.V., Guang X., Fontaine D, Kern G., Khan T. K., Brandt J., Konishi Y., Nebe-von-Caron G., White III C. L., and Alkon D. L., "Morphometric imaging biomarker identifies Alzheimer's disease even among mixed dementia patients." Sci Rep 12, 17675 (2022). 2. Chirila F.V., Khan T. K., and Alkon D. L., "Spatiotemporal complexity of fibroblast networks screens for Alzheimer's disease." J. Alzheimer's Dis. 33, 165-176 (2013). 3. Chirila, F. V., Khan, T. K., and Alkon, D. L., 'Fibroblast Aggregation Rate Converges with Validated Peripheral Biomarkers for Alzheimer's Disease.' 1279 – 1294 (2014). 4. Khan T. K., Sen A., Hongpaisan J., Lim C. S., Nelson T. J., Alkon D, L., "PKCε deficits in Alzheimer's disease brains and skin fibroblasts." J. Alzheimer's Dis., 43(2):491-509 (2015). 5. Zhao W. Q., Ravindranath L., Mohamed A. S., Zohar O., Chen G. H., Lyketsos C. G., Etcheberrigaray R., AlkonD. L., "MAP Kinase Signaling Cascade Dysfunction Specific to Alzheimer's Disease in Fibroblasts" Neurobiol. Dis 11(1), 166-183 (2002). 6. Khan T. K., Alkon D. L., "An internally controlled peripheral biomarker for Alzheimer's disease: Erk1 and Erk2 responses to the inflammatory signal bradykinin." Proc. Natl. Acad. Sci. U S A 103(35), 13203-7 (2006). 7. Spellman P., Sherlock G., Zhang M.Q., Iyer V. R., Anders K., Eisen M. B., Brown P.O., Botstein D, Futcher B.,» Comprehensive identification of cell cycle-regulated genes of the yeast Saccharomyces cerevisiae by microarray hybridization» Mol. Biol. Cell. 9(12):3273-97(1998).

LP051- INVESTIGATING SEX-SPECIFIC BLOOD BIOMARKERS ASSOCIATED WITH MEMORY CHANGES IN MIDDLE-AGED ADULTS: INSIGHTS FROM THE FRAMINGHAM HEART STUDY.

H. Ding[1] , C. Liu[2], Y. Li[2], T.F.A. Ang[1] , S. Devine[1] , Y. Liu[1] , R. Au[1] , P.M. Doraiswamy[3] *(1. Boston University Chobanian & Avedisian School of Medicine - Boston (United States), 2. Boston University School of Public Health - Boston (United States), 3. Duke University School of Medicine - Boston (United States))*

Background: Memory decline among middle-aged adults is a significant concern, and the role of sex-specific blood biomarkers in this context remains poorly understood. In this study, we aimed to bridge this gap in knowledge by utilizing the extensive data from the Framingham Heart Study (FHS) to explore the relationship between sex-specific blood biomarkers and memory changes in middle-aged adults. **Methods:** We included participants under 60 years of age from the FHS Offspring Cohort, with an average age of 53 years and a range spanning 33 to 59 years; notably, 55.5% of the participants were women. Our investigation encompassed a wide range of exposures including age, sex, education, apolipoprotein-E genotype, body mass index, ventricular heart rate, systolic and diastolic blood pressure, resistin, fasting blood glucose, fasting blood insulin, hemoglobin A1C, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL), total cholesterol, amyloid β 40 and 42, C-reactive protein, interleukin 6 and 18, tumor necrosis factor-alpha, adiponectin, and fibrinogen. The primary outcome of our study was the annualized memory change, calculated based on results from 6 neuropsychological test measures administered between two assessment points, with an average interval of 4.3 years. To analyze the association between blood biomarkers and annualized memory change, we employed linear regression, adjusting for baseline age, education, and baseline cognition score. Furthermore, in order to construct causal dose-response curves linking annualized memory change with the blood biomarkers found to be significantly associated, we employed the generalized propensity score (GPS), taking into account age, sex, and education [1, 2]. Besides, a partial correlation analysis was conducted to explore the relationship between each individual biomarker and annualized memory change. **Results:** Higher levels of adiponectin and HDL were significantly associated with a slower or no memory decline in the pooled sample (beta = 0.028, P = 0.008) and women (beta = 0.0085, P = 0.015), while a higher level of fasting blood glucose was associated with faster memory decline (beta = -0.0048, P = 0.020). In women, higher hemoglobin A1C was also significantly associated with a faster memory decline (beta = -0.20, P = 0.020). The results from partial correlation analyses also supported the findings of adiponectin and FBG in association testing with memory change. The casual dose-response curve shows a U-shaped relationship between HDL levels and memory change. No significant associations were found for the other blood biomarkers (e.g. Aβ42) with memory change. **Conclusions:** As far as our understanding goes, this study presents the inaugural sex-specific network analysis of blood biomarkers linked to midlife memory decline within a prospective cohort study. The implications of our findings underscore the significance of addressing cardio-metabolic risks and emphasize the necessity to authenticate mid-life specific biomarkers that can expedite the formulation of primary preventive strategies. **Key words:** Sex difference, Memory decline, Blood biomarkers, Association, Middle-aged adults. **Disclosures:** PMD has received research grants, advisory/board

fees and/or stock from several companies and is a co-inventor on several patents related to the diagnosis and treatment of dementia. Other authors declare that they have no conflict of interests. **References:** 1. Galagate D. Causal inference with a continuous treatment and outcome: Alternative estimators for parametric dose-response functions with applications. University of Maryland, College Park; 2016. 2. Kobrosly RW. causal-curve: A Python Causal Inference Package to Estimate Causal Dose-Response Curves. Journal of Open Source Software 2020;5(52):2523.

LP052- VALIDATION OF AN ULTRA-SENSITIVE METHOD FOR PHOSPHO-TAU 217 (PTAU-217) QUANTITATION IN HUMAN PLASMA, SERUM, AND CSF. H. Zhang[1], J. Liu[1], N. Zhang[1], Z.J. Lin[1] *(1. Frontage Laboratories Inc. - Exton (United States))*

Background: Both blood-based (plasma and serum) and CSF tau phosphorylated at Threonine 217 (pTau-217) have been shown to be able to discriminate early to mild Alzheimer's disease (AD) from non-AD neurodegenerative disorders and healthy controls with high sensitivity and specificity. Here we present the fully validated ultra-sensitive pTau-217 assays for human plasma, serum, and CSF using the Quanterix Simoa HD-X platform. It is a new addition to the established protein biomarker assays (pTau-181, GFAP, and NfL) that we have validated in support of clinical trials and for the diagnosis of neurodegenerative diseases. **Methods:** pTau-217 Simoa CARe Advantage kit from ALZpath/Quanterix has been used for the method development and validation of pTau-217 assay for human plasma, serum, and CSF. All three validations followed the 2018 FDA BMV and 2022 ICH M10 guidelines. pTau-217 assay sensitivity and concentration detection range, minimum required dilution (MRD), freeze/thaw, benchtop, and refrigerated temperature stability, hemolytic and lipemic interferences have been validated for all three matrices. pTau-217 detectability was tested in normal plasma, serum, and CSF samples, versus AD plasma and CSF samples. **Results:** Validation of pTau-217 quantitation in human plasma, serum, and CSF has demonstrated that the validated pTau-217 assay has an analytical LLOQ of 0.00977 pg/mL, is one of the most sensitive assays with a minimal sample volume requirement of only 33.3 μl for plasma and serum, and 5 μl for CSF, and is cost-effective, compared to the current published data [see reference 1-4]. The minimum required dilution (MRD) is 1:3 for plasma and serum and 1:20 for CSF. The analyte is stable in plasma, serum, and CSF for up to 24 hours when refrigerated, 6 hours at ambient temperatures, and up to 5 freeze/thaw cycles. It tolerates up to 3% hemolytic, and up to 300 mg/DL lipemic plasma and serum. pTau-217 was able to be detected in 100% normal plasma, 90.0% normal serum and 92.3% normal CSF samples, and 100% AD plasma and CSF samples. The validated assay was successfully applied in the sample analysis and the data show dramatic differences on the pTau-217 levels between normal subjects and AD patients in both plasma and CSF. **Conclusions:** Validation of the pTau-217 Simoa assay in human plasma, serum, and CSF demonstrated that it is a novel approach with ultra sensitivity, high accuracy, and assay robustness. Together with the established sensitive pTau-181, GFAP, and NfL assays , these assays are available for application in clinical trials and diagnosis of neurodegenerative diseases. **Key words:** pTau-217, Simoa, Human Plasma, Serum, CSF, Full Method Validation. **Disclosures:** The authors declared no competing interests. **References:** 1. Mattsson-Carlgren N, et al. Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease. Brain. 2020;143:3234–3241. doi: 10.1093/brain/awaa286; 2. Palmqvist S, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. JAMA. 2020;324:772–781. doi: 10.1001/jama.2020.12134; 3. Thijssen EH, et al. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. Lancet Neurol. 2021;20:739–752. doi: 10.1016/S1474-4422(21)00214-3; 4. Janelidze S, et al. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. Brain. 2023 Apr 19;146(4):1592-1601. doi: 10.1093/brain/awac333.

LP053- BASELINE REGIONAL FLORTAUCIPIR PROFILES IN PRECLINICAL ALZHEIMER'S DISEASE. W. Zhu[1], S.Y. Shin[1], J. Latourelle[1] *(1. Aitia - Somerville (United States))*

Background: Aitia's Digital Twins are powerful tools for generating patient-level predictions of Alzheimer's disease features and progression. Here, in collaboration with Global Alzheimer's Platform Foundation (GAP), we evaluated diverse clinical and molecular data sources as screening tests to identify individuals with positive amyloid PET results for a more cost-effective and convenient alternative, accessible to a larger at-risk population. **Methods:** GAP's Bio-Hermes1 study profiled high-dimensional blood and digital biomarkers from more than 1,000 multi-ethnoracial volunteers; covering demographics, vital signs, APOE genotype, p-tau 217, p-tau 181, beta amyloid, cognitive tests, proteomics (Somalogic), PET imaging among many. Our training dataset included ~7,000 features from 780 multi-ethnoracial participants (45% Healthy Controls, 32% MCI and 22% probable AD). A left-out test set with less complete features (N=~150) was retained for out-of-sample validation. The prevalence of a positive amyloid was 0.35 in the training set, and 0.41-0.49 in the test sets. Aitia's REFSTM platform2 developed an ensemble of Bayesian multivariate models for 14 separate input pools composed of different features of interest, to predict amyloid PET positivity. The predictive ability of the models was measured by the area under ROC curve (AUC), and further evaluated through 5-fold cross-validation and out-of-sample validation. Model performance was tested between models (DeLong's test) to compare predictive value of different data types. **Results:** The highest level of predictive performance was observed when using all available data, all blood biomarkers, and p-tau 217 alone, as well as when looking at wither all data or all biomarkers excluding p-tau 217 (in-sample AUC ranged from 0.9 to 0.94, tier 1). Predicting Amyloid+ using only proteomics or APOE4 also demonstrated strong performance (in-sample AUC of 0.84 and 0.80, tier 2). The remaining seven models based on various combinations of non-molecular clinical and cognitive measures including a set of "easily accessible" self-reported clinical- and digitally assessed cognitive test data comprised the last tier (in-sample AUC ranged from 0.68 to 0.75, tier 3). The performance of the different models was generally observed to be slightly reduced in the healthy cohort compared to MCI and AD and consistently ordered among the three tiers. Performance was also generally consistent across ethnoracial groups, and these findings were validated in the cross-validation and independent left-out samples. **Conclusions:** We quantified the contribution of different data features and modalities to the prediction of amyloid PET positivity in the large-scale multi-ethnoracial Bio-Hermes study data. Digital Twins showed that p-tau 217 is the most effective biomarker in general, corroborating previous

studies. We further demonstrate that equivalent predictive performance can be maintained with other blood biomarkers even in the absence of p-tau 217 and that even much more easily accessible and self-reported data may provide a cost-effective screening strategy in various situations. Digital Twins can be further explored for causal inference including understanding the causal relationships among biomarkers, proteins, and disease features, potentially allowing rich understanding of biomarkers, surrogate endpoints, and disease mechanisms. The Digital Twins will be continuously updated as new data become available to further refine and improve these applications. **Key words:** Digital Twins, Amyloid PET, p-tau 217, Causal Inference. **References:** 1. https://globalalzplatform.org/biohermesstudy/; 2. Latourelle JC, et al. Lancet Neurol. 2017. PMID: 28958801. https://doi.org/10.1016/S1474-4422(17)30328-9

LP054- CHANGES OF CSF AND PLASMA BIOMARKERS DURING 18-MONTH PERIOD IN A PHASE II CLINICAL TRIAL WITH BIOMARKER PROVEN ALZHEIMER'S DISEASE PATIENTS. C. Teunissen[1], M. Koel-Simmelink[1], M. Oosthoek[1], N. Prins[2], P. Van Bokhoven[3], T. Okuda[4], P. Scheltens[5] *(1. Neurochemistry Laboratory, Department of Neurochemistry, Amsterdam UMC - Amsterdam (Netherlands), 2. Brain Research Center - Amsterdam (Netherlands), 3. IXA-Neuroscience, Amsterdam Neuroscience, Amsterdam UMC location Vrije Universiteit - Amsterdam (Netherlands), 4. FUJIFILM Toyama Chemical Co., Ltd. - Tokyo (Japan), 5. Amsterdam UMC - Amsterdam (Netherlands))*

Background: Edonerpic maleate (T-817MA) is an orally available small molecule compound which has potent neuroprotective actions. In a past phase 2 study (NCT02079909) significant reduction of p-tau 181 in the cerebrospinal fluid (CSF) at week 52 was observed in a subset of patients agreed to undergo lumbar punctures (N=17-24). Based on these finding a disease-modifying effect of T-817MA was suggested. To clarify its potential as a therapeutic in an earlier stage of AD, we designed the T817MAEU201 study (NCT04191486) in which AD pathology-relevant biomarkers were measured in CSF and plasma at baseline, and week 52 and 78 as proof of concept. **Methods:** T817MAEU201 is a phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of T-817MA in patients with mild cognitive impairment (MCI) or mild dementia due to AD, as evidenced by abnormal CSF Aβ 42 and p-tau 181 at screening. Other key inclusion criteria were 50-80 years of age, MMSE score of 24-30. Randomized patients were treated by either 448 mg of T-817MA or placebo for 78 weeks. To evaluate changes in biomarker concentrations during the treatment period, CSF and plasma samples were collected at baseline, and week 52 and 78. Concentrations of CSF biomarkers, p-tau 181, p-tau-217, total tau, Aβ42, Aβ40, Aβ42/Aβ40 ratio, neurogranin, neurofilament light chain (NFL) and chitinase 3-like 1 (YKL-40) were measured. Concentrations of plasma biomarkers, p-tau 181, p-tau-217, Aβ 42, Aβ 40, Aβ42/Aβ40 ratio, NFL and glial fibrillary acidic protein (GFAP) were measured. The primary endpoint of this study was change of CSF p-tau 181 from baseline to week 78. **Results:** 221 patients were randomized. 188 completed 78 weeks of treatment (14.9% premature discontinuation). 159 CSF samples were collected for biomarker analysis at week 78. Baseline values of the CSF and plasma biomarkers confirmed underlying AD pathology of randomized patients. No differences in CSF p-tau 181 were observed after 78 weeks between T-817MA treated patients vs placebo. Among all other CSF/plasma biomarkers significant increases were observed in plasma NFL and plasma GFAP between T-817MA treated patients vs placebo. Additional analysis regarding biomarker changes during 18-months observation, correlation between CSF and plasma and correlations among biomarkers will be presented. **Conclusions:** No differences in changes in CSF p-tau 181 were observed as a result of the intervention vs placebo. The observations of CNS biomarker trend in 18 months in the placebo groups during this very controlled observation interval is valuable for designing clinical trials in future and understanding drug effect. **Key words:** CSF biomarkers, plasma biomarkers, Phase 2, edonerpic. **Clinical Trial Registry:** NCT04191486; https://clinicaltrials.gov. **Disclosures:** CT is employed by Amsterdam UMC. She has grants or contracts for Research of the European Commission (Marie Curie International Training Network, grant agreement No 860197 (MIRIADE), Innovative Medicines Initiatives 3TR (Horizon 2020, grant no 831434) EPND (IMI 2 Joint Undertaking (JU), grant No. 101034344) and JPND (bPRIDE), National MS Society (Progressive MS alliance), Alzheimer Drug Discovery Foundation, Alzheimer Association, Health Holland, the Dutch Research Council (ZonMW), including TAP-dementia, a ZonMw funded project (#10510032120003) in the context of the Dutch National Dementia Strategy, Alzheimer Drug Discovery Foundation, The Selfridges Group Foundation, Alzheimer Netherlands. She is recipient of ABOARD, which is a public-private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). CT is also a contract researcher for ADx Neurosciences, AC-Immune, Aribio, Axon Neurosciences, Beckman-Coulter, BioConnect, Bioorchestra, Brainstorm Therapeutics, Celgene, Cognition Therapeutics, EIP Pharma, Eisai, Eli Lilly Fujirebio, Grifols, Instant Nano Biosensors, Merck, Novo Nordisk, Olink, PeopleBio, Quanterix, Roche, Siemens, Toyama, Vivoryon, and the European Commission. CT has received payment or honoraria from Roche, Novo Nordisk, and Grifols, where all payments were made to her institution. She also serves on editorial boards of Medidact Neurologie/Springer; and in Neurology: Neuroimmunology & Neuroinflammation. CT is editor of Alzheimer Research and Therapy. MKS declares nothing to disclose MO has received consultancy fees from New Amsterdam Pharma (paid to her institute). NP is co-PI of the current trial with Fuji Film Toyama Chemical. NP performed consultancy work for Aribio, Amylyx, Eli-Lilly and Janssen and received a speaker fee from Biogen. NP is CEO and co-owner of Brain Research Center, the Netherlands. PVB declares nothing to disclose. TO is an employee of FUJIFILM Toyama Chemical Co., Ltd. PS is a full time employee of EQT Life Sciences (formerly LSP) and Professor Emeritus at Amsterdam University Medical Centers. PS has received consultancy fees (paid to the university) from Alzheon, Brainstorm Cell and Green Valley. Within his university affiliation PS was global PI of the phase 1b study of AC Immune, Phase 2b study with FUJI-film/Toyama and phase 2 study of UCB. PS is past chair of the EU steering committee of the phase 2b program of Vivoryon and the phase 2b study of Novartis Cardiology and presently co-chair of the phase 3 study with NOVO-Nordisk.

LP055- ANALYTICAL AND CLINICAL VALIDATION OF THE SIMOA JANSSEN PLASMA P217+ TAU AS A CLIA LAB DEVELOPED TEST (LDT) FOR CLINICAL USE.

D. Wilson[1], G. Triana-Baltzer[2], A.J. Vasko[1], K. Copeland[3], L. Hesterberg[4], M. Khare[1], M. Wolfe[1], P. Sheehy[1], Z. Fernandes[1], H. Kolb[2], M. Roskey[1], M. Miller[1] *(1. Quanterix - Billerica (United States), 2. Janssen R&D - La Jolla (United States), 3. Boulder Statistics - Steamboat Springs (United States), 4. HCS, Inc - Denver (United States))*

Background: The intersection of new therapeutic options for Alzheimer's disease (AD), the emergence of accurate blood based tests for AD, and the anticipated health system log jam for confirmatory diagnostic testing with traditional modalities, has elevated the need for accurate blood test alternatives for identifying amyloid pathology to an urgent level. Plasma p-Tau 217 has emerged as a biomarker with sufficient sensitivity and specificity to rule out and rule in amyloid pathology with high confidence, potentially serving as a readily scalable non-invasive test to facilitate AD diagnosis and identifying patients who could benefit from drug therapy. In this presentation, we describe analytical and clinical validation of a lab developed test for plasma p-Tau 217 suitable for clinical use. **Methods:** The Janssen p217+ tau assay has been described [1]. In brief, the assay is a fully automated 3-step bead-based digital ELISA with femtogram/mL sensitivity enabling measurement plasma p-tau 217 in both AD and non-AD patients. For analytical validation, we employed CLSI-based protocols following CLIA guidelines, and for setting cutoffs and clinical validation, we utilized the prospective BioHermes trial [2]. BioHermes was designed to evaluate blood based biomarkers to detect brain amyloid in recruited participants from 17 US clinical sites. The study included >20% representation from racial/ethnic minority participants. Participants 60-85 years old were clinically assessed and assigned to one of three cohorts: cognitively normal (CN, n=417), mild cognitive impairment (MCI, n=312), or mild AD (n=273). Clinical assessment was followed by amyloid PET. The prevalence of amyloid positivity was 21%, 34%, and 62%, and the proportion of minority groups was 19%, 25%, and 32% for CN, MCI and AD cohorts respectively. Aligning with recently updated draft NIA-AA guidelines, a three-range approach was chosen in recognition of negative/positive overlap with an indeterminant zone. To establish and validate cutoffs, the cohorts were divided into training and validation groups. Cutoffs were set in the training cohort to provide positive and negative concordance rates with amyloid PET of at least 95%, with confidence intervals of approximately ±5% and an indeterminant range ≤20%. **Results:** Limits of detection and quantification were 0.002 pg/mL and 0.037 pg/mL respectively. Repeatability and reproducibility across 3 reagent lots using samples across the measuring range were 4.26% (95% CI: 2.87-5.67) and 8.42% (4.42-12.23). Linearity per CLSI EP06-A gave ≤15% deviation at all dilutions. Receiver operating characteristics across training and validation groups gave an area under the curve (AUC) of 0.93 (CI 0.87-0.98). Lower (95% sensitivity, <0.09 pg/mL) and upper (95% specificity, >0.11 pg/mL) cutoffs derived from the training group gave overall positive and negative percent agreements of 95.3% and 91.5% respectively for the validation group. The overall indeterminant range between the two cutoffs was 17%. **Conclusions:** The assay demonstrated acceptable analytical performance for CLIA implementation as an LDT for clinical use. The two cutoff approach resulted in high concordance with PET with an acceptable indeterminant range for rule-out and rule-in applications to support diagnostic evaluation for AD. Further validation is needed to support the use of the test for confirmatory diagnostic purposes. **Key words:** Plasma p-Tau 217, BioHermes, LDT. **Disclosures:** No competing disclosures. **References:** Triana-Baltzer G, et al. Alzheimers Dement (Amst). 2021;13(1):e12204. doi:10.1002/dad2.12204; Mohs R, et al. Alzheimer's Dement (in review).

LP056- THE ROLE OF NEUROINFLAMMATION IN ALZHEIMER'S DISEASE: A SYSTEMATIC LITERATURE REVIEW.

M.T. Heneka[1], S. Gauthier[2], C.A. Sagar[3], J. Hahn-Pedersen Hviid[3], M. Bentsen[3], H. Zetterberg[4] *(1. Luxembourg Centre for Systems Biomedicine, Université du Luxembourg - Belvaux (Luxembourg), 2. AD and Related Disorders Research Unit, McGill Center for Studies in Aging, Departments of Neurology & Neurosurgery, Psychiatry, and Medicine at McGill - Montreal (Canada), 3. Novo Nordisk A/S - Søborg (Denmark), 4. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg - Mölndal (Sweden))*

Background: Recent studies on neuroinflammation in the pathogenesis of Alzheimer's disease (AD) are of significance but require further investigation [1]. Several mediators of neuroinflammation can serve as therapeutic targets for AD as well as biomarkers for prognostic purposes [2]. This systematic literature review (SLR) aims to investigate the role of neuroinflammation in AD and explores the association of neuroinflammation with AD disease progression. **Methods:** An SLR was conducted as per the Cochrane Handbook for Systematic Reviews of Interventions, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Systematic searches were conducted on 10 Feb 2023 using MEDLINE®, Embase®, and PsycInfo® databases to search for articles in English from 2012 on AD or mild cognitive impairment due to AD, using neuroinflammation or other immune search strings. Two independent reviewers screened titles and examined full-text records for relevance. **Results:** The SLR identified 3669 articles from the three databases. After eligibility screening and review, 114 studies were included in the SLR report and detailed data extracted from 56 studies. Cerebrospinal fluid (CSF) inflammatory biomarkers – namely YKL-40 (6 studies), sTREM2 (5 studies), and GFAP (4 studies) were identified to have a key role in AD neuroinflammation. Significantly higher levels of CSF YKL-40 (6/6 studies), CSF sTREM2 (4/5 studies), and CSF GFAP (4/4 studies) were found in patients with dementia due to AD compared with cognitively normal control subjects. CSF sTREM2 changes were found to be sensitive to preclinical stages of AD. Levels of CSF YKL-40 were higher in the dementia stage of AD compared with the mild cognitive impairment (MCI) stage of AD, and control patients. Prognostic value of plasma or serum GFAP biomarker was observed in three studies (3/5 studies). In cognitively normal people or those with subjective cognitive decline, higher baseline levels of serum or plasma GFAP predicted steeper rate of cognitive decline and clinical progression to dementia stage of AD. In AD patients with dementia, higher levels of plasma GFAP were associated with greater change in MMSE score and poor cognitive outcome during follow-up. CSF YKL-40 increased longitudinally in patients with all-cause MCI and AD patients with dementia but not in cognitively normal individuals, and highest baseline levels of CSF YKL-40 in subjects with all-cause MCI predicted progression to dementia due to AD with a hazard ratio of 3. CSF sTREM2 levels also showed prognostic value in predicting rate of cognitive decline in AD. **Conclusions:** Evidence from

fluid biomarkers consolidates the role of neuroinflammation in pathophysiology of AD and supports clinical use of GFAP for prognostic purpose as recommended in the draft NIA-AA Revised Criteria for Diagnosis and Staging of Alzheimer's Disease 2023 guidelines. The link between neuroinflammation and the degree of cognitive impairment varied depending on the specific biomarkers. More clinical evidence is needed before these fluid biomarkers (CSF GFAP, CSF TREM2, and CSF YKL-40) can be widely introduced into therapeutic practice. Larger longitudinal observational studies in diverse AD populations are needed to investigate the role of neuroinflammation in AD and its association with long-term clinical outcomes. **Key words:** Alzheimer's disease, mild cognitive impairment, neuroinflammation, fluid biomarkers. **Disclosures:** MTH serves on scientific advisory boards for Alector, the Dementia Discovery Fund, IFM Therapeutics, Muna Therapeutics, the Paris Brain Institute and UK-DRI, and T3D Therapeutics. He has received honoraria for consultations and/or oral presentations from AC Immune, Biogen, Eisai, Novo Nordisk, and Roche. SG has served on scientific advisory boards for Advantage Therapeutics, Alzheon, AmyriAD, Biogen Canada, Eisai Canada, Enigma, Lilly Canada, Lundbeck, Medesis, Roche Canada, Sharon Francis Foundation, and TauRx. SAC, JHH-P, and MB are employees of Novo Nordisk. HZ has served on scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZpath, Annexon, Apellis, Artery Therapeutics, Inc., AZTherapies, Inc., Cognition Therapeutics, Inc., Denali Therapeutics, Eisai, NervGen, Novo Nordisk, OptoCeutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave Life Sciences. He has given lectures in symposia sponsored by AlzeCure, Biogen, Cellectricon, Fujirebio, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). **References:** 1. Webers A, et al. Immunol Cell Biol 2020; 98 (1): 28–41. http://doi: 10.1111/imcb.12301. 2. Simrén J, et al. Adv Clin Chem 2023; 112: 249–281. http://doi: 10.1016/bs.acc.2022.09.006.

LP057- PROTEOMIC ANALYSIS IN A PHASE 2 CLINICAL TRIAL STUDYING CT1812 TO IDENTIFY CSF AND PLASMA PHARMACODYNAMIC BIOMARKERS AND MOLECULAR CORRELATES OF EEG IN ALZHEIMER'S DISEASE PATIENTS.

V. Di Caro[1], K. Pandey[2], B. Lizama[1], E. Cho[1], D. Duong[3,4], W. De Haan[5,6], M. Grundman[7], N. Seyfried[4], A. Caggiano[1], E. Vijverberg[6], M. Hamby[1] *(1. Cognition Therapeutics, Inc. - Pittsburgh (United States), 2. Emtherapro Inc, Systems Biology. - Atlanta (United States), 3. Emtherapro Inc, Systems Biology - Atlanta (United States), 4. Emory University School of Medicine, Biochemistry - Atlanta (United States), 5. Department of Clinical Neurophysiology and MEG Center, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 6. Alzheimer Center, Department of Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC - Amsterdam (Netherlands), 7. Global R&D Partners, LLC and Dept of Neurosciences University of California - San Diego (United States))*

Background: CT1812 is an oral small molecule sigma-2 receptor (S2R) modulator in development for Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). Preclinical and clinical evidence indicate that CT1812 can displace toxic amyloid-β oligomers (AβO) from binding to neuronal synapses leading to a displacement of AβO into the CSF. A phase 2, single site, double-blind, placebo controlled, crossover design study was conducted in 16 participants with mild to moderate AD (NCT04735536) to evaluate the effect of the S2R modulator CT1812 on quantitative electroencephalography (EEG) activity, safety, and exploratory biomarkers. The full analysis of an unbiased assessment of CSF and plasma proteomics to identify pharmacodynamic biomarkers of CT1812 will be presented herein. **Methods:** Participants were randomized to receive four weeks of either CT1812 (300 mg, PO, qD) or placebo during the first treatment period. Following a two-week washout, participants then switched treatment for another four-week period. Tandem-mass tag mass spectrometry (TMT-MS) proteomics was performed on CSF and plasma collected at baseline, day 29 (immediately after the first treatment period) and day 72 (immediately following the second treatment period) for longitudinal assessments. Treatment effects were assessed through differential abundance analyses using two statistical levels ($p<0.1$, $p<0.05$) followed by pathway analyses (MetaCore, STRING). To identify correlates to EEG, Pearson correlation analyses were performed across several EEG parameters and each protein in the CSF proteome ($p<0.05$). **Results:** Across all samples, 2,612 proteins were detected in CSF and 2,365 were detected in plasma. During the first period, 163 CSF proteins (as assessed at $p<0.05$) and 68 plasma proteins (as assessed at $p<0.1$) were differentially abundant in participants treated with CT1812 compared to placebo. Hierarchical clustering and MSD analyses ($p<0.05$) demonstrated stratification of patients by treatment. Inflammatory, amyloid-β, and synaptic pathways were identified as significantly (at $p<0.1$ and $p<0.05$) altered in plasma; whereas in CSF, pathways linked to cholesterol, lipoprotein biology, and Wnt signaling were found to be significantly represented ($p<0.05$). Sets of proteins were identified to be significantly correlated ($p<0.05$) with regional and global EEG parameters (relative theta and alpha power). Several biological processes were identified via pathway analyses to be associated with regional and global theta and alpha power, including that linked to changes in brain activity ($p<0.05$). **Conclusions:** These results provide insight into potential pathway engagement biomarkers of CT1812 after four week treatment and identify potential molecular correlates to parameters of EEG that are known to be disrupted in AD patients. Results support the continued clinical development of CT1812 in mild to moderate AD (NCT03507790), early AD (NCT05531656) and DLB (NCT05225415). This study was supported by a grant from the National Institute on Aging (AG058710). **Key words:** Amyloid-beta oligomers, TMEM97, S2R. **Clinical Trial Registry:** NCT04735536; https://clinicaltrials.gov/show/NCT04735536. **Disclosures:** MH, AC, VD, EC, BL are employees and shareholders of Cognition Therapeutics; MG is an employee of Global R&D partners and a consultant to Cognition Therapeutics. WH is an employee of the Amsterdam UMC EEG lab, which performs centralized EEG analysis for multicenter pharmaceutical trials by Cognition Therapeutics, Vivoryon, Immunobrain, Toyama Fujifilm, Cervomed and Treeway. EV is or has been PI for PI for DIAN TU trials, AC immune, Alnylam, CogRX therapeutics, New Amsterdam Pharma, Janssen, UCB, Roche, Vivoryon, ImmunoBrain, GemVax and Alector, Eli Lilly, Biogen and Fuij Film Toyama. Consultant for New Amsterdam Pharma, Treeway, ReMynd, Vivoryon, Biogen, Vigil Neuroscience, and Roche. KP and DD are employees of Emtherapro.

LP058- CHANGES IN EEG THETA/ALPHA RATIO DURING AN 18-MONTH PERIOD IN A PHASE II CLINICAL TRIAL WITH BIOMARKER-CONFIRMED ALZHEIMER'S DISEASE PATIENTS.

W. De Haan[1], N. Prins[2], P. Van Bokhoven[3], T. Okuda[4], P. Scheltens[5] *(1. Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location Vumc - Amsterdam (Netherlands), 2. Brain Research Center - Amsterdam (Netherlands), 3. IXA-Neuroscience, Amsterdam Neuroscience, Amsterdam UMC location Vrije Universiteit - Amsterdam (Netherlands), 4. FUJIFILM Toyama Chemical Co., Ltd. - Tokyo (Japan), 5. Amsterdam UMC - Amsterdam (Netherlands))*

Background: Quantitative electroencephalography (EEG) is an easily accessible, non-invasive tool for the direct assessment of neuronal and synaptic function. The most prominent neurophysiological hallmark of AD is gradual diffuse slowing of spontaneous oscillatory activity, and this can be described by an increase in slow theta (4-8 Hz) as well as a decrease in faster alpha (8-13 Hz) activity. The theta/alpha ratio has been demonstrated to be a fairly robust marker for the diagnosis and disease course of Alzheimer's disease (AD). However, the potential of the theta/alpha ratio to monitor treatment effects has not been fully investigated. We used the theta/alpha ratio as one of the secondary endpoints in a phase 2 study to evaluate efficacy and safety of edonerpic maleate (T-817MA) in patients with early stages of Alzheimer's disease (AD). **Methods:** T817MAEU201 is a phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of T 817MA in patients with mild cognitive impairment (MCI) or mild dementia due to AD, as evidenced by abnormal CSF Aβ 42 and p-tau 181 at screening. The primary endpoint of this study was change of CSF p-tau 181 from baseline to week 78. To verify the disease modifying effect of the compound from various aspects, eyes-closed, resting-state EEG theta/alpha ratio was chosen as one of the secondary endpoints. Randomized patients were treated by either 448 mg of T-817MA or placebo for 78 weeks. During the treatment period, the EEG theta/alpha ratio was calculated in visually selected, artefact-free epochs (n=4 for each EEG, averaged) at baseline, week 52 and week 78. **Results:** 221 patients were randomized. 188 completed 78 weeks of treatment (14.9% premature discontinuation). Time-dependent increase in the EEG theta/alpha ratio was observed during the 78-week treatment of placebo. Estimated change from baseline (LSMEAN) of the theta/alpha ratio in the placebo group was 0.026 at week 52 (n=105) and 0.047 at week 78 (n=101). A consistent trend towards theta/alpha ratio stabilization, but no significant differences were found in the T-817MA group at week 52 or week 78. **Conclusions:** The EEG theta/alpha ratio was explored as neurophysiological efficacy marker of T-817MA treatment in AD. Although a trend towards theta/alpha ratio stabilization was observed in the treated group, the difference with the placebo group was non-significant. Its usefulness as therapeutic marker needs further validation. **Key words:** EEG, theta/alpha ratio, Phase 2, edonerpic. **Clinical Trial Registry:** NCT04191486; https://clinicaltrials.gov. **Disclosures:** WH heads the Amsterdam UMC EEGlab, which performs centralized EEG analysis for multicenter pharmaceutical trials by Cognition Therapeutics, Vivoryon, Immunobrain, Toyama Fujifilm, Cervomed and Treeway. NP is co-PI of the current trial with Fuji Film Toyama Chemical. NP performed consultancy work for Aribio, Amylyx, Eli-Lilly and Janssen and received a speaker fee from Biogen. NP is CEO and co-owner of Brain Research Center, the Netherlands. PVB declares nothing to disclose. TO is an employee of FUJIFILM Toyama Chemical Co., Ltd. PS is a full time employee of EQT Life Sciences (formerly LSP) and Professor Emeritus at Amsterdam University Medical Centers. PS has received consultancy fees (paid to the university) from Alzheon, Brainstorm Cell and Green Valley. Within his university affiliation PS was global PI of the phase 1b study of AC Immune, Phase 2b study with FUJI-film/Toyama and phase 2 study of UCB. PS is past chair of the EU steering committee of the phase 2b program of Vivoryon and the phase 2b study of Novartis Cardiology and presently co-chair of the phase 3 study with NOVO-Nordisk.

LP059- ASSESSMENT OF PLASMA BIOMARKERS COMBINED WITH CLINICAL MEASURES IN MILD COGNITIVE IMPAIRMENT, AD DEMENTIA, AND NORMAL AGING.

M. Sabbagh[1], M. Thomas[1], J. Wilson[2], G. Malaty[1], B. Decourt[3] *(1. Barrow Neurological Institute - Phoenix (United States), 2. Arizona State University - Tempe (United States), 3. Texas Tech University - Lubbock (United States))*

Background: There would be tremendous value for having biomarker panels as screening tools for the assessment of AD pathology. Technologies that increase the sensitivity and accuracy of the measurement of plasma Aβ42, total Tau (t-Tau), phosphorylated Tau (P-tau),) have emerged. **Objective:** The specific aim of the present study was to assess the accuracy of plasma Aβ42, total Tau (t-Tau), and pTau combined with clinical measures in identifying mild cognitive impaired (MCI), NC and AD cases. **Methods:** The total sample size was 66 subjects including 37 NC, 16 MCI [NIA-AA Criteria, Alberts 2011], 13 AD dementia [McKhann criteria] and. NC subjects reported no demonstrable cognitive complaints, were intact functionally and cognitively. The variables included age, education, MOCA, and FAST. Plasma biomarkers were assayed by ImmunoMagnetic Reduction (IMR) technology (MagQu, Inc). **Results:** MOCA scores were lower in the aMCI and AD groups. The sensitivities using biomarkers (abeta42xT-Tau) or MoCA individually to discriminate aMCI from NC are 0.625 to 0.92, respectively. When the threshold for the Ab1-42xT-Tau + MoCA is set at 0.306, the sensitivity = 0.929, specificity = 0.833, AUC =0.921 for differentiating NC from aMCI. **Conclusions:** In this study, we found that plasma biomarker product, Ab1-42xT-Tau, when used in combination with the MoCA screening tool, increases the specificity for distinguishing aMCI from NC

LP060- MULTIOMIC BLOOD-BASED BIOMARKERS EXHIBIT HIGH SPECIFICITY IN PREDICTING ALZHEIMER'S DISEASE FROM PREDEMENTIA.

B. Souchet[1], A. Michail[1], M. Heuillet[2], A. Dupuy-Gayral[2], E. Haudebourg[2], C. Pech[2], A. Berthemy[2], F. Autelitano[2], B. Billoir[1], K. Domoto-Reilly[3], C. Fowler[4], T. Grabowski[3], S. Jayadev[3], C.L. Masters[4], J. Braudeau[1] *(1. AgenT - Paris (France), 2. Evotec - Toulouse (France), 3. University of Washington - Seattle (United States), 4. University of Melbourne - Victoria (Australia))*

Background: The primary criteria for diagnosing mild cognitive impairment (MCI) or dementia resulting from Alzheimer's disease (AD) rely partly on cognitive assessments and the presence of amyloid plaques, as substantiated in scientific literature [1, 2]. While these criteria exhibit high sensitivity in predicting AD among cognitively impaired patients, their specificity is comparatively low [3-5]. In fact, as much as 25% of individuals with amyloid plaques may be misdiagnosed with AD when they are actually suffering from a different brain disorder. Consequently, there is an imperative need to develop novel biomarkers characterized by

high specificity. These biomarkers would not only enable earlier diagnosis but also facilitate swift therapeutic interventions and more effective monitoring of clinical trials. **Methods:** We devised targeted mass spectrometry assays for 81 blood-based biomarkers, encompassing 45 proteins and 36 metabolites, that had been previously identified in AAV-AD rats [6]. We analyzed blood samples from 345 participants with cognitive impairment, including 193 with Mild cognitive impairment and 152 with dementia, at their baseline visits and subsequently followed them clinically for up to 13 years. The participants' ultimate diagnoses, either AD or a different brain disorder, were determined at their last clinical assessments, adhering to the specific clinical diagnostic criteria associated with each disorder subtype. Of the participants, 82.9% had available amyloid status data at baseline, with 61.9% testing positive for amyloid. Both amyloid-positive and amyloid-negative individuals were present within each clinical group. We developed predictive machine learning models specifically for identifying AD participants (including 123 with Prodromal AD and 126 with AD dementia) within the group of individuals with non-AD brain disorders (comprising 96 participants). The training dataset (70% of the total) was employed for selecting a subset of biomarkers, training the algorithm, and defining the cutoff values, while the external test dataset (30% of the total) was used to blindly validate the predictive model. **Results:** Utilizing a combination of 19 blood biomarkers and age, our model demonstrated the capability to distinguish AD participants (41 with Prodromal AD and 43 with AD dementia) from non-AD participants (25 individuals) with a remarkable specificity of 92.0% and sensitivity of 52.4% during external blind validation (AUROC=71.8%, p=0.001). When the amyloid status data (derived from CSF or PET scans) and our predictive machine learning model were applied in association, with individuals being categorized as AD if they tested positive in both assessments, we achieved a perfect specificity of 100% along with a sensitivity of 39.7%. **Conclusion:** Our multiomics blood-based peripheral biomarkers exhibit a high predictive accuracy for identifying AD patients within the cognitively impaired population, resulting in a low rate of false positives. When used in conjunction with amyloid screening, these biomarkers hold the potential to identify a nearly pure AD patient population. **Key words:** Alzheimer's, Biomarkers, Prodromal AD, Artificial Intelligence, Machine Learning. **Disclosures:** BS, AM, BB & JB are AgenT's employees. **References:** 1. McKhann, G. M. et al. Alzheimers Dement 7, 263-269 (2011). https://doi.org:10.1016/j.jalz.2011.03.005; 2. Albert, M. S. et al. Alzheimers Dement 7, 270-279 (2011). https://doi.org:10.1016/j.jalz.2011.03.008; 3. Martinez, G. et al. Cochrane Database Syst Rev 11, CD012216 (2017). https://doi.org:10.1002/14651858.CD012216.pub2; 4. Ritchie, C. et al. Cochrane Database Syst Rev 2014, CD008782 (2014). https://doi.org:10.1002/14651858.CD008782.pub4; 5. Kokkinou, M. et al. Cochrane Database Syst Rev 2, CD010945 (2021). https://doi.org:10.1002/14651858.CD010945.pub2; 6. Audrain, M. et al. Cereb Cortex 28, 3976-3993 (2018). https://doi.org:10.1093/cercor/bhx260

CLINICAL TRIALS: COGNITIVE AND FUNCTIONAL ENDPOINTS

P098- BETWEEN-COUNTRY COMPARISONS OF QUALITY OF LIFE AND ACTIVITIES OF DAILY LIVING IN MULTINATIONAL ALZHEIMER'S DISEASE CLINICAL TRIALS.

S. Machizawa[1], E. Appleman[1], J. Stenclik[1], A. Lacob[2], R. Kamat[1] *(1. Signant Health - Blue Bell (United States), 2. Signant Health - Bucharest (Romania))*

Background: With an increasing number of Alzheimer's disease (AD) clinical trials conducted globally, it is increasingly important to understand the impact of geo-cultural factors on clinical outcome measures. Previous research [1] reported geo-cultural heterogeneity in patient characteristics and clinical outcomes in multinational AD trials. Thus, sponsors should be aware of these differences to plan global trials appropriately. The present study investigated regional between-country differences in the AD Cooperative Study-Activities of Daily Living for Mild Cognitive Impairment (ADCS-MCI-ADL) and Quality of Life in AD (QoL-AD) in Asia and Europe while controlling the baseline cognitive status among the participants. **Methods:** This study used data from two multinational, randomized, controlled Phase 3 AD trials, specifically on the ADCS-MCI-ADL, QoL-AD, and AD Assessment Scale-Cognitive Subscale (ADAS-Cog). Data were pooled for participants in Asia (n = 215, 240, and 153 for China, Japan, and South Korea, respectively) and Europe (n = 95, 43, 75, 212, 35, and 60 for France, Germany, Italy, Spain, Sweden, and the UK, respectively) at baseline and Week 76-79 from these studies. **Results:** There was statistically significant heterogeneity at baseline on the QoL-AD scores within Europe and Asia (Kruskal-Wallis test; p<.001) and on the ADCS-MCI-ADL scores within Europe (Kruskal-Wallis test; p<.001) after controlling the cognitive status based on the baseline ADAS-Cog scores. Within Europe, scores in Sweden were significantly higher across scales. Specifically, the ADCS-MCI-ADL scores in Sweden were higher than those in Italy, Spain, and the UK; Participant QoL-AD scores were higher than those in Germany, Italy, and the UK (Dunn's test; p<.001); and Caregiver QoL scores were higher than those in France, Germany, Italy, and Spain (Dunn's test; p<.001). Within Asia, Caregiver and Subject QoL scores at baseline were higher in China than in Japan and South Korea, with Japan being the lowest (Dunn's test; p<.001). No difference was found in the ADCS-MCI-ADL scores within Asia. When examining mean change on these rating scale scores from baseline to Week 76-79 after controlling the baseline cognitive status, no between-country differences were noted either within Europe or Asia. **Conclusion:** This study found there was significant between-country variation in self-reported and caregiver-reported participants' QoL at baseline within Europe and Asia when their baseline cognitive status was controlled. Additionally, there was between-country variation in participants' ADL within Europe but not Asia. However, the course of change over time on these rating scale scores was similar across countries within each region. One might attribute the variation in the QoL across countries to its multidimensional nature. For example, the QoL of older adults may be influenced by various non-cognitive cultural and/or societal factors such as political and economic stability, gender equality, health services, costs and income, safety, and commonly accepted values. Nevertheless, given the similar course of change over time, the regional heterogeneity in the QoL and ADL scores may not be an imminent concern in multinational AD clinical trials. **Key words:** Multinational clinical trial, Alzheimer's disease, Quality of Life, Activity of Daily Living, Between-country, cross-

cultural. **Disclosures:** The authors have no actual or potential conflict of interest in relation to this presentation. **References:** 1. Cummings, J, et al. Alzheimer's Research & Therapy; 2018, 10:116. https://doi.org/10.1186/s13195-018-0443-2

P099- THE EFFECT OF GLOBAL FUNCTIONING ON PARTICIPANT AND STUDY PARTNER RATINGS OF QUALITY OF LIFE IN PARTICIPANTS WITH PRODROMAL TO MILD ALZHEIMER'S DISEASE. J. Stenclik[1], A. Aedo[1], S. Machizawa[1], R. Kamat[1], E. Appleman[1], A. Iacob[1] *(1. Signant Health - Blue Bell (United States))*

Background: Multinational clinical trials for dementia commonly include measures of both global functional status and quality of life (QoL) to assess disease severity and impact. Study partner and participant ratings of participant QoL may be impacted differentially by functional deficits specific to a participant's memory ability, orientation status, problem solving, community engagement, household duties, and self-care capability. This study examined the relationship between cognitive and functional status as rated by the Clinical Dementia Rating Scale (CDR) and participant and study partner ratings of participant QoL as rated by the Quality of Life - Alzheimer's Disease (QoL-AD) while controlling for severity of cognitive impairment on the Alzheimer's Disease Assessment Scale- Cognitive subscale (ADAS-Cog). We hypothesize that the CDR will be significantly correlated with both participant and study partner ratings of participant QoL. **Methods:** This study utilized electronic scales of the QoL-AD (both participant and study partner ratings of participant QoL), CDR, and ADAS-Cog13 to assess QoL, cognitive and functional status, and cognitive impairment. Data were collected from two multinational cohorts comprised of prodromal to mild AD participants and their respective study partners (n=3251). Ratings at baseline visits were utilized. ADAS-Cog scores were then employed to control for the impact of participant cognitive impairment on study partner or participant ratings. **Results:** Participant reported QoL-AD scores were significantly correlated with each CDR domain: Memory $r(3250) = -.09$, $p < .001$, Orientation $r(3250) = -.15$, $p < .001$, Judgment $r(3250) = -.13$, $p < .001$, Community Affairs $r(3250) = -.21$, $p < .001$, Home and Hobbies $r(3249) = -.21$, $p < .001$, and Personal Care $r(3250) = -.15$, $p < .001$. In contrast, participant QoL-AD scores as rated by the study partner were not correlated with any of the six CDR domains. **Conclusions:** Consistent with our hypothesis, findings indicate that participants' ratings of QoL were correlated with cognitive and functional status as assessed by the CDR. Poorer participant performance across all functional domains of the CDR was associated with reduced QoL. More specifically, participants who experienced greater difficulty on tasks related to community engagement, home activities, and hobbies endorsed a more pronounced reduction in QoL. This suggests these domains may reflect a participants' diminished engagement and independence with regard to enjoyable activities, peer interaction, and community engagement. In contrast, study partner's ratings of participant QoL were not correlated with participant level of functioning on the CDR. These findings suggest that study partners may have insufficient insight into a participant's perception of life satisfaction and well-being and may underestimate their quality of life. Future research should examine the role of participant functional and cognitive status on participant and study partner ratings of QoL.

P100- BLOOD PRESSURE VARIABILITY VIA AMBULATORY MONITORING AND RISK FOR DEMENTIA IN THE SPRINT MIND TRIAL. I. Sible[1], D. Nation[2] *(1. University of Southern California - Los Angeles (United States), 2. University of California Irvine - Irvine (United States))*

Background: Blood pressure (BP) variability (BPV) is an emerging risk factor for cognitive impairment, Alzheimer's disease, and cerebrovascular disease, independent of traditionally studied/targeted mean BP levels. Recent work suggests higher BPV measured over months to years remains a risk for cognitive decline, mild cognitive impairment (MCI), and probable dementia, despite strict control of mean BP levels. However, BP fluctuations can also be studied over shorter intervals, such as 24 hours, via ambulatory monitoring. Less is known how BPV over 24 hours may relate to risk for dementia under specific antihypertensive strategies. We examined whether 24-hour BPV is related to dementia risk based on antihypertensive treatment type. **Methods:** In this post hoc analysis of the ambulatory BP monitoring ancillary study of the SPRINT MIND trial, 798 participants underwent 24-hour ambulatory BP monitoring mean 27.6 (0.7 SD) months after treatment randomization (standard vs intensive BP lowering). BPV over the 24-hour period was calculated as the average real variability. Participants also underwent cognitive testing at study baseline and every two years during the planned 4-year follow-up. Cognitive scores were used to determine adjudicated clinical outcomes of normal cognition, MCI, probable dementia, and MCI/probable dementia composite. Our primary outcome for the present study was incident probable dementia and secondary outcomes were MCI and MCI/probable dementia composite. We used Cox proportional hazards models to examine the potential effect of 24-hour BPV on the rate of cognitive outcomes under intensive vs standard BP lowering, with adjustment for age, sex, education, race/ethnicity, and 24-hour mean BP. **Results:** Higher BPV over 24 hours via ambulatory monitoring was associated with increased risk for probable dementia in the standard treatment group (adjusted hazard ratio [HR]: 2.57 [95% CI 1.16, 5.67], $p = 0.02$) but not in the intensive treatment group (adjusted HR: 0.53 [95% CI 0.23, 1.24], $p = 0.15$). Ambulatory 24-hour BPV was not significantly associated with risk for MCI ($p's = 0.37 - 0.48$) or MCI/probable dementia composite ($p's = 0.11 - 0.71$) in either treatment group. **Conclusion:** Higher 24-hour BPV remains a risk factor for dementia despite strictly controlled mean BP levels, in the standard treatment group. Findings are consistent with prior work examining BPV over months to years and suggest that BP fluctuations captured over 24 hours via ambulatory monitoring may also be an emerging vascular risk factor associated with cognitive impairment and dementia. **Key words:** blood pressure variability; dementia; ambulatory blood pressure monitoring. **Clinical Trial Registry:** ClinicalTrials.gov; NCT01206062. **Disclosures:** The authors declare no competing interests.

P101- LONGITUDINAL RESTING-STATE EEG ALONG THE ALZHEIMER'S DISEASE CONTINUUM: THE ROAD TO SUCCESSFUL CLINICAL TRIAL IMPLEMENTATION. E.P. Scheijbeler[1], W. De Haan[1], C.J. Stam[1], J.W.R. Twisk[1], A.A. Gouw[1] *(1. Amsterdam UMC location VUmc - Amsterdam (Netherlands))*

Background: To enable successful inclusion of electroencephalography (EEG) outcome measures in Alzheimer's disease (AD) clinical trials, we retrospectively mapped the progression of resting-state EEG measures over

time in amyloid-positive subjects along the AD continuum. **Methods:** Resting-state 21-channel EEG was recorded in 173 subjects positive for amyloid deposition (subjective cognitive decline (SCD), n = 16; mild cognitive impairment (MCI), n = 94; dementia due to AD, n = 63). Two or more EEG recordings were available for all subjects. We computed whole-brain and regional relative power (i.e., theta (4-8Hz), alpha1 (8-10Hz), alpha2 (10-13Hz), beta (13-30Hz)), peak frequency, signal variability (i.e., theta Permutation Entropy) and functional connectivity values (i.e., alpha and beta corrected Amplitude Envelope Correlation, theta Phase Lag Index, weighted Symbolic Mutual Information, inverted Joint Permutation Entropy). Whole-group linear mixed effects models were used to model the development of EEG measures over time. Group-wise analysis was performed to investigate potential differences in change trajectories between diagnostic groups. The longitudinal relation between EEG and global cognition was evaluated. Finally, we estimated the minimum sample size required to detect a stabilizing treatment effect using EEG measures, in hypothetical clinical trials of 1- or 2-year duration. **Results:** Whole-group analysis revealed significant regional and global oscillatory slowing over time (i.e., increased relative theta power, decreased alpha2 and beta power), with strongest effects for temporal and parieto-occipital regions. Signal variability showed stronger decline on global than regional scale. Disease severity at baseline influenced the EEG measures' rates of change, with fastest deterioration in MCI subjects. Only MCI subjects displayed a significant decrease of parieto-occipital functional connectivity strength over time. Lower parieto-occipital peak frequency, temporal relative alpha2 and beta power, as well as higher temporal relative theta power, were significantly associated with a decrease in Mini Mental State Examination score. We estimate that 1-year trials, focusing on amyloid-positive MCI subjects, require 148 subjects per arm (2 arms, 1:1 randomization) to detect a stabilizing treatment effect on temporal relative theta power. **Conclusion:** Resting-state EEG measures could facilitate early detection of treatment effects on neuronal function in AD patients. Their sensitivity depends on the region-of-interest and disease severity of the study population. Conventional spectral measures, particularly recorded from temporal regions, still present the most robust measures for longitudinal effect monitoring in AD clinical trials. **Key words:** Longitudinal; Electroencephalography; Surrogate marker; Sample size; Alzheimer's disease. **Disclosures:** W.H. and A.G. are founders of the EEGlab at Amsterdam UMC, location VUmc, The Netherlands. E.S. is part of the EEGlab research team. The EEGlab performs central EEG analysis for clinical trials funded by Vivoryon, EIP-Pharma, Fujifilm Toyoma, Immunobrain and Treeway. This funding does not involve personal support. C.S. and J.T. did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

P102- THE EEG AS FUNCTIONAL ENDPOINT IN AD TRIALS. W. De Haan[1,2], E. Scheijbeler[1,2], A. Gouw[1,2,3], C.J. Stam[2,4] *(1. Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc - Amsterdam (Netherlands), 2. Amsterdam Neuroscience, Neurodegeneration, - Amsterdam (Netherlands), 3. Clinical Neurophysiology and MEG Center, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, - Amsterdam (Netherlands), 4. Clinical Neurophysiology and MEG Center, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc - Amsterdam (Netherlands))*

Background: Electroencephalography (EEG) is the most efficient method for monitoring treatment effects on brain dynamics in clinical trials. Its relatively direct representation of neuronal and synaptic function, and its ability to capture changes in short timespans compared to other modalities makes it particularly attractive for drug development in AD. However, brain dynamics are highly variable and complex by nature, and making the right methodological choices can be a challenge. What can we learn from previous trials? **Methods:** In this study, we conducted a comprehensive review of the literature on currently active and completed clinical trials in Alzheimer's disease (AD) that employed EEG-related outcome measures. We analyzed all current registrations in the clinicaltrials.gov database (n=103) and consulted other relevant aggregated evidence sources. Our review focused on study design, methodology, results, feasibility and new developments. **Results:** Over the past years, there has been a notable increase in the utilization of EEG-based outcome measures in clinical trials for AD. Notably, a significant proportion of recent trials utilizing EEG involve non-invasive brain stimulation as a treatment modality. The most widely adopted outcome measures are based on spectral and functional connectivity analysis of resting-state, eyes-closed EEG [2]. Successful implementation of EEG in multicenter trials hinges on effective harmonization of multicenter data and systematic centralized quality checks throughout the study [3]. New developments include longer and remote (home-based) EEG registrations and machine-learning-based analysis techniques. **Conclusion:** EEG-based outcome measures are increasingly being employed in clinical trials for AD, encompassing both pharmacological and non-pharmacological interventions. Based on the wide range of outcome measures, their treatment monitoring characteristics, and the practical feasibility of EEG in this population, it appears to be an increasingly appreciated tool. With the recent emergence of clinically relevant treatments for AD, EEG as a functional biomarker may hold even greater value, as identifying the changes in brain activity associated with successful treatment can deepen our understanding of AD pathophysiology. **Key words:** EEG, Alzheimer, neurophysiology, clinical trial. **Disclosures:** None. **References:** 1. www.clinicaltrials.gov; 2. Babiloni ea., (2021). Measures of resting state EEG rhythms for clinical trials in Alzheimer's disease: Recommendations of an expert panel. Alzheimer's & Dementia, 17(9), 1528-1553. https://doi-org.vu-nl.idm.oclc.org/10.1002/alz.12311; 3. de Haan, ea., Chapter 36 in Alzheimer's Disease Drug Development: Research and Development Ecosystem. Cummings, J ea., Cambridge University Press, 2022.

P103- RATES OF PROGRESSION IN PATIENTS WITH ALZHEIMER'S DISEASE DEPENDING ON APOLIPOPROTEIN E GENOTYPE AND CONCOMITANT MEDICATIONS. C. Wattmo[1] *(1. Cognitive Disorders Research Unit, Department of Clinical Sciences, Malmö, Lund University - Malmö (Sweden))*

Background: The apolipoprotein E (APOE) e4 allele is associated with higher cholesterol levels, and an increased risk of developing Alzheimer's disease (AD) and amyloid-related imaging abnormalities after initiation of amyloid-modifying therapies. A worse cognitive response to cholinesterase inhibitor (ChEI) treatment and longitudinal outcome in APOE e4-carriers has been observed. Based on these clinical findings, cholesterol and the APOE e4 allele may affect beta-amyloid burden, metabolism, and inflammation in the brain. Younger age at onset and at diagnosis of AD have also been reported in APOE e4-carriers. Younger persons usually have less comorbidity and fewer concomitant medications that may affect the outcome of AD. **Objectives:** This longitudinal study examined potential differences in cognitive and functional progression rates in AD between patients with different APOE genotypes and concomitant medications. **Methods:** The Swedish Alzheimer Treatment Study (SATS) is a prospective observational clinical practice-based multicenter study for evaluation of long-term effectiveness of ChEI therapy. Here, 999 outpatients (320 APOE non-e4-carriers and 679 e4-carriers) clinically diagnosed with mild-to-moderate AD (Mini-Mental State Examination [MMSE] score, 10–26) at the start of ChEI treatment (baseline) were enrolled. Participants were assessed for cognitive (MMSE) and functional performance (Instrumental Activities of Daily Living scale [IADL] and Physical Self-Maintenance Scale [PSMS]) at baseline and every 6 months for 3 years. Univariate general linear models were used to investigate whether usage of specific concomitant medications (antihypertensive/cardiac therapy, antidiabetic drugs, asthma medication, thyroid therapy, lipid-lowering agents, estrogens, nonsteroidal anti-inflammatory drugs/acetylsalicylic acid, antidepressants, antipsychotics, and anxiolytics/sedatives/hypnotics) affected the rates of disease progression in patients with or without the APOE e4 allele. The outcomes were adjusted for sex, age at baseline, years of education, and cognitive and functional abilities at baseline. **Results:** Annual cognitive decline was faster in APOE non-e4-carriers receiving lipid-lowering agents vs. nonusers (p=0.036). In contrast, cognitive progression rate was slower in e4-carriers receiving lipid-lowering agents vs. nonusers (p=0.006). Cognitive decline was faster in APOE e4-carriers receiving anxiolytics/sedatives/hypnotics vs. nonusers (p=0.034); this difference was not found in non-e4-carriers. A faster annual progression rate in both IADL and basic ADL was demonstrated in APOE non-e4-carriers receiving antidepressants vs. nonusers (p<=0.012); these differences were not observed in e4-carriers. Moreover, APOE non-e4-carriers receiving antipsychotics had faster IADL deterioration vs. nonusers (p=0.003); this difference was not detected in e4-carriers. **Conclusion:** Various concomitant medications and comorbidities might affect the cognitive and functional outcomes of AD differently depending on APOE genotype. APOE e4-carriers, but not non-e4-carriers, who received lipid-lowering agents showed a slower cognitive decline than nonusers. Because the APOE e4 allele is known to be associated with higher cholesterol levels and has been implicated in AD-related processes, such as beta-amyloid burden and inflammation, e4-carriers may benefit more from use of statins. A risk factor for faster cognitive decline among APOE e4-carriers only was treatment with anxiolytics/sedatives/hypnotics, suggesting that these individuals might be more prone to the related adverse effects. In non-e4-carriers, neuropsychiatric symptoms were risk factors for faster functional deterioration, particularly in IADL, which is an important measure of independent living. **Disclosures:** The author reports no conflict of interest.

P104- EFFECTS OF MELISSA OFFICINALIS EXTRACT CONTAINING ROSMARINIC ACID FOR ALZHEIMER'S DISEASE IN HUMAN. M.S. Shinohara[1], K.O. Ono[1] *(1. Kanazawa University - Kanazawa (Japan))*

Background: In our previous study, we found that rosmarinic acid (RA) inhibits the formation of amyloid-β protein (Aβ) fibrils and destabilizes preformed Aβ fibrils in vitro [1]. It also inhibits the Aβ oligomerization, thereby reducing Aβ oligomer-induced synaptic toxicities [2]. Moreover, it has been reported that RA inhibits both oligomerization and Aβ deposition in Alzheimer's disease (AD) transgenic mice (Tg2576) [3]. Next, we made Melissa officinalis (M. officinalis) extract capsule which containing 500 mg of RA. To explore the safety and beneficial effects of M. officinalis extract containing RA on cognition, we conducted three randomized double-blind placebo-controlled trials in human. The first one was performed in healthy individuals to assess the tolerability and safety of M. officinalis extract capsule, the second one aimed to show the safety, tolerability, and efficacy in patients with mild AD dementia, and the third one investigated the effects on cognition in older adults without dementia. **Methods:** In the first study, we investigated pharmacokinetics of M. officinalis extract containing RA in healthy individuals (n = 11). The second study was conducted about the safety and tolerability of M. officinalis extract containing RA in patients with mild dementia due to AD (n = 20). The third study aimed to assess the effects of M. officinalis extract containing RA supplementation (500 mg of RA per day) period of 96 weeks on cognition in older adults without dementia (n = 323). The primary outcome of the third study was change in cognitive performance from baseline to 48- or 96-week follow-up examinations. **Results:** M. officinalis extract containing RA was tolerable and safe in healthy individuals as well as in patients with mild AD dementia. Additionally, M. officinalis extract containing RA helped prevent worsening of AD-related neuropsychiatric symptoms. Regarding non-demented older adults, there were no significant differences in cognitive measures between the placebo and M. officinalis groups. However, based on the analysis of Clinical Dementia Rating Sum of Boxes scores in participants without hypertension, the score was found to be increased by 0.006 and decreased by 0.085 in the M. officinalis containing RA and placebo groups, respectively; this difference was statistically significant (P = 0.036). **Conclusions:** These results indicate that M. officinalis extract containing RA is tolerable and safe in human and shows preventive effects for AD-related neuropsychiatric symptoms. In addition, M. officinalis extract containing RA may help prevent cognitive decline in older adults without hypertension. **Key words:** Alzheimer's disease, rosmarinic acid, Melissa officinalis extract. **Clinical Trial Registry:** UMIN000007734, UMIN000004997, UMIN000021596, and jRCTs041180064. **References**: 1. Ono K, et al. Curcumin Has Potent Anti-Amyloidogenic Effects for Alzheimer's β-Amyloid Fibrils In Vitro. J Neurosci Res, 2004, 75, 742-750. 2. Ono K, et al. Phenolic Compounds Prevent Amyloid β-Protein Oligomerization and Synaptic Dysfunction by Site-specific Binding. J Biol Chem, 2012, 287, 14631-14643.

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P105- TRAILBLAZER-ALZ 2: HETEROGENEITY IN PERFORMANCE OF CLINICAL OUTCOME ASSESSMENTS ACROSS GEO-CULTURAL AREAS.

G. Tronchin[1], W.W. Ye[1], X. Mi[2], A.M. Wessels[1] *(1. Eli Lilly and Company - Indianapolis (United States), 2. TechData Services Company - King Of Prussia (United States))*

Background: TRAILBLAZER-ALZ 2 is a phase 3 study evaluating safety and efficacy of donanemab in individuals with early symptomatic Alzheimer's disease (AD), with evidence of tau and amyloid pathology. Clinical trials occur globally, and although the commonly-used neuropsychological batteries for dementia are translated in multiple languages, test performance can potentially be affected by cultural aspects including: cultural values, familiarity, language usage, and patterns of abilities [1]. Cross-cultural differences also affect how caregivers understand and approach dementia, including symptom interpretation, help-seeking behaviors, and expectations [2], which feed into scoring of informant-reported scales. This study's objective was to assess performance across five geo-cultural areas in Clinical Dementia Rating Global Score (CDR-GS), CDR-sum of boxes (CDR-SB), integrated AD Rating Scale (iADRS), Mini-Mental State Examination (MMSE), and specific CDR domains, at randomization in eight countries. **Methods:** Baseline scores in CDR-GS, CDR-SB, iADRS, and MMSE in TRAILBLAZER-ALZ 2 were evaluated. The iADRS score was derived from the administered scales of AD Assessment Scale-Cognitive subscale (ADAS-Cog13) and AD Cooperative Study-Instrumental Activities of Daily Living (ADCS-iADL). Raters were qualified based on educational, clinical, and scale administration experience, and received training on scale administration and scoring. Scales were administered using an electronic Clinical Outcome Assessment tablet. Study data spanned 5 geo-cultural areas: Oceania (n=17), North America (n=1389), Western Europe (n=61), Eastern Europe (n=181), and East Asia (n=88). Analysis of Covariance (ANCOVA) adjusting for age, sex, education, acetylcholinesterase inhibitors and/or Memantine use, and time since AD onset, was performed to assess the differences in all scales across five geo-cultural areas. Adjusted p-value from Tukey adjustment method considered multiple comparisons between-group differences. P-value <0.05 indicated statistical significance. **Results:** For CDR-SB and CDR-GS baseline scores, Eastern Europe showed significantly worse performance than North America, East Asia (all p<0.001), and Western Europe (CDR-SB p=0.003; CDR-GS p<0.001). Within individual domains on the CDR, Eastern Europe performed significantly worse than North America and East Asia on memory (p=0.002; p=0.038), judgement and problem-solving (both p<0.001), orientation (p=0.005; p=0.013), home and hobbies (both p<0.001), and personal care (only North America p=0.040). Eastern Europe's performance for judgement and problem-solving (p=0.018), home and hobbies (p<0.001), and personal care (p=0.045) domains was also significantly worse than Western Europe. No significant differences between geo-cultural areas were observed for community affairs domain. Eastern Europe performed significantly worse than North America (p<0.001), Western Europe (p<0.001; p=0.004), and East Asia (p=0.008; p<0.001) for iADRS and MMSE scales, respectively. **Conclusions:** Significantly worse performance identified in CDR, MMSE, and iADRS in Eastern Europe, reflects greater baseline cognitive and functional impairment compared to other countries. Worse baseline performance in ADAS-Cog, ADCS-iADL, and CDR-SB for Eastern Europe was previously shown [3]. These results also suggest that performance differences across geo-cultural areas are not driven by whether the scale is informant-reported or performance-based. Additional analyses to characterize this population are warranted to confirm that patients at later disease stage are enrolled in Eastern Europe compared to other countries, and whether factors such as later disease identification and diagnosis are contributing to this pattern. **Key words:** Geo-cultural areas; cognitive assessments; functional assessments; disease stage. **Clinical Trial Registry:** NCT04437511. **Disclosures:** Giulia Tronchin, Wendy Wenyu Ye, and Alette M. Wessels are full-time employees and minor shareholders of Eli Lilly and Company. Xiaojuan Mi is a full-time employee of TechData Services Company. **References:** 1. The Impact of Culture on Neuropsychological Test Performance In International Handbook of Cross-Cultural Neuropsychology, BP Uzzell MP, A Ardila, ed. (2007) Taylor and Francis, New York. 2. Gray HL, Jimenez DE, Cucciare MA, Tong HQ, Gallagher-Thompson D (2009) Ethnic differences in beliefs regarding Alzheimer disease among dementia family caregivers. Am J Geriatr Psychiatry 17, 925-933. 3. Henley DB, Dowsett SA, Chen YF, Liu-Seifert H, Grill JD, Doody RS, Aisen P, Raman R, Miller DS, Hake AM, Cummings J (2015) Alzheimer's disease progression by geographical region in a clinical trial setting. Alzheimers Res Ther 7, 43.

P106- ASSESSING 'TRUE' NON-PROGRESSION RATE IN EARLY ALZHEIMER'S DISEASE ACCOUNTING FOR WITHIN-SUBJECT VARIATION.

M. Pang[1], W. Huijbers[1], A. Gabelle[1], A. Gafson[1], R. Hughes[1], S. Belachew[1], S. Changyu[1] *(1. Biogen - Cambridge (United States))*

Background: Patients with early Alzheimer's disease (AD) have been a primary target population for the testing of medical interventions intended to slow the clinical progression of the disease. Multiple anti-amyloid therapeutic agents, including aducanumab, lecanemab and donanemab, have demonstrated efficacy in reducing the worsening of cognition and function in randomized controlled trials (RCTs) of patients with early AD. Data from these RCTs also suggest that some patients in the placebo arm may not show any clinical progression. The percentage of these "non-progressors", as defined by the target clinical outcome assessment, has strong and critical implication on the design of an RCT, the interpretation of the result from an RCT and the development of more sensitive measures to capture disease progression. Additionally, direct calculation based on the observed worsening from baseline in general leads to a biased estimate of the percentage of non-progressors due to the within-subject variation of the clinical measures. Recently developed statistical methodology offers an opportunity to address this limitation. **Methods:** We estimated the percentage of non-progressors as measured by the Clinical Dementia Rating Sum of Boxes (CDR-SB) using pooled data from the placebo arms of the EMERGE (NCT 02484547) and ENGAGE (NCT02477800) trials. For each patient in the pooled placebo arms, we estimated a linear model that approximated the true longitudinal change of CDR-SB. The estimated change from baseline to week 78 (in the unit of its standard error) was used as an input to an Empirical Bayes deconvolution algorithm, which further generated the estimate of the distribution of the true CDR-SB change at week 78 in the pooled placebo arms of EMERGE and ENGAGE. The probability of zero CDR-SB change under this distribution represents the proportion of non-

progressors (with respect to CDR-SB). **Results:** Among patients in the placebo arms of EMERGE and ENGAGE trials who had a CDR-SB measure at week 78, 23.1% had no worsening of CDR-SB (CDR-SB at week 78 ≤ CDR-SB at baseline). Using the Empirical Bayes deconvolution method, we estimated that 27.2% (95% CI: 21.3%-33.2%) of the pooled population of EMERGE and ENGAGE, did not progress in terms of CDR-SB during an 18-month follow-up. **Conclusion:** Over a quarter of the patient population targeted by the EMERGE and ENGAGE trials did not progress with respect to the primary endpoint, CDR-SB, even without treatment. This represents a significant proportion of the early AD population with multiple implications. First, as current disease modifying therapies only slow clinical progression, instead of reversing its trajectory, the non-progressors cannot by definition 'benefit' from a drug. As such the effect size among progressors is actually higher than the reported effect size from an RCT but is diluted by the non-progressors. Second, sample size considerations for future RCTs need to consider whether non-progressors can be accurately identified at screening in order to avoid/mitigate diluting the effect size. Third, more research is needed to better understand the nature of clinical manifestations of early AD progression for the non-progressors and develop novel measures to capture it.

P107- VIDEO-BASED ASSESSMENT OF COGNITIVE FRAILTY IN OLDER ADULTS WITH COGNITIVE IMPAIRMENT.

R.K. Mishra[1], M. Lee[2], J. Beom[2], M.D. Rouzi[2], A. Vaziri[1], B. Najafi[1] *(1. Ph.D. - Boston (United States), 2. Baylor College of Medicine, Houston (United States))*

Background: Cognitive impairment (CI) and physical frailty (PF) can be interdependent, with each condition influencing the severity and progression of the other. Consequently, the presence of both CI and PF can be a significant indicator for the rapid cognitive decline in individuals with Alzheimer's disease (AD). Several tools have been created to measure PF objectively. However, subjective surveys rely on patient memory, and objective tests like grip strength and walking assessments can present difficulties in regular assessment, especially for individuals with AD. To address this problem, we developed a video-based frailty assessment tool to objectively measure PF that can be remotely administered. The upper extremity Frailty Meter (FM), a 20-second repetitive elbow flexion-extension test, measures frailty index (FI) and frailty phenotypes (slowness, weakness, rigidity, and exhaustion) [1]. **Methods:** The upper extremity Tele-FM was administered among participants aged 20-85 conducted [2]. The participants' elbow motion was recorded using a webcam as they flexed and extended their dominant arm for 20 seconds under two different conditions: single task and dual task. In the dual-task condition, participants simultaneously performed elbow rotation while counting backward. Cognitive impairment was assessed using the Montreal Cognitive Assessment (MOCA) [3] and PF was determined using the FI derived from Tele-FM assessment [4]. Participants were classified regarding cognitive impairment (Intact/CI+; Impaired/CI-) and physical frailty (Intact/PF+; Frail/PF-). The FI and associated traits like flexion time (slowness), power (weakness), range of motion, ROM (rigidity), and power reduction (exhaustion) [1, 2, 4, 5] were analysed, allowing for comparison among the four subgroups. **Results:** The study involved 82 participants (average age=59.20 ± 18.09 years; body mass index=28.41 ± 6.07 kg/m2; 76.83% female) who completed a Tele-FM assessment in single and dual-task conditions. They were categorized into four groups: Robust (CI+/PF+, n=28), High Cognition (CI+/PF-, n=17), High Physical (CI-/PF+, n=21), and Worst (CI-/PF-, n=16). Results showed significant interaction effect between CI and PF on outcomes involving slowness, weakness, and FI. Notably, exhaustion levels amplified from the Robust to the Worst group, illustrating the combined effect of cognitive impairment and physical frailty on the exhaustion phenotype. **Conclusion:** This study demonstrated the feasibility of using the 20-second Tele-FM technique to evaluate physical frailty and cognitive decline remotely for remote patient monitoring, as well as for use in clinical trials. These results demonstrate the complex relationship between CI and PF. The combined impact of CI and PF intensifies frailty symptoms, as assessed by the FI. Incorporating Tele-FM into routine telehealth assessments could enable timely interventions and potentially slow dementia progression. It might also help identify underlying factors affecting cognitive reserve in older adults with AD. **Key words:** frailty, cognition, telehealth, remote patient monitoring, digital health, digital biomarkers. **Clinical Trial Registry:** NCT05754021 https://clinicaltrials.gov/ct2/show/NCT05754021. **Disclosures:** Ram Kinker Mishra has received personal compensation for serving as an employee of BioSensics. Bijan Najafi has received personal compensation in the range of $100,000-$499,999 for serving as a Consultant for BioSensics. Bijan Najafi has received personal compensation in the range of $5,000-$9,999 for serving as a Consultant for Mölnlycke Health Care. Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. **Funding:** Research reported in this publication was supported by the National Institute On Aging of the National Institutes of Health under Award Number R44AG061951. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. **References:** 1. Toosizadeh N, et al. PloS one 2017;12(2), e0172766. DOI: https://doi.org/10.1371/journal.pone.0172766; 2. Zahiri M, et al. IEEE Access 2020; 8, 219391-219399. DOI: 10.1109/ACCESS.2020.3042451; 3. Nasreddine Z, et al. Journal of the American Geriatrics Society 2005; 53(4), 695-699. DOI: https://doi.org/10.1111/j.1532-5415.2005.53221.x; 4. Najafi B, et al. JAMA Network Open 2020; 3(11), e2020161-e2020161. DOI:10.1001/jamanetworkopen.2020.20161; 5. Lee H, et al. Gerontology 2018; 64(4), 389-400. DOI: https://doi.org/10.1159/000484241

P108- THERAPEUTIC DRUG MONITORING FOR DOSE OPTIMIZATION IN ALZHEIMER'S DISEASE AND IN DEMENTIA WITH LEWY BODIES.

P. Høgh[1], M. Fischer[1] *(1. Department of Neurology, Zealand University Hospital - Roskilde (Denmark))*

Introduction: Current anti-dementia drugs for symptomatic treatment of Alzheimer's Dementia and Dementia with Lewy Bodies belong to either the class of acetylcholinesterase inhibitors or Methyl-D-Aspartate-receptor antagonists. Previous evidence suggests that serum concentrations of the most widely prescribed acetylcholinesterase inhibitor Donepezil vary widely within clinical populations and that a higher dose than normally prescribed may have a positive effect on cognition compared to the standard dose. Therapeutic drug monitoring (TDM) is a tool for dose optimization whereby treatment is adjusted based on previous quantification of serum or plasma concentrations of the prescribed drug from blood collected from the patient. **Methods:** A single-blinded 1:1 randomized controlled study

in an outpatient memory clinic. Eligible participants newly diagnosed with either Alzheimer's dementia, dementia with Lewy bodies or Parkinson's disease dementia treated with either Donepezil or Memantine. The control group received standard care treatment. The intervention group had treatment optimized according to TDM. Change of clinical outcomes on the Mini-Mental State Examination, Addenbrooke's Cognitive Examination, Neuropsychiatric Inventory Questionnaire and Disability Assessment in Dementia from baseline to 12 months follow-up were compared between the intervention and control group. In addition, data on the incidence and severity of adverse reactions were collected, as well as the proportion of participants having a serum concentration within the therapeutic reference range. **Results:** 132 participants with either Alzheimer's Dementia or Dementia with Lewy Bodies were recruited of whom 107 completed the study. Statistical analysis did not reveal any differences between groups for clinical outcomes. No significant difference in frequency of adverse reactions was found. Adverse reactions were not found to be caused by abnormally high serum concentrations. **Conclusion:** Treatment optimization based on TDM did not significantly improve clinical outcomes nor did TDM reduce the frequency of adverse reactions. However, the study population was broad and too small to allow for subgroup analysis. It is plausible that TDM based dose optimization for a select group of patients is beneficial. **Clinical Trial Registry:** NCT04117178. **Disclosures:** the authors declared no competing interests

P109- TIMING THE CHANGE IN THE PRE-CLINICAL ALZHEIMER'S COGNITIVE COMPOSITE SCORE WITH AMYLOID-B IN PRE-CLINICAL ALZHEIMER'S DISEASE. T. Cox[1], R. Shishegar[1], C. Fowler[2], S. Rainey-Smith[3,4,5,6], H. Sohrabi[3,4], S. Markovic[3,4], V. Dore[1,7], P. Bourgeat[8], J. Fripp[8], R. Martins[6,9], V. Villemagne[10], C. Masters[2], C. Rowe[2,7], J. Doecke[8] *(1. Australian E-Health Research Centre, CSIRO - Parkville (Australia), 2. The University of Melbourne, The Florey Institute - Melbourne (Australia), 3. Centre for Healthy Ageing, Murdoch University - Murdoch (Australia), 4. Australian Alzheimer's Research Foundation - Perth (Australia), 5. University of Western Australia - Perth (Australia), 6. Edith Cowan University, School of Medical and Health Sciences, Centre of Excellence for Alzheimer's Disease Research & Care - Perth (Australia), 7. Department of Molecular Imaging & Therapy Austin Health - Melbourne (Australia), 8. Australian E-Health Research Centre, CSIRO - Brisbane (Australia), 9. Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University - Sydney (Australia), 10. Department of Psychiatry, University of Pittsburgh School of Medicine - Pittsburgh (United States))*

Introduction: With two drugs now shown to reduce Amyloid-β (Aβ) and slow cognitive decline in symptomatic AD, it is important to understand cognitive decline in preclinical stages to inform study design testing disease modifying therapies for primary and secondary preventions. A neuropsychological endpoint such as the Pre-Clinical Alzheimer's Cognitive Composite (PACC) score has been designed to characterise cognitive decline in the early stages of AD. Understanding of how this outcome varies over the entire disease course could improve our understanding of AD development and inform methods to select participants. This research aims to increase the precision of recruitment and design of trials in preclinical AD through defining the timing of abnormality for PACC and Aβ, and demonstrate that both cognition and Aβ level need to be considered for recruitment. **Methods:** Data from 933 participants (Cognitively Unimpaired [CU] N: 426, Mild Cognitive Impairment [MCI] N: 265, AD N: 242) from the Australian Imaging Biomarkers and Lifestyle (AIBL) study of ageing with PET-Aβ imaging and neuropsychological assessment was used. Participants classified as Aβ accumulators with a Centiloid (CL) value of >20 or a positive slope for CL ^{3}3 visits and at least one measurement over 0 CL were selected for analyses. CL and PACC were transformed into Z-scores (PACC inverted) to fit the one axis and analysed simultaneously using a multivariate fit to a trajectory. To align the timing between PACC scores and CL values, years taken from Aβ positivity to PACC scores between -0.5 and -1.5 were computed. Rates of change in PACC were also computed (standard deviations calculated via 500 bootstraps), with an abnormal score derived at the 95% of CU Aβ- group. Sample size to define a 30% reduction in PACC decline was computed. **Results:** Using Aβ positivity at 20CL as disease time zero, the time taken for the PACC score to reach abnormal levels of -0.5, -0.75, -1, -1.25 and -1.5 was 5.4 (SD:3.3), 10.2 (SD:2.9), 12.6 (SD:2.9), 14.8 (SD:2.9) and 16.5 (SD:2.9) years respectively. At CL levels 30, 40, 50, and 60, the aligned PACC scores were -0.41 (SD:0.10), -0.47 (SD:0.11), -0.53 (SD:0.12) and -0.60 (SD:0.13). 95% of CU Aβ- participants had rates of change in PACC of less than -0.187/year while at 20, 40 & 60 CL the mean change were -0.023(SD:0.05), -0.032 (SD:0.008), and -0.044 (SD:0.012) per year respectively. At CL values between 50-60, 1,165 participants per treatment arm are required to detect a 30% reduction in PACC decline over three years ($p<0.05$; power=80%). Given an enrolment into a pre-clinical study requires Ab loadat 40 CL, the models indicate criteria should specify PACC scores below -0.47, such that treatment related reductions in cognitive decline can be met. **Conclusions:** Using multivariate trajectory analyses, we defined a clinically meaningful range of abnormal PACC scores aligned with Aβ levels that could inform trial design in pre-clinical AD. The rates of change in PACC at specific CL levels along with their related PACC values demonstrate the necessity to use a combination of the expected rate of change in PACC and Aβ for recruitment.

P110- IMPACT OF STUDY PARTNER TYPE ON PRIMARY ENDPOINT VARIABILITY IN TWO PHASE 3 REGISTRATION TRIALS IN MILD-TO-MODERATE ALZHEIMER'S DISEASE. M. Ryan[1,2,3], D. Gillen[1,2], J. Grill[1,4,5] *(1. Institute for Memory Impairments and Neurological Disorders, UC Irvine - Irvine (United States), 2. Department of Statistics, UC Irvine - Irvine (United States), 3. Department of Biostatistics, Yale School of Public Health - New Haven (United States), 4. Department of Psychiatry and Human Behavior, UC Irvine - Irvine (United States), 5. Department of Neurobiology and Behavior, UC Irvine - Irvine (United States))*

Background: Background: In Alzheimer's disease (AD) clinical trials, participants are required to enroll with a study partner (SP) who ensures compliance and completes outcomes assessing participant cognitive and functional ability. The SP role is commonly filled by spouses and other family members. Spouse and non-spouse SPs differ in numerous ways, including average time in contact with the participant. These differences may impact variability of SP-reported assessments, which may in turn impact trial integrity. We quantified the impact of SP type on the variance of SP-reported Disability Assessment for Dementia (DAD) scores. **Methods:** We analyzed data from the Bapineuzumab 301 (APOE e4 non-carriers) and 302 (APOE e4 carriers) phase 3 trials in mild-to-moderate AD, provided by the trial sponsor, Janssen Research & Development, LLC for use in these analyses. We compared the sample variances for

end-of-study DAD scores for spousal and non-spousal SPs in each trial. We computed 95% confidence intervals (CIs) for the corresponding parameters via bootstrapping. We used similar methods to compare the variances in the difference between baseline and end-of-study DAD scores for SP types. **Results:** Among the 1,231 and 1,097 participants analyzed from trials 301 and 302, 818 (66.5%) and 837 (76.3%) had spousal SPs at baseline, respectively (Table 1). On the other hand, 674 (674/958=70.4%) and 699 (699/898=77.8%) of those who completed the end-of-study visit in each trial had spousal SPs, respectively. In trial 301, the variance of end-of-study DAD scores for spousal SPs were observed to be 16% lower compared to non-spousal SPs (spousal/non-spousal = 629.45/747.04 = 0.84, 95% CI = [0.72, 1.01]). In trial 302 this relative decrease was observed to be 11%, though with less precision (spousal/non-spousal = 611.35/688.76 = 0.89, 95% CI = [0.73, 1.10]). Neither trial had significant differences in spousal vs non-spousal variances of the change-from-baseline DAD scores (Trial 301: spousal/non-spousal = 377.43/424.43 = 0.90, 95% CI = [0.66, 1.23]; Trial 302: spousal/non-spousal = 353.44/323.88 = 1.09, 95%CI = [0.85, 1.43]). Differences in the linear trend of DAD variance were significantly different between SP types in trial 301 (Est.: -1.74, 95% CI: [-3.37, -0.08]), but were not significantly different in trial 302 (Est.: 0.99, 95% CI: [-3.64, 5.60]). **Conclusions:** SP type was associated with differential change in variation across study time in SP-reported endpoints in the non-carrier study. Overall, though, no significant difference in variance of change-from-baseline scores in either trial indicates SP type has limited impact on trial primary analyses. **Key words:** Alzheimer's disease, study partner, clinical trial, variation. **Clinical Trial Registry:** ClinicalTrials.gov numbers: NCT00575055 and NCT00574132; EudraCT number: 2009-012748-17. **Disclosures:** The authors declared no competing interests

P111- EFFECTS OF PHYTONCIDE INHALATION ON STROOP TASK PERFORMANCE IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT: AN FNIRS PILOT STUDY.

D.H. Kim[1], S. Park[1], J. Kim[1] *(1. Chuncheon Sacred Heart Hospital Hallym University College of Medicine - Chuncheon (Korea, Republic of))*

Background and purpose: Several studies have reported the therapeutic effects of phytoncides on various physical and mental disorders. However, little is known about the therapeutic effects of phytoncides on mild cognitive impairment (MCI), a prodromal stage of dementia. In this pilot study, we aimed to clarify the effect of inhaled phytoncides on the cognitive function of patients clinically diagnosed with MCI. **Methods:** In total, 21 patients with MCI were randomly assigned to either a saline(no-odor) group(N=10) or phytoncide group(N=11), subsequently inhaled saline or phytoncide for 30 min indoors, respectively. To evaluate changes in cognitive function, we implemented functional near-infrared spectroscopy along with the Stroop task and compared task performance and hemodynamic responses in the dorsolateral/ventrolateral part of the prefrontal cortex (DLPFC/VLPFC) before and after inhalation. **Results:** While the saline group showed no significant difference in task performance before and after inhalation (Wilcoxon W=18.50; p=0.385), the phytoncide group represented a significant improvement in Stroop task performance, answering 6.65 more correct responses after inhalation (Wilcoxon W=1.50; p=0009). A significant reduction of HbO2 level was found in the left VLPFC showing hemodynamic attenuation in the phytoncide group after inhalation (Wilcoxon W=56.00; p=0.042), while no significant before- vs. after-inhalation difference was found in other regions or in the saline group. Since compensatory task-related prefrontal hyperactivation represents one of the neural indicators of cognitive dysfunction in MCI, our findings shed light on the beneficial effects of phytoncide on cognitive function in patients with MCI. **Conclusions:** Phytoncide may have a therapeutic benefit to improve cognitive function in patients with MCI. **Clinical Trial Registration:** The study was registerd in the Clinical Trials Registry of Korea. The trial number is KCT0007317 (30/07/2021). **Key words:** phytoncide, Stroop task, mild cognitive impairment, dementia, functional near-infrared spectroscopy.

P112- THE USE OF COMPOSITE Z-SCORES IN PLACE OF NORMATIVE-BASED SCALING TO IMPROVE SIGNAL DETECTION IN CLINICAL TRIALS INVOLVING NEURODEGENERATIVE DISEASES.

E. Jacobs[1], C. Randolph[1,2], D. Schoemaker[1], D. Digregorio[1], S. Negash[1], R. Blattner[1] *(1. WCG Clinical - Princeton (United States), 2. Loyola University Medical Center - Chicago (United States))*

Background: Population-based norming for neuropsychological tests such as the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is necessary for diagnostic purposes and useful for clinical interpretation of performance in research settings as well. The scaling procedures used to transform raw scores into index scores have the effect of constraining score ranges at the upper and lower limits of performance. This may reduce the sensitivity of such tests to detect change at the outer limits of score ranges. This study explored the potential utility of a z-score analysis in capturing a greater range of performance in comparison to index scores in clinical trials of two different neurodegenerative disorders. **Method:** We examined data from pooled clinical trials of Alzheimer disease (AD) and pooled data from progressive supranuclear palsy (PSP) trials. The standard index score data were compared to a composite z-score approach to scoring that followed the domain and total scale index score composites, but using the AD and PSP baseline data, respectively, for z-score calculations Index score and z-score distributions and effect sizes of change over time were compared. **Result:** The AD and PSP samples were both close to two standard deviations below the normal age-adjusted mean at baseline, as measured by the RBANS total scale index score. In both the AD and PSP samples, the z-score methodology resulted in more normal distribution and larger effect sizes due to disease progression over time than the normative based index score approach. **Conclusions:** The z-score methodology resulted in more normal distributions and was significantly more sensitive to change due to disease progression than the index score approach. We recommend the use of the z-score methodology for tracking change in study populations where performance is expected to fall at or below these levels relative to the normal population. **Key words:** Alzheimer's disease, neurodegenerative disease, clinical trials, endpoints. **Disclosures:** Authors are employees of WCG. **References:** Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 20: 310-319

P113 THE EXPANDED BRIEF ASSESSMENT OF COGNITION (BAC) FOR THE ASSESSMENT OF COGNITIVE IMPAIRMENT IN MILD ALZHEIMER'S DISEASE. D. Schoemaker[1], A.S. Atkins[1], C. Abraham[1], H. Evans[1], M. Welch[1], B.L. Plassman[2], C. Madsen[2], N. Sickel[2], J. Sedway[1], K.A. Welsh-Bohmer[1], R.S.E. Keefe[1] *(1. WCG - Cary (United States), 2. Duke University - Durham (United States))*

Background: With a growing focus on the preclinical and mild stages of Alzheimer's Disease (AD), clinical trials are in urgent need of validated cognitive assessment tools with increased sensitivity to early cognitive decline. The Brief Assessment of Cognition (BAC) is a battery of cognitive tasks that can be administered on a tablet, allowing for the standardization of administration and automatization of scoring (Keefe et al., 2008, Atkins et al., 2017). The BAC has been used in multiple academic and industry-sponsored trials. An expanded version of the BAC (i.e, Expanded BAC) including additional subtests specifically targeting hippocampal-dependent cognitive functions has been developed to improve sensitivity to cognitive impairment observed at the earliest stages of AD. Here, we present results of a recent study assessing the sensitivity of the Expanded BAC to cognitive impairment in subjects with mild cognitive impairment (MCI) and mild AD. **Methods:** Participants included 78 adults with clinical diagnoses of MCI or mild-AD (NIA-AA criteria), 178 healthy adults (HA) aged less than 65 years, 133 older adults aged 65 years or more with no subjective cognitive decline (healthy older adults, HOA), and 32 older adults with subjective cognitive decline as identified based on a score ≥4 on the Mail-In Function Cognitive Screening Instrument (SCD). Participants from the HA, HOA, or SCD groups did not present objective cognitive impairment on standard cognitive testing. Performance on the Expanded BAC individual subtests and composite score (i.e., sum of Z-scores derived from all subtests) was compared across groups using ANCOVAs, with age, gender, and education as additional covariates. Pairwise comparisons between groups were assessed using Tukey LSD tests. In the MCI/mild-AD group correlations were computed between the Expanded BAC composite score and well-established clinical outcome measures, the MMSE and CDR Sum-of-Boxes (CDR-SB). **Results:** After adjusting for age, education, and sex, there was no difference in the Expanded BAC composite score between HA and HOA ($p>0.05$). The MCI/mild-AD group performed significantly worse on the Expanded BAC composite score compared to the HA ($p< 0.001$), HOA ($p< 0.001$), and SCD ($p< 0.001$) groups. Finally, individuals from the SCD group had reduced composite scores compared to HOA ($p=0.003$). The Categorized List Learning and Delayed Recognition were the two subtests yielding the greatest effect size ($\eta 2$) when contrasting performance of subjects with MCI/mild-AD or SCD against that of subjects with no evidence of cognitive decline. When looking at associations with well-established clinical outcome measures, the Expanded BAC composite score was significantly associated with the CDR-SB ($r=-0.51$, $p<0.001$) and the MMSE score ($r=0.31$, $p=0.01$). **Conclusions:** Performance on the Expanded BAC is sensitive to cognitive impairment in subjects with SCD and MCI/mild-AD. Additionally, performance on the Expanded BAC is significantly correlated with clinical and cognitive staging instruments commonly used in AD clinical trials. These findings suggest that the Expanded BAC could be a valuable tool to assess and track cognitive impairment associated with the early stages of AD. **Key words:** Cognition, Computerized Cognitive Assessment, Mild Cognitive Impairment, Mild Alzheimer's Disease. **Disclosures:** DS, CA, HE, MW, and JS are a full-time employee of WCG. ASA is a full-time employee of Eli Lilly. KAWB served as a consultant for Biogen and Roche-Genentech, and is currently a contractual employee at WCG. RSEK serves as a consultant to WCG, Karuna, Novartis, Kynexis, Gedeon-Richter, Pangea, Merck, Boehringer-Ingelheim, and receives royalties for the BAC, BACS and VRFCAT. The other authors have no disclosures to report. **References:** Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophrenia research, 68(2-3), 283-297. Atkins, A. S., Tseng, T., Vaughan, A., Twamley, E. W., Harvey, P., Patterson, T., ... & Keefe, R. S. (2017). Validation of the tablet-administered Brief Assessment of Cognition (BAC App). Schizophrenia Research, 181, 100-106.

P114- STANDARDIZED IMPLEMENTATION OF PERSONALIZED ENDPOINTS FOLLOWING FDA'S DRAFT GUIDANCE 4 ON PATIENT-FOCUSED DRUG DEVELOPMENT: GOAL ATTAINMENT SCALING IN A PHASE 2 STUDY OF XPRO IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE. G. Sevinc[1], C. Chapman[1], T. Lehner[2], C. Barnum[2], J. Jaeger[2,3,4], K. Rockwood[1,5,6] *(1. Ardea Outcomes - Nova Scotia (Canada), 2. INmune Bio, Inc - Florida (United States), 3. CognitionMetrics, LLC - Connecticut (United States), 4. Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine - New York (United States), 5. Division of Geriatric Medicine, Dalhousie University, - Nova Scotia (Canada), 6. Geriatric Medicine Research Unit, Nova Scotia Health Authority, - Nova Scotia (Canada))*

Background: The Food and Drug Agency's recent draft guidance, part of four patient-focused documents, describes methods to incorporate the patient experience into drug development and regulatory decision-making1. Personalized endpoints, such as Goal Attainment Scaling (GAS), have been endorsed with an emphasis on standardized implementation. Here we present how we implemented GAS in a Phase 2 study of pegipanermin (XPro1595), a six-month, blinded, randomized, placebo-controlled trial in 201 patients with early Alzheimer's disease and biomarkers of inflammation. **Methods:** First, an electronic Data Capture platform, GoalNav®, designed for GAS was employed to ensure consistency across sites/patients. Second, GAS interviewers were trained and certified to help patients and study partners to set personally meaningful goals that are realistic, and potentially targeted by the product being evaluated. Further, patients/study partners were oriented to GAS by a handout that includes a goal inventory. The handouts familiarize patients/study partners with goal-setting processes and introduce potential goals (symptoms and/or challenges) prior to the screening interview. The goal inventory was prepared by disease experts, with special consideration to product's proposed MoA. Goals are mapped to domains including cognition, behavior, daily function, executive function, and physical manifestations. The patients/study partners were encouraged to set one goal per domain and minimum three goals to capture multiple domains. They can further personalize items in the goal inventory or add new ones. The frequency with which specific goals occur, or cluster by domain, offers target areas to monitor, potentially helping to elucidate the drug's MoA. Third, standardized implementation and improved quality were targeted through systematized goal reviews by two independent GAS experts. Using enhanced SMART goal setting criteria (specific, measurable, achievable, realistic, timebound), they reviewed each interviewer's first

set of goals immediately after the screening visit. This allowed personalized feedback to each rater, within a seven-day window, before baseline. This personalized feedback with supplementary training was provided until the rater reached a predefined competency level. Fourth, ongoing interviewer support on GAS techniques and specialized data monitoring further safeguarded systematized collection of personalized input. Finally, the protocol also included assessment of all relevant symptoms and domains using standardized outcome measures such as EMACC – a composite battery of validated neuropsychological tests sensitive to change in early Alzheimer's. Critically, at each follow-up visit, together with attainment level for each goal, information on newly emergent symptoms was collected. This step fulfills the Agency's requirement to detect newly occurring and worsening symptoms, not just those assayed by standardized measures and/or biomarkers. **Results:** Personalized endpoints such as GAS, when implemented diligently, can capture clinically meaningful effects, especially when the model of disease treatment has yet to be specified. **Conclusion:** Human trials of innovative treatments offer a way to focus understanding of cogent mechanisms of action. In this, systematic inventories of where treatment effects might arise can be a valuable adjunct to current outcome measures. The standardized implementation outlined above, of an inherently patient-centered approach that quantifies, and records individual experiences can enhance drug development efforts in Alzheimer's disease, especially with novel products. Manufacturer name/location: XPro1595, INmune Bio, Inc., San Diego, CA, USA. **Clinical Trial Registry:** NCT05318976; https://clinicaltrials.gov. **References:** 1https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

P115- VERBAL LEARNING OVER FIVE DAYS: LEARNING CURVES, AGE-INDEPENDENCE, AND SLEEP SENSITIVITY. A. Kaula[1], N. Taptiklis[1], N. Sen[1], F. Cormack[1,2], N. Cashdollar[1], K. Zavitz[1] *(1. Cambridge Cognition - Cambridge (United Kingdom), 2. University of Cambridge - Cambridge (United Kingdom))*

Background: Associative memory and its relationship with age has long been an area of interest. Classic tasks such as Paired Associate Learning (PAL) and Verbal Paired Associates (VPA) show sensitivity to age and are often used in assessing memory in health and disease. Recently, Learning Over Repeated Exposures (LORE) has been shown to be sensitive to beta-amyloid pathology that did not affect performance in single-visit associative memory tasks. We have developed a LORE version of VPA that uses Text-To-Speech (TTS) and Automatic Speech Recognition (ASR) remotely, at scale. We previously reported on the feasibility of this task, and now investigate its properties further in a larger, demographically balanced sample. This allows us to examine the psychometric properties of the task among a wide age-range, as well as affording sufficient power to address relationships between this task and other, classic neuropsychological measures. **Methods:** A demographically balanced sample (N=170) was recruited via the Prolific platform for remote online testing. During the week preceding the five-day LORE burst, participants completed a baseline battery of CANTAB tasks (including PAL and VPA). On each day of the burst, participants answered the single-item Karolinska Sleepiness Scale to give a subjective measure of alertness, and then proceeded immediately to the VPA-LORE task. The LORE paradigm is as follows: on the first day, eight word-pairs are presented verbally, and participants are asked immediately to recall them. On subsequent days a recall phase is followed by re-presentation of the word pairs for further learning. On the final day, only recall is tested. Recall scores are obtained on each of the five days, with a certain amount of forgetting expected between the first days' immediate recall, and the second days' recall. Individual learning curve slopes were obtained (OLS), and learning was explored using a Linear Mixed Effects model. **Results:** Linear Mixed Effects modelling with linear and quadratic terms provided a good fit to learning curves in our sample, $X2 = 40.08$, $p < .001$, and including daily KSS alertness scores improved model fit further ($p = .020$). Significant correlations were found between baseline PAL Total Errors Adjusted (PALTEA) and VPA-LORE scores on days one, two, and three ($rp's = -.244, -.246 -.165$ respectively), but not between PALTEA and LORE learning slopes. Furthermore, while performance on PAL significantly correlated with age ($rp = .412$), no such association was observed for the VPA-LORE measures. **Conclusion:** Our findings provide support for the utility of the VPA-LORE paradigm in capturing associative learning in a low-burden manner. We find that whereas PAL shows sensitivity in our sample to age, acquisition of word-pair associates over a longer burst does not. We characterise learning curves and find additionally that self-reported sleepiness was a good predictor of daily LORE performance, suggesting a desirable sensitivity to sleep quality in this learning task. The lack of a correlation between learning slope and PAL performance and VPA LORE measures and age may suggest a somewhat separable learning mechanism.

P116- A META-ANALYSIS TO DEMONSTRATE THE INCIDENCE OF PLACEBO EFFECT IN ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT TRIALS: MITIGATING FOR IMPACTS ON TRIAL ENDPOINTS. M. Carbo[1], M. Moberg[1], R. Avrumson[1] *(1. Worldwide Clinical Trials - Doylestown (United States))*

Background: Placebo effect is a known confound across many Alzheimer's Disease (AD) and Mild Cognitive Impairment trials. There is the potential for response bias in trials with patient and study partner reported outcomes, most often identified as the primary or secondary endpoints in AD and MCI studies. A study participant's expectations of treatment benefits, increased standard of care, or anticipated side effects of the experimental drug, can influence test performance, trial commitment, study partner relationships and bias towards endpoint reporting (Hrobjartsson, Kaptchuck & Miller, 2011). The quality of data collection and overall trial outcome may be impacted, warranting efforts towards the implementation of mitigation strategies. **Methods:** A multinational meta-analysis of 14 AD and MCI placebo-controlled efficacy studies (18 effects) evaluating cognition, behavior, and function was completed. The study population reviewed (N= 6940) included participants with diagnosed MCI, Early-Stage to Severe AD, and AD patients with clinically significant agitation. All studies required the participation of a study partner in support of primary and secondary outcome measures: Clinical Dementia Rating Scale Sum of Boxes, ADCS-Clinical Global Impression of Change, ADCS-Activities of Daily Living and Disability Assessment for Dementia. The studies were of mixed results[CM1] and revealed a high incidence of adverse event reporting. Further exploration into the placebo and treatment assigned groups was conducted with consideration to the participant's experience of AEs and its potential influence on cognitive and functional endpoint

reporting. A literature review of such impacts covered placebo control strategies. **Results:** There were 3085 placebo and 3855 Donepezil participants reviewed across common adverse event categories: Gastrointestinal, Anorexia, Sleep Disturbance, and Behavioral. Moderate (d=0.68, 95% CI $0.81<\delta<0.58$) and homogeneous (Q=25.23[17], p=0.09) effects were found in AD and MCI groups for Donepezil and placebo AEs. The data indicates no significant difference in AEs between Donepezil and placebo with a further analysis of specific common adverse event categories to be presented. Methods to control the placebo response were not noted across studies. This suggests an absence of mitigation strategies for patients and study partners in support of reliable data collection across endpoints. **Conclusion:** The value in applying methods towards the control of placebo response in MCI and AD clinical trial design is well supported by this data. This analysis revealed a placebo effect across trials as evidenced through high incidence of AE reporting between groups. Trial participants assigned to placebo experienced common adverse effects with those assigned to treatment. Most studies reporting positive outcomes separated from placebo; however, a strong placebo response may have confounded results in the trials that did not produce symptomatic improvement or where clinical benefit was uncertain. Introducing placebo mitigation practices through participant and study partner education, site training, the practice of neutrality in the research environment and overall management of site and participant expectations, may prove to reduce the placebo response in future AD and MCI trials forward. **References:** Burns, A., Rossor, M., Hecker, J., et al. (1999). The Effects of Donepezil in Alzheimer's Disease – Results from a Multinational Trial. Dementia, Geriatric, and Cognitive Disorders, 10(3): 237-244. Hommea, A., Takeda, M., Imai, Y., et al. (2000). Clinical Efficacy and Safety of Donepezil on Cognitive and Global Function in Patients with Alzheimer's Disease: A 24-Week, Multicenter, Double-Blind, Placebo-Controlled Study in Japan. Dementia, Geriatric, and Cognitive Disorders, 11(6). 299-313. Hrobjartsson, A., Kaptchuk, T. & Miller, F. (2011). Placebo Effect Studies Are Susceptible to Response Bias and to Other Types of Biases. Journal of Clinical Epidemiology, 64(11): 1223-1229. Ito, K., Corrigan, B., Romero, K., et al. (2013). Understanding Placebo Responses in Alzheimer's Disease Clinical Trials from the Literature Meta-Data and CAMD Database. Journal of Alzheimer's Disease, 37: 173-183. Johannsen, P., Salmon, E., Hampel, H., et al. (2006). Assessing Therapeutic Efficacy in a Progressive Disease: A Study of Donepezil in Alzheimer's Disease. CNS Drugs, 20: 311-325.

P117 CAPTURING CLINICALLY MEANINGFUL CHANGE IN ALZHEIMER'S DISEASE: THE ELECTRONIC PERSON SPECIFIC OUTCOME MEASURE APPROACH.

S. Saunders[1,2], J. Gomes-Osman[1,3], A. Jannati[1,4], S. Tobyne[1], J. Pobst[1], C. Ritchie[5,6], S. Luz[2], G. Muniz-Terrera[2,7], Á. Pascual-Leone[1,8] *(1. Linus Health Inc - Boston (United States), 2. University of Edinburgh - Edinburgh (United Kingdom), 3. University of Miami Miller School of Medicine - Miami (United States), 4. Harvard Medical School - Boston (United States), 5. Scottish Brain Sciences - Edinburgh (United Kingdom), 6. University of Edinburgh - Edinburgh (United Kingdom) - Edinburgh (United Kingdom), 7. University of Ohio - Ohio (United States), 8. Hebrew SeniorLife - Boston (United States))*

Background: Recent advances in pharmacological interventions for Alzheimer's disease (AD) offer evidence of emerging treatments able to change AD pathology and slow down cognitive decline. It is critical to relate any intervention's biological effectiveness to clinically meaningful changes that are personally important to the individual through patient reported outcome (PRO) measures. However, PROs have traditionally posed a challenge to quantify. One recently developed solution is the electronic Person Specific Outcome Measure (ePSOM) tool which captures the most important things that individuals want to continue doing even if their brain health declined through conditions such as AD. The ePSOM approach facilitates the shift from measuring generic outcomes to meaningful personalised outcomes both in AD research and clinical practice. **Methods:** We are currently conducting a US-based study to collect primarily free text data on what matters most to people about their brain health. Target enrolment is 6,000 participants, including individuals with and without cognitive impairment. We use natural language processing (NLP) techniques to create themes of brain health priorities across the sample, which are combined with the existing UK-based data set of 80,000 free text responses (n=5,808) [1]. Additionally, we mapped 184 brain health themes derived from the UK-based data to neurocognitive and motor functions required for each. We developed machine learning (ML) algorithms to cluster US-based study data with the existing themes to facilitate evidence-based recommendations for how to maintain neurocognitive/motor function. **Results:** At time of submission, 233 individuals have completed the ePSOM US survey (mean age 58.37 [SD=5.87]; n=73 [31%] women; n=160 [69%] men; n=40 [17%] individuals with and n=193 [83%] without self-reported diagnosis of mild cognitive impairment or AD-related dementias). An analysis of brain health priorities focusing on differences in key sociodemographic groups and individuals with and without self-reported diagnosis of neurodegenerative disease will be presented at the conference. The 184 pre-existing themes mapped onto nine neurocognitive domains with 44 sub-domains and three motor function domains with two sub-domains. Initial results indicate our ML algorithm is able to map new free text responses to existing themes in real-time and display personally meaningful recommendations linked with each theme/function. **Conclusion:** The ePSOM tool is an approach for incorporating personally meaningful brain health outcomes into AD trials and monitoring of function in priority areas for the individual. The tool uses a digital interface and is designed to have robust psychometric properties enabling the tool to be used in regulatory trials. Employing PRO measures alongside objective clinical measures in AD clinical trials offers a secondary endpoint to establish an intervention's clinical meaningfulness. Separately, use of the ePSOM tool in clinical practice would allow personalised recommendations for how to maintain function in the individual patient's priority areas for as long as possible. **Disclosures:** Stina Saunders, Joyce Gomes-Osman, Ali Jannati, Sean Tobyne, Jeff Pobst and Álvaro Pascual-Leone receive salary from Linus Health. The authors declared no competing interests. **References:** [1] Saunders, S., Muniz-Terrera, G., Sheehan, S., Ritchie, C.W., Luz, S. (2021). A UK-Wide Study Employing Natural Language Processing to Determine What Matters to People about Brain Health to Improve Drug Development: The Electronic Person-Specific Outcome Measure (ePSOM) Programme. Journal of Prevention of Alzheimer's Disease link

LP062- TRACKING SHORT-TERM COGNITIVE CHANGES AMONG COGNITIVELY UNIMPAIRED OLDER ADULTS WITH DIFFERENT AMYLOID (A) AND TAU (T) PROFILES USING THE BOSTON REMOTE ASSESSMENT FOR NEUROCOGNITIVE HEALTH (BRANCH). R. Jutten[1], D. Soberanes[2], E. Weizenbaum[1], C. Molinare[1], S. Hsieh[1], M. Farrell[1], D. Rentz[1,2], G. Marshall[1,2], K. Johnson[1], R. Sperling[1,2], R. Amariglio[1,2], K. Papp[1,2] *(1. Massachusetts General Hospital, Harvard Medical School - Boston (United States), 2. Brigham and Women's Hospital, Harvard Medical School - Boston (United States))*

Background: Remote, digital cognitive assessments provide the opportunity to assess cognition more frequently, resulting in test paradigms that can capture cognitive changes more rapidly than standard in-clinic single-timepoint cognitive assessments. The Boston Remote Assessment for Neurocognitive Health (BRANCH) was designed to improve the detection and tracking of subtle cognitive changes in preclinical Alzheimer's disease (AD), by leveraging a multi-day learning curve (MDLC) paradigm. We previously showed that BRANCH MDLCs obtained over 7 days can reveal cognitive deficits in Aβ+ cognitively unimpaired (CU) older adults. Here, we investigated whether repeating BRANCH MDLCs longitudinally could track cognitive change in CU individuals with different Aβ (A) and tau (T) biomarker profiles. **Methods:** CU older adults (n=102, age=73.4±7.6, 66% female, 16.6±2.4 years of education) from three well-characterized cohorts completed multi-day BRANCH at baseline and after 15±4 months follow-up. BRANCH includes the Face-Name Associative Memory Exam (FNAME) and a processing speed test with an associative memory component (Digit Sign Test). For each test, identical stimuli are used for all seven days, with new stimuli to be learned at each longitudinal follow-up assessment. Using an area under the curve method allowing for the combination of day 1 performance and learning over the subsequent six day, a summary MDLC score is computed for each individual test as well as for a FNAME-Digit Sign composite. All participants underwent [11C]Pittsburgh compound-B and [18F]flortaucipir PET within 0.7±0.5 years of BRANCH baseline. Participants were grouped as biomarker +/- based on amyloid PET (A; global amyloid burden, DVR, cutoff 1.14) and tau PET (T; inferior-temporal lobe tau, SUVr cutoff 1.30), resulting in n=58 participants (56.9%) classified as A-/T-, n=26 (25.5%) as A+/T- and n=15 as A+T+ (14.7%). The 3 participants (2.9%) classified as A-/T+ and were excluded from analyses. Linear mixed effect (LME) models correcting for age, sex and years of education were used to examine MDLCs on the composite score as well as individual measures across A/T groups, with A-T- group used as reference group. **Results:** The A+T+ group showed diminished MDLCs on the composite at baseline (A+T+ b= -0.08, 95%CI[-0.15,-0.02], p=0.016), but baseline A/T status was not associated with change in MDLCs at follow-up. A similar pattern was observed when looking just at the FNAME; with the A+T+ group performing worse at baseline (A+T+ b= -0.11, 95%CI[-0.20,-0.02], p=0.018) but no group differences observed over time. However, on the Digit Sign Test, the A+T- group exhibited lower MDLCs at baseline (A+T- b= -0.05, 95%CI[-0.10,-0.01], p=0.04), as well as diminished MDLCs over time (Time*A+T- b= -0.02, 95%CI[-0.05,-0.01], p=0.04), with the A+T+ group showing similar effect-sizes albeit at trend-level (A+T+ b= -0.05, 95%CI[-0.11,0.00], p=0.09; Time*A+T+ b= -0.02, 95%CI[-0.04,0.1], p=0.19). **Conclusion:** These results show that the BRANCH MDLC paradigm can detect subtle cognitive deficits in CU individuals who harbor both amyloid and tau pathology. In addition, our preliminary longitudinal findings suggest that repeating MDLCs over one year may track AD-related cognitive decline. By showing sensitivity to change over relatively short time-intervals, paradigms like BRANCH MDLCs have the potential to accelerate future AD secondary prevention trials.

LP063- FACTORS ASSOCIATED WITH FLOOR AND CEILING EFFECTS IN THE LATAM-FINGERS NEUROPSYCHOLOGICAL BATTERY. M. Yassuda[1], C. Suemoto[1], L. Crivelli[2], I. Calandri[2], P. Caramelli[3], F. Lopera[4], S. Brucki[1], R. Nitrini[1], A.L. Sosa[5], R. Salinas[5], L. Velilla[4], G. Sevlever[2], M. Kivipelto[6], M. Carrillo[7], R. Allegri[2] *(1. University of São Paulo - São Paulo (Brazil), 2. Fleni - Buenos Aires (Argentina), 3. Universidade Federal de Minas Gerais - Belo Horizonte (Brazil), 4. Antioquia Medical School - Antioquia (Colombia), 5. Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez - Ciudad De México (Mexico), 6. Karolinska Institutet - Stockholm (Sweden), 7. Alzheimer's Association - Chicago (United States))*

Background: The LatAm-FINGERS team selected tests previously used in the WW-FINGERS Network, which were developed in high-income countries. Although most of the tests had been previously validated in one or more countries in Latin America (LA), multinational studies are not available to indicate whether such tools are adequate for the region that is characterized by heterogeneous culture and education. Therefore, we aimed to assess floor and/or ceiling effects in the LatAm-FINGERS neuropsychological battery, in the baseline evaluation, and to investigate associated sociodemographic factors. **Methods:** The LatAm-FINGERS study is a two-year non-pharmacological intervention to improve cognition, in which 12 LA countries apply harmonized assessments. The present analyses included the following tests: Free and Cued Selective Reminding Test (FCSRT) (sum of the three immediate free recall trials alone and added to the immediate cued recall trials, delayed free recall, delayed total score - free plus cued recall); Logical Memory (immediate and delayed recall); Digit Symbol Substitution Test, Digit Span (Forward, Backward and Sequencing), and the Mini-Mental State Examination (MMSE). Floor and ceiling effects were identified when the test mean was less than two standard deviations (SD) from the lowest or highest score possible, respectively. This pattern indicates that a substantial number of scores cluster near the bottom or top of the scale. Age, sex, education, and race were investigated as factors that could be associated with such effects. **Results:** In 1,123 participants, 73.1 % were women, with mean age and education of 67.4 (4.7) and 12.9 (3.7) years, 58% were Mestizo, 28% were White, 7% were Black, and 6% were from other races. There was a floor effect in the Backward Digit Span test (1.56 SD units from the minimum score), which was associated with race (Mestizos and Black participants) and lower education. Ceiling effects were observed for the FCSRT sum of the immediate free and cued recall trials (0.39 SD units from the maximum score); FCSRT delayed free recall (1.39 SD); FCSRT delayed total score (0.28 SD); and MMSE (1.57 SD). Ceiling effects were associated with higher education for all tests, female sex for FCSRT trials, race (Black participants less likely for the FCSRT immediate free and cued recall trials, and Mestizos more likely for the FCSRT delayed free recall), and older age for the FCSRT delayed free recall. **Conclusions:** Floor effect was observed in the Backward Digit Span test. Ceiling effects were observed in the FCSRT, mainly for cued recall scores. The fact that the FCSRT controls for inattention in encoding and that it includes three consecutive immediate free and cued recall trials may explain the observed ceiling effects. Overall, results suggest the tests are performing adequately in this sample from LA.

LP064- ROBUSTNESS AND GENERALIZABILITY OF A SPEECH BASED COMPOSITE SCORE FOR MEASURING DISEASE PROGRESSION IN AD. M. Spilka[1], M. Xu[1], J. Robin[1], W. Simpson[1] *(1. Winterlight Labs - Toronto (Canada))*

Background: Changes in speech and language are evident in Alzheimer's disease (AD). Natural language processing and computational linguistics can help objectively quantify language impairment and provide novel measures of disease progression. We previously developed a novel speech-based composite score by analyzing patient verbal responses from the Clinical Dementia Rating (CDR) interview. We found that this composite score was both sensitive to longitudinal language change and significantly associated with clinical endpoints in a sample of AD participants. In the current analysis, we examined the generalizability of this composite to speech obtained from a brief picture description task in a separate AD sample. We compared the composite performance to established clinical endpoints and other language-based task scores. **Methods:** 148 English-speaking participants with mild-to-moderate AD who were randomized into the placebo arm of a Phase 2/3 clinical trial completed clinical assessments and an app-based speech assessment at baseline, and at 3-month, 6-month, and 12-month follow-up. Speech assessment included two picture description tasks in which participants were shown a drawing of a scene and asked to describe it in their own words. A set of nine speech and language features (for the speech-based composite score) and an objective measure of picture description performance ("object content score") were extracted for each participant from transcribed speech recordings. The longitudinal trajectory and magnitude of change for the composite score were compared to those of the clinical study endpoints (e.g., ADAS-Cog) and the object content score. Results were compared against our previously published performance of the composite derived from CDR interview speech. We further examined associations among speech-based scores and clinical endpoints, and whether combining speech-based scores increased sensitivity. **Results:** In this separate AD sample, the speech-based composite showed significant longitudinal change over time ($p < .001$), which paralleled longitudinal trajectories of both the ADAS-Cog and object content scores. The magnitude of change from baseline to endpoint was similar for the composite ($d = 0.37$) and object content score ($d = 0.46$) but smaller than for the ADAS-Cog ($d = 0.81$). The composite score showed significant moderate correlations with the ADAS-Cog ($r = 0.48$) and object content score ($r = -0.41$). When compared to the original development study where the composite score was obtained from CDR interview speech, the current composite generated from the picture description task had a 50% smaller magnitude of longitudinal change. Adding the object content score to the composite led to greater change from baseline but this was comparable to the magnitude of change for the object content score alone. **Conclusions:** The performance of a novel speech-based composite score obtained from open-ended interview speech was broadly generalizable to shorter, more structured picture description task speech, albeit with a lower effect size. The composite was sensitive to progressive speech changes in early AD and associated with clinical endpoints, demonstrating robustness across different speech sources. Results further validate digital speech assessments as a clinically relevant tool to measure disease progression in AD.

LP065- COGNITIVE FUNCTIONAL COMPOSITE DETECTED TIME-DEPENDENT WORSENING OF COGNITION AND FUNCTION DURING 18-MONTH PERIOD IN A PHASE II CLINICAL TRIAL WITH BIOMARKER PROVEN ALZHEIMER'S DISEASE PATIENTS. S. Sikkes[1], M. Postema[1], N. Prins[2], P. Van Bokhoven[3], T. Okuda[4], P. Scheltens[5] *(1. Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location Vumc - Amsterdam (Netherlands), 2. Brain Research Center - Amsterdam (Netherlands), 3. IXA-Neuroscience, Amsterdam Neuroscience, Amsterdam UMC location Vrije Universiteit - Amsterdam (Netherlands), 4. FUJIFILM Toyama Chemical Co., Ltd. - Tokyo (Japan), 5. Amsterdam UMC - Amsterdam (Netherlands))*

Background: Cognitive-Functional Composite (CFC) is a brief measure of both cognition and function, comprising seven existing cognitive tests focusing on memory and executive functioning and the Amsterdam IADL Questionnaire (A-IADL-Q). CFC was previously demonstrated as a suitable assessment to capture clinically meaningful cognitive decline in early dementia, therefore it was used as a secondary endpoint in T817MAEU201 study (NCT04191486) to evaluate efficacy and safety of edonerpic maleate (T-817MA) in patients with early stages of Alzheimer's disease (AD). Here, we explore change in CFC and its subcomponents over an 18-month follow-up in both treatment and placebo groups. **Methods:** T817MAEU201 is a phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of T 817MA in patients with mild cognitive impairment (MCI) or mild dementia due to AD, as evidenced by abnormal CSF Aβ 42 and p-tau 181 at screening with change of CSF p-tau 181 from baseline to week 78 as primary outcome. Randomized patients were treated by either 448 mg of T-817MA or placebo for 78 weeks. Cognition and function as secondary endpoints were evaluated using the CFC, encompassing cognitive composite (subtasks of ADAS-COG, Category fluency, Letter fluency, Digital Span, Digit Symbol Substition) and everyday functioning as assessed by the study partner reported A-IADL-Q, as well as the Clinical Dementia Rating Scale Sum of Boxes (CDR-sb). During the treatment period, CFC was assessed at baseline, week 28, week 52 and week 78. The difference between placebo and T-817MA was analyzed for total score of CFC (Z-score, both cognition and function) and each subscale using MMRM. And the difference between baseline and each visit in each group was analyzed using paired samples t-test. **Results:** 221 patients were randomized, of which 188 (85%) completed 78 weeks of treatment (14.9% premature discontinuation). Baseline age was 69.7 ± 6.5 years (mean ± SD) with 60.3% of female and mean MMSE and CDR-sb at baseline were 26.6 ± 1.8 and 2.72 ± 1.65, respectively. Baseline characteristics and diagnostic groups were well-balanced between treatment groups. In both groups, time dependent worsening in total CFC score was observed with significant change from baseline to week 28, 52 and 78 (all p-values<.05). Estimated change from baseline (LSMEAN) of total CFC at week 78 was -0.361 in placebo group (n=102) and -0.365 in T-817MA group (n=84). The difference in decline between treatment and placebo was not statistically significant (p=0.959). Both the cognitive and the functional component of the CFC showed significant decline over time from baseline to 28 weeks and beyond (all p-values<.05). Time-dependent decline in each subscales of cognitive component was also observed. **Conclusions:** The CFC showed time-dependent worsening of both cognition and function, and these did not differ between intervention and placebo. The observations of CFC decline in

18 months in the placebo group is valuable for designing future clinical trials and understanding drug effects. **Key words:** CFC, Phase 2, edonerpic. **Clinical Trial Registry:** NCT04191486; https://clinicaltrials.gov. **Disclosures:** SS provided consultancy services for Toyama, Aribio, Biogen, Boehringer, Prothena Biosciences, and she is part of the Scientific Advisory Board of Cogstate. All fees are paid to the institution. SS is the developer of the Amsterdam IADL Questionnaire and the Cognitive Functional Composite. All license fees are paid to the institution. SS receives funding from Health~Holland, Topsector Life Sciences & Health (PPP-allowance; LSHM19051, LSHM20084, LSHM22026-SGF), ZonMW (www.tap-dementia.nl, #10510032120003) in the context of Onderzoeksprogramma Dementie, part of the Dutch National Dementia Strategy, as well as ZonMW (#7330502051 and #73305095008), and SPREAD+. All funding is paid to the institution. MP declares nothing to disclose. NP is co-PI of the current trial with Fuji Film Toyama Chemical. NP performed consultancy work for Aribio, Amylyx, Eli-Lilly and Janssen and received a speaker fee from Biogen. NP is CEO and co-owner of Brain Research Center, the Netherlands. PVB declares nothing to disclose. TO is an employee of FUJIFILM Toyama Chemical Co., Ltd. PS is a full time employee of EQT Life Sciences (formerly LSP) and Professor Emeritus at Amsterdam University Medical Centers. PS has received consultancy fees (paid to the university) from Alzheon, Brainstorm Cell and Green Valley. Within his university affiliation PS was global PI of the phase 1b study of AC Immune, Phase 2b study with FUJI-film/Toyama and phase 2 study of UCB. PS is past chair of the EU steering committee of the phase 2b program of Vivoryon and the phase 2b study of Novartis Cardiology and presently co-chair of the phase 3 study with NOVO-Nordisk.

LP067- MEASURING WHAT MATTERS MOST TO PEOPLE LIVING WITH ALZHEIMER'S DISEASE AND CARE PARTNERS: WHAT MATTERS MOST QUALITATIVE RESEARCH. C. Romano[1], E. Bratlee-Whitaker[1], W.L. Herring[1,2], L.F. Callahan[3], K. Raimundo[4], J. Taylor[5], G. Taylor[5], I. Kremer[6], D. Lappin[7], T. Frangiosa[7], K. Gnanasakthy[1], D. Goss[1], R. Paulsen[8], A. Hartry[9], D. Dibenedetti[1] *(1. RTI Health Solutions - Research Triangle Park (United States), 2. Care Sciences and Society, Karolinska Institute - Stockholm (Sweden), 3. University of North Carolina at Chapel Hill - Chapel Hill (United States), 4. Genentech - San Francisco (United States), 5. Memory Advocate Peers (MAP) - New York (United States), 6. LEAD Coalition (Leaders Engaged on Alzheimer's Disease) - Washington, D. C. (United States), 7. Faegre Drinker Consulting - Washington, D. C. (United States), 8. UsAgainstAlzheimer's - Washington, D. C. (United States), 9. Biogen Inc - Cambridge (United States))*

Background: Understanding experiences and concepts important to people living with Alzheimer's disease (PLWAD) and to their care partners is critical to developing drugs and services that provide meaningful benefit. The What Matters Most (WMM) research program previously identified 42 WMM concepts encompassing treatment-related needs and preferences of PLWAD and their care partners [1, 2]. Round two of the research aims to build upon previous WMM work to verify WMM concepts identified as meaningful by extending to a more diverse population and providing greater context for the lived experience of Alzheimer's disease (AD) in consideration of stages across the AD continuum. **Methods:** A cross-sectional, single-visit observational study was conducted with PLWAD and care partners of PLWAD using semistructured, web-based interviews. Interviews sought to contextualize WMM concepts and determine whether concepts can be prioritized. To ensure that all needs, preferences, and priorities were assessed, participants were clinically confirmed and classified in 1 of 5 AD populations, ranging from Group 1 (people with AD risk or pathology, or their care partners) to Group 5 (care partners of people with severe AD). Interview data were systematically coded and reviewed using qualitative content analysis and thematic analysis methods [3]. Important concepts and dominant trends were identified and compared across interviews [4]. Descriptive statistics were summarized for demographic and clinical data. **Results:** The study population included 64 PLWAD (n=24) and care partners (n=40) spanning experiences across the full AD spectrum, from at-risk through severe disease. Both PLWAD and care partners were demographically diverse, representing a mix of sex, age, educational level, race, and ethnicity. Participants endorsed the importance of all 42 original WMM concepts and their categorization within the hypothesized domains of thought processing (14 concepts), daily activity (12), emotion (6), independence (4), communication (3), and social life/activity (3). Additionally, participants identified a few new candidate WMM concepts and suggested repositioning existing concepts to better describe the lived experience of AD. Respondents selected the descriptor "impact" most frequently to describe WMM concepts in their lived AD experience. Further, participants prioritized concepts, consistently articulated most and least important items across multiple example questions, and provided rationale for their rankings. Thought processing was most frequently identified as the most important treatment benefit (55%), though this decreased to 46% when PLWAD were analyzed separately. Additionally, treatment benefits affecting communication and independence were considered most important by more PLWAD (18% and 15%, respectively) than care partners (2% and 9%, respectively). **Conclusions:** This phase of the WMM research program demonstrated endorsement of previously identified WMM concepts and their domain placement in a conceptual disease model and greater characterization of WMM by participants representing PLWAD and care partners across the AD continuum. These findings provide context for understanding WMM in AD and allows for refinement of the conceptual disease model. This model may serve as a useful roadmap to identify best-fit clinical outcome assessments and guide future clinical studies. Finally, our WMM research will inform development of a refined WMM survey for additional stakeholders, including clinicians, payers, and policymakers. **Key words:** Alzheimer's Disease, Qualitative Interviews, Symptoms and Impacts, Preferences and Priorities. **Disclosures:** CR, EB, WLH, KG, DG, and DB are full-time employees of RTI Health Solutions, an independent nonprofit research organization, which was retained by AD PACE to conduct the research that is the subject of this abstract. Their compensation is unconnected to the studies on which they work. LFC is an employee of the University of North Carolina at Chapel Hill. KR is an employee of Genentech. JT and GT are living with AD. IK is a consultant serving as LEAD Coalition executive director. AH is an employee of Lilly & Co. DL and TF are employees of Faegre Drinker Consulting. RP is an employee of UsAgainstAlzheimer's. **Trademarks:** What Matters MostTM; UsAgainstAlzheimer'sTM. **References:** 1. DiBenedetti DB, et al. Alzheimers Res Ther 2020; 12(1): 90. doi:http://dx.doi.org/10.1186/s13195-020-00659-6. 2. Hauber B, et al. Neurol Ther 2023; 12(2): 505-527. doi:http://dx.doi.org/10.1007/s40120-023-00445-0. 3. Hsieh HF, Shannon SE. Qual Health Res 2005; 15(9): 1277-1288. doi:http://dx.doi.org/10.1177/1049732305276687. 4. Boeije H. Qual Quant 2002; 36(4): 391-409. doi:http://dx.doi.org/10.1023/a:1020909529486.

LP068- THE DOWN SYNDROME – CLINICAL GLOBAL IMPRESSION OF CHANGE (DS-CGIC). J. Gray[1], A. Strydom[2], O. Sol[1], J. Fortea[3], M. Rafii[4] *(1. AC Immune - Lousanne (Switzerland), 2. King's College - London (United Kingdom), 3. Hospital San Pau - Barcelona (Spain), 4. USC - San Diego (United States))*

Background: Alzheimer's disease (AD) is an inevitable consequence of the increased production of beta-amyloid in persons with Down syndrome (DS), who are on average diagnosed with dementia at 54 years of age. Increased accumulation of amyloid plaques and tau tangles have been well-documented by longitudinal PET imaging in older individuals with DS and studies are ongoing to better document the natural history of the associated cognitive and functional decline. **Objectives:** With the recent successes of amyloid lowering antibodies, studies are underway or planned to treat and ultimately prevent AD dementia associated with DS. These studies require sensitive instruments to detect changes over time. The measurement of change in overall clinical function over time using a clinician's global impression of change is a well-recognised approach in many areas of medicine including in individuals with AD. Yet current instruments have not been adapted to the special issues of persons with DS. In the context of a multicentre study of an anti-amyloid vaccine, ACI-24 (the ABATE study part 2 (participants with DS)) a semi-structured interview for use with the caregiver of participants with DS has been developed, the DS-CGIC. **Methods:** Three areas are assessed - Cognition, daily living function and mood/behavior during a semi-structured interview with the caregiver lasting around 20 minutes. Items to probe in these areas were developed empirically by clinicians familiar with AD in persons with DS. 11 items are probed for cognition, 8 for daily living function and 6 for behaviour/mood. For each domain, a general item is included to cover areas of importance for the participant which are not part of the regular probes. At baseline, the caregiver is interviewed about performance in these areas but not scored. For visits at which change from baseline is scored, the caregiver is interviewed and asked about changes in each item. Then, for each of the 3 domains, a change score is assigned on a 7-point scale where 1 is marked improvement, 2 is moderately improvement, 3 is minimal improvement, 4 is no change, 5 is minimal worsening, 6 is moderate worsening and 7 is marked worsening. Finally, an overall score is assigned using the same 7-point scheme. **Conclusions:** The changes over time on the DS-CGIC will be examined as an exploratory measure both on placebo and active treatment. Comparison of the changes over time with those on other instruments will help to establish the validity of the scale, as will its use in natural history studies such as the Trial Ready Cohort – Down syndrome (TRC-DS).

LP069- THE LONGITUDINAL IMPACT OF COVID-19 LOCKDOWN ON MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE. H.H. Lee[1,2], Y.S. Cho[3], J.Y. Lee[1] *(1. Department of Psychiatry, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea - Seoul (Korea, Republic of), 2. Interdisciplinary Program in Cognitive Science, Seoul National University, Republic of Korea Interdisciplinary Program in Cognitive Science - Seoul (Korea, Republic of), 3. Keimyung University School of Medicine & Institute for Medical Science - Daegu (Korea, Republic of))*

Background: The COVID-19 pandemic has significantly impacted older adults, potentially affecting their health due to social distancing and quarantine measures. However, the specific longitudinal impact of COVID-19 lockdown measures on individuals with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) remains unclear. This study investigates changes in cognitive, psychological, and behavioral functioning in individuals with MCI and AD, utilizing a two-year pre-pandemic baseline and longitudinal follow-up data spanning the COVID-19 pandemic. The primary objective is to assess the pandemic's influence on the cognitive faculties of MCI and AD patients. **Methods:** We retrospectively recruited 130 patients aged 59-94 from a medical center in Korea who had undergone psychiatric assessments four times consecutively from January 2018 to December 2021. Assessment scores from the initial lockdown period in Korea (March 22, 2020) were recalculated using interpolation. Mixed-effects models were employed to assess changes in cognitive, psychological, and behavioral functioning in MCI/AD patients, comparing the periods before the pandemic (January 2018 - February 2020) with the pandemic period (March 22, 2020 - December 2021). The slopes of the score differences between 1) the pre-pandemic and lockdown periods (March 2020) and 2) the lockdown and during-pandemic periods (up to December 2021) were compared to identify the lockdown's effects. Exploratory regression analysis identified factors associated with changes in clinical dementia rating sum of boxes (CDR-SB). **Results:** Compared to their pre-pandemic baseline, both MCI and AD patients exhibited deteriorating scores in clinical dementia ratings, cognitive functioning, and activities of daily living (ADL, IADL) during the pandemic. Specifically, AD patients showed a significant decline in cognitive functioning. Patients with higher education levels (7 years or more) experienced a more rapid decline in cognitive function compared to those with lower education levels (6 years or less, or no formal education). Regression analysis revealed a significant association between reduced activities of daily living, MMSE scores, and the Clinical Dementia Rating sum of boxes. **Conclusions:** This study provides valuable insights into the longitudinal impact of COVID-19 lockdown measures on cognitive functioning in individuals with cognitive impairment. The findings demonstrate that lockdown measures resulted in a significant deterioration in cognitive abilities, particularly among AD patients, with these changes being closely tied to established risk factors for dementia. Additionally, the enforced social isolation during lockdowns constrained daily activities, exacerbating cognitive decline in this vulnerable population. This underscores the complex interplay between environmental factors and cognitive health, emphasizing the need for targeted interventions and support for individuals with cognitive impairment during times of crisis. **Key words:** dementia, neuropsychological tests, COVID-19. **Disclosures:** No Disclosures to Report. **References:** 1. Arce Rentería M, Vonk JMJ, Felix G, Avila JF, Zahodne LB, Dalchand E, Frazer KM, Martinez MN, Shouel HL, Manly JJ. Illiteracy, dementia risk, and cognitive trajectories among older adults with low education. Neurology. 2019 Dec 10;93(24):e2247-e2256. doi: 10.1212/WNL.0000000000008587. Epub 2019 Nov 13. PMID: 31722961; PMCID: PMC6937498. 2. Gan J, Liu S, Wu H, Chen Z, Fei M, Xu J, Dou Y, Wang X and Ji Y (2021) The Impact of the COVID-19 Pandemic on Alzheimer's Disease and Other Dementias. Front. Psychiatry 12:703481. doi: 10.3389/fpsyt.2021.703481. 3. Kang M, Lee I, Hong H, Kim J, Kang H. Predictors of Changes in Cognitive Function in Older Korean Adults: The 2006-2018 Korean Longitudinal Study of Aging. Int J Environ Res Public Health. 2021 Jun 11;18(12):6345. doi: 10.3390/ijerph18126345. PMID: 34208163; PMCID: PMC8296181. 4. Zhao Q, Zhou B, Ding D, Teramukai S, Guo Q, et al. (2014)

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COGNITIVE ASSESSMENT AND CLINICAL TRIALS

P118- THE VIEWMIND AI SOLUTION (VIMAS) ADDRESSES INEQUITIES AND DISPARITIES IN THE ASSESSMENT OF DEMENTIA RISK. M.A. Parra[1], A. Gonzalez-Hernandez[2], J. Bonilla-Santos[2], R.A. Gonzalez-Montealegre[2], D. Yisela-Cala[2], G. Fernandez[3], D. Verge[4] *(1. University of Strathclyde - Glasgow (United Kingdom), 2. Universidad Surcolombiana - Huila (Colombia), 3. ViewMind - Bahia Blanca (Argentina), 4. ViewMind - West Chester (United States))*

Background: Dementia has been declared a global challenge. However, solutions to address this problem are far from global (Parra et al., 2019). A key factor precluding the validity and generalizability of novel developments in the field of early diagnosis is their cultural bias. The Professional Interest Area on Diversity and Disparities from ISTAART highlighted the urgent need to harmonise assessments across the global north and global south if we are to better understand and detect these globally devastating disorders earlier (Babulal et al., 2019). The novel ViewMind AI Solution which combines state of the art cognitive markers, high precision eye-tracking metrics (ET), and AI has been subjected to the investigation of these outstanding needs. Here we present preliminary results from a large population-based study in southern regions of Colombia aimed at investigating the validity of a novel digital neurocognitive biomarkers to detect dementia risk in underrepresented populations. **Methods:** The ViewMind AI Solution records ET variables during memory binding (Parra et al., 2011). The task assesses low-level integrative memory abilities, and it has been proposed as a novel memory marker for AD (Costa et al., 2017). We analysed a small sample of 29 individuals of whom 8 met criteria for Mild Cognitive Impairment (MCI). Healthy control (HC) and MCI participants were matched according to age (HC: 61.8±6.68, MCI: 62.5±5.2, p=0.398) but were significantly different with regard to years of education (HC: 12.3±6.0, MCI: 5.87±5.6, p=0.007). They all underwent standard clinical, functional, and neuropsychological assessments. Multivariate analyses were conducted to investigate if groups differed in the neuropsychological (i.e., a battery comprising memory, attention, language, praxis, and executive functions tests), cognitive (i.e., behavioural responses during the integrative memory task), and biomarker (i.e., ET metrics) domains, when education was and was not added to the models as a confounding factor. **Results:** The non-controlled model addressing the neuropsychological domain yielded significant group effects [F=2.69, p=0.034, β=83%], but these disappeared when we covaried for education [F=1.78, p=0.143, β=61%]. The cognitive domain proved uninformative. The biomarker domain revealed group differences with the non-controlled model which were significant [F=3.83, p=0.007, β=94%] and increased after removing the variance accounted for by years of education [F=4.10, p=0.005, β=95%]. These ET findings emerged during the memory encoding phase of the integrative memory task only. **Conclusion:** Traditional neuropsychological assessments proved uninformative to detect dementia risk among individuals with very low education. As we have previously shown, biological data drawn from ET metrics taken during the memory encoding phase outperformed pure behavioural scores drawn from the integrative memory task (Fernandez et al., 2018; Fernández & Parra, 2021). This profile mirrors that seen in patients with or at risk of Alzheimer's disease dementia. Of note, such ET metrics detected significant group differences with statistical power above 80% whether models controlled for years education or not. These results support our proposal of ViewMind AI Solution as a culture-free neurocognitive biomarker for the early detection of dementia in underrepresented populations. **Key words:** Dementia, Diversity and Disparity, Eye-Tracking, Cognitive Markers, AI, Biomarkers, Preclinical Detection. **Disclosures:** MAP is a consultant for ViewMind serving as Neuroscientific Officer. GF is ViewMind Chief Scientific Officer. **References:** Babulal, G. M., Quiroz, Y. T., Albensi, B. C., Arenaza-Urquijo, E., Astell, A. J., Babiloni, C., Bahar-Fuchs, A., Bell, J., Bowman, G. L., Brickman, A. M., Chetelat, G., Ciro, C., Cohen, A. D., Dilworth-Anderson, P., Dodge, H. H., Dreux, S., Edland, S., Esbensen, A., Evered, L., . . . O'Bryant, S. E. (2019). Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: Update and areas of immediate need. 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P119- CLINICAL DEMENTIA RATING SCALE (CDR®) DOMAIN SCORES DIFFER BY DIAGNOSIS IN HISPANIC AND NON-HISPANIC WHITE SAMPLES. G. Pilonieta[1], D. Geldmacher[1] *(1. The University of Alabama at Birmingham - Birmingham (United States))*

Background: The CDR® dementia staging instrument is a clinician-rated global assessment widely used as part of the diagnostic methods in clinical and research settings and as a primary endpoint in clinical trials. However, recent studies suggested the influence of cultural and linguistic factors on CDR scores. [1] This study aims to investigate potential differences in CDR ratings in the National Alzheimer's Coordinating Center (NACC) database by ethnicity. **Methods:** We compared demographics, clinical characteristics, and Clinical Dementia Rating Scale (CDR®) domain ratings across consensus diagnostic groups (Cognitive Normal [CN], impaired-not-Mild Cognitive Impairment [INMCI], Mild

Cognitive Impairment [MCI], or dementia) in non-Hispanic White (NHW) (N=7,719; 91.88%) and Hispanic (N=682, 8.12%) adults in the NACC cohort. Data included Version 3.0 of the UDS, collected at initial visits by 37 ADRCs from March 2015 to June 2022 (alz.washington.edu). ANCOVA tests were performed to evaluate associations of CDR domain ratings across consensus diagnostic groups by ethnicity and to ascertain differences in CDR ratings by ethnicity among consensus diagnostic groups. **Results:** Among 8,401 participants, 4,610 (54.87 %) were women, mean age at baseline was 70.27 (SD 8.36), and mean education was 16.18 (SD 2.82) years. Compared to NHW, Hispanic participants had a higher proportion of women $\chi 2$ (1, N=8,401) = 21.4978, p <.0001, were younger (t=3.07, p =0.0021), had completed significantly fewer years of education (t= 21.33, p =<.0001), and reported significantly higher depressive symptoms (t=-3.33, p =0.0009). CDR ratings by domain significantly differed across consensus diagnosis groups in both subsamples. When stratified by consensus diagnosis groups, analyses showed variations in several domain ratings. Hispanics had higher orientation ratings in the INMCI (p=0.0494) and dementia groups (p=0.0050) than NHW. In the MCI group, Hispanics had statistically significantly lower scores than NHW in all the ratings except personal care ($p < 0.05$). These differences remained after controlling for demographics and clinical variables. Interestingly in the dementia group, analyses showed variations in CDR Global Score, CDR-Sum of Boxes, memory, judgment and problem solving, and community affairs ratings. However, these differences were not retained after controlling for demographics and the presence of depressive symptoms. **Conclusions:** Our study found that cross-sectional CDR ratings differed between Hispanic and non-Hispanic White participants. Cultural factors might influence the expression and reporting of cognition and function, but these differences may be attenuated as severity increases. Future research with more racially and ethnically heterogeneous samples and culturally and linguistically diverse raters may help to explore the impact of different perceptions of ADRD-related changes among underrepresented groups on dementia staging. **Key words:** Alzheimer's disease, Dementia diagnosis, CDR®, Global rating, Race, Ethnicity. **Disclosures:** Dr. Pilonieta reports no disclosures. Dr. Geldmacher has received research funding paid to his employer from Biogen, Eisai, Genentech, Janssen, and Vaccinex, as well as NIH and the US Department of Defense. He has received consulting income from Eisai, Genentech, Lilly, and Premier Applied Science. **References:** 1. Kamat, R., Appleman, E.R., Chen, Z., Stenclik, J., Machizawa, S. and Feaster, H.T. (2022), Geo-cultural influences on the relationship between the CDR and MMSE. Alzheimer's Dement., 18:e060203. https://doi.org/10.1002/alz.060203

P120- SEX BIAS AND THE ASSOCIATION OF DEMENTIA LIFESTYLE RISK FACTORS WITH SUPERAGER STATUS.

M. Mcphee[1], L. Mcketton[2], A. Laplume[3], A. Troyer[1,4], N. Anderson[2,4,5] *(1. Neuropsychology and Cognitive Health, Baycrest - Toronto (Canada), 2. Rotman Research Institute, Baycrest Academy for Research and Education - Toronto (Canada), 3. Douglas Research Centre, McGill University and Centre for Research at the Geriatrics Institute of the University of Montreal - Montreal (Canada), 4. Department of Psychology, University of Toronto - Toronto (Canada), 5. Department of Psychiatry, University of Toronto - Toronto (Canada))*

Background: Superagers are defined as 80 to 89 year olds with intact cognition and memory equivalent to at least average performance of individuals 20 to 30 years younger. This study examined the impact of sex in superager group classification and whether dementia risk factors distinguish those with typical-for-age cognitive abilities ('typical-agers') from superagers. **Methods:** Data were drawn from participants who completed the Cogniciti Brain Health Assessment in n = 9,233 (70% female) aged 50-69 (normative comparison group) and n = 469 (67% female) aged 80-89 (superager group). As part of the assessment, participants completed a questionnaire of demographic and modifiable lifestyle dementia risk factors (informed primarily by Livingston's 2020 model), followed by four cognitive tasks that assess associative memory, working memory, set shifting, and cognitive inhibition. **Results:** The use of sex-stratified normative comparisons for superager classification amplified the difference in cognitive performance between superagers and typical-agers, suggesting the presence of sex-based bias in superager classification. Of the tested individual risk factors, hearing loss was associated with a 48% reduction of the likelihood of superager group membership (p = .015) for females (OR = 0.520, 95% CI [0.304, 0.876]) but not males (OR = 1.169, 95% CI [0.510, 2.813]). Other lifestyle dementia risk factors were unrelated to superager status. Superagers out-performed typical-agers on measures of working memory, set shifting, and cognitive inhibition, though effect sizes were very small. **Conclusions:** These findings revealed that sex can moderate the relationship between dementia risk factors and probability of superager status by introducing bias in classification methods that have implications for the generalizability of study results. We highlight the unique role of hearing loss in female's superager status. Future studies of the superager construct should take into consideration the role that sex differences may play.

P121- OBJECTIVE MONITORING OF INSTRUMENTAL ACTIVITIES OF DAILY LIVING IN DEMENTIA.

R.K. Mishra[1], M. Lee[2], A.S. Nunes[3], M.K. York[2], M.E. Kunik[2], A. Vaziri[3], B. Najafi[2] *(1. Biosensics - Boston (United States), 2. Baylor College of Medicine - Houston (United States))*

Background: Background: Instrumental activities of daily living (IADLs) play an important role in Alzheimer's disease (AD) by providing insights into a person's functional abilities and limited IADL indicates high fall risk. IADLs refer to complex activities necessary for independent living, including meal preparation, medication management, and handling household chores. However, the current assessment of IADLs is subjective and reliant on the patient's memory. This study presents intermediate results from an ongoing clinical trial investigating the feasibility of novel technology-based platform, IADLSys, for home-based remote monitoring of IADL among individuals with AD. **Methods:** The IADLSys system comprises three key elements: (1) wireless physical tags (pTAG) that are affixed to objects of interest, (2) a pendant-sensor that monitors physical activities and detects interactions with the pTAGs, and (3) an interactive tablet serving as a gateway for transferring data to a secure cloud. When a pTAG near the pendant is activated by the movement, the pendant sensor records the IADL interaction data using Bluetooth technology. Participants were identified as fallers if their score on the Falls Efficacy Scale International (FES-I) was greater than 25. Additionally, life-space, depression, and quality of life were administered using the subjective questionnaires. **Results:** The study involved 25 individuals with AD, consisting of 16 non-fallers (age = 69.1 ± 7.3 years, female = 82%, BMI = 29.7 ± 6.4 kg/m2) and 9 fallers (age = 67. 8 ± 4.7 years, female = 67%, BMI = 32.1 ± 7.3 kg/m2). Among the fallers group, participants exhibited

fewer visits to the kitchen (effect size d = 0.395), lower use of medication box (d = 0.736), lower cadence during walking (steps/minute, d = 0.785), and longer durations of sitting (d = 0.52) compared to non-fallers. Additionally, fallers had significantly lower life-space mobility compared to non-fallers (effect size d = 0.73). **Conclusion:** The implementation of smart home technology such as IADLSys for remote monitoring of instrumental activities of daily living (IADL) holds potential in offering personalized support to individuals with cognitive impairment, while also enabling the tracking of both physical and cognitive decline. In the context of Alzheimer's disease (AD), individuals with a high fear of falls typically exhibit lower levels of IADL performance and physical functioning compared to those who do not experience falls. Lastly, an objective and remote assessment of IADL will provide an objective monitoring biomarker for AD, and facilitate reliable assessment of functional abilities in the clinical trials. **Key words:** Dementia caregiving, Digital Health, Caregiving burden, Smart Home, AD clinical trials. **Clinical Trial Registry:** NCT05703490; https://clinicaltrials.gov/ct2/show/NCT05703490. **Disclosures:** Ram Kinker Mishra has received personal compensation for serving as an employee of BioSensics. Adonay S. Nunes has received personal compensation for serving as an employee of Biosensics. Ashkan Vaziri has received personal compensation for serving as an employee of BioSensics. Michele K. York has received personal compensation in the range of $0-$499 for serving on a Scientific Advisory or Data Safety Monitoring board for RAD-PD. The institution of Michele K. York has received research support from Michael J. Fox Foundation. The institution of Michele K. York has received research support from NIH. The institution of Michele K. York has received research support from Takeda. Mark E. Kunik has received personal compensation in the range of $500-$4,999 for serving as an Expert Witness for County probate courts and attorneys. The institution of Mark E. Kunik has received research support from VA. The institution of Mark E. Kunik has received research support from NIH. Bijan Najafi has received personal compensation in the range of $100,000-$499,999 for serving as a Consultant for BioSensics. Bijan Najafi has received personal compensation in the range of $5,000-$9,999 for serving as a Consultant for Mölnlycke Health Care. Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. **Funding:** Research reported in this publication was supported by the National Institute On Aging of the National Institutes of Health under Award Number R42AG060853. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

P122- ERRORS IN CLINICAL DEMENTIA RATING ADMINISTRATION AND SCORING: IDENTIFYING TARGETS FOR INTERVENTION.

R. Kamat[1], J. Massa[1], A. Aedo[1], G. Barbati[1], S. Machizawa[1], J. Stenclik[1], E. Appleman[1], A. Iacob[1] *(1. Signant Health - Blue Bell (United States))*

Background: The Clinical Dementia Rating (CDR) scale is one of the most widely used cognitive outcome measures in Alzheimer's Disease (AD) clinical trials1. The CDR is a global assessment developed to facilitate dementia severity staging. Based on study partner and participant interviews, the rater evaluates the participant's abilities in 6 cognitive/ functional categories along 5 levels of impairment (no dementia to severe dementia). Given the widespread use of this scale in AD clinical trials, it is important to ensure reliability. Administration and scoring errors can have a substantial impact on trial results. These errors may increase variability in data thus masking accurate estimates of treatment effects. To our knowledge, error types on the CDR have not been formally investigated. In this study, we aimed to examine the type and frequency of errors made by raters participating in multinational AD clinical trials. **Methods:** We reviewed 13,147 screening and baseline visits from two multinational AD clinical trials. Participants who were administered the CDR but subsequently did not meet the study inclusion criteria were not included in these analyses. Raters varied in educational background as well as AD and scale experience. All raters received standardized CDR training and assessment of ability to score the scale. The audio recordings and scale data from these visits were reviewed by independent, local-language experts who identified errors in administration and scoring. The reviewers were trained to ensure consistency. We examined the frequency of administration and scoring errors in each of the six CDR domains. **Results:** Administration and Scoring errors were detected across all domains. Overall, administration errors (3.64% - 19% of visits) were more common than scoring errors (1.58% - 6.18% of visits). Administration errors were most frequent in the Memory (19%) and Judgment and Problem Solving (9.58%) domains. Examples of administration errors included using an incorrect time frame (i.e., 1 week or 1 month) for study partner's report of recent event in the Memory domain and gathering insufficient details from the study partner regarding the participant's prior versus current abilities in the Judgment and Problem Solving domain. Scoring errors were most frequent in the Orientation (6.18% of visits) and Community Affairs (4.87%) domains. Examples included not synthesizing study partner responses with participant performance when scoring the Orientation domain or selecting "Sometimes" when the study partner response indicates meaningful participation in activities outside the home (Question 7; Community Affairs domain). **Conclusions:** All CDR domains were vulnerable to errors, with Memory, Judgment and Problem Solving, Orientation domains being most likely to be administered or scored incorrectly. These errors may impact the ability to detect treatment effects in AD clinical trials. Future directions include examining the relationship between rater characteristics (i.e. educational background, AD and scale experience) and CDR error type and frequency. Our findings highlight the need for customized, enriched training for raters targeting the most common errors in administration and scoring. Additionally, these findings support ongoing monitoring of CDR assessments. Both these actions serve to improve inter-rater reliability and data quality in clinical trials. **Key words:** Clinical trial, dementia, Alzheimer's disease, assessment errors. **Disclosures:** No disclosures to report

P123- LEVERAGING AI METHODS TO DETECT COGNITIVE DECLINE AND DEMENTIA OVER THE TELEPHONE: A PROMISING NEW SCREENING TOOL.

C. Diaz-Asper[1], C. Chandler[2], S. Turner[3], B. Reynolds[3], B. Elvevåg[4] *(1. Marymount University - Arlington (United States), 2. University of Colorado, Boulder - Boulder (United States), 3. Georgetown University - Washington Dc (United States), 4. University of Tromsø - the Arctic University of Norway - Tromsø (Norway))*

Background: Timely and accurate recognition and monitoring of early cognitive decline is crucial for Alzheimer's disease (AD) clinical trials to facilitate accurate diagnosis,

establish baselines, track disease progression, measure treatment efficacy, and ensure participant safety. However, the identification of reliable signs of AD at the preclinical stage remains challenging, especially for clinicians, and as a result, many individuals may be missed for inclusion in clinical trials which could have significant implications for treatment options, quality of life, and cost of care. Currently, the detection of early cognitive decline requires a comprehensive clinical examination, which is both time consuming and expensive. By contrast, a few minutes of speech collected remotely via telephone in naturalistic settings and analyzed with innovative computational methods could provide accurate metrics. **Methods:** Participants (N=91) were community-dwelling English speakers, recruited via the Memory Disorders Program (MDP) at Georgetown University, and were cognitively healthy (n=29) or carried a diagnosis of mild AD (n=30) or amnestic MCI (n=32). Clinical diagnoses of AD and MCI followed established criteria. All participants had been evaluated with the Mini Mental State Exam (MMSE) within the last 6 months, had adequate hearing, and no self-reported history of neurological disease, drug or alcohol abuse, psychiatric hospitalization, current cancer treatment, stroke or heart attack within the last year. The study was approved by the institutional review boards of Marymount University and Georgetown University (MU IRB#260). Participants were at home, and were called by a trained research assistant for a short telephone interview at a time convenient for them. The interview consisted of a standardized telephone cognitive screening tool (the modified Telephone Interview for Cognitive Status, TICS) as well as two prompts to elicit speech: animal fluency (generating the names of as many animals as possible in one minute) and autobiographical recall (a favorite memory from childhood). Speech responses were digitally recorded and a range of natural language (lexeme, syntactic, semantic) and acoustic features were extracted to build a multimodal machine learning model to classify diagnostic groups. **Results:** Participants rated the interview favorably in terms of enjoyment, ease and lack of anxiety produced [1]. The multimodal approach was 75% accurate overall in predicting group membership (cognitively healthy, aMCI, or AD) which outperformed traditional speech-based screening tools (MMSE and TICS) and an expert human who read transcripts of participants' autobiographical recall [2]. Importantly, this method was able to extract meaningful information from real-world speech samples of variable recording quality. Language, acoustic, and crossmodal animal fluency features, and language and acoustic autobiographical recall features were predictive of diagnostic groups, with varied levels of discriminability. For animal fluency, the most discriminable language-based features were variations of the maximum number of animals per category. For autobiographical memory, the Mel Frequency Cepstral Coefficient (MFCC) acoustic features, measures of semantic coherence, and individual word probabilities were highly predictive of cognitive decline [3]. **Conclusion:** This new approach of combining advances in AI with the convenience of the telephone demonstrates proof of concept for the development of a screening tool for cognitive decline that can improve the science and technology of clinical assessment via its focus on the automated analysis of speech and language. Since the collection of speech data can be achieved remotely, rapidly, at low cost, and without specialized equipment, these methods hold potential for large-scale screening and monitoring of cognitive decline. Further, many traditional neuropsychological assessment tools are poorly suited for monitoring and tracking purposes because they suffer from documented biases and practice effects. In contrast, by training machine learning models on speech from diverse samples, regular, accurate and unbiased screening of cognitive decline can be achieved. **Key words:** Cognitive screening, Speech and Language, Natural Language Processing, Machine Learning. **Clinical Trial Registry:** N/A. **Disclosures:** RST - research support to Georgetown University from Alector, Biogen, Cognition Therapeutics, Eisai, Lilly, Janssen, Vaccinex, and Vivoryon. The authors declare no competing interests. **References:** 1. Diaz-Asper, C., Chandler, C., Turner, R. S., Reynolds, B., & Elvevåg, B. (2021). Acceptability of collecting speech samples from the elderly via the telephone. Digital Health. https://doi.org/10.1177/20552076211002103; 2. Diaz-Asper, C., Chandler, C., Turner, R. S., Reynolds, B., & Elvevåg, B. (2022). Increasing access to cognitive screening in the elderly: applying natural language processing methods to speech collected over the telephone. Cortex, 156, 26-38. https://doi.org/10.1016/j.cortex.2022.08.005 3. Chandler, C., Diaz-Asper, C., Turner, R. S., Reynolds, B., & Elvevåg, B. (under review). An explainable machine learning model of cognitive decline derived from speech. Alzheimer's and Dementia

P124- INFLUENCE OF COVID-19 PANDEMIC TO SELF-PERCEIVED MEMORY DECLINE: CONTRIBUTION TO COGNITIVE CHANGE ONE-YEAR LATER. K. Sato[1,2], Y. Niimi[2], R. Ihara[3], K. Suzuki[4], A. Iwata[3], T. Iwatsubo[1,2] *(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: Subjective cognitive complaints and their indexed score, Cognitive Function Index (CFI), are known as important markers of cognitive decline, development of dementia, and the pathological basis of Alzheimer's disease (AD). As one of the CFI items, a simple question "self-perceived memory decline compared to one-year ago" might also have an important potential to predict future cognitive decline or the development of dementia. Meanwhile, the "self-perceived memory decline" is reported as associated with depression or anxiety, and the COVID-19 pandemic in 2020 has also been known to have had brought about many kinds of psychiatric symptoms including depression or anxiety to the elderly individuals. **Objectives:** These earlier observations suggest that the contribution of the self-perceived memory decline to the prediction of cognitive decline may have been altered or influenced during the COVID-19 pandemic or lock-down period to uncertain extent: if it is true, it may require us to adjust the CFI scores depending on the period of measurements in relation to the COVID-19 pandemic, in the analysis of clinical studies or clinical trials of AD treatment where CFI score is frequently measured. In this study, we aimed to investigate the contribution of the self-perceived memory decline compared to a year ago as well as its interaction with the COVID-19 pandemic to the actual cognitive change one-year later. **Methods:** We used data of thousands of elderly individuals from the National Health And Aging Trends Study (NHATS), which collects annual interviews of nationally representative samples of older adults among Medicare beneficiaries in the United States. We utilized mixed model with repetitive measures (MMRM) to examine the effect of "self-perceived memory decline" and its interaction with the COVID-19 pandemic to the cognitive function in the next year. Zero-inflated Poisson model was used for regression. Sociodemographic features were simultaneously imputed as

covariates. **Results:** We included approximately 6,700 elderly individuals whose interview was recorded annually since 2011 until 2021. Higher age, being men, not being white race, education history of highschool diplomacy or lower, lower ADL, lower iADL, poorer social activity, having depression symptoms, lower annual income, or having "self-perceived memory decline" were significantly associated with the higher risk of worse cognitive function in the next year. Meanwhile, the interaction of the self-perceived memory decline and the COVID-19 pandemic (as a dummy variable denoting survey in 2020) was not associated with. Similar results were obtained even when we analyzed only those without apparent cognitive decline. **Conclusions:** Current analysis using a large-scale annual survey data suggested that the "self-perceived memory decline" is by itself associated with the cognitive decline one-year later irrespective of other related factors such as ADL, depressive symptoms, or the disruption during COVID-19 pandemic, and that it may be a useful marker widely and consistently applicable to general population as one of the simple prediction markers of cognitive decline.

P125 NILI: DIGITAL HEALTH SOLUTION FOR DEMENTIA CARE COORDINATION AND MANAGEMENT.

R.K. Mishra[1], M. Lee[2,3], M.K. York[3], M.E. Kunik[4,5], B. Najafi[2,3], A. Vaziri[1] *(1. BioSensics LLC - Newton (United States), 2. Department of Surgery, Baylor College of Medicine - Houston (United States), 3. Neurology and Psychiatry & Behavioral Sciences, Baylor College of Medicine - Houston (United States), 4. Menninger Department of Psychiatry and Behavioral Science, Baylor College of Medicine, - Houston (United States), 5. Michael E. DeBakey Veterans Affairs Medical Cente - Houston (United States))*

Background: Dementia is an age-related chronic disease leading to progressive cognitive impairment and affecting patients' independence. This condition burdens patients, caregivers, and families with significant physical and emotional stress. To alleviate this, we developed 'Nili', a technology-driven platform designed to streamline dementia care coordination and management. Nili aims to lessen caregiver strain, enhance patients' physical function and improve adherence to care routines. This study discusses Nili's feasibility and acceptability among dementia patients, caregivers, and providers. We also detail our ongoing randomized control trial (RCT) studying Nili's effectiveness in reducing caregiving burden and stress, and enhancing the lives of patients with dementia. **Methods:** Nili provides a comprehensive approach to dementia care coordination, promoting adherence to daily tasks. It uses gamified tasks for patient engagement and offers caregivers a holistic view of patient adherence to care plans. Additionally, it facilitates social engagement through multimedia sharing and video calls within the patient's care network. To gauge factors like perceived usefulness (PU), ease of use (PEoU), technology anxiety, and intended use (IU), we conducted a mixed-methods study. This involved interviewing a focus group of 11 dementia care experts, 10 dementia patients, and 14 caregivers, using the Technology Acceptance Model (TAM) questionnaire and a five-point Likert scale. We are currently conducting six-month RCT with 100 individuals with dementia and their caregivers to determine the efficacy of Nili in reducing caregiving burden and stress, as well as improving patient task adherence, physical function, and quality of life. **Results:** Results from our focus group affirmed high acceptability, PEoU, PU, and IU, with satisfaction levels between 70% and 100%. These outcomes were statistically significant compared to the natural level ($p < 0.05$), with low concerns about privacy and technology anxiety. Secondary analyses revealed that age negatively affected PEoU among IWDs ($r = -0.68$, $p = 0.03$), while PEoU positively influenced IU among caregivers ($r = 0.73$, $p < 0.01$). Our Phase II RCT study has just commenced, with five IWDs and their caregivers already participating. Although the data is preliminary, early results indicate Nili's acceptability and feasibility for daily routine use. **Conclusion:** This study presents an innovative, interactive, digital care coordination system designed to alleviate caregiver burden for individuals with dementia. Our feasibility findings confirm the system's acceptability and scalability, though acceptability decreases with user age. While all stakeholders rated the system's PU highly, scalability proved to be highly dependent on the PEoU. In the ongoing RCT, early results from the first 10 participants (five dementia patients and their caregivers) suggest that simplifying the system enhances daily routine adoption. However, these results are preliminary, and larger sample sizes are necessary for confirmation. **Key words:** Dementia caregiving, Digital Health, Caregiving burden, Smart Home. **Clinical Trial Registry:** NCT04308512; https://clinicaltrials.gov/ct2/show/NCT04308512. **Disclosures:** Ram Kinker Mishra has received personal compensation for serving as an employee of BioSensics. Adonay S. Nunes has received personal compensation for serving as an employee of BioSensics. Ashkan Vaziri has received personal compensation for serving as an employee of BioSensics. The authors declared no competing interests. Michele K. York has received personal compensation in the range of $0-$499 for serving on a Scientific Advisory or Data Safety Monitoring board for RAD-PD. The institution of Michele K. 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Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. **Funding:** Research reported in this publication was supported by the National Institute On Aging of the National Institutes of Health under Award Number R44AG066360. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

P126- USING SPEECH BIOMARKERS FOR DETECTION AND MONITORING OF COGNITIVE DECLINE.

A.S. Nunes[1], G. Cay[2], M. Lee[2], M.D. Rouzi[2], N. El-Refaei[2], A. Momin[2], R.K. Mishra[1], B. Najafi[2], A. Vaziri[1] *(1. BioSensics LLC - Boston (United States), 2. Interdisciplinary Consortium on Advanced Motion Performance (iCAMP), Michael E. DeBakey Department of Surgery, Baylor College of Medicine - Houston (United States))*

Introduction: Existing cognitive assessment tools have certain limitations, including challenges related to floor/ceiling effects, reduced psychometric performance in mild cases, and biases arising from repeated evaluations. In our study,

we aim to explore the potential of utilizing digital speech analysis as an innovative approach for detecting cognitive impairment. Our focus is on identifying unique digital speech biomarkers that correlate with cognitive impairment and its severity, presenting a promising diagnostic tool within the field of cognitive neuroscience. **Methods:** We conducted our research with a diverse group of older adults, encompassing varying cognitive states, including individuals with Alzheimer's disease. Their speech was recorded during a reading task. We used BioDigit Speech (BioSensics, Newton, MA) to measure speech parameters such as timing, pitch, and loudness. Group differences were assessed using Cohen's effect size, and correlations were established with the Montreal Cognitive Assessment (MoCA). To distinguish cognitive states based on speech data and predict MoCA scores, we employed a stepwise approach utilizing a Random Forest model, which identified highly correlated features. **Results:** Our study cohort comprised 59 participants, with 36 individuals (age mean ± SD: 66±9, 25 females) exhibiting cognitive impairment and 23 individuals (age mean ± SD: 69±6, 14 females) serving as cognitively intact controls. Timing parameters, specifically, Speech to pause ratio, stood out with the most significant effect size (d=0.656, p=0.017) between these groups. Among the assessed parameters, Dynamic Time Warping (DTW)-based similarity demonstrated a substantial positive correlation (rho=0.529, p<0.001), while the ratio of extra words, revealed the strongest negative correlation (rho=-0.441, p<0.001) with MoCA scores. By combining four key speech parameters—total pause time, speech-to-pause ratio, DTW-based similarity, and the ratio of extra words—we achieved optimal discriminative performance. Precision and balanced accuracy scores were determined to be 84.3 ± 1.5% and 75.0 ± 1.4%, respectively. **Discussion:** Speech data analysis is a promising avenue for distinguishing individuals with cognitive impairment from cognitively intact, age-matched older adults. Specifically, parameters related to timing and similarity within speech data offer valuable insights into the severity of cognitive impairment. These findings substantiate the premise that speech analysis can potentially serve as a valuable digital biomarker, enabling early detection and continuous monitoring of cognitive impairment. The implications of such advancements extend to the realm of dementia care and management, offering novel avenues for research and targeted interventions, as well as in clinical trials. **Key words:** Dementia, Digital Health, speech, cognitive impairment, remote patient monitoring. **Disclosures:** Adonay Nunes Sastre has received personal compensation for serving as an employee of BioSensics. Ashkan Vaziri has received personal compensation for serving as an employee of BioSensics. The authors declared no competing interests. Bijan Najafi has received personal compensation in the range of $100,000-$499,999 for serving as a Consultant for BioSensics. Bijan Najafi has received personal compensation in the range of $5,000-$9,999 for serving as a Consultant for Mölnlycke Health Care. Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. Bijan Najafi has received intellectual property interests from a discovery or technology relating to health care. **Funding:** Research reported in this publication was supported by the National Institute On Aging of the National Institutes of Health under Award Number R44AG080861 The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

P127- VALIDATION OF A TICS-M CUTOFF SCORE FOR IDENTIFICATION OF COGNITIVE IMPAIRMENT DURING TELEPHONE PRE-SCREENING ASSESSMENT.

E. Fischer[1] , A. O'connell[2], S. Gaussoin[3], S. Lockhart[1] , S. Craft[1]
(1. Wake Forest School of Medicine, Department of Internal Medicine - Gerontology - Winston-Salem (United States), 2. Wake Forest School of Medicine, Department of Internal Medicine - Gerontology - Winston-Salem (United States) - Winston-Salem (United States), 3. Wake Forest School of Medicine, Department of Biostatistics and Data Science - Winston-Salem (United States))

Background: Successful and timely enrollment into Alzheimer's disease (AD) clinical trials targeting prodromal and preclinical AD necessitates pre-screening participants for cognitive eligibility prior to an in-person screening visit. Distinguishing between those with mild cognitive impairment (MCI) versus normal cognition (NC) is especially challenging, as most with MCI do not have a previous clinical evaluation to determine cognitive status. The modified Telephone Interview for Cognitive Status (TICS-m) is an efficient, accessible method of assessment, but existing research does not provide clear evidence of cutoff scores likely to identify MCI. We used data collected from well-characterized clinical research participants at the Wake Forest Alzheimer's Disease Research Center (ADRC) to determine a reliable TICS-m cutoff score that can distinguish between NC and likely cognitive impairment. **Method:** Participants [N= 368, age 70(8.1), education 15.7(2.5), 64% female, 72% white, 49% normal cognition, TICS-m 35.7(4.7)] complete a phone screen evaluation (PSE), which includes the TICS-m, report of subjective memory concerns, and collection of demographic data. Those who then enroll in the ADRC Clinical Core study complete a clinician interview and physical/neurological exam, neuropsychological battery, and the Clinical Dementia Rating Scale (CDR). An adjudication panel determines a cognitive impression of NC, MCI, or dementia. A variation of the preclinical Alzheimer's cognitive composite (PACC5) was generated from baseline assessments (MMSE, Craft Story recall, Digit Symbol Coding, FCSRT, and category fluency). To compare applicability of a TICS-m cutoff between different methods of cognitive evaluation, a logistic regression was completed for four separate models: (A) consensus panel impression, (B) ≤-1 SD PACC5, (C) ≤-1 SD PACC5 and CDR global score ≥0.5, and (D) ≤-1 SD PACC5 score and ≥1 item endorsed on subjective concerns. All models categorized cognitive status by Impaired (MCI or dementia)/ Not Impaired (NC). Each model included demographics (age, race, sex, education), the TICS-m total score, and five yes/no subjective concern questions. **Results:** The logistic regression analyses showed the TICS-m score was statistically significant as a predictor of impairment (p <0.0001) in all models. Other predictors (family/friends concern, sex, education, self-report concern) were statistically significant (p<0.05) but inconsistent across models. The datasets were partitioned into training and test sets using an 80:20 ratio and classification tree analyses were completed. A TICS-m cutoff score of <35 was the initial determinate for all models, with other variables (family/friends concern, age, sex, education) as subsequent branches mixed across models. Across the models, a TICS-m ≥35 correctly classified participants (72% - 93%) as not impaired. The consensus panel impression (Model A) is often held as the gold-standard, yet all models achieved comparable results. Model A achieved a misclassification rate (MCR) of 0.22 and demonstrated 73.5% sensitivity and 81.8% specificity. Model B (MCR = 0.15, 66.7% sensitivity and 92.9% specificity), Model C (MCR = 0.16, 64.2% sensitivity and 88.9% specificity), and

Model D (MCR = 0.13, 73.7% sensitivity and 91.8% specificity) demonstrated similar results. **Conclusion:** Applying a TICS-m score cutoff of 35 provides an efficient method for identifying participants with likely cognitive impairment versus normal cognition to enable referral to clinical trials. **Key words:** TICS-m, Cognitive Impairment, Prescreening, Classification. **Disclosures:** The authors declared no conflict of interests.

P128- THE PRE-CLINICAL ALZHEIMER'S COGNITIVE COMPOSITE SCORE: INFORMING CLINICAL MEANINGFULNESS THROUGH THE ALZHEIMER'S DISEASE CONTINUUM.

J.D. Doecke[1], M. Cespedes[1], T. Cox[2], R. Shishegar[3], C.J. Fowler[4], S. Rainey-Smith[5,6,7,8], H. Sohrabi[9,10], S. Markovic[9,10], J. Fripp[1], C. Gillis[11], N. Maserejian[11], Y.Y. Lim[12], J. Hassenstab[13,14], P. Maruff[15] *(1. Australian E-Health Research Centre, CSIRO - Herston (Australia), 2. Australian E-Health Research Centre, CSIRO - Canberra (Australia), 3. Australian E-Health Research Centre, CSIRO - Parkville (Australia), 4. The University of Melbourne, The Florey Institute - Parkville (Australia), 5. Centre for Healthy Ageing, Murdoch University - Murdoch (Australia), 6. Australian Alzheimer's Research Foundation - Perth (Australia), 7. University of Western Australia - Perth (Australia), 8. Edith Cowan University, School of Medical and Health Sciences, Centre of Excellence for Alzheimer's Disease Research & Care - Joondalup (Australia), 9. Centre for Healthy Ageing, Health Futures Institute, Murdoch University - Murdoch (Australia), 10. Australian Alzheimer's Research Foundation, Sarich Neuroscience Research Institute - Nedlands (Australia), 11. Biogen - Boston (United States), 12. Turner Institute for Brain and Mental Health, School of Psychological Sciences - Monash (Australia), 13. Knight Alzheimer Disease Research Center, Washington University School of Medicine - St Louis (United States), 14. Department of Neurology, Washington University School of Medicine - St. Louis (United States), 15. Cogstate - Melbourne (Australia))*

Background: Following the trajectory of cognitive decline across pre-clinical, prodromal and dementia stages of Alzheimer's disease (AD), is important for understanding disease progression and treatment efficiency. With prospective cognitive data from international studies converging on strong clinical-pathological models of cognitive change in AD, it now becomes necessary to consider how to utilize such models for guiding clinical decisions including the meaningfulness of cognitive change at different stages of the disease. Here we translate findings from our sigmoid model of cognitive change by aligning participants pre-clinical Alzheimer's cognitive composite (PACC) scores to this disease trajectory model. This model contends decline in cognitive scores passing the model inflection point defines a clinically meaningful change; a criterion that is useful to inform both clinical practice and clinical trial design. **Methods:** Participants classified as cognitively unimpaired (CU), mild cognitive impairment (MCI), or AD-dementia with at least 36 months of follow-up from the Alzheimer's Dementia Onset and Progression in International Cohorts (ADOPIC) study were included. The PACC score, consisting of the California Verbal Learning Test (CVLT), Weschler Logical Memory (LMII), Digit Symbol Coding and the Mini-Mental State Examination (MMSE) was harmonised prior to transformation to fit the sigmoid trajectory. Transformed data for participants were then classified as being cognitively stable (no score passing through the sigmoid inflection point) or having cognitive decline (at least one score past the population sigmoid inflection point. A subset of data with PET Amyloid-β (PET-Aβ) was used for pre-clinical & prodromal specific analyses. Information from participants with AD dementia was used to define the full population sigmoid curve. Participant slopes for the PACC score were assessed across clinical classification, between pre-clinical and prodromal stages, and between APOE ε4 carriers/non-carriers. **Results:** 2,861 participants, including 1774 CU (62%), 864 MCI (30%) and 223 AD (8%) were assessed. Average age was 75.7 years (SD:7.2), 51% were female, 38% carried at least one APOE ε4 allele, and the average years of education was 14.9 (SD:3). PET-Aβ was available for 2,126 (74%) participants. Mean annual rates of change (ARC) for those with cognitive decline (past the sigmoid inflection point) in CU, MCI and AD groups was -0.09 (SD: 0.10), -0.25 (SD: 0.20) and -0.51 (SD: 0.19) respectively compared to those with stable cognition CU -0.003 (SD: 0.05) or with stable MCI -0.01 (SD: 0.05). For pre-clinical disease where cognition was declining, the mean ARC was -0.14 (SD: 0.13) whilst for prodromal this increased to -0.31 (SD: 0.2). Carrying an APOE ε4 allele increased the mean ARC in pre-clinical disease although this was not significant (ε4- -0.12 [SD: 0.11], ε4+ -0.15 [SD: 0.15], p=0.63). The effect was more pronounced for prodromal disease (ε4- -0.28 [SD: 0.20], ε4+ -0.33 [SD: 0.20], p=0.009). **Conclusions:** Using the sigmoid method to investigate cognitive change provided clinically important information on both understanding pre-clinical/prodromal disease, and placement of individuals on the population disease trajectory. Such a model of cognitive change provides a statistically robust criterion for clinical meaningfulness, which does not depend upon clinical disease stage.

P129- AUTOMATED LINGUISTIC METRICS FROM A NOVEL, REMOTE, SMARTPHONE-BASED SELF-ASSESSMENT OF CUED NARRATION AND FREE RECALL CORRELATE WITH BRAIN ATROPHY IN LANGUAGE AND MEMORY NETWORKS IN EARLY ALZHEIMER'S DISEASE.

I.T. Kurniawan[1], M.K. Kosek[2], R.M. Ullmann[1], A.M. Wolfer[1], S. Holiga[1], E.A. Aponte[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. - Basel (Switzerland), 2. Roche Global IT Solution Centre, - Warsaw (Poland))*

Background: The earliest stages of preclinical and overt Alzheimer's disease are associated with changes in language and semantic/episodic memory. Identification and monitoring of these subtle changes require sensitive, reliable and neuroanatomically valid tasks which ideally can be administered remotely at scale. **Objectives:** To determine preliminary psychometric, clinical, and functional neuroanatomic validity of Story Time task (ST), a novel smartphone-based assessment of cued narration and recall, for the early AD spectrum. **Methods:** 123 demographically-matched adults participated in a multi-center study: 31 healthy controls (HC), 31 amyloid PET negative subjective cognitive decline (SCDn), 31 amyloid PET positive SCD (SCDp) and 30 early AD (eAD) participants. Each received a preconfigured smartphone with the AD digital assessments suite (AD-DAS) for unsupervised, at-home testing over a 30-day period, including 9 ST administrations. The ST was developed collaboratively between Oxford University, F. Hoffmann-La Roche Ltd. and Eli Lilly. It instructed participants to narrate a story depicted in cartoon strips out loud (narration), and retell stories immediately and one day later without visual cues (short- and long-delay recall, respectively). The smartphone recorded spoken speech, from which the following metrics were extracted: noun rate, word count and relative speech durations

(i.e, speech to pauses; delayed recall to narration). Test-retest reliabilities were assessed with intra-class correlations (ICC), preliminary clinical validity with regularized ridge regression models predicting Boston Naming Test (BNT) and known-groups validity with proportional odds logistic regression models (POLR). Nominal p-values are reported. Covariates were age, gender, education, study site. High-resolution anatomic, T1-weighted MRIs were processed using a whole-brain voxel-based morphometry (VBM) pipeline to determine regions where ST metrics correlated with brain atrophy (additional covariate: total intracranial volume). Statistical parametric maps were thresholded at $p<0.001$ uncorrected (voxel-level) and family-wise error corrected $p<0.05$ (cluster-level). Cluster peak voxels, t- and FWE-corrected p-values are reported. **Results:** Test-retest reliabilities were mostly in the moderate to good range (ICCs 0.63-0.89). Narration noun rate, and short- and long-delay word counts and relative speech durations correlated with BNT (all adjusted-$R2>0.02$, $p<0.03$). During narration, noun rate differentiated eAD from all other groups (log odds ratio - $LOR>1.05$, $p<0.03$), and word count eAD from HC ($LOR=1.16$, $p<0.03$). At short-delay, noun rate differentiated eAD from all groups ($LOR>1$, $p<0.05$), and word count eAD from SCDp ($LOR=1.4$, $p<0.007$). At long-delay, word count differentiated eAD from both SCD groups ($LOR>1.05$, $p<0.04$). Relative speech durations at both delays differentiated eAD from all groups ($LOR>1.25$, $p<0.02$). Reduced narrative speech correlated with atrophy in the left angular, supramarginal and middle temporal gyri ($x=-57,y=-62,z=24$; $t=4.05$; $p<0.031$) and left cerebellum ($-26,-77,-24$; $t=4.1$; $p<0.016$). Relatively terser short-delay recall correlated with atrophy in language, memory and visual networks including left middle ($-57,-18,-2$; $t=5.47$; $p<0.0001$) and anteromedial temporal lobes ($23,-20,-11$; $t=5.15$; $p<0.031$). Relatively terser long-delay recall correlated with right superior medial frontal lobe atrophy ($10,44,48$; $t=5.71$; $p<0.004$). **Conclusion:** These preliminary findings indicate that remote, smartphone-based assessments of cued speech and free recall may generate reliable and valid estimates of atrophy in language and memory networks in individuals on the early AD spectrum.

P130- CHARACTERISING PROGRESSIVE DECLINE ACROSS MULTIPLE COGNITIVE DOMAINS IN PRECLINICAL ALZHEIMER'S DISEASE. R. Shishegar[1], T. Cox[2], H.R. Sohrabi[3], S. Markovic[3], J. Fripp[4], V. Doré[1], P. Bourgeat[4], J. Hassenstab[5], Y.Y. Lim[6], P. Maruff[7], C.L. Masters[8], J.D. Doecke[8] *(1. Australian E-Health Research Centre, CSIRO - Melbourne (Australia), 2. Australian E-Health Research Centre, CSIRO - Canberra (Australia), 3. Centre for Healthy Ageing, Murdoch University - Murdoch (Australia), 4. Australian E-Health Research Centre, CSIRO - Brisbane (Australia), 5. Department of Psychological and Brain Sciences, Washington University in Saint Louis - Saint Louis (United States), 6. Turner Institute of Brain and Mental Health, School of Psychological Sciences, Monash University - Clayton (Australia), 7. Cogstate Ltd. - Melbourne (Australia), 8. The University of Melbourne, The Florey Institute - Melbourne (Australia))*

Background: In cognitively unimpaired (CU) older adults, preclinical Alzheimer's disease (AD) is defined by the presence of abnormally high amyloid (Ab+), and characterised by a subtle but relentless decline in cognition which ultimately becomes sufficient to meet clinical criteria for symptomatic AD. Additionally, whilst most studies examining cognitive change in preclinical AD have used linear modelling, the rate of cognitive decline from preclinical to symptomatic AD is likely to be non-linear. However, small sample sizes have limited the extent to which non-linear modelling of cognitive change across preclinical through to symptomatic AD has been possible. By harmonizing data across three large cohorts (AIBL, ADNI and OASIS) as part of the Alzheimer's Dementia Onset and Progression in International Cohorts (ADOPIC) effort, there is now the opportunity to challenge current models of cognitive change in AD. This work aims to understand clinically meaningful acceleration of cognitive decline and the temporal ordering of domain specific cognitive decline and identify those markers which represent linear/non-linear change across the complete AD-continuum. **Methods:** Participants (n=2080, 51% female, mean age 73.3 ±6.9, 37% APOE e4 carriers) from the Alzheimer's Dementia Onset and Progression in International Cohorts (ADOPIC) study were included based on having at least one Ab PET scan and three cognitive assessments over 36 months. Data were harmonized using a previously established machine learning algorithm1 to provide five cognitive composite scores: Preclinical Alzheimer Cognitive Composite (PACC), executive function, episodic memory, language, and attention. Linear mixed models (LMM) were used to compute rates of change, for each clinical group (CU, mild cognitive impairment (MCI), AD-dementia). Aβ status was classified as Ab+ (Centiloid >20 CL) or normal (Ab-) at baseline. Participants' individual rates of change for each composite were plotted against their mean score, where a quadratic fit indicated whether the data would align to a sigmoid trajectory. **Results:** LMMs indicated the greatest separation between slopes for CU Ab- and CU Ab+ was seen for PACC (CU Ab- slope: 0.007 [SE: 0.005], CU Ab+ slope: -0.025 [SE 0.006], $p=0.0009$), episodic memory (CU Ab- slope: 0.061 [SE: 0.005], CU Ab+ slope: 0.03 [SE 0.006], $p=0.004$), language (CU Ab- slope: 0.004 [SE: 0.006], CU Ab+ slope: -0.003 [SE 0.007], $p=0.03$), whilst for executive function (CU Ab- slope: -0.001 [SE: 0.005], CU Ab+ slope: -0.020 [SE 0.006], $p=0.08$), and attention (CU Ab- slope: 0.005 [SE: 0.004], CU Ab+ slope: -0.001 [SE 0.005], $p=0.98$)), the separation was not significant ($p>0.05$). Three composite scores including PACC, language and executive function were identified as suitable for fitting to a sigmoid trajectory. Composite score for episodic memory and attention were found to have a slow linear trajectory rather than a sigmoid trajectory. **Conclusion:** In preclinical AD, clinically meaningful decline was seen in the PACC score, and in episodic memory and language domains. Whilst PACC and language demonstrated a fit to a sigmoid trajectory, episodic memory did not. Information from assessment of large datasets serves to add to our understanding of clinical progression, thereby informing clinical trial endpoints and prognostic practice in clinical settings. **Disclosures:** The authors declare no competing interests. **References:** 1. Shishegar R, et al. Sci Rep. 2021 Dec 10;11(1):23788. doi: 10.1038/s41598-021-02827-6.

P131- DO ALZHEIMER'S RISK GENES ALSO PREDICT COGNITIVE DECLINE? S. Fernandez[1,2], R. Shishegar[3], P. Maruff[4,5], C. Masters[4], V. Villemagne[6,7], T. Cox[3], V. Doré[3,7], T. Porter[1,2], S. Laws[1,2] *(1. Centre for Precision Health, Edith Cowan University - Perth (Australia), 2. Collaborative Genomics and Translation Group, School of Medical and Health Sciences, Edith Cowan University - Perth (Australia), 3. Australian E-Health Research Centre, CSIRO - Melbourne (Australia), 4. Florey Institute of Neuroscience and Mental Health, The University of Melbourne - Melbourne (Australia), 5. Cogstate Ltd - Melbourne (Australia), 6. Department of Psychiatry, University of Pittsburgh, - Pittsburgh (United States), 7. Department of Molecular Imaging and Therapy and Centre for PET, Austin Health, - Melbourne (Australia))*

Background: Background: It is a primary goal for novel Alzheimer's disease (AD) therapeutics to slow the progression of clinical symptoms and thus preserve quality of life and independent function for those affected. However, it is difficult for clinical trials to demonstrate evidence for such an effect in the current setting of poorly understood heterogeneity in rates of change over the disease course. The identification of contributing factors will facilitate more appropriate partitioning of variance in statistical models and thus enhance the signal of effective therapeutics. Here, individual genetics are an intuitive but underexplored candidate. While many AD risk genes have now been identified, early evidence suggests the same genes are not associated with rates of cognitive decline. **Methods:** Participants were drawn from the Australian Imaging Biomarkers and Lifestyle (AIBL), Alzheimer's Disease Neuroimaging Initiative (ADNI), and Open Access Series of Imaging Studies (OASIS) cohorts (n = 2,755) and split into discovery GWAS (n = 2,755) and PRS development validation (n = 1,397) datasets. The performance of AD risk polygenic risk scores (PRSAD) was compared against that of PRSs directly informed by genome wide association studies (GWAS) of cross-sectional (PRScog-cs) and longitudinal cognition (PRScog-long) in their predictive utility for the same cognitive phenotypes in the independent validation dataset. Cognition was measured with a verbal episodic memory cognitive composite previously associated with AD risk and progression. All analyses were covaried for age, sex, education years, the top genetic principal component, and diagnosis (where appropriate) and were performed first across a pooled cohort and then by diagnostic classification substrata (cognitively unimpaired [CU], mildly cognitively impaired [MCI], and AD). **Results:** For all groups, cross-sectional cognitive performance was better predicted by PRScog-cs than PRSAD and there was little overlap across the genes represented in either PRS. While this effect was of little practical significance for most analyses (max R2 = 0.01), PRScog-cs in the MCI group analysis achieved an R2 of 0.11 in an independent validation set. Of 60 validated variants selected in this PRS, 58 came from the Mediator of DNA Damage Checkpoint 1 (MDC1) gene for which there exists evidence of a role in microtubule stability. Follow up analyses showed a genome wide association for these variants in longitudinal hippocampal volume in MCI participants only, and a nominal association with longitudinal cognition also in MCI participants only. MDC1 did not contribute to PRSAD. Neither PRSAD nor PRScog-long was able to predict longitudinal cognition in any group. **Conclusions:** These results highlight the difficulty of longitudinal cognition as a phenotype, and we discuss the development of alternative approaches to build more advanced statistical models of cognitive change that may improve the sensitivity for future genetic analyses in this setting. We also present evidence for a potential role of MDC1 in disease progression at the MCI stage that appears independent of global AD risk. **Key words:** Cognitive decline, genetics, polygenic risk score, statistical modelling. **Disclosures:** The authors declared no competing interests

P132- FORECASTING FUTURE DEMENTIA RISK USING A DIGITAL CLOCK DRAWING ASSESSMENT IN AN AFRICAN AMERICAN POPULATION. J. Pobst[1], S. Tobyne[1], A. Jannati[1,2], R. Banks[1,3], D. Libon[1,4], R. Swenson[1,5], M. Lamar[6,7], L. Barnes[6,7,8], D. Bates[1], J. Showalter[1], A. Pascual-Leone[1,2,9] *(1. Linus Health, Inc. - Boston, Massachusetts (United States), 2. Department of Neurology, Harvard Medical School - Cambridge, Massachusetts (United States), 3. Michigan State University - East Lansing, Michigan (United States), 4. Rowan University - Stratford, New Jersey (United States), 5. University of North Dakota School of Medicine and Health Sciences - Fargo, North Dakota (United States), 6. Rush Alzheimer's Disease Center - Chicago, Illinois (United States), 7. Department of Psychiatry and Behavioral Sciences, Rush University Medical Center - Chicago, Illinois (United States), 8. Department of Neurological Sciences, Rush University Medical Center - Chicago, Illinois (United States), 9. Hinda and Arthur Marcus Institute for Aging Research, Deanna and Sidney Wolk Center of Memory Health, Hebrew Senior Life - Boston, Massachusetts (United States))*

Background: Early detection of elevated risk of developing Alzheimer's Disease (AD) and related dementia (ADRD) provides patients, caregivers, and clinicians the opportunity to plan ahead and intervene early to improve cognitive health trajectories. In addition, early detection could assist researchers to improve group selection and assignment in clinical trials. Despite the clear value of early detection, existing solutions are time-consuming and lack the sensitivity required to identify presymptomatic individuals at risk for future disease. Recently, a commercial version of the well established digital clock drawing assessment, the DCTclock™ (Linus Health, Boston, MA), was introduced and has demonstrated good predictive power for detecting both general cognitive impairment (CI) and the presence of AD pathology in cognitive unimpaired populations. **Methods:** Longitudinal data from 1161 participants (median age=72.4±6.4, median years of education=14±3.4, 78% female, 99% African American) were gathered as part of the Minority Aging Research Study (MARS) and the Rush Alzheimer's Disease Center (RADC) Clinical Core. Participants were followed longitudinally for up to 18 years (median=7 years). At each yearly visit, participants completed a full clinical evaluation and an extensive neuropsychological assessment protocol, including DCTclock™. Participants were diagnosed for probable or possible AD dementia or non-AD dementia according to the NINCDS/ADRDA criteria. Participants were also grouped into three CI groups based on patterns of performance on neuropsychological testing. Statistical comparisons were used to determine whether DCTclock™ summary scores at baseline were associated with future conversion to dementia or CI. Survival analyses were conducted to quantify differences in cognitive health trajectories (time to dementia or CI) based on baseline DCTclock™ performance. **Results:** DCTclock summary scores (range 0-100) for participants that converted to dementia within four years were significantly lower from those that remained unimpaired (mean DCTclock™ score=39.1±23.5 vs 61.1±19.6, p<0.0001, Kolmogorov–Smirnov test). dCDT performance for participants who experienced any cognitive impairment within four years were also significantly lower (mean DCTclock™ score=48.2±23.8 vs. 61.1±19.6, p=0.023). Significant differences for conversion to

dementia or cognitive impairment were also observed at three, two, and one years to conversion (all p<0.001). Survival analyses showed clear, statistically significant differences in cognitive health trajectory over five years when baseline DCTclock™ scores were less than 60 for participants who converted to dementia (log rank test, $\chi2=7.33$, $p=0.007$) or cognitively impaired ($p=0.001$, $\chi2=10.8$) compared to participants with a baseline DCTclock™ score greater than 75. **Conclusion:** This work demonstrates the potential of DCTclock™ to predict an elevated risk of developing cognitive impairment or dementia up to five years in the future. Forecasting future risk to motivate behavioral interventions to mitigate risk, identifying patients for disease modifying treatments, and screening participants for enrollment in clinical trials for preventative treatments could be enhanced by leveraging digital assessment to capture previously unattainable behavior. Importantly, these results were derived from a sample of nearly 100% African Americans - a historically underrepresented population in ADRC research. **Key words:** early detection, forecasting, dementia, digital cognitive assessment. **Disclosures:** Jeff Pobst, Sean Tobyne, Ali Jannati, Russell Banks, David Bates, John Showalter, and Álvaro Pascual-Leone receive salary from Linus Health. Alvaro Pascual-Leone serves as a paid member of the scientific advisory boards for Neuroelectrics, Magstim Inc., TetraNeuron, Skin2Neuron, MedRhythms, and Hearts Radiant. All other authors declared no competing interests. **References:** Barnes LL, Shah RC, Aggarwal NT, Bennett DA, Schneider JA. The Minority Aging Research Study: ongoing efforts to obtain brain donation in African Americans without dementia. Curr Alzheimer Res. 2012 Jul;9(6):734-45. doi: 10.2174/156720512801322627. PMID: 22471868; PMCID: PMC3409294. Souillard-Mandar W, Penney D, Schaible B, Pascual-Leone A, Au R and Davis R (2021) DCTclock: Clinically-Interpretable and Automated Artificial Intelligence Analysis of Drawing Behavior for Capturing Cognition. Front. Digit. Health 3:750661. doi: 10.3389/fdgth.2021.750661. Souillard-Mandar, W., Davis, R., Rudin, C. et al. Learning classification models of cognitive conditions from subtle behaviors in the digital Clock Drawing Test. Mach Learn 102, 393–441 (2016). https://doi.org/10.1007/s10994-015-5529-5

P133- BRIDGING THE ASSESSMENT GAP: NEWLY DEVELOPED NEUROPSYCHIATRIC COGNITIVE ASSESSMENTS ON THE COGNIVUE® PLATFORM SHOW STRONG CORRELATION WITH TRADITIONAL GOLD STANDARD TESTS.

J. Galvin[1] *(1. University of Miami Comprehensive Center for Brain Health - Miami (United States))*

Background: Many tools for assessing decline in cognitive function have limited utility due to issues of accuracy, testing bias [1], and uptake among clinicians [2]. Cognivue is an FDA-cleared cognitive assessment device based on modern cognitive neuroscience, that allows clinicians and patients to move beyond the questions and answers approach of traditional cognitive tests. The automated Cognivue technology utilizes adaptive psychophysics and assesses the patient's motor skills and visual acuity, eliminating biases that can be found in common paper & pencil (or paper/pencil on an iPad) cognitive testing mechanisms. Cognivue developed and adapted five additional gold-standard neuropsychiatric tests that were added to the Cognivue testing platform to provide a more tailored approach to patient testing. **Methods:** This was a multi-site, validity and reliability study that enrolled 1,575 subjects at 14 study sites throughout the United States. Demographic information including age, sex, race, ethnicity, and education was captured and used to ensure a diverse representation of study subjects. Subjects were randomized for order of testing at each study site to complete six gold-standard neuropsychiatric cognitive tests adapted by Cognivue on the Cognivue platform; 1) Gating/ Gaiting, 2) Reaction Time (Auditory & Visual), 3) Digit Span (Auditory & Visual), 4) Stroop (Acoustic Amplitude & Color Word), 5) Cued Visual Go-No, and 6) Delayed Recall. Analyses included: regression analyses for agreement and retest reliability, rank linear regression, bivariate correlation analysis and factor analysis for psychometric comparisons. **Results:** Our study aimed to investigate the correlation between the Cognivue suite of newly developed cognitive assessments on the Cognivue platform and five traditional gold standard tests of cognitive function. The study included a sample of 1,575 participants who underwent both the Cognivue assessments and the six gold-standard neuropsychiatry tests. The results revealed a remarkably high correlation between the Cognivue suite of assessments and the traditional gold standard tests. This strong correlation indicates a robust relationship and demonstrates the reliability and validity of the Cognivue platform in measuring cognitive performance. **Conclusion:** Our study demonstrated that the newly developed neuropsychiatric cognitive assessments implemented on the Cognivue platform exhibit a high level of correlation with traditional gold standard tests. validate the effectiveness and reliability of the Cognivue platform in accurately measuring cognitive performance in individuals, independent of age, race, ethnicity, sex, or education. The high correlation supports the potential of the newly developed gold-standard correlated assessments to serve as an additional valuable tool for clinicians and researchers in evaluating cognitive function and monitoring treatment outcomes. The integration of these innovative assessments into clinical practice has the potential to enhance diagnostic accuracy, improve treatment planning, and optimize patient care [3]. **Key words:** Digital Assessment, Cognition, Biomarker. **Clinical Trial Registry:** NCT05712005. Data Deposition: https://clinicaltrials.gov/ct2/show/NCT05712005. **Disclosures:** James Galvin is a scientific consultant for Cognivue. Joel Raskin is a scientific Consultant for Cognivue. The additional authors claim no competing interests. **References:** 1. Ranson, J, et al. Neurol Clin Pract 2019, 9 (2) 109-117; DOI: 10.1212/CPJ.0000000000000566; 2. Gorodeski, E, et al. Clinical Cardiology 2019, 43 (2) 179 – 186; https://doi.org/10.1002/clc.23318 3. Mattke, S, et al. Alzheimer's Dement. 2023; 1- 8. https://doi.org/10.1002/alz.13051

P134- EFFICIENT AND AUTOMATED COGNITIVE PRE-SCREENING FOR CLINICAL TRIALS USING THE MONTREAL COGNITIVE ASSESSMENT (MOCA) XPRESSO TOOL AND AUTOMATED REPORT.

S. Klil-Drori[1], K. Bodenstein[2], L. Kojok[2], S.M. Sun[3], Y. Ghantous[2], Z. Nasreddine[2] *(1. McGill University - Montreal, QC (Canada), 2. MoCA Cognition Clinic and Institute - Montreal, QC (Canada), 3. Harvard University - Cambridge, MA (United States))*

Introduction: Clinical trials on Alzheimer's disease (AD) require screening many patients in search of a specific population with a relatively narrow range of cognitive scoring. The inclusion criteria for cognitive scoring in most clinical trials for AD encompass the mild cognitive impairment (MCI) to mild dementia spectrum. However, screening for the specific range of cognitive scores is time-consuming, costly, and requires trained staff. Therefore, a brief self-administered cognitive pre-screening tool with automated results may easily identify

the relevant population and provide efficient screening. **Methods:** We recently developed the MoCA-XpressO: a brief self-administered cognitive pre-screening tool for the general public that includes an automated report of the test results. The MoCA-XpressO is a novel screening tool that is different than the classic MoCA test. It includes different gaming tasks that evaluate 3 cognitive domains: memory task, logical task (evaluation of executive functions), and processing speed. The MoCA-XpressO was validated compared to the digital MoCA test (version 8.1) as a gold standard in a crossover validation study. A logistic regression model was built, and the accuracy of the model was evaluated by the sensitivity, specificity, and area under the Receiver Operating Characteristic (ROC) curve. The automated report for the results of the MoCA-XpressO was designed to facilitate screening for clinical trials on AD: the results are presented on a scale according to each trial's specific inclusion and exclusion cognitive criteria. **Results:** The MoCA-XpressO pre-screening tool evaluates 3 cognitive domains: memory, executive functions, and processing speed. Analysis of the MoCA-XpressO validation study compared to the digital MoCA (n=88) showed a strong association between: (1) MoCA Memory Index Score (MIS) and MoCA-XpressO memory task score (p-values<.001); (2) MoCA Executive Index Score and MoCA-XpressO logical task score (p-values<.03); and (3) total scores of the classic MoCA test and MoCA-XpressO (p-values<.007). The Area Under the ROC Curve (AUC) for logistic regression showed sensitivity of 91.3%with MoCA-XpressO cutoff score of 0.31, and specificity of 90.5% for 0.59 as the MoCA-XpressO cutoff score. The MoCA-XpressO automated report provides rapid interpretation of the results, including: (1) Score of the MoCA-XpressO; (2) Processing speed; and (3) Probability to meet a specific range of the cognitive inclusion or exclusion criteria for the clinical trial. The automated report indicates if the patient's cognitive scores are likely to: (a) meet the inclusion criteria; (b) meet the exclusion criteria below the cognitive threshold; or (c) meet exclusion criteria above the cognitive threshold. The latter is of significant importance as it allows identifying the population that may meet inclusion criteria in the future and could be re-screened after >3 months. **Conclusion:** The MoCA-XpressO is a brief cognitive self-administered tool that allows efficient pre-screening for clinical trials on AD: it is strongly predictive of the standard MoCA score and provides a rapid automated report of the results designed specifically to present the probability of meeting the study's inclusion and exclusion criteria. Moreover, differentiating exclusion criteria below the cognitive threshold compared to above the cognitive threshold allows continuous follow-up for patients who may meet inclusion criteria in the future. **Key words:** cognitive screening, self-assessment, screening tool, automated report. **Clinical Trial Registry:** NCT05879562 https://clinicaltrials.gov/. **Data Deposition:** N/A. **Disclosures:** Dr. Nasreddine is the Copyright owner of MoCA Test and received funding for clinical trials and advisory board from Lilly, Biogen, Eisai. Dr. Ghantous is VP for Medical Affairs at MoCA Cognition. Sivan Klil-Drori, Katie Bodenstein and Lara Kojok are part-time employees at MoCA Cognition. **References:** 1. Nasreddine, Z. et al. J. Am. Geriatr. Soc. 53, 695–699 (2005). 2. Julayanont, P., et al. J. Am. Geriatr. Soc. 62, 679–684 (2014). 3. Borson, S., et al. Int. J. Geriatr. Psychiatry 21, 349–355 (2006). 4. Riley McCarten, J. et al. J. Am. Geriatr. Soc. 60, 210–217 (2012).

P135- ATTACHING CLINICAL MEANINGFULNESS TO CDR-SB SCORE. D. Digregorio[1], C. Randolph[1,2], S. Negash[1], E. Jacobs[1], R. Blattner[1] *(1. WCG - Princeton (United States), 2. Loyola University Medical Center - Chicago (United States))*

Background: The Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) is the sole primary endpoint in most clinical trials of early symptomatic Alzheimer's Disease (AD) and has been deployed as such in recent trials of monoclonal antibodies against beta amyloid that have received FDA approval. These approvals have put a renewed spotlight on what is meaningful change and measuring the rate of progression of disease. The CDR is not a tool that is commonly used in clinical practice, however, and there is some lack of clarity as to what relatively small differences in CDR-SB score changes between treatment and placebo arms in clinical trials translate to in terms of clinical meaningfulness for study participants and families. **Methods:** To explore this, we examined the functional status of participants as measured by the Amsterdam Independent Activities of Daily Living (A-IADL) scale in trials where the CDR and the A-IADL scale were administered at the same visits. We collated data from 7 secondary prevention and early symptomatic trials involving AD biomarker-positive participants. **Results:** A total of 6,452 pairs of CDR-SB and A-IADL scores were obtained, with CDR-SB scores ranging from 0-6. In addition to plotting the relationship between the CDR-SB and the A-IADL total scores, we identified specific functional items that were lost at each CDR-SB stepwise increase in score. **Conclusion:** As we approach the advent of approved FDA treatment for early symptomatic AD there is a growing need for real world data on the meaningfulness of the change on statistical analyses for what would constitute meaningful change. We believe the results presented showing the relationship between loss of function as a study participant progresses in the stages of their disease provide a more concrete, "real-world" understanding the association between CDR-SB scores and functional status in AD trial participants. **Key words:** Alzheimer's Disease, Meaningful Change, Clinical Dementia Rating Scale- Sum of Boxes, Amsterdam Independent Activities of Daily Living scale. **Disclosures:** Authors are employees of WCG. **References:** Morris JC. The clinical dementia rating (CDR): current version and scoring rules. Neurology 1993;43:2412-4. Sikkes SA, de Lange-de Klerk ES, Pijnenburg YA, et al. A new informant-based questionnaire for instrumental activities of daily living in dementia. Alzheimer's Dement. 2012;8(6):536-43. U.S. Food and Drug Administration (FDA). FDA grants accelerated approval for Alzheimer's drug. FDA News Release; 2021. Available from: https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug. Accessed November 14, 2021.

P136- ANALYSIS OF AB(1-42) OLIGOMERS BY CYCLIC ION MOBILITY SPECTROMETRY IN SPIKED HUMAN CEREBROSPINAL FLUID. M. Vlk[1], J. Hey[2], W. Korfmacher[2], A. Muck[3], M. Hubálek[1], J. Cvačka[1] *(1. Institute of Organic Chemistry and Biochemistry of the CAS, Mass Spectrometry Group - Prague (Czech Republic), 2. Alzheon - Framingham (United States), 3. Waters Corporation, Analytical Professional Services EMEA - Wilmslow (United Kingdom))*

Background: Amyloid beta (Aβ) peptide aggregation into soluble oligomers and further formation of fibrils and plaques are hallmarks of Alzheimer's disease (AD). Studies have shown that the toxic effects of soluble oligomers on synaptic function

play a crucial role in AD pathogenesis. Understanding the dynamics of Aβ oligomer formation and its quantification can enable the study of disease progression, development of potential treatments, and early diagnosis. Our work focuses on detection of soluble Aβ(1-42) oligomers in water and Aβ(1-42) spiked CSF utilizing state-of-the-art cyclic ion mobility mass spectrometry (cIM-MS) system. Model samples were used to optimise the instrumental parameters to enhance the transmission of oligomer ions and ion mobility separation of the isobaric monomer and oligomer ions. The goal of this research is to develop a quantitative analytical assay for the spectrum amyloid Ab oligomers in human CSF. **Methods:** Samples of Aβ(1-42) in water were incubated to enhance the generation of soluble oligomers and used for cIM-MS method optimization. Samples of Aβ(1-42) spiked hCSF were pre-fractionated using weight cut-off (MWCO) sample filters. Ion mobility mass spectrometry detection was performed using a SELECT SERIES Cyclic IMS instrument (Waters) with a static nanoelectrospray ion source operated with in-house pulled borosilicate emitters. **Results:** The optimised cIM-MS method was used to analyse the aqueous and hCSF Aβ(1-42) samples. Oligomer species ranging from dimers to dodecamers (9 – 54 kDa) were detected along with the monomer. A two-step sample preparation method was applied to the Aβ(1-42) spiked hCSF samples. **Conclusion:** Our results show that Cyclic IMS can be employed to detect, characterise, and measure soluble Aβ(1-42) oligomeric species in aqueous and hCSF in vitro. Optimisation of instrumental parameters and the application of two-step sample preparation and pre-fractionation method enabled the detection of Aβ(1-42) oligomers in aqueous samples as well as in spiked hCSF samples.

P137- SEX DIFFERENCES IN PREDICTING PROGRESSION IN COGNITIVELY UNIMPAIRED ADNI PARTICIPANTS USING COGNITIVE TEST PERFORMANCEE. A. Diaz[1,2], M.J. Miller[1,2], M. Mila Aloma[1,3], Z. Hausle[1,3], P. Zobel-Thropp[1,3], D. Tosun[3], R. Nosheny[4], L.M. Shaw[5], M.W. Weiner[1,2] *(1. Northern California Institute for Research and Education (NCIRE) - San Francisco (United States), 2. Department of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases - San Francisco (United States), 3. University of California, San Francisco, Department of Radiology and Biomedical Imaging - San Francisco (United States), 4. University of California, San Francisco, Department of Psychiatry and Behavioral Sciences - San Francisco (United States), 5. University of Pennsylvania, Perelman School of Medicine - Pennsylvania (United States))*

Background: As we move into the treatment era for Alzheimer's disease (AD), identifying individuals likely to progress from cognitively unimpaired (CU) to Mild Cognitive Impairment (MCI) or dementia across the AD continuum is critical. Despite previous studies indicating some sex/gender biases in clinical cognitive assessments, which could limit their uniform application and interpretation, these tests remain among the gold standards in clinical diagnosis of AD and are routinely used as inclusion criteria and endpoints in clinical trials [1-6]. The goal of this study was to assess baseline performance on clinical tests predicts progression in clinical diagnosis in the Alzheimer's Disease Neuroimaging Initiative (ADNI) with particular attention to how the sensitivity of these tests varies with self-reported sex. **Methods:** Of 898 ADNI participants (n=389 males; n=509 females) were CU at their baseline visit, 148 (n=79 males; n=69 females) progressed to cognitive impairment (MCI or AD) at a future time point. We analyzed the data in a logistic regression framework to estimate the association between subjects' performance on various cognitive tests, and the odds of disease progression using the AUROC. We further evaluated the performance of each model as a predictor of disease progression. For each cognitive assessment, we compare the performance of a sex-adjusted model that includes sex as a co-variate, a model that includes an interaction between sex and assessment performance, and sex-specific models. ADNI clinical assessments examined include PACC (digit span; trails), CDR-SB, MMSE, ADAS-COG, informant ECog, FAQ, and MOCA. **Results:** Base model (including sex, age, and years of education) showed significant associations between each of these variables and disease progression. The base model produced AUCs of 0.60 for males and 0.66 for females under sex-specific models, and 0.64 in the sex-adjusted model. We found a significant association ($p<0.05$) between performance and disease progression with every clinical test except the MMSE and FAQ. The models that included MMSE and FAQ failed to outperform the base model in AUROC, while the inclusion of any other test resulted in a model with higher AUC in men, but which underperformed the base model in women. This trend of improved predictive performance on the male cohort was particularly notable in models that included PACC (trails male AUC = 0.68; trails female AUC = 0.65) and CDR sum of boxes (male AUC = 0.65; female AUC = 0.65, and the effect was most pronounced with MOCA (male AUC = 0.79; female AUC = 0.70), which also demonstrated the greatest predictive performance for both sexes of any test that we considered. **Conclusions:** In ADNI, clinical assessments show stronger predictive value for risk of clinical progression from CN to MCI/AD for males compared to females, suggesting sex/gender related differences in early clinical presentation of cognitive impairment. This could be influenced by factors like women masking symptoms or a higher verbal cognitive reserve [7,8]. These results raise questions about potential biases in clinical tests or the diagnostic paradigm and may be specific to the ADNI cohort. Regardless, further investigation is warranted for this intriguing initial finding. **Key words:** Clinical assessments, cognitively unimpaired, MCI, sex. **Disclosures:** Diaz – Nothing to declare; Miller – Nothing to declare; Mila Aloma – Nothing to declare; Hausle – Nothing to declare; Zobel-Thropp – Nothing to declare; Tosun – Nothing to declare; Nosheny – Funding to institution from NIH, California Department of Public Health, Genetech Inc. Shaw – Nothing to declare; Weiner – Funding to institution from NIH. **References:** 1. Mielke M.M., Clinical Epidemiology 2014; 6:37-48. DOI: 10.2147/CLEP.S37929; 2. Gerstorf D., The Journals of Gerontology: Series B 2006; 61:245–249. https://doi.org/10.1093/geronb/61.4.P245; 3. Nebel R.A., Alzheimer's & Dementia 2018; 14:1171-1183. https://doi.org/10.1016/j.jalz.2018.04.008; 4. Porsteinsson A.P., J Prev Alzheimers Dis 2021; 8:371–386. https://doi.org/10.14283/jpad.2021.23; 5. Sperling R.A., Sci Transl Med 2014; 6(228):228fs13. doi: 10.1126/scitranslmed.3007941; 6. Rafii M.S., Alzheimers Dement 2023; 19:1227-1233. doi: 10.1002/alz.12748; 7. Sundermann E.E., Neurology 2016; 87:1916-1924. DOI: 10.1212/WNL.0000000000003288; 8. Sundermann E.E., Neurology 2016; 86:1368-1376. DOI: 10.1212/WNL.0000000000002570

LP070- ASSOCIATION OF SPEECH AND LANGUAGE FEATURES WITH BIOMARKERS IN EARLY STAGE ALZHEIMER PATIENTS. A. König[1,2], S. Köhler[3], J. Tröger[1], E. Mallick[1], N. Linz[1], J. Priller[4,5,6,7], M. Donix[8,9], J. Wiltfang[10,11,12], I. Zerr[10,13], D. Düzel[14,15,16], A. Spottke[17,18], F. Brosseron[19], M. Wagner[19,20], A. Ramirez[19,20,21,22], S. Teipel[3,23] *(1. ki:elements GmbH - Saarbrücken (Germany), 2. Cobtek (Cognition-Behaviour-Technology), Université Côte d'Azur - Nice (France), 3. Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Standort Rostock/Greifswald, - Rostock/greifswald (Germany), 4. Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE) - Berlin (Germany), 5. Department of Psychiatry and Psychotherapy, Charitéy - Berlin (Germany), 6. School of Medicine, Technical University of Munich; Department of Psychiatry and Psychotherapy, - Munich (Germany), 7. University of Edinburgh and UK DRI, - Edinburgh (United Kingdom), 8. Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE) - Dresden (Germany), 9. Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden,y. - Dresden (Germany), 10. German Center for Neurodegenerative Diseases (DZNE) - Goettingen (Germany), 11. Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, University of Goettingen y - Goettingn (Germany), 12. Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveirol - Aveiro (Portugal), 13. Department of Neurology, University Medical Center, Georg August University,. - Goettingen (Germany), 14. German Center for Neurodegenerative Diseases (DZNE) - Magdeburg (Germany), 15. Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University - Magdeburg (Germany), 16. Institute of Cognitive Neuroscience, University College London. - London (United Kingdom), 17. German Center for Neurodegenerative Diseases (DZNE) - Bonn (Germany), 18. Department of Neurology, University of Bonn, - Bonn (Germany), 19. German Center for Neurodegenerative Diseases (DZNE) - Bonn (Germany), 20. Department of Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, - Bonn (Germany), 21. Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD) University of Cologne - Cologne (Germany), 22. Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry, University of Cologne, Medical Faculty, - Cologne (Germany), 23. University Medical Center Rostock, - Rostock (Germany))*

Introduction: Future AD trials on new disease modifying drugs will require a shift to very early identification of individuals at risk of dementia. Subtle changes in speech and language are early features of Alzheimer's disease (AD) and consequently, analysing speech performance may be a promising new digital biomarker for detecting AD [1]. Digital markers of language and speech may offer a method for screening of at-risk populations that are at the earliest stages of AD. To this end, a screening battery was developed consisting of speech-based neurocognitive tests (Semantic verbal fluency and Verbal learning test) from which next to classical scores additional features such as temporal clustering, semantic switching or mean utterances are extracted. The automated test performs a remote primary screening using a simple telephone and chatbot technology. The study aims to validate speech biomarkers for identification of individuals with early signs of AD by comparing them to clinical gold standard measures such as neurocognitive tests and biomarker data [2]. **Methods:** Speech samples and clinical data were collected from 93 participants (52% females) from the German DESCRIBE and DELCODE cohorts [3]. 20 participants present a Mild Cognitive Impairment (MCI) and 73 are considered cognitively unimpaired. Spearman rank correlations were performed between the speech biomarkers and the MMSE and CDR scores as well as with CSF p/t-tau and abeta42 levels (only for 29 participants available). Group differences between diagnostic groups were calculated using Mann-Whitney test. **Results:** Only mild to moderate correlations were found with both MMSE score ($r = 0.32$, $p < 0.01$) and CDR score ($r = -0.21$, $p < 0.061$) which may be due to ceiling effects in this early stage population. Correlations were found as well between the TMT B scores and temporal clustering in Semantic Verbal Fuency ($r = 0.43$, $p < 0.01$) as well as in the Verbal learning test ($r = 0.37$, $p < 0.03$). Strongest correlations were found between the speech biomarkers for cognition composite score (ki:e SB-C) and t-tau ($r = 0.62$, $p < 0.001$) and memory related speech features and p-tau ($r = 0.62$, $p < 0.001$). Speech features from the Verbal learning test such as mean utterance distances and temporal clustering correlated significantly with Abeta 42 ($r = - 0.55$, $p < 0.002$). Abeta group comparisons were not significant. **Conclusion:** Strongest associations were found between the speech biomarkers and p-tau and t-tau levels in an early AD stage cohort population. The results are in line with other biomarker findings showing that tau-related pathology contributes to cognitive decline. Results are encouraging and point towards potential application of speech biomarkers in future pharmaceutical research in AD [4]]. **Disclosure:** AK, JT, EM and NL are employed at the company ki:elements. Stefan Teipel served on Advisory Boards of Roche, Eisai, and Biogen and is member of the Independent Data Safety and Monitoring Board of the Study ENVISION (Biogen). All other authors declare no competing interests. **References:** 1. de la Fuente Garcia S, Ritchie CW, Luz S. Artificial Intelligence, Speech, and Language Processing Approaches to Monitoring Alzheimer's Disease: A Systematic Review. Journal of Alzheimer's disease: JAD. 2020;78(4):1547-74; DOI: 10.3233/JAD-200888. 2. König A, Linz N, Baykara E, Tröger J, Ritchie C, Saunders S, Teipel S, Köhler S, Sánchez-Benavides G, Grau-Rivera O, Gispert JD, Palmqvist S, Tideman P, Hansson O. Screening over Speech in Unselected Populations for Clinical Trials in AD (PROSPECT-AD): Study Design and Protocol. J Prev Alzheimers Dis. 2023;10(2):314-321. doi: 10.14283/jpad.2023.11. PMID: 36946458; PMCID: PMC9851094. 3. Jessen, F., Spottke, A., Boecker, H. et al. Design and first baseline data of the DZNE multicenter observational study on predementia Alzheimer's disease (DELCODE). Alz Res Therapy 10, 15 (2018). https://doi.org/10.1186/s13195-017-0314-2. 4. Boccalini C, Ribaldi F, Hristovska I, Arnone A, Peretti DE, Mu L, Scheffler M, Perani D, Frisoni GB, Garibotto V. The impact of tau deposition and hypometabolism on cognitive impairment and longitudinal cognitive decline. Alzheimers Dement. 2023 Aug 9. doi: 10.1002/alz.13355. Epub ahead of print. PMID: 37555516.

LP071- A BLUEPRINT FOR EARLY DETECTION OF COGNITIVE IMPAIRMENT IN PRIMARY CARE SETTINGS. T. Macleod[1] , J. Murray[1] , C. Bielak[2], K. Selzler[1] *(1. Davos Alzheimer's Collaborative Health System Preparedness - Wayne (United States), 2. Bridgeable - Toronto (Canada))*

Background: With more than 55 million people worldwide currently living with Alzheimer's or other forms of dementia [1], healthcare systems worldwide are not prepared to care for today's Alzheimer's patients or the growing wave of patients to come. There is insufficient evidence on how to best evaluate the impact of novel interventions in real-world settings. Classic studies indicate that it takes 17–20 years to

get clinical innovations into practice; moreover, fewer than 50% of clinical innovations ever make it into general usage [2]. The goal of Davos Alzheimer's Collaborative Healthcare System Preparedness (DAC-SP) is to catalyze global healthcare system transformation that allows Alzheimer's patients quicker access to life-changing innovations and new therapies. DAC-SP uses implementation science to evaluate global pilot programs focused on seeding health system change with clear actions and goals aimed at sustainable solutions. The first DAC-SP program focused on early detection of cognitive impairment which is a critical building block for system preparedness including identifying the right patients at the right time for disease-modifying therapies and enrollment in clinical trials. The learnings fromt this program were synthesized into a practical, digital blueprint designed as an enduring resource for other healthcare systems seeking to adopt best practices for modernizing Alzheimer's care. **Methods:** The DAC-SP Early Detection Program was initiated in 2021 in seven flagship healthcare systems across six countries including Brazil, Jamaica, Japan, Mexico, Scotland, and two sites in the United States. The goal was to increase early detection of cognitive impairment in primary care settings [3]. The program implemented innovative screening tools including a digital cognitive assessment (DCA) and a blood-based biomarker (BBM) test for Alzheimer's disease pathology in a non-specialty setting. Over the past 2 years, leaders from each flagship site formed a Community of Practice (CoP), which met regularly to discuss operational and clinical challenges, collaborate on solutions, and co-design the digital blueprint based on the learnings from their respective studies. Data was collated from these facilitated CoP meetings as well as interviews and workshops with site leaders. **Results:** The blueprint synthesizes key learnings, insights, and resources captured from the CoP. It provides field-tested implementation strategies, key tasks and resources required to implement those strategies, and solutions to common bottlenecks in an accessible and dynamic digital platform. The blueprint was informed by rigorous cross-site implementation evaluation of the program and was co-designed using human-centered design best practices to ensure the material is highly usable and actionable. Although every healthcare system is different, the blueprint allows users to leverage experiences from others so new innovations and therapies can be applied more efficiently in clinical practice. **Conclusions:** Establishing an early detection program for cognitive impairment is a valuable step in supporting system readiness while providing much needed screening and care for patients and their families. Alzheimer's patients and their families do not have 17-20 years to wait for research to reach clinical practice. This digital blueprint provides an operational roadmap that can be adopted by other healthcare systems to expedite the transformation of the Alzheimer's care pathway. **Key words:** early detection, cognitive impairment, implementation science. **References:** 1. Alzheimer's Disease International (ADI) Dementia Facts and Figures. Accessed Sept 2023. 2. Bauer, M. and Kirchner, J. Psychiatry Research. 2020; Volume 283. 3. Ball, D. et al. Alzheimer's Dement. 2023; 19: 1568– 1578.

LP072- IMPLEMENTING COGNITIVE ASSESSMENT AND RETISPEC RETINAL SCREENING IN COMMUNITY-BASED SETTINGS: ENHANCING EARLY DETECTION OF ALZHEIMER'S DISEASE. S. Cohen[1], A. Kurzman[2,3,4], J. Giordano[2], R. Naureen[2], A. Hansen[1], M. Martinez[1], M. Bietenhader[2], N. Sohbati[5], N. Abdulla[6], C. Cameron[7], S. Estreicher[7], S. Semwel[7], C. Bornbaum[2] *(1. Toronto Memory Program - Toronto (Canada), 2. RetiSpec, Inc. - Toronto (Canada), 3. University of California, Irvine - Irvine (United States), 4. Davos Alzheimers Collaborative - Philadelphia (United States), 5. Victoria Village Optometry - Toronto (Canada), 6. Summerhill Optometry - Toronto (Canada), 7. Alzheimer Society of Toronto - Toronto (Canada))*

Background: Canada faces a critical need to increase screening rates for Alzheimer's disease (AD) given anticipated new treatments for AD. In Ontario, primary care providers (PCPs) are the gatekeepers to medical care; however, primary care settings are not equipped to effectively assess cognition resulting in significant under-diagnosis of AD. This study aimed to assess the feasibility of a novel, community-based AD screening program to increase rates of cognitive and retinal assessments. Primary and secondary endpoints were to increase rates of assessments performed and have 10% of all referrals for assessments originate from optometry, respectively. **Methods:** An observational study assessed the utility of leveraging community-based settings to increase rates of cognitive assessment (conducted by Alzheimer Society social workers) and RetiSpec's AI-based eye test to detect biologic signatures of AD. Eligible participants were adults ages ≥55 years with self-reported memory concerns. Screening occurred via either the local Alzheimer Society chapter for cognitive assessment (Boston Naming Test (BNT) and Montreal Cognitive Assessment (MoCA), or BNT and Mini-Mental State Examination (MMSE) plus Clock Drawing Test (CDT), as per education level) or optometry clinic for a RetiSpec scan (bilateral retinal images using a standard fundus camera with a hyperspectral sensor, plus a brief survey on scan experience). Cognitive assessment results were shared with the participant's PCP or study-appointed Nurse Practitioner (NP) and a visit to discuss results was facilitated. **Results:** In total, N=916 individuals were screened (60.2% from optometry settings); N=134 participants enrolled with the mean age of 73.8 years (SD=6.9). 63.7% identified as female; self-identified race and ethnicity included: 60.5% White, 16.9% Asian, 5.6% Black, 1.6% Hispanic, and 13.7% Mixed/Other races. N=124 participants received a cognitive assessment: 118 MoCA and 124 BNT assessments were administered with mean scores of 24.7 (SD=3.7) and 13.3 (SD=2.0), respectively. Mean MMSE and CDT scores for n=6 participants were 18.7 (SD=5.7) and 1.2 (SD=1.2), respectively. Individuals enrolled through optometry settings (N=36, 29.0% of enrollment) showed slightly better cognitive results than those entering through the Alzheimer Society (mean MoCA and BNT scores: 25.2 (SD=3.2) and 13.8 (SD=1.7) vs 24.5 (SD=4.0) and 13.1 (SD=2.1), respectively.) To date, 89.5% of participants discussed their cognitive assessment results with a clinician; 39.6% participants consulted the study-appointed NP. 72.6% participants who received a cognitive assessment underwent a RetiSpec scan (n=90); 70.0% completed a post-scan survey. Survey results showed that participants had a positive experience with the eye scan (4.2/5, SD=1.3) and were interested in sharing the scan results with their PCP (5.0/5; SD=0.0). Cognitive screening assessments and hyperspectral retinal scans were integrated into existing community workflows; endpoint 1 was met with 13.8% cognitive

assessments/month compared to 1.8/month in the 12-month pre-study period. Endpoint 2 was met with 29.0% of individuals screened originating from optometry clinics. **Conclusions:** Utilizing community-based settings, including optometry clinics and Alzheimer Society social workers, demonstrates a promising approach to AD screening. Technology to evaluate amyloid status that leverages existing imaging infrastructure, including RetiSpec's AI-based eye exam, may offer a pragmatic, affordable, and scalable way to increase AD screening rates via optometry settings.

LP073- CONCURRENT DETECTION OF COGNITIVE IMPAIRMENT AND AB PET STATUS WITH A SHORT AI-ENABLED DIGITAL COGNITIVE ASSESSMENT. D. Bates[1], A. Jannati[1,2], K. Thompson[1], C. Toro-Serey[1], J. Gomes-Osman[1,3], R. Banks[1], J. Pobst[1], C. Higgins[1], J. Showalter[1], S. Tobyne[1], A. Pascual-Leone[1,2,4] *(1. Linus Health, Inc. - Boston (United States), 2. Department of Neurology, Harvard Medical School - Boston (United States), 3. Department of Neurology, University of Miami Miller School of Medicine - Miami (United States), 4. Hinda and Arthur Marcus Institute for Aging Research and Deanna and Sidney Wolk Center for Memory Health, Hebrew SeniorLife - Boston (United States))*

Background: Early identification Alzheimer's disease (AD) is essential to maximize benefits from lifestyle interventions and emerging disease-modifying treatments. Additionally, due to a high screen failure rate and costly prescreening protocols for clinicals trials of AD-modifying treatments, an efficient and cost-effective solution is urgently needed. Critically, it is important to not only establish AD biomarker positivity, but also the level of cognitive impairment. Digital cognitive assessments (DCAs) are often touted as a solution, however they have historically fallen short of expectations in practice. The goal of this study was to compare the accuracy of traditional and digital cognitive assessments and blood biomarkers to identify brain amyloid-beta (Aβ) status and cognitive impairment. We also evaluated the added value of combining cognitive assessments and blood-based biomarkers in predicting brain Aβ status. **Methods:** Bio-Hermes-001, a prospective, cross-sectional study during 2021-2023 comprising 3 visits over an average of 59 days was conducted at ambulatory testing facilities at academic, clinical, and commercial research organizations. 930 participants (>23% racial/ethnic minorities; mean age 72.0±6.7; 56.8% female; Mini-Mental Status Examination (MMSE) score 20-30) were classified as cognitively unimpaired, mild cognitive impairment, or probable Alzheimer's dementia per study protocol. Tests included 18F-florbetapir positron emission tomography (PET); blood biomarkers Aβ42/40, pTau-181, and pTau-217; and cognitive evaluation by MMSE, RAVLT, Cognivue Clarity, and the Digital Clock and Recall (DCR). The performance of each cognitive assessment and blood biomarker alone, or their combinations, to classify cognitive impairment or PET Aβ status was evaluated using the area under the receiver operating characteristic curve (AUC). Superiority, non-inferiority, or inferiority were established by comparing bootstrapped confidence intervals for classification accuracy with a 10% margin. **Results:** 35% of participants were Aβ+ on PET. Aβ42/40, pTau-181, and pTau-217 poorly classified cognitive impairment (AUCs: 0.63; 0.66; 0.72, respectively), but accurately classified Aβ status (AUCs: 0.81; 0.78; 0.89, respectively). The DCR accurately classified cognitive impairment (AUC=0.85) and Aβ status (AUC=0.83). The DCR was superior or non-inferior to MMSE, RAVLT, and Cognivue for cognitive-impairment classification despite having the shortest and most consistent completion time (~3 min), and to Aβ42/40, pTau-181, and pTau-217 for Aβ PET classification. Combination of the DCR with each blood biomarker improved their Aβ predictivity more than any other cognitive test, with DCR–pTau-217 combination being the strongest predictor (AUC=0.91). **Conclusions:** Blood-based biomarkers and traditional cognitive assessments alone cannot accurately assess both the cognitive consequences and pathological substrates of AD. However, the DCR achieved success in both areas. Moreover, the DCR added value to blood biomarkers in predicting brain Aβ status. Digital cognitive assessments that leverage AI process metrics, such as the DCR, present opportunities for cost-effective integration into clinical trial pre-screening to decrease high screen-failure rates and in clinical workflows to ensure the most suitable candidates for disease-modifying treatments are prioritized for specialist referral.

LP075- A PILOT TEST TO EXAMINE THE UTILITY OF THE MONTREAL COGNITIVE ASSESSMENT (MOCA) IN PREDICTING REPEATABLE BATTERY FOR THE ASSESSMENT OF NEUROPSYCHOLOGICAL STATUS (RBANS) SCORE FOR ELIGIBILITY IN ALZHEIMER'S DISEASE (AD) TRIALS. E. Sosa[1], J. Mitolo[1], T. Parnitvithikul[1], J. Serrano-Sanchez[1], C. Karmar[1] *(1. Irvine Clinical Research - Irvine (United States))*

Background: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a widely used instrument to assess cognitive decline. The RBANS is a validated measure that has demonstrated diagnostic accuracy across different populations [1]. Studies have found that individuals with Alzheimer's Disease (AD) perform most poorly on the delayed memory index (DMI) of the assessment [2]. A DMI score of ≤85 is used as a key inclusion criterion in some AD clinical trials [3]. Therefore, efforts are needed to better identify qualifiable participants who would meet this DMI criterion. The current research represents an initial test of the utility of the Montreal Cognitive Assessment (MoCA) in predicting eligibility based on RBANS DMI scores. Prior research has revealed significant correlations between total MoCA and RBANS scores [4]. This research expands on prior works by including examinations of the total, delayed recall, and memory index (MIS) scores. MIS is calculated by assigning 3 points for the number of words remembered on free delayed recall, 2 points for category cued recall, and 1 point for multiple choice cued recall. This domain specific score has been used to predict AD diagnosis [5] and can provide valuable insight on participant selection. **Methods:** Participants were administered the MoCA as part of a clinical trial pre-qualification process. Total (N = 37), delayed recall (N = 40), and MIS (N = 29) scores were compared with RBANS DMI scores for those who proceeded to screen for trials. A series of analyses were conducted to examine the relationship between MoCA (total, delayed recall, and memory index) and screening DMI scores. **Results:** Simple regression analyses revealed that the MoCA memory index score (MIS), $F(1,27) = 7.89$, $p = .009$, $R2 = .23$, free delayed recall score, $F(1,38) = 21.49$, $p < .001$, $R2 = .36$, and total score, $F(1,35) = 4.99$, $p = .032$, $R2 = .13$, were predictive of RBANS DMI score. The regression equation from these analyses indicated that a DMI score of 85 can be expected from individuals whose score, on average, are as follows: MIS = 9.54, free delayed recall = 1.97, total MoCA = 22.62. **Conclusions:** The current study provides initial insight into how the MoCA can be used to better identify eligible

candidates for AD trials with a RBANS DMI criterion. **Key words:** Cognitive assessments, MoCA, RBANS, Alzheimer's dementia, clinical trial eligibility. **References:** 1. Shura, R.D., Brearly, T. W., Rowland, J. A., & Martindale, S. L. (2018). RBANS validity indices: A systematic review and meta-analysis. Neuropsychology Review, 28(3), 269-284. 2. Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary clinical validity. Journal of Clinical and Experimental Neuropsychology, 20(3), 310-319. 3. Haeberlein, S. B., von Hehn, C., Tian, Y., Chalkias, S., Muralidharan, K. K., Chen, T., Wu, S., Skordos, L. A., Nisenbaul, L., Rajagovidan, R., Dent, G., Harrison, K., Nestorov, I., Zhu, Y., Mallinckrodt, D., & Sandrock, A. (2020). Emerge and engage topline results: Phase 3 studies of aducanumab and early Alzheimer's disease: Developments in clinical trials and cognitive assessment. Alzheimer's & Dementia, 16. 4. Paul, R., Lane, E., Tate, D., Heaps, J., Romo, D., Akbudak, E., Niehoff, J., & Conturo, T. E. Neuroimaging signatures and cognitive correlates of the Montreal Cognitive Assessment screen in a nonclinical elderly sample. Archives of Clinical Neuropsychology, 26(5), 454-460. 5. Julayanont, P., Brousseau, M., Chertkow, H., Phillips, N., & Nasreddine, Z. (2014). Montreal Cognitive Assessment index score (MoCA-MIS) as a predictor of conversion from mild cognitive impairment to Alzheimer's disease. Journal of the American Geriatrics Society, 62(4), 679-684.

LP076- IDENTIFYING THE SEVERITY OF DEMENTIA BASED ON COGNITIVE PERFORMANCE AND INDEX OF INDEPENDENCE IN BASIC ACTIVITIES OF DAILY LIVING. D. Huynh[1], B. Huang[1], R. Hosseini Ghomi[1,2] *(1. BrainCheck Inc. - Austin (United States), 2. Frontier Psychiatry - Billings (United States))*

Background: Alzheimer's disease and related dementias (ADRD) are characterized by impairments in an individual's cognitive and functional abilities. Severe levels of these impairments can make the patient incapable of carrying out even basic self-care tasks. Computerized cognitive tests have been shown to be effective in detecting mild cognitive impairment and ADRD but whether they can stage the ADRD disease remains to be studied. This study examines: (1) the correlation between a battery of BrainCheck cognitive assessments (BC-Assess) with the total scores of the Katz Index of Independence in Activities of Daily Living (ADL) [1] and Dementia Severity Rating Scale (DSRS) [2], and (2) the accuracy of using BC-Assess and ADL scores to identify dementia stage determined by DSRS total score. **Methods:** Retrospective analysis was performed on a BrainCheck dataset containing 3861 patients with cognitive impairment who received a care plan from their providers between 02/2022 and 06/2023. These patients were 60 years of age or older and had available DSRS, ADL, and BC-Assess data. The DSRS total score was used to identify patients' stage of impairment: 3,151 mild-dementia patients (score 0-18), 600 moderate-dementia patients (score 19-26) and 110 severe-dementia patients (score 37-54)2. Pearson correlation was calculated to assess the strength of associations between BC-Assess, ADL, and DSRS scores. A three-way Multivariate-Analysis-of-Variance (MANOVA) was used to examine how ADL and BC-Assess scores combined differ by dementia stage after controlling for age group and gender. Multinomial logistic regression was used to evaluate the possibility of using patients' ADL and/or BC-Assess scores to predict their dementia stage. **Results:** ADL and BC-Assess scores decrease with increasing dementia severity. For both scores, the distribution is systematically skewed towards the high values for the mild group, towards the low values for the severe group, and more evenly distributed for the moderate group. Results from the three-way MANOVA and post-hoc analysis show that these two scores vary significantly across dementia stages, but to different extents across age groups and genders. Correlations between scores are moderate. A stronger correlation was found between DSRS and ADL scores (r=-0.66) than that between DSRS and BC-Assess scores (r=-0.59) and between ADL and BC-Assess scores (r=0.46). ROC analysis of the logistic regression shows that, although either ADL or BC-Assess score can effectively predict dementia stage, highest accuracy is when both scores are included in the model (ROC AUC: mild=0.94; moderate=0.77; severe=0.9; micro-average=0.93). Except for a low sensitivity in identifying the moderate group, a sensitivity/specificity of at least 76% was observed for all models and groups. **Conclusions:** Our results suggest a progressive decline in both cognitive and functional abilities as patients move through the stages of dementia. Among patients with dementia, performance in a cognitive assessment or in basic activities of daily living is informative of severity diagnosis. However, consideration of both cognitive (BC-Assess) and functional (ADL) measures generates highest accuracy. **Key words:** Dementia, cognitive impairment, functional activities, cognitive assessment, BrainCheck. **Disclosures:** The study was funded by BrainCheck. All authors receive stock options from BrainCheck. **References:** 1. Wallace M, Shelkey M; Hartford Institute for Geriatric Nursing. Katz Index of Independence in Activities of Daily Living (ADL). Urol Nurs. 2007 Feb;27(1):93-4. PMID: 17390935. 2. Clark CM, Ewbank DC. Performance of the dementia severity rating scale: a caregiver questionnaire for rating severity in Alzheimer disease. Alzheimer Dis Assoc Disord. 1996;10(1):31–9.

LP077- COMPARING PSYCHOMETRIC CHARACTERISTICS OF A COMPUTERIZED COGNITIVE TEST (BRAINCHECK-ASSESS) AGAINST THE MONTREAL COGNITIVE ASSESSMENT (MOCA). D. Huynh[1], B. Huang[1], R. Hosseini Ghomi[1,2] *(1. BrainCheck Inc. - Austin (United States), 2. Frontier Psychiatry - Billings (United States))*

Background: Previous validation studies demonstrated that BrainCheck Assess (BC-Assess), a computerized cognitive test battery, can reliably and sensitively distinguish individuals with different levels of cognitive impairment (i.e., normal cognition (NC), mild cognitive impairment (MCI), and dementia) [1, 2]. Compared with other traditional paper-based cognitive screening instruments commonly used in clinical practice, the MoCA is generally accepted to be among the most comprehensive and robust screening tools, with high sensitivity/specificity in distinguishing MCI from NC and dementia [3-5]. In this study, we examined: (1) the linear relationship between BC-Assess and MoCA and their equivalent cut-off scores, and (2) the extent to which they agree on their impressions of an individual's cognitive status. **Methods:** A subset of participants (N=55; age range 54-94, mean/SD=80/9.5) from two previous studies [1, 2] who took both the MoCA and BC-Assess were included in this analysis. Linear regression was used to calculate equivalent cut-off scores for BC-Assess based on those originally recommended for the MoCA to differentiate MCI from NC (cut-off=26), and dementia from MCI (cut-off=19) [6]. Impression agreement between the two instruments were measured through overall agreement (OA), positive percent agreement (PPA), and negative percent agreement (NPA). **Results:** A high Pearson correlation coefficient of 0.77 (CI =

0.64 - 0.86) was observed between the two scores. According to this relationship, MoCA cutoffs of 26 and 19 correspond to BC-Assess scores of 89.15 and 68.92, respectively. These scores are consistent with the currently recommended BC-Assess cutoffs (i.e. 85 and 70). The two instruments also show a high degree of agreement in their impressions based on their recommended cut-offs: (i) OA=70.9%, PPA=70.4%, NPA=71.4% for differentiating dementia from MCI/NC; (ii) OA=83.6%, PPA=84.1%, NPA=81.8% for differentiating dementia/MCI from NC. **Conclusions:** This study provides further validation of BC-Assess in a sample of older adults by showing its high correlation and agreement in impression with the widely used MoCA. **Key words:** Dementia, mild cognitive impairment, MoCA, BrainCheck. **Disclosures:** The study was funded by BrainCheck. All authors receive stock options from BrainCheck. **References:** 1. Ye S, Sun K, Huynh D, Phi HQ, Ko B, Huang B, Hosseini Ghomi R. A Computerized Cognitive Test Battery for Detection of Dementia and Mild Cognitive Impairment: Instrument Validation Study. JMIR Aging [Internet]. 2022 Apr 15 [cited 2022 Dec 23];5(2):e36825. 2. Groppell S, Soto-Ruiz KM, Flores B, Dawkins W, Smith I, Eagleman DM, Katz Y. A Rapid, Mobile Neurocognitive Screening Test to Aid in Identifying Cognitive Impairment and Dementia (BrainCheck): Cohort Study. JMIR Aging. 2019 Mar 21;2(1):e12615. 3. Carson N, Leach L, Murphy KJ. A re-examination of Montreal Cognitive Assessment (MoCA) cutoff scores. Int J Geriatr Psychiatry 2018 Feb;33(2):379-388. 4. Dautzenberg G, Lijmer J, Beekman A. Diagnostic accuracy of the Montreal Cognitive Assessment (MoCA) for cognitive screening in old age psychiatry: Determining cutoff scores in clinical practice. Avoiding spectrum bias caused by healthy controls. Int J Geriatr Psychiatry 2020 Mar 27;35(3):261-269. 5. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005 Apr;53(4):695-699. 6. Davis DHJ, Creavin ST, Yip JLY, et al. Montreal cognitive assessment for the diagnosis of Alzheimer's disease and other dementias. Cochrane Database Syst Rev. 2015 Oct 29; 2015(10): CD010775.

LP078- COGNITIVE EFFECTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 36-WEEK CLINICAL TRIAL OF CITRUS PHYTOCHEMICALS IN SUBJECTIVE COGNITIVE DECLINE. Elena Gatti[1], Giovanni Sgro[2,3], Natale Salvatore Bonfiglio[4], Andrea Geviti[4], Salvatore Genovese[5], Serena Fiorito[5], Lucia Palumbo[5], Giovanni B. Frisoni[6], Michela Pievani[1], Francesco Epifano[5], Samantha Galluzzi[1] *(1. Laboratory Alzheimer's Neuroimaging and Epidemiology, IRCCS Istituto Centro San Giovanni Di Dio Fatebenefratelli, Brescia (Italy), 2. Molecular Markers Laboratory and 3. Clinical Trial Service, IRCCS Istituto Centro San Giovanni Di Dio Fatebenefratelli, Brescia (Italy), 4. Service of Statistics, IRCCS Istituto Centro San Giovanni Di Dio Fatebenefratelli, Brescia, (Italy), 5. Laboratory of Phytochemistry and Chemistry of Natural Products, Department of Pharmacy, University "G. d'Annunzio" of Chieti-Pescara, Chieti, (Italy), 6. University Hospitals and University of Geneva, Geneva (Switzerland))*

Background: We designed a clinical trial to evaluate cognitive and biological effects of a 36-week treatment with citrus peel extract in older adults with subjective cognitive decline (SCD) (ClinicalTrials.gov identifier: NCT04744922). Here we present the results of cognitive outcomes. **Methods:** Eighty subjects were enrolled between April 2021 and August 2022, and randomly assigned to receive either active treatment (400 mg citrus peel extract standardized in content of auraptene - 0.1 mg - and naringenin – 3 mg) or placebo in a 1:1 ratio for 36 weeks. The primary end point was the change from baseline at 36 weeks in the total score of the Repeatable Battery for the Assessment of Neuropsychological Status (R-BANS). Secondary cognitive outcomes included changes in verbal and non-verbal memory, attention, executive and visuospatial functions, and subjective memory concerns. The statistical analysis was performed using the intention-to-treat approach with generalized linear mixed models. **Results:** The subjects enrolled had an average age of 69.2+4.3 years, a high level of education (13.7+3.5 years) and were in prevalence females (75%), without significant differences between treatment and placebo groups. At baseline, cognitve tests were similar between groups, except for the Wisconsin Card Sorting Test – Global Score, where the treatment group performed better than placebo group (27.9±21.6 vs 40.7±32.2, p=0.040, respectively). We found a significant effect of time (p<.001), but not time*treatment interaction (p=.662) on the R-BANS total score. The analysis of the R-BANS subtests showed that this time effect was driven by changes in immediate (p<.001) and delayed memory (p<.001). For secondary outcomes, we found a significant time, but not time*interaction effect, on tests of verbal memory (California Verbal Learning test (immediate, short, and long delayed recall, p<.001) and meta-memory (Multifactorial Memory Questionnaire, Satisfaction p<.001, Ability p<.001 and Strategies p=.026). We found a significant time*treatment effect on the Stroop Test - Error Interference (p=.047) and the Wisconsin Card Sorting Test - Global Score (p=.005). **Conclusion:** Our results showed that both treatment and placebo groups improved in the primary cognitive outcome, suggesting a placebo-effect. The analysis of biological outcomes and correlations with cognitive outcomes will help us better understand the effect of citrus phytochemicals in our population. **Key words:** Subjective cognitive decline, Randomized clinical trial, Auraptene, Naringenin. **Clinical Trial Registry:** NCT04744922 https://classic.clinicaltrials.gov/ct2/show/study/NCT04744922

LP080 ECO-EXPOSOME AND MILD COGNITIVE IMPAIRMENT: LINKING ENVIRONMENTAL AND SOCIAL VULNERABILITY INDICES TO THE COG-IT CLINICAL TRIAL. A. Adhikari[1], A. Nwosu[1], C. Hellegers[1], J. Phillips[2], J. Petrella[3], D. Devanand[4], M. Doraiswamy[1] *(1. Neurocognitive Disorders Program, Department of Psychiatry, Duke University School of Medicine - Durham (United States), 2. Department of Psychiatry, Columbia University Medical Center, and the New York State Psychiatry Institute - New York City (United States), 3. Department of Radiology, Duke University School of Medicine - Durham (United States), 4. Department of Psychiatry, Columbia University Medical Center, and the New York State Psychiatry Institute - New York City (United States))*

Background: While environmental risk factors of Alzheimer's disease (AD) have been studied over several decades, neither socioeconomic nor environmental data had been captured comprehensively at the neighborhood scale. Integrating such data may allow a deeper understanding of the interplay between environmental risk factors, social determinants and mild cognitive impairment (MCI). The Environmental Justice index (EJI) and Area Deprivation Index (ADI) are two new measures that allow for such data integration. **Methods:** COG-IT was a 78-week, clinical trial of 109 MCI participants. We extracted 40 unique neighborhood social and environmental vulnerability indices (including indices pertaining to quality of water, air, and home as well as

green spaces, access to transportation) from the EJI and ADI and examined their relationship to measures of cognition, function, and brain atrophy. **Results:** We observed relationships between the functional activities questionnaire and specific EJI modules. We also observed significant differences between white and minority populations for environmental and social rankings on the EJI as well as the state decile rankings of the ADI. **Conclusions:** To our knowledge, this is the first study to link EJI indices to an MCI clinical trial. Future studies should aim to gather longitudinal exposure data in larger, more cognitively diverse samples. **Key words:** Alzheimer's Disease (AD), mild cognitive impairment (MCI), environment, neighborhood, risk factors, health disparities. **Disclosures:** Data collection for the COG-IT study was supported by National Institute on Aging NIH grant number 1R01AG052440. Supported by National Institutes of Health, National Institute on Aging Grant Number 1R01AG052440. **References:** Centers for Disease Control and Prevention and Agency for Toxic Substances Disease Registry Environmental Justice Index (EJI) Technical Documentation. 2022. University of Wisconsin School of Medicine and Public Health, 2021 Area Deprivation Index v4. 2021. Devanand, D.P., et al., Computerized Games versus Crosswords Training in Mild Cognitive Impairment. NEJM Evid, 2022. 1(12).

LP121- MEMTEST, A DIRECT-TO-CONSUMER SELF-ADMINISTERED DIGITAL COGNITIVE TEST SELF COMPLETED IN UNDER 10 MINUTES ON MOBILE (ANDROID OR IPHONE), PC, OR TABLET TO INCREASE CLINICAL TRIAL PARTICIPATION AND DECREASE SCREEN FAILS FOR VERBAL SCREENING TESTS AND FLUID BIOMARKERS IN ALZHEIMER'S DISEASE CLINICAL TRIALS. D. Watson[1], S. Stanton[2], R. Guilfoyle[3], T. Mareck[3], B. Lenox[1] *(1. K2 Medical Research - Maitland (United States), 2. K2 Medical Research - Winter Park (United States), 3. Recall Technologies - Orlando (United States))*

Background: Research sites need to track how triaged subjects perform on Inclusion criteria, to reduce screen failures on scales and fluid biomarkers. The ability to predict a subject's immediate and delayed recall on traditional paper and pencil tests such as CVLT, RAVLT, and ISLT is a current issue in clinical studies that accounts for 60-85% of the initial screen fail rate. Fluid biomarkers like TAU, Amyloid, and ApoE have also contributed to between 40-70% (Goldman et al 2020)) in disease modifying studies in Alzheimer's Disease and over 80% in asymptomatic or prodromal studies. Traditional verbal list learning screening tests take approximately 20 minutes to administer and require a delayed word recall at least 10 minutes before a delayed recall task is given. With fluid markers we have begun to see this take shape in clinical trials, but it adds at least 30 days in the screening process with a high screen failure rate.Lengthy prescreening processes significantly decrease the number of subjects a site can prescreen in a day. memTEST was created using natural learning process (NLP) to be SELF administered in less than 10 minutes on a mobile device (android and iPhone), tablet, or personal computer to assess memory decline through auditory verbal learning and compared to, in person, traditional verbal learning screening tools and fluid biomarkers (Amyloid, TAU, and ApoE). **Methods:** memTEST was performed on 201 subjects that wanted to participate in clinical trials for Alzheimer's Disease. Of the 201, 200 of them completed an in-person verbal and auditory list learning l assessment and 181 volunteered for a fluid biomarker assessment using PrecivityAD2. The results of the fluid biomarkers were not part of the process to include people in clinical trials as results came in 10 months after collection, due to logistics and backlog. Specimens were collected and shipped in real-time, but the results were delayed and could not become a dynamic element of the study. We also collected demography that included, but is not limited to, age, diagnosis, race, gender, education, family history, medical history, and social history. We also measured the downstream effect of these tools collecting the number of people that participated in a clinical trial, Amyloid PET, TAU PET, MRI, and other screening diagnostics that could create efficiency to decreasing unnecessary screens. **Results:** Only 1 subject did not have the re-test performed and withdrew participation. 20 Subjects did not have the peripheral biomarker measured due to voluntary withdrawal. 148 of the subjects wanted to participate in a clinical trial (81%), 97 (52%) were screened into a study. We reviewed threshold composite scores on the traditional learning tests and found we can reduce screen fails by 35% using the paper and pencil scales. memTEST was able to reduce the screen fail rate by another 20% making the system over 50% more efficient. We will present the correlation to blood biomarkers, but biostatistics are in the final stages of review. The correlation to the traditional learning test was low (65%) but when we altered the self-administered tests threshold composite score to account for self-administration environmental testing variance and it predicted memory decline in nearly all the subjects tested. **Conclusions:** memTEST is a fast and easy Self-administered assessment tool completed on mobile devices, PC, or tablet to determine risk in memory decline, that increases awareness and would decrease the number of unnecessary screens. We also found subjects engaged in understanding the clinical trial process using this safe and noninvasive tool. There are further studies required to determine the best threshold but as a population risk tool it increased participation and decreased would decrease screen fails. It is possible with more data that this tool could be used in population health to increase clinical trial awareness for Alzheimer's disease and help more people access risk at home to then seek a more comprehensive evaluation (blood-based biomarker or validated cognitive tool) in clinic, medical research unit, or home health.

LP122- VALIDATING ENHANCED BEHAVIORAL MEASURES OF WORD RECALL BASED ON UNDERLYING COGNITIVE PROCESSES. J. Bock[1,2], H. Hara[1,3], D. Fortier[1], T. Mangrola[1], 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: Underlying the behavior of memory performance are cognitive processes, which include encoding and recall and which, when quantified, can enable better understanding of individuals' cognitive health. Quantified cognitive processes (qCPs) can be generated with a hierarchical Bayesian cognitive processing (HBCP) model, applied to item response data from commonly used wordlist memory (WLM) tests. Seven qCPs have been well validated, each representing probability of information processing through different encoding (N1, N2, N3, or N4) or retrieval (R1, R2, or R3) paths and storage states (pre-task, transient, or durable storage). Previously, we showed that qCPs, when summated as recall probability (M), highly resemble observed behavior of total word recall for a WLM test. These generalized measures are a valuable bridge between underlying processes and observed behaviors. In the present study, we generated an enhanced

set of M parameters and validated their ability to identify individuals with mild cognitive impairment (MCI) due to Alzheimer's disease (AD). **Methods:** Item response data was obtained from ADAS-Cog WLM tests (n = 1,842) in the ADNI, along with participant demographics, CSF AD biomarkers (most recent within 2 years), Clinical Dementia Rating-Global Score (CDR-GS), and qCPs. Participants were assigned to one of two groups based on CDR-GS and ATN status (amyloid, tau, neurodegeneration): CN (n assessments = 726) if CDR-GS = 0 and ATN-, and MCI (n assessments = 1,116) if CDR-GS = 0.5 and ATN+. We generated qCPs for each assessment and calculated newly developed M parameters from these processes. MIFR1, MIFR2, MIFR3, and MDFR1 measure the latent recall rate for a generalized word during a respective immediate or delayed free recall task, and MTran and MDura measure latent recall rate for a generalized word retrieved through transient or durable storage. With an even split into training and testing subgroups, we assessed two Bayesian logistic regression models on the training subgroup: demographics, MIFR3, and MDFR1 in the task model, and demographics, MTran, MDura, and MDFR1 in the storage model. Bayes factors were calculated for each factor. Subsequently, we applied coefficients to the testing group to generate prediction probabilities and performed an ROC analysis. **Results:** The task model M coefficients (βMIFR3 M = -9.38, SD = 1.61; βMDFR1 M = -13.69, SD = 1.20) demonstrated extreme evidence in favor of the alternative hypothesis (BFs > 1,000). The storage model MDura (M = -29.15, SD = 3.52) and MDFR1 (M = -9.45, SD = 1.35) also demonstrated extreme evidence in favor of the alternative (BFs > 1,000). ROC AUCs = .91 and .90 for the task and storage models, respectively. **Conclusions:** The current study validates qCPs as underlying cognitive measures that can reconstruct observed behavior and demonstrates their ability to identify MCI due to AD, using only a wordlist memory test. These measures, both qCPs and generalized behavioral measures, enable identification and measurement of subtle changes that cannot be observed with traditional neuropsychological testing approaches in early AD, when mild symptoms require the greatest precision.

LP123- ARC-DS: A DIGITAL COGNITIVE OUTCOME MEASURE FOR DOWN SYNDROME-ASSOCIATED AD PREVENTION TRIALS. J. Hassenstab[1], L. Del Hoyo Soriano[2], O. Wagemann[3], A. Baksh[4], A. Aschenbrenner[1], B. Ances[1], J. Fortea[2], J. Levin[3], M. Schöll[5], E. Surace[6], A. Strydom[4] *(1. Washington University in St. Louis - St. Louis (United States), 2. Sant Pau Hospital - Barcelona (Spain), 3. Ludwig-Maximilian-University - Munich (Germany), 4. King's College London - London (United Kingdom), 5. University of Gothenburg - Gothenburg (Sweden), 6. FLENI Institute - Buenos Aires (Argentina))*

Background: Almost all individuals with Down syndrome (DS) develop pathological indicators of Alzheimer's disease (AD) by age 35 and are symptomatic typically in their late 40s. AD is the leading cause of death among adults with DS, yet those with DS are routinely excluded from AD prevention trials. One major limitation is that there are no cognitive outcomes for DS populations that have been designed and purpose-built for culturally and linguistically diverse groups. Because of the rarity of the DS population, and to establish meaningful cognitive change in multiple cultures for regulatory approvals, DS-AD trials will enroll participants in different languages and regions. Our approach, used to successfully develop and deploy a digital cognitive outcome in 10 languages in 22 countries in the DIAN and DIAN-TU studies, will provide a global outcome measure that has undergone extensive accessibility and validity testing that can be administered remotely on participants personal smartphones in local languages. **Method:** The Ambulatory Research in Cognition-Down Syndrome (ARC-DS) smartphone platform uses principles from ecological momentary assessment (EMA) to deliver high-frequency cognitive assessments in a measurement "burst" design. Participants receive notifications at quasi-random intervals up to four times per day for a one-week period, once per year. Notifications of test availability are delivered via text message containing a link which then presents the survey and cognitive tests via a version of a web browser. Participants have up to two hours to respond to the notification. The tests and surveys rely on audio instructions and a graphically rich and intuitive for individuals with DS who have mild intellectual disability (ID). Use of text is minimal due to literacy constraints in this population. For convergent validity comparisons, we will administer conventional cognitive measures used in other DS-AD cohort studies. **Results:** In phase one of the ARC-DS study, we have completed initial psychometric studies indicating that the measures are feasible and reliable in DS individuals with mild ID. We completed extensive user experience research (UXR) with 15 participants and their study partners (typically their parents or other family members) to identify so-called "pain points". We found several areas to focus on for future development. We removed all reading requirements as several participants with moderate ID struggled with literacy. We also recalibrated the tests in several ways to avoid ceiling and floor effects. We will present additional test data and describe in detail each cognitive measure in the presentation. We will also describe the ARC-DS study structure, aims, and validation methods in the presentation. **Conclusion:** There is a tremendous need for validated and sensitive cognitive measures appropriate for global AD prevention trials for individuals with Down syndrome. The ARC-DS study will attempt to address these needs with a purpose-built, culturally- and linguistically-adapted digital platform compliant with security and privacy regulations that will be open-source and freely available to the DS-AD research community and industry partners. **Key words:** Down syndrome, cognition, clinical trials, digital biomarker. **Disclosures:** The study is funded by NIH grant R01AG081394. The authors report no conflicts of interest with the present work.

BEHAVIORAL DISORDERS AND CLINICAL TRIALS

P138- EFFECTS OF BREXPIPRAZOLE ON AGITATION ASSOCIATED WITH DEMENTIA DUE TO ALZHEIMER'S DISEASE: ANALYSIS OF POOLED EFFICACY DATA FROM TWO PHASE 3 FIXED-DOSE TRIALS BY BASELINE AGITATION FREQUENCY. J. Aggarwal[1], D. Lee[1], N. Hefting[2], D. Chen[1], D. Chang[1], Z. Zhang[1], M. Miguelez[1], S. Behl[1] *(1. Otsuka Pharmaceutical Development & Commercialization Inc. - Princeton, New Jersey (United States), 2. H. Lundbeck A/S - Valby, Copenhagen (Denmark))*

Background: Neuropsychiatric symptoms are among the most difficult and stressful aspects of Alzheimer's disease (AD) for patients and caregivers. Agitation – a burdensome neuropsychiatric symptom – is a prevalent clinical manifestation of AD. Brexpiprazole was recently approved by the FDA for the treatment of agitation associated with dementia due to AD, making it the first approved medication for this indication in the USA. The aim of these analyses was

to evaluate the impact of baseline agitation frequency on improvements during brexpiprazole treatment, using data from two fixed-dose trials of patients with agitation associated with AD. **Methods:** Studies 283 and 213 were Phase 3, 12-week, randomized, double-blind, placebo-controlled, parallel-arm trials of brexpiprazole in patients with agitation associated with dementia due to AD (NCT01862640, NCT03548584). Agitation was assessed using the Cohen-Mansfield Agitation Inventory (CMAI), which measures the frequency of 29 agitated behaviors (29 items, each rated 1–7 [1=never, 7=several times an hour; total score range 29–203]). The primary efficacy endpoint of each study was the change from baseline to Week 12 in CMAI Total score. In the present analyses, data were pooled for Studies 283 and 213 (brexpiprazole doses of 2 or 3 mg/day). Patients were grouped by baseline CMAI Total score as follows: ≤65 (lower tertile; i.e., a lower baseline frequency of agitated behaviors), 66–80 (middle tertile), >80 (upper tertile; i.e., a higher baseline frequency of agitated behaviors), and treatment differences over 12 weeks were determined in each tertile (mixed model for repeated measures). Additionally, across all patients in each treatment group, CMAI behaviors were grouped by baseline frequency (i.e., data for all items with a baseline frequency of 7 [several times an hour] were pooled, then items with a score of 6, etc.), and mean score changes over 12 weeks were determined (descriptive statistics). **Results:** In the lower, middle, and upper tertiles, the respective treatment differences for brexpiprazole 2 or 3 mg/day versus placebo in mean change in CMAI Total score from baseline to Week 12 were: -0.65 (brexpiprazole n=101, placebo n=81, p=0.67); -6.73 (brexpiprazole n=126, placebo n=72, p=0.0020); and -5.73 (brexpiprazole n=136, placebo n=94, p=0.020). In the analysis of changes in CMAI behaviors by baseline frequency, the greatest treatment effect was observed on the most frequently occurring CMAI behaviors. For example, in the brexpiprazole group, behaviors that occurred 'several times an hour' at baseline (score of 7) decreased, on average, to a frequency of 'several times a week', with a mean -2.9-point change in CMAI item score over 12 weeks. Placebo-treated patients experienced lesser reductions in agitation, with behaviors occurring 'several times an hour' at baseline showing a mean -1.9-point change in CMAI item score, to a frequency of '1–2 times a day'. **Conclusions:** Across two trials of patients with agitation associated with dementia due to AD, reductions in baseline agitation were greater in patients treated with fixed-dose brexpiprazole 2 or 3 mg/day versus placebo. Improvements were generally greater in patients with more frequent agitated behaviors at baseline. **Key words:** Agitation, Dementia, Alzheimer's disease, Brexpiprazole. **Disclosures:** Jyoti Aggarwal, Daniel Lee, Dalei Chen, Denise Chang, Zhen Zhang, Maia Miguelez and Saloni Behl are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA. Nanco Hefting is a full-time employee of H. Lundbeck A/S, Valby, Copenhagen, Denmark.

P139- EFFECTS OF BREXPIPRAZOLE ON AGITATION ASSOCIATED WITH DEMENTIA DUE TO ALZHEIMER'S DISEASE: ANALYSIS OF POOLED RESPONSE DATA FROM TWO PHASE 3 FIXED-DOSE TRIALS. D. Lee[1], J. Aggarwal[1], N. Hefting[2], D. Chen[1], D. Chang[1], S. Behl[1]
(1. Otsuka Pharmaceutical Development & Commercialization Inc. - Princeton, New Jersey (United States), 2. H. Lundbeck A/S - Valby, Copenhagen (Denmark))

Background: Neuropsychiatric symptoms of dementia due to Alzheimer's disease, including agitation, are among the most difficult and stressful aspects of the disease for patients and caregivers. Brexpiprazole has recently been approved by the FDA as a treatment for agitation associated with dementia due to Alzheimer's disease. The aim of this analysis was to explore response rates based on meaningful thresholds, from two fixed-dose trials of brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease. **Methods:** The two fixed-dose trials were Phase 3, 12-week, randomized, double-blind, placebo-controlled, parallel-arm trials of brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease (NCT01862640, NCT03548584). The first fixed-dose trial investigated brexpiprazole doses of 1 and 2 mg/day, and the second fixed-dose trial investigated brexpiprazole doses of 2 and 3 mg/day. In both trials, the Cohen-Mansfield Agitation Inventory (CMAI) was used to measure the frequency of 29 agitated behaviors, and the primary efficacy endpoint was the change from baseline to Week 12 in CMAI Total score. The total improvement in agitation over the study period was also measured using the mean Clinical Global Impression – Improvement (CGI-I) score, as related to agitation (secondary endpoint). Other secondary/exploratory endpoints included the CMAI response rate (pre-defined as ≥40%, ≥30%, or ≥20% reduction from baseline to Week 12 in CMAI Total score), and the CGI-I response rate (pre-defined as a CGI-I score of 1 [very much improved] or 2 [much improved]). In the present analysis, data for brexpiprazole 2 or 3 mg/day are pooled from the two fixed-dose trials, and compared with corresponding pooled placebo data. All response data are based on last observation carried forward analyses. **Results:** Across the two fixed-dose trials (pooled), 363 patients randomized to brexpiprazole 2 or 3 mg/day and 247 patients randomized to placebo were included in these analyses. In the pooled sample, CMAI response rates for brexpiprazole 2 or 3 mg/day versus placebo at Week 12 were as follows: ≥40% reduction, 25.1% versus 14.2% (p=0.0003); ≥30% reduction, 42.7% versus 30.8% (p=0.0023); ≥20% reduction, 65.3% versus 50.6% (p=0.0014). The rate of CGI-I response at Week 12 was 51.2% with brexpiprazole 2 or 3 mg/day versus 43.3% with placebo (p=0.047). **Conclusions:** Across two trials of patients with agitation associated with dementia due to Alzheimer's disease, fixed-dose brexpiprazole 2 or 3 mg/day was associated with higher response rates compared with placebo, across all defined response criteria. **Key words:** Agitation, Alzheimer's disease, Brexpiprazole, Response rates. **Disclosures:** Daniel Lee, Jyoti Aggarwal, Dalei Chen, Denise Chang and Saloni Behl are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA. Nanco Hefting is a full-time employee of H. Lundbeck A/S, Valby, Copenhagen, Denmark.

P140- DESIGN OF ADEPT-2, A PHASE 3, PARALLEL GROUP STUDY TO EVALUATE KARXT (XANOMELINE–TROSPIUM) AS A TREATMENT FOR PSYCHOSIS ASSOCIATED WITH ALZHEIMER'S DISEASE. M. Kang[1], C. Watson[1], J. Cummings[2], G. Grossberg[3], R. Marcus[1], P. Yeung[1]
(1. Karuna Therapeutics - Boston (United States), 2. Chambers-Grundy Center for Transformative Neuroscience, University of Nevada, Las Vegas - Las Vegas (United States), 3. Department of Psychiatry & Behavioral Neuroscience, Saint Louis University School of Medicine - Saint Louis (United States))

Background: Psychosis represents a major unmet medical need in patients with Alzheimer's disease (AD) dementia. With no approved medications for AD dementia psychosis (ADP), current treatment relies on off-label uses of antipsychotics with limited efficacy and significant safety concerns. Xanomeline is an M1/M4 preferring muscarinic receptor agonist that has

previously been shown to have antipsychotic effects in subjects with AD [1]. While xanomeline had promising efficacy for potentially treating psychosis in AD, cholinergic adverse events limited further clinical development of xanomeline. KarXT is an investigational treatment that combines xanomeline with trospium, an FDA-approved non-specific muscarinic receptor antagonist. Unlike xanomeline, trospium does not measurably cross the blood-brain barrier, providing a mechanism to mitigate peripheral cholinergic effects of xanomeline while maintaining its muscarinic receptor agonist activities in the brain. **Methods:** ADEPT-2 trial is a phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of KarXT for the treatment of ADP. Subjects aged 55-90 years with moderate to severe psychosis associated with mild to severe AD dementia will be enrolled into the study. Eligible subjects will be randomized to receive either KarXT or placebo in a double-blinded manner for 12 weeks and subjects who complete the study will be eligible to participate in a one-year, open-label safety extension study. **Results:** The primary efficacy endpoint of the study is change from baseline to end of Week 12 in the Neuropsychiatric Inventory-Clinical (NPI-C): Hallucinations and Delusions (H+D) score and the key secondary efficacy endpoint is change from baseline to end of Week 12 in the Cohen-Mansfield Agitation Inventory (CMAI). The safety endpoints include the evaluation of safety and tolerability of KarXT compared with placebo in subjects with ADP. The study is planned to start in 2023 and will enroll approximately 360 subjects with psychosis associated with AD dementia. **Conclusion:** ADEPT-2 is designed to assess the safety and efficacy of KarXT for the treatment of psychosis in patients with AD dementia. If ADEPT-2 is successful, KarXT has the potential to be the first in a new class of pharmacologic treatment for AD psychosis based on muscarinic receptor agonism. **Disclosures:** MK, CW, RM, and PY are employees of and hold equity in Karuna Therapeutics. JC has provided consultation to Acadia, Alkahest, Alpha Cognition, AriBio, Biogen, Cassava, Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, Lilly, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Ono, Otsuka, PRODEO, Prothena, reMYND, Resverlogix, Roche, Signant Health, Suven, and United Neuroscience and is supported by NIGMS grant P20GM109025, NINDS grant U01NS093334, NIA grant R01AG053798, NIA grant P20AG068053, NIA grant P30AG072959, NIA grant R35AG71476, Alzheimer's Disease Drug Discovery Foundation (ADDF), Ted and Maria Quirk Endowment, and the Joy Chambers-Grundy Endowment. GG is a consultant for Acadia, Avanir, Axsome, Biogen, BioXcel, Genentech, Karuna, Lundbeck, Otsuka, Roche, and Takeda; has received research support from Neuromodulatory Therapies and Nia; and is on safety monitoring committees for Anavex, EryDel, Merck, Oligomerix, and Newron. **References:** 1. Bodick NC, et al. Arch Neurol 1997; 54(4):465-73. doi: 10.1001/archneur.1997.00550160091022.

LP124- A REVIEW OF MEANINGFUL CHANGE IN AGITATION BEHAVIORS ASSOCIATED WITH ALZHEIMER'S DISEASE AND THE POTENTIAL IMPACT OF BREXPIPRAZOLE.

J. Aggarwal[1], B. Talon[2], P. Such[3], M. Brubaker[1], D. Wang[3], A. Atri[4,5,6,7] *(1. Otsuka Pharmaceutical Development & Commercialization Inc. - Princeton (United States), 2. H. Lundbeck A/S - Deerfield (Denmark), 3. H. Lundbeck A/S - Valby, Copenhagen (Denmark), 4. Banner Sun Health Research Institute - Sun City (United States), 5. Banner Alzheimer's Institute - Phoenix (United States), 6. Brigham and Women's Hospital - Boston (United States), 7. Harvard Medical School - Boston (United States))*

Background: Agitation is a common and heterogeneous neuropsychiatric symptom of Alzheimer's disease (AD), which is associated with substantial burden and costs to patients and caregivers. Meaningful treatment benefits in AD are a complex latent construct that involve multiple stakeholders and perspectives, subject to measurement in various ways; this necessitates assessment of meaningful change from different perspectives and using multiple methods. A literature review was conducted to identify what constitutes a meaningful change in agitation behaviors in patients with AD, from the perspectives of patients, caregivers, and clinicians. Qualitative and quantitative published findings were used to assess meaningful benefits of brexpiprazole for the treatment of agitation behaviors associated with dementia due to AD. **Methods:** The literature search was conducted using Medline, Embase, and Biosis for journal publications (2018–2023). Separately, congress proceedings (AAIC, AAGP, CTAD, ASCP, IPA) were reviewed (2021–2023). The review included qualitative and quantitative perspectives on meaningful change, plus supportive studies that contribute to overall understanding of the relationship between the Cohen-Mansfield Agitation Inventory (CMAI), commonly used in clinical trials to measure agitation behavior frequency, and other patient or caregiver outcomes (e.g., quality of life, burden, likelihood of depression and anxiety, health care resource utilization and costs). The literature findings, including anchor-based analyses utilizing the Clinical Global Impression – Severity of illness (CGI-S) as related to agitation, provided context for evaluating the potential meaningful benefit of brexpiprazole treatment in patients with agitation associated with dementia due to AD, using data from two pivotal Phase 3 trials that supported brexpiprazole's FDA approval. **Results:** The journal search yielded 174 results, of which 26 were reviewed in full. Four additional studies were identified from congress proceedings. Change in agitation behavior frequency was reported by caregivers as important, with decreased frequency perceived as a meaningful improvement. Other changes considered by caregivers to be meaningful included changes in behavior intensity, intent to disturb or cause harm, potential to cause serious harm, amount of harm caused, and level of worry, frustration, or isolation. Published thresholds for meaningful within patient change on the CMAI ranged from -15 to -25 points. Studies comparing the CMAI to other measures, such as the Zarit Burden Interview (ZBI), showed strong correlations and demonstrated that different CMAI agitation behaviors are related to caregiver burden and caregiver and patient quality of life. Across the two pivotal Phase 3 trials of brexpiprazole, greater reductions in the frequency of agitation behaviors were observed with brexpiprazole than placebo, and a higher proportion of brexpiprazole- versus placebo-treated patients achieved a -20-point reduction in CMAI score. **Conclusions:** Based on integration of qualitative and quantitative research, reductions in the frequency of agitation behaviors can reflect

meaningful change. Further underscoring the importance of caregiver perspectives, data show a reduction in the frequency of agitation behaviors, as measured by the CMAI, to be associated with improvements in caregiver burden and caregiver and patient quality of life. These findings provide further support for clinically meaningful change and treatment benefits in agitation behaviors for patients with dementia due to AD treated with brexpiprazole. **Key words:** Agitation, Alzheimer's disease, Meaningful change, Literature review. **Disclosures:** Jyoti Aggarwal and Malaak Brubaker are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA. Brian Talon and David Wang are full-time employees of Lundbeck LLC, Deerfield, IL, USA. Pedro Such is a full-time employee of H. Lundbeck A/S, Valby, Copenhagen, Denmark. Alireza Atri has received honoraria for consulting; participated in independent data safety monitoring boards; provided educational lectures, programs, and materials; served on advisory boards; or received travel/hotel from AbbVie, Acadia, Allergan, the Alzheimer's Association, Alzheimer's Disease International (ADI), Axovant, AZ Therapies, Biogen, Eisai, Grifols, JOMDD, Lundbeck, Merck, Prothena, Roche/Genentech, Novo Nordisk, Qynapse, Sunovion, Suven and Synexus. Dr. Atri's institutional receives institutional research grant/contract funding for sponsored research (industry, foundation, Research Consortia, NIH, State) in which he is involved, including from several industry-sponsored trials, NIA/NIH 1P30AG072980, AZ DHS CTR040636, Washington University St Louis, Foundation for NIH (FNIH), and Gates Ventures. Dr. Atri receives royalties from Oxford University Press for a textbook on dementia principles and practices.

LP125- LONGITUDINAL EFFECTS OF CAREGIVING BURDEN ON INFLAMMATORY BIOMARKERS IN SPOUSAL CAREGIVERS OF INDIVIDUALS WITH COGNITIVE IMPAIRMENTS.

J. Jeon[1] *(1. Department of psychiatry, Chungnam National University College of Medicine - Daejeon (Korea, Republic of))*

Background: Caring for spouses with cognitive impairments poses considerable emotional and physiological challenges. This study aimed to longitudinally assess the connection between neuropsychiatric symptoms, as measured by the Neuropsychiatric Inventory (NPI), and levels of the inflammatory biomarker Oxidized Low-Density Lipoprotein Receptor-1 (OLR1) among spousal caregivers. **Methods:** From May 2020 to May 2023, clinical evaluation and blood tests were conducted for patients who visited Chungnam National University Hospital Geriatric Neuropsychiatric Clinic with their spouse. Twenty spousal caregivers of individuals diagnosed with cognitive impairments who completed baseline and one-year follow up assessment participated in the study. NPI scores were obtained to gauge neuropsychiatric symptoms at baseline, and 12 months. Blood samples were also collected at these time points to measure OLR1 levels. Longitudinal analyses, adjusted for age, sex, and baseline cognitive status, were employed to examine the dynamics of the relationship between NPI scores and OLR1 levels. **Results:** Initial findings suggest a significant positive correlation between baseline NPI scores and OLR1 levels($p=0.038$). Furthermore, over the course of a year, changes in NPI scores were positively correlated with changes in OLR1 levels ($p=0.017$). Spousal Caregivers who reported increased burden of care-recipient showed a consistent rise in OLR1 levels over the 12-month observation period. **Discussion:** The results indicate that the neuropsychiatric challenges associated with caregiving might be linked with heightened inflammatory responses, as reflected by OLR1 levels. This connection could offer insights into the physiological pathways influenced by the stresses of caregiving for spouses with cognitive impairments. The potential implications for the caregivers' own cognitive and cardiovascular health warrant further exploration.

LP126- FEASIBILITY AND ACCEPTABILITY OF USING TECHNOLOGY IN CAREGIVERS AND ALZHEIMER'S DISEASE PATIENTS WITH AGITATION.

H. Okhravi[1], A. Gupta[2], S. Jain[3], K. Maly[2], C. Nesbitt[2], I. El Moudden[1], S. Alyaan[2] *(1. Eastern Virginia Medical School - Norfolk (United States), 2. Old Dominion Univiersity - Norfolk (United States), 3. Stony Brook University - New York (United States))*

Background: The ability of mobile technologies and wearables to passively and continuously collect data holds much potential to improve the quality and efficiency of clinical research studies1,2. However, they pose technological challenges to participants and their caregivers3. This becomes more important in patients with dementia who also exhibit behavioral issues such as agitation. We explored the acceptability of using technology (wearables, electronic form data completion and submission, sleep, and real time agitation episode collection) in Alzheimer's disease (AD) patients with agitation and their caregivers. **Methods:** 24 participants ages 56 – 88, with Mini-Mental State Exam (MMSE) score 5-28 were recruited. Caregivers underwent baseline assessment with Zarit Burden Interview (ZBI), Cohen-Mansfield Agitation Index (CMAI) and Neuropsychiatric Inventory (NPI), followed by a 16-week enrollment in a CBD oil clinical trial for agitation. At week 16 caregivers filled out a questionnaire assessing their experiences with the technology aspects (setup, maintenance, troubleshooting, and technology experience) throughout the study. To investigate the impact of patients' neuropsychiatric symptoms, cognition, caregiver burden and demographic factors on the ease of using technology, we studied correlations between CMAI, NPI, MMSE, ZBI, age, and education with the 4 aforementioned technology aspects. **Results:** Total scores from baseline assessment metrics were analyzed using the Pearson correlation coefficients, with each of the 4 technology aspects. For the 24 users, we found very low ($\sigma<0.25$) correlation between the baseline scores and their experiences with technology. Age and education also, exhibited low correlation with technology. For specific technology aspects, we observe overall acceptability. The mean score of acceptability on a scale of 1-5, 5 indicating highest ease of use across all participants, were 4 for technology setup, 4.1 for technology maintenance, 3.5 for technology troubleshooting and user experience. The overall mean across all users and all 4 technology aspects was 3.8. **Conclusion:** Our results indicate overall good to high acceptance of technology among caregivers and patients with AD and agitation. There is no correlation between the level of patients' NPS, cognitive status, caregivers' burden or their age and education with level of technology burden. **References:** Galetsi, P., Katsaliaki, K., & Kumar, S. (2023). Exploring benefits and ethical challenges in the rise of mHealth (mobile healthcare) technology for the common good: An analysis of mobile applications for health specialists. Technovation, 121, 102598. Hayes, C. J., Dawson, L., McCoy, H., Hernandez, M., Andersen, J., Ali, M. M., Bogulski, C. A., & Eswaran, H. (2023). Utilization of Remote Patient Monitoring Within the United States Health Care System: A Scoping Review. Telemedicine and e-Health, 29(3), Original Research. Published online: March 10, 2023. doi:

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Conflict of Interest: This project is entirely funded by Ecofibre Company, the manufacturer of the study product utilized in this research. We confirm that the sponsor has not been involved or had any role in the creation of this abstract or its contents.

HEALTH ECONOMICS AND CLINICAL TRIALS

P141- IMPLICATIONS OF TREATMENT DURATION AND INTENSITY ON THE VALUE OF ALZHEIMER'S TREATMENTS.

S. Mattke[1], T. Ozawa[1], M. Hanson[1] *(1. USC - Los Angeles (United States))*

Background: Disease-modifying Alzheimer's disease (AD) treatments will probably become available soon. However, the benefit of the treatment will be attenuated by the highly complex process of intravenous delivery and ARIA monitoring, which will create additional cost and caregiver burden, as many patients will probably have to be accompanied for their visits. Thus, the beneficial effect of an AD treatment on caregiver burden because of slower disease progression will be reduced, and the added cost of treatment delivery needs to be taken into account when calculating overall value. We estimated the value of a hypothetical Alzheimer's treatment using different assumptions for treatment duration and intensity. **Methods:** We estimated the life-time value of a treatment that reduces progression from mild cognitive impairment (MCI) by 30% from a payer perspective, which considers cost offsets, i.e., reduced medical and formal social care costs, and QALYs gains, and a societal perspective, which adds reduction in caregiver burden. Estimates for gross value of the treatment were based on a prior publication1, medical cost on Medicare payment rates, and caregiver time use on a survey of 16 clinical sites. Caregiver time was monetized based on the April 2023 U.S. average hourly wage for lost work hours and 0.35 times average hourly wage for lost leisure hours. Future costs were inflated by 3% annually. We analyzed five scenarios for treatment delivery: treatment until the patient progresses to moderate dementia with (1) bi-weekly and (2) four-weekly infusions, and infusions every four weeks for (3) 72, (4) 52 and (5) 24 weeks. Cost of the office visit for treatment was assumed to be $70.82 and for infusion delivery $61.15 based on 6% of lecanemab's list price. We assumed MRIs without contrast (cost of $266.72) at week 10, 14, 28 and 52 for ARIA monitoring and then once per year while on treatment. **Results:** Treatment until progression to moderate dementia would take 7.24 years on average. Its gross value in 2023 USD would be $183,360 in direct cost offsets, $828,920 from a payer and $863,388 from a societal perspective, respectively. In the five scenarios, added medical cost would be $30,272, $16,639, $3,594, $2,915 and $1,457, and caregiver time cost $6,035, $3,108, $573, $432, and $270, respectively. Thus, chronic treatment every 2 or 4 weeks would reduce cost offsets by 17% and 9%, respectively, and caregiver benefit by 18% and 9%, respectively, whereas reductions of benefit under all three time-limited treatment scenarios would be 1-2%. **Conclusion:** Direct medical cost and caregiver burden of a chronic AD treatment would be substantial because of the long duration. While these estimates do not yet account for differential ARIA incidence and discontinuation and re-treatment patterns for the five scenarios, the net value generation of time-limited treatment is projected to be substantially larger than that of chronic treatment, assuming similar effectiveness and safety. Such determination of lifetime net value can be useful to determine value-based prices for different types of AD treatments.

P142- AMYLOID PET: THE CASE FOR QUANTIFICATION IN CLINICAL ROUTINE..

P. Kuo[1], W. Jagust[2], G. Farrar[3] *(1. U Arizona - Tuscon (United States), 2. UC Berkeley - Berkeley (United States), 3. GE Healthcare - Amersham (United Kingdom))*

Background: Amyloid PET has been commercially available since 2013 with the approval of [18F]florbetapir, [18F]florbetaben and [18F]flutemetamol. According to the Prescribing Information (PI), all tracers should be interpreted via specific visual read methodology. Although generally available in Nuclear Medicine the use of quantitative software tools is not covered in the tracer PIs. The work here highlights the value of adding quantitative methodology to amyloid PET tracer interpretation. Major goals are to standardise image analysis and improve inter-reader agreement in an era when amyloid PET is required to initiate and manage newly approved therapies. **Methods:** The authors assessed evidence from peer reviewed publications, appropriate use recommendations, clinical trial data, labelling language and documents from US health system stakeholders to demonstrate the added value of quantitation to both the analysis and utility of amyloid PET. **Results:** Visual read assessment of amyloid PET has been validated through comparison with neuropathology and is ~90% accurate. Trained readers are reliably able to distinguish positive from negative in the vast majority of cases. However, a small fraction of false positive (FP) and false negative (FN) cases are observed which could be obviated with the adjunctive use of quantitation. The US IDEAS study reported a comparable 86.5% agreement between local visual read and Centiloid values (using a 24.1 CL threshold) with 7.5% of cases read visually positive but in the negative CL zone (Zelter et al 2022) (whilst 6% were observed to be FN). A similar FP scenario could have occurred in the Phase III Lecanemab study where trial participants were included based on amyloid PET by visual read, but when measured by Centiloid Units in the sub study the lower bound of the range was minus 16.6 CL in the treated group and minus 17.0 CL in the placebo group (Van Dyck et al 2023). Alternatively, the Phase III Donanemab study (Sims et al 2023) used a Centiloid cut-off of 37 to include subjects for therapy intervention and used amyloid PET to direct cessation of therapy once amyloid burden reduced below specific threshold levels. Language in the recent NCD decision memo issued by CMS points to the futility of treating amyloid negative patients with amyloid targeted therapies and based upon integrated data from both IDEAS and the latest ICER reports (Lin et al 2023) savings of at least $200M drug costs alone could be made by using a quantitative measure to exclude a minority of potential 'false positive' visual read cases. **Conclusion:** Here we present both scientific and economic rationales for the inclusion of quantitation to supplement visual interpretation of amyloid PET scans. The Centiloid scale is a proven tracer independent measure that could be further utilised for a standardised approach to image assessment for both initial diagnosis and therapy monitoring and to gain financial savings. **Key words:** Amyloid PET, quantitation, visual read, anti-amyloid therapies, therapy initiation, therapy monitoring, economic savings. **Disclosures:** Phillip H. Kuo: PHK is a consultant and/or speaker for Blue Earth Diagnostics, Chimerix, Eli Lilly, Fusion Pharma, General Electric Healthcare, Invicro, Novartis, Radionetics, and Telix Pharmaceuticals. He

is a recipient of research grants from Blue Earth Diagnostics and General Electric Healthcare. William J Jagust: WJ consults for Lilly, Eisai, Roche, and prothema pharmaceuticals and has equity in Molecular Medicine and Optoceutics. Gill Farrar: GF is a full-time employee of GE Healthcare. **References:** CMS National Coverage Analysis Proposed Decision Memo. Beta amyloid positron emission tomography in dementia and neurodegenerative disease. Ref CAG-00431R https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&ncaid=308. Lin GA, Whittington MD, Wright A, Agboola F, Herron-Smith S, Pearson SD, Rind DM. Beta-Amyloid Antibodies for Early Alzheimer's Disease: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, April 17, 2023. https://icer.org/assessment/alzheimers-disease-2022/#timeline. Sims JR, Zimmer JA, Evans CD et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ2 Randomised Clinical Trial. JAMA (2023) Aug 8; 330 (6): 512-527. Van Dyck CH, Swanson CJ, Aisen P et al. Lecanemab in Early Alzheimer's Disease. N Eng J Med (2023) Jan 5; 388 (1): 9-21. Zeltzer E, Mundada NS, La Joie R et al. Quantitative analysis of 6,150 real-world amyloid Positron Emission Tomography (PET) scans from the Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) study. Data presented at AAIC 2022

P143- ASSESSING HEALTH SYSTEM CAPACITY FOR DELIVERY OF A DISEASE-MODIFYING THERAPY FOR ALZHEIMER'S DISEASE: A MULTI-COUNTRY ANALYSIS.

I. Mirik Danaci[1], V. Crowell[1], N. Budd[2], H.B. Nygaard[3] *(1. F. Hoffmann-La Roche Ltd - Basel (Switzerland), 2. F. Hoffmann-La Roche Ltd - Mississauga (Canada), 3. Division of Neurology and Djavad Mowafaghian Centre for Brain Health - Vancouver (Canada))*

Background: Recent estimates suggest 100 million people globally are afflicted with Alzheimer's disease (AD), many in the early stages. Disease modifying therapies (DMTs) for early AD have now received regulatory approval , however, health systems still face enormous challenges to detect, diagnose and treat all patients who could benefit. Understanding the nature and magnitude of health system bottlenecks is essential for health system planning, resource allocation and selection of optimal solutions to ensure broad and equitable patient access to AD DMTs. **Methods:** A model was developed to estimate the difference between required and available resources at each step of the AD care pathway in the near term (1-3 years) following DMT introduction. Resources considered were health care personnel, magnetic resonance imaging (MRI) and positron emission tomography (PET) scanners. Patient demand and available resources were informed by a pragmatic review of literature on AD care-seeking, provider behavior, epidemiology, and health system variables in France, Canada,Germany, Italy, Spain, the United Kingdom (UK) and the United States (US). Assumptions about required resources were sourced from clinical trial protocols, literature and expert opinion. Annual total and satisfied demand at each patient journey step, additional resources required to meet total patient demand, and, in Canada, the US and the UK, the additional patients that could be served by a shift away from PET to cerebrospinal fluid (CSF) amyloid beta testing were estimated. The time required of primary care providers (PCP) to detect possible cases of early AD was also estimated. **Results:** Given current health system resources in these countries, only 1-5% of patient demand for DMTs could be met. The largest bottlenecks occurred at diagnosis and eligibility. Satisfied demand for diagnosis was highest in Germany, where AD specialists are more numerous, and lowest in France; however, in both countries only 2- 3% of demand for treatment could be met. In Canada, the UK and the US, greater reliance on PET scans resulted in only 1-2% of demand for eligibility testing being satisfied. Neurologists, MRIs and PET scans were the largest bottlenecks across countries. Neurologist capacity was particularly limited in France, the UK and the US, where their numbers would need to increase by 41, 18 and 17 fold, respectively, to fill the gap. MRI capacity would need to increase by 10-19 fold, while Canada, Germany, the UK and the US would require 31-79 fold existing PET scan capacity. Through a shift to 90% CSF testing, two to five times more patients in Canada, the UK and the US could be tested for DMT eligibility. Detection of early AD would require an estimated 4.0 to 11.3 hours of PCP time per month. **Conclusion:** Current health system capacity is radically insufficient to deliver access to AD DMTs. The confirmation of the presence of Amyloid-β (Aβ) to determine treatment eligibility using CSF can increase diagnostic capacity at this step. Additionally, early detection solutions to facilitate patient triage in primary care, such as blood-based biomarkers, and alternative DMT formulations to reduce administration burden, will be essential. Investments in human resources and infrastructure will also be critical to alleviate health system bottlenecks.

EPIDEMIOLOGY AND CLINICAL TRIALS

P144- STATE DEPARTMENT OF MOTOR VEHICLES CLINICIAN REPORTING MANDATES OF DEMENTIA DIAGNOSES: EVIDENCE FOR RISKS AND BENEFITS.

H. Jun[1], Y. Liu[2], E. Chen[2], A. Becker[2], S. Mattke[1] *(1. Harvard Medical School - Boston (United States), 2. University of Southern California - Los Angeles (United States))*

Background: With older drivers representing the fastest growing group among the driver population and dementia prevalence increasing with age, policymakers face the challenge of balancing the objectives of ensuring road safety and mobility of elderly individuals. In the U.S., 14 states require the patient, and 4 states the treating clinician to report a dementia diagnosis to the state Department of Motor Vehicles (DMV), which may lead to revoking patients' driver's licenses. In turn, patients in states with reporting mandates may be reluctant to disclose symptoms of cognitive decline and clinicians to probe for those, potentially leading the missed or delayed diagnoses. The risk-benefit implications of these policies are unknown. Here, we reviewed the evidence of benefits and analyzed underdiagnosis rates by state. **Methods:** We calculated the observed number of patients with a dementia diagnosis for each primary care clinician with at least 25 patients in the 100% Medicare fee-for-service and Advantage Plan data from 2017 to 2019. We then estimated each clinician's expected number of dementia cases using a predictive model based on patient characteristics: age, sex, race/ethnicity, and dual eligibility status. The ratios between clinicians' observed and expected diagnosis rates are their dementia detection rates. We predicted a clinician's probability of underdiagnosing dementia, defined as a detection rate below the lower bound of the estimated 95% confidence interval of the detection rate as a function of state reporting statutes and patient panel composition. We searched for evidence of the association of reporting mandates and road safety using the published literature and 2017 to 2019 motor vehicle death data from the National Safety Council. **Results:** Primary care clinicians in states with clinician reporting mandates have an adjusted 14% probability of underdiagnosing dementia compared to 9% in states with patient reporting and

no mandates, a 56% relative difference (p<0.001). We did not find statistically different rates in clinician reporting states compared to other states for traffic deaths per 10,000 motor vehicles (1.2 vs. 1.3, respectively) and 100,000,000 motor vehicle miles (1.2 vs. 1.1, respectively). In addition, we identified a publication that found no difference in dementia diagnoses among drivers hospitalized for car accidents between states with clinician mandates and other states [1]. **Conclusions:** State statutes to mandate clinician reporting of dementia diagnoses to the DMV were associated with a higher likelihood of underdiagnosing dementia, thus creating the risk of missed or delayed diagnoses. As we did not find evidence that those mandates would improve road safety, the net effect of such policies appears negative. **References:** 1. Agimi Y, Albert SM, Youk AO, Documet PI, Steiner CA. Dementia and motor vehicle crash hospitalizations. Role of physician reporting laws. 2018;90(9):e808-e813. **Keywords:** older drivers, driver's license, dementia, primary care, underdiagnosing, reporting mandate. **Disclosures:** SM serves on the board of directors of Senscio Systems, Inc., and the scientific advisory board of AiCure Technologies, Alzpath and Boston Millennia Partners. He has received consulting or speaker fees from Biogen, C2N, Eisai, Novartis, Novo Nordisk and Roche/Genentech.

P145- AGE-SPECIFIC RELATIVE COMORBIDITY BURDEN OF MILD COGNITIVE IMPAIRMENT: A US DATABASE STUDY. G. Li[1], N. Toschi[2], V. Devanarayan[1], R. Batrla[1], T. Boccato[2], M. Cho[1], M. Ferrante[2], F. Frech[1], J. Galvin[3], D. Henley[4], S. Mattke[5], S. De Santi[1], H. Hampel[1] *(1. Eisai Inc - Nutley (United States), 2. University of Rome Tor Vergata - Rome (Italy), 3. University of Miami - Miami (United States), 4. Janssen Research & Development - New Brunswick (United States), 5. University of Southern California - Los Angeles (United States))*

Background: Early identification of Alzheimer's disease (AD) is crucial for increasing the likelihood of effective treatment outcomes, because treatments, such as recently approved amyloid-targeting drug lecanemab, are labeled for use in the mild cognitive impairment (MCI) or mild dementia stage of AD. However. MCI detection rates in primary care have been reported to be only 6-15%. We investigated the association of MCI with known comorbidities for Alzheimer's disease and related dementia (ADRD) to assess the potential of these chronic conditions to predict MCI risk. We investigated whether their predictive potential varied by age. **Methods:** MarketScan claims data were used to identify individuals aged ≥50 years with a diagnosis of MCI (but without one of dementia) and matched individuals without a diagnosis of MCI or dementia. The association between individual MCI and ADRD comorbidities, which were reported in the literature, was assessed via logistic regression. The predictive potential of comorbidities shown to be associated with MCI to discriminate MCI from propensity-score matched non-MCI individuals was evaluated via Bayesian logistic lasso regression (BLLR, a machine learning algorithm). Prediction performance was first assessed via 10-fold cross-validation within a training set of 2/3rd of the subjects, and then verified and summarized in the hold-out group of the remaining 1/3rd of the individuals via the area under the receiver-operating characteristic curve (ROC-AUC). Analyses were conducted for the overall population and by age group (50-64, 65-79, and ≥80 years). **Results:** All literature-reported 25 ADRD comorbidities had significantly higher frequencies in MCI (n=5185) compared to non-MCI (n=15,555) and could thus be considered as also comorbidities for MCI ($p < 0.05$). The association between comorbidities and MCI weakened with increasing age groups, e.g., odds ratios (ORs, MCI vs non-MCI) in 50-64, 65-79, and ≥80 years, respectively, for depression (4.4, 3.1, 2.9); stroke/transient ischemic attack (TIA) (6.4, 3.0, 2.1); and hearing loss (2.5, 2.0, 1.9) ($p \leq .05$ for all comparisons). The combined predictive potential of these risk factors for MCI also decreased in older age groups, with the ROC-AUCs of 0.75, 0.70, and 0.66 respectively, with significantly higher performance for the youngest age group ($p \leq .05$). Depression, stroke/TIA, and hearing loss were significant predictors across age groups. However, certain risk factors were age-specific predictors. Obstructive sleep apnea, for example, was significant only for the two youngest age groups but not for the 80+ age group. Weight loss was not significant for the 50 to 64 years age group. Furthermore, insomnia, bipolar, chronic pulmonary disease, metabolic syndrome, psychosis, chronic kidney disease, hyperlipidemia, and ischemic heart disease were only significant comorbidities for the youngest age group. **Conclusion:** The comorbidity burden of MCI relative to non-MCI is age dependent. A model based on comorbidities alone predicted an MCI diagnosis with reasonable accuracy. The presence of these comorbidities and other routinely collected health care information can help primary care physicians (PCPs) triage individuals, especially in younger age groups, by elevated risk for MCI, thereby focusing scarce time and resources. **Key words:** mild cognitive impairment (MCI); MCI risk prediction; Alzheimer's disease; electronic health records (EHR). **Disclosure:** Authors of this study were supported by Eisai Inc via employment or contract. The authors declared no competing interests. **References:** 1. Anderson ND. 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P146- COMORBIDITIES OCCURRING BEFORE AND AFTER DIAGNOSIS OF MILD COGNITIVE IMPAIRMENT OR ALZHEIMER'S DISEASE: A LARGE US NATIONWIDE ELECTRONIC HEALTH RECORD COHORT STUDY.

L. Vinikoor-Imler[1], O. Sanchez-Solino[1], E. Xiaomeng Yue[1], I. Boroje[1] *(1. AbbVie Inc. - Chicago (United States))*

Background: Individuals diagnosed with mild cognitive impairment (MCI) and/or Alzheimer's disease (AD) are typically at an advanced age and may be managing multiple comorbidities in addition to cognitive impairment. Understanding the comorbidities associated with MCI and AD, in the context of diverse populations, is important in clinical trials and real-world clinical practice. The primary objective of this study was to characterize comorbidities occurring before and after diagnosis of MCI and AD, compared with matched controls, in a US real-world setting. The secondary objective was to describe these diagnoses stratified by gender and race/ethnicity. **Methods:** A retrospective cohort study was conducted using electronic health records and insurance claims from the Optum® Market Clarity database. The study included patients ≥18 years old and diagnosed with MCI and/or AD between January 2017 and September 2021 using ICD-9 and ICD-10 diagnosis codes. Patients enrolled in the database for ≥12 months before receiving a diagnosis of MCI and/or AD were included in this study. The prevalence of morbidities was determined using diagnosis codes and/or specific medications and included all time available prior to the first MCI or AD diagnosis. For the subset of the population with ≥3 years of data after the first MCI or AD diagnosis, morbidities were determined post-MCI or AD diagnosis using all time prior plus these 3 years. The occurrence of these diagnoses and comorbidities were stratified by gender and race/ethnicity. Controls were matched based on age, gender, race/ethnicity, and time in the database. **Results:** The study identified 134,565 patients with MCI (56.5% female) and 65,672 patients with AD (62.3% female). The mean age at diagnosis was 69.0±15.0 years for MCI and 78.9±8.5 years for AD. The most prevalent conditions experienced before and after MCI or AD diagnoses were cardiovascular disease, hypertension, and diabetes (comorbidities any time prior until date of MCI or AD diagnosis: 75.4%, 70.4%, and 29.4%, respectively, for MCI and 80.2%, 76.3%, and 31.9%, respectively, for AD; comorbidities prior and through 3 years after MCI or AD diagnosis: 79.9%, 74.7%, and 31.2%, respectively, for MCI and 83.9%, 79.7%, and 33.6%, respectively, for AD). Within all categories of gender and race/ethnicity, patients with MCI had a higher prevalence of stroke prior to diagnosis, compared with matched controls (Standard Mean Difference>0.1). History of obesity was more frequent among controls than patients with AD (Standard Mean Difference >0.1) and a similar trend was noted for cardiovascular disease among men in some race/ethnicity groups. **Conclusions:** The proportion of patients with MCI and/or AD diagnosed with comorbidities prior to or within 3 years of diagnosis was high, as would be expected for an aging population. Comorbid cardiovascular disease and hypertension were reported with the highest prevalence. Prior stroke was more prevalent in patients with MCI than controls, and history of obesity was more frequent among controls than patients with AD. These results demonstrate that, due to the high prevalence of comorbidities, care must be taken to consider comorbidities among patients with MCI and/or AD. **Key words:** Mild Cognitive Impairment, Alzheimer's disease, Comorbidities, Cardiovascular disease. **Disclosures:** LVI, EY, and OSS are full-time employees of AbbVie and may hold AbbVie stock and/or stock options. IB is a contractor with AbbVie.

P147- BIOMARKER AND CLINICAL CORRELATIONS FOR AMYLOID TARGETING MONOCLONAL ANTIBODY (MAB) TREATMENT RESPONSES.

J. Wagg[1], N. Fournier[1], G. Lucken[1], C. Schumer[2], O. Sol[1], J. Gray[1], M. Vukicevic[1], M. Kosco-Vilbois[1], A. Pfeifer[1], J. Streffer[1] *(1. AC Immune SA - Lausanne (Switzerland), 2. EPFL - Lausanne (Switzerland))*

Background: Pathological features of Alzheimer disease include Amyloid plaques and neurofibrillary tangles. Clinical trials have demonstrated positive clinical outcomes for lecanemab, donanemab and aducanumab, specifically linking Amyloid PET lowering to clinical benefit. While not achieving clinical benefit bapineuzumab, gantenerumab and solanezumab added to and are in line with this correlation. A growing body of treatment response data is accumulating including clinical assessment, Amyloid PET, and fluid biomarker outcome data for aforementioned mAbs. The objectives of the present work

were to: (i) extract and quantify treatment response effect sizes for amyloid targeting mAbs; (ii) explore quantitative relationships between treatment responses across these mAbs. **Methods:** A prior meta-analysis of amyloid targeting mAbs was updated [1]. Public domain documents reporting clinical trial treatment responses for one or more such mAbs were sourced and response data for placebo and active treatment arms extracted including corresponding variability measures. Treatment response effect sizes were calculated as the difference between active and placebo arm changes from baseline (CBL) standardized by the estimated pooled standard deviation for these CBLs. Pairwise linear correlations between response effect sizes were calculated provided these were available for at least 3 mAbs. For all pairings, Pearson's correlation coefficients and corresponding p-values were calculated. A predefined p-value of <0.05 was deemed statistically significant. **Results:** Relationship between clinical assessment and biomarker effect sizes: Linear correlations between ADAS-Cog effect sizes versus corresponding biomarker effect sizes were strong for Amyloid PET (r=0.77, p<0.001), CSF Abeta 1-42 (r=-0.74, p= 0.036) and CSF pTau181 (r=0.79, p=0.002) but moderate for plasma pTau181 (r=0.64, p=0.087) and weak for CSF Total Tau (r=0.25, p=0.592). Linear correlations of CDR-SB effect sizes versus corresponding biomarker effect sizes were strong for Amyloid PET (r=0.7, p=0.003) and plasma pTau181 (r=0.72, p=0.043), while only weak to moderate for other fluid biomarkers. Relationship between Amyloid PET and fluid biomarker effect sizes: Linear correlations of Amyloid PET effect sizes versus corresponding fluid biomarker effect sizes were strong for plasma pTau181 (r=0.94, p<0.001), CSF Abeta 1-42 (r=-0.85, p= 0.008) and CSF pTau181 (r=0.72, p=0.009). Relationship between fluid biomarker effect sizes: None of the linear correlations between fluid biomarker effect sizes (plasma pTau181, CSF pTau181, CSF Total Tau, CSF Abeta1-42) were statistically significant. Dynamics of Amyloid PET and pTau lowering: Lecanemab and donanemab demonstrate large effect sizes for Amyloid PET and pTau lowering. For both mAbs, the time courses of Amyloid PET and plasma pTau lowering were well described by mono-exponential declines with half-lives of approximately 9.5-weeks and 15-weeks, respectively. **Conclusions:** There is a strong statistically significant correlation between clinical benefit and corresponding Amyloid PET as well as CSF pTau181 effect sizes. Amyloid PET effect sizes were strongly correlated with corresponding plasma pTau181, CSF Abeta 1-42 and CSF pTau181 effect sizes. This confirms the strong utility of biomarkers in AD drug development and in this case specifically the conversation from a target related pharmacodynamic marker (Amyloid PET) to a downstream marker (specifically pTau 181) demonstrating impact on disease modification in addition to clinical response. **Disclosures:** All authors except CS are employees of AC Immune. CS was previously employed by AC Immune. **References:** 1. Avgerinos K.I. et al. Effects of monoclonal antibodies against amyloid-β on clinical and biomarker outcomes and adverse event risks: A systematic review and meta-analysis of phase III RCTs in Alzheimer's disease. Ageing Research Reviews 2021;68:101339

P148- HIGH PREVALENCE OF AMYLOID CEREBRAL PATHOLOGY IN OLDER ADULTS WITH COGNITIVE FRAILTY - AN INDICATION FOR ANTI-AMYLOID THERAPIES? S. Sourdet[1], G. Soriano[1], B. Vellas[1] *(1. Gerontopôle - Toulouse (France))*

Background: Cognitive decline is not well understood in frail older adults. Amyloid brain deposition may be a mechanism linking frailty and cognitive decline in this population. The main objective of this study is to evaluate the prevalence of subjects with a positive amyloid cerebral status in cognitively frail older adults. **Methods:** The COGFRAIL study is an observational study of frail and pre-frail (meeting ≥ 1 Fried criteria) older adults with cognitive impairment (Clinical Dementia Rating Scale at 0.5 or 1, and with Mini Mental State Examination score³20). Cerebral amyloid pathology was assessed in 215 subjects using amyloid Positron Emission Tomography (PET) or amyloid-beta (Aβ) level in cerebrospinal fluid (CSF). Positive amyloid status was determined using either cortical/cerebellum standardized uptake value ratio (SUVR) or abnormal CSF b-amyloid-1-42 or CSF Aβ42/Aβ40 ratio values. Clinical (socio-demographics, comorbidities), physical (Fried criteria, Short Physical Performances Battery), nutritional (MNA score, BMI), cognitive (neuropsychological battery), biological and MRI data were collected at baseline, and confronted to amyloid and frailty status. **Results:** At baseline, 215 participants with an amyloid status, the mean age was 82.5 (± 4.9) years, 65.6% women, 43.3% were frail (≥3 frailty criteria) and 56.7% pre-frail (1 or 2 frailty criteria. The mean MMSE score was 24.5 (± 4.9). A total of 27.4% subjects were apolipoprotein E4 carriers. The prevalence of subjects with amyloid positive status was 58.1% (CI 95%: 51.2%-64.8%) (n=199; PET and n=16; CSF). There was no significant difference between prevalence of amyloid positive status between prefrail (63.1%) and frail (51.6%) subjects (adjusted p=0.190). Few significant differences were identified between frail and prefrail older adults according to their amyloid status. **Conclusion:** Prevalence of amyloid cerebral pathology is high in older adults with cognitive frail subjects. These results rise the question of the indication of anti-amyloid therapies in this population, and their potential benefit on both cognitive and physical function. **Disclosures:** The authors have no conflict of interest.

P149- ACCULTURATION-RELATED CHARACTERISTICS ASSOCIATED WITH RESEARCH ATTITUDES AMONG UNDERREPRESENTED POPULATIONS RECRUITED TO AN ALZHEIMER'S DISEASE PRECLINICAL TRIAL. C.R. Salazar[1], H. Shin[1], M.B. Tallakson[1], E. Duran[1], R. Eunji[1], M. Corona[1], R. Romero[1] *(1. UC Irvine Institute for Memory Impairments and Neurological Disorders - Irvine (United States))*

Background: Alzheimer's disease (AD) clinical trials remain disproportionately lacking in representation from minoritized populations, many of whom are immigrants. This study investigates the potential role of acculturation - the assimilation process into a host culture - in influencing research attitudes among immigrant populations, and its implications on their recruitment into the AHEAD 3-45 clinical trial. **Methods:** A collaboration with National Hispanic, Philippine, and Korean nurse organizations facilitated the recruitment of Hispanic/Latino, Korean, and Filipino older adults for the AHEAD 3-45 trial. Over a year, we conducted 21 recruitment events in marginalized communities of Orange County, California. We gathered sociodemographic data including acculturation-related factors (primary language, nativity status, length of U.S. residency, and immigration age) through structured

questionnaires. Research attitudes were assessed using the 7-item Research Attitude Questionnaire (RAQ). Logistic regression models were constructed to examine the associations between acculturation-related characteristics and RAQ scores, accounting for potential confounders. **Results:** Our outreach engaged around 630 Hispanic/Latino, and Asian American and Pacific Islander adults, with 472 completing the surveys. Participants were predominantly immigrants (84%) with a non-English primary language (67%), average age 58 years, and one fifth with high school education or less. Attending the event for information and concerns about memory loss were the main motivations reported by participants. Spanish and Korean speakers had lower odds (51% and 45% respectively) of scoring ≥28 on the RAQ after adjustment for age and sex (adjusted odds ratio [aOR] for Spanish language=0.49, 95% confidence interval [CI]=0.27–0.90; aOR for Korean language=0.65, 95% CI=0.36–1.19). These associations were attenuated after further adjustment by education. However, a 10-year increase in U.S. residence duration increased the odds of scoring ≥28 on the RAQ by 51%, adjusting for age, sex, and education (aOR 1.51, 95% CI=1.11–2.05). An opposite trend was observed with immigration age, where a 10-year increase resulted in 44% lower odds after similar adjustments (aOR 0.66, 95% CI=0.49–0.90). **Conclusion:** Our findings highlight the imperative of incorporating acculturation-related factors in the recruitment strategies of Alzheimer's disease clinical trials, particularly when targeting underrepresented immigrant populations. Recruitment efforts should employ culturally-sensitive approaches that are attuned to a range of acculturation experiences and language proficiencies. Future longitudinal studies are needed to determine the potential impact of acculturation on enrollment and retention in Alzheimer's disease trials. **Key words:** Recruitment; Alzheimer clinical trials; Underrepresented populations; Acculturation; Research Attitudes. **Disclosures:** Authors have no disclosures to report

P150- SILDENAFIL IS A CANDIDATE DRUG FOR ALZHEIMER'S DISEASE: REAL-WORLD PATIENT DATA OBSERVATION. F. Feixiong[1], P. Pengyue[12], J. Cummings[3] *(1. Cleveland Clinic - Cleveland (United States), 2. Indiana University - Bloomington (United States), 3. University of Nevada Las Vegas - Las Vegas (United States))*

Background: Alzheimer's disease (AD) is the main form of dementia and become one of the most expensive burdening diseases in the United States. As the traditional anti-tau or anti-amyloid selective drug discovery approaches did not benefit the AD patients, we developed an endo-phenotype disease module-based methodology for AD drug repurposing and identified sildenafil (a phosphodiesterase type 5 (PDE5) inhibitor) as a candidate drug for AD. **Methods:** We performed new patient data analyses using both the MarketScan® Medicare Supplemental database (n=7.23 million older [>65 years] subjects) and the OPTUM database (n=11.52 million older subjects). We selected a new calcium channel blocker (nifedipine) and three diuretics (bumetanide, furosemide, and spironolactone) as comparator drugs and conducted propensity score-matched observations. **Results:** We adjusted sex, age, race, and 13 comorbidities in the OPTUM analyses, as well as sex, age, geographic location, and 18 comorbidities in the MarketScan analyses. We found sildenafil usage to be associated with reduced likelihood of AD across all four drug cohorts, including bumetanide, furosemide, spironolactone, and nifedipine. Specifically, we found sildenafil vs. spironolactone was associated with a 46% reduced prevalence of AD in MarketScan (HR = 54%, 95% CI 0.32-0.66, p-value = 3.33x10-5) and a 30% reduced prevalence of AD in OPTUM (HR = 70%, 95% CI 0.49-1.00, p-value = 0.05). Subgroup analysis further revealed sildenafil usage in individuals with hypertension to be associated with reduced likelihood of AD across all four drug cohorts. Sildenafil treatment can reduce phosphorylated tau (pTau181 and pTau231), phosphorylated GSK-3b and CDK5 in the AD patient-iPSC-derived neuron model, mechanistically supporting its potential therapeutic effect in Alzheimer's disease. **Conclusion:** The new real-world patient data observation provides further support for reduced AD prevalence in patients exposed to sildenafil, suggesting that future clinical studies are warranted to identify causal relations between sildenafil use and reduced incidence of AD.

LP081- BRIDGING THE GAP: ENHANCING REPRESENTATION IN ALZHEIMER'S CLINICAL TRIALS THROUGH STRATEGIC COLLABORATION WITH PRIMARY CARE CLINICS IN DIVERSE COMMUNITIES. B. Quaning[1], S. Santeli[2], S. Carmona Torres[2], L. Lenox[2], B. Warner[2], S. Baez-Torres[2] *(1. Metro Health Inc. - Orlando (United States), 2. K2 Medical Research - Orlando (United States))*

Background: African American and Hispanic populations are at a greater risk of developing Alzheimer's Disease compared to other ethnic groups. However, there is a significant lack of participation from these communities in clinical trials related to Alzheimer's. Partnerships within research dedicated clinics and local primary care clinics have emerged as a promising solution to address the underrepresentation of diverse populations in Alzheimer's research. These partnerships aimed to leverage the existing trust and rapport that primary care clinics have established with their diverse patient populations. Primary care clinics play a vital role as gatekeepers to healthcare services, particularly for underserved communities. They are deeply embedded within the communities they serve; this unique position provides primary care clinics with a valuable opportunity to engage patients in research initiatives. This study aims to evaluate the impact of a research dedicated clinic and a local geriatric primary care clinic in increasing diverse participation rates in Alzheimer's clinical trials. **Methods:** We conducted a descriptive, retrospective study, including all subjects that participated in Alzheimer's related trials and were referred to our site by geriatric primary care clinics from November 2022 to May 2023. Demographic data was collected from the medical records. The database was checked for errors and corrected to keep patient 's confidentiality. Simple descriptive statistics were generated to summarize distributions and proportions on study variables. Data was described using percentages. **Results:** Of 200 patients, 124 were female (62%). The mean age was 72.02 ± 8.90 years (range, 40-98 years), and the median age was 73 years. Most patients were white non-Hispanic (44.5 %), 54 were black non-Hispanic (27 %), 47 were white-Hispanic (23.5 %), and the rest of participants native Hawaiians, and Asians. Of 200 patients prescreened, 66 participated in Alzheimer's trials (33%). **Conclusion:** Partnerships between research dedicated clinics and local primary care clinics serving diverse communities have demonstrated significant potential in increasing research participation rates. By leveraging the existing trust, rapport, and accessibility of primary care clinics, these partnerships have the ability to address the underrepresentation of diverse populations in research studies. The collaborative approach allows for seamless integration of research participation into routine primary care

visits, improving convenience for patients and facilitating the translation of research findings into clinical practice. By implementing such partnerships, we can strive towards more inclusive and representative research outcomes, ultimately advancing medical knowledge and promoting equitable healthcare interventions.

LP082- PREDICTORS OF RESPONSE RATE TO A MAILED INVITATION TO PARTICIPATE IN A DEMENTIA PREVENTION LIFESTYLE INTERVENTION TRIAL (U.S. POINTER): HOUSTON SITE EXPERIENCE.

V. Pavlik[1], M. Yu[1], H. Shields[1], A. Alexander[2], R. Trevino-Whitaker[2], J. Valenta[2], R. Elbein[3], A.M. 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. We assessed the demographic predictors of response rate to a mailed recruitment letter inviting participation in a multi-modal lifestyle intervention trial to prevent cognitive impairment in individuals aged ages 60-79 with two or more risk factors for dementia (the U.S. POINTER trial). **Methods:** Two clinic systems serving a large, racially and ethnically diverse metropolitan area in the south-central U.S. collaborated to serve as one of five sites for the U.S. POINTER trial. Potentially eligible participants were identified through an 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 utility of a mailed letter campaign as a recruitment tool in a diverse patient population, we identified the demographic variables associated with the response rates to the recruitment letter, including age, sex, racial and ethnic group identification, area deprivation index (ADI), and recruitment period (to account for secular trends in response). The ADI, a measure of average neighborhood education and income, ranges from 1 to 100, with lower scores indicating the least amount of neighborhood deprivation. Using descriptive statistics and logistic regression modeling, we identified significant predictors of response. **Results:** 101,651 individuals of 104,993 who received a letter had addresses that could be matched to NDI data and were included in the analysis. The self-identified racial and ethnic group distribution of letter recipients was 47.7% White/Caucasian, 24.5% Black/African-American, 16.5% Hispanic/Latino, and 11.3% other. Forty-four percent of African-American letter recipients and 38.1% of Hispanic recipients were in the highest (worst) quartile of ADI, compared to 9.5% of Caucasian recipients. Overall, 2404 (2.4%) contacted the study web site to begin the enrollment process. Response rates across racial and ethnic group categories were 3.3%, 1.7%, 1.4% and 1.6% respectively ($p<.001$). Females were slightly more likely to respond than males (2.6% versus 2.1%, $p<.001$). Response rate was inversely correlated with ADI, from 1.4% in the highest quartile (greatest neighborhood deprivation) to 3.1% in the lowest quartile (least neighborhood deprivation). All demographic variables contributed significantly and independently to response rate in multiple logistic regression analysis. There was no significant interaction between ADI quartile and racial/ethnic group classification in altering the probability of response. Although racial/ethnic group identity and area deprivation independently affected the odds of response, 62% of African-American individuals, and 55% of Hispanic individuals who responded were from neighborhoods above the median ADI (i.e., worse deprivation). **Conclusion:** In spite of lower response rates to a recruitment letter by patients from under-represented groups identified through an EMR query, the resulting sample was both ethnically and socioeconomically diverse. Recruitment to clinical trials from large EMR databases in demographically diverse communities can be an effective tool to increase diversity.

LP083- ALZHEIMER'S DISEASE LINKAGE TO EVIDENCE (AD-LINE) STUDY: AN ANALYSIS OF CONCORDANCE BETWEEN CLINICAL DIAGNOSIS AND EVIDENCE OF AD DIAGNOSIS IN REAL-WORLD US CLAIMS DATA.

H. Fillit[1,2], S. Seleri Assunção[3], C. Wallick[3], I.M. Abbass[3], C. Ng[3], T.M. To[3], K. Raimundo[3], T. Majda[3], D. Glazebrook[3], O.V. Tcheremissine[4] *(1. Alzheimer's Drug Discovery Foundation, - New York City (United States), 2. Departments of Geriatric Medicine, Medicine, and Neuroscience, Icahn School of Medicine at Mount Sinai - New York City (United States), 3. Genentech, Inc., a member of the Roche Group - South San Francisco (United States), 4. Department of Psychiatry, Atrium Health Behavioral Health Charlotte - Charlotte (United States))*

Background: Randomized controlled trials are considered the gold standard for evidence generation; however, they often lack generalizability to the real world. Real-world evidence shows that Alzheimer's disease (AD) diagnosis is frequently missed or delayed until later stages. Here we demonstrate a novel linkage study design between real-world Medicare claims data and data from the GRADUATE phase 3 clinical trials of gantenerumab. In this analysis, we sought to understand differences in diagnosis of AD in the real world using US data, compared to trial participants with early symptomatic AD (ie, mild cognitive impairment [MCI] due to AD or mild AD dementia) as determined GRADUATE trial investigators. **Methods:** Alzheimer's Disease Linkage to Real-World Evidence (AD-LINE) is a noninterventional cohort study of patients aged ≥66 years with early symptomatic AD and beta-amyloid pathology confirmed via amyloid PET or CSF who were enrolled in the GRADUATE studies and in Medicare Fee-for-Service or Medicare Advantage plans in the US. Medicare claims data containing an MCI, dementia, or AD diagnosis on any type of claim were analyzed behind a firewall and the Research Data Assistance Center used participant's clinical trial subject identifier, Medicare beneficiary identifier (MBI), date of birth, and sex for linkage. Although not a planned analysis, rates of MCI, dementia, or AD diagnosis in real-world Medicare claims were used to determine concordance with clinically confirmed diagnoses of MCI due to AD or mild AD dementia among the AD-LINE cohort. Due to the Centers for Medicare & Medicaid Services (CMS) sample size reporting restrictions, only descriptive statistics related to concordance are reported. **Results:** In total, 111 US GRADUATE participants consented to having their claims linked. After ensuring linkable MBIs, Medicare Parts A/B enrollment, and no health maintenance organization (HMO) enrollment (for which claims are not required to be submitted to CMS), claims data from 61 of the 111 participants were eligible for linking and analysis. The mean age among the 61 participants was 74.8 years (SD: 5.5); 35 participants (57.4%) were female. At clinical trial entry, 30 participants (49.2%) had MCI due to AD and 31 (50.8%) had mild AD dementia. Collectively, 85.25% of the overall participants had a claim with an MCI, dementia, or AD diagnosis within the 12 months prior to clinical trial

entry, whereas 80.65% of participants entering the trial with mild AD dementia had a claim with an AD diagnosis. In the overall cohort, 39.34% had a claim for MCI, 32.79% had a claim for dementia, and 67.21% had a claim for AD. Additional data on healthcare resource utilization and AD progression in the AD-LINE cohort will be distributed as they become available. **Conclusions:** Overall, there was a relatively high concordance between the rates of clinically confirmed diagnosis and evidence of diagnosis in real-world US claims data, supporting the use of real-world data in early symptomatic AD. This analysis helps to confirm the validity of this type of data linkage to key stakeholders (eg, healthcare professionals, payers, population health decision makers, and researchers) that may benefit from the insights it provides. **Key words:** early symptomatic Alzheimer's disease, real-world evidence. **Disclosures:** HF is an unpaid consultant for Roche/Genentech. OVT is a consultant for Roche/Genentech and received research support from Athira, Eli Lilly, Concept, and Genentech/Roche. KR, SSA, IMA, CN, TMT, and TM are employees/shareholders of Genentech, Inc. CW was an employee and shareholder of Genentech, Inc., at the time this study was conducted. **Sponsor:** Genentech, Inc., a member of the Roche Group

LP127- CHARACTERISTICS OF ADULTS WITH INCIDENT COGNITIVE IMPAIRMENT IN A POPULATION-BASED STUDY OF COGNITIVE AGING. K. Ghoniem[1], J. A. Aakre[2], A. M. Castillo[2], M. Elminawy[1], E. A. Brauer[1], P. Vemuri[3], C. R. Jack Jr.[3], J. Graff-Radford[1], D. S. Knopman[1], R. C. Petersen[1], M. Vassilaki[1] *(1. Department of Neurology, Mayo Clinic - Rochester (United States), 2. Department of Quantitative Health Sciences, Mayo Clinic - Rochester (United States), 3. Department of Radiology, Mayo Clinic - Rochester (United States))*

Background: As treatment for Alzheimer's disease (AD) is becoming available, the characteristics of older adults in the community who are diagnosed with mild cognitive impairment and dementia need to be clearly described so that clinical trial populations represent those at risk for cognitive impairment and new treatments are generalizable to the community. **Methods:** The Mayo Clinic Study of Aging (MCSA) is a population-based cohort study of cognitive aging in Olmsted County (MN) with serial comprehensive cognitive evaluations every 15 months. The study aimed to describe the characteristics of community-dwelling participants when they were diagnosed with incident (new) mild cognitive impairment (MCI) or mild dementia diagnosis (Clinical Dementia Rating global score 0.5-1) at a follow-up visit. All participants for the current study were cognitively unimpaired and 50 years old or older at MCSA baseline. **Results:** There were 965 MCSA participants with an incident diagnosis of MCI (n=926) or mild dementia (n=39) during follow-up; 49.2% were female, and 308 (32.4%) were apolipoprotein E ε4 carriers. The mean age (standard deviation (SD)) at the visit was 83.2 (7.4) years for incident MCI and 84.1 (8.8) years for incident dementia cases. Participants had a mean (SD) Mini-Mental State Exam score of 25.7 (1.8) for MCI and 22.3 (3.5) for dementia cases, and a Functional Activities Questionnaire mean (SD) score of 2.3 (4.3) for MCI and 13.8 (9.3) for dementia cases. Participants also presented with hearing (334 (36.7%)), visual (156 (17.2%)), and walking/balance (384 (42.3%)) difficulties that interfered with everyday activities. Twelve percent (n=104) had Beck Depression Inventory-II>13 (more than minimal depressive symptoms), and 152 (17.0%) had Beck Anxiety Inventory>7 (more than minimal anxiety symptoms). Twenty-six percent (n=250) of the participants had diabetes, 787 (81.8%) had hypertension, and 90 (9.8%) of MCI cases and 9 (23.1%) of dementia cases had a history of stroke. Forty-four percent (n=422) of the participants had coronary artery disease, 190 (19.8%), had congestive heart failure, 206 (21.3%) had chronic kidney disease, 224 (26.8%) had obesity (body mass index>=30) and 192 patients (20.8%) were taking anticoagulants. Thirty-two percent (n=304) of the participants had a history of cancer (ever). Most participants with incident cognitive impairment (69.3%) (N=669) had four or more medical conditions. They had a mean (SD) of 3.2 (1.7) cardiometabolic conditions and a Charlson comorbidity index (excluding dementia) of 5.5 (3.8). **Conclusions:** The most probable community-dwelling candidates for clinical trials and new treatments for Alzheimer's disease and related dementias will be older adults with multiple medical conditions. **Key words:** Mild cognitive impairment, mild dementia, chronic conditions, clinical trial candidates. **Disclosures:** Khaled Ghoniem, Jeremiah A. Aakre, Anna M. Castillo, Mohamed Elminawy, and Emma A. Brauer have no disclosures. C.R. Jack Jr. has no financial conflicts to disclose; he receives research support from NIH and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic. P. Vemuri receives research funding from NIH. J. Graff-Radford receives support from the NIH, serves on the DSMB for StrokeNET, and is an investigator in clinical trials sponsored by Eisai and the Alzheimer's Treatment and Research Institute at the University of Southern California. D.S. Knopman serves on a Data Safety Monitoring Board for the Dominantly Inherited Alzheimer Network Treatment Unit study. He served on a Data Safety Monitoring Board for a tau therapeutic for Biogen (until 2021) but received no personal compensation. He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the University of Southern California. He has served as a consultant for Roche, Samus Therapeutics, Magellan Health, Biovie, and Alzeca Biosciences but receives no personal compensation. He attended an Eisai advisory board meeting for lecanemab on December 2, 2022, but received no compensation. He receives funding from the NIH. R.C. Petersen serves as a consultant for Roche, Inc., Eisai, Inc., Genentech, Inc., Eli Lilly, Inc., and Nestle, Inc., served on a DSMB for Genentech, receives royalties from Oxford University Press and UpToDate, and receives NIH funding. M. Vassilaki received research funding from F. Hoffmann-La Roche Ltd and Biogen in the past and consulted for F. Hoffmann-La Roche Ltd, unrelated to this work; she currently receives research funding from NIH and has equity ownership in Amgen, Johnson and Johnson, Medtronic, and Merck.

LP128- STUDY PARTNER EFFECT ON RETENTION IN ALZHEIMER'S DISEASE TRIALS. S.Y. Ryu[1], M. Nuño[1], D. Gillen[2], J. Grill[2] *(1. University of Southern California - Los Angeles (United States), 2. University of California, Irvine - Irvine (United States))*

Background: Study retention is crucial to clinical trial success since greater than expected dropout rates can lead to reduced power and biased results. Because Alzheimer's disease trials require the enrollment of a study partner and a participant, the success of these trials also depends on the study partner. Previous work has shown that the study partner requirement is often a barrier to recruitment into Alzheimer's disease trials (Grill and Karlawish 2010), and that there may be differences in trial outcomes for different study partner types. It is unclear whether there are also differences in dropout rates by study partner type. **Objective:** To investigate whether study partner type was associated with the risk of dropout in two large

phase 3 registration trials. **Methods:** We used data from two trials of bapineuzumab for patients with mild-to-moderate AD, one for APOE e4 carriers and one for non-carriers. Data were provided by the sponsor of the trials, Janssen Research & Development, LLC for use in these analyses. The co-primary endpoints were the change from baseline to week 78 in the Disability Assessment for Dementia (DAD) and the 11-item AD Assessment Scale (ADAS Cog-11). Completers were defined as participants with baseline and week 78 scores on ADAS Cog-11 or DAD. Participants were excluded from our analyses if they did not declare a study partner type in the Resource Utilization in Dementia-Lite (RUD-Lite) or if they were missing ADAS Cog-11 and DAD at baseline. Time-to-dropout was defined as the time from study enrollment to the time of the last visit during which ADAS Cog-11 or DAD were conducted. Cox proportional hazards models were used to compare the risk of dropout for different study partner dyad types. Age, sex, MMSE, DAD, and ADAS-Cog 11 at baseline were selected a priori as potential confounders. **Results:** Data were available for 1,234 participants in the non-carrier study and 1,221 participants in the carrier study. Of these patients, 1,229 from the non-carrier and 1,097 from the carrier study were included in our analysis. In both trials, we observed a higher proportion of participants enrolled with a spouse (non-carriers: 817, 66.3%; carriers: 837, 76.3%). Participants who enrolled with an adult child were older, on average, compared to participants who enrolled with a non-child study partner. Approximately half of the sample was female, with a higher percentage of females among adult child dyads. Observed completion rates were higher among spousal dyads in both studies. In the non-carrier trial, approximately 75% of spousal dyads completed the trial while 60% of adult-child dyads and 54% of dyads with other study partners completed the trial. Differences in the proportion of completers were lower in the carrier study, with approximately 75%, 73%, and 70% of completers among spousal, adult child, and "other" dyads. After adjusting for a priori selected potential confounders, the estimated hazard ratios in the non-carrier trial were 1.67 (95% CI: 1.29, 2.18) and 2.06 (95% CI: 1.56, 2.73) when comparing child dyads to spousal dyads and "other" dyads to spousal dyads, respectively. In the carrier trial, the estimated hazards ratios were 0.81 (95% CI: 0.57, 1.14) and 1.26 (95% CI: 0.84, 1.90) when comparing child and other spousal dyads, respectively. **Conclusion:** We found that a higher proportion of spousal dyads completed the trials compared to other dyad types. Differences in the completion rates, however, were lower in the carrier study compared to the non-APOE4 carrier study. The reasons for these differences are unclear. Potential contributors include differential barriers to and motivation toward continued study participation. Future work will further investigate potential explanations for the differences in the results of the two studies. Understanding the factors driving these differences may help understand reasons for dropout, aiding in the development of new retention strategies. **Conflicts of Interest:** JDG has received research support from Biogen, Eli Lilly, Genentech, Eisai, BrightFocus Foundation, the Alzheimer's Association, and the National Institute on Aging and has consulted for SiteRx, Cogniciti, and Flint Rehab. He is a paid section editor for Alzheimer's & Dementia. The other authors do not have conflicts of interest to declare. **References:** Grill, Joshua D., and Jason Karlawish. 2010. Alzheimer's Research & Therapy 2 (6): 34. https://doi.org/10.1186/alzrt58.

ANIMAL MODEL

P151- DECIPHERING THE MECHANISMS OF ACTION OF COGNITIVE GAIN USING THE MULTIDOMAIN LIFESTYLE INTERVENTION PROTOCOL – FROM HUMAN RCTS TO MICE.

V. Alanko[1,2], F. Eroli[2], A. Solomon[3,4], K. Håkansson[1], T. Ngandu[5], T. Hartmann[6,7], P. Nilsson[2], M. Kivipelto[1,4,8], S. Maioli[2], A. Matton[1,2,4] *(1. Division of Clinical Geriatrics, Department of NVS, Karolinska Institutet - Solna (Sweden), 2. Division of Neurogeriatrics, Department of NVS, Karolinska Institutet - Solna (Sweden), 3. Institute of Clinical Medicine/Neurology, University of Eastern Finland - Kuopio (Finland), 4. Ageing Epidemiology (AGE) Research Unit, Imperial College London - London (United Kingdom), 5. Population Health Unit, Finnish Institute for Health and Welfare - Helsinki (Finland), 6. Deutsches Institut für Demenz Prävention (DIDP), Saarland University - Homburg (Germany), 7. Department of Experimental Neurology, Medical Faculty, Saarland University - Homburg (Germany), 8. Theme Inflammation and Aging, Karolinska University Hospital - Solna (Sweden))*

Background:AD/dementia is multifactorial, involving abnormalities in several cellular and molecular pathways. Therefore, multimodal interventions targeting multiple risk factors and disease mechanisms early in the disease process are most likely to be effective. This was shown by the multimodal lifestyle FINGER RCT in at-risk older adults without substantial cognitive impairment. The FINGER RCT is not only providing a protocol to prevent or delay dementia onset but also provides a model to better understand molecular mechanisms of cognitive gains which is important for developing more tailored interventions and new drug targets. **Methods:** We are currently studying blood biomarkers in samples from the FINGER RCT (eg. brain derived neurotrophic factor (BDNF), inflammatory markers and -omics, AD biomarkers). Yet, since systemic changes in plasma not only reflect brain-specific mechanisms we have set up a novel protocol to study multimodal lifestyle intervention in mice. The protocol was developed to recapitulate the FINGER and MIND-AD clinical trials. In the lifestyle Prevention of Alzheimer's Working-mechanimsms (PAW) group, mice were given access to running wheels (voluntary exercise), Fortasyn Connect (healthy diet), and subjected to cognitive training in an IntelliCage (IC) environment. To separately investigate the effects of an intervention resembling vascular monitoring, a group of mice was given Atorvastatin and Enalapril mixed in the diet. Control mice were housed in normal conditions. Blood pressure and blood samples were collected at baseline and at the end of the protocol. A full battery of cognitive tests were performed at the end of the protocol and after scarifying the mice a range of tissues were dissected and stored for future analyses. **Results:** In the FINGER human RCT we show that levels of proBDNF, but not mature BDNF, predicted memory gains over the 2-year intervention (b: 0.647, p=0.002). Participants who increased their proBDNF significantly improved their memory over time. Furthermore, the mouse PAW study aimed to evaluate the feasibility of an innovative housing setup that provides a lifestyle intervention for mice allowing to study brain specific changes. Definite strengths of the protocol are the minimal need for mouse handling, the possibility of group housing, and that the intervention runs fully in a homecage environment, thus reducing stress. PAW mice on a group level were able to reduce the error rates (incorrect corner visits) by approximately 25% in all paradigms showing that the cognitive training was succesful. At the end of the protocol both PAW and pharma groups had

significantly lowered their blood pressure compared to the control group. Importantly the PAW group also improved in memory compared to controls whereas the pharma group did not change. In a next step, we will analyze the molecular changes. **Conclusion:** In concert with blood sample analyses of samples from the FINGER RCT we here created an innovative programme to study brain mechanisms of cognitive gains in mice. We constructed a way of performing multimodal lifestyle intervention in mice in a homecage environment. Moreover, our protocol minimizes stress due to handling and provides quantitative data for both cognitive training and exercise. The future steps involve studying animal models of cognitive decline, Alzheimer's disease and vascular/metabolic dysfunction to assess mechanisms impacted by lifestyle change. **Clinical Trial Registry:** FINGER: NCT01041989; https://clinicaltrials.gov. **Disclosures:** The authors declared no competing interests.

P152- SUBCELLULAR AND SECRETORY EFFECTS OF THE APPNL-F KNOCK-IN IN MICE NEURONS. S. Schediin-Weiss[1], Y. Yu[1], R.Z. Zhou[1], L.O. Tjernberg[1] *(1. Karolinska Institutet - Solna (Sweden))*

Background: Several rodent models have been developed to enable studies on the mechanisms behind Alzheimer disease (AD). Many of these models have focused on overexpressing the Aβ precursor protein (APP), leading to increased levels of not only Aβ but also APP and APP-derived fragments. To overcome the problems associated with overexpression, the knock-in mouse model AppNL-F was developed [1]. Here, we characterize the effects of these mutations at a cellular and subcellular level. **Objective:** Our aim is to elucidate how the APP processing pathway is affected in the AppNL-F mouse model. **Methods:** To truly resolve the subcellular compartments, we used the super-resolution microscopy technique Stimulated Emission Depletion (STED) microscopy to study fluorescently labeled proteins of interest in primary neurons. We used validated antibodies directed to the amyloid precursor protein (APP), its C-terminal fragments (CTFs) and Aβ42 in combination with subcellular markers, with a similar approach as we used previously in wild-type (WT) mice [2]. We quantified the colocalization of APP/APP-CTF with the organelle markers and compared the distribution in neurons from AppNL-F compared to WT mice. Intracellular and secreted levels of Aβ42 were measured with ELISA. **Results:** In AppNL-F hippocampal neurons, the levels of APP/APP-CTF were enriched in clathrin-coated pits and/or clathrin-coated vesicles in soma and in early endosomes in neurites. Importantly, the levels of APP/APP-CTF were significantly elevated in axons in AppNL-F neurons, while the level of APP-CTF in mature synapses was decreased. Aβ42 levels measured by ELISA were slightly elevated in neuronal lysates but, in contrast, several-fold increased in the medium. **Conclusion:** APP endocytosis, transport and processing is enhanced in neurons derived from AppNL-F compared to WT mice. The subcellular compartments along this pathway where accumulations occur are clathrin-coated pits and/or clathrin-coated vesicles in soma as well as immature presynapses along axons. These data could be used to design subcellular-targeting treatment strategies by making molecules that inhibit APP-processing pathways in specific subcellular compartments. **References:** 1. Saito, T., et al., Single App knock-in mouse models of Alzheimer's disease. Nat Neurosci, 2014. 17(5): p. 661-3. 2. 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.

LP084- TREM2 AGONISM AFFECTS HUMAN MICROGLIA RESPONSE IN THE PRESENCE OF AMYLOID PATHOLOGY IN VIVO. P. Flagstad[1], I. Geric[1,2,3], M. Polydoro[1], L. Wolfs[2,3], A. Misbaer[1,2,3], A. Nair[2,3], L. Sans[1], M. Dalby[1], J. Zheng[1], T. Sommer Bisgaard[1], L.C. Roenn[1], R. Balice-Gordon[1], B. De Strooper[2,3,4], N. Plath[1] *(1. Muna Therapeutics - Copenhagen (Denmark), 2. Centre for Brain and Disease Research, Flanders Institute for Biotechnology (VIB) - Leuven (Belgium), 3. Department of Neurosciences and Leuven Brain Institute, KU Leuven - Leuven (Belgium), 4. UK Dementia Research Institute at UCL, University College London - London (United Kingdom))*

Background: Pharmacological activation of TREM2 represents a novel therapeutic approach to slow Alzheimer´s disease (AD) progression. Loss-of-function variants in TREM2 have been linked to early- and late-onset AD and exacerbate amyloid pathology in animal models of disease. Genetic ablation of TREM2 function has been shown to lock microglia in a homeostatic state, preventing a switch to a disease-associated state supporting the phagocytotic clearance of misfolded proteins and cellular debris. Monitoring the impact of TREM2 activation in vivo requires humanized animal models due to low TREM2 gene sequence homology, inherent differences in immune responses and phenotypic disparities in vitro and in vivo between mouse and human microglia. Here, we study the impact of TREM2 agonism on xenografted human microglia in a mouse model of amyloid pathology. **Methods:** To study the impact of TREM2 agonism on human microglia in the presence of amyloid pathology in vivo, hESC-derived microglia were transplanted into the brain of Rag2 -/- | IL2rg-/- | hCSF1 KI | APPNL-G-F mouse pups. At 7 months of age, xenografted animals were treated systemically with the selective, potent and brain penetrant TREM2 agonist MTX-298 (50 mg/kg, twice daily for one day) or vehicle. 24h after the first dose, human microglia were isolated from the brain of xenografted mice and analyzed for changes in gene expression by qPCR and single cell RNA sequencing. **Results:** The activation of TREM2 on human microglia by MTX-298 led to differential gene expression across range of functionally related genes, including an increase in expression of selected cytokines and chemokines. Interestingly, changes were observed in xenografted human microglia in the presence of amyloid pathology, but not in mouse microglia cells. Other changes in the transcriptome profile indicate a shift in microglia subpopulations towards immune reactive states in TREM2-agonist-treated xenografted APPNL-G-F mice. These effects were observed at exposures consistent with activation of TREM2 in vitro and in vivo assessed by pSYK and sTREM2 levels. **Conclusion:** The human microglia xenograft mouse model is a highly valuable tool to study the impact of pharmacological TREM2 activation and other manipulations on human microglia in the presence and absence of neuropathology. **Key words:** TREM2, microglia, xenografted mice, gene expression. **Disclosures:** Presenting author is full time employee of Muna Therapeutics.

LP085- KIT-13, AN INNOVATIVE PLASMALOGEN DERIVATIVE, IMPROVED MEMORY AND COGNITION THROUGH SUPPRESSION OF NEUROINFLAMMATION IN MURINE MODELS. M.S. Hossain[1], S. Mawatari[1], M. Honsho[2], T. Fujino[3] *(1. Institute of Rheological Functions of Food - Fukuoka (Japan), 2. Kyushu University - Fukuoka (Japan), 3. Neurocores - Boston (United States))*

Background: Background: Plasmalogens (Pls) are specialized phospholipids crucial for brain health. Their depletion with age and exposure to stress is linked to the disease pathologies

involving cognitive decline and neuroinflammation. In recent years, a wide array of beneficial effects of plasmalogens, including cell signaling modulation and inhibition of neuroinflammation [1, 2], have been elucidated. Also, a promising memory-enhancing effect of scallop-derived natural Pls (sPls) in various stages of Alzheimer's disease (AD) patients [3] has been reported from our clinical studies. To provide more potent efficacy with the same safety profiles as sPls, we developed a blood-brain barrier-transmissible plasmalogen derivative, KIT-13, using our technology and its anti-neuroinflammatory and cognitive improvement effects were investigated in this study. **Methods:** We synthesized and rigorously analyzed a Pls derivative, designated as KIT-13, utilizing techniques such as NMR, IR, and Mass spectrometry assays. We assessed KIT-13's entry into the mouse brain following oral ingestion through LC-Mass/Mass spectrometry assays. Neuroinflammation was evaluated by characterizing the morphology of astrocytes (GFAP positive) and microglia (Iba1 positive) cells using immunohistochemistry (IHC) assays in adult male mice (C57BL/6J). Neuronal cell apoptosis was confirmed using the In Situ Cell Death Detection Kit (Roche). In vitro studies were conducted in mouse-derived microglial cells (MG6 and BV2) to confirm nuclear entry of the NF-kB protein (p65) and assess the anti-neuroinflammatory effects of Pls and its derivative in an LPS-induced inflammation model. Neurogenesis (DCX positive neurons) and BDNF expression were examined to gauge the impact of KIT-13 and sPls on neuronal plasticity. ELISA assays were performed to screen pro-inflammatory cytokines. **Results:** Oral administration of the novel Pls derivative, KIT-13, reduced the LPS-induced NF-kB activation in microglial cells and downregulated the expression of pro-inflammatory cytokines (TNF-alpha, MCP-1, IL-1beta). Additionally, KIT-13 induced BDNF expression in the hippocampus of mouse brains (in vivo) and neuronal cell lines (in vitro) while preventing neuronal apoptosis by enhancing the activation of ERK and AKT proteins. KIT-13 also promoted neurogenesis (DCX-positive neurons in the hippocampus). LC-MS/MS data indicated the presence of KIT-13 in the brain following oral administration, suggesting its ability to cross the blood-brain barrier. KIT-13 effectively mitigated learning and memory impairment induced by LPS injection in adult male mice, with more pronounced memory enhancement than sPls. **Conclusion:** Natural scallop-derived plasmalogens (sPls) have been reported to improve cognition in AD patients. KIT-13, a plasmalogen derivative, is designed and developed to produce more effects directly in the brain. KIT-13 has shown potent efficacy in inhibiting neuroinflammation, promoting neurogenesis, and enhancing memory compared to sPls. KIt-13 can be a potent therapeutic candidate to treat Alzheimer's disease with its multimodal actions, including cognitive improvement in the brain. **Key words:** plasmalogen derivative, neuroinflammation, memory improvement, neurogenesis, Alzheimer's diseases. **Disclosures:** We declare no competing interests related to present our research data. **References:** 1. Goodenowe D.B. et al. Front Cell Dev Biol 2022; 10:864842. https://doi.org/10.3389/fcell.2022.864842; 2. Hossain M.S. et al. Brain Research Bulletin. 2023 Jan;192:56-61. https://doi.org/10.1016/j.brainresbull.2022.11.005; 3. Fujino T. et al. EBioMedicine. 2017 Mar; 17: 199–205. https://doi.org/10.1016/j.ebiom.2017.02.012

LP086- PROTECTIVE EFFECTS OF NEW COMBINATION DRUG FPT-03 IN OXIDATIVE DAMAGES AND COGNITIVE IMPAIRMENTS AGAINST TRAUMATIC BRAIN INJURY.

W. Chao[1], B. Chen[1], C.Y. Tseng[2] *(1. Future PharmTech - Taipei (Taiwan, Republic of China), 2. Chung Yuan Christian University - Taoyuan (Taiwan, Republic of China))*

Background: A traumatic brain injury (TBI) causes abnormal proliferation of neuroglial cells and over-release of glutamate. This may induce oxidative stress and inflammation, and lead to neuronal death, memory deficits and even vascular cognitive impairment (VCI) if the condition is severe. Many of these factors are also linked to increased risk of Alzheimer's.However, there are currently no FDA-approved drugs specifically for the treatment of VCI. However, some medications that are used to treat Alzheimer's disease, such as cholinesterase inhibitors (donepezil, galantamine, and rivastigmine), may also be prescribed off-label to help manage symptoms of vascular dementia. These medications can help improve cognitive function and may also help with behavioral and psychological symptoms. **Method:** Sildenafil is a medication that is commonly used to treat erectile dysfunction and pulmonary arterial hypertension. While evidence from animal studies and small clinical trials has suggested that sildenafil may improve cognitive function in people with vascular dementia (1, 2). Here we use the investigational product, FPT-03, a new combination drug containing sildenafil and two other compounds as a potential treatment for vascular dementia in SD rat model. **Result:** This study examined whether FPT-03 inhibits the production of reactive oxygen species and inflammatory response, thereby protecting neurons from glutamate excitotoxicity, promoting the regeneration of injured neurites, and ultimately alleviating TBI-induced spatial memory deficits. We found that FPT-03 inhibits the generation of intracellular reactive oxygen species induced through glutamate excitotoxicity and reduces neuronal death in cortical neurons. In neurite injury assay, the length of the regenerated neurite was longer in the FPT-03-treated group than that of the control group. Our SD rat model has determined that FPT-03 alleviates TBI-induced spatial memory deficits, expedites the restoration of the injured areas, and induces the secretion of brain-derived neurotrophic factors and lowers the production of astroglia. **Conclusion:** In conclusion, FPT-03 protects neurons from TBI-induced oxidative stress and glutamate excitotoxicity, promotes nerve fiber regeneration, and reduces TBI-induced vascular cognitive impairment. **Key words:** FPT-03, TBI, VCI, dementia. **Disclosures:** CY Tseng received a grant from Future PharmTech. The authors declared no competing interests. **References:** 1. Xiong Y, Wintermark P. The Role of Sildenafil in Treating Brain Injuries in Adults and Neonates. Frontiers in Cellular Neuroscience [Internet]. 2022 [cited 2023 Mar 26];16. Available from: https://www.frontiersin.org/articles/10.3389/fncel.2022.879649; 2. Venkat P, Chopp M, Zacharek A, Cui C, Landschoot-Ward J, Qian Y, et al. Sildenafil treatment of vascular dementia in aged rats. Neurochemistry International [Internet]. 2019 Jul 1 [cited 2023 Mar 26];127:103–12. Available from: https://www.sciencedirect.com/science/article/pii/S019701861830559X

LP087- NONFIBRILLAR DUTCH MUTANT AMYLOID BETA (AB) AGGREGATES (OLIGOMERS) REVEALED BY ANTI-PREFIBRILLAR OLIGOMER ANTIBODY A11 AND FITC-PEPTIDE IMAGING ARE ASSOCIATED WITH AGING-RELATED SYNAPTIC DYSFUNCTION BUT CAUSE NO DETECTABLE INFLAMMATION. S. Gandy[1], E. Castranio[1] , M. Varghese[1] , E. Argyrousi[2], K. Tripathi[3], C. Glabe[4], E. Levy[5], M. Wang[1], B. Zhang[1], W. Lubell[6], B. Guerin[7], S. Rahimipour[8], D. Dickstein[9], O. Arancio[2], M. Ehrlich[1] *(1. Icahn School of Medicine - New York (United States), 2. Columbia U - New York (United States), 3. Bar Ilan U - Raman Gat (Israel), 4. U Calif Irvine - Irvine (United States), 5. NYU & NKI - New York (United States), 6. U Montreal - Montreal (Canada), 7. U Sherbrooke - Sherbrooke (Canada), 8. Bar Ilan U - Raman Gat (Canada), 9. Uniformed Health Sci U - Bethesda (United States))*

Background: Clinicopathological studies of Alzheimer's disease (AD) have demonstrated that synaptic or neuronal loss and clinical cognitive decline do not reliably correlate with the burden of fibrillar amyloid. We created a transgenic mouse model overexpressing Dutch (E693Q) mutant human amyloid precursor protein (APP) driven by the pan-neuronal Thy1 promoter [1]. The Dutch mutation disrupts the formation of antiparallel β-sheets, thereby preventing fibrillogenesis and favoring the accumulation of nonfibrillar oligomeric Aβ peptide (oAβ). Nonamyloidogenic APP α-carboxyl-terminal fragments also accumulate in the brains of Dutch transgenic mice with the highest levels detected at age 24 months. The mice develop an impaired learning phenotype directly related to the cortical levels of oAβ. The current study advances our understanding of the localization and molecular and subcellular basis for the learning behavior deficit in the Dutch mice. **Methods:** Male and female TgAPPE693Q mice and wildtype controls were subjected to learning behavior studies, and their brains were examined by immunohistochemistry, transmission electron microscopy, electrophysiology, and RNA sequencing. **Results:** Brain levels of nonfibrillar oAβ in Dutch mice showed an aging-dependent increase, using A11 immunohistochemistry and peptide-FITC microscopy. Electrophysiological characterization of hippocampal synapses in adult Dutch and wildtype mice at ~7 and ~11 months of age revealed no change in basal excitatory transmission, consistent with normal density and morphology of mGluR2/3+ synapses in the CA1 region of the hippocampi of 12-month-old Dutch and age-matched wildtype mice. One exception was that post-synaptic density area was increased in non-perforated mGluR-2/3+ synapses in the Dutch mice. Functional characterization of the presynaptic terminals in Dutch mice revealed abnormalities in post-tetanic potentiation, synaptic fatigue, and synaptic vesicle replenishment after depletion. Single cell RNA-sequencing to elucidate cell-type specific transcriptional responses to oAβ revealed altered transcriptional profiles in multiple cell types. Unexpectedly, there were no obvious differences between the transcriptional profiles of microglia from Dutch mice compared to those from wildtype mice, consistent with our observation that Iba1-like immunofluorescence was normal. These results suggest the absence of detectable inflammation in the brains of Dutch mice. In contrast, excitatory neurons showed the most altered transcriptomic profile, which was associated with the biological processes of 'translation' and 'oxidative phosphorylation'. Ultrastructural analysis of presynaptic mitochondria at excitatory synapses revealed fewer mitochondria in the presynaptic terminals of Dutch mice. **Conclusions:** Despite the absence of Aβ fibrils, the profound learning deficits in Dutch mice are apparently associated with presynaptic functional deficits and mitochondrial abnormalities in excitatory neurons of the hippocampus, suggesting potential mechanisms associated with nonfibrillar oAβ toxicity that may be therapeutic targets. Nonfibrillar oAβ deposits were revealed by co-localization of A11 immunoreactivity with peptide-FITC microscopy. Mice that accumulate nonfibrillar oAβ exclusively may be a useful experimental system for further characterization of the cyclic azaglycine peptide PET tracer Lys(64Cu/NOTA)1]-CP7 that shows robust PET signal from the brains of 44-day-old presymptomatic 5xFAD mice [2]. **Key words:** A11, amyloid, cyclic azagylycine peptide, fibrillogenesis, nonfibrillar, NOTA (triazacyclononane-1,4,7-triacetic acid), PET. **Disclosures:** Dr. Gandy is a co-founder of Recuerdo Pharmaceuticals. He has served as a consultant in the past for J&J, Diagenic, and Pfizer, and he currently consults for Cognito Therapeutics, GLG Group, SVB Securities, Guidepoint, Third Bridge, MEDACORP, Altpep, Vigil Neurosciences, and Eisai. He has received research support in the past from Warner-Lambert, Pfizer, Baxter, and Avid. Dr. Arancio consults for Neurokine Therapeutics and Appia Pharmaceuticals. **Disclaimer:** The opinions expressed herein are those of the authors and are not necessarily representative of those of the government of the United States, the Uniformed Services University of the Health Sciences, the Department of Defense (DoD), or the United States Army, Navy or Air Force or the Henry M. Jackson Foundation for the Advancement of Military Health, Inc. **References:** 1. Gandy S, et al. Days to criterion as an indicator of toxicity associated with human Alzheimer amyloid-beta oligomers. Ann Neurol. 2010 Aug;68(2):220-30. doi: 10.1002/ana.22052. PMID: 20641005; PMCID: PMC3094694. 2. Habashi M, et al. Early diagnosis and treatment of Alzheimer's disease by targeting toxic soluble Aβ oligomers. Proc Natl Acad Sci U S A. 2022;119(49):e2210766119. doi: 10.1073/pnas.2210766119. PMID: 36442093; PMCID: PMC9894226. **Grants:** E.L.C. (P30 AG066514 to Mary Sano with Developmental Pilot Award), S.G. 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LP088- HUMANIZED MODEL TO STUDY THE ROLE OF KV1.3 BLOCKADE ON MICROGLIA IN NEUROINFLAMMATION. I. Geric[1], L. Baltussen[2], L. Wolfs[2], A. Misbaer[1], N. Afrang[2], L. Sans[1], M. Dalby[1], A. Koustrup[1], D. Kuczek[1], J. Valadas[1], L.C. Roenn[1], M. Terndrup Pedersen[1], R. Balice-Gordon[1], B. De Strooper[2,3,4], N. Plath[1] *(1. Muna Therapeutics - Copenhagen (Denmark), 2. Centre for Brain and Disease Research, Flanders Institute for Biotechnology (VIB) - Leuven (Belgium), 3. UK Dementia Research Institute at UCL - London (United Kingdom), 4. Department of Neurosciences and Leuven Brain Institute, KU Leuven - Leuven (Belgium))*

Background: Microglia are key players in neuroinflammation linked to neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Several studies have shown that pharmacological blockade of the potassium channel Kv1.3 in rodent microglia reduces neuroinflammation and enhances neuroprotection, indicating its potential as a promising novel therapeutic approach. Although extensive literature supports the role of Kv1.3 in rodent microglia cell physiology in vitro and in vivo, the role of Kv1.3 in human microglia biology

and function has been less well studied, especially regarding processes involved in neurodegeneration. To address this, we have studied the role of Kv1.3 blockade in human microglia in vitro and in vivo using a xenotransplantation model. **Methods:** To study the impact of small molecule-mediated Kv1.3 blockade on pro-inflammatory responses in vitro, human stem cell (hESC)-derived microglia were co-treated with the Kv1.3 tool blocker PAP-1 in the presence of LPS or amyloid beta oligomers and cytokine production measured. In vivo assessments were conducted on hESC-derived microglia transplanted into the brain of Rag2 -/- | IL2rγ -/- | hCSF1 KI mouse pups [1]. Adult, xenografted mice injected icv with amyloid-beta received systemic treatment with either a Kv1.3 blocker (PAP-1, MTX-004) or vehicle for 3 days. Endogenous mouse and xenografted human microglia were subsequently isolated and assessed using RNA-seq. **Results:** We observed that treatment with small molecule Kv1.3 blockers reduces amyloid beta induced cytokine expression in hESC-derived microglia in vitro and in vivo. Transcriptional analyses confirmed that a pro-inflammatory gene signature was downregulated in human microglia after pharmacological blockade of Kv1.3 in vivo. Interestingly, effects of Kv1.3 blockade differed between mouse and human microglia, underscoring the necessity of humanized models to study microglia cells in the context of neuroinflammation. **Conclusions:** Our results support the hypothesis that Kv1.3 represents an compelling novel target for the treatment of human diseases with inflammatory drivers of pathology. Importantly, we demonstrate that mice xenografted with hESC-derived microglia constitute a powerful model for studying human microglia in the context of neuroinflammation, and for assessing pharmacological modulation of their activation in the context of disease pathology. **Reference:** 1. Fattoreli N, Martinez-Muriana A, Wolfs L, Geric I, De Strooper B, Mancuso R. Nat Protoc. 2023 16: 1013-1033.

LP089- IMPACT OF 'MASKED' 40 HZ LIGHT THERAPY ON COGNITIVE DECLINE AND ASSOCIATED NEUROPATHOLOGY IN A MOUSE MODEL OF ALZHEIMER'S DISEASE. M. Browne[1], O. Curreri[1], S. Ancheta[1], L. Jiwu[1], S. Wu[1], L. Yang[1], Y. Yao[1], M. Carstensen[2,3], M. Nguyen[2], D. Kaufer[1], L. Kriegsfeld[1] *(1. University of California, Berkeley - Berkeley (United States), 2. Optoceutics ApS - Copenhagen (Denmark), 3. Technical University of Denmark - Lyngby (Denmark))*

Background: Coordinated oscillations of excitatory and fast-spiking inhibitory neurons in the 20-50-Hz range, called gamma oscillations, underlie cognitive functioning and are dampened in Alzheimer's disease (AD). Several reports to date indicate that visual stimulation with 40 Hz light enhances gamma rhythmicity and improves cognition and microglial phagocytosis of extracellular amyloid-beta plaques1; although one recent study found no impact of 40 Hz light stimulation on amyloid-beta or microglia morphology2. Studies to date have used 40 Hz light stimulation that is stroboscopic and may have potential side effects of administration (e.g., discomfort, fatigue, migraines, seizures) in vulnerable individuals. The current study employed a novel 40 Hz lighting technology in which the perceived flashing light is grossly reduced to examine the efficacy in induction of gamma oscillations and the impact of this novel lighting source on cognitive function and neuropathology in a mouse model of AD. **Methods:** In the present study, a novel light source that produces 40 Hz 'invisible' spectral flicker (ISF) was used. This technology applies multiple single-color LEDs to produce white light where spectral composition alternates at a modulation frequency, resulting in 40 Hz stimulation3. Using EEG, we confirmed that ISF lighting produces 40 Hz cortical oscillations comparable to stroboscopic light. We then exposed 5-month-old 5xFAD (a mouse model of AD) and WT mice to 1 h a day of ISF light, stroboscopic light, or static light for one month. Mice were examined on cognitive and behavioral tasks prior to collecting brain tissue for further analysis. Brain tissue was immunofluorescently labeled for ionized calcium binding adaptor molecule 1 (Iba1; a marker of microglia/macrophages), cluster of differentiation 68 (CD68; a marker of microglial activation), and an antibody against amyloid-beta protein. **Results:** Chronic treatment with 40 Hz ISF light led to a non-significant (p=0.06) reduction in the time to find a hidden platform in the Morris water maze in 5xFAD animals relative to mice treated with static light. ISF and stroboscopic lighting treatment significantly increased activated microglia associated with extracellular plaque deposits in the hippocampus relative to static lighting controls. Similarly, ISF, but not stroboscopic-light-treated, mice exhibited increased clustering of Iba1-positive cells around amyloid-beta plaques in the visual cortex relative to static lighting controls. The total and percent area of beta-amyloid labeling was not significantly reduced in the hippocampus or visual cortex. Work using more quantitative measures of beta-amyloid deposition is ongoing. **Conclusions:** These findings suggest that ISF lighting represents a viable alternative to stroboscopic lighting in generating gamma oscillations and the potential amelioration of AD symptomatology and neuropathology. **Key words:** non-invasive, 40 Hz, gamma, neuroinflammation. **Disclosures:** Some authors are employed at OptoCeutics APS, a company in which ISF lighting is being developed to treat AD. Partial funding for the work was provided by OptoCeutics APS. **References:** 1. Iaccarino HF, et al. Nature 2016; 540: 230–235. doi: 10.1038/nature20587; 2. Soula M, et al. Nat Neurosci 2023; 26(4): 570-578. doi: 10.1038/s41593-023-01270-2; 3. Carstensen MS, et al. Proc SPIE 2020; XV(112210L). doi.org/10.1117/12.2544338

NEW THERAPIES AND CLINICAL TRIALS

P153- IMPACT OF ADHERENCE ON COGNITIVE OUTCOMES IN A PILOT STUDY OF THE COGSTIM MODEL. R.L. Ownby[1] *(1. Nova Southeastern University - Fort Lauderdale (United States))*

Background: Given limited progress in developing pharmacologic treatments for dementing illnesses, interest in lifestyle interventions for dementia prevention has increased (1). Given the myriad factors related to risk and protection from these illnesses, however, patients may have difficulty prioritizing which factors to address in developing more brain healthy lifestyles and not know how to initiate and maintain behavior change. We developed a cognitive behavioral shared decision-making model (Cogstim model) to help patients and clinicians address these issues. This study was conducted during the COVID-19 pandemic completely online. We previously reported outcomes from this study with respect to noncognitive outcomes (2). The purpose of this report is to provide information about the degree of adherence to the computer-based cognitive training incorporated in the study intervention and its relation to cognitive outcomes. **Methods:** Participants were randomly assigned to receive either the model-based intervention (psychoeducation plus structured goal setting and behavior change techniques) or treatment as usual (TAU). All participants completed an online cognitive

assessment battery (Cognifit® Assessment for persons 65 and older) and then were encouraged to complete cognitive training as they desired; the software program tracked the time spent in training. Given large differences in time spent training, we also assessed the impact of training time on cognitive test results. We divided participants into two groups based on whether, over the course of the 12-week study, they spend more or less than one hour in computer-based training. **Results:** Eighteen individuals (6 men 12 women, 2 Black and 16 White persons, average age 72.7 years, average years of education 17.9) were enrolled; 16 completed the study. The number of hours spent on computer-based training ranged from 0 to 10.5 (median 1.25 hours). Evaluation of training effects on the Cognifit® cognitive measures before and after the study intervention showed, in general, evidence of modest improvements in cognitive domain scores consistent with practice effect (the improvement in test performance commonly found when a test is administered a second time). When time spent training was included in models, however, the effect approached conventional levels of significance and was associated with a large effect size (e.g., for attention, $\chi 2$ [1] = 2.88, p = 0.09, d = 0.93 [95th CI -0.14-2.02]; for working memory, $\chi 2$ [1] = 2.46, p = 0.12, d = 1.07 [95th CI -0.04-2.19). Unplanned comparisons of those who completed at least one hour of cognitive training compared to those who did not substantiated the impact of training on posttest scores, with a significant time by group (trained vs. not) on the motor coordination subtest that was associated with a very large effect size ($\chi 2$ [1] = 9.57, p = 0.002, d = 2.44 [95th CI 0.89-3.98]). **Conclusions:** These results support others' observations (1) of the importance of taking participant adherence into account for outcomes in multimodal interventions for brain health. **Key words:** Alzheimer, cognition, computer cognitive training, adherence. **Clinical Trial Registry:** NCT04822129; https://clinicaltrials.gov. **Disclosures:** The author has nothing to disclose. **References:** 1. Ngandu J et al. Lancet, 385(9984), 2255-2263. https://doi.org/10.1016/S0140-6736(15)60461-5; 2. Ownby, RL. J Prevent Alzheimers Dis, 9, S110-S111.

P154- PIVOTAL TRIAL OF LOW-INTENSITY PULSED ULTRASOUND THERAPY FOR EARLY STAGE OF ALZHEIMER'S DISEASE (LIPUS-AD) –RATIONALE AND DESIGN-. H. Shimokawa[1,2], M. Akishita[3], M. Ihara[4], S. Teramukai[5], A. Ishiki[6], Y. Nagai[7], H. Kato[2], M. Fukushima[8] *(1. International University of Health and Welfare - Narita (Japan), 2. Sound Wave Innovation Inc. - Tokyo (Japan), 3. University of Tokyo - Tokyo (Japan), 4. National Cerebrovascular and Cardiovascular Center - Suita (Japan), 5. National Cerebrovascular and Cardiovascular Center - Kyoto (Japan), 6. Tohoku Medical and Pharmaceutical University - Sendai (Japan), 7. Kyoto University - Kyoto (Japan), 8Learning Health Society Institute - Nagoya (Japan))*

Background: Along with society aging, the prevalence of Alzheimer's disease (AD) has been rapidly increasing worldwide. There are lines of evidence suggesting an involvement of vascular pathology in AD. Indeed, endothelial dysfunction with reduced nitric oxide (NO) availability has been reported to play an important role in the pathogenesis of AD. Furthermore, the combination of amyloid pathology and cerebral ischemic pathology has been found as major triggering mechanisms of dementia. Thus, vascular dysfunction, especially cerebral microcirculatory dysfunction, should 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 [1]. We demonstrated that the LIPUS therapy ameliorates cognitive declines in mouse models of AD and vascular dementia (VaD) [2]. The effects of the LIPUS therapy is mainly mediated by upregulation of eNOS as its beneficial effects are absent in eNOS-deficient mice [2]. Based on these experimental findings, we performed a pilot trial of the LIPUS therapy for early stage of AD, suggesting its efficacy and safety for the disorder [3]. The Japanese government has designated the LIPUS device as the first breakthrough medical device in Japan [4]. Thus, we are performing a pivotal clinical trial (LIPUS-AD) to finally address the efficacy and safety of our LIPUS therapy in patients with early AD in Japan. **Methods:** LIPUS-AD is a randomized, double-blind, placebo-controlled pivotal trial, in which a total of 220 patients with early stage of AD (mild AD and MCI due to AD), who are positive for amyloid beta (Ab) PET, are enrolled. They will be divided in a 1:1 fashion into LIPUS and placebo groups. The LIPUS therapy is performed for the whole brain through the bilateral temporal bones alternatively for one hour 3 times per week as one session under the special conditions (32 cycles, 0.5MHz, 0.25W/cm2). The LIPUS therapy is performed for 6 sessions with a 3-month interval in the LIPUS group for 72 weeks, while placebo group is treated in the same manner but without LIPUS irradiation. They are further followed up for additional 6 months after the LIPUS/placebo therapy. Before and at 72 weeks of the trial, all subjects undergo brain Ab PET and MRI and cognitive functions tests, including ADAS-J-cog-14, CDR sum boxes, MMSE-J, NPIQ-J, J-ZBI, WMS-R, FAQ, EQ-5D-5L, and ABC. The primary efficacy endpoint is the changes in ADAS-J-cog-14 scores from baseline to 72 weeks. The secondary efficacy endpoints include those in the cognitive functions scores mentioned above at 24, 48, 72, and 96 weeks, the prevalence of responders at 24, 48, 72, and 96 weeks defined as those with no deterioration or even improvement in ADAS-J-cog-14 scores, and the transition rate from MCI due to AD to AD at 24, 48, 72, and 96 weeks. The safety endpoints include adverse symptoms until 96 weeks and any abnormal MRI findings at 72 weeks. **Conclusion:** LIPUS-AD addresses efficacy and safety of the LIPUS therapy in patients with early AD. **Key words:** Alzheimer's disease, Low-intensity pulsed ultrasound, Medical device, Nitric oxide. **References:** 1. Shindo T, Shimokawa H. Ann Vasc Dis. 2020;13:116-125. http:// doi: 10.1093/cvr/cvaa221. 2. Eguchi K, et al. Brain Stim. 2018;11:959-973. http:// doi: 10.1016/j.brs.2018.05.012. 3. Shimokawa H, et al. Tohoku J Exp Med. 2022;258:167-175. http://doi: 10.1620/tjem.2022.J078. 4. https://www.mhlw.go.jp/content/11123000/000335171.pdf (2022). **Conflict of interest:** HS is the founder and CMO of the Sound Wave Innovation, Inc.

P155- MASUPIRDINE (A PURE 5-HT6 RECEPTOR ANTAGONIST) FOR THE TREATMENT OF AGITATION IN PATIENTS WITH DEMENTIA OF ALZHEIMER'S TYPE - RATIONALE AND PHASE-3 STUDY DESIGN. R. Nirogi[1], J. Ravula[1], S. Jetta[1], V.K. Goyal[1], P. Jayarajan[1], V. Benade[1], A. Shinde[1], S.K. Pandey[1], R. Subramanian[1], A.R. Mohammed[1], V. Jasti[1] *(1. Suven Life Sciences Ltd - Hyderabad (India))*

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the presence of cognitive symptoms (i.e., loss of memory, language, problem-solving and other thinking abilities). In addition, majority of AD patients exhibit non-cognitive symptoms i.e., neuropsychiatric symptoms (NPS) during the course of the disease. Agitation is one of the most common NPS. Agitation is associated with increased morbidity and mortality in patients, caregiver burden

and earlier placement in long-term care facilities. Currently, treatment options are limited to psychosocial interventions and few pharmacological agents. Psychosocial interventions have limitations, and pharmacological agents possess modest efficacy and several safety concerns in patients with dementia. Thus, there is an unmet need for newer and safer agents. Serotonin-6 (5-HT6) receptors are G-protein-coupled receptors with unique localization and specific distribution in the brain regions. Several of the clinically used psychotropics have strong affinity for 5-HT6 receptors. Thus, 5-HT6 receptors antagonist may have a potential therapeutic utility for the management of agitation. **Methods:** Masupirdine (SUVN-502) is a pure, potent and orally active 5-HT6 receptor antagonist. In animal models of aggression like resident-intruder task and dominant-submissive assay, treatment with masupirdine attenuated aggressive behaviors compared to vehicle treatment. In the brain region (cortex) having a role in behavioral modulation, masupirdine significantly modulated the levels of dopamine and norepinephrine in animal models. In a post hoc analysis of the Phase-2 study (NCT02580305) in probable AD, potential treatment benefits were observed on agitation in the masupirdine treatment arms. Significant decreases in agitation/aggression scores were observed at Week 13 and Week 26 in the masupirdine 50 mg and 100 mg treatment arms compared to placebo. In addition, masupirdine was generally safe and well tolerated in AD patients. Relying on the observations from the animal models and AD patients, a Phase-3 study has been initiated to explore the beneficial effects of masupirdine for agitation in patients with dementia of Alzheimer's type (NCT05397639 and EudraCT 2021-003405-22). The Phase-3 study is a double-blind, randomized, placebo-controlled, parallel group, global study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of masupirdine. The study will recruit patients (male or female, 50-90 years of age, both inclusive) with agitation per International Psychogeriatric Association (IPA) provisional consensus definition of agitation in cognitive disorders. The study will enroll ~375 patients from USA and Europe. Patients will be randomly assigned in a 1:1:1 ratio to receive either 50 mg or 100 mg masupirdine or placebo for 12 weeks. Cohen-Mansfield Agitation Inventory items score aligning to the IPA agitation criteria domains and the Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change score as related to agitation are the primary and key secondary efficacy endpoints, respectively. **Results:** The subject enrolment is expected to be completed by Q3 2024. **Conclusion:** The Phase-3 study (NCT05397639) may provide evidence for the potential utility of masupirdine for the treatment of agitation in dementia of Alzheimer's type. Phase-3 study data readout is anticipated in Q1/Q2 2025. **Key words:** Masupirdine, agitation, Alzheimer's, dementia. **Clinical Trial Registry:** NCT05397639; https://clinicaltrials.gov

P157- BIOMARKER AND EDEMA ATTENUATION IN INTRACEREBRAL HEMORRHAGE (BEACH): A PHASE 2A PROOF-OF-CONCEPT TRIAL OF A NOVEL ANTI-NEUROINFLAMMATORY SMALL MOLECULE DRUG CANDIDATE. L. Van Eldik[1], W. Ziai[2], L. Sansing[3], D. Hanley[2] *(1. University of Kentucky - Lexington (United States), 2. Johns Hopkins University - Baltimore (United States), 3. Yale University - New Haven (United States))*

Background: Non-traumatic spontaneous intracerebral hemorrhage (ICH) is a major medical problem with few effective therapies. ICH causes considerable mortality and morbidity, especially in older adults, possibly due to increased prevalence of vascular co-morbidities, cerebral amyloid angiopathy, and hypertension. In addition to the primary injury caused by the hemorrhage and hematoma expansion, secondary neuroinflammatory events after ICH can further damage the brain and lead to increased risk of neurologic complications including Alzheimer's disease and related dementias. Previous work [1, 2] suggests that the robust proinflammatory cytokine increase in the brain that occurs in the first few days after injury is a key contributor to cerebral edema, long-term neurological damage, and cognitive deficits. The mechanistic linkage of the acute cytokine surge to progression of ICH-induced injury, plus the attractive therapeutic time window of hours to days post-injury, provide a rational therapeutic target for intervention in the acute care setting. To address the clear and urgent need for interventions that improve neurologic recovery and outcomes, we developed [3] the investigational drug candidate, MW01-6-189WH (MW189). MW189 is a novel, CNS-penetrant, small molecule developed as a selective suppressor of injury- and disease-induced proinflammatory cytokine overproduction associated with destructive neuroinflammation/synaptic dysfunction cycles. In animal models of acute brain injury, MW189 at low doses attenuated neuroinflammation, reduced cerebral edema, and improved functional and cognitive performance [4]. MW189 was also safe and well tolerated in phase 1a and phase 1b clinical trials in healthy adults [5], supporting the further development of MW189 for patients with acute brain injury. Therefore, we designed the first-in-patient exploratory trial with the aim to determine safety and tolerability of MW189 in patients with acute spontaneous ICH. **Methods:** The Biomarker and Edema Attenuation in IntraCerebral Hemorrhage (BEACH) trial is a first-in-patient phase 2a, proof-of-concept study of MW189 in patients with ICH. This multicenter, prospective, randomized, double-blind controlled trial will enroll 120 non-traumatic ICH participants, with an anticipated average age in their mid-60s and substantial numbers of individuals with cerebral small vessel disease and cerebral amyloid angiopathy. Patients will be randomly assigned 1:1 to receive intravenous MW189 (0.25 mg/kg) or placebo (saline) within 24 hours of symptom onset and every 12 hours for up to 5 days or until hospital discharge. **Results:** The BEACH trial is actively enrolling participants. The primary outcome is all cause-mortality within 7 days post-randomization between treatment arms. Secondary endpoints include all-cause mortality at 30 days, perihematomal edema volume after symptom onset, adverse events, vital signs, pharmacokinetics of MW189, and proinflammatory cytokine concentrations in plasma (and cerebrospinal fluid if available). Other exploratory endpoints are functional outcomes collected on days 30, 90, and 180. **Conclusions:** Success with MW189 in ICH patients will further de-risk the compound for subsequent larger trials of acute CNS injury and/or to develop the drug for Alzheimer's and other age-related dementias. The study will also generate important information about the utility of targeting the acute proinflammatory cytokine aspects of neuroinflammation in older adults with vascular disease. **Keywords:** hemorrhagic stroke, neuroinflammation, cytokine, perihematomal edema. **Clinical Trial Registry:** NCT05020535; https://clinicaltrials.gov. **Disclosures:** BEACH is supported by the National Institute on Aging (multi-PI grant R01 AG069930 to DFH and LVE) and directed by the University of Kentucky and by the division of Brain Injury Outcomes at Johns Hopkins University. The Trial Innovation Center is supported by the National Center for Advancing Translational Sciences, National Institute on Aging, under award number U24TR001609. LVE is an inventor on patents covering MW189

and a scientific founder of ImmunoChem Therapeutics, LLC, a start-up formed to commercialize MW189. **References:** 1. Landreneau MJ, et al. Ann Clin Transl Neurol 2018; 5(8): 962-970. doi: 10.1002/acn3.595; 2. Askenase MH, et al. Sci Immunol 2021;6(56):eabd6279. doi: 10.1126/sciimmunol.abd6279; 3. Hu W, et al. Bioorg Med Chem Lett 2007; 17(2): 414-418. doi: 10.1016/j.bmcl.2006.10.028; 4. James ML, et al. Anesthesiology 2012;116(6): 1299-1311. doi: 10.1097/ALN.0b013e318253a02a; 5. Van Eldik LJ, et al. Clin Pharm Drug Dev 2021;10: 131-143. doi: 10.1002/cpdd.795

P158- TREATMENT OF EARLY SYMPTOMATIC ALZHEIMER'S DISEASE WITH NASAL PROTOLLIN TO ACTIVATE MONOCYTES AND CLEAR AMYLOID BETA.

P. Kolypetri[1], P. Da Silva[1], L. Liu[1], C.D. Gauthier[1], T.J. Saraceno[1], T. Singhal[1], S.A. Gale[1], T. Chitnis[1], D.J. Selkoe[1], H.L. Weiner[1]
(1. Department of Neurology, Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School - Boston (United States))

Background: Amyloid beta (Aβ) accumulation is a primary initiating event in AD and anti-amyloid antibody therapy has shown positive clinical effects in AD. Monocytes have been shown to play an important role in modulating disease in animals (1) and we found that nasal administration of Protollin - a proteosome-based adjuvant acting as a TLR2/TLR4 agonist – activates monocytes to enter the brain, clear Aβ and improve cognition in both young and old animals (2-5). Thus, nasal Protollin it is a novel anti-amyloid approach to treat AD. We investigated the safety and immune effects of nasal Protollin in early AD in a double blind, Phase 1, ascending dose trial. **Methods:** Sixteen early symptomatic AD patients (4/group) received two doses of 0.1, 0.5, 1.0 or 1.5 mg of Protollin or placebo intranasally two weeks apart. Blood tests and physical examination were performed, and the immune profile of monocytes was investigated by RNA sequencing. **Results:** Protollin was safe and well-tolerated. Prominent immune effects on monocytes and other immune cells were seen at the 1.0 and 1.5 mg doses. Protollin induced the differential expression of 327 genes in classical monocytes involved in the IL-4, IL-12 signaling, glucocorticoid receptor, HIF-1-alpha, c-myb transcription factor and antigen processing and presentation pathways. A Protollin-modulated, transcriptional signature consisting of 38 differentially expressed (DE) genes occurred in classical monocytes as potential biomarkers. Intermediate and nonclassical monocytes also underwent transcriptional changes (54 and 83 DE genes, respectively) including the TNF-α, IFN-γ response, complement and hypoxia pathways as well as the EGFR1, c-myb transcription factor, cell cycle and mitotic G2/M phase pathways, respectively. We also found DE genes involved in common pathways in transcriptional profiles of CD8+, CD4+ T cells and B cells including the phagosome, antigen processing and presentation and interferon-g-mediated signaling. **Conclusion:** Nasal Protollin is safe in early AD subjects and induces immune changes in monocytes, B cells and T cells. Protollin is a novel peripheral immunomodulatory approach for the treatment of AD by inducing monocytes to clear amyloid in the brain. **Key words:** Protollin, blood monocyte subsets, early AD patients. **Disclosures:** Jiangsu Nhwa Pharmaceutical (NHWA),I-Mab Biopharma (I-Mab) and Inspirevax are responsible for the development, manufacturing and marketing of the immune modulator Protollin. The authors declare there is no conflict of interest. **References:** 1. Jorfi M. et al., Genome Med 2023; 15(1): 6. https://doi.org/10.1186/s13073-023-01155-w; 2. Frenkel D. et al., Journal of Clinical Investigation 2005; 115: 2423-2433. https://doi.org/10.1172/JCI23241; 3. Frenkel D. et al., Ann. Neurol. 2008; 63: 591-601. https://doi.org/10.1002/ana.21340; 4. Frenkel D. et al., Nat Commun 2013; 4: 2030. https://doi.org/10.1038/ncomms3030; 5. Lifshitz V. et al., Neurobiol. Aging 2012; 33 (2): 432.e1-e13. https://doi.org/10.1016/j.neurobiolaging.2011.01.006

LP090 THE PURELY THERMODYNAMIC ANTI-PRIONIC MODE OF ACTION FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES.

D. Willbold[1]
(1. Forschungszentrum Jülich - Jülich (Germany))

Background: Neurodegenerative protein-misfolding diseases, like Alzheimer's (AD) and Parkinson's disease (PD), are driven by prion-like self-replicating and propagating protein assemblies of amyloid β (Aβ), α-synuclein, and many more. The conformation these proteins have in the aggregated state is thermodynamically more stable than their physiological monomer conformation, which is often intrinsically disordered. Therefore, we have developed all-D-enantiomeric peptide ligands that bind the monomeric protein of interest with high affinity, thereby stabilizing the physiological intrinsically disordered monomer structure. These ligands are eliminating already existing aggregates by disassembling them into monomers. This purely thermodynamic driven mode of action (MoA) is truly "anti-prionic", because it is eliminating already existing oligomers and fibrils, thus disrupting prion-like replication and propagation of toxic protein aggregates. The MoA is realized by all-D-enantiomeric peptides that are specific for the target protein. The objective of the presentation will be the demonstration of the MoA for α-synuclein in vitro, and for Aβ ex vivo, as well as efficacy in patients with mild cognitively impairment (MCI) due to AD and mild AD. **Methods:** atomic force microscopy (AFM), dynamic light scattering (DLS), surface plasmon resonance spectroscopy (SPR), nuclear magnetic resonance spectroscopy (NMR), and a clinical study: 20 MCI and mild AD patients were recruited to participate in a single center, randomized, placebo-controlled, double-blind study. Patients received once daily oral doses of 300 mg PRI-002 or placebo for 28 days. **Results:** The all-D-enantiomeric ligand for α-synuclein, SVD-1a, disassembled preformed α-synuclein fibrils (PFF) as shown by AFM and DLS analysis. SPR and NMR demonstrated picomolar affinity of SVD-1a to α-synuclein monomers, while keeping them in their physiological IDP conformation. The all-D-enantiomeric ligand for Aβ, RD2, demonstrated ex vivo target engagement and disassembled Aβ oligomers obtained from brain tissue of former AD patients [1]. A clinical phase Ib, double-bind, placebo-controlled study with 20 mild cognitively impaired (MCI) due to AD and mild AD patients treated once daily orally with RD2 or placebo for 4 weeks with an additional 4 weeks follow up period yielded good safety and tolerability. Also, as demonstrated and published before with four different animal models in four different laboratories, patients treated with RD2 improved their short term memory abilities significantly, as shown with the Word List assay of the CERAD battery of neurocognitive testing. A phase II study is scheduled later this year with 270 patients and 12 to 24 months treatment. I will also acknowledge the many contributors of both developments that are too many to be included here in the abstract. **Conclusion:** The unique anti-prionic mode of action for the treatment of AD, PD and other protein misfolding diseases is promising. **Reference:** 1. Kass et al., Cell Rep. Med. 3, 100630 (2022). **Key words:** anti-prionic mode of action, ex vivo target engagement, clinical trial phase Ib. **Clinical Trial Registry:** EudraCT 2020-003416-27;

NCT 04711486; https://clinicaltrials.gov. **Disclosures:** DW is co-inventor of patents related to the work described. DW is co-owner of Priavoid GmbH, which is owner of the patents related to the work.

LP091- RATIONALE FOR A TRIAL IN TYPE 2 DIABETES AND/OR CORONARY ARTERY DISEASE: COMBINED INTERVENTION WITH EXERCISE AND A SOLUBLE EPOXIDE HYDROLASE INHIBITOR. M. Ruthirakuhan[1,2], N. Anita[1,2,3], J.S. Rabin[2,3,4], M. Goubran[2], N. Herrmann[2], P.I. Oh[5], A.Y. Taha[6], S.E. Black[2,5], C. Tartaglia[7], A.C. Andreazza[1], H. Cogo-Moreira[8], J. Edwards[9], K. Lanctot[1,2,3,10], W. Swardfager[1,2,3] *(1. Department of Pharmacology & Toxicology – University of Toronto - Toronto (Canada), 2. Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute - Toronto (Canada), 3. KITE Research Institute, Toronto Rehabilitation Institute-University Health Network - Toronto (Canada), 4. Rehabilitation Sciences Institute, Temerty Faculty of Medicine, University of Toronto - Toronto (Canada), 5. Department of Medicine (Neurology), Sunnybrook Health Sciences Centre, University of Toronto - Toronto (Canada), 6. Department of Food Science and Technology, College of Agriculture and Environmental Sciences, University of California, Davis; West Coast Metabolomics Center, Genome Center, University of California - Davis; Center for Neuroscience, One Shields Avenue, University of California - Davis, Ca (United States), 7. Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto - Toronto (Canada), 8. Department of Education, ICT and Learning, Østfold University College - Østfold (Norway), 9. School of Epidemiology and Public Health-University of Ottawa - Ottawa (Canada), 10. Department of Psychiatry, Sunnybrook Health Sciences Centre, University of Toronto - Toronto (Canada))*

Background: Vascular inflammatory conditions of aging such as coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) are risk factors for vascular cognitive impairment (VCI) and dementia. Recent consensus recommendations strongly support lifestyle interventions for dementia prevention, of which physical activity is one of the most potent actions known to combat cognitive decline. Nonetheless, not everyone benefits. Notably, people with CAD or T2DM show highly variable cognitive responses. Therefore, identifying novel targets and treatments to enhance the cognitive benefits of exercise in those with T2DM and/or CAD is an important clinical priority. **Methods:** Here, we rationalize the need for an interventional trial to improve cognition in individuals with T2DM and/or CAD in four steps: 1) We investigated potential target populations for intervention, based on the results of studies quantifying the effects of exercise on cognition in individuals undertaking exercise-based rehabilitation for cardiovascular diseases. 2) We identified evidence supporting a detrimental effect of cerebral small vessel disease (SVD) on cognitive outcomes based on neuroimaging markers of SVD. 3) In multiple clinical populations, we identified peripheral blood markers of SVD that implicate a specific targetable lipid pathway. 4) We conducted the Pro-Resolving Inflammatory Mediators in Neurovascular Gains in Aerobic Training study (PRIMiNG-AT), in which we investigated relationships between targetable lipid pathway markers and cognitive outcomes over the course of a 6-month exercise intervention for people with T2DM and/or CAD. **Results:** 1) The 2020 report of the Lancet Commission includes physical exercise as one of the most potent activities known to combat cognitive decline. However, individuals with CAD [1, 2] and T2DM [3] have demonstrated variability in cognitive response following the completion of a structured exercise-based rehabilitation program. 2) In individuals with CAD, cognitive non-response to exercise was linked to white matter hyperintensities (WMH), a neuroimaging marker of SVD [4]. This finding implicates SVD as a barrier to benefitting cognitively from exercise. 3) In individuals with stroke, neuroimaging markers of SVD were related to peripheral markers of the soluble epoxide hydrolase (sEH) pathway (WMH:β1,79=.364,p<.001; MRI-visible perivascular spaces:β1,79=0.302,p=0.011)(Yu 2023). Furthermore, in individuals with transient ischemic attack[5], stroke [6], and T2DM [7], products of the sEH enzyme were associated with poorer VCI scores. These findings implicate the sEH pathway as a treatment target for SVD. 4) Here we report from our PRIMING-AT study, an interaction between exercise and sEH markers, such that higher sEH markers predicted poorer cognitive outcomes with exercise (F1,45=5.4,p=.03). These findings specify a link between sEH markers and cognitive non-response to exercise in this population. **Conclusions:** Our work has implicated sEH in small vessel VCI, and in limiting the cognitive benefits of exercise in individuals with T2DM and/or CAD. These findings present new opportunities to boost the brain benefits of exercise by combining it with the use of an sEH inhibitor. This offers new potential to preserve cognitive performance into later decades of life for those living with chronic ischemic /neuroinflammatory comorbidities that can impair the cerebral microvasculature with aging. **Key words:** diabetes, cardiovascular disease, clinical trials, exercise intervention. **Disclosures:** The authors report no competing interests. **References:** 1. Swardfager W, Herrmann N, Marzolini S, Saleem M, Kiss A, Shammi P, et al. Cardiopulmonary Fitness Is Associated with Cognitive Performance in Patients with Coronary Artery Disease. J Am Geriatr Soc 2010;58:1519–25. https://doi.org/10.1111/j.1532-5415.2010.02966.x. 2. Saleem M, Bandaru VVR, Herrmann N, Swardfager W, Mielke MM, Oh PI, et al. Ceramides predict verbal memory performance in coronary artery disease patients undertaking exercise: a prospective cohort pilot study. BMC Geriatr 2013;13:135. https://doi.org/10.1186/1471-2318-13-135. 3. 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LP092- PERSONALIZED HIPPOCAMPAL NETWORK-TARGETED STIMULATION FOR ALZHEIMER'S DISEASE: A RANDOMIZED CONTROLLED TRIAL. Y.H. Jung[1], H. Jang[2], S. Park[3], H.J. Kim[2], S.W. Seo[2], G.B. Kim[4], D.L. Na[5] *(1. Myongji Hospital, College of Medicine, Hanyang University - Goyang (Korea, Republic of), 2. Samsung Medical Center - Seoul (Korea, Republic of), 3. Hanyang University - Seoul (Korea, Republic of), 4. Anymed - Seoul (Korea, Republic of), 5. Sungkyunkwan University - Seoul (Korea, Republic of))*

Background: In the context of the demand for effective treatment for Alzheimer's disease (AD), repetitive transcranial magnetic stimulation (rTMS) has emerged as a safe and promising intervention. We investigate the effect of a four-week personalized hippocampal network-targeted rTMS on cognitive and functional performance as well as functional connectivity in AD. **Methods:** This randomized, sham-controlled, participant- and evaluator-blinded trial was conducted between May 2020 and April 2022. We recruited 44 patients with early AD with evidence of amyloid deposition on positron emission tomography (PET) or cerebrospinal fluid testing. Of them, 41 participants who met the inclusion criteria were randomly assigned to receive either hippocampal-network-targeted or sham stimulation. Twenty sessions of personalized rTMS targeting the left parietal area, which is functionally connected to the hippocampus based on individualized fMRI maps, over four weeks. Sham stimulation was defined as the sound of the pulses without actual magnetic stimulation. A personalized 3D-printed frame was used to fix the rTMS coil to the optimal target site. The primary outcome was the change in the Alzheimer's Disease Assessment Scale-Cognitive Subscale test (ADAS-Cog) score eight weeks after baseline. Secondary outcomes included changes in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) and Seoul-Instrumental Activity Daily Living (S-IADL) scales and resting-state fMRI connectivity between the hippocampus and cortical areas. **Results:** Among 30 participants (rTMS, n=18; sham, n=12) who completed the 8-week trial, the mean age was 69.8 years; 18 participants (60 %) were female. As the primary outcome, the change in ADAS-Cog score at 8 weeks was significantly different between the rTMS and sham groups (P=0.002). Changes in the CDR-SOB (P=0.007) and S-IADL (P=0.004) scores were significantly different between the groups favoring rTMS. fMRI connectivity analysis revealed that rTMS increased functional connectivity between the hippocampus and precuneus, and these changes were associated with improvements in ADAS-Cog (P=0.005). **Conclusion:** The positive effects of rTMS on cognitive and functional performance, combined with the observed plastic changes in the hippocampal-cortical network, support the use of rTMS as a potential non-pharmacological treatment for AD. **Key words:** Hippocampal network targeted stimulation, transcranial magnetic stimulation, Alzheimer's Disease, treatment, Cognition. **Clinical Trial Registry:** clinicaltrial.org identifier: NCT04260724. **Disclosure:** Dr. Jung was supported by a faculty grant from the Myongji Hospital (2205-09-01) and a fund from the Korea Centers for Disease Control and Prevention (2023-ER1003-00). Dr. Jang was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (NRF-2020R1A2C1009778) and by the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) and Korea Dementia Research Center (KDRC), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (HU20C0414). Dr. Kim was supported by grants from the National Research Foundation of Korea (NRF-2021R1A2C2011648), Hanyang University (HY-202000000002753), and the Institute for Basic Science (IBS-R015-D1). REMED Co. Ltd. provided funding for the clinical trials, including TMS treatment and fMRI experiments. We thank Dr. Voss in the University of Chicago for his detailed and helpful comments on the earlier version of the manuscript. We specially thank the individuals who have participated in this randomized and sham-controlled clinical trial. **References:**
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LP093- EFFICACY AND SAFETY OF AXS-05 IN AGITATION ASSOCIATED WITH ALZHEIMER'S DISEASE: RESULTS FROM ACCORD, A PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RELAPSE PREVENTION TRIAL. J. Cummings[1], G. Grossberg[2], C. Andersson[3], G. Eglit[3], C. Streicher[3], H. Tabuteau[3] *(1. University of Nevada, Las Vegas - Las Vegas, NV (United States), 2. Saint Louis University School of Medicine - St. Louis, MO (United States), 3. Axsome Therapeutics - New York, NY (United States))*

Background: Background: Agitation is reported in up to 70% of individuals with Alzheimer's disease (AD) and is characterized by emotional distress, aggressive behaviors, disruptive irritability and disinhibition [1]. Agitation is associated with increased caregiver burden, decreased functioning, accelerated cognitive decline, earlier nursing home placement, and increased mortality [1, 2, 3]. AXS-05 (dextromethorphan-bupropion) is a novel, oral NMDA receptor antagonist and sigma-1 receptor agonist approved for the treatment of major depressive disorder and under evaluation for Alzheimer's disease-related agitation (ADA). **Methods:** ACCORD (Assessing Clinical Outcomes in Alzheimer's Disease Agitation; NCT04797715) was a Phase 3, randomized,

discontinuation, double-blind, placebo-controlled, multi-center trial to evaluate efficacy and safety of AXS-05 in individuals with ADA. Participants with a diagnosis of probable AD and clinically meaningful agitation were enrolled into a 9-week, open-label period during which they were treated with AXS-05 and monitored for sustained clinical response defined as a ≥30% improvement from baseline in the Cohen Mansfield Agitation Inventory (CMAI) total score and improvement on the Patient Global Impression of Change (PGI-C; score of ≤3) that were both maintained for at least 4 consecutive weeks. Participants who experienced a sustained clinical response during the open-label period were then randomized (1:1) to continue treatment with AXS-05 or placebo in a double-blind fashion for up to 26 weeks. Treatment was continued until either a relapse of agitation symptoms or the end of the double-blind period, whichever occurred first. The primary endpoint in the study was time from randomization to relapse of agitation. The key secondary endpoint was the percentage of participants who relapsed. **Results:** 178 individuals were enrolled into the open-label period and treated with AXS-05 (mean CMAI total score at baseline = 70.9). Statistically significant improvement on the CMAI was seen with open-label AXS-05 treatment at all timepoints starting at Week 1 ($p<0.001$) with mean reductions from baseline of 6.7 points at Week 1 and 20.6 points at Week 5 ($p<0.001$). In the randomized discontinuation phase of the trial, 108 participants were randomized to continue AXS-05 (n=53) or switched to placebo (n=55). AXS-05 met the primary endpoint by substantially delaying the time to relapse of agitation symptoms as compared to placebo, with a hazard ratio for time to relapse of 0.275 ($p=0.014$), representing a 3.6-fold lower risk of relapse compared to placebo. AXS-05 also met the key secondary endpoint of relapse prevention (7.5% relapse incidence rate for AXS-05; 25.9% for placebo, $p=0.018$). The rates of adverse events observed in the double-blind period were 28.3% AXS-05, 22.2% placebo. Discontinuations due to adverse events were 0% AXS-05, 1.9% placebo. There was no evidence of cognitive decline for participants treated with AXS-05. AXS-05 was not associated with sedation. **Conclusion:** ACCORD met its primary outcome as treatment with AXS-05 substantially reduced the risk of relapse and was generally well-tolerated for participants who achieved sustained clinical response in the preceding open label treatment period. These data support the continued development of AXS-05 as an efficacious and safe novel treatment for ADA. **Key words:** Alzheimer's disease agitation, AXS-05, NMDA receptor antagonist. **Disclosures:** JC has provided consultation to Acadia, Alkahest, AlphaCognition, AriBio, Biogen, Cassava, Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, Lilly, LSP, Merck, NervGen, Novo Nordisk A/S, Oligomerix, Ono, Otsuka, PRODEO, Prothena, ReMYND, Resverlogix, Roche, Signant Health, Suven, and United Neuroscience pharmaceutical, assessment, and investment companies. He is supported by US National Institute of General Medical Sciences (NIGMS) grant P20GM109025; National Institute of Neurological Disorders and Stroke (NINDS) grant U01NS093334; National Institute on Aging (NIA) grants R01AG053798, P20AG068053, P30AG072959, and R35AG71476; the Alzheimer's Disease Drug Discovery Foundation (ADDF); the Ted and Maria Quirk Endowment; and the Joy Chambers-Grundy Endowment. GG has provided consultation to Acadia, Alkahest, Avanir, Axovant, Axsome, Biogen, BioXcel, Genentech, Karuna, Lundbeck, Otsuka, Roche, and Takeda. He has provided research support for Lilly, Roche, and the National Institute on Aging. He has served on a Speaker's Bureau for Acadia, Biogen, and Eisai and has served on Safety Monitoring Committees for Anavex, EryDel, IntracellularTherapies, Merck, Newron and Oligomerix. CA, GE, CS, and HT are employees of Axsome Therapeutics. **References:** 1. Tractenberg RE, et al. J Neuropsychiatry Clin Neurosci. 2002;14:11-18. Doi. org/10.1176/jnp.14.1.11. 2. Porsteinsson AP,et al. Expert Opin Pharmacother. 2017;18:611-620. Doi: doi.org/10.1080/14656566.2017.1307340. 3. Rabins PV, et al. Alzheimers Dement. 2013;9:204-207. DOI: 10.1016/j.jalz.2012.01.003

LP094- A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SAFETY, TOLERABILITY, PHARMACOKINETIC, AND PHARMACODYNAMIC STUDY OF ESCALATING SINGLE AND MULTIPLE DOSES OF DGX-001 IN HEALTHY VOLUNTEERS FOLLOWED BY A STRESS EXPOSURE RESILIENCE PANEL (SERP).

T. Polasek[1], T. Plattel[2], R. Kim[2], S. Smith[2], I. Grachev[2], N. Schwartz[2], D. Smith[2] *(1. Monash University - Melbourne (Australia), 2. Viage - Palo Alto (United States))*

Background: DGX-001 is a novel, orally administered peptide neurotherapeutic planned to be studied as a potential treatment for cognitive impairment in Alzheimer's disease, Parkinson's disease, or depression. DGX-001 is unique in that it acts exclusively in the gut without systemic exposure to modulate vagal nerve activity and potentially cognition. In preclinical studies, DGX-001 reproducibly reversed depressive behavior in mouse models of induced stress, and improved cognition in a model of induced short-term memory loss. **Methods:** Healthy adults, aged 18-65, were enrolled in 3 parts. Part 1, single ascending dose (SAD), consisted of 30 participants in 4 single-dose cohorts (S1 to S4) randomized 6:2 to receive a single oral dose of DGX-001 (60 mg, 180 mg, and 540 mg per day) or placebo under fasted conditions. Assessments occurred on Days 1, 7, and 14. Part 2, multiple ascending dose (MAD), consisted of 24 participants in 3 multiple-dose cohorts (M1 to M3) randomized 6:2 to receive an oral dose of DGX-001 (60 mg, 180 mg, and 540 mg) or placebo once a day for 7 days after overnight fasting. Assessments occurred on Days 1, 14, and 21. Part 3 (SERP) consisted of 14 participants who were enrolled to explore the pharmacodynamic (PD) effects of DGX-001. Participants were randomized 1:1 to receive either 540 mg DGX-001 or placebo. Subjects were then sleep deprived for 24 hours on Day 7 in a 2-period, 2-sequence, cross-over design. PD assessments included qEEG, cognitive tests (DET, GMLT and OCL), depressive mood score (m-PHQ-9), and a sleepiness scale (modified-Insomnia Severity Index, m-ISI). **Results:** No plasma samples had detectable DGX-001 at or above the lower limit of quantification (20 ng/mL). In all parts of the study, there were no serious adverse events or study discontinuations. Most treatment-emergent adverse events were mild or moderate in intensity and occurred in the System Organ Class of Respiratory, Thoracic, and Mediastinal Disorders (mostly throat irritation) and Gastrointestinal Disorders (mostly nausea and vomiting, dry mouth). There were no clinically meaningful trends in safety labs, vital signs, and ECG readings. In exploratory PD assessments (MAD and SERP), potential changes were observed on Day 7 on qEEG, cognitive test scores, self-reported depressive mood scores, and sleepiness scores. **Conclusions:** DGX-001 is safe and well tolerated in healthy adults. The exploratory PD assessments suggested improved cognitive function and sleep quality following administration of DGX-001. DGX-001 will next be tested in a transdiagnostic phase 2 study to determine its ability to alleviate cognitive impairment observed in patients with Alzheimer's, Parkinson's,

or depression. **Key words:** DGX-001, Phase 1, Alzheimer's, gut-brain. **Clinical Trial Registry:** NCT05121831; https://clinicaltrials.gov. **Data Deposition:** https://clinicaltrials.gov/study/NCT05121831. **Disclosures:** There are no financial interests, relationships, or conflicts of interest to disclose.

LP095- NEURORESTORE ACD856, A TRK-PAM IN CLINICAL DEVELOPMENT FOR ALZHEIMER'S DISEASE SHOWS NEUROPROTECTIVE AND NEURORESTORATIVE EFFECTS. P. Forsell[1,2], V. Lidell[1,2], A. Rasti[1,2], G. Nordvall[1,2], J. Sandin[1,2], M. Jönsson[1,2] *(1. AlzeCure Pharma AB, Huddinge (Sweden), 2. Division of Neuroscience, Care and Society, Karolinska Institutet, Solna (Sweden))*

Background: Neurotrophins are a family of proteins that play a crucial role in the development, maintenance, and survival of neurons in the nervous system. One of the most well-known neurotrophins is brain-derived neurotrophic factor (BDNF), and others include nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). They bind and mediate their effects through the tropomyosin-receptor kinase (Trk) receptors (TrkA, TrkB and TrkC). A large body of scientific data suggests that neurotrophins could play a significant role in Alzheimer's (AD) and other neurodegenerative diseases, mediating effects on neuronal survival and plasticity, cognitive function, neuroregeneration and neuroprotection. AlzeCure Pharma has developed novel positive allosteric modulators of Trk-receptors and the lead candidate ACD856 has recently successfully completed phase I clinical trials. This compound has shown potent cognitive-enhancing properties in several animal models as well as antidepressant effects. Based on the extensive scientific data supporting a role for neurotrophins in AD, the objective of these studies was to assess whether ACD856 displays any effect on neuroprotection or neuronal plasticity that would support also potential disease-modification effects of this molecule. **Methods:** PC12 cells were incubated with DMSO or increasing amounts of ACD856 in the presence of 3 ng NGF/mL for 5 days and neurite outgrowth, as measured by neurite total length, was studied. SNAP25 levels were analyzed in NGF-treated PC12 cells in the presence of increasing concentrations of ACD856. Neuroprotective effects were studied using primary cortical cells exposed to 10 μM Aβ1-42 for 96 h with or without ACD856, and the levels of SNAP-25 in neurites were determined by immunocytochemistry. BDNF levels in vitro was assessed using primary cortical neurons incubated with increasing concentrations of ACD856, and the levels of BDNF were thereafter determined. For the in vivo BNDF studies, twenty-one months old mice were dosed with 5 mg/kg ACD856 once daily for 4 weeks by s.c. injection. The left hemisphere of each brain was homogenized, and the BDNF levels were determined by ELISA. **Results:** In the functional in vitro studies, ACD856 enhanced NGF-induced neurite outgrowth, both as measured by neurite total length per neuron and by neurite total length per well. Furthermore, ACD856 also increased the levels of the pre-synaptic protein SNAP-25 in neurites. In the neuroprotection assay, ACD856 was able to significantly protect the cortical neurons from Aβ42-induced toxicity. Furthermore, ACD856 increased the levels of BDNF in both isolated nerve cells and in brain of aged animals which have a natural reduction in the levels of BDNF. Combined, these studies suggest a neurorestorative effect of ACD856. **Conclusion:** We established that NeuroRestore ACD856 had neurotrophic effects, stimulating neurite outgrowth and increasing SNAP25 levels in PC12 cells. Additionally, it displayed neuroprotective effects, significantly decreasing Aβ1-42-induced toxicity. ACD856 was also able to increase levels of BDNF in vitro and in vivo suggesting effects that are long lived due to the function and role of BDNF on surrounding tissues. These data support potential disease-modifying effects of ACD856, which combined with cognitive-enhancing properties, would provide a step-change in future therapy management for AD patients and potentially also other neurodegenerative diseases. **Key words:** BDNF, NGF, neurotrophin, Trk-receptor, neuroprotection, Alzheimer's disease, Neurodegenerative diseases. **Disclosures:** All listed authors are employees at AlzeCure Pharma.

LP096- PHASE 1 SAD/MAD DATA AND PHASE 2 STUDY DESIGN FOR LHP588, A SECOND-GENERATION GINGIPAIN INHIBITOR FOR THE TREATMENT OF P. GINGIVALIS-POSITIVE ALZHEIMER'S DEMENTIA. M. Kurihara[1], R. Ihara[1], K. Ishibashi[2], K. Ishii[2], K. Kanemaru[1], A. Iwata[1] *(1. Lighthouse Pharmaceuticals - San Francisco (United States), 2. Barrow Neurological Institute - Phoenix (United States), 3. University of California, San Francisco, CA - San Francisco (United States), 4. Pentara Corp - Millcreek (United States))*

Background: Gingipains are toxic protease virulence factors from the bacterial pathogen P. gingivalis (Pg) that were discovered in postmortem brains of patients with Alzheimer's disease (AD). Gingipain levels correlated with AD diagnosis and tau pathology, and oral infection of wild-type mice with Pg resulted in brain inflammation, neurodegeneration, and AB42 production that was blocked by gingipain inhibitors [1]. LHP588 is a second-generation orally bioavailable and brain-penetrant lysine-gingipain inhibitor that reduces the toxicity of Pg and the bacterial load. In a prior Phase 2/3 study of COR388 (atuzaginstat) (NCT03823404), a first-generation lysine-gingipain inhibitor, the primary intent-to-treat prespecified endpoint was not met. However, prespecified subgroup analyses indicated efficacy in patients with Pg-positive saliva (Pg+) (N = 244), slowing cognitive decline compared with placebo on the ADAS-Cog11 by 57% in the high-dose group (p =0.02) [2]. Changes in Pg DNA in saliva correlated significantly with changes on the ADAS-Cog, CDR-SB, and MMSE. Atuzaginstat was generally well tolerated but development was discontinued because of liver transaminase elevations that demonstrated significant correlations with high levels of an inactive metabolite, M9. The supportive data from the atuzaginstat clinical trial informed the development of the approach, target, and population for clinical testing of LHP588 in mild-to-moderate AD with biomarker evidence of Pg infection. We will review new data from the LHP588 SAD/MAD, and the design of the Phase 2b study. **Methods:** The Phase 1 study of LHP588 enrolled 32 healthy volunteers in the SAD component with 4 cohorts and concurrent placebo (25 mg, 50 mg, 100 mg, 200 mg) and 24 healthy volunteers in the 10-day MAD portion, with 3 cohorts and concurrent placebo (50, 100 mg, and 200 mg). There were also tests of the effect of food on the PK, and of brain penetrance by assessment of LHP588 exposure in CSF. **Results:** The second-generation lysine gingipain inhibitor LHP588, which doesn't create the M9 metabolite produced by atuzaginstat, was well-tolerated in the SAD and 10-day MAD study. Adverse events in the active arms were mild and sporadic and fewer than the placebo arm. PK with once-daily dosing achieved target concentrations predicted to be sufficient for reduction of systemic Pg infection at doses >25 mg of LHP588, and exposures equivalent or greater than those achieved with the high dose of atuzaginstat. LHP588 was also detected in the CSF.

The dose of 200mg, 4x the highest dose planned for further development (50mg), achieved approximately 7x the exposure of the 50 mg dose, further supporting the overall safety index. **Conclusion:** LHP588 was well-tolerated in healthy volunteers without evidence of hepatic safety signals to date, and its PK profile was supportive of once daily dosing. The Phase 2 trial of LHP588 will be similar in design to the prior atuzaginstat study but will be restricted to subjects with Pg+ saliva. **Key words:** Phase 2, LHP588, P. gingivalis, Alzheimer's. **Clinical Trial Registry:** NCT04920903; https://clinicaltrials.gov/study/NCT04920903. **Disclosures:** MD, MS, JB, JW, MR, LJH, CL, SD own Lighthouse Pharmaceuticals stock. The other authors declared no competing interests. **References:** 1. Dominy SS, et al. Sci Adv 2019; Jan 23;5(1):eaau3333. doi: 10.1126/sciadv.aau3333; 2. Detke MJ, et al. AD/PD Conference 2022; Mar 23: https://www.vjdementia.com/video/tjympcjxwx0

LP097- ALZHEIMER'S DISEASE RESEARCH RECRUITMENT IN A WORLD WITH DISEASE MODIFYING TREATMENTS ON MARKET. I. Goodman[1], D. Gautieri[1], E. Beck[1], M. Stalder[1] *(1. SiteRx - New York (United States))*

Background: The last several years have provided significant progress toward bringing Alzheimer's disease treatments to the market. Following 2021's FDA approval of Biogen's Aduhelm under the accelerated approval pathway, Eisai and Biogen's Leqembi received full approval in July 2023. According to recent news, a positive decision is also expected for Eli Lilly's Donanemab in the near future. With no prior drugs approved since over a decade prior, these potential breakthroughs mark a significant shift in the paradigm for research recruitment, which remains an active area of investment in life sciences. According to Cummings et al, over 57,000 participants were necessary to enroll 187 AD trials that were registered on clinicaltrials.gov as of the beginning of 2023. In early AD, for which recent approvals have been indicated, there are over 20,000 participants needed in Phase 3 trials alone. **Objectives:** Understanding prescription versus research referral preferences and behaviors among providers treating AD patients will be critical for establishing effective recruitment strategies for ongoing and future drug development. SiteRx aims to conduct a survey to understand physicians' perceptions of emerging treatments, expected use, and impact on clinical research referral patterns. **Methods:** SiteRx works with community-based neurologists across the United States to facilitate their offering of expanded treatment options, including clinical research trials, to their patients using SiteRx's proprietary technology platform and services. SiteRx aims to conduct an online survey to physicians (n=100). The survey will collect information on: (A) the physician (e.g. provider type, practice type, health system affiliation), (B) details on patients under their care (e.g. percent ADRD, percent AD by severity, monthly volume, demographic characteristics), (C) Diagnostic and care management practices, (D) anticipated/observed prescription behaviors, and (E) anticipated/observed clinical research referral behaviors as it relates to emerging AD treatment options. **Results:** This research will expand on results of an initial survey conducted in July 2023. The initial survey included 46 neurologists. One-third of respondents indicated eagerness to prescribe approved-treatments immediately, while one-fourth are not planning to prescribe in the near future. Drivers and barriers to prescribing included 70% of physicians identifying need for better access to diagnostics, 55% needing more data on amyloid mAbs, and less than 20% citing CMS Registry requirements as a challenge. One-third of respondents indicated that many/most patients are inquiring about recently approved treatments, while one-fifth claim no inquiry by patients. Late breaking additional surveying will expand on number and characterization of respondents, as well as additional topics like referral barriers and behaviors. **Conclusion:** Neurologists are generally excited, yet cautious, as new amyloid mAbs enter the market. Much of the caution is due to a lack of information and knowledge on how best to navigate this new world, and the next 1 to 2 years hold a lot of uncertainty. With clinical development having reached its first real breakthroughs in Alzheimer's Disease over the last two decades, research efforts continue to grow exploring existing and novel targets to help progress medical care in a highly unmet area of medicine. With new breakthroughs, neurologists are showing signs of growing interest in research in addition to exploring newly approved Alzheimer's Disease therapies.

LP129- TREATMENT OF ALZHEIMER'S DISEASE SUBJECTS WITH EXPANDED NON-GENETICALLY MODIFIED NATURAL KILLER CELLS (SNK01) WITH ENHANCED ACTIVITY — FINAL REPORT OF A PHASE I DOSE ESCALATION STUDY. C.H. Zuniga Gil[1], B.I. Acosta Gallo[1], R. Menchaca Diaz[1], C.A. Amescua[1], S. Hong[2], L. Hui[2], H. Lee[2], J. Mata[2], P.Y. Chang[2], K. Betito[2], P.Y. Song[2] *(1. Hospital Angeles - Tijuana (Mexico), 2. NKGen Biotech - Santa Ana (United States))*

Background: Natural Killer (NK) cells play a profound role in the innate immune system and their importance in neurodegenerative disease has largely been overlooked despite preclinical studies demonstrating their ability to reduce neuroinflammation (by identifying and eliminating autoreactive T cells), degrade and reduce amyloid protein aggregates, and even remove damaged neurons. SNK01 is autologous non-genetically modified NK cell product with highly enhanced cytotoxicity, activating receptor expression, and strong ability to cross the blood brain barrier. We hypothesize that SNK01 can be safely infused to reduce neuroinflammation and proteins in AD patients. **Methods:** In this Phase 1 dose escalation study, SNK01 was administered IV every three weeks for a total of 4 treatments using a 3+3 dose escalation design (1, 2 and 4 x 109 cells) in subjects with either mild, moderate, or severe AD (Median MMSE was 14). Cognitive assessments (CDR-SB, ADAS-Cog, MMSE and ADCOMS) and CSF biomarker analyses were performed at baseline and at 1 and 12 weeks after the final dose. The primary endpoint was safety and secondary endpoints included changes in cognitive assessments and biomarker levels. **Results:** Ten subjects were enrolled in the three dose-escalation cohorts. No treatment related adverse events have been observed to date. Despite 70% of subjects being treated at relatively low doses of SNK01, 50-70% of all enrolled subjects in the trial had either stable or improved CDR-SB, ADAS-Cog and/or MMSE, and 90% had stable or improved composite ADCOMS scores at one-week post-treatment. Furthermore, 60% of subjects showed a trend of improvement (mean change of 14.9%) while on treatment, with 1 subject changing from moderate AD to mild AD, based on ADCOMS scores. At week 22 (12 weeks post last dose), 44% continued to be stable from their week 11 ADCOMS scores, and 22% remain improved from their baseline exam. Furthermore, in both week 11 and 22, we saw a dose-dependent improvement in some neuroinflammatory biomarker levels and protein levels. **Conclusions:** SNK01 was safe and well tolerated. SNK01 appears to have clinical activity in AD

while reducing neuroinflammation and protein levels. These results justify a larger trial with a higher dosing and longer treatment duration which will be initated in late 2023. **Key words:** natural killer cells, neuroinflammation. **Clinical Trial Registry:** NCT04678453; https://classic.clinicaltrials.gov/ct2/show/NCT04678453. **Disclosures:** Authors Song, Betito, Chang, Mata, Lee, Hui, and Hong are all employees and shareholders of NKGen Biotech who is the sponsor of this trial.

LP130- ANTI-ABETA LIPOSOMAL VACCINE, ACI-24.060, INDUCES ANTI-ABETA ANTIBODIES WITH BINDING PROFILES MIRRORING CLINICALLY VALIDATED MONOCLONAL ANTIBODIES. E. Fiorini[1], C. Babolin[1], R. Carpintero[1], S. Rigotti[1], S. Siegert[1], C. Morici[1], M. Verardo[1], J. Wagg[1], P. Donati[1], S. Delpretti[1], J. Streffer[1,2], A. Pfeifer[1], M. Kosco-Vilbois[1], M. Vukicevic[1] *(1. AC Immune SA - Lausanne (Switzerland), 2. University of Antwerp - Antwerp (Belgium))*

Background: Active immunization is an attractive approach in development for the treatment and prevention of Alzheimer's disease and other neurodegenerative disorders. Its key advantage over other therapies is the induction of sustained antibody responses which can be easily boosted with occasional immunizations. The recent clinical evidence of targeting pathological species of amyloid with monoclonal antibodies (mAbs) such as lecanemab or donanemab, has validated the relevance of anti-Abeta immunotherapies. ACI-24.060 is a liposomal anti-Abeta vaccine, having Abeta 1-15 as immunogen. In this study in non-human primates (NHP), the antibodies produced post administration of ACI-24.060 were compared to the binding preferences towards different Abeta species of lecanemab and donanemab. **Methods:** ACI-24.060, generated using the liposomal SupraAntigen® platform, was used to immunize cynomolgus monkeys (NHP) monthly for 7 months. Immune sera obtained at various times were tested using a competitive inhibition assay involving preincubation of immune sera or lecanemab with Abeta 1-40 monomers or Abeta1-42 oligomers (1). The binding profile was established for the vaccine-induced antibodies and lecanemab. Binding to the pathological pyroglutamate species of Abeta was assessed using an ELISA-based assay (2). **Results:** Immunization of NHP with ACI-24.060 induced a sustained polyclonal response with strong binding to Abeta toxic species, i.e., Abeta oligomers and pyroglutamate-Abeta. The competitive inhibition assay demonstrated that the antibodies generated by active immunization of NHP with ACI-24.060 gave a 3 log differential for oligomeric over monomeric species of Abeta, similar to lecanemab. Binding of the vaccine-induced immune sera to pyroglutamate-Abeta was similar to the binding of around 10 ug/mL of donanemab, which is the range of clinically relevant concentrations (above 4.43 ug/mL) associated with amyloid plaque reduction in human patients (3). **Conclusion:** In NHP, a liposomal anti-Abeta vaccine, ACI-24.060 induced antibody responses with strong binding to pathological Abeta oligomers and pyroglutamate-Abeta species. Importantly, the preference in binding of the polyclonal antibodies to oligomeric versus monomeric Abeta mirrored that of lecanemab, with a similar 3 log differential. Binding of the polyclonal antibodies to pyroglutamate-Abeta was in the range of binding of clinically relevant concentrations of donanemab. Altogether, these data confirmed that ACI-24.060 induces robust levels of anti-Abeta antibodies, with an excellent binding profile, combining the properties of lecanemab and donanemab. Therefore, ACI-24.060, with FDA Fast Track designation, represents a potential breakthrough active immunotherapy for Alzheimer's disease. It is currently in clinical development in both Altheimer's and Down syndrome individuals, with the first clinical readouts expected in the first half of 2024. **References:** Söderberg L, et al. Neurotherapeutics 2023; 20:195–206. https://doi.org/10.1007/s13311-022-01308-6. Vukicevic M, et al. Brain Commun 2022; 4(1). https://doi.org/10.1093/braincomms/fcac022. Gueorguieva I, et al. Alzheimers Dement 2023; 9(2):e12404. https://doi.org/10.1002/trc2.12404. **Disclosures:** All authors are employees of AC Immune SA, Lausanne, Switzerland

PROOF OF CONCEPT/TRANSLATIONAL RESEARCH FOR ALZHEIMER DRUG DEVELOPMENT INTERVENTIONS

P159- D-PEPTIDE-MAGNETIC NANOPARTICLES DISAGGREGATE TAU FIBRILS AND RESCUE BEHAVIORAL DEFICITS IN A MOUSE MODEL OF ALZHEIMER'S DISEASE. K. Hou[1], H. Pan[1], D. Eisenberg[1] *(1. UCLA - Los Angeles (United States))*

Background: Abnormal tau aggregation is increasingly accepted as a cause of neuronal death and brain atrophy in Alzheimer's disease (AD). Diminishing tau aggregation is a promising strategy in the search for an efficacious AD therapeutic. Previously, we used the atomic structure of a segment (VQIVYK) from the tau fibril core as a template and designed a D-amino-acid peptide D-TLKIVW that binds the ends of tau fibrils to cap their growth [1]. Here we further designed a D-TLKIVWC, which is a C-terminal D-cysteine extension of D-TLKIVW. **Methods:** We used ThT assay, transmission electron microscopy, and other techniques to investigate whether D-TLKIVWC can inhibit recombinant tau aggregation and disaggregate tau fibrils. We studied whether D-TLKIVWC can block the spread of tau pathology in the tau biosensor cell line and whether D-TLKIVWC can protect neuronal cells from tau-induced toxicity with MTT assay. We further conjugated D-TLKIVWC to magnetic iron oxide nanoparticles (MNPs-DP) to help D-TLKIVWC cross the blood-brain barrier. We used the PS19 transgenic mice that overexpress the P301S mutant form of human microtubule-associated protein tau as a tauopathy model to investigate the therapeutic efficiency of MNPs-DP against AD-related tauopathy. Two-month-old male PS19 mice were stereotaxically injected with tau K18+ fibril seeds to induce similar and consistent levels of tau pathology in cohorts of PS19 mice. 10 mg/kg body weight of MNPs-DP or vehicle (PBS) were tail vein-injected into PS19 transgenic mice weekly for ten weeks (n = 13 per group). Finally, we assessed the spatial cognition and memory of these mice using the Barnes maze test and novel object recognition. The biosafety of MNPs-DP was evaluated by aspartate aminotransferase (AST) blood and histological analysis of the main organs. **Results:** We find D-TLKIVWC not only prevents tau aggregation but also disaggregates recombinant tau fibrils and tau fibrils isolated from autopsied brains of AD patients. It can prevent tau spreading in the tau biosensor cell line and protect neuronal cells from tau-induced toxicity. The MNPs-DP complex retains the inhibition and disaggregation properties of D-TLKIVWC. Ten weeks of MNPs-DP significantly reversed neurological deficits in the PS19 mouse model of AD compared with the PBS-treated group ($p = 0.042$, $n = 13$) while not causing apparent toxic side effects. **Conclusion:** We provide preclinical data demonstrating the in vitro tau-disaggregating activity and the in vivo therapeutic potential of D-TLKIVWC and one intravenously bioavailable formulation, MNPs-DP. Our work supports the future Phase I

evaluation of D-TLKIVWC formulations including MNPs-DP in humans with Alzheimer's disease and other tauopathies. If safe and acutely effective against tauopathy biomarkers, this new class of highly specific structurally designed tau disaggregators could be rapidly optimized and further developed for clinical use. **Key words:** Tau disaggregation, D-peptide, Magnetic nanoparticle. **Disclosures:** K.H. received an Alzheimer's Association Research Fellowship (AARF-21-848751). D.S.E. received grants from the National Institutes of Health (1R01AG070895 and RF1AG065407). D.S.E. is the SAB chair and equity holder of ADRx, Inc. **References:** S. A. Sievers, J. Karanicolas, H. W. Chang, A. Zhao, L. Jiang, O. Zirafi, J. T. Stevens, J. Münch, D. Baker, D. Eisenberg, Structure-based design of non-natural amino-acid inhibitors of amyloid fibril formation. Nature 475, 96-100 (2011).

P160- STRUCTURAL DYNAMICS OF AMYLOID-B PROTOFIBRILS AND ACTION OF LECANEMAB AS OBSERVED BY HIGH-SPEED ATOMIC FORCE MICROSCOPY. K. Ono[1], T. Nakayama[2], M. Tsuji[3], K. Umeda[2], T. Oguchi[3], H. Konno[2], M. Shinohara[1], Y. Kiuchi[3], N. Kodera[2], D.B. Teplow[4] *(1. Kanazawa University Graduate School of Medical Sciences - Kanazawa (Japan), 2. Nano Life Science Institute, Kanazawa University - Kanazawa (Japan), 3. Showa University School of Medicine - Tokyo (Japan), 4. David Geffen School of Medicine at UCLA - Los Angeles (United States))*

Background: Amyloid-β (Aβ) aggregation intermediates, including oligomers and protofibrils (PF), have attracted attention as neurotoxic aggregates in Alzheimer's disease. At the end of last year, it was reported that the anti-Aβ PF antibody lecanemab had positive results in Phase 3 Clarity AD, but the details of the mechanism of its action were unknown. **Methods:** Here, we investigated the structure of Aβ42 PF at the single-molecule level using high-speed atomic force microscopy, which is capable of acquiring both structural and kinetic information with a microcantilever that can capture moving images in 0.001-second increments. We observed the kinetics of PF, and the interaction of lecanemab with PF and oligomers of Aβ. **Results:** PF was found to be a curved nodal structure with stable binding angles between individual nodes. PF was also a dynamic structure that associates with other PF molecules and undergoes intramolecular cleavage. Lecanemab remained stable in binding to PF and globular oligomers of Aβ, inhibiting the formation of large aggregates as well as reducing their cytotoxicity by alleviating membrane damage. **Conclusion:** Our results provide direct evidence for the mechanism by which lecanemab directly interferes with Aβ aggregation process to reduce cytotoxicity.

P161- APOE-TARGETED EPIGENOME THERAPY FOR ALZHEIMER'S DISEASE: PRE-CLINICAL STUDIES. O. Chiba-Falek[1,2], B. Kantor[1,2] *(1. Duke University - Durham (United States), 2. CLAIRIgene, LLC - Durham (United States))*

Background: There is an urgent need to shift the paradigm of Alzheimer's disease (AD) drug discovery to the development of new targets. Apolipoprotein E gene (APOE) is the strongest and most reproducible genetic risk factor for late-onset AD (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. In this study we developed an epigenome therapy platform to reduce APOEe4 expression by targeted modification of the epigenome landscape across APOE locus. **Methods:** We developed epigenome therapy based on CRISPR/deactivated(d) Cas9 editing technology fused with a repressor molecule and delivered by viral vehicle. We designed a set of gRNAs to target regulatory elements in APOE region and within exon 4 overlapping the SNP that defines the APOEe4 allele. We validated our epigenome therapy platform in vitro using human induced pluripotent stem cell (hiPSC)-derived models and in vivo using mouse models including: (1) wild-type (WT) mouse, (2) human APOEe4 knock-in mouse (B6.129P2-Apoetm3(APOE*4)Mae N8, hereafter E4KI), and (3) our newly developed humanized mouse model in which the entire mouse region was replaced with the human (h)APOE and the adjacent hTOMM40 loci including their upstream and downstream flanking regulatory sequences (hereafter, TR hAPOE-TOMM40). **Results:** The viral dCas9-repressor vector showed a robust decrease, ~50%, in APOE-mRNA levels in hiPSCs and the derived cholinergic neurons, microglia, and cerebral organoids models. The system specifically targeted the APOEe4 allele exhibiting the reduction effect in all hiPSC-derived cellular and organoids models with the e4-allele while there was no effect in the isogeneic hiPSC-derived models homozygous for the e3-allele. Further examination of the transduced e4/4 cerebral organoids demonstrated that the specific reduction in APOEe4 expression led to lower Aß42/40 levels and a significant decrease in the level of phosphorylated-Tau (pTau). Next, we moved onto in vivo studies by stereotactic injection of the AAV-dCas-repressor vector into the mice hippocampus followed by evaluation of the efficacy of the platform. In the WT mouse we observed a significant decrease, amounting to ~70%, in mouse endogenous Apoe expression. Similar significant and robust effects were observed in both APOE-humanized mouse models. Thus, the E4KI and the TR hAPOE-TOMM40 mice showed a 75% reduction in human APOE expression. Altogether, these results demonstrated a strong and specific repression effect in vivo. **Conclusions:** Collectively, our results provided in vitro and in vivo proof-of-concept for the utility, efficacy, and specificity of the APOE-targeted epigenome therapy. Our epigenome therapy strategy for targeted fine-tuning of APOEe4 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. **Key words:** APOE, gene therapy, hiPSC, cerebral organoids, APOE-humanized mouse model. **Disclosures:** Drs. Kantor and Chiba-Falek are Co-Founders at CLAIRIgene. CLAIRIgene has an exclusive, worldwide option agreement from Duke for the related patent portfolio for all fields of use. This work was funded in part by the National Institutes of Health/National Institute on Aging (NIH/NIA) [R41 AG077992 to CLAIRIgene, LLC].

P162- A POSSIBLE PATHOGENIC PSEN2 GLY56SER MUTATION IN A KOREAN PATIENT WITH EARLY-ONSET ALZHEIMER'S DISEASE. D.E. Jeong[1], M.J. Kang[1] *(1. Department of Neurology, Veterans Health Service Medical Center - Seoul (Korea, Republic of))*

Background: With a prevalence of 5%, early-onset Alzheimer's disease (EOAD) is a relatively rare neurogenetic cognitive disorder. The major causal factors of AD pathogenesis were identified as genetic variants from the presenilin 1 (PSEN1), presenilin 2 (PSEN2), and APP genes. The presenilin 1 (PS1) and presenilin 2 (PS2) proteins were enzymatic parts of γ-secretase, which could cleave and process the APP. The production of Aβ peptide species may be impacted by

mutations in these genes. In this study, we described a clinical data of a Korean EOAD patient with Gly56Ser mutation in PSEN2. To address the pathogenicity of the mutation, in silico analysis and structural predictions were also conducted. **Methods:** A 64-year-old right-handed woman with 12 years of education presented with a 4-year history of progressive cognitive impairment. Her symptoms occurred insidiously, with short-term memory loss and insomnia. The patient scored 24/30 in a Mini-Mental State Examination (MMSE). The subscores seven serial calculations were 3 out of 5 and the delayed word recall score was 0 out of 3, with a 0.5 Clinical Dementia Rating (CDR). Brain magnetic resonance imaging showed that the volume of the bilateral hippocampus was reduced, without any ischemic changes or lesions (Figure 1). 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) showed bilateral temporoparietal association cortices, precuneus, inferior parietal lobule, and middle temporal gyrus hypometabolism, a typical pattern of glucose metabolism in patients with AD. A blood sample (5 mL) was collected from the patient in an EDTA-containing tube and stored at −20 ◦C for further use. Genomic DNA from blood cells was purified using a QIAamp DNA Blood Maxi Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Purified DNA was stored at −20 ◦C until analysis. Whole-exome sequencing was performed to screen for variants in the genes associated with AD. **Results:** From in silico analysis, the bulkiness score of mutant PS2 was higher than that of the wild-type protein (Figure 2). The hydrophobicity score of the mutant protein was markedly lower than that of the wild-type one. Based on the 3D structural modeling of the secondary structure, the positions of Gly56 and Ser56 of the wild-type and mutant proteins, respectively, were anticipated to be located within loop structures without definite structures. Glycine is the smallest amino acid, and serine is a polar amino acid with a hydroxymethyl group on its side chain, which could form hydrogen bonds and phosphorylation. Based on a model of the mutant protein, Ser56 displayed the potential interactions with Met1, Ala6, Asp8, and Glu54. Interestingly, in mutant model 2, a hydrogen bond formed between Ser56 and Leu396 that reduced the distance between the loop and the helix region in PS2. **Conclusion:** Substitution with serine may affect interactions with other residues and/or phosphorylation, promoting AD pathogenicity. Future functional studies will be required to fully understand disease progression and mechanisms. **Key words:** Alzheimer's disease; mutation; presenilin 2; phosphorylation; PSEN2 Gly56Ser mutation. **Disclosures:** The authors declared no competing interests. **References:** 1. Zhang X, et al. Front Aging Neurosci. 2018 ;10:359. doi: 10.3389/fnagi.2018.00359. 2. Murphy MP, et al. J Alzheimers Dis. 2010 ;19(1):311-23. doi: 10.3233/JAD-2010-1221. 3. Caldeira C, et al. Front Aging Neurosci. 2017;9:277. doi: 10.3389/fnagi.2017.00277.

P163- EFFECT OF SPECTRAL BINNING IN X-RAY SCATTERING METHOD FOR NON-INVASIVELY CHARACTERIZING AMYLOIDS. E. Dahal[1], S. Amer[1], K. Suresh[1], O. Sandvold[2], P. Noël[2], A. Badano[1] *(1. U.S. Food and Drug Administration - Silver Spring (United States), 2. University of Pennsylvania - Philadelphia (United States))*

Background: We recently demonstrated a label-free in vivo method using spectral small-angle x-ray scattering (sSAXS) to estimate amyloid burden in mice studies. For clinical translation of this technology to measure amyloid burden in the human brain, here we report on evaluating the technique for use with a clinical three-threshold or four bin photon-counting detector currently used in spectral CT systems. **Methods:** We used a prototype system integrating a polychromatic x-ray source (tungsten anode) and a 2D spectroscopic photon-counting detector (80 x 80 pixels) made from cadmium telluride. The incident x-ray beam was pinhole collimated to create a 1-2~mm pencil beam to irradiate up to 16 cm thick objects (plastic) with and without the target mimicking amyloid plaques. The detector was placed 220 to 300 mm from the irradiated object to collect scattered photons at small angles (<10°). By varying the number of energy bins from 2 to 200 with respective bin sizes from 28 to 1 keV, we assessed the recovery of the scattering signature from targets along with its relative scattering intensity proportional to the target concentration. The effect of sample thickness when using a limited number of energy bins in the diagnostic x-ray energy range was evaluated to understand the source of signal degradation. **Results:** Measurements show characteristic scattering peaks of amyloid plaques recovered without significant spectra degradation in reciprocal q-space up to four energy bins. For measurements using two energy bins with 28 keV bin size, we saw significant change in the scattering profile of amyloid plaques with distorted signal in comparison to the reference measurement using 200 energy bins. **Conclusions:** Our initial results support the feasibility of using a clinical three-threshold photon-counting detector currently used in spectral CT systems to measure amyloid burden in the human brain using the scattering signature of amyloid plaques. The sample thickness effect in the diagnostic x-ray energy range and degradation of scattering features should be taken into account while using a limited number of energy bins. **Key words:** photon-counting detector, limited energy bins, amyloid burden, scattering signal. **Disclosures:** The authors declared no competing interests.

P164- NOVEL BRAIN SHUTTLE PLATFORM FOR PRECISION DELIVERY OF ALZHEIMER'S DISEASE THERAPEUTICS. L. Wang[1], J. Santos[2], A. England[1], Y. Lu[1], A. Graveline[1], M. Sanchez[1], T. Barata[2], D. Teixeira[2], D. Ingber[1], J. Gorman[1] *(1. Wyss Institute at Harvard University - Boston (United States), 2. FairJourney Biologics - Porto (Portugal))*

Background: Drug delivery to the brain and to specific diseased brain cells and brain compartments remains a formidable challenge for the development of effective treatment for Alzheimer's disease (AD). More than 99% AD drug trials have failed [1, 2], frequently without achieving therapeutic concentration and target saturation in the brain. The blood-brain barrier (BBB), comprising a monolayer of highly specialized brain microvascular endothelial cells (BMECs), astrocytes and pericytes, stops toxins and harmful molecules from getting into the brain [3]. As a result, the BBB also prevents most therapeutics from reaching the brain. Only 0.01-0.1% of large biologic drugs can cross the BBB and reach brain parenchyma [4, 5]. The therapeutic hypothesis of this study is that dramatically enhancing brain uptake and target engagement of drugs will significantly increase their efficacy in the treatment of AD. **Methods:** Using BMEC receptor-mediated transcytosis pathways, the Wyss Institute's Brain Targeting Program has developed 3 panels of brain shuttles, each of which binds to a receptor that is highly abundant and enriched on BMECs. To assess and rank the transcytosis ability of the shuttles, we performed in vivo brain uptake screening of each shuttle in humanized transcytosis receptor knock-in (KI) mice. The extracellular domain of the mouse receptor is replaced with its human counterpart in these KI mice to allow binding and transcytosis of human brain shuttles

across the BBB. Ab concentrations in parenchymal brain lysates and plasma were determined using a human Fc ELISA. Using an immunostaining approach, we also characterized the cellular distribution of the lead brain shuttles in brain tissues. Peripheral organ biodistribution studies were used to analyze the peripheral sink. Additional shuttle characterizations included cyno target binding, affinity, epitope binning and sequence liabilities. **Results:** We have identified lead brain shuttles for each panel that can increase the brain parenchymal uptake of therapeutic IgGs by 10-30-fold compared to IgG alone. Further, the shuttles showed differentiated brain PK and expression profiles. The anti-TfR brain shuttles crossed the BBB and reached brain parenchyma rapidly, while the anti-CD98hc and Target 3 shuttles have lower Cmax and higher AUC, indicating sustained brain exposure. To tailor our shuttles for AD drug development, we will perform proof-of-concept studies in mouse models. We will first generate shuttle-drug fusion molecules by linking each of our 3 lead brain shuttles to Ab or oligo drugs targeting tau or amyloid beta. We will then assess brain PK, brain distribution, target engagement and biodistribution of each fusion molecule in efficacy mouse models. The parental drugs without a shuttle will be used as controls. To increase target engagement of the fusion molecules in cytosol or nucleus, we test endosomal escape approaches built on our shuttle platform. **Conclusion:** With enhanced brain uptake and intracellular targeting of diseased cells, our brain shuttle platform can significantly aid AD therapeutic development. Efficient brain shuttle-mediated drug targeting may also lower the dose required to reach therapeutic concentration in brain. Finally, we are exploring shuttle modifications with the goal of reducing ARIA. **Key words:** Drug delivery, brain shuttle, precision medicine, Alzheimer's disease. **Disclosures:** This work is supported by a grant from Mass Life Sciences Center and by industry sponsorship. The authors declared no competing interests. **References:** 1. Cummings, Jeffrey et al. Alzheimer's research & therapy vol. 11,1 76. 31 Aug. 2019, doi:10.1186/s13195-019-0529-5; 2. Cummings, Jeffrey L et al. Alzheimer's research & therapy vol. 6,4 37. 3 Jul. 2014, doi:10.1186/alzrt269; 3. Abbott, N Joan et al. Neurobiology of disease vol. 37,1 (2010): 13-25. doi:10.1016/j.nbd.2009.07.030; 4. St-Amour, Isabelle et al. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism 2013; 33,12:1983-92. doi:10.1038/jcbfm.2013.160; 5. Pardridge, William M. Pharmaceutics 2022 Jun; 14,6 1283. doi:10.3390/pharmaceutics14061283

P165- EQUILIBRATIVE NUCLEOSIDE TRANSPORTER 1 (ENT1) AS A PROMISING THERAPEUTIC TARGET TO RESCUE PATHOLOGICAL FEATURES AND ALLEVIATE COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE. C.Y. Lin[1,2], C.P. Chang[1,2], K.C. Wu[2,3], C.W. Wu[1,2], C.J. Lin[2,3], Y. Chern[1,2] *(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))*

Background: Alzheimer's disease (AD) is the most prominent neurodegenerative disorder in aging societies that poses a substantial healthcare burden. The major pathological features of AD include energy dysfunction, extracellular amyloid plaques, intracellular neurofibrillary tangles, neuroinflammation, oxidative toxicity, cognitive impairment, and memory loss. Although recent FDA-approved antibody drugs targeting amyloid offer some promise, effective treatments remain in high demand. ENT1 is a bidirectional transporter that transports adenosine in a concentration-dependent manner. Disruption of adenosine homeostasis in the brain is known to result in energy dysfunction associated with mitochondrial impairment and reduced energy production in AD. Thus, developing drugs that modulate energy metabolism may offer a promising approach for treating AD. Our recent publication suggests that blocking ENT1 using JMF3464 (J4) ameliorates the symptoms of AD in mice by modulating adenosine homeostasis and improving neuronal energy failure during AD. **Objectives:** We set out to determine the efficacy and safety for J4, an orally active small inhibitor of ENT1, by monitoring various behavioral and physiological indicators in animal models. **Methods:** To evaluate the therapeutic effects, we tested two distinct AD mouse models (APP/PS1 for amyloidosis and THY-Tau22 for tauopathy) with the onset of memory deficiency occurring at the age of 6 months were tested. In the disease stage (11-12 months old), AD mice were orally administered J4 at a dosage of 3 mg/kg/day dissolved in drinking water containing 1% HPβCD for one month. We monitored the therapeutic efficacy of J4 using maze tests, pathological analyses, and PET scans, including mitochondria-, FDG-, amyloid-, and Tau-PET). Furthermore, rats and dogs were used to assess the safety pharmacology and general toxicology of J4. **Results:** Nonclinical efficacy studies conducted on two AD mouse models, APP/PS1 and THY-Tau22, have shown that J4 exhibits superior therapeutic effects. These effects include the ability to alleviate cognitive dysfunctions and impaired spatial memory, reduce the accumulation of misfolded Aβ and tau proteins, oxidative stress, and neuroinflammation, as well as elevated mitochondrial and glucose metabolic activities in the brain. Additionally, acute administration of J4 led to elevated glucose uptake in the brain, suggesting that fluorodeoxyglucose-positron emission tomography (FDG-PET) may serve as an effective means to assess the pharmacodynamic effect of J4. Moreover, the safety profile of J4 is encouraging, with acceptable tolerability in GLP toxicology and safety pharmacology studies. Collectively, J4 represents a novel compound that provides a first-in-class approach to address the fundamental issue of insufficient energy supply in neurons affected by AD. **Conclusion:** The results of our nonclinical studies demonstrate that oral administration of J4 provides therapeutic effects in treating AD and shows acceptable tolerability in GLP toxicology studies. In addition, a combination of PET images (e.g., mitochondria-, amyloid-, Tau- and FDG-PET) was established in the preclinical study, which can potentially serve as biomarkers in clinical usage. Our findings indicate that J4 is a novel and promising new chemical entity for treating AD by inhibiting ENT1 and modulating adenosine homeostasis. Further clinical studies are necessary to evaluate its efficacy and safety in humans. **Conflict of interest statement:** Yijuang Chern holds patents on J4 for the treatment of neurodegenerative diseases.

P166- STUDY OF NOVEL COPPER AND ZINC BINDING ANALOGUE OF GMP-1 IN TG4510 TAUOPATHY MOUSE MODEL. B. Winblad[1], Z. Zhao[1], P. Pavlov[1] *(1. Karolinska Institutet - Solna (Sweden))*

Background: We have previously described GMP-1, a small molecule with ability to chelate copper and zinc inhibiting amyloid beta fibrillization and oxidative stress and improving memory in the transgenic drosophila and mouse models that overexpress beta amyloid [1, 2]. However, the effect of GMP-1

and its analogues on memory and pathological tau aggregates was not yet investigated. Metal attenuating compounds such as PBT2 and clioquinol were previously shown to decrease brain tau aggregation and improve memory in the Tg4510 tau transgenic mouse model [3, 4]. This study aims to investigate the potential of a GMP-1 analogue to improve memory function as well as tau hyperphosphorylation/aggregation in Tg4510 mouse model. **Methods:** Copper/zinc binding: Metal binding by GMP-1 analogue was assayed by UV-vis spectroscopy. Pharmacokinetic study: Plasma and brain samples were collected and analyzed by liquid chromatography-mass spectrometry. Treatment conditions: 8-12 months-old Tg4510 mice were treated with vehicle (0.1% DMSO) or with 16.7 mg/kg/day of GMP-1 analogue in the drinking water ad libitum. The treatment lasted for 4 weeks followed by memory testing using Y-maze and contextual fear conditioning tests. Furthermore, brains were collected and analyzed for tau aggregation and hyperphosphorylation markers, gliosis as well as for neurodegeneration. **Results:** Spectroscopy studies confirm specific Cu2+/Zn2+ binding by GMP-1 analogue. PK studies of GMP-1 analogues are ongoing. Behavioral assessment of Tg4510 treated with vehicle or GMP-1 analogue revealed a trend towards memory improvement of context $p = 0.0583$ and cued $p = 0.0573$ fear conditioning test. Immunohistochemical assessment of brain pathology is ongoing. **Conclusion:** We showed that metal-attenuating compounds can rescue tau-associated memory dysfunction in the Tg4510 taoupathy model. **Disclosures:** The authors declare no conflict of interest. **Key words:** cognition; tauopathy; GMP-1 analogue. **References:** 1. Pavlov PF, et al., (2018) Cell Mol Med. 22, 3464-3474; 2. Kumar R, et al., (2020) J Alzheimers Dis. 73, 695-705; 3. Sedjahtera A, et al., (2018) Metallomics. (2018) 10, 1339-1347; 4. Lei P et al., (2015) Neurobiol Dis. 81, 168-175.

P167- NOVEL SMALL MOLECULE POLY-DISAGGREGATOR THERAPEUTICS FOR AD, ALS AND FTD REDUCE TDP-43 OLIGOMERIZATION, AGGREGATION, AND PATHOLOGY.

M. Kokes[1], V. Mathur[1], E. Shao[1], S. Arya[1], C. Planey[1] *(1. Acelot - Palo Alto (United States))*

TDP-43 pathology is a hallmark in most cases of Amyotrophic Lateral Sclerosis (ALS) and defines frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP). It is also present in over 30% of Alzheimer's Disease patients. TDP-43 pathology features cytoplasmic accumulation of insoluble TDP-43 aggregates. Notably, aggregates of several other amyloidogenic proteins appear alongside TDP-43 aggregates as co-pathology or multiple co-pathologies in the majority of AD, ALS and FTLD-TDP cases, including amyloid-β, α-synuclein, and tau. Furthermore, one amyloidogenic protein species can cross-seed aggregates or toxic oligomers of another distinct amyloidogenic protein species and accelerate overall disease progression. Together, these features underscore the potential therapeutic benefit of simultaneously targeting multiple amyloidogenic proteins. Using our novel machine learning platform, we identified small-molecule compounds that can disrupt toxic oligomers and aggregates of amyloidogenic proteins including TDP-43, amyloid-β, α-synuclein, and tau. We experimentally identified compounds that potently prevent in vitro aggregation and induce disaggregation of a minimal amyloidogenic TDP-43 (307-319) peptide as well as full length amyloid-β, α-synuclein, and tau using a dye-based aggregation assay. We find that one of the most potent compounds, ACE-339 dose-dependently reduced cytoplasmic TDP-43 aggregates in a human cellular TDP-43 aggregation model. TDP-43 and other amyloidogenic proteins can assemble into oligomers as an intermediate step to aggregation and these oligomers are considered to induce gain-of-function neuronal toxicity and degeneration. Using high resolution ion-mobility mass spectrometry to specifically identify small oligomers, we find that ACE-339 reduced oligomers and restored monomers and dimers formed by the TDP-43 peptide, suggesting that ACE-339 inhibits TDP-43 oligomerization. Furthermore, ACE-339 shows low plasma and brain homogenate binding, high metabolic stability, is orally bioavailable, and highly blood-brain barrier permeable. We tested ACE-339 in a doxycycline-repressible human iTDP-43A315T mouse model of ALS/FTD. Two months of daily oral dosing at two doses was well tolerated and ACE-339 was detectable at high concentrations in the brains of the mice at the end of the experiment. Notably, ACE-339 reduced TDP-43 pathology in the brain and showed partial behavioral rescue in iTDP43A315T mice. We found that ACE-339 reduced all markers of pathological forms of TDP-43 tested, including significantly reduced TDP-43 phosphorylation and TDP-43 insolubility, and cytoplasmic localization and ubiquitination trended lower with ACE-339 treatment. ACE-339 also improved motor performance and disinhibition deficits characteristic of iTDP-43A315T mice. Taken together, these in vitro, cell-based, and in vivo results indicate that the Acelot machine learning platform can identify small molecules that act as 'poly-disaggregators' on multiple amyloidogenic protein targets and have valuable therapeutic potential for AD, ALS, FTLD-TDP and other amyloid-associated diseases.

P168- DIFFERENCES IN GLUTAMINYL CYCLASE PROTEIN LEVELS IN MILD COGNITIVE IMPAIRMENT SUBJECTS.

X. Morato[1], A. Cano[1], S. Valero[1], R. Nuñez[1], R. Puerta[1], J.A. Allué[1], L. Sarasa[1], A. Ruiz[1], M. Boada[1] *(1. FUNDACIO ACE - Barcelona (Spain))*

Background: In addition to wide described amyloid β (Aβ) peptides, several N-terminally truncated fragments of Aβ peptides have been shown to contribute to Alzheimer's disease (AD) pathophysiology. Among them, N-terminal truncated Aβ forms pyroglutamated at the 3 and 11 positions play a key role in the neurotoxicity of AD. These forms rapidly adopts a β-sheet conformation, with enhanced aggregation propensities and resistance to most peptidases. Glutaminyl cyclase (QC) is the enzyme responsible of the pyroglutamation of N-terminal truncated Aβ peptides in the brain. So, the inhibition of QC activity has been proposed as a promising strategy for the development of novel AD treatments. Moreover, monitoring biofluid QC levels could have a theragnostic value in clinical trials evaluating the efficacy of QC inhibitors in early AD patients. Thus, the aim of this work is the evaluation of QC activity and levels in Mild Cognitive Impairment (MCI) subjects stratified by AT(N) categories. **Methods:** QC protein levels were measured in paired plasma and CSF samples of 90 patients with MCI using both Somascan (n=90) and Olink (n=45) platforms. QC activity was measured using the commercial SensoLyte®Green Glutaminyl Cyclase Activity Assay Kit. CSF Aβ42, Aβ40 and pTau181 were measured using the Lumipulse G600 II automatic platform and N-terminal variants of Aβ peptides Aβ3-40, Aβ11-40 and Aβ11-42 were quantified by liquid chromatography tandem mass spectrometry. MCI subjects were stratified by AT(N) categories (30 MCI A-T-N-, 30 MCI A+T-N- and 30 MCI A+T+N+) to perform the analysis of correlations. **Results:** No significant correlation

was observed between QC protein levels in plasma and CSF using Olink (r=.220, p=.151) or Somascan (r=.095, p=.377). QC protein levels measured using both Olink and Somalogic proteomic platforms correlates in CSF with QC activity (r=0.83, p =<.001 and r=0.95, p=<.001 respectively) and significant differences in QC protein levels were observed between A+T-N- and A+T+N+ (p < .001) subgroups in CSF but not in plasma. In all MCI, a high correlation of QC protein levels and CSF Aβ40 levels was observed (r =.733, p < .001). When considering all study subjects together, the correlations of QC with CSF Aβ42 (r=.332) and pTau181 (r=.477) levels were moderate. However, when evaluating each MCI subgroup separately, we observed higher correlations in the A-T-N- subgroup of QC activity with CSF Aβ42 levels (r=.640) and pTau181 (r =.560). Truncated amyloid peptides Aβ3-40, Aβ11-40, Aβ11-42 showed moderate correlation coefficients for QC protein levels (r=.436, r=.290 and r=.277 respectively) and CSF pTau181 levels (r=.351, r=.295 and r=.218, respectively). **Conclusions:** This PoC study based on the analysis of 90 MCI stratified by different AT(N) subgroups has identified some differences in the QC activity and levels. Deeper analysis of QC distribution in larger cohorts of MCI and AD patients, could be relevant to understand the importance of this enzyme for patient selection in clinical trials and the success of QC inhibitors. **Key words:** Alzheimer's disease, Mild cognitive Impairment, Cerebrospinal fluid, Glutaminyl cyclase, QC, Amyloid beta. **Disclosures:** MB, AC, SV, RN, RP, PG, JAA, LS, AR and XM are employees of the Ace Alzheimer Center and have no conflicts of interest to declare. **References:** 1. Christopher P. Sullivan et al. Neuroscience Letters 505 (2011) 109– 112. https://doi.org/10.1016/j.neulet.2011.09.071; 2. Vijverberg et al. Alzheimer's Research & Therapy (2021) 13:142 https://doi.org/10.1186/s13195-021-00882-9

P169- WHITE MATTER HYPERINTENSITY ACCUMULATION IS RELATED TO CEREBRAL AMYLOID ANGIOPATHY AND NEURODEGENERATION IN AUTOSOMAL DOMINANT AND SPORADIC AD.

Z. Shirzadi[1], S. Schultz[1], W.Y. Yau[1], N. Friedrichsen[2], K. Kantarci[3], G. Preboske[3], C. Jack Jr[3], B. Gordon[2], E. Mcdade[2], T. Benzinger[2], R. Bateman[2], S. Greenberg[1], R. Sperling[1], A. Schultz[1], J. Chhatwal[1] *(1. Massachusetts General Hospital, Brigham and Women's Hospital, Harvard Medical School - Boston (United States), 2. Washington University in St. Louis School of Medicine - St. Louis (United States), 3. Mayo Clinic, Radiology - Rochester (United States))*

Background: Increased white matter hyperintensity (WMH) volume is a common MRI finding in both autosomal dominant Alzheimer's disease (ADAD) and late-onset Alzheimer's disease (LOAD), but it remains unclear whether WMH is reflective of AD-intrinsic processes or evidence of white-matter injury secondary to elevated systemic vascular risk factors (e.g., small vessel ischemic changes suggestive of mixed vascular and AD pathologies). Using longitudinal data from three cohorts of ADAD and LOAD, we estimated the contributions of AD-intrinsic processes (neurodegeneration, cerebral amyloid angiopathy (CAA), and parenchymal amyloidosis) on WMH accumulation. We also examined whether systemic vascular risk explains WMH beyond these AD-intrinsic processes. **Methods:** We used data from the Dominantly Inherited Alzheimer's Network (DIAN), Alzheimer's Disease Neuroimaging Initiative (ADNI), and the Harvard Aging Brain Study (HABS), which included 1141 cognitively impaired and unimpaired individuals (252 pathogenic variant carriers from DIAN; 889 older adults from ADNI and HABS). We assessed the independent contributions of neurodegeneration (gray matter volume), parenchymal amyloidosis (amyloid PET), CAA (evidenced by cortical microbleeds; CMBs), and systemic vascular risk (Framingham Heart Study cardiovascular disease risk score (FHS-CVD)) on cross-sectional and longitudinal WMH volume while controlling for demographics. Lastly, we examined the relationship between baseline WMH burden and the development of CMB during longitudinal follow-up using survival analysis. **Results:** We observed that longitudinal increases in WMH volume were: (1) greater in individuals with CMBs compared to those without (DIAN: t=3.2, p=0.001; ADNI: t=2.7, p=0.008); (2) associated with gray matter atrophy (DIAN: t=-3.1, p=0.002; ADNI: t=-5.6, p<0.001; HABS: t=-2.2, p=0.03); (3) greater in older individuals (DIAN: t=6.8, p<0.001; ADNI: t=9.1, p<0.001; HABS: t=5.4, p<0.001); and (4) not significantly correlated with systemic vascular risk in ADAD and LOAD after accounting for gray matter volume, CMB presence, and amyloid burden. In older adults without CMBs at baseline, greater WMH volume was predictive of CMB development during longitudinal follow-up (Cox Hazard ratio=2.63 (CI:1.72-4.03), p<0.001). Notably, adjusting for age, gray matter volume, amyloid burden, and FHS-CVD did not alter the survival analysis results. **Conclusions:** Increased WMH volume in AD is associated with the AD-intrinsic processes of neurodegeneration, CAA, and parenchymal amyloidosis and may not reflect the effects of elevated systemic vascular risk. Additionally, increased WMH volume may represent an early sign of CAA, preceding the emergence of CMBs. These results suggest that white matter injury markers in ADAD and LOAD are independently associated with gray matter atrophy and CAA physiology. These results support the development of optimized WMH measures that may be useful as CAA biomarkers in the pre-CMB stage of the disease. This disease stage currently lacks a reliable imaging biomarker. Such markers are particularly important for AD clinical trials to identify individuals with latent CAA pathophysiology at risk of hemorrhagic lesions.

P170- SYSTEMATIC IN SILICO ANALYSIS OF CLINICALLY TESTED DRUGS FOR REDUCING AMYLOID BETA PLAQUE ACCUMULATION IN ALZHEIMER'S DISEASE.

S. Head[1], R. Das[1], B. Campbell[2], D. Zweifel[2], J. Burke[1], J. Apgar[1], F. Hua[1] *(1. Applied BioMath - Concord, Massachusetts (United States), 2. Prothena Biosciences Inc. - South San Francisco, California (United States))*

Background: Recent clinical trials of Aβ antibodies have established a relationship between plaque reduction and positive clinical and functional outcomes. Therefore, Applied BioMath undertook an exercise to quantitatively assess the antibody characteristics that predict Aβ plaque clearance by evaluating the effect of various classes of anti-Aβ therapeutics to better predict potential clinical benefit. To that end, we developed a quantitative systems pharmacology (QSP) model using eight different Aβ targeting approaches (aducanumab, lecanemab, crenezumab, solanezumab, bapineuzumab, elenbecestat, verubecestat, and semagacestat). **Methods:** Ordinary differential equations were used to model the production, transport, and aggregation of Aβ; pharmacology of the drugs; and their impact on plaque. **Results:** The calibrated model predicts that endogenous plaque turnover is slow, with an estimated half-life of 2.75 years. The model indicates that binding to plaque and inducing antibody-dependent cellular phagocytosis (ADCP) predicts CNS Aβ plaque reduction. This conclusion is further supported by results from inhibitors of

Aβ production (e.g. secretase inhibitors), monomer-selective antibodies (e.g. solanezumab), and antibodies with reduced Fc-mediated effector function (e.g. crenezumab) that all show relatively little plaque reduction. **Conclusions:** A QSP model calibrated to clinical data for multiple drugs with different target species and modalities enables meaningful comparisons between therapeutic strategies. The model simulations provide novel insights into clinical results and guidance for future therapeutic development. **Key words:** quantitative systems pharmacology, mathematical modeling, amyloid plaque. **Disclosures:** Portions of the presented results were supported by funding from Othair Prothena Ltd, Dublin, Ireland, a member of the Prothena Corporation plc group, and by the National Institutes of Health under award number 4R44AG058411-02. The authors declare no competing interests.

P171- IN SILICO SIMULATION OF DEMENTIA-ALZHEIMER-SYNDROME: APPLICATION OF HYBRID COMPUTING APPROACH TO THE STUDY OF EMERGENT BEHAVIOR. A. Khachaturian[1], Z. Khachaturian[1], J. Bouteiller[2], E. Troppová[3], V. Snášel[4], V. Vondrák[4], J. Damborský[5], S. Mazurenko[5], J. Šivic[3], V. Dočkal[3] *(1. Campaign to Prevent Alzheimer's Disease - Rockville (United States), 2. University of Southern California - Los Angeles (United States), 3. Czech Institute of Informatics, Robotics and Cybernetics, Czech Technical University - Prague (Czech Republic), 4. Technical University of Ostrava - Ostrava (Czech Republic), 5. International Clinical Research Center of St. Anne's University Hospital - Brno (Czech Republic))*

Background: Although there is growing recognition that dementia-Alzheimer syndrome and other related chronic brain disorders have polygenic origins, the field lacks the appropriate analytical tools to study the multi-faceted complexity of this condition. A distinctive feature of 'complex systems' lies in the dynamic, unpredictable, and multi-dimensional relationships among its interconnected parts. Thus, a prospective conceptual model of dementia must deal with the non-linearity of relationships and phenomena of emergent behavior. One major challenge in developing interventions for chronic brain disorders is the lack of appropriate models and computational algorithms to simulate and investigate the complex neurobiology of dementia. With the advent of novel advanced technologies beyond the capabilities of current high-performance computing (HPC), e.g., quantum (QC) and/or hybrid computing (HPCQC), it will be possible to simulate the intricate interactions among the multiple variables that underlie the neurodegenerative processes. Brain neural systems consist of sets of spatial hierarchies of networks with increasing levels of complexity. Ultimately, human behavior emerges from gated interactions between these different spatial scales across multiple temporal scales. However, the system is non-linear, i.e., changes in emerging behavior are not always proportional to the corresponding changes at lower scales, e.g., at the molecular or protein level. Thus, cognitive impairment and other clinical manifestations of dementia can be regarded as emergent behaviors and the expression of the complexity in the non-linear transfer of functions in the constituent components of the neural net involved. **Methods:** Simulation studies of non-linear coupling across critical elements of the neural system will demand computational power far beyond current HPC capacities. Classical computing and HPC provide computing power for solving significant problems with a low-order polynomial scaling. However, many problems exhibit high polynomial or non-polynomial scaling. Extending (in problem size or computational realism) such a problem model leads to collision with the polynomial, exponential, or combinatorial scaling wall, that is impossible to overcome with classical methods. The complexity of synaptic connections demonstrates the need for QC power in brain research. Many computing problems in brain research can be solved only by combining multiple algorithms, spawning a mixture of polynomial and nonpolynomial scaling computational kernels (solvable by HPCQC). **Results:** HPCQC with artificial intelligence/machine learning (AI/ML) can help us create suitable models of complex, multidimensional interconnected processes owing in part to the use of neural networks and the computational ability to process yottabytes of clinical and biological data. This approach was presented by academic partners led by INDRC in the EU Teaming for Excellence grant proposal CLARA. It strives for the interdisciplinary center of excellence focused on the next generation of AI/ML applications and HPCQC tools to solve the etiology of neurodegeneration. **Conclusions:** HPCQC with AI/ML represents an emerging technology challenging the frontier of research in neurodegeneration, particularly dementia-Alzheimer syndrome, by examining non-linear interactions between the molecular, behavioral, and clinical features of brain disorders. **Key words:** Alzheimer´s disease, artificial intelligence, brain research, high-performance computing, hybrid computing, quantum computing, neurodegenerative disorders, machine learning. **Disclosures:** There are no financial conflicts of interest to disclose.

P172- NEUROPROTECTIVE AND MNESIC-IMPROVING EFFECTS OF FLUOROETHYLNORMEMANTINE (FENM) IN THE Aβ25-35 MOUSE MODEL OF ALZHEIMER'S DISEASE. A. Carles[1], A. Freyssin[2], F. Perin-Dureau[2], G. Rubinstenn[2], T. Maurice[1] *(1. MMDN, Univ Montpellier, EPHE, INSERM, Montpellier (France), 2. ReST Therapeutics, Paris (France))*

Objectives: Fluoroethylnormemantine (FENM) is an analogue of Memantine originally synthesized as a precursor for PET imaging. We previously published, in Swiss mice intracerebroventricularly injected with oligomerized Aβ25–35 peptide, an acute model of Alzheimer's disease, that FENM prevented toxicity, neuroinflammation and learning deficits. Moreover, in behavioral testings, FENM showed superior efficacy to Memantine without any amnesic effect even at high doses. In this toxic AD model but with another genetic background (C57BL/6) we now aim to i) reproduce superiority of FENM over Memantine, ii) investigate FENM effect in mice previously treated with Memantine after vanishing of initial efficacy of this latter iii) compare two ways of administration of FENM, intraperitoneally daily versus subcutaneously continuously. **Methods:** Animals' spatial working memory was evaluated once-a-week throughout the whole experiments. The mnesic scores of animals were based on measurement of spontaneous alternation in the Y-maze test. i) and ii) FENM (0.3 mg/kg) and Memantine (0.3 mg/kg) were intraperitoneally injected daily with different agenda of treatments duration/discontinuation/switch. iii) FENM dose range administration (0.01-0.03-0.1-0.3 mg/kg) was performed either through intraperitoneally daily repeated injections (ip-repeated) or via surgically implanted Alzet pumps allowing a subcutaneous continuous infusion. **Results:** i) FENM (0.3 mg/kg) was efficient on mice spatial working memory preservation throughout its 8 weeks of administration, whereas Memantine (0.3 mg/kg) was only efficient during the first 4 weeks then lost its effect during the last 4 weeks of treatment. Furthermore, even after FENM discontinuation, mice maintained excellent mnesic scores for 3 more weeks. ii) In mice having received 5 weeks

of Memantine we therefore observe the loss of its efficacy and the reemergence of cognitive disturbances seen in this AD model. Then, introduction of FENM during 3 weeks allows the recovery of working memory. Even after FENM discontinuation (as described above) mice maintained excellent mnesic scores for 3 more weeks. iii) In behavioral tests performed as soon as after 1 week of treatment, ip-repeated FENM was effective at 0.3 mg/kg, whereas sc-Alzet FENM was effective at as low as 0.1 mg/kg/day (and above). **Conclusions:** We confirm in cognitive paradigm the previously published histopathological observations of a neuroprotective effect of FENM, which appears to be superior to Memantine. This efficacy is further increase with a continuous mode of administration via Alzet pump. Finally, whereas Memantine effects is transient, FENM' efficacy is long lasting, non-vanishing and sustained even after treatment discontinuation strongly suggesting a disease modifying activity. After having been recently granted of a positive scientific advice from EMA, the First-In-Human FENM administration in healthy volunteers will start in Q3 2023. **Disclosures:** AF, GR, FPD are employees of ReST, AC is a PhD sudent from UM under ReST contract. TM, GR, AF are inventors in patents on FENM application to AD.

P173- NANOLITHIUM HAS A DUAL POTENTIAL IN ALZHEIMER'S DISEASE: TO TREAT NEUROPSYCHIATRIC SYMPTOMS AND MODIFY DISEASE COURSE. M.E. Soto-Martin[1], S. Guilliot[2], P.J. Ousset[1], K. Bennys[3], C. Paquet[4], J. Touchon[5], E.N. Wilson[§] *(1. Alzheimer's disease Memory Research & Clinical center, Department of Geriatrics, Gerontopole, Hôpital Lagrave - Toulouse (France), 2. Medesis Pharma - Baillargues (France), 3. Alzheimer's disease Memory Research & Clinical center, Department of Neurology, University Hospital Gui de Chauliac - Montpellier (France), 4. Cognitive Neurology Center, Lariboisière Fernand-Widal Hospital APHP Université de Paris Cité - Paris (France), 5. University of Montpellier - Montpellier (France), 6. Neurology & Neurological Sciences, Stanford School of Medicine - Stanford (United States))*

Background: Lithium has a pleiotropic effect in neurodegenerative diseases such as Alzheimer's Disease (AD), which confers it a dual potential as a symptomatic treatment (of neuropsychiatric symptoms associated with the disease) and as a disease modifier. The benefit of Lithium in AD has been studied however its narrow therapeutic index precluded further developments. Medesis Pharma is currently studying Lithium associated with its drug delivery technology, called Aonys®, optimizing active ingredient bioavailability. **Results:** Aonys® is a water-in-oil microemulsion composed of self-assembled specific polar lipids, surfactant, and co-surfactants, all generally recognized as safe compounds. Nanolithium, Aonys® associated to an aqueous solution of lithium citrate, has a different absorption and distribution profile than lithium classical solution. The combination deposited on the buccal mucosa is loaded as a lipidic object in lipoprotein. The lipoproteins then act as trojan horse, circulating through the lymph and transiting further to the general circulation to release their cargo inside the cells including brain cells via lipoprotein receptors such as the scavenger receptor B1 (SR-B1). Using a different cell penetration mechanism bypasses voltage dependent ionic channel and enable a pharmacological activity at doses largely inferior to the ones needed with classical lithium solution. Moreover, a different cell penetration mechanism obviates most of the toxicity of lithium. As classical lithium, Nanolithium mechanism of action is exerted mainly through inhibition of Glycogen Synthase Kinase-3β. Over-activity of GSK-3β has been proposed to be involved in tau hyper-phosphorylation, increased β-amyloid production, and local plaque-associated microglial-mediated inflammatory responses; all of which are hallmark characteristics of AD. Nanolithium inhibitory effect on GSK-3β has been demonstrated in an animal model. Reduced production of toxic amyloid, rescued deficits in learning and memory have also been observed, supporting the cognitive benefit of the study drug. Beyond its effects on disease specific pathways, Nanolithium also showed a consistently positive effect on neuroinflammation, oxidative damage, neuroplasticity and neuroprotection in AD and other neurodegenerative diseases models. **Perspectives & Conclusions:** The ongoing proof-of-concept clinical study on Nanolithium in AD (NCT05423522) aims to exemplify the clinical efficacy of Nanolithium versus placebo, on the progression of neuropsychiatric symptoms between baseline and 12 weeks, supporting a symptomatic effect. Early intervention on neuropsychiatric symptoms and proper management has also been proposed as a mean to slow disease progression for patients with such manifestations. Analysis of the effect on Nanolithium after 9 to 12 months (depending on treatment arm) on each NPI-12 items, could also help identifying a subset of patients who can particularly benefit from early treatment with Nanolithium. The secondary objectives of the study are to elucidate the disease modifying potential through evaluation of the efficacy of Nanolithium after 9 to 12 months of treatment on progression of functional and cognitive performance, progression of cortical hypometabolism, progression of biological peripheral biomarkers (β-amyloid, Neurofilaments, BDNF, pTau, and inflammatory cytokines). Confirming lithium disease modifying potential in a formulation that is adapted for AD patient population would represent a promising therapeutic option for AD.

P174- ADVANCING DIVERSE RECRUITMENT BY ASSESSING FACILITATORS AND BARRIERS TO PARTICIPATION IN ALZHEIMER'S AND DEMENTIA-RELATED RESEARCH. J. Lucas[1], S. Green[1], M. Robinson[1], A. Spaulding[1] *(1. Mayo Clinic - Jacksonville (United States))*

Background: People who identify as Black/African American (AA) remain underrepresented in clinical trials. This study explored facilitators and barriers to AA participation in the AHEAD clinical trial. **Methods:** This study, conducted by [RMTM1] an urban medical center in the southern US, consisted of 12 focus groups within the local AA community employing scripts developed and delivered in collaboration with African American community advisors. Investigators followed a content analysis and grounded theory approach to data analysis, resulting in identification of 3,640 codes which were collapsed into overarching categories. Resultant themes were then applied to an adaptation of the transtheoretical model stages of behavior change, focused on facilitators and barriers to changing individual behavior to engage participants in clinical trials. The social-ecological model was then used to map opportunities for the medical research community to overcome these barriers at each included level, all suggested by focus group participants. After analyses, a member checking/give-back session was held to ensure themes were accurate and to provide participants recognition and appreciation for their efforts. **Results:** Self-identified AA participants (n=84) represented 4 broad stakeholder groups, including: individuals enrolled in observational research on aging and dementia (n=35); caregivers and family members of those with dementia (n=23); clergy and funeral directors (n=9); and community members not engaged in research (n=17). In the social-ecological

model and transtheoretical model adaptation, the need for AA representation in clinical trials was universally recognized across focus groups at the intrapersonal, interpersonal, and community levels. Motivation to participate included potential benefits gained by the participant or their family members and altruistic reasons to benefit the community and future generations, which are also included in the model. Barriers to enrollment included themes of feeling uninvited or excluded, several dimensions of fear and mistrust, personal experiences with racism, lack of understanding (the disease, the study, or benefits of participation), and logistical issues. Themes reflecting opportunities to increase awareness and enrollment were also identified and mapped using the social-ecological model levels as a guide. Suggestions included utilizing messaging by trusted community members (physicians, clergy, civic leaders); employing culturally reflective, one-on-one recruitment strategies; and ensuring a culturally comforting and familiar environment where the trial is being conducted. During the subsequent member-checking phase, participants confirmed the accuracy of identified themes. They provided additional examples of lack of understanding (e.g.,need to understand the necessity for all study components and length of study commitment) and mistrust (e.g., perception that the consent process protects the investigator, not the participant). **Conclusion:** Participants in our study were eager for African Americans to be involved in clinical trials despite the extensive barriers they cited, suggesting that clinical trial sponsors and investigators have opportunities to develop trust, provide education, communicate transparently, and engage the AA community in ways that will achieve greater inclusion. The socio-ecological model adaptation developed in this study provides a framework for healthcare providers and researchers seeking to optimize recruitment efforts to engage and enroll AA community members in clinical trials. **Key words:** barriers to participation, African American, qualitative research, grounded theory. **Disclosure:** The authors have no conflicts of interest to declare*

P175- FOSGONIMETON, A SMALL-MOLECULE POSITIVE MODULATOR OF THE HGF/MET SYSTEM, ATTENUATES AMYLOID-BETA TOXICITY IN PRECLINICAL MODELS OF ALZHEIMER'S DISEASE. S. Reda[1], S. Setti[1], A.A. Berthiaume[1], W. Wu[1], J. Johnston[1], R. Taylor[1], K. Church[1] *(1. Athira Pharma, Inc. - Bothell (United States))*

Background: Positive modulation of the hepatocyte growth factor (HGF)/MET system may represent a promising therapeutic strategy for Alzheimer's disease (AD) based on its multimodal neurotrophic, neuroprotective, and anti-inflammatory effects addressing the complex pathophysiology of neurodegeneration. We have previously shown that fosgonimeton, a small-molecule positive modulator of the HGF/MET system, is neuroprotective in preclinical models of dementia [1]. In human trials, treatment with fosgonimeton showed in post hoc analyses consistent improvement on plasma biomarkers of neurodegeneration and neuroinflammation, which also significantly correlated with improvements in clinical outcomes in people with mild-to-moderate AD [2, 3]. Herein, we highlight a proposed mechanism by which fosgonimeton induces neuroprotective effects to attenuate amyloid-beta (Aβ)-induced toxicity in preclinical models of AD. **Methods:** To evaluate the effects of fosgonimeton in vitro, primary rat cortical neurons were treated with the active metabolite of fosgonimeton, fosgo-AM, challenged with Aβ (Aβ1-42; 15 μM) for 24 hours, and co-immunostained for microtubule-associated protein-2 and phospho-tau. Immunofluorescence analyses were used to determine neuronal survival, neurite network integrity (total neurite length), and phospho-tau levels. To elucidate intracellular mechanisms, the effects of fosgo-AM on Aβ-induced mitochondrial dysfunction and apoptotic signaling (cytochrome C) were investigated. Protein analyses via western blot were conducted to assess downstream signaling effectors such as ERK, AKT, and GSK3β. In addition, we investigated the effect of fosgo-AM on autophagic signaling as mediated by ULK1 and Beclin-1. In vivo, we assessed the effects of fosgonimeton in an intracerebroventricular (ICV) Aβ25-35-induced model of cognitive impairment. Adult male rats were injected with Aβ25-35, and subcutaneously administered with fosgonimeton (0.125, 0.25, 0.5, 1, or 2 mg/kg) or vehicle for 14 days, at which time rats underwent the passive avoidance acquisition paradigm. On day 15, rats were placed into the passive avoidance apparatus once more and assessed for step-through latency in a retention trial for cognitive function. **Results:** Fosgo-AM treatment significantly improved survival of cortical neurons, protected neurite networks, and reduced tau hyperphosphorylation after injury with Aβ1-42. Interrogation of intracellular events indicated that cortical neurons treated with fosgo-AM exhibited a significant decrease in mitochondrial oxidative stress and cytochrome C release, effects that are expected to counteract Aβ-mediated toxicity and promote neuronal survival. Additionally, fosgo-AM significantly enhanced activation of pro-survival effectors ERK and AKT, and reduced activity of GSK3β, one of the main kinases involved in tau hyperphosphorylation. Fosgo-AM also mitigated Aβ-induced deficits in ULK1 and Beclin-1, suggesting that it may restore autophagic function to facilitate clearance of toxic proteins. In vivo, fosgonimeton administration led to functional improvement in the ICV-Aβ25-35 model of AD, as it significantly restored cognitive function at all doses tested in the passive avoidance test. **Conclusions:** Our data demonstrate the ability of fosgonimeton to counteract mechanisms of Aβ-induced toxicity, reduce tau pathology, and promote neuronal survival in vitro. Furthermore, treatment with fosgonimeton leads to cognitive rescue in an Aβ-driven rat model of AD, suggesting that the cellular effects of fosgonimeton translate to functional benefits. Overall, our data continue to support the therapeutic development of fosgonimeton for AD. Fosgonimeton is currently in clinical trials for mild-to-moderate AD (NCT04488419; NCT04886063). **Key words:** Amyloid, Tau, Neuroprotection, Small molecule therapeutic. **Disclosures:** S.M.R., S.E.S., A.A.B., W.W., J.L.J., R.W.T., K.J.C. are employees of Athira Pharma, Inc. (Athira), and hold shares of stock and/or stock options in Athira. **References:** 1. Johnston J, et al. Fosgonimeton, a Novel Positive Modulator of the HGF/MET System, Promotes Neurotrophic and Procognitive Effects in Models of Dementia. Neurotherapeutics 2023 Mar; 20(2):431-451. doi: 10.1007/s13311-022-01325-5. 2. Moebius H, et al. Fosgonimeton provides congruent benefit on diverse biomarkers of neurodegeneration, significantly correlating with a composite clinical score of cognition and function in Alzheimer's disease. Clinical Trials in Alzheimer's Disease 2022; Poster LP79, https://www.athira.com/scientific-publications-ctad-2022/. 3. Moebius H, et al. Fosgonimeton Provides Congruent Improvements on Neurodegeneration Biomarkers, Significantly Correlating With Composite Clinical Score of Cognition and Function in Alzheimer's Disease. American Academy of Neurology 2023; Poster S26, https://www.athira.com/aan-2023-fosgonimeton-moebius/

P176- DESIGNED PEPTIDE TARGETING A-SHEET AMYLOID-B OLIGOMERS DECREASES TOXIC OLIGOMER BURDEN AND IMPROVES BEHAVIOR IN AD MOUSE MODELS. C. Tallon[1], C. Gajera[1], J. Posakony[1], G. Block[1], V. Daggett[1] *(1. AltPep Corporation - Seattle (United States))*

Background: Alzheimer's disease (AD) is characterized by the accumulation of β-sheet-rich amyloid-β (Aβ) plaques within the brain; however, this accumulation does not correlate with cognitive decline in AD patients while toxic soluble oligomers do. These soluble oligomers have been demonstrated to assume a nonstandard secondary structure called "α-sheet", which forms during the peak of Aβ cytotoxicity. We have designed a de novo α-sheet Soluble Oligomer Binding Inhibitor (SOBIN) peptide, SOBIN-01, that tightly binds and inhibits the toxic oligomers. **Methods:** Using our Soluble Oligomer Binding Assay (SOBA) for detection of toxic Aβ oligomers, we evaluated whether α-sheet oligomers were detectable in the Tg2576 AD mouse model and if SOBIN-01 could reduce toxic oligomer levels. 12-week-old Tg2576 mice, an age that precedes pathology and symptomatic behavioral deficits, were dosed intranasally (IN) with a single dose of vehicle (PBS) or 200 - 0.01 μg of SOBIN-01. The brains were collected 3 days later and were analyzed with SOBA. We next examined SOBIN-01's efficacy in an induced AD mouse model where α-sheet-enriched Aβ was ICV infused into 6-month-old female C57BL/6 mice. Mice were given a single 100 μg IN dose of SOBIN-01 and their behavior was examined in the open field and Morris water maze (MWM) tests 1- and 3-weeks post dosing. **Results:** The Tg2576 mice contained high levels of toxic oligomers as measured by SOBA compared to the WT controls. The SOBIN-01 treated Tg2576 mice showed a complete reduction in the SOBA signal. In the acute, induced-AD model, the Ab treated mice had deficits during the learning acquisition trials with increased escape latency and distance to platform. SOBIN-01 rescued Ab oligomer-induced learning and memory deficits both 1 and 3 weeks after a single dose in the MWM assay. In a 24h long-term memory probe, Ab-treated mice receiving only vehicle were unable to distinguish between the target quadrant of the MWM and neighboring quadrant, while both the PBS infused control and SOBIN-01 treated mice spent significantly more time in the target quadrant. **Conclusions:** The presence of α-sheet oligomers was detected with SOBA in a Tg mouse model of AD well before the onset of any pathological markers. Infusing normal mice with these α-sheet oligomers was sufficient to induce cognitive deficits after one and three weeks. Treatment with SOBIN-01 reduced the SOBA signal in Tg2576 AD mice and improved behavioral deficits in the ICV Ab mice. Ongoing efforts are examining SOBIN-01's long-term efficacy in the Tg2576 AD model. Taken together, SOBIN-01 targets the earliest forms of toxic oligomers, providing a potential opportunity for improving upon, and or complementing, current therapeutics in the AD space. **Key words:** Amyloid β, α-sheet, toxic soluble oligomers, Alzheimer's disease, therapeutic peptide, SOBA. **Disclosures:** All authors are current employees or affiliates of AltPep Corporation. V.D. is a named inventor on patents pertaining to SOBIN-01.

P177- UNRAVELING THE THERAPEUTIC POTENTIAL OF NOVEL HYALURONIC ACID ESTRADIOL CONJUGATE ND108E IN ALZHEIMER'S DISEASE: MECHANISTIC INSIGHTS AND FUTURE DIRECTIONS. C.L. Hou[1], S.Y. Lee[1], J.C. Wang[1], T.A. Chen[1], K.T. Chang[1], M.H. Chen[2], H.C. Lin[2], T. Chao[2], T.J. Wang[3], J.R. Chen[2] *(1. Holy Stone HealthCare - Taipei (Taiwan, Republic of China), 2. National Chung-Hsing University - Taichung (Taiwan, Republic of China), 3. National Taichung University of Science and Technology - Taichung (Taiwan, Republic of China))*

Background: Epidemiological studies show an increased risk of Alzheimer's disease (AD) with age-related loss of sex hormones. AD is more prevalent in postmenopausal women and young women who undergo surgical menopause were more prone to experiencing cognitive decline associated with increased neuropathology of AD. Recent studies suggest that reduction of brain-derived estrogen, rather than circulating estrogen may play an important role in AD development, while retaining normal brain estradiol (E2) can prevent AD progression. Estrogen supplementation may sustain effective E2 levels to slow down AD progression. This program developed a therapeutic approach of brain E2 supplementation for AD. ND108E is a hyaluronate conjugated drug (HACD), a conjugate of biological polymer sodium hyaluronate and E2. The studies were to demonstrate HACD can penetrate the blood-brain barrier (BBB), and ND108E can restore cognitive functions, facilitate a prolonged release profile of E2, and mitigate the risk of side effects associated with estrogen supplementation. **Methods:** Effects of HACD on BBB penetration was explored by distribution of HA-dye in brain. After administration of HA-Rhodamine to C57BL/6J mice intravenously, immunostaining of hippocampus was performed using anti-Rhodamine antibody, and results were obtained through confocal microscopy. In vivo cognitive functions were studied using ovariohysterectomy (OHE) rat model. ND108E was administrated via intravenous injection twice per week for 2 weeks. The cognitive performance of OHE rats were assessed using Morris water maze (MWM) task. To evaluate the neuronal functions, spine density of neuron dendrites was measured. Lucifer yellow was microinjected into the neurons in hippocampal CA1 pyramidal layer, and the spine number was calculated using fluorescence microscopy. In vitro functional modulation of non-amyloid pathway was evaluated in SH-SY5Y-APP cells. Western blotting was employed to determine levels of phosphorylated Tau, phosphorylated GSK3beta, soluble APP fragment (sAPPα), C83 c-terminal APP fragments (C83), and α-secretase (MMP-9). **Results:** The fluorescence of HA-Rhodamine in the hippocampus increases twofold compared to Rhodamine alone suggesting that HACD significantly enhances the penetration of Rhodamine across the BBB. In vivo behavioral studies, OHE rats treated with ND108E exhibited preference in the MWM task compared to untreated OHE rats. The results of latency and probe behavioral testing indicated the learning and memory ability of ND108E-treated OHE rats were restored as that of normal rats. Furthermore, an increase in the density of spine in hippocampal pyramidal neurons was observed following ND108E treatment. These findings suggest the increase in spine formation may contribute to the effects of ND108E on learning and memory functions. ND108E was identified as a modulator inhibiting Abeta formation and phosphorylation of Tau. The increase in sAPPα, C83 and MMP-9 indicated ND108E altered APP processing through enhanced α-secretase. The decrease in phosphorylation of Tau and GSK3beta indicated ND108E

inhibited Tau hyperphosphorylation via GSK3beta pathway. **Conclusion:** These studies suggested beneficial effects of ND108E for cognitive decline. ND108E promote spine plasticity and contribute to improvement in learning and memory. The inhibition of Abeta formation and hyperphosphorylation of Tau indicated a neuroprotective effects in preventing the progression of AD pathology. These finding collectively highlight the promising therapeutic potential of ND108E in the treatment of AD.

P178- STRUCTURAL AND BIOCHEMICAL SIMILARITIES OF PROTOFIBRILS AND PLAQUE FIBRILS: IMPLICATIONS FOR ANTI-AMYLOID IMMUNOTHERAPY. A. Stern[1], Y. Yang[2], S. Jin[1], K. Yamashita[2], A. Meunier[1], W. Liu[1], Y. Cai[1], M. Ericsson[3], L. Liu[1], M. Goedert[2], S. Scheres[2], D. Selkoe[1] *(1. Ann Romney Center For Neurologic Diseases, Brigham And Women's Hospital, Harvard Medical School - Boston (United States), 2. MRC Laboratory for Molecular Biology - Cambridge (United Kingdom), 3. Harvard Medical School - Boston (United States))*

Background: Lecanemab has been described to bind preferentially to Aβ protofibrils compared to fibrils, a distinction hypothesized to explain its clinical efficacy compared to other anti-amyloid monoclonal antibodies.1,2 However, there is no structural definition of a protofibril, nor is there detailed biochemical analysis of protofibrils from human brain. **Methods:** We used a gentle "soaking" method to isolate aqueously diffusible Aβ aggregates from the grey matter of postmortem human Alzheimer disease brains, a pool of Aβ thought to contain "soluble protofibrils" or "oligomers". We used differential centrifugation, immunoelectron microscopy, and cryoelectron microscopy to describe the structure and properties of these aqueously diffusible aggregates and their reactivity with clinical antibodies. **Results:** Virtually all aqueously diffusible Aβ aggregates (i.e., protofibrils) could be pelleted by sufficient centrifugal force (>250,000 g), implying they are particulate (insoluble). These aqueously diffusible aggregates had the same atomic structure as Sarkosyl-insoluble (i.e., amyloid plaque-derived) Aβ aggregates. Donanemab, lecanemab, aducanumab, and gantenerumab all immunoprecipitated Aβ42 from soaking extracts and labeled the Aβ fibrils therein. **Conclusions:** There may not be Aβ protofibrils in human brain distinct from amyloid plaque fibrils in atomic structure or immunoreactivity to clinical anti-amyloid monoclonal antibodies. **Key words:** amyloid; Aβ; donanemab; lecanemab; aducanumab; gantenerumab; cryoEM; immunotherapy; Alzheimer disease. **Disclosures:** DJS is a director and consultant to Prothena Biosciences. The other authors declare no conflicts of interest. **References:** 1. Lannfelt L et al. (2014) Alzheimers Res Ther 6:16. 2. Tucker S et al. (2015) J Alzheimers Dis 43:575-588.

LP098- HUMAN SPECIFIC A7NACHR-DEPENDENT ADAPTATION TO MECHANICAL PROPERTIES OF THE EXTRACELLULAR ENVIRONMENT. I. Ihnatovych[1], R.P. Dorn[1], E. Nimmer[1], Y. Heo[1], Y. Bae[1], K. Szigeti[1] *(1. University at Buffalo - Buffalo (United States))*

Background: CHRFAM7A, a human restricted gene associated with neuropsychiatric and neurodegenerative disorders, is expressed in 99.3% of the human population. It is present in different copy number (0-4) and orientation (direct or inverted alleles). CHRFAM7A translated from the direct allele incorporates into the α7 nicotinic acetylcholine receptor (α7nAChR) leading to a hypomorphic receptor . Our results of multiomics analysis of post mortem brains from the ROSMAP dataset have demonstrated that CHRFAM7A gene expression level is associated with actin cytoskeleton gain of function. As the actin cytoskeleton is implicated in adaptation to the mechanical properties of the brain, we explored the role of CHRFAM7A in adaptation to the extracellular environment in the human context. **Methods:** We utilized a human isogenic CHRFAM7A iPSC model and polyacrylamide hydrogels corresponding to Young's modulus 2 kPa (soft) and 5 kPa (stiff), the shift between rodent and human brain stiffness, to study human specific adaptation to the mechanical properties of the brain. Medial ganglionic eminence (MGE) progenitors generated from CHRFAM7A null (0 copy number) and CHRFAM7A knock-in (CHRFAM7A KI) lines were contrasted using fluorescent phalloidin immunocytochemistry, atomic force microscopy (AFM) and small G-protein activation assay. **Results:** We found distinct differences in growth cone (GC) morphology, polarization pattern, small GTPases activity, and intracellular elastic modulus between the medial ganglionic eminence (MGE) progenitors generated from CHRFAM7A null (0 copy number) and CHRFAM7A KI lines. In response to an increased matrix stiffness, null MGE progenitors developed pronounced and multidirectional GCs with filopodia morphology, while CHRFAM7A GCs demonstrated lamellipodia structure. In the stiffer environment, null cells became predominantly multipolar, while CHRFAM7A_KI cells became mostly bipolar. Preferred membrane structure and cell polarity correlated with small GTPases activity: in null MGE progenitors, the CDC42 activity was higher than RhoA in the soft environment, promoting bipolar polarization of the cells opposed to multipolar morphology (high RhoA activity) in the stiff environment. In contrast, MGE progenitors derived from the CHRFAM7A KI line activated both CDC42 and Rac1 and with limited RhoA activation. CHRFAM7A KI MGE progenitors were able to invade the stiffer environment by adapting intracellular stiffness. The adaptation was inhibited by Rac1 inhibitor (EHT1864). The invasion was associated with increased MMP2 and MMP9 expression suggesting increased ECM degradation consistent with lamellipodia driven cellular motility. Inhibition of Rac1 led to a decrease in both MMP2 and MMP9 levels only in the CHRFAM7A KI line. **Conclusions:** Our results provide evidence that the presence of human specific CHRFAM7A positively affects neuronal ability to adapt to matrix stiffness. CHRFAM7A may facilitate neuronal adaptation to changes in the brain environment in physiological and pathological conditions (inflammation, Amyloid deposition, myelination, aging, glioma, stroke) which may lead to benefit or risk based on the disease context. **Key words:** CHRFAM7A, actin cytoskeleton, small GTPases, extracellular matrix. **Disclosures:** The authors have nothing to disclose.

LP099- MECHANISTIC INSIGHTS INTO THE TRANSLATIONAL GAP FOR CHOLINERGIC THERAPIES IN ALZHEIMER'S DISEASE. K. Szigeti[1], I. Ihnatovych[1], N. Rosas[1,2], R.P. Dorn[1], E. Notari[1], Z. Chen[1], E. Cortes Gomez[3], M. He[1], M. Del Regno[1], D.A. Bennett[4], A. Pralle[1], Y. Bae[1], J. Wang[3], G. Wilding[1] *(1. University at Buffalo - Buffalo (United States), 2. Universidad Nacional de San Martin - Buenos Aires (Argentina), 3. Roswell Park Comprehensive Cancer Center - Buffalo (United States), 4. Rush Alzheimer's Disease Center - Chicago (United States))*

Background: Recent advancements in imaging techniques and concerted efforts have led to major strides in deciphering the human brain. Despite this progress, the human brain remains elusive for successful interventions and represents

some of the most persistent translational gaps in medicine. Understanding the fundamental differences between the human and pre-human brain is a prerequisite to designing meaningful models. CHRFAM7A, a human restricted fusion gene is associated with decreased AD risk and decreased response to cholinergic therapy. Utilizing human brain gene expression, iPSC model, cognitive and MRI data the mechanistic insights into the physiological role of CHRFAM7A in human brain is presented to decipher this conundrum. **Methods:** Multiomics approach on 600 post mortem human brain tissue samples (ROSMAP) generated mechanistic hypotheses are tested and validated in an isogenic hiPSC model of CHRFAM7A knock-in medial ganglionic eminence progenitors and neurons. Pilot study of neurocognitive and MRI correlation with the CHRFAM7A carrier status using ANCOVA explores human brain structural-functional readouts. Proof of Principle Double Blind Pharmacogenetic Study on the effect of AChEI therapy based on CHRFAM7A carrier status was performed in two paradigms: response to drug initiation and DMT effect. Mini Mental Status Examination (MMSE) was used as outcome measure. Change in MMSE score from baseline was compared by 2-tailed T-test. Longitudinal analysis of clinical outcome (MMSE) was performed using a fitted general linear model, based on an assumed autoregressive covariance structure. Model independent variables included age, sex, and medication regimen at the time of the first utilized outcome measure (AChEI alone or AChEI plus memantine), APOE4 carrier status (0, 1 or 2 alleles as categorical variables) and CHRFAM7A genotype. **Results:** CHRFAM7A incorporation into the a7 nAChR pentamer results in a hypomorphic receptor in iPSC derived MGE progenitors with decreased channel open probability. The hypomorphic receptor has diminished response to pharmacological modulation; concomitantly the hypomorphic receptor changes Ca2+ dynamics leading to Rac1 activation. Rac1 activation leads to a dynamic actin cytoskeleton and remodeling of membrane protrusion from filopodia to lamellipodia. The actin cytoskeleton GOF reinforces the neuronal structure measured by a more compact and more efficient human brain. **Conclusions:** In the presence of CHRFAM7A the hypomorphic a7 nAChR receptor mediates cytoskeletal gain of function in the human brain through Ca2+ signaling. The outcome is a more resilient brain in CHRFAM7A carriers (CNV GWAS association) but diminished AChEI treatment response due to the hypomorphic receptor. **Key words:** CHRFAM7A, translational gap, Alzheimer's disease, cholinergic therapy. **Disclosures:** The authors have nothing to disclose.

LP100- HUMAN RESTRICTED CHRFAM7A GENE MAY ENHANCE BRAIN EFFICIENCY. K. Szigeti[1], R.P. Dorn[1], M. Del Regno[1], J. Dejan[2], N. Bergsland[2], M. Ramanathan[1], M.G. Dwyer[2], R.H. Benedict[1], R. Zivadinov[1] *(1. University at Buffalo - Buffalo (United States), 2. Buffalo Neuroimaging Analysis Center - Buffalo (United States))*

Background: CHRFAM7A, a uniquely human fusion gene, has been associated with neuropsychiatric disorders including Alzheimer's disease, schizophrenia, anxiety, and attention deficit disorder. Understanding the physiological function of CHRFAM7A in the human brain is the first step to uncovering its role in disease. Using human brain multiomics and isogenic iPSC, CHRFAM7A was identified as a potent modulator of intracellular calcium and an upstream regulator of Rac1 leading to actin cytoskeleton reorganization and a switch from filopodia to lamellipodia implicating a more efficient neuronal structure. We performed a neurocognitive-MRI correlation pilot study on 46 normal human subjects to explore the effect of CHRFAM7A on human brain. **Methods:** Dual locus specific genotyping of CHRFAM7A was performed on genomic DNA to determine copy number (TaqMan assay) and orientation (capillary sequencing) of the CHRFAM7A alleles. As only the direct allele is expressed at the protein level and affects a7 nAChR function, direct allele carriers and non-carriers are compared for neuropsychological and MRI measures. Subjects underwent neuropsychological testing with a battery to measure motor (Timed 25-foot walk test, 9-hole peg test), executive function (Symbol Digit Modalities Test), Learning and memory (California Verbal Learning Test immediate and delayed recall, Brief Visuospatial Memory Test – Revised immediate and delayed recall) and Beck Depression Inventory - Fast Screen, Fatigue Severity Scale. All subjects underwent MRI scanning on the same 3T GE scanner using the same protocol. T2 lesion volume was determined by an experienced neuroimager using a semi-automated iso-contouring technique. Global and tissue-specific volumes were determined using validated cross-sectional algorithms including FSL's Structural Image Evaluation, using Normalisation, of Atrophy (SIENAX) and FSL's Integrated Registration and Segmentation Tool (FIRST) on lesion-inpainted images. The cognitive tests were age and years of education-adjusted using analysis of covariance (ANCOVA). Age-adjusted analysis of covariance (ANCOVA) was performed on the MRI data. **Results:** CHRFAM7A direct allele carrier and non-carrier groups included 33 and 13 individuals, respectively. Demographic variables (age and years of education) were comparable. Motor function and depression were similar between the groups. Cognitive domain, executive function, learning and memory were higher in the carrier-group, reaching statistical significance in visual immediate recall ($p=0.003$). The two groups had similar lateral ventricular volume ($p=0.708$) and T2-lesion volume ($p=0.876$). Intriguingly, direct allele carriers had smaller whole brain ($p=0.046$), white matter ($p=0.077$), gray matter ($p=0.082$) and deep gray matter volume ($p=0.050$). **Conclusions:** These pilot data suggest that direct allele carriers harbor a more efficient and compact brain consistent with the cellular biology of actin cytoskeleton and synaptic gain of function. Further larger human studies of cognitive measures correlated with MRI and functional imaging are needed to decipher the impact of CHRFAM7A on brain function. **Key words:** CHRFAM7A, neuropsychological assessment, structural MRI, human brain diversity. **Disclosures:** The authors have nothing to disclose.

LP101 COMBINED E2 AND CHRISTCHURCH GAIN-OF-FUNCTION VARIANTS OF THE HUMAN APOE GENE DELIVERED BY AAVRH.10 EFFECTIVELY SUPPRESSES BOTH AMYLOID AND TAU PATHOLOGY IN THE CNS OF MURINE MODELS OF APOE4 HOMOZYGOUS ALZHEIMER'S DISEASE. C. Günaydın[1], D. Sondhi[1], S. Kaminsky[1], H. Lephart[1], P. Leopold[1], R. Khanna[2], R. Crystal[1] *(1. Weill Cornell Medical College - New York (United States), 2. LEXEO Therapeutics - New York (United States))*

Background: The common apolipoprotein E alleles (APOE2, 3 and 4) are important genetic risk factors for late-onset Alzheimer's disease, with the E4 allele increasing risk and reducing the age of onset and the E2 allele decreasing risk and markedly delaying the age of onset. The focus of this study is to assess the ability of gene delivery of apolipoprotein E (APOE) gain-of-function alleles, APOE2 (C112/C158), and the

rare human "hyper" gain-of-function Christchurch (R136S) mutation to suppress Alzheimer's disease (AD)-related to pathology associated with homozygous inheritance of the AD-high risk APOE4 allele. **Methods:** We assessed adeno-associated serotype AAVrh.10 delivery of APOE2 vs combining the APOE Christchurch variant with the APOE2 variant to suppress both the amyloid and tau-associated pathology in murine models of APOE4 homozygous AD. We tested the hypothesis that AAVrh.10-mediated CNS delivery of the combined human APOE2 allele with the Christchurch mutation (AAVrh.10hAPOE2Ch, referred to as "E2Ch"), will provide greater protection against development of APOE4-associated AD-related pathology compared to the unmodified APOE2 allele (AAVrh.10hAPOE2, referred to as "E2"). These vectors along with controls AAVrh.10Null and PBS were tested in two models of AD: APP.PSEN1/TRE4 humanized APOE4 "amyloid mice" that develop amyloid plaques with progressive neurodegeneration and dysfunction; and P301S/TRE4, humanized APOE4 "tau mice" that develop neurofibrillary tangles and tauopathy with progressive neurodegeneration and dysfunction. The vectors or controls were administered to the hippocampus (2x1010 gc, 2 μl) of amyloid mice at age 2.5 months with assessment 3 months post-administration and to tau mice at age 5.5 months with assessment after 3 months. **Results:** Both the E2Ch and E2 vectors prevented Aβ42 and Aβ40 accumulation in amyloid mice compared to controls ($p<0.01$) but only the E2Ch vector suppressed total tau and p-tau levels in tau mice ($p<0.01$). Both the E2Ch and E2 vectors decreased β-amyloid aggregates in amyloid mice but a decrease in tau tangles in tau mice was observed only with the E2Ch vector ($p<0.01$). Microglial activation (Iba1 staining) and reactive astrocytes (GFAP staining) were significantly suppressed with both vectors in amyloid mice ($p<0.01$), but only the E2Ch vector mediated significant suppression of Iba1 and GFAP in tau mice ($p<0.01$). Both amyloid and tau mice treated with the E2 and E2Ch vectors were assessed using behavioral assays (nesting, Y maze, novel object recognition, Barnes maze). In the amyloid mice, the E2 and E2Ch vectors had similar benefits, but in the tau mice, the E2Ch vector markedly outperformed the E2 vector, with E2Ch improvement in all 4 behavioral assays compared to E2. **Conclusions:** In summary, while the E2 vector is effective in suppressing APOE4-associated amyloid pathology, only the combined Christchurch and APOE2 variant provided a "hyper" gain-of-function APOE variant that effectively treats both the amyloid and tau pathology of murine models of APOE4 homozygous AD, supporting the development of AAVrh.10APOE2Ch as a therapy for APOE4-associated AD. **Key words:** gene therapy, APOE4, APOE2, APOE Christchurch. **Disclosures:** DS, SK, RGC have equity in LEXEO Therapeutics

LP102- NEW APPROACH TO ALZHEIMER'S DISEASE - NOVEL CHIMERIC GAS6 FUSION PROTEIN. S.M. Ji[1], H.J. Han[1], J.K. Lee[1], S.H. Park[1], W.S. Chung[1,2], C.H. Kim[1,2] *(1. Illimis Therapeutics., Inc. - Seoul (Korea, Republic of), 2. Department of Biological Sciences, Korea Advanced Institute of Science and Technology (KAIST) - Daejeon (Korea, Republic of))*

Background: Aβ immunotherapy has been acknowledged as a promising approach in treating Alzheimer's disease (AD). Recent Aβ-antibodies have shown substantial reduction of Aβ burden in the brain, proving Aβ as a prominent biomarker in Alzheimer's disease. Limitations such as adverse reactions including but not limited to antibody-induced inflammation, subsequent amyloid-related imaging abnormalities (ARIA), and cerebral microbleeding has been observed [1]; especially with ApoE carrier populations remain to be resolved [2]. Here we developed a novel chimeric protein platform, GAS6-mediated anti-inflammatory adaptor (GAIA). GAIA platform utilizes Tyro3, Axl, and Mer-TK (TAM) receptors that are expressed on glial cells and mediate phagocytosis without inflammatory response. **Methods:** We have developed a GAIA-based novel chimeric protein (αAβ-GAS6) with two distinct functional domains; a single-chain variable fragment of Aducanumab that selectively binds to Aβ, fused with GAS6, a TAM receptor-binding domain. Aβ clearance and phagocytosis-associated inflammatory responses to the αAβ-GAS6 were studied in comparison with Aducanumab. **Results:** The αAβ-GAS6 displayed selective uptake of oligomeric Aβ (oAβ) through phagocytosis in vitro. While the Aducanumab induced phagocytosis only in primary microglia, the αAβ-GAS6 significantly induced phagocytosis in both cultured microglia and astrocyte. Treatment with the αAβ-GAS6 secreted significantly lower amount of pro-inflammatory cytokines in comparison to the Aducanumab, such as TNF, IL-6, and IL-1β. Further analysis with scRNA sequencing of brain samples from αAβ-GAS6 treatment group in comparison to the Aducanumab group demonstrated reduction in pro-inflammatory signatures in microglia, while significant reduction of ApoE was observed in astrocytes. In line with anti-inflammatory effects of the αAβ-GAS6, ARIA, a major severe side effect of Aβ immunotherapy linked to CAA (cerebral amyloid angiopathy)-related inflammation, was thoroughly investigated using a CAA-like animal model. As expected, treatment with the αAβ-GAS6 had significant reduction of CAA-like microhemorrhage that was aggravated by the Aducanumab [3]. **Conclusion:** Our novel chimeric fusion protein αAβ-GAS6 have shown efficient Aβ clearance with significantly reduced neuroinflammatory response, and cerebral microbleeding compared to conventional antibody therapeutic, Aducanumab. Clinical application of this novel immunotherapeutic agent will overcome the antibody-induced inflammation, vascular damage, and subsequent ARIA with favorable safety and efficacy. Beyond AD, we intend to explore its therapeutic potential in APoE carrier as well as in AD patients with CAA. **Key word:** CAA, ApoE, Alzheimer's disease, fusion protein, Gas6, TAM, efferocytosis. **Disclosures:** Dr. Won-Suk Chung and Dr. Chan Hyeok Kim are the scientific co-founders of Illimis Therapeutics. All other authors are employees of Illimis Therapeutics. **References:** 1. Cummings., Drugs, 2023, PMID: 37060386. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10195708/; 2. Van Dyck., Biological Psychiatry, 2018. https://doi.org/10.1016/j.biopsych.2017.08.010; 3. Chung et al., Nature Medicine, 2022, PMID: 35927581. https://www.nature.com/articles/s41591-022-01926-9

LP104- MICROGLIA-SPECIFIC APOE-TARGETED EPIGENOME THERAPY FOR ALZHEIMER'S DISEASE. O. Chiba-Falek[1], E. Korsakova[2], K. Boris[1] *(1. Duke University - Durham (United States), 2. CLAIRIgene - Durham (United States))*

Background: The key role of microglia in the etiology of Alzheimer's disease (AD) has been well established. Apolipoprotein E gene (APOE), the strongest and most reproducible genetic risk factor for late-onset AD (LOAD), is abundantly expressed in microglia and accumulating evidence suggested the pathogenic effect of the e4 risk-allele in the microglia. Furthermore, using single-nucleus transcriptomic analysis we and others showed a significant increase in APOE expression levels in microglia from LOAD brain tissues

compared to age- and sex- matched healthy controls. Our data also demonstrated that APOE overexpression was correlated with more open chromatin sites in diseased microglia. Our overarching goal is to shift the paradigm of LOAD drug discovery towards the development of cell type- and gene-specific therapeutics targets. In this study we developed an epigenome therapy platform to reduce APOEe4 expression precisely in the microglia by targeted modification of the epigenome landscape across APOE regulatory region. **Methods:** Our epigenome therapy platform is based on all-in-one AAV vector comprises of CRISPR/deactivated(d)Cas9, fused with a synthetic repressor molecule and driven by an engineered microglia-specific promoter. We validated the efficacy and specificity of our epigenome therapy platform in vitro using human induced pluripotent stem cell (hiPSC)-derived microglia like cells from LOAD patient homozygote for the APOEe4 allele. **Results:** In a prior study, stereotactic injection of the AAV/dCas-repressor vector into the hippocampus of a humanized mouse model, created by targeted replacement of the mouse with the human APOE-TOMM40 genomic region, showed a robust and significant reduction in the expression of the human APOE amounting to 75%. In the current study we further developed and optimized the platform to achieve microglia specific and beneficial effect. First, we screened several AAV serotypes and found that AAV2.6 resulted in the most efficient transduction into microglia cell-type detected by GFP expression. Next, we engineered regulatory sequences based on promoters of human microglia genes for specific and efficient expression of the therapeutic platform in microglia cells. Transduction of the lead therapeutic AAV vector driven by an engineered human microglia regulatory sequence demonstrated a significant microglia-specific reduction in APOE-mRNA levels, amounting to ~30% lower levels compared to the control vector. The repression of APOEe4 expression in the hiPSC-derived microglia resulted in a significant increase in Ab clearance such that the increased Ab uptake was similar to that of APOEe3 microglia. In addition, evaluation of inflammatory response and activated microglia markers validated that the reduction in APOEe4 expression rescued inflammation, characteristic of APOEe4 microglia cells. **Conclusions:** Collectively, our results provided in vitro proof-of-concept for the utility, efficacy, and specificity of the APOE-targeted microglia-specific epigenome therapy. Our technology is translational toward the development of a novel therapeutic strategy to prevent, delay onset and/or halt the progression of LOAD and promotes precision medicine in LOAD.

LP105- ABVAC40 INDUCES ANTI-ABX-40 PLASMA SPECIFIC ANTIBODIES THAT BIND WITH AB VASCULAR DEPOSITS IN BRAIN SLICES FROM HUMANS WITH CEREBAL AMYLOID ANGIOPATHY.

M. Montañes[1], J. Canudas[1], I. Martinez[1], A.M. Lacosta[1], M. Pascual-Lucas[1], J. Terencio[1,2] *(1. Araclon Biotech-Grifols - Zaragoza (Spain), 2. Grifols - Barcelona (Spain))*

Background: ABvac40 was designed as the first active immunotherapy against the C-terminal end of amyloid-beta 40 (Aβ40). With established excellent safety profile and robust immune response in AB1601 phase 2 clinical trial [1], characterizing the binding profile of ABvac40-elicited antibodies is pivotal for mechanistic insights and specificity. To this end, in this study we have comprehensively investigated the ability of the antibodies raised by ABvac40 in the AB1601 study to target different species and aggregation forms of Aβ. In addition, we have tested its reactivity against vascular amyloid deposition in human brains with cerebral amyloid angiopathy (CAA), which is highly prevalent among Alzheimer's disease patients [2]. **Methods:** Dot blot assays were conducted using synthetic Aβ peptides of different lengths, truncated at both the N-terminal and C-terminal ends. Nitrocellulose membranes were probed with pre-immune and post-immune (after five ABvac40 or placebo inoculations) plasma samples from patients in the placebo and ABvac40 arms (study details were previously presented [1]). Western blot assays were performed using in vitro-generated oligomers, composed of either Aβ40, Aβ42, or a combination of both [3]. The membranes were incubated with plasma samples from ABvac40-treated patients (pre-immune and after seven doses of ABvac40). Immunohistochemistry analysis were carried out on post-mortem human brain paraffin-embedded sections from three patients diagnosed with CAA and three healthy controls (provided by CIEN Foundation Tissue Bank, Madrid). These histological sections were incubated with post-immune plasma samples (after seven doses of ABvac40), using pre-immune plasma of the same patients as negative control. **Results:** Plasma samples of ABvac40-treated patients presented specific dot-blot immunobinding against Aβx-40 peptides, whereas they did not bind to amyloid peptides terminating at amino acids 38, 42 or 43. Neither the pre-immune plasma of these patients nor that from patients who received placebo, recognized any peptides investigated in the study. Western blot analysis demonstrated that plasma samples from ABvac40-treated patients recognized monomers, dimers, trimers and higher oligomers composed of Aβ40. These antibodies did not recognize Aβ42 in either monomeric or aggregated states. Staining of brain tissue sections from CAA patients revealed strong immunoreactivity against Aβ vascular deposits. Additionally, some senile plaques were also recognized. These signals were absent when using plasma samples taken prior immunization. The staining specificity was confirmed through pre-adsorption of post-immune plasma with the specific antigen. **Conclusions:** This study demonstrates the specificity of plasma antibodies triggered by ABvac40, which recognize the C-terminal region of Aβx-40 peptides in different aggregated states (monomeric, oligomeric, and brain deposits). Binding of ABvac40-elicited antibodies to vascular and parenchymal amyloid brain deposits could have an important role in the mechanism of action of ABvac40. We hypothesize that the interaction of anti-Aβ40 antibodies with vascular amyloid could lead to a reduction of amyloid deposition in cerebral vessels. This could enhance the clearance of brain waste through perivascular spaces, potentially contributing to cognitive improvement, while maintaining an excellent safety profile as demonstrated. However, additional studies are needed to better understand the mechanism of action of ABvac40. **Key words:** ABvac40, vaccine, Aβ40, immunotherapy, epitope characterization, CAA. Clinical Trial Registry: NCT03461276, https://clinicaltrials.gov/. **Disclosures:** MM, JC, IM, AML and MPL are full-time employees of Araclon Biotech-Grifols. JT is a full-time employee of Grifols. **References:** 1. Molina, E. et al Alzheimer's & Dementia 2022, 18, S10. https://doi.org/10.1002/alz.065633; 2. Jäkel, L. et al 2022. Alzheimer's & Dementia 18(1), 10-28. https://doi.org/10.1002/alz.12366; 3. Barghorn, S. et al. 2005. Journal of neurochemistry, 95(3), 834-847. https://doi.org/10.1111/j.1471-4159.2005.03407.x

LP106- CENTILOID SCALE EXPRESSION USING NEUROPHET SCALE PET WITH DIVERSE TRACER COMPARISON. C. Yeong Sim[1], L. Min-Woo[1], K. Hajin[1], L. Jiyeon[1], M. Youngjoon[1], L. Minho[1], K. Donghyeonv, K. Regina Ey[1] *(1. Research Institute, Neurophet Inc. - Seoul (Korea, Republic of))*

Background: Centiloid scale is a standardized method for quantifying b-amyloid PET tracers from participants' dataset of amyloid-positive diagnosed with Alzheimer's disease and amyloid-negative with normal cognition under 45 years. There is, however, limited software available to calculate the Centiloid scale. The aim of this study is to validate and provide Centiloid scale corresponding to Neurophet SCALE PET (Neurophet Inc., Seoul, Republic of Korea) pipeline. **Methods:** We used 286 participants who underwent amyloid PET (11C-PiB, 18F-Florbetaben, 18F-Flutemetamol, 18F-Florbetapir, and 18F-NAV4694) and 3D T1 weighted MR images in GAAIN dataset (https://www.gaain.org/centiloid-project). We processed the SUVR calculation using SCALE PET in global cortical regions (including frontal, lateral parietal, lateral temporal, cingulate cortices, and striatal regions) and cerebellum as reference region in the original T1 space and converted it to Centiloid scale with PiB SUVR translation. The calculated Centiloid scale was compared to the original method using SPM12 proposed in MATLAB R2018a (The MathWorks Inc., Massachusetts, United States). **Results:** Our results showed a great correlation (slope = 1.00, intercept = 0.02 R2 = 0.99) to the original method using SPM12. Individual tracers showed the dynamic range of slope in SUVR from SCALE PET comparing with PiB SUVR, 18F-NAV4694 showed a slope closer to 1.0 (0.997) and 18F-Florbetapir showed a farther value (0.51) from 1.0. After converting SUVR to Centiloid scale, most of tracers showed high R2 (0.89~0.99), slope (1.00~1.07), and intercept (0.14~2.52) compared to the original Centiloid scales. Only 18F-Florbetapir showed the larger intercept (2.52), however, other tracers showed smaller than 2.0 (18F-Florbetaben: 0.46, 11C-PiB: 0.82, 18F-Flutemetamol: 1.07, 18F-NAV4694: 1.90) and were appropriate as Centiloid scale. **Conclusion:** Centiloid scale using SCALE PET measured in the original T1 space showed a high correlation with the standard method for both cortical and subcortical regions and was applicable in the study. **Key words:** Alzheimer's disease, Amyloid PET, Centiloid, SUVR, Standardization. **Disclosures:** The authors declared no competing interests. **References:** 1. Klunk WE, et al., Alzheimer's and Dementia, 2015, 11(1), 1-15.e154. doi:10.1016/j.jalz.2014.07.003; 2. Rowe CC, et al., J Nucl Med. 2016, 57(8):1233-7. doi: 10.2967/jnumed.115.171595; 3. Rowe CC, et al., Eur J Nucl Med Mol Imaging. 2017;44(12):2053-2059. doi:10.1007/s00259-017-3749-6; 4. Battle, M. R., et al., EJNMMI research, 2018, 8(1), 107. doi.org/10.1186/s13550-018-0456-7 [5] Navitsky M, et al., Alzheimer's Dement. 2018, 14(12):1565-1571. doi: 10.1016/j.jalz.2018.06.1353 [6] Lee J, et al., Diagnostics (Basel), 2022, 12(3):623. doi:10.3390/diagnostics12030623

LP107- SIMUFILAM'S PRIMARY MECHANISM OF ACTION CONFIRMED BY TIME-RESOLVED FRET. E. Cecon[1], J. Dam[1], L.H. Burns[2], R. Jockers[1] *(1. Université Paris Cité, Institut Cochin, INSERM, CNRS - Paris (France), 2. Cassava Sciences, Inc. - Austin, Tx (United States))*

Background: Simufilam is a novel drug candidate in Phase 3 clinical trials for Alzheimer's Disease (AD) dementia. This oral small molecule targets an altered form of filamin A (FLNA) found in AD. The drug disrupts FLNA's aberrant linkage to the α7 nicotinic acetylcholine receptor (α7nAChR), thereby blocking soluble amyloid beta1-42 (Aβ42)'s signaling via α7nAChR that hyperphosphorylates tau [1]. Simufilam has reduced levels of Aβ42–α7nAChR complexes in brains of transgenic AD mice and lymphocytes of AD patients (oral treatment) and in postmortem human AD brain (ex vivo incubation) [2, 3]. We also previously showed that simufilam reduced binding affinity of Aβ42 for α7nAChR by 1000- to 10,000-fold using direct binding of labelled simufilam [2]. The current work measured simufilam's effect on the Aβ42–α7nAChR interaction using time-resolved fluorescence resonance energy transfer (TR-FRET) [4], a robust technology to detect highly sensitive molecular interactions. **Methods:** To monitor Aβ42 binding to α7nAChR by a TR-FRET assay, HEK293T cells were transfected to express SNAP-α7nAChR prior to SNAP-α7nAChR labelling with the fluorophore Terbium cryptate. Cells were incubated with varying concentrations of simufilam or unlabelled Aβ42 together with 10 nM Aβ42-FAM (5-carboxyfluorescein-labelled Aβ42) and read in a Tecan F500 plate reader after precise excitation and detection of the FRET signal. Data are expressed as the acceptor/donor ratio normalized as % of maximal Aβ42-FAM binding. The mean pIC50 was calculated from 4 separate experiments. **Results:** Simufilam reduced Aβ42 binding to α7nAChR with a pIC50 of 10.9 compared to 11.9 for unlabeled Aβ42 (direct competition) and similar to previously published pIC50s of several agonists, partial agonists or competitive antagonists of α7nAChR (range: 8.4 to 12.7 pIC50). The full inhibition by simufilam was also very close to that of unlabeled Aβ42. **Conclusions:** A robust technology designed to detect highly sensitive molecular interactions confirmed simufilam's primary mechanism of action. Simufilam's high potency in reducing Aβ42–α7nAChR binding, measured by time-resolved FRET, appears unprecedented for a mechanism of binding a receptor-associated protein. The picomolar IC50 in reducing this interaction corroborates previous data showing a reduced binding affinity of Aβ42 for α7nAChR as well as the picomolar IC50s for simufilam's inhibition of the Aβ42–α7nAChR interaction, tau hyperphosphorylation, and FLNA linkages to α7nAChR and TLR4 shown by other techniques. **Key words:** nicotinic receptor, TR-FRET, binding, amyloid beta. **Disclosures:** EC is an employee of the CNRS and JD and RJ are employees of Inserm; they report no conflicts of interest. LHB is an employee of Cassava Sciences. **References:** 1. Burns, L.H., Pei, Z. and Wang, H-Y. (2023). Targeting α7 nicotinic acetylcholine receptors and their protein interactions in Alzheimer's disease drug development. Drug Dev Res DOI: 10.1002/ddr.22085. 2. Wang, H-Y., Lee, K-C., Pei, Z., Khan, A., Bakshi, K., Burns, L.H. (2017). PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis. Neurobiol Aging, 55: 99-114. 3. Wang H-Y., Pei, Z., Lee, K-C., Lopez-Brignoni, E., Nikolov, B., Crowley, C., Marsman, M., Barbier, R., Friedmann, N., Burns, L.H. (2020). PTI-125 reduces biomarkers of Alzheimer's disease in patients. J Prevent Alzheimer's Disease, 7: 256-264. 4. Wang, H-Y., Cecon, E., Dam, J. Pei, Z., Jockers, R. and Burns, L.H. (2023) Simufilam reverses aberrant receptor interactions of filamin A in Alzheimer's disease. Int J Mol Sci in press.

LP108- PREDICTION OF GLOBAL STANDARDIZED UPTAKE VALUE RATIO AND AMYLOID STATUS WITH BOTH T1-WEIGHTED AND T2-FLAIR IMAGE USING DEEP LEARNING. M.W. Lee[1], H.S. Yang[1], H.W. Kim[1], Y.S. Choe[1], J.M. Kang[1], S.H. Jeon[1], Y.J. Moon[1], D.H. Kim[1], M.H. Lee[1], D.W. Kang[2], S.Y. Jeon[3], S.J. Son[4], Y.M. Lee[5], R. Kim[1], H.K. Lim[6] *(1. Research Institute, Neurophet Inc. - Seoul (Korea, Republic of), 2. Department of Psychiatry, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of), 3. Department of Psychiatry, Chungnam National University Hospital - Daejeon (Korea, Republic of), 4. Department of Psychiatry, Ajou University School of Medicine - Suwon (Korea, Republic of), 5. Department of Psychiatry, Medical Research Institute, Pusan National University Hospital - Busan (Korea, Republic of), 6. Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of))*

In Alzheimer's disease, quantifying cerebral amyloid accumulation using a global standardized uptake value ratio (SUVR) is essential for amyloid positivity readings. We developed a deep learning model that predicts global SUVR to classify amyloid positivity using only Magnetic Resonance Imaging (MRI) images. 1,974 T1-weighted (T1w) images, T2-Fluid Attenuated Inversion Recovery (T2-FLAIR) images, and amyloid Positron Emission Tomography (PET) images pair sets were acquired from Alzheimer's Disease Neuroimaging Initiative (ADNI) and six domestic hospitals. For both T2-FLAIR and PET images, co-registration was performed on the T1w images. The reference region of global SUVR was set to the whole cerebellum. All images were resized to 128x128x128. The training, validation, and test sets were randomly distributed according to the subjects in a ratio of 8:1:1. To predict SUVR well, it is necessary to consider both images and personal characteristics. As a key objective in this study, we constructed a deep learning model structure that effectively observes input images in detail without overfitting personal characteristics. We propose DenseSET, a combination of DenseNet, which connects each feature layer to every other feature layer in a feed-forward fashion, and Squeeze-Excitation (SE), which has good recalibration ability. The SE block input range has been expanded to include images and personal characteristics. This block combines the input image and personal characteristics to determine features from a Convolutional Neural Network (CNN) and channel attention to the selected features. The proposed DenseSET structure is a customized DenseNet that combines a SE block after each pooling layer. Accuracy, sensitivity, and specificity were calculated to determine how effective the SUVR obtained from the proposed model was for classifying Amyloid positivity. As a result of performing amyloid status prediction on the SUVR predicted by the proposed model according to the cut off set for each tracer (AV45; 1.11, FBB; 1.20, FMM; 1.03), in the train and test set performance, accuracy of 0.87 and 0.80, sensitivity of 0.84 and 0.72, and specificity of 0.88 and 0.84, respectively. Our deep learning model can predict global SUVR to classify amyloid positivity. Proposed model may support the clinical decisions and enhance the accuracy of classifying amyloid positivity of radiologists.

DIGITAL HEALTH/E-TRIALS

P179- DEVELOPMENT OF A MILD COGNITIVE IMPAIRMENT RISK PREDICTION MODEL USING ELECTRONIC HEALTH RECORD DATA. G. Li[1], V. Devanarayan[1], R. Halpern[2], R. Batrla[1], S. De Santi[1], F. Frech[1], J. Vandercappellen[1], A.S. Khachaturian[3], R. Crislip[4], S. Mattke[5], H. Hampel[1] *(1. Eisai - Nutley (United States), 2. Optum - Eden Prairie (United States), 3. Prevent Alzheimer's Disease 2020, Inc. - Rockville (United States), 4. OptumCare - Phoenix (United States), 5. University of Southern California - Los Angeles (United States))*

Introduction: As the currently available disease-modifying treatments (DMTs) are indicated for patients with Alzheimer's disease (AD) at mild cognitive impairment (MCI) or mild dementia stage, the importance of early identification of MCI has increased dramatically. Primary care providers (PCPs) are in the best position to detect early signs of MCI, especially given that cognitive function assessment has been incorporated into Medicare annual wellness visit requirements. As documented in the literature, MCI detection rate by PCPs in the normal course of clinical practice is only 6-15%. The low detection rate has been attributed to lack of familiarity with early MCI symptoms and inadequate time and resources. We are building on previous claims data analyses by utilizing electronic health record (EHR) data, which include clinical information, to identify additional risk factors and build a predictive model for MCI risk. **Methods:** We are conducting a retrospective analysis using the Optum EHR database. Individuals ≥40 years old are identified from January 2016 – March 2021 and assigned to MCI or non-MCI cohorts. The MCI cohort has ≥1 diagnosis record with an International Classification of Diseases, Tenth Revision, Clinical Modification diagnosis code G31.84; the first record sets the index date. The non-MCI cohort index date will be set on a randomly selected diagnosis record. All individuals will be observed for 2 years pre-index. The MCI cohort will have no diagnosis or abstracted note records for MCI or AD or related dementias (ADRD) pre-index and the non-MCI cohort will have no evidence of MCI or ADRD in the entire study period. Potential predictors of MCI have been identified from literature and clinical input; they include (1) individual characteristics, eg, smoking and body mass index (2) diagnoses, eg, hypertension, heart disease, diabetes; and (3) abstracted note records derived via natural language processing related to relevant clinical conditions such as memory impairment. MCI risk factors will be identified via logistic regression. Prediction models based on risk factors for discriminating between MCI and non-MCI individuals will be constructed via various machine-learning algorithms. Model performance will be evaluated via 10-fold cross-validation using data from two-thirds of the subjects and then verified in the remaining one-third. Results from one of the best performing algorithms will be reported, with preference given to simpler models with clear interpretation. **Results:** Current results include a preliminary MCI cohort of 20,865 individuals. Preliminary MCI individuals were 71.1 years old on average, 59.1% female, 83.7% Caucasian, 10.7% African American, and 3.6% Hispanic. After the final MCI and non-MCI cohorts are identified, the two cohorts will be compared to identify the significant MCI predictors and modeled for MCI risk prediction as described above. **Conclusion:** We aim to use the prediction model from this study to improve the ability to discriminate between MCI and non-MCI individuals and, ultimately, to develop a triage tool for PCPs to identify individuals at elevated MCI risk for further workup, using the data available to them. **Key words:** mild cognitive impairment

(MCI), electronic health record data, MCI risk prediction, Alzheimer's disease. **Disclosures:** Eisai is sponsoring this study, and Gang Li, Viswanath Devanarayan, Richard Batrla, Susan De Santi, Feride Frech, Jo Vandercappellen, and Harald Hampel are employees of Eisai. Rachel Halpern and Richard Crislip are employees of Optum; Optum was contracted by Eisai to conduct this analysis. Soren Mattke is a paid consultant to Eisai. Ara S. Khachaturian is an employee of PAD 2020 and PAD 2020 is contracting with Eisai to participate in this study. **References:** Borson S, et al. Int J Geriatr Psychiatry 2006 Apr;21(4):349-55. doi: 10.1002/gps.1470. Kaduszkiewicz H, et al. J Nutr Health Aging 2010 Oct;14(8):697-702. doi: 10.1007/s12603-010-0038-5. Sawa GM, Arthur A. Age and Ageing 2015;44:642047. doi: 10.1093/ageing/afv020. Sabbagh MN et al. Early Detection of Mild Cognitive Impairment (MCI) in Primary Care. J Prev Alzheimers Dis. 2020;7(3):165-170. doi: 10.14283/jpad.2020.21. Boada M et al. Alzheimers Dement 2022 Jun;18(6):1119-1127. doi: 10.1002/alz.12441. Bernstein Sideman A, et al. J Alzheimers Dis 2022;86(2):655-665. doi: 10.3233/JAD-215106. O'Brien K, et al. J Gen Intern Med 2022 Sep 26. doi: 10.1007/s11606-022-07824-7. Pandhita SG, et al. Neuroepidemiology 2020;54(3):243-250. doi: 10.1159/000503830.

P180- VALIDATING A NOVEL DIGITAL COGNITIVE PLATFORM: SENSITIVITY TO CHANGE FOLLOWING AN ALCOHOL CHALLENGE. J. Dyer[1], F. Barbey[2], M.D. Islam[2], J. Jaeger[3,4], B. Murphy[2], N. Kennedy[5] *(1. Cumulus Neuroscience - Belfast (United Kingdom), 2. Cumulus Neuroscience - Dublin (Ireland), 3. CognitionMetrics - Stamford, CT (United States), 4. Albert Einstein College of Medicine - Bronx, NY (United States), 5. University of Ulster - Coleraine (United Kingdom))*

Background: Detecting cognitive change over time (especially differences between placebo and treated groups) is a critical outcome measure for the success/failure of a compound and better testing tools are needed. Tools like ADAS-Cog and CDR-SB – while commonly used – are insensitive in very early disease, prone to measurement noise, can have practice effects, and require clinical staff to administer during in-person site visits. These factors necessitate longer and larger clinical trials, with cognition measured at 6+ month intervals. Digital technology could address these problems via automated testing, at higher frequencies (e.g. 'burst' designs), at home, curtailing measurement noise and thereby reducing the size and length of clinical trials. Numerous such measures have been proposed, but few have been validated with respect to sensitivity to change. Here we report on the validation of a small suite of tablet-based tasks which were developed for frequent real-world use by patients. An alcohol challenge was used as an accelerated model of cognitive decline in neurodegeneration. We administer very-high-frequency testing via the Cumulus Neuroscience platform, using cognitive tests which target functions typically impaired in early Alzheimer's Disease (paired episodic memory; working memory; reaction time; symbol-coding). **Methods:** After massed practice (3 administrations), 30 healthy younger adults (20F, 10M; 18-44yrs, mean 23yrs) were each dosed with alcohol (target BAC 0.08-0.1%) and placebo (mixer only) across two sessions in counterbalanced order, 1-2 weeks apart (single blind). Cognitive performance was assessed using the battery at set intervals (8 administrations per lab day), tracking intoxication over time. Tests were self-administered on an Android tablet, with BAC% measured throughout using a breathalyser. Test order was counterbalanced within and across participants. **Results:** Alcohol impaired performance on all cognitive tests, with performance reverting to baseline by the end of the session. Linear mixed models (LMM) revealed that from 45m after dose, performance was significantly impaired on symbol coding ($t = -3.982$; $p < 0.001$); episodic memory ($t = -3.426$; $p = 0.005$); reaction time ($t = 4.060$; $p = 0.001$); and working memory ($t = -2.947$; $p = 0.026$). Wilcoxon tests across massed practice sessions revealed a small practice effect on the symbol-coding task between practice 1 and 2 ($Z = 52$; $p = 0.045$), and LMM detected improvement across the two in-lab testing days (equivalent of +2.8 correct responses; $p < 0.001$). No other practice effects were observed. All p values are Holm-Bonferroni corrected. **Conclusion:** The tablet battery can sensitively measure change in dementia-relevant cognitive functions over the timescale of acute alcohol intoxication and return to sobriety. These digital tests are repeatable at high frequency with minimal practice effects, which could increase statistical power in clinical trials via reduction of within-subject variance. In a decentralized clinical trial, digital 'burst' testing has potential to detect cognitive signals of drug effect earlier, and perhaps with smaller N, than traditional approaches. Repeatable tests like those in the current battery might be appropriate for use in the early disease, where sensitive tools are lacking. Further validation research with a large sample of AD patients is underway. **Key words:** Cognitive testing; mobile device; sensitivity to change; alcohol challenge; cognitive impairment; at-home testing; real-world data; decentralised trials; episodic memory; working memory; executive function; psychomotor speed. **Disclosures:** Authors JD, FB, NI and BM are employees of Cumulus Neuroscience and hold share options in the company. Author JJ is a paid consultant for Cumulus Neuroscience.

P181- THE EFFECTS OF HOME-BASED, SEMI-COMPUTERIZED COGNITIVE TRAINING ON COGNITIVE FUNCTION IN COMMUNITY DWELLING OLDER ADULTS. G.H. Kim[1], B.R. Kim[2], H.E. Kim[3], J.H. Jeong[4] *(1. Department of Neurology, Ewha Womans University, College of Medicine - Seoul (Korea, Republic of), 2. Ewha Medical Research, InstituteEwha Womans University - Seoul (Korea, Republic of), 3. Department of Artificial Intelligence Convergence, Ewha Womans University - Seoul (Korea, Republic of), 4. Ewha Womans University - Seoul (Korea, Republic of))*

Background: Cognitive intervention (CI) has been known to improve cognition and to delay cognitive decline in older adults. Although computerized cognitive interventions have been tried for older adults, sometimes it is noted that some older adults have difficulty adapting to computer-related new devices, which may further lead to lower compliance and adherence. The purpose of this study was whether semi-computerized cognitive training (CCT) for 12 weeks improved cognitive performance in older adults without dementia. **Methods:** Semi-CCT consists of a smart pad connected to a book. Various tasks or problems are presented on the smart pad, and patients can interact by touching the corresponding answers on the book. The smart pad records and displays the correctness of the response, indicating whether the answer is correct or not. A single-blind randomized controlled trial was conducted in 70 older adults without dementia. All participants underwent the Mini-Mental State Examination (MMSE), and only those who scored above -1 SD compared to the norm were recruited for this study. Participants were randomized into the two groups: the CI with semi-CCT (CCT) (n=35) group and waitlist control group without cognitive intervention (Control) (n=35). The A total of 12 cognitive training programs provided to the participants targeting for attention, memory, visuospatial,

calculation, language and frontal executive functions. The semi-CCT comprised 30-min-session per day for 12 weeks at home. The primary 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. Two participants from each group were dropped out. After 12 week intervention, semi-CCT group demonstrated improvement in memory and attention domain compared to the control group. **Conclusions:** Our results suggest that the 12 week home- based, semi-CCT could help improve cognitive function in older adults. **Key words:** semi-computerized cognitive intervention. [This work was supported by Institute of Information & communications Technology Planning & Evaluation (IITP) grant funded by the Korea government(MSIT) (No. RS-2022-00155966, Artificial Intelligence Convergence Innovation Human Resources Development (Ewha Womans University)]

P182- COMPARING THE EFFECTS OF COMBINED COGNITIVE AND FUNCTIONAL SKILLS TRAINING TO SKILLS TRAINING ALONE: BURST TRAINING INCREASES TRAINING GAINS WITHOUT INCREASING DROP-OUTS. P. Harvey[1], P. Kallestrup[2], 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. CCT commonly fails to generalize to real-world functioning across conditions, so skills training interventions 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, administered concurrently in the same training sessions led to synergistic gains in cognition and functional skills compared to skills training alone (Harvey et al., 2022). However, in those studies, despite considerable improvements in both cognition and functional skills performance, drop-out rates were highest in the combined condition. **Objectives:** 1: to examine the comparative efficacy of remotely delivered cognitive and functional skills training for improvements in performance on computerized measures of functional skills in rigorously diagnosed participants with MCI across two different training conditions. 2: to examine rates of treatment discontinuation across combined cognitive and skills training interventions and skills training alone. **Methods:** 90 participants with MCI (Jak-Bondi criteria) and 72 NC constitute the sample. 44 of the participants with MCI were randomized to FUNSAT alone while 46 received combined training. 25% of participants in both groups were fully assessed and trained in Spanish. All NC received FUNSAT alone. Participants graduated from the each of the 6 training tasks (Ticket Purchase, ATM Banking, Medication Management, Medication Refill, Internet Banking, Internet Shopping) when they performed all of the subtasks with one or fewer errors. Training in FUNSAT alone includes two 1-hour training sessions per week for 12 weeks. Combined treatment includes a training burst of 3 weeks with twice-weekly BrainHQ followed by 9 weeks of FUNSAT training. Outcomes were measured with several indices of training gains, including total training gains (completion time and errors), training grains on the first training session, and average training gains across all training session. Participants were provided with a Chromebook device, along with accounts and passwords for accessing training software. **Results:** Effect sizes for improvement in time to completion from baseline to end of training across the 6 tasks in MCI participants ranged 1.03 to 1.56, with changes in errors essentially identical, ranging from 1.04 to 1.62. As an example, average time to completion of the medication management task was 1339 seconds at baseline; endpoint performance averaged 643 seconds There are no overall differences in training gains associated with combined vs. FUNSAT only training, although combined participants received 33% less skills training. Changes in performance at the first training session were significantly greater for 4 of the 6 tasks in participants who received cognitive training before skills training, all; $p<.01$. Drop-out rates were low and similar (5% and 7%) across the conditions. **Conclusions:** A fully remotely deliverable functional skills and CCT training program is feasible and shows evidence of substantial efficacy. 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 9 weeks of FUNSAT training following a 3-week burst of CCT. **Grant Support:** R44 AG057238-03. **Clinical Trials Registration:** NCT04679441

P183- A REAL-WORLD, LONGITUDINAL OBSERVATIONAL STUDY IN PATIENTS WITH ALZHEIMER'S DISEASE DEMENTIA AND HEALTHY CONTROLS, USING FREQUENT REPEATED DIGITAL MEASUREMENTS PERFORMED AT-HOME ON THE CUMULUS PLATFORM: A PRELIMINARY REPORT. A. Buick[1], A. Alexander-Sefre[1], S. Diggin[1], J. Dyer[1], B. Murphy[2], H. Nolan[2], L. Rueda-Delgado[2], J. Rowe[3], K. Muhammed[4] *(1. Cumulus Neuroscience Ltd - Belfast (United Kingdom), 2. Cumulus Neuroscience Ltd - Dublin (United Kingdom), 3. Department of Clinical Neurosciences, University of Cambridge - Cambridge (United Kingdom), 4. Nuffield Department of Clinical Neurosciences, University of Oxford - Oxford (United Kingdom))*

Background: Conventional tools that measure cognitive decline give an infrequent 'snapshot' in an atypical environment and are costly to administer. Home-based digital technology gives the opportunity for repeated sampling in a natural environment, combined with AI/data analytics techniques that extract more discriminatory power from multiplex data. The Cumulus Neuroscience Platform is designed specifically to realise this potential with longitudinal measurement of electrophysiology, cognition, and behaviourally-relevant symptoms within a single unified platform, that participants can use at home. Here we describe a real-world study of the feasibility of Cumulus to measure neurocognitive function at-home in people with Alzheimer's disease (with mild/early dementia) and healthy adult controls. The objectives were to assess the scientific and technical capability of the Cumulus Platform through comparison with standard tools for measuring AD dementia. **Methods:** 119 participants (59 AD and 60 matched controls) were enrolled in a 52-week study involving at-home digital assessments; repeated 30-minute sessions wearing a 16-channel dry EEG headset synchronized with cognitive and behavioural tasks on a mobile tablet, followed by a sleep EEG headset at night. Using a tapered sampling

design, participants completed a familiarisation period before a 2-week burst of sampling on an almost-daily basis; then, sampling every 2 weeks until week 26, and monthly thereafter. Conventional neurocognitive paper-and-pen assessments (including ADAS Cog, and subtests from WMS-IV and WAIS-IV) were conducted at baseline, 26 and 52 weeks. Preliminary analyses are presented here, focusing on cross-sectional analysis of endpoints during the initial burst period, and usability/feasibility for participation to-date. **Results:** Patient participants at baseline were aged 73.7 (s.d. 6.7) years with an ADAS-Cog score of 25.1 (s.d. 7.9), whilst controls were aged 71.1 (s.d. 7.1) years with an ADAS-Cog score of 9.0 (s.d. 5.0). Withdrawal rates are currently 20.3% and 6.7% for patients and controls respectively. Based on 103 participants currently enrolled (or finished participation), session adherence was 81.1% for patients and 85.7% for controls. To date, all participants have passed the initial burst period, 61 have completed 6 months, and 8 have completed the full year of participation. A gamified executive function task (DSST) differentiated strongly between groups (t(98)=10.32, p=4.8e-16), and correlated highly with the corresponding paper-based benchmark (rho=0.76, p=4.5e-20). The gamified associative memory task performance differed strongly (t(98)=8.11, p=2.4e-11) and correlated with a verbal memory pen-and-paper benchmark (rho=0.75, p=6.2e-19). EEG features elicited by a gamified 2-stimulus oddball task showed characteristic sensory and higher cognitive processing, with reduced and delayed P300 in the patient group. We confirmed the reduction of alpha-power in resting-state EEG in patients. **Conclusions:** Based on provisional data from a sub-set of participants in the ongoing study, digital assessments through the Cumulus Platform can be frequently used by people with mild symptomatic AD at-home. Preliminary analysis indicates these types of digital technology have construct validity, distinguishing groups, correlating with conventional benchmarks, and confirming EEG predictions. We propose the Cumulus Platform as feasible to provide objective, frequent and patient-centred tracking of functional neurophysiology, facilitating future use of these digital biomarkers in tracking decline or treatment response. **Key words:** EEG, digital biomarker, cognition, decentralized Trials. **Disclosures:** AB, AAS, SD, JD, BM, HN and LR are employees of Cumulus Neuroscience Ltd.

P184- ENHANCING AUTOMATED TRANSCRIPTION FOR SPEECH-BASED SCREENING IN ALZHEIMER'S DISEASE. U. Meepegama[1], C. Skirrow[1], M. Ropacki[2], E. Fristed[1], J. Weston[1] *(1. Novoic - London (United Kingdom), 2. Strategic Global Research & Development - Temecula (United States))*

Background: Changes in speech patterns are noted in the early stages of Alzheimer's disease (AD), and can be detected with end-to-end automation of linguistic and speech content analysis. Transcription is an early stage of the analysis pipeline, whose accuracy may impact on the sensitivity of speech biomarkers. However, automated speech recognition (ASR) systems often fail to transcribe clinically-relevant features like disfluencies and filled pauses. **Methods:** 200 participants (MCI, mild AD or cognitively unimpaired) were recruited into the AMYPRED-UK (NCT04828122) and AMYPRED-US (NCT04928976) studies, completing optional remote speech-based assessments for up to 8 days on their own smart devices. Analyses were carried out on two immediate and one delayed recall of two stories from the Automatic Story Recall Task, administered in a prespecified test session. Speech samples, including disfluencies and filled pauses, were manually transcribed using a standardised procedure. ASR was conducted using two approaches: an off-the-shelf transcription system (Google Speech-to-text); and a custom transcription model, a multilingual encoder-decoder Transformer, optimised to capture disfluencies and filled pauses. Word error rate (WER) evaluated the ASR accuracy against manual transcription, with and without removal of all disfluencies and filled pauses. WER was averaged across the three story recalls, and explored in relation to demographic variables and clinical diagnostic status. The impact of transcription method was evaluated on G-match, a measure of proportional recall, calculated as the cosine text similarity between the textual embeddings of the source text and transcribed retelling for the three stories, averaged for each participant. Prediction of MCI/Mild AD from G-match was carried out with a logistic regression model and 5-fold cross-validation. **Results:** 103 adults (46 Male, 57 Female; 47 MCI/mild AD, 56 cognitively unimpaired; mean age=69.5) completed the prespecified remote speech assessments. Qualitative review of transcripts showed that disfluencies and filled pauses were accurately captured using the custom method, but not by Google Speech-to-text. The custom method also generated around 30% fewer transcription errors, regardless of data cleaning method (WER=0.07- 0.1 for custom method versus WER=0.1- 0.14 for off-the-shelf system, p<0.001). WER consistently differed between MCI/mild AD and cognitively unimpaired participants (p<0.01, r=0.27-0.35), but did not differ by participant sex (p>0.15), or correlate with age (all p>0.4). G-match prediction of MCI/Mild AD was consistent for all transcription methods (custom method: AUC=0.82, Google Speech-to-text: AUC=0.81, manual: AUC=0.82; all p>0.3). **Conclusions:** Novel methods can improve the authenticity and quality of automated transcription in speech-based screening for Alzheimer's disease. Clinical predictions derived from proportional recall on the Automated Story Recall Task were robust to variation in transcription accuracy. Further research is now needed to evaluate if additional sensitivity is conferred by disfluencies and filled pauses, which can be captured with novel transcription methods, and are known to be sensitive to early speech-based changes in AD. **Disclosures:** All authors are employed by, or option- or shareholders of Novoic. **Key words:** Alzheimer's disease, transcription, automatic speech recognition, speech-based tasks.

P185- A HYBRID DEEP LEARNING AUDIO-VISUAL APPROACH FOR MILD COGNITIVE IMPAIRMENT PREDICTION: I-CONECT STUDY. F. Far Poor[1], M. Alsuhaibani[1], M.H. Mahoor[1], L. Chen[2], H.H. Dodge[2] *(1. Department of Electrical and Computer Engineering, University of Denver - Denver (United States), 2. Department of Neurology, Massachusetts General Hospital, Harvard Medical School - Boston (United States))*

Background: It is now well documented that even at an early stage of MCI, subtle cognitive decline can be associated with changes in speech (linguistic and acoustic characteristics), head pose, eye gaze, and facial expressions in older adults. The recent development of Artificial Intelligence (AI) allows extracting high signal features among a large set of features that are potentially associated with early cognitive decline. Using free conversations between older adults and interviewers recorded via Internet/webcam, we aimed to examine whether multimodal fusion of features (e.g., language and facial expression) extracted from the video recording could lead to improved detection of MCI, compared with those using unimodal features. **Methods:** Data came from the Internet-

Based Conversational Engagement Clinical Trial (I-CONECT) (NCT02871921) which examined the effects of frequent social interactions, specifically conversational interactions, could enhance cognitive reserve and decelerate cognitive decline among socially isolated non-demented subjects (MCI or normal cognition (NC), 1:1 ratio) aged 75 and older. 156 participants were randomized either into the control or experimental group. The participants in the experimental group engaged in free conversations with interviewers prompted by daily themes and associated pictures 4 times per week for 6 months and twice per week for additional 6 months. Each session consists of 30 minutes of conversations using the Internet and user-friendly devices/webcam. Around 6000 video sessions were recorded. Conversations were transcribed using Automatic Speech Recognition specifically developed for older subjects. Out of 150 themes (i.e., discussion topics) used in the trial, we selected 4 themes with adequate sample sizes of good video qualities using criteria including brightness, without eyeglasses, and proper distance between face and camera. Selected themes (sample size) included: Summertime (30 participants), Halloween (32), Self-care (30), and Cities & Towns (34). The dataset is balanced with half being diagnosed with MCI. In this study, facial features were extracted from video frames through a convolutional Autoencoder. Bidirectional Encoder Representations from Transformers (BERT) model captured temporal facial information. Linguistic features are extracted through Linguistic Inquiry Word Count (LIWC). We trained four separate Random Forest models for each of the 4 themes to generate the probability of being MCI. The probability scores are fused using the majority voting method (selecting the highest probability features) for classification. **Results:** We used a 10-fold cross-validation approach on the subject level to train and test the models. Accuracy, F1 score, sensitivity, specificity, and area-under-the-curve (AUC) were assessed. The accuracies of unimodal methods in percentage (only language, only video-extracted features) for Summertime, Halloween, Self-care and Cities & Towns were (80.8, 68.3), (90.9, 73.0), (91.3, 61.0) and (95.5, 69.3), respectively. On the other hand, audio-visual fusion led to promising results for each theme: 92.6, 98.0, 95.3, and 94.9 respectively. **Conclusion:** The results of our study showed that the proposed multimodal approach improved the accuracy of the AI multimodal fusion in distinguishing MCI from NC. The conversations used in this study were recorded using the Internet/webcam at participants' homes. The approach can provide a home-based cost-effective detection of MCI, although further validation study is required.

P186- FEASIBILITY OF THE CUMULUS ELECTROPHYSIOLOGICAL NEUROCOGNITIVE PLATFORM TO ENABLE DE-CENTRALISED TRIALS IN ALZHEIMER'S DISEASE. F.M. Barbey[1], C.J. Barnum[2], A.R. Buick[3], J.F. Dyer[3], M.N. Islam[1], J. Fogarty[4], H. Nolan[1], B. Murphy[1] *(1. Cumulus Neuroscience Ltd. - Dublin (Ireland), 2. INmune Bio Inc. - Boca Raton (United States), 3. Cumulus Neuroscience Ltd. - Belfast (United Kingdom), 4. Nanyang Technological University - Singapore (Singapore))*

Background: Neurofunctional biomarkers (e.g., haemodynamic or electrophysiological) give direct and objective access to the functional effects of drug action. Typically, this requires travel to a clinical trial centre equipped for specialised imaging, but such visits became harder to justify during the pandemic. Conversely, digital endpoints can be deployed easily, to broader populations, at lower risk and inconvenience to patients, but are only surrogates of the brain network activities that neurofunctional methods record. We report on a Covid-era deployment of a patient-friendly at-home neurophysiological biomarker tool, as an adaptive addition to a phase 1b trial of an experimental Alzheimer's therapy. We focus on the platform's feasibility, including adherence and data quality. **Methods:** We present feasibility data collected during the Phase 1b open-label, dose-identification study of XPro1595 in patients with Alzheimer's disease and biomarkers of inflammation (https://clinicaltrials.gov/ct2/show/NCT03943264), which was subsequently advanced to Phase 2. The Cumulus digital platform was a late addition to mitigate reluctance of patients to visit clinical centres during the peak of the Covid-19 pandemic. Patients visited the clinic for weekly XPro1595 injections, over 12 weeks, and three individuals were recruited to use the Cumulus platform. Recordings were captured in-clinic around the time of weekly injections aimed at capturing acute drug effects, together with regular burst sampling in the home to observe a pre-intervention baseline, and organisational changes over the course of the trial. The tasklist included a 15-min MMN task, a 15-min P300 task, and a 7-min resting state. Patients had the option to complete passive tasks only (e.g., the MMN and resting state) if the P300 active task proved to be too difficult based on their impairment level. **Results:** Three mild to moderate AD patients with MMSE scores of 13, 15 and 25 (one male, two female) completed 14 weeks of at-home recordings, with the assistance of a study partner. A total of 111 sessions were collected out of 116 requested across all participants (adherence to protocol was 100%, 91.9%, 97.3%, respectively). The two patients with a higher level of impairment chose to only conduct passive tasks in the home. The core feature expected in human EEG Power Spectral Density (spectral power decay) was observable in all patients, and only the mild AD patient exhibited a clear alpha peak between 8 to 12Hz. The morphology, and scalp topography of the EEG signals extracted from the MMN and P300 tasks were canonical, with lower MMN amplitude in the most impaired patients - consistent with the AD literature. Although the N was small, and there was no placebo condition, the hypothesised increase in alpha band power and P300 amplitudes were seen acutely after the infusions, while expected increases in P300 amplitude and reduction in theta power were observed over the following weeks, consistent with organisational changes. **Conclusions:** The Cumulus platform can be frequently and correctly used by mild to moderate AD patients in the home over long periods of time (e.g., >3 months) including 'burst' measurement periods in-lab or at-home. Digital technology grounded in the brain has the potential to provide objective, frequent and patient-centred tracking of biomarkers of AD-relevant functional neurophysiology. **Clinical Trial Registry:** NCT03943264; https://clinicaltrials.gov. **Disclosures:** FB, AB, JF, JD, MNI, HN and BM are employees of Cumulus Neurosciences Ltd., the technology provider and hold share options as part of their employment package.

P187- ACCELERATING SUSTAINABLE ADOPTION AND JUSTIFICATION OF DIGITAL CLINICAL DETECTION APPLICATIONS FOR COGNITIVE IMPAIRMENT AND DEMENTIA INTO ESTABLISHED HEALTHCARE SYSTEMS. A. Khachaturian[1], B. Cassin[2], G. Finney[3], P. Barkman Ferrell[4], E. Klein[4], M. Boustani[5], Z. Khachaturian[1]
(1. Campaign to Prevent Alzheimer's disease - Rockville (United States), 2. DigiCARE Realized Inc. - Old Bridge (United States), 3. Geisinger Health - Danville (United States), 4. Eli Lilly and Company - Indianapolis (United States), 5. Indiana University - Indianapolis (United States))

Background: Cost estimates for care for those living with dementia and other cognitive impairments are rising and are now estimated to approach US$1 trillion globally by 2025 [1]. This is the devastating economic strain of Alzheimer's disease and related dementias (AD/ADRD). The lack of specialized personnel, infrastructure, diagnostic capabilities, and healthcare access impedes the timely identification of patients progressing to dementia, particularly in underserved populations [2]. Despite several new intervention options for AD/ADRD, the international healthcare infrastructure systems may not be able to handle the existing cases, not to mention additional sudden increases among those with underrecognized cognitive impairment and dementia [3-5]. Delivering timely, dependable, and quality clinical care for those at-risk/with cognitive difficulties must overcome many challenges. Bioinformatics offers potentially quicker access to health services. However, adopting digital clinical decision intelligence applications (CDIAs) in established healthcare systems will be essential to address the increasing demands for earlier detection of cognitive impairments and dementia. **Methods:** A modified Delphi method was used to develop a systematic approach for a demonstration project to identify the necessary adoption parameters among different types of healthcare systems, necessary and sufficient to support a decision to use CDIAs in routine clinical daily practice[6]. The effort gathered, convened, and analyzed expert opinions from relevant stakeholders from non-Federal healthcare systems, Federal healthcare systems, healthcare professionals, patient advocacy groups, industries allied with digital health, and health policy leaders. The effort involved repeated rounds of surveys and expert feedback to reach a consensus on solutions as well as to identify differing perspectives. By involving multiple participants in an iterative process, the modified Delphi method ensured that varied perspectives were considered while minimizing the influence of any individual's opinion. This approach can be beneficial when a precise answer is unavailable or significant uncertainty exists around an issue. While the process is time intensive, the approach provides more informed decisions and reflects the collective experience of experts. **Results:** The expert panel identified several key factors that could influence the successful deployment, implementation, and healthcare adoption of CDIAs. First, establishing and cultivating trust and providing seamless ease of use for healthcare professionals in artificial intelligence/machine learning (AI/ML)-driven CDIAs is paramount. Second, the development of evidence to support claims of improving the cost-effectiveness of diagnostic services, mitigating preventable readmissions, and optimizing the overall cost of care. Third, the imperative to enhance clinical care operational efficiency by streamlining processes, mitigating care service gaps, minimizing system slack, preparing health system for transitioning AD/ADRD treatment plans, and navigating primary care and specialist capacity constraints. Fourth, incorporating relevant factors, including environmental and social components, risk-benefit profiles for different communities, lifestyle considerations, affordability constraints, and other unbiased socioeconomic variables to provide a fundamental basis for achieving health equity. **Conclusions:** Healthcare bioinformatics offers a potential route for quicker access to brain healthcare services; however, better preparedness plans must be implemented to provide decision-makers with evidence to make decisions. The most critical consideration for adopting AI/ML-driven clinical decision intelligence applications (CDIA) is ensuring patients, practitioners, and healthcare systems act on the information provided. **Key words:** Dementia, Alzheimer, healthcare systems, artificial intelligence, machine learning, clinical decision applications, healthcare system preparedness, technology adoption. **Disclosures:** Ara S. Khachaturian, Ph.D. is an Officer and director of the Campaign to Prevent Alzheimer's Disease (PAD 20/20) and; Officer, director and employee of Khachaturian and Associates; Founding executive-editor of Alzheimer's & Dementia, The Journal of the Alzheimer's Association (retired), Founding executive-editor of Alzheimer's & Dementia: Translational Research & Clinical Intervention (retired), Founding executive-editor of Alzheimer's & Dementia: Diagnoses, Assessment & Disease Monitoring (retired); Executive Officer and Director, Brain Watch Coalition; Senior Research Fellow, University of Nevada Las Vegas, National Supercomputing Institute & Dedicated Research Network; Received payments through organizational affiliations for grants, contracts, consulting fees, honoraria, meeting support, travel support, in-kind research/professional support over the last 36 months from the Alzheimer's Association, Acadia Pharmaceuticals, Alzheon, Biogen, Clinical Trials Alzheimer's Disease Conference, Davos Alzheimer's Consortium, Eisai, Eli Lilly & Company, RELX Plc, High Lantern Group, International Neurodegenerative Disorders Research Center, and Serdi Publishing. **References:** 1. 2022 Alzheimer's disease facts and figures. 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P189- CORRELATION BETWEEN ALTOIDA'S DIGITAL COGNITIVE ASSESSMENT AND STANDARD NEUROPSYCHOLOGICAL TESTS IN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT AND COGNITIVELY HEALTHY VOLUNTEERS. E. Streel[1], A. Tort Merino[2], A. Ferrari[3], G. Sanchez-Benavides[4,5,6,7], C. Minguillon[4,5], S.F. Fallone[8], R. Harms[9], I. Tarnanas[10], M. Balasa[2], M.F. Iulita[11] *(1. Altoida Inc. - Washington (United States), 2. Hospital Clinic, IDIBAPS - Barcelona (Spain), 3. Altoida Inc. - Rome (Italy), 4. Barcelonaβeta Brain Research Center (BBRC) - Barcelona (Spain), 5. Pasqual Maragall Foundation - Barcelona (Spain), 6. Hospital del Mar Medical Research Institute - Barcelona (Spain), 7. (CIBERFES), Instituto de Salud Carlos III - Madrid (Spain), 8. Altoida Inc. - Maastricht (Netherlands), 9. Altoida Inc. - Nijmegen (Netherlands), 10. Altoida Inc. - Thessaloniki (Greece), 11. Altoida Inc. - Barcelona (Spain))*

Background: Digital biomarkers are increasingly utilized as exploratory endpoints and screening tools for inclusion in clinical trials, offering advantages over traditional neuropsychological batteries. They facilitate rapid, frequent, and unbiased measurements of cognitive and functional status, without requiring a trained clinical rater. Altoida Inc. developed a tabled-based assessment using augmented reality (AR) which simulates activities of daily living and evaluates cognitive and motoric abilities in approximately 10 minutes. We investigated the correlation between Altoida's digital biomarker assessment (DNS-MCI score) and standard neuropsychological tests, including the Mini-Mental State Examination (MMSE), the Free and Cued Selective Reminding Test (FCSRT) and the Trail Making Test (TMT). **Methods:** This is a dual center, cross-sectional cohort study (n=186; 51.6% female; mean age 68.6 (6.3) years). We included 82 (44.1%) participants from the Alzheimer's disease and other Cognitive Disorders Unit at Hospital Clinic Barcelona and 104 (55.9%) participants from the β-AARC cohort1 established at the Barcelonaβeta Brain Research Center. Participants received a neurological evaluation, neuropsychological test battery, and Altoida's digital biomarker assessment. They were classified according to their clinical status, as cognitively normal (CN; n=126; mean age: 67.6 (6.4) years; mean MMSE score: 28.5 (1.4) points; Clinical Dementia Rating (CDR)=0) or as having mild cognitive impairment (MCI; n=60; mean age: 70.8 (5.6); mean MMSE score: 25.8 (2.6) points; CDR=0.5). Mixed effect linear regression analysis with Wald's test on the coefficients was used to evaluate the correlation between DNS-MCI scores and neuropsychological tests; patient ID was used as random effect. A subset had known amyloid status based on CSF Aβ42 determinations (Lumipulse, Fujirebio). Two-group comparisons were evaluated with Student's t-test. **Results:** DNS-MCI scores showed significant positive correlations with the MMSE ($R2=0.25$, $p<0.001$) and the immediate and delayed FCSRT subtests ($R2=0.24$-0.37, $p<0.001$), as well as negative correlations with the TMT test ($R2=0.15$, $p<0.001$). DNS-MCI scores were significantly lower in individuals presenting with MCI than CN ($p<0.001$). Participants who were identified as MCI Aβ+ showed significantly lower DNS-MCI scores than those who were MCI Aβ- ($p<0.001$). ROC curves showed very good diagnostic performance of the DNS-MCI in the discrimination between CN vs MCI (AUC=0.82, 95%CI [0.76-0.88]) and of MCI Aβ- vs MCI Aβ+ (AUC=0.80, 95%CI [0.69-0.92]). **Conclusions:** Altoida DNS-MCI score correlated with classical neuropsychological tests commonly used as a battery (lasting approximately 60-90 minutes) when evaluating patients in clinical research and clinical practice. Altoida's digital biomarker assessment allows excellent discrimination of MCI and those with amyloid positivity. **Key words:** digital biomarkers, cognitive assessment, clinical trials, endpoints, augmented reality. **Disclosures:** ES, AF, SF, RH, IT and MFI are employees of Altoida, Inc and may hold stock options in the company. **ClinicalTrials.gov Identifier:** NCT04935372.

P190- BUILDING AN EVIDENCE CATALOG OF DIGITAL MEASUREMENT TECHNOLOGIES TO ACCELERATE ENDPOINT DEVELOPMENT IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS CLINICAL TRIALS. S.A. Lott[1], E. Streel[2], P. Fromy[3], J. Goldsack[4], O.B.O. The Dime Core Digital Measures Of Adrd Project Team[4] *(1. The Digital Medicine Society - Johnstown (United States), 2. Altoida - Washington, DC (United States), 3. The Digital Medicine Society - Saumur (France), 4. The Digital Medicine Society - Boston (United States))*

Background: Measurement in clinical trials of Alzheimer's Disease and Related Dementias (ADRD) has traditionally focused on clinician reported outcome measures, such as the clinical dementia rating scale sum of boxes, and supplemented with clinical outcome assessments reported by care partners and patients, such as the Activities of Daily Living for Mild Cognitive Impairment scale. While these scales are useful and have been shown to relate to aspects of life that are important to the patient, they are typically measured at clinic visits spaced across lengthy intervals. Digital measurement technologies (DHTs) can employ sensor based hardware and software based applications to measure meaningful aspects of a patient's life more regularly and in a home environment. These technologies can also be developed to measure very specific and meaningful aspects of a patient's health. As such, digital measurement technology can supplement the in-clinic patient assessment to allow for a more voluminous data collection strategy at a finer resolution. This in turn could lead to additional responsive endpoint measures, and potentially reduce the sample size requirements of a trial. **Objectives:** To create a well-referenced online catalog of existing electronic clinical outcomes assessments technologies in the ADRD space. **Methods:** A focused review of the literature was conducted to identify potential manuscripts that detailed the use of digital measurement technology in the ADRD space. This initial list was screened to select appropriate measurement technologies. Once a list of potential DHTs was defined, the project team requested input from a convenience sample of ADRD experts and asked them to report any missing technologies. Then, technology developers were contacted to complete an online survey where they were able to upload additional evidence in the form of manuscripts, poster presentations, white papers, and technical documentation as well as open-access algorithms and datasets. The data supplied through this process was added to the evidence arising from the literature review and compared against evidence standards defined by the project team and based on the literature. Evidence standards had two levels: required evidence and supplemental evidence. In order to reach the required evidence standards, a DHT needed to have published evidence of at least 1 element of the V3 framework (Verification, Analytical Validation or Clinical Validation) to an acceptable level based on selected elements of the EValuatIng connecteD sENsor teChnologiEs (EVIDENCED) checklist. Supplementary evidence was not a requirement, but was collected on the basis of the following categories to enrich the catalog: • The NICE Evidence Standards Framework Standard 5: embed good data practices in the design of the DHT; • The NICE Evidence Standards Framework Standard 7:

show processes for creating reliable health information; • Use in healthcare settings; • Use in clinical trial settings; • Regulatory acceptance; • Payer acceptance; • Use as a prognostic or diagnostic biomarker including differentiation between ADRD stages/conditions; • Use in diverse populations; • Detail around the cost of implementation; • Detail around language availability; • Detail around usability. Acceptable technologies and associated evidence were collated in an open-access online resource for public use. **Results:** The literature review resulted in a total of 1744 hits which were screened down to 156 relevant manuscripts. From these 156 relevant manuscripts, 116 technologies were identified. At the time of writing, 43 additional technologies have been identified by external experts leading to a total of 159 identified technologies. Currently, over 100 developers have been contacted for additional evidence and 20 have responded to the request. Evidence covered a broad range of required and supplementary evidence. The proportion of DHTs meeting the required evidence standards is still under review by the project team. **Conclusion:** This work marks the start of a tool designed to accelerate knowledge and research in digital measurement in ADRD clinical trials. As the request for evidence went to developers only a week prior to this writing, there is currently a low response rate. However, we expect additional evidence to be forthcoming and developers will continue to be contacted for this evidence. The catalog will be updated periodically and will also allow technology developers to submit new technologies, supporting evidence, datasets, and algorithms for further use and future development.

P191- ADVANCING COMPUTERIZED COGNITIVE ASSESSMENT: COGNIVUE'S® ENHANCED NORMATIVE RANGE DATA SETS THE NEW GOLD STANDARD FOR SENSITIVITY AND PATIENT PROFILING. J. Galvin[1] *(1. University of Miami Comprehensive Center for Brain Health - Boca Raton (United States))*

Background: The great challenge in nearly all U.S. clinical trials is that their study cohorts are overwhelmingly European White, male, and highly educated with post college degrees. The Further the Objective and Clinical Understanding of Cognivue Study had a 37 percent research participation rate of historically underserved and underrepresented populations compared to typical scientific studies of this size that draw on average between two to 16 percent diverse participation [1]. This study showcases Cognivue's innovative approach to computerized cognitive assessment by introducing additional normative range data, resulting in enhanced sensitivity and improved patient profiling. By redefining the computerized cognitive assessment category, Cognivue set a new gold standard for comprehensive cognitive evaluation in diverse populations. **Methods:** This was a multi-site, validity and reliability study that enrolled 1,575 subjects at 14 study sites throughout the United States. Demographic information including age, sex, race, ethnicity, and education was captured and regularly assessed during enrollment to ensure a diverse representation of study subjects. This study confirmed a neutral test application for the study and eliminated common cognitive assessment biases by stratifying by the demographic categories. Analyses included: regression analyses for agreement and retest reliability, and rank linear regression, bivariate correlation analysis and factor analysis for psychometric comparisons. **Results:** Over 28 percent of subjects from 14 sites in 11 states in the study identified their race as Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or other non-white, while over 12 percent of participants identified their ethnicity as Hispanic or Latino. This is twelve times more than the average Hispanic/Latino participation in U.S. clinical trials, recorded as less than one percent by the Food and Drug Administration [2]. The results of the study demonstrated that incorporating diverse subject participation significantly improved the accuracy of normative ranges. The inclusion of individuals from various backgrounds provides a broader perspective, enabling the establishment of more comprehensive and inclusive norms. These normative ranges account for the natural variations observed in different demographic groups, resulting in a more precise scoring system. **Conclusion:** The refined normative ranges generated in this study by incorporating diverse demographic factors offer valuable insights for clinicians, researchers, and practitioners. These ranges enable more precise interpretations of testing and test results, enhancing the accuracy of Cognivue neuropsychiatric assessments and addressing the most commonly found challenges related to cognitive assessments [3]. This study highlights the importance of accounting for the diverse characteristics of individuals to ensure equitable and effective assessments and treatment strategies in addition to the applicability of Cognivue cognitive assessment screening products within the general population by confirming total scoring, age-specific normative ranges, test-retest reliability, and sensitivity and specificity as compared to other frequently used paper and digital assessments. **Key words:** Gold-Standard Cognitive Assessment. **Clinical Trial Registry:** NCT05712005. **Data Deposition:** https://clinicaltrials.gov/ct2/show/NCT05712005. **Disclosures:** James Galvin is a scientific consultant for Cognivue. Joel Raskin is a scientific advisor for Cognivue. The additional authors claim no competing interests. **References:** 1. Ramamoorthy A, et al. Clin Pharmacol Ther. 2015 Mar;97(3):263-73. doi: 10.1002/cpt.61; 2. Lolic M, et al. J Clin Pharm Ther. 2021 Dec; 46(6):1576-1581. doi: 10.1111/jcpt.13532; 3. Tripathi R, et al. Dement Neuropsychol. 2014 Apr-Jun;8(2):148-154. doi: 10.1590/S1980-57642014DN82000010

P192- THE BRAIN HEALTH CHAMPION STUDY: A HEALTH COACHING INTERVENTION WITH MOBILE TECHNOLOGY IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT OR RISK FACTORS FOR DEMENTIA- AN UPDATE. K. Riera[1], A. Park[1], B. Mcfeeley[1], D. Babazadeh[1], A. Altman[1], K. Daffner[1], S. Gale[1] *(1. Brigham and Women's Hospital - Boston (United States))*

Background: Cumulative evidence suggests adhering to brain-healthy behaviors can decrease dementia risk and rate of cognitive decline. We previously demonstrated that a health coaching intervention, including weekly phone calls, facilitated adherence to lifestyle recommendations in older adults with mild cognitive impairment (MCI) or mild dementia. The current study extends this research to include cognitively normal, older adults at risk for dementia, and adds wearable fitness trackers and a mobile health platform for texting, video sessions, and photographing food intake. Since our last report, additional participants have enrolled, and further analyses completed. **Methods:** Participants, age 60-79, with MCI due to suspected Alzheimer, cerebrovascular, or "mixed" disease, or older adults with dementia risk factors, are being randomized to the Brain Health Champion (BHC) intervention or a counseling and education (CE) control. In BHC, under the guidance of health coaches, participants set personalized goals, reinforced by weekly video calls, mobile messaging, and one dietitian consult. In CE, usual care is supplemented by physician counseling and educational materials sent every six weeks. Changes in physical

activity, diet, social/cognitive engagement, neurocognitive battery test scores, and behavioral health metrics are measured over six months using questionnaires, wearable fitness trackers, and photographed food logs. Maintenance of behavior changes are also assessed 6 months post-intervention. **Results:** Fifty-five participants (17 MCI, 38 cognitively normal/at risk) have enrolled in the study, with 36 (19 BHC, 17 CE) completers to date. All participants successfully operated the mobile technology alone or with care partners' assistance. When compared to the CE group, BHC participants tend to show increased physical activity, measured by the Physical Activity Scale for the Elderly (PASE), and quality of life, measured by Flanagan Quality of Life (FQoL) scale. While both arms showed improved adherence to a Mediterranean diet, the BHC group demonstrates statistically significant greater reported improvement. Participants from both arms show increases in cognitive activity, step counts by their fitness tracker, and scores on neurocognitive assessment. Qualitative data collected through post-study feedback surveys revealed all participants in the BHC arm were satisfied with their weekly encounters, relationships with coaches, and the study overall. Feedback also points to a trend in BHC toward increased brain health knowledge and overall change in brain healthy behaviors compared to CE, which did not report as much satisfaction in their education component nor readiness to commit to lifestyle changes. Generally, participants in both arms attribute their improved diet to the education and recommendations they received, despite having received the information differently. **Conclusions:** Both mobile technology-augmented personalized health coaching and provider counseling and education interventions can promote evidence-based brain healthy behaviors that reduce risk of cognitive decline. Data trends suggest that coaching may be more effective in terms of increasing physical activity, quality of life, and adherence in a Mediterranean diet. **Key words:** Brain health coaching, Nonpharmacological clinical trials for Alzheimer disease, Digital health, Cognitive impairment. **Disclosures:** The authors have no relevant disclosures.

LP109- DEVELOPMENT AND CLINICAL VALIDATION OF ICOBRAIN ARIA – AN AI-BASED ASSISTIVE SOFTWARE TOOL FOR AUTOMATED DETECTION AND QUANTIFICATION OF AMYLOID-RELATED IMAGING ABNORMALITIES.

D.M. Sima[1], T.V. Phan[1], S. Van Eyndhoven[1], S. Vercruyssen[1], R. Magalhães[1], C. Maes[1], J. Guo[2], R. Hughes[2], R. Gabr[2], P. Saha-Chaudhuri[2], G.G. Curiale[3], S. Belachew[2], W. Van Hecke[1], A. Ribbens[1], D. Smeets[1] *(1. icometrix - Leuven (Belgium), 2. Biogen Digital Health - Cambridge, Massachusetts (United States), 3. Biogen - Cambridge, Massachusetts (United States))*

Background: Amyloid-related imaging abnormalities (ARIA) are brain magnetic resonance imaging (MRI) findings associated with the use of amyloid beta-directed monoclonal antibody therapies in Alzheimer's disease (AD). ARIA monitoring is important to inform treatment dosing decisions and might be improved through assistive software. We developed an artificial intelligence (AI)-based software, icobrain aria, for assisting radiological interpretation of brain MRI scans in patients monitored for ARIA, and assessed its diagnostic performance. **Methods:** We conducted a multiple-reader multiple-case study to compare the diagnostic performance of radiologists assessing ARIA on MRI scans from patients treated with aducanumab, both unassisted and assisted by the icobrain aria software. The study encompassed 199 cases from the EMERGE, ENGAGE and PRIME clinical trials and 16 U.S. board certified radiologists with a range of experience. Radiologists reported the presence and severity of ARIA-E (edema/sulcal effusion) and ARIA-H (microhemorrhage and superficial siderosis), either assisted or unassisted by icobrain aria. Of all cases, 44 did not contain any ARIA findings, 84 had both ARIA-E and ARIA-H and the remaining cases had either ARIA-E (n = 39) or ARIA-H (n = 36) only. The co-primary study endpoints were the difference between assisted and unassisted detection accuracy of ARIA-E and ARIA-H separately, assessed with the area under the receiver operating characteristics curve (AUC), where the assisted and unassisted assessments for ARIA severity were compared against a gold standard consensus of 3 experts. **Results:** Radiologists assisted by icobrain aria were significantly better in detecting ARIA. icobrain aria-assisted reading performance was superior (vs unassisted) for both ARIA detection co-primary endpoints, with an AUC difference of 0.051 (95% CI: 0.020, 0.083) for ARIA-E (p=0.001) and 0.044 (95% CI: 0.017, 0.070) for ARIA-H (p=0.001). The average assisted AUC was 0.873 (95% CI: 0.835, 0.911) for ARIA-E detection, and 0.825 (95% CI: 0.781, 0.869) for ARIA-H detection. Sensitivity increased significantly from 70.9% (unassisted) to 86.5% (assisted) for ARIA-E detection, and from 68.7% to 79.0% for ARIA-H detection, while specificity remained above 80% for the detection of both ARIA types. **Conclusion:** Radiological reading performance for ARIA detection and diagnosis is significantly improved when using icobrain aria. Hence, icobrain aria can be a clinically impactful tool to improve safety monitoring and management of AD patients treated with amyloid beta-directed monoclonal antibody therapies. **Key words:** multiple-reader multiple-case study, amyloid-related imaging abnormalities (ARIA), software-assisted radiological reading, icobrain aria. **Disclosures:** D.M. Sima, T.V. Phan, S. Van Eyndhoven, S. Vercruyssen, R. Magalhães, C. Maes, A. Ribbens, D. Smeets are employees at icometrix. W. Van Hecke is founder and CEO of icometrix. J. Guo, R. Hughes, R. Gabr, P. Saha-Chaudhuri, G.G. Curiale, S. Belachew are employees and stakeholders of Biogen.

LP110- THE MOBILE TOOLBOX (MTB) AS A NOVEL OUTCOME MEASURE FOR ASSESSING COGNITION REMOTELY IN ALZHEIMER'S DISEASE CLINICAL TRIALS: VALIDATION WITH IN-CLINIC COGNITIVE ASSESSMENTS AND AD BIOMARKERS.

J. Burling[1], R. Jutten[1], M. Properzi[1], R. Amariglio[2], G. Marshall[2], K. Papp[2], K. Johnson[3], R. Sperling[2], D. Rentz[2] *(1. Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA - Boston (United States), 2. Department of Neurology, Massachusetts General Hospital, Harvard Medical School & Department of Neurology, Brigham and Women's Hospital, Harvard Medical School - Boston (United States), 3. Department of Neurology/Radiology, Massachusetts General Hospital, Harvard Medical School - Boston (United States))*

Background: Paper-pencil tests are considered the gold standard to assess cognitive efficacy in Alzheimer's disease (AD) clinical trials. A challenge of these tests is in-clinic administration, limiting the ability to reach remote community cohorts. At-home, smartphone-based assessments have the potential to overcome these limitations. One such assessment, the Mobile Toolbox (MTB), has shown good reliability and validity [1, 2], making it a promising tool to measure cognition outside the clinic. Here, we compared MTB-based composites to the Preclinical Alzheimer's Cognitive Composite-5 (PACC5) and explored associations between the MTB and AD biomarkers on positron emission tomography (PET) imaging. **Methods:**

The MTB was administered to 78 cognitively unimpaired (CU) older adults from four observational studies: the Harvard Aging Brain Study, the Subjective Cognitive Decline Study, Serial MK6240 Study, and Instrumental Activities of Daily Living Study. All participants had in-clinic PACC5 testing available, and a subsample had PiB-PET (n=57) and FTP-PET (n=35). The MTB includes six measures of Fluid Cognition, including episodic memory (Picture Sequence Memory (PSM) and Face-Name Associative Memory Exam (FNAME)), executive functions (EF) (Dimensional Change Card Sort (DCCS), Flanker), working memory (Memory for Sequence (MFS)), and processing speed (Number-Symbol Match (NSM)), and two measures of Crystallized Cognition (Spelling and Vocabulary). We hypothesized that a combination of the MTB measures PSM, FNAME (episodic memory), NSM (processing speed), and Vocabulary (as a general measure of cognition) would correlate with the PACC5, resulting in an MTB-PACC-like composite. Next, we created multiple MTB-based composites, consecutively adding measures of working memory and EF, resulting in the MTB-composite-3 (PSM, FNAME, MFS); MTB-composite-4 (PSM, FNAME, MFS, NSM); MTB-composite-5A (PSM, FNAME, MFS, NSM, DCCS) and MTB-composite-5B (PSM, FNAME, MFS, NSM, Flanker). Linear regression models correcting for age, sex and years of education compared various MTB-composites to the PACC5, global amyloid burden (PiB DVR) and tau deposition (FTP SUVr, PVC) in the medial temporal lobe. **Results:** Preliminary MTB baseline data was available on 78 participants (age 70.9±9.18, 61.5% female, 16.6±2.5 years of education). The theoretically derived MTB-PACC-like composite was associated to PACC5 (corrected b=0.35, 95%CI[0.15,0.55], p=0.001), as were the MTB-composite-3 (corrected b=0.29, 95%CI[0.10,0.48], p=0.003), MTB-composite-4 (corrected b=0.36, 95%CI[0.17,0.56], p=0.001), MTB-composite-5A (corrected b=0.37, 95%CI[0.17,0.57], p<0.001) and MTB-composite-5B (corrected b=0.38, 95%CI[0.17,0.59], p=0.001). No significant associations were observed with MTB composites and global amyloid, although we observed a trend-level association between amyloid and the MTB-composite-3 (corrected b=-0.07, [-0.16,0.30], p=0.156). The following MTB composites were associated with entorhinal tau: MTB-composite-3 (corrected b=-0.23, 95%CI[-0.40,-0.05], p=0.012), MTB-composite-4 (corrected b=-0.21, 95%CI[-0.39,-0.03], p=0.025), MTB-composite 5A (corrected b=-0.20, 95%CI[-0.37,-0.02], p=0.029) and MTB-composite 5B (b=-0.22, 95%CI[-0.42,-0.03], p=0.028). **Conclusions:** Various combinations of MTB-based composites done at home are similarly associated with in-clinic PACC5 performance. Further, our preliminary results suggest that the most efficacious MTB-composites for detecting cognitive deficits related to AD pathology included only measures of episodic memory, processing speed and EF. Overall, these findings suggest that the MTB might be a promising tool to remotely monitor cognition in AD clinical trials. Future work will focus on determining the optimal MTB-composite to detect AD-related cognitive change over time.

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LP111- IMPROVING COGNITIVE TESTING AND CARE PROCESSES FOR OLDER ADULTS AT RISK OF COGNITIVE DECLINE IN A LARGE HEALTH CARE SYSTEM.

D. Gitelman[1,2,3], J. Mishos[1], C.M. Canda[1], P. Pagel[1,4], L. Dimitris[1], M. Malone[1,4,5] *(1. Advocate Health, Neuroscience Service Line – Midwest Region - Downers Grove, IL (United States), 2. Rosalind Franklin University of Medicine and Science, Department of Medicine - North Chicago, IL (United States), 3. Northwestern University / Feinberg School of Medicine, Department of Neurology - Chicago, IL (United States), 4. Aurora Health Care, Department of Senior Services - Milwaukee, WI (United States), 5. University of Wisconsin School of Medicine & Public Health - Madison, WI (United States))*

Background: In the United States, primary care clinicians (PCPs) typically diagnose and treat most patients who have or who may be developing neurocognitive disorders (NCDs) [1]. However, nearly two-thirds of patients remain underdiagnosed, misdiagnosed or experience a delay in diagnosis [1-3]. Many barriers to care have been cited for these failures in diagnosis including limitations in PCP time and expertise, and inadequate technical, financial, and staffing resources [1, 4]. Diagnostic delays may particularly impact minority populations. In contrast, an early diagnosis is important for providing prognosis, advanced care planning, increasing patient safety, and initiating non-pharmacological interventions that may preserve cognitive function and enhance quality of life. Furthermore, with the recent development of beta-amyloid antibodies, early diagnosis is critical for access to this therapy. **Methods:** The project was formulated as a quality improvement initiative as part of the Davos Alzheimer's Collaborative Healthcare System Preparedness early detection grant, and was exempted from IRB review. Physicians and advanced practice clinicians (APCs) were initially recruited through discussions with primary care leadership, and later through word-of-mouth. To address limitations in PCP time, clinic staff were trained to administer the BrainCheck digital cognitive testing tool. Testing typically takes 10-15 min, can be performed remotely or before the visit and provides immediate results. The tool has good sensitivity and specificity for detecting early cognitive impairment [5, 6]. To enhance PCP efficiency a comprehensive Epic EMR SmartSet has been developed that includes diagnostic, treatment and patient guidance sections that can be rapidly selected during an office visit. Finally to address limitations in PCP expertise educational tools include 1) A series of brief lectures (slides and video), for which CME credit will be available, that review basic aspects of Alzheimer's disease and dementia care. 2) Access to a new internal SharePoint site that serves as a resource hub with information on dementia diagnosis, treatment, community resources and guidance for caregivers. 3) Weekly Project ECHO® based Memory Care Case Conferences (CME provided) where guidance can be provided on patient care, and 4) an implementation of eConsults that allows for quick linkage between PCPs and dementia experts in order to answer questions about patient care. **Results:** Forty-six clinicians representing 24 practices have been recruited over the past 12 months of the project, which was consistent with the recruitment goals. Five hundred sixty-two BrainCheck assessments have been performed. Project ECHO® Memory Care Case conferences have been attended by 120 clinicians, of various types, per month. Implementing this comprehensive program was associated with multiple challenges in PCP adoption of new tools and workflows, information technology requirements, educational material development, and effective communication strategies to enable full utilization of the new

resources. **Conclusions:** The outcomes of this project have allowed us to design more effective strategies for increasing cognitive testing and improving the management of patients with dementia at the health system level. Detection of cognitive impairment at the earliest stages in the Alzheimer's disease time course will also help to ensure that newly diagnosed patients are eligible for promising disease modifying treatments. **Key words:** Digital Tools, Cognitive testing, Primary care, Early Diagnosis. **Disclosures:** Darren Gitelman, consultant for: Abbvie, Eisai, Lilly, Genentech/Roche, Novo-Nordisk. Institution receives clinical trial funding from: Biogen, Cassava, Eisai, Lilly. Michael Malone, Stock Ownership: Abbott Labs, Abbvie. Jennifer Mishos, Cristybelle-Marie Canda, Patti Pagel, Lisa Dimitris: Nothing to disclose. **Support:** This project was supported by a Davos Alzheimer's Collaborative Healthcare System Preparedness grant and from the Frisbie endowment to the Advocate Foundation. **References:** 1. Bernstein, A., et al. BMC Health Serv Res, 2019; 19(1), 919. doi:10.1186/s12913-019-4603-2; 2. Boustani, M., et al. J Gen Intern Med, 2005; 20(7), 572-577. doi:10.1111/j.1525-1497.2005.0126.x; 3. Boise, L., et al. Gerontologist, 1999; 39(4), 457-464. doi:10.1093/geront/39.4.457; 4. Liss, J. L., et al. J Intern Med, 2021; 290(2), 310-334. doi:10.1111/joim.13244; 5. Groppell, S., et al. JMIR Aging, 2019; 2(1), e12615. doi:10.2196/12615; 6. Ye, S., et al. medRxiv. 2021; doi:10.1101/2020.11.10.20229369

LP112- FEASIBILITY AND ACCEPTABILITY OF A REMOTE AND FULLY-AUTOMATED PHONE SCREENING FOR COGNITIVE IMPAIRMENT IN THE AUTONOMY PHASE II STUDY. S. Schäfer[1], S. Ruhmel[2], J. Tröger[1], D. Henley[2], F. Dörr[1], J. Warken[1], N. Linz[1], J. Herrmann[1], K. Langel[2], A. König[1] *(1. ki elements GmbH - Saarbrücken (Germany), 2. Janssen Research & Development, LLC - Raritan (United States))*

Background: Remote and automatic cognitive screening tools offer a cost-effective approach for conducting large-scale assessments. These tools are of particular interest for clinical trials in which the recruitment of a substantial cohort of eligible participants is paramount. Furthermore, they are valuable for accessing potential participants that are less mobile or underrepresented participants living in geographically hard-to-reach regions. However, to ensure adherence and prevent selective drop-outs of participants, it is essential that those tools provide an intuitive user experience. In this work, we evaluated the feasibility and acceptance of a remote and fully-automated phone screening for assessing cognition in older adults within the context of Janssen's phase 2 Autonomy study. **Methods:** The Autonomy trial expands site-based enrollment with a global outreach strategy targeting a broad population. For selected sites in the US, the ki:elements Speech Biomarker for Cognition (ki:e SB-C) is integrated into a digital patient recruitment funnel and uses an automated bot to call participants via a standard phone call. The SB-C collects speech during word list learning, semantic verbal fluency, and free-speech tasks, extracting up to 100 speech features resulting in scores for different cognitive domains, culminating in an overall cognition score. The SB-C assessment lasts ~10 minutes. Responders are classified into referrals (MCI) and non-referrals (healthy or dementia) based on a pre-screening machine learning model using the SB-C scores as input. To evaluate performance of this approach, the pre-screening engine does not affect the invitation to the on-site screening. Participants specified a 2-hour time window for their availability. They were called twice daily for up to 7 days or until they completed the assessment. They could also initiate the call by themselves. Participants had to authenticate themselves using a code provided upon signing up for the study. No incentives were given for participation. Calls were investigated regarding: - frequency and reason for dropouts, - time of day of successful assessments, - ratio of outgoing to incoming calls, - user experience rating (1 - 10), - correlation of these variables with call success. **Results:** Out of 249 participants, 72 completed the assessment, with 70 having successful biomarker calculations. One hundred twelve participants dropped out because they were unreachable or found the call timings inconvenient, 49 could not authenticate, 6 ended the call during the assessment, and 5 declined voice recording. The most successful call time was between 10:00 AM to 12:00 PM, with no difference among age groups. Successful calls correlated with how often participants called the system themselves ($r = 0.25$, $p < .001$). The average user experience rating of participants who successfully performed the assessment was $M = 5.92$ out of 10. **Conclusions:** In this project, participants mainly dropped out before the actual assessment started. Few left during the assessment, suggesting the main barriers are accessibility and authentication, not technical problems, or assessment burden. Reducing early dropouts might be achieved by increasing participant motivation and implementing different authentication methods that do not require a random code. Moreover, enabling the callback option is strongly recommended for automated systems. **Key words:** User behavior, automated phone assessments, automated screenings. **Disclosures:** SS, JT, FD, JW, NL, JH, AL are employed at the digital biomarker company ki:elements. JT, NL, JH own shares of the company. SR, DH, KL are employed at the pharma company Janssen. The authors have no conflicting interests to report.

LP113- OLDER PEOPLE WITH MILD COGNITIVE IMPAIRMENT EXHIBIT LOWER SEMANTIC NOISE AFTER SIX MONTHS OF FREQUENT SOCIAL CONVERSATIONS. L. Chen[1], M. Asgari[1], H. Dodge[2] *(1. Department of Pediatrics, Oregon Health & Science University - Portland (United States), 2. Massachusetts General Hospital, Harvard Medical School - Boston (United States))*

Background: The Internet-Based Conversational Engagement Clinical Trial (I-CONECT, www.I-CONECT.org, NCT02871921PI: Dodge) intervention was designed to deliver online conversation sessions to socially isolated older old to prevent the development of Alzheimer's Disease and Related Dementia (ADRD). We are interested in whether intervention effects participants' ability of focusing on a conversation. Semantic noise (SN) is a linguistic measurement that quantifies how well the conversation focuses on topics they are discussing. We hypothesized that by engaging in high frequent conversation which aimed to enhance cognitive reserve, the SN observed in older people's conversations with mild cognitive impairment (MCI) would resemble those with normal cognition (NC). **Method:** We analyzed transcriptions from a behavioral intervention randomized controlled trial, I-CONECT, which involved semi-structured conversations between facilitators and participants. In the project, the experimental group engaged in 30-minute semi-structured conversations (four times per week for 6 months) via video-chats. Every video-chat is oriented to a predefined topic which was provided in a standardized order (e.g., dancing is the 1st conversation topic in the 2nd week). Out of 186 subjects randomized into the trial, 64 participants were randomized into the experimental group. Among them, 52 participants (26 MCI and 26 normal based on NACC D1)

with sufficient recording quality during the 2nd week of the intervention (baseline) and during the last week (i.e., 24th) before the month 6 (M6) post-intervention assessments (post-trial assessments at M6) were used in this analysis. We utilized an automatic speech recognition (ASR) system to transcribe these recordings and measured each transcription's SN. We analyzed the statistical difference of MSN (mean SN) between participants with MCI and those with NC at baseline (2nd week) and M6 (24th week). **Results:** Using two-tailed t-test, we found that at the baseline, MSN in MCI group was significantly higher than NC group (MCI: 2.09(0.34), NC: 1.87(0.35), p-value: 0.024). After six months of social interaction, MCI and NC group were not significantly different (MCI: 1.81(0.47), NC: 1.95(0.47), p-value: 0.280). Moreover, in MCI group, baseline's MSN was significantly higher than M6' (p-value: 0.017), while, in NC group, there was no significant difference between baseline and M6 (p-value: 0.465). **Conclusions:** We showed that, through six months of social interaction, MCI group's MSN reduces from significantly higher than NC group at the baseline to not significantly different from NC group at M6. This indicates that the high dosage of interactive conversations reduces MSN in the MCI group. Quantitatively analyzing the impact of conversation frequency to MSN will be our future research direction.

LP114- DEVELOPMENT AND PRELIMINARY VALIDATION OF A VIRTUAL REALITY MEMORY TEST FOR ASSESSING VISUOSPATIAL MEMORY. K.W. Kim[1], J.D. Choi[2], J. Chin[3], B.H. Lee[3], C. Jee Hyun[4] *(1. Jeonbuk National University Medical School and Hospita - Jeonju (Korea, Republic of), 2. Seers Technology Company Ltd - Seongnam (Korea, Republic of), 3. Samsung Medical Center - Seoul (Korea, Republic of), 4. Korea Institute of Science and Technology - Seoul (Korea, Republic of))*

Background: Alzheimer's disease often presents with visuospatial memory impairment, but standard memory tests fail to capture its impact on everyday life adequately. **Methods:** To address the challenges of locating and recalling misplaced objects faced by patients, we introduced an innovative visuospatial memory assessment known as the Hidden Objects Test (HOT), conducted within a virtual environment. HOT scores were categorized into prospective memory, item free-recall, place free-recall, item recognition, and place-item matching. To validate the VR memory test, we compared HOT scores across Alzheimer's disease dementia (ADD), amnestic mild cognitive impairment (aMCI), and normal controls (NC), also contrasting them with conventional neuropsychological test results. Participants' virtual movement paths were tracked, assessing fundamental metrics like total distance, duration, and speed. We additionally conducted walking trajectory pattern analysis, including outlier and stay-point detection. **Results:** We developed the HOT to replicate a house's living room, evaluating participants' capacity to locate hidden objects. Preliminary findings revealed significant differences in total HOT scores among ADD patients (n=17), aMCI patients (n=14), and NC participants (n=15) ($p < 0.001$). The total HOT score displayed a positive correlation with traditional memory test results ($p < 0.001$). Analysis of walking trajectories indicated that ADD and aMCI patients often meandered instead of taking a direct route to the concealed objects. In terms of fundamental metrics, ADD patients exhibited significantly longer durations compared to NC participants ($p = 0.008$). Trajectory pattern analysis indicated a significantly higher count of outliers—trajectories deviating over 95% from the estimated path—in ADD patients compared to NC participants ($p = 0.002$). Moreover, the count of stay-points, indicating positions where participants remained stationary for over 2 seconds, was significantly higher in both ADD and aMCI patients compared to NC participants (ADD vs. NC: $p = 0.003$, aMCI vs. NC: $p = 0.019$). **Conclusion:** The HOT, which emulates real-life scenarios, demonstrates potential as an ecologically valid method for assessing visuospatial memory function in daily life. Analysis of walking trajectories suggests that individuals with ADD and aMCI tend to wander rather than pursuing a direct path to hidden objects. **Key words:** Alzheimer's disease, Virtual reality, Spatial memory, Spatial navigation, Head mounted display. **Disclosures:** The authors declared no competing interests. **References:** 1. Mrakic-Sposta S, et al. Front Aging Neurosci. 2018 Oct 1;10:282. doi: 10.3389/fnagi.2018.00282. 2. Liu Y, et al. Front Aging Neurosci. 2019 Oct 18;11:280. doi: 10.3389/fnagi.2019.00280.

LP115- ASSESSING THE IMPACT OF DONEPEZIL ON VISUOSPATIAL ABILITIES IN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT: A PRELIMINARY STUDY UTILIZING EYE-TRACKING METRICS. K.W. Kim[1], Q. Wang[1], B.S. Shin[1] *(1. Jeonbuk National University Medical School - Jeonju (Korea, Republic of))*

Background: There is limited supporting evidence regarding the impact of Cholinesterase Inhibitors (ChEIs) on cognitive test scores among individuals with Mild Cognitive Impairment (MCI). However, the existing trials and outcomes from previous meta-analyses exhibit certain limitations. Notably, the selection of MCI participants did not consistently involve the use of Alzheimer's disease (AD) biomarkers for diagnosis. This raises the possibility that the efficacy of ChEIs might be more pronounced for MCI cases linked to AD pathology, while potentially being less impactful for cases with diverse underlying causes of MCI. Additionally, the sensitivity of cognitive tests and clinical assessment scores, which were utilized as primary outcome measures, might not be optimal for capturing subtle changes in individuals with MCI. Therefore, a more nuanced approach is necessary, potentially incorporating surrogate markers that can discern the effects of ChEIs more sensitively compared to traditional cognitive tests or clinical rating scores. **Methods:** To address these gaps, we propose the implementation of a randomized controlled trial. This trial aims to meticulously evaluate the effects of donepezil—an established ChEI—specifically in patients diagnosed with MCI attributed to AD pathology, confirmed through amyloid positron emission tomography (PET) scans. We conducted an assessment using eye-tracking metrics during the administration of the modified Rey Complex Figure Test (RCFT). The main objective was to observe any alteration in the ratio of fixations made within the working space relative to the perceptual space while participants engaged with the simplified RCFT. This ratio change was tracked over a span of 12 weeks, starting from baseline. Our analytical focus was primarily centered on evaluating the divergence in change patterns between the donepezil and control groups in terms of the aforementioned primary outcome. The statistical analysis was carried out using the Mann-Whitney U test. **Results:** Our initial findings from 16 participants (8 in each study arm) revealed a significant observation. Notably, the ratio of fixations, calculated as the quotient between fixations within the working space and those within the perceptual space, exhibited a substantial increase in the group receiving donepezil after the 12-week intervention period ($p = 0.028$). Furthermore, when examining the alteration in the aforementioned fixation ratio between the baseline and the 12-week mark, the donepezil

group displayed a notably higher change compared to the control group (p = 0.007). These outcomes contribute to our evolving understanding of the effects of donepezil in this context. **Discussion:** This study was designed to determine whether eye-tracking metrics can detect the effect of donepezil on visuospatial dysfunction more sensitively in patients with MCI. **Key words:** Cholinesterase inhibitors, mild cognitive impairment, eye-tracking metrics. **Clinical Trial Registratry:** KCT0006236; https://cris.nih.go.kr. **Disclosures:** This research was supported by Eisai Korea Inc. **References:** Kim et al. Trials 2022 Sep 27;23(1):813. doi: 10.1186/s13063-022-06781-0.

LP116- THE EFFECT OF ROBOT-BASED DIGITAL COGNITIVE TRAINING ON COGNITIVE PERFORMANCE OF DEMENTIA PATIENTS. J.W. Oh[1,2], J.H. Lee[3], M.H. Hong[4], W.S. Kang[5], J.W. Kim[3,5] *(1. Department of Neurology, Brigham and Women's Hospital - Boston, Massachusetts (United States), 2. Whydots Inc. - Bucheon (Korea, Republic of), 3. Department of Psychiatry, Kyung Hee University Hospital - Seoul (Korea, Republic of), 4. Seodaemun-gu Center for Dementia - Seoul (Korea, Republic of), 5. Department of Psychiatry, Kyung Hee University College of Medicine - Seoul (Korea, Republic of))*

Background: Cognitive training is known to be effective in improving or preserving the cognitive functions of early-stage dementia patients. Robot PIO (Whydots Inc., South Korea) is a parrot-inspired interactive robot that can communicate with patients and offer an automated, personalized digital cognitive training program [1]. This study aims to evaluate the effectiveness of the robot-based digital cognitive training program in improving dementia patients' cognitive performance. **Methods:** This study compared the domain-specific cognitive performance of subjects before and after their participation in the robot-based cognitive training program. Thirty-six subjects with CDR 0.5 or 1 were enrolled through a public dementia center in Seoul, Korea, and twenty-seven subjects completed the robot PIO-based cognitive training program, which was conducted twice a week, 50 min/session, for six weeks [1]. Subjects' cognitive performances were evaluated at baseline and after completing the program with the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) neuropsychological battery, which enabled comprehensive assessment of cognitive function through eight different neuropsychological tests (J1-J8) evaluating verbal fluency, naming, mental state, word recognition/memory/recall, and constructional praxis/recall [2]. **Results:** The mean age of the study population was 77.1 (SD 6.6) years, and 59.3% of the subjects were female. The average years of education was 6.4 (SD 4.5) years, and the average CDR at baseline was 0.69 (SD 0.25). After completing the robot-based cognitive training program, there was significant improvement in naming (J2 Boston Naming Test; before: 7.6 (SD 3.3), after: 8.3 (SD 3.5), p=0.01), Mini-Mental State Examination (J3; before: 20.1 (SD 4.5), after: 20.7 (SD 5.1), p=0.03), and word list recognition (J7; before: 5.9 (SD 3.1), after: 6.5 (SD 3.1), p=0.01). Other test scores were stable without significant change. **Conclusion:** Our results suggest that the automated digital cognitive training program based on social robot PIO may improve or preserve the cognitive function of patients in the early stages of dementia. This implies a potential use of robots and related digital health technology to reduce the public health burden of dementia by assisting patient's cognitive training. **Key words:** Digital health, Social robot, Cognitive training program. **Disclosures:** JWO and MHH are former employees of Whydots Inc. Otherwise, the authors have no conflicts of interest. **References:** 1. Dementia Care Robot PIO. Whydots Inc.; 2023. Accessible: https://www.whydots.com/en/robot-pio-1; 2. Lee, et al. The J of Gerontology: Series B 2002; 57(1):47-53. https://doi.org/10.1093/geronb/57.1.P47

LP117- THE DIGITAL LITERACY PREDICTS THE QUALITY OF LIFE IN NORMAL OLD AGE GROUP BUT NOT IN DEMENTIA GROUP. L. So-Yeong[1], L. Jung-In[1], L. Jun-Young[1,2] *(1. SMG-SNU Boramae Medical Center - Seoul (Korea, Republic of), 2. Department of Psychiatry, Seoul National University College of Medicine - Seoul (Korea, Republic of))*

Background: This study used to test the digital literacy levels can predict the quality of life in the old age population according to the level of cognitive impairment. **Methods:** The survey was conducted by dividing into 3 groups (Normal, MCI, AD) to measure changes according to cognitive decline. A total of 283 participants were recruited in this study (NC, 121; MCI, 88; AD, 93). One-way ANOVA and multivariate multiple regression analysis were conducted to examine the relationship between the quality of life and literacy. All participants completed a survey on basic demographic statistical questions, EQ-5D, digital literacy, and health literacy. **Results:** First, EQ-5D Index score($F=28.646$, $p<.001$), digital literacy score($F=29.883$, $p<.001$), and health literacy score($F=3.098$, $p=.047$) showed significant differences in the three groups of NC, MCI, and AD. Second, all of NC ($F=90.05$, $p<.001$), MCI ($F=22$, $p<.001$), and AD ($F=54.05$, $p<.001$), digital literacy had a significant effect on health literacy. Third, in NC, EQ-5D Index score was influenced by both digital literacy ($p=.003$) and health literacy($p=.003$). However, EQ-VAS was only influenced by health literacy ($p<.001$). Fourth, in MCI, EQ-5D Index score wasn't affected by both digital literacy ($p=.056$) and health literacy ($p=.269$). However, EQ-VAS was only affected by digital literacy ($p<.001$). Fifth, in AD group, EQ-5D Index score wasn't affected both by digital literacy ($p=.329$) and health literacy ($p=.063$), and EQ-VAS also wasn't affected by digital literacy ($p=.272$) and health literacy($p=.123$). **Conclusion:** As cognitive decline worsens, literacy scores decrease, ultimately weakening the association between literacy and quality of life. Consequently, digital literacy significantly predicts both EQ-5D Index score and EQ-VAS in NC, but the same predictive power does not hold true for the dementia group. **Key words:** Digital literacy, Health literacy, EQ-5D, Alzheimer's, Mild cognitive impairment, Cognitive impairment patient, dementia. **Disclosures:** This work was supported by the Technology Innovation Program (or Industrial Strategic Technology Development Program-The bio industry technology development) (20018143) funded By the Ministry of Trade, Industry & Energy(MOTIE, Korea). The authors have no potential conflicts of interest to disclose. **References:** 1. The Report on the Digital Divide (2022). from the National Information Society Agency, Korea. https://www.nia.or.kr/site/nia_kor/ex/bbs/View.do?cbIdx=81623&bcIdx=25353&parentSeq=25353. 2. Neter, E., & Brainin, E. (2012). eHealth literacy: extending the digital divide to the realm of health information. Journal of medical Internet research, 14(1), e19.

LP131- OBSERVER-REPORTED OUTCOME OF FUNCTIONAL DECLINE USING CONTINUOUS EXPERIENCE SAMPLING: FINDINGS FROM THE RADAR-AD STUDY. S. Sikkes[1,2], M. Postema[1], M. Tewolde[1], M. Verrijp[3], M. Muurling[1], C. De Boer[1], S. Vairavan[4], D. Aarsland[5], A.K. Brem[5], G. Wittenberg[4], M. Dubbelman[6], R. Jutten[7], P. Scheltens[1], P.J. Visser[1], W. Van Der Flier[1] *(1. Amsterdam UMC - Amsterdam (Netherlands), 2. VU University - Amsterdam (Netherlands), 3. Brain Research Center - Amsterdam (Netherlands), 4. Janssen Neuroscience R&D - Titusville, NJ (United States), 5. Kings College London - London (United Kingdom), 6. Brigham and Womens Hospital - Boston, MA (United States), 7. Harvard Medical School - Boston, MA (United States))*

Background: The FDA recently underlined the importance of capturing clinically meaningful concepts in clinical trials (FDA guidance, April 2023). One essential clinical outcome measure in Alzheimer's disease (AD) is functional decline, as captured with instrumental activities of daily living (IADL). These everyday activities, including managing finances and handling technology strongly rely on cognitive abilities, and are typically measured using single-time point subjective rating scales, such as the study-partner reported Amsterdam IADL Questionnaire (A-IADL-Q). Continuous sampling of people's current experiences in their natural environment could provide improved real-time IADL measurements whilst minimizing response burden. The aim of this study was to compare the A-IADL-Q to a set of continuous experience sampling versions of the A-IADL-Q, with regards to construct validity, measurement error and known groups validity. **Methods:** Data was collected as part of the cross-sectional RADAR-AD study. Amyloid biomarker-confirmed participants were included with preclinical AD, prodromal AD, and mild-to-moderate AD, as well as healthy controls, from 13 clinical sites in 12 European countries. Two versions of the A-IADL-Q were completed by the study partner: (1) the A-IADLQSV30, a 30-item (cross-culturally) validated version, (2) Experience sampling short forms of the A-IADL (A-IADL-QES) consisting of 7-8 items, constructed balancing content and difficulty level. Four different versions were administered weekly during 8 weeks. Both A-IADL-QSV30 and A-IADL-QES were scored using item response theory scoring, resulting in a latent trait score and standard error. Correlation coefficients between IADL scores, age, sex, education and MMSE were calculated. Clinical IADL classification according to previously established cut-off values was compared between both forms. Linear regression analyses were performed with A-IADL-Q scores as dependent variable, and with diagnostic group, version, age, sex and gender as independent variables. **Results:** A total of 222 individuals (49% female, M(age)=69±SD=8) were included. Both AIADL-Q versions showed low correlations with education (range -0.01;0.05), and age (range -0.05;-0.02) and high correlations with MMSE (range 0.69;0.74), supporting construct validity. For the A-IADL-QES, 76% of respondents had a standard error >5, indicating considerate measurement imprecision. In contrast, for the A-IADL-QSV30, only 0.9% of respondents had a standard error >5. As expected, healthy controls obtained the highest A-IADL-Q scores (M(A-IADLQSV30)=68.20±2.63; M(A-IADL-QES)=63.16±1.74), reflecting 'no IADL problems'. Participants with preclinical AD had slightly more IADL problems (M(A-IADLQSV30=66.11±3.90; M(A-IADL-QES)=61.76±3.73), but also scored within the 'no IADL problems' category. For prodromal AD, the mean score was reflective of 'mild IADL problems' (M(A-IADL-QSV30=58.62±7.12; M(A-IADL-QES)=56.58±7.12), and for mild-moderate AD scores fell in the 'moderate IADL problems' range (M(A-IADLQSV30=46.81±7.96; M(A-IADL-QES)=46.21±8.50). Linear regression showed that both versions differentiated between diagnostic groups and healthy controls, when controlling for age, sex and education (all p-values <.05). **Conclusions:** We compared different administration modalities of the A-IADL-Q, using an experience sampling design. Our findings support the use of experience sampling for IADL with regards to construct and known groups validity, as well as clinical IADL classification. Measurement precision was compromised in the experience samplingversion, and future studies should focus on whether this is reflective of day-to-day fluctuations, which could aid in enhancing the measurement of clinically meaningful concepts.

LP133- A ONE-STOP-SHOP FOR TELEHEALTH GUIDED APOE TESTING, BLOOD BASED BIOMARKERS, AND MULTI-DOMAIN LIFESTYLE INTERVENTION: EARLY LEARNINGS FROM A PROOF-OF-CONCEPT. A. Rao[1], L. Anderson[1], T. Wilkes[1], S. Verdooner[1] *(1. Neurovision Inc - Sacramento (United States))*

Background: With the ongoing limitations of our healthcare system, the care gaps are often widest with behavioral and cognitive care. Unfortunately, this has led to long wait times and delayed care which can ultimately limit treatment options when cognitive impairment progresses. Solutions for accessible, scalable and affordable cognitive care are critical to prevent further disparities and fully realize the potential of emerging advancements. **Methods:** To address clinical gaps in care, BrainHealth.net was created as a one-stop-shop for patients and their referring physicians to access APOE testing, blood-based biomarkers (BBMs), and lifestyle intervention services via telehealth. The platform and telehealth program utilizes a HIPAA compliant electronic medical record (EMR) and supports video care visits, wearable data integration, and daily patient brain health education and engagement. For this study, patients were recruited by direct physician electronic referral after being evaluated by a neurologist and through word-of-mouth. All patients underwent a risk assessment by a trained Brain Health Educator (BHE) who typically was a RN or allied healthcare professional. Patients opted-in to share wearable data and participate in a 3-month telehealth lifestyle intervention program aimed at improving diet, sleep, and exercise. Patients were also invited to participate in a Laboratory Developed Test (LDT) for APOE genotyping (e2, e3, e4), using a simple cheek-swab at home, and online counseling. A panel of BBMs and rule out blood tests were also available to all patients. **Results:** The proof of concept began through a multi-site recruitment process, and a total of 12 patients were referred, and 8 were enrolled, 4 patients were referred directly by a neurologist, and 4 patients were referred by word-of-mouth. After 2 months, there was no attrition in the program and there were 138 logins per patient into the electronic medical record system operated by Brainhealth.net. The average duration of a telehealth visit was 30-45 minutes, and patients had completed 5 tele brain health lifestyle intervention sessions which had compromised of diet, sleep, exercise education modules. 4 patients engaged daily with the BHE and provided insight into their daily diet, sleep, and exercise habits. Patients were enrolled from 4 different geographic states across the United States. Ages ranged from 59-79, 62% white, 38% Asian, 25% Male, 75% Female. Patient's chronic medical conditions included: MCI, ADRD, Stroke, Autoimmune encephalitis, Multiple Sclerosis, Epilepsy. During submission of this research, patients were offered APOE

genotyping and a BBM panel. **Conclusion:** This proof of concept is an alternative care access and delivery model for patients seeking cognitive risk assessment, APOE genotyping, BBMs, and lifestyle intervention program all from a "one-stop-shop". Brainhealth.net works collaboratively with health systems and physician practices to create a modular add-on service program to augment busy clinical practices that may have long wait times and limited staff to provide cognitive care services and lifestyle intervention. As the population ages, there will be increased demand for appropriate screening, lab tests and documentation to optimize the patient journey. This workflow and proof of concept provides a framework to address clinical gaps and improve patient outcomes. **Key words:** telehealth, care delivery, brainhealth, healthsystem, clinical workflow, proof of concept, apoe, blood-based biomarkers, lifestyle intervention. **Conflicts of Interest:** AR and TW are consultants to Neurovision. **References:** 1. Alzheimer's Association. 2023 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2023;19(4). DOI 10.1002/alz. 2. Dall, Timothy M et al. "Supply and demand analysis of the current and future US neurology workforce." Neurology vol. 81,5 (2013): 470-8. doi:10.1212/WNL.0b013e318294b1cf

BEYOND AMYLOID AND TAU

P193- ANGIOGENIC MECHANISMS IN ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW OF NEUROPATHOLOGICAL EVIDENCE.

A. Kapoor[1], D. Nation[1]
(1. University of California, Irvine - Irvine (United States))

Background & Objectives: Cerebrovascular dysfunction can trigger angiogenic processes and contribute to the pathophysiology of Alzheimer's disease. Whether the process of angiogenesis is beneficial or detrimental in the context of Alzheimer's disease remains unknown. Moreover, pathological hallmarks of Alzheimer's disease, such as amyloid beta (Aβ), may interact with angiogenic cells and proteins to influence disease processes. In this review, we examined studies utilizing post-mortem brain tissues of individuals with Alzheimer's disease to investigate expression of angiogenic markers and explore the role of angiogenesis in Alzheimer's disease. **Methods:** Using Medline (1946 to August 04, 2021), the literature was systematically searched for articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Angiogenesis and Alzheimer's disease terms were searched as keywords and mapped to MeSH headings. A total of 2203 records were screened; 209 studies were assessed for eligibility, 120 met all criteria and 20 specifically examined post-mortem brain tissue and were included in this review. **Results:** The included studies evaluated multiple angiogenesis markers in different brain regions, including hippocampus, frontal cortex and precuneus, in both white and gray matter. Four studies consistently showed reduced pericyte protein platelet derived growth factor receptor beta (PDGFRβ) in Alzheimer's disease brains and two found corresponding increase in the levels of ligand PDGF-BB. Eight studies demonstrated elevated levels of vascular endothelial growth factors (VEGF), with two studies showing reduction in VEGF expression and others observing an association between Aβ levels and VEGF-A deposition. Four studies showed conflicting findings on expression of endothelin-1 (EDN1) in Alzheimer's disease brains. **Discussion:** This systematic review highlights the key angiogenic proteins and signaling pathways that may be involved in the pathogenesis of Alzheimer's disease based on neuropathological evidence. The limitations of the current literature include the lack of distinct delineation between Alzheimer's disease, vascular dementia and mixed dementia, which may lead to differential expression of angiogenic proteins. Future studies should also consider disease severity, given that levels of growth factors, such as VEGF, may be elevated early in disease processes but may decrease in severe cases. Moreover, these studies suggest co-accumulation and interaction of Aβ with angiogenic proteins, which could elucidate the role of vascular mechanisms in the development of Alzheimer's disease and reveal potential therapeutic targets.

P194- DO MOUSE DATA LIE? FOR BUNTANETAP THEY TOTALLY PREDICT HUMAN OUTCOMES ALL THE WAY TO CLINICAL EFFICACY.

M. Maccecchini[1], C. Fang[1]
(1. Annovis Bio - Berwyn (United States))

Background: Overexpression of neurotoxic proteins drives downstream events that dysregulate axonal transport, lead to inflammation, nerve cell death, and loss of function [1]. By inhibiting the translation of neurotoxic aggregating proteins - amyloid precursor protein, tau, alpha-synuclein etc., buntanetap restores axonal transport, lowers inflammation, and protects nerve cells from dying. In three double-blind, placebo controlled, phase 1/2 clinical studies in both Alzheimer (AD) and Parkinson (PD) patients buntanetap showed statistically significant improvement in movement in PD and cognition in AD [2]. **Method:** Here we want to compare our animal data with our human data to evaluate if animal models are predictive of human outcomes. We are comparing data from APP/PS1 AD mice [3], Ts65Dn Down Syndrome mice [4], and two Phase 1 /2 double-blind, placebo-controlled human AD studies: Discover study run by ADCS and AD/PD study run by Annovis. **Result:** Buntanetap is a translational inhibitor of APP by pulse-chase experiment in mice and by stable isotope labeling kinetics (SILK) in humans [5]. Our drug inhibits APP/Abeta, tau/pTau in a dose-dependent manner in animals [3, 4, 6] and humans [7]. The biomarker dose-response is seen at a much higher dose than the efficacy dose-response. We see a statistical improvement in cognition in animals and in humans [2, 3]. Buntanetap is currently being developed in Phase 3 clinical trial in PD and Phase 2/3 in AD. **Conclusion:** In all our studies conducted to date in mice and humans, we have obtained consistent data on the mechanism of action, on lowered levels of neurotoxic aggregating proteins, and on improvements in cognition after buntanetap treatment. **Disclosure:** Maria Maccecchini and Cheng Fang are employees of Annovis Bio. **References:** 1. Chen XQ, Barrero CA, Vasquez-Del Carpio R, Reddy EP, Fecchio C, Merali S, Deglincerti A, Fang C, Rogers J, Maccecchini ML. Posiphen Reduces the Levels of Huntingtin Protein through Translation Suppression. Pharmaceutics. 2021 Dec 7;13(12):2109. doi: 10.3390/pharmaceutics13122109. PMID: 34959389; PMCID: PMC8708689. 2. Fang C, Hernandez P, Liow K, Damiano E, Zetterberg H, Blennow K, Feng D, Chen M, Maccecchini M. Buntanetap, a Novel Translational Inhibitor of Multiple Neurotoxic Proteins, Proves to Be Safe and Promising in Both Alzheimer's and Parkinson's Patients. J Prev Alzheimers Dis. 2023;10(1):25-33. doi: 10.14283/jpad.2022.84. PMID: 36641607. 3. Teich AF, Sharma E, Barnwell E, Zhang H, Staniszewski A, Utsuki T, Padmaraju V, Mazell C, Tzekou A, Sambamurti K, Arancio O, Maccecchini ML. Translational inhibition of APP by Posiphen: Efficacy, pharmacodynamics, and pharmacokinetics in the APP/PS1 mouse. Alzheimers Dement (N Y). 2018 Jan 18;4:37-45. doi: 10.1016/j.trci.2017.12.001. PMID: 29955650; PMCID: PMC6021259. 4. Chen XQ, Salehi A, Pearn ML, Overk

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P195- FLUID BIOMARKER RESULTS FROM AN OPEN-LABEL PILOT STUDY OF SENOLYTIC THERAPY FOR ALZHEIMER'S DISEASE, STOMP-AD. M.E. Orr[1,2,3], V.R. Garbarino[4,5], J.P. Palavicini[4], T.F. Kautz[4,5], S.K. Dehkordi[5,6], H. Zare[5,6], P. Xu [7,8], B. Zhang[7,8], J. Melendez[9,10], N. Barthelemy[9,10], R.J. Bateman[9,10], M.M. Gonzales[5,11] *(1. Wake Forest University School of Medicine, Gerontology and Geriatric Medicine, - Winston-Salem (United States), 2. Wake Forest Alzheimer's Disease Research Center - Winston-Salem (United States), 3. Salisbury VA Medical Center - Salisbury (United States), 4. University of Texas Health Science Center at San Antonio, Department of Medicine, - San Antonio (United States), 5. Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases - San Antonio (United States), 6. University of Texas Health Science Center at San Antonio Department of Cell Systems and Anatomy, - San Antonio (United States), 7. Icahn School of Medicine at Mount Sinai, Department of Genetics and Genomic Sciences, - New York (United States), 8. Mount Sinai Center for Transformative Disease Modeling - New York (United States), 9. Washington University School of Medicine, Department of Neurology - St Louis (United States) - St Louis (United States), 10. The Tracy Family SILQ Center - St Louis (United States), 11. University of Texas Health Science Center at San Antonio, Department of Neurology - San Antonio (United States))*

Background: Senescent cells accumulate in the body with advanced age and contribute to disease and dysfunction [1]. Removing senescent cells with dasatinib and quercetin (D+Q) reduces neuropathological burden in mouse models of Alzheimer's disease (AD) [2]. We previously reported that orally administered D+Q was well tolerated in participants with early-stage AD, and that D was detected in cerebrospinal fluid (CSF) after treatment [3]. Here we analyzed exploratory outcome measures of proteomics, lipidomics and transcriptomics in blood and CSF to gain preliminary insights into broad treatment effects and begin developing biomarker panels associated with senescent cell clearance. **Methods:** We analyzed blood and CSF from the five participants with early-stage AD that completed the open-label pilot trial [3, 4]. CSF levels of Aβ40, Aβ42, total and phosphorylated tau were evaluated before and after treatment using multiple platforms including Lumipulse, Simoa, and multidimensional mass spectrometry. Target engagement was assessed by investigating post-treatment changes in plasma and CSF markers of senescence with Meso Scale Discovery Immunoassays, lipidomics and transcriptomics. Paired t-tests were used to examine differences in biomarker levels pre- and post-treatment. **Results:** In four out of five participants, CSF levels of Aβ42 increased and the p-tau181/ Ab42 ratio decreased. Lipidomics detected 194 lipid species; ten significantly changed in abundance with treatment when applying an unadjusted $p<0.05$ cut-off. In peripheral blood mononuclear cells, we detected treatment-dependent differences in the expression of 7 of 53 genes involved in the conserved transcriptional response to adversity, which is activated by chronic stress. **Conclusions:** Exploratory outcomes on fluid biomarkers suggest that senescent cell clearance improves amyloid AD biomarkers, modulates lipid species and the cellular response to chronic stress. Fully powered, double-blind, placebo-controlled studies will be critical to confirm these preliminary findings and evaluate the potential of disease modification with the novel approach of targeting cellular senescence in AD [5], e.g., NCT04685590. **Key words:** biology of aging, cellular senescence, geroscience, biomarkers. **Clinical Trial Registry:** NCT04685590. https://clinicaltrials.gov. **Disclosures:** This work was made possible by grants through the Alzheimer's Drug Discovery Foundation GC-201908-2019443, the UTHSCSA Center for Biomedical Neuroscience, the San Antonio Claude D. Pepper OAIC (P30AG044271) and the Tracy Family SILQ Center at Washington University. **References/** 1. T. Tchkonia, J. L. Kirkland, Aging, Cell Senescence, and Chronic Disease: Emerging Therapeutic Strategies. JAMA 320, 1319-1320 (2018). 2. N. Musi et al., Tau protein aggregation is associated with cellular senescence in the brain. Aging Cell 17, e12840 (2018). 3. M. Orr et al., Senolytic therapy to modulate the progression of Alzheimer's Disease (SToMP AD) - Outcomes from the first clinical trial of senolytic therapy for Alzheimer's disease. Res Sq, (2023). 4. M. M. Gonzales et al., Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD): A Pilot Clinical Trial. J Prev Alzheimers Dis 9, 22-29 (2022). 5. M. M. Gonzales et al., A geroscience motivated approach to treat Alzheimer's disease: Senolytics move to clinical trials. Mech Ageing Dev 200, 111589 (2021).

P196- PLASMA AND CEREBROSPINAL FLUID PROTEOMIC ASSOCIATION DURING ALZHEIMER'S DISEASE (AD) PROGRESSION SUGGESTS POSSIBLE NEW TARGETS FOR TREATING AD PATIENTS. Y. Wang[1], R. Gonzalo[2], C. Minguet[2], A.M. Ortiz[2], S. Lohr[1], M. Boada[3], O. López[4], A. Paez[2], J. Loscos[5], J. Canudas[5], M. Pascual[5], J. Terencio[2], M. Costa[2], C. Feng[1], 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), 5. Araclon, a Grifols company - Zaragoza (Spain))*

Background: Despite extensive research over decades, our understanding of the mechanisms of Alzheimer's disease (AD) is still limited. One of the reasons is that the brain is a highly protected organ, nearly isolated from the rest of the body by the blood-brain barrier (BBB). The crosstalk between plasma and cerebrospinal fluid (CSF) proteomes is not well studied partially due to the challenges to obtain paired plasma and CSF samples. Here we took the advantage of two AD clinical trials to study the relationships between the plasma-CSF proteomes

during AD progression and/or in response to AD treatment and compared the results to a recent study with age and sex matched AD patients and healthy controls (HC) [1]. **Methods:** Paired plasma and CSF samples from three AD populations: AMBAR (Alzheimer's Management by Albumin Replacement, phase IIb/III, treated with Plasma exchange with Albumin replacement—PE-Alb, n=134), ABvac40 (phase II, treated with a vaccine against amyloid-beta 40, n=92), Emory-AD (n=17), and one HC population (Emory-HC, n=18) were included in this analysis. The aptamer-based proteomic technology SomaScan (SomaLogic, Boulder, Colorado, US) was used to measure more than 7k proteins from both fluids. The plasma-CSF correlations were measured by Spearman correlation (rho). Absolute rho>0.5 and a BH (Benjamini-Hochberg) adjusted p-value<0.05 were the criteria used to identify proteins with median-to-high plasma-CSF correlation in AD patients from AMBAR and ABvac40 samples at baseline. Pathway enrichment analysis was then performed using Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome databases. The difference in plasma-CSF correlations of identified proteins between HC and AD patients or among different AD severity groups were tested by linear mixed model or paired t-test, respectively. Finally, the PE-Alb treatment effect on plasma-CSF correlations was examined by a linear mixed model. **Results:** A total of 70 proteoforms with significant median-to-high plasma-CSF correlations in AD patients were identified. They were mostly originating from peripheral tissues and involved in immune-related and digestion pathways. Correlations for these identified proteins were significantly higher in each of these 3 AD populations than the correlation in age-&sex-matched HC (all p.values<0.01). Furthermore, we observed significantly higher plasma-CSF proteomic correlation in mild AD patients than the correlation in MCI (mild cognitive impairment) patients (p.value=0.003, from ABvac40 baseline data), but not between mild-AD and moderate-AD patients (p.value=0.637) nor during one-year progression in placebo group (p.value=0.064, from AMBAR study). Intriguingly, they were significantly decreased after one year of PE-Alb treatment in treated group comparing to the correlation in placebo group (p.value=0.003). **Conclusion:** Our analyses identified 70 proteoforms with median-to-high plasma-CSF correlations and these correlations were increased in AD patients compared to HC. We also observed that PE-Alb treatment decreased these correlations to the levels closer to those observed in HC. These findings emphasize the important role of plasma-CSF proteomic crosstalk during early AD progression and suggest possible new targets for AD therapy. **Key words:** Alzheimer's disease, proteomics, plasma-CSF proteomic association. **Disclosures:** Y.W., S.L., C.F., and B.L. are full-time employees of Alkahest, a Grifols company, R.G., C.M., P.L., A.M.O., A.P., J.T., and M.C. are full-time employees of Grifols and J.L., J.C., and M.P. are full-time employees of Araclon, a Grifols company. **References:**

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P197- WHOLE TRANSCRIPTOMIC CELL FREE MESSENGER RNA CHARACTERIZATION OF ALZHEIMER'S DISEASE IN CEREBROSPINAL FLUID COMPARED TO PLASMA FROM HUMAN SUBJECTS.

R. De Sota[1], R. Rissman[2], J. Brewer[2], S. Khoury[1], S. Toden[1], J. Sninsky[1] *(1. Molecular Stethoscope - South San Francisco (United States), 2. University of California, San Diego - San Diego (United States))*

Background: The development of effective therapies and diagnostics for Alzheimer's Disease (AD) has been demanding due to an incomplete understanding of the underlying multifactorial pathology and the brain tissue's limited accessibility. Extracellular carriers in biological fluids have diverse cargoes including different ribotypes and have been implicated in intercellular communication and signals of disrupted cellular homeostasis. We previously demonstrated AD subjects have a distinct plasma cell free messenger RNA (cf-mRNA) profile compared to non-cognitively impaired (NCI) individuals and developed a diagnostic classifier using machine learning. **Objectives:** We sought to determine if cerebrospinal spinal fluid (CSF) would be an enriched source of cf-mRNA from the brain which may provide granular insight into the molecular dysregulations underlying AD pathology. We then considered their prioritization for inclusion in feature selection for cf-mRNA classifiers developed from human plasma. **Methods:** Human CSF and plasma samples were collected from 45 AD and 12 NCI subjects of similar age distribution from University of California San Diego. Thirteen of the AD subjects had matched CSF and plasma. RNA was isolated from CSF and plasma then exon enrichment libraries were generated and sequenced. Using our cf-mRNA sequencing machine learning platform, we examined the cf-mRNA composition of CSF and plasma, and then performed comparative analysis of tissue- and cell-associated cf-mRNA transcripts. Principal Component Analysis (PCA) analysis was used to discern gene transcript differences between matched CSF and plasma samples. GTEx and Tabula Sapiens datasets were used to estimate the abundance of brain- and cell-associated transcripts. Differential expression analysis was performed to identify differentially expressed genes and associated biological pathway analyses (Gene Ontology, Reactome and KEGG) were determined. Logistic regression with L2 regularization was performed to highlight the key gene transcripts involved. **Results:** PCA analysis revealed human CSF cf-mRNAs were distinct from plasma cf-mRNA. Lack of cf-mRNA from circulating cells in blood permitted a marked increase in detection sensitivity of brain associated CSF cf-mRNA compared to plasma. We identified 2211 dysregulated genes in the CSF cf-mRNA of AD patients. CSF cf-mRNAs were enriched in biological processes associated with AD, including brain development, synaptic signaling, viral mRNA translation, and vesicle-mediated transport. We identified 1055 correlated genes in the CSF and plasma cf-mRNA transcriptomic profile across AD patients. We evaluated the expression levels of retroelement nucleocapsid genes believed to be involved in memory consolidation and synaptic plasticity. The absence of cf-mRNA from circulating cells in plasma resulted in a 5-fold higher relative detection of nucleocapsid gene transcripts in CSF compared to plasma. Of particular note, ARC, RTL8C, and PNMA2 nucleocapsid genes were differentially expressed in AD. **Conclusion:** This is the first study to characterize the cf-mRNA transcriptome in CSF and compare cf-mRNA of matched CSF and plasma from human AD subjects. CSF cf-mRNA pathway analysis recapitulates known mechanisms of AD. Matched CSF and plasma cf-mRNA

analysis further highlights the increased presence of brain derived cell free mRNA transcripts in both CSF and plasma. The detection of retroelement nucleocapsid gene transcripts adds to the accumulating evidence for the involvement of extracellular retroelements in AD pathology.

P198- CSF PROTEOMICS IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE HIGHLIGHTS PARALLELS WITH SPORADIC DISEASE.

C. Teunissen[1], E.L. Van Der Ende[2], S.I.'. Veld[2], I. Hanskamp[2], S. Van Der Lee[3,4], J. Dijkstra[5], J.C. Van Swieten[6], D.J. Irwin[7], A. Chen-Plotkin[7], W.T. Hu[8], A. Lemstra[9], Y.A.L. Pijnenburg[9], W.M. Van Der Flier[9,10], M. Del Campo[9,11], L. Vermunt[2,9] *(1. Amsterdam UMC - Amsterdam (Netherlands), 2. Neurochemistry Laboratory, Department of Clinical Chemistry, Amsterdam Neuroscience, Amsterdam UMC, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 3. lzheimer Center Amsterdam, Department of Neurology, Amsterdam UMC, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 4. Genomics of Neurodegenerative Diseases and Aging, Human Genetics, Amsterdam UMC, Vrije Universiteit Amsterdam - Amsterdam (Pays-Bas) - Amsterdam (Netherlands), 5. Genomics of Neurodegenerative Diseases and Aging, Human Genetics, Amsterdam UMC, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 6. Alzheimer Center and Department of Neurology, Erasmus University Medical Center - Rotterdam (Netherlands), 7. Department of Neurology, Perelman School of Medicine, University of Pennsylvania - Philadelphia (United States), 8. Department of Neurology, Emory University School of Medicine - Atlanta (United States), 9. Alzheimer Center Amsterdam, Department of Neurology, Amsterdam UMC, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 10. Department of Epidemiology and Data Science, Amsterdam Neuroscience, Amsterdam UMC, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 11. Barcelonabeta Brain Research Center (BBRC) - Barcelona (Spain))*

Introduction: Autosomal dominant Alzheimer's disease (ADAD) offers a unique opportunity to study pathophysiological changes in a relatively young population with few comorbidities. A comprehensive investigation of proteome changes occurring in ADAD could provide valuable insights into AD-related biological mechanisms and uncover novel biomarkers and therapeutic targets. Furthermore, ADAD might serve as a model for sporadic AD, but in-depth proteome comparisons are lacking. We aimed to identify dysregulated CSF proteins in ADAD and determine the degree of overlap with sporadic AD. **Methods:** We measured 1472 proteins in CSF of PSEN1 or APP mutation carriers (n=22) and age- and sex-matched controls (n=20) from the Amsterdam Dementia Cohort using proximity extension-based immunoassays (PEA) by Olink. We compared protein abundance between groups with two-sided t-tests and identified enriched biological pathways. Using the same protein panels in paired plasma samples, we investigated correlations between CSF proteins and their plasma counterparts. Finally, we compared our results with recently published PEA data from an international cohort of sporadic AD (n=230) and non-AD dementias (n=301). All statistical analyses were false discovery rate-corrected. **Results:** We detected 66 differentially abundant CSF proteins (65 increased, one decreased) in ADAD compared to controls ($q<0.05$). The most strongly upregulated proteins (fold change >1.8) were related to immunity (CHIT1, ITGB2, SMOC2), cytoskeletal structure (MAPT, NEFL) and tissue remodeling (TMSB10, MMP-10). Significant CSF-plasma correlations were found for the upregulated proteins SMOC2 and LILR1B. 36 of the 66 differentially expressed proteins had been previously measured in the sporadic dementias cohort, 34 of which (94%) were also significantly upregulated in sporadic AD, with a strong correlation between the fold changes of these proteins in both cohorts ($rs=0.730$, $p<0.001$). 29 of these 36 proteins (81%) were also upregulated among non-AD patients with suspected AD co-pathology. **Conclusions:** This CSF proteomics study demonstrates substantial biochemical similarities between ADAD and sporadic AD, suggesting involvement of the same biological processes. Besides known AD-related proteins, we identified several relatively novel proteins, such as TMSB10, MMP-10 and SMOC2, which have potential as novel biomarkers. With shared pathophysiological CSF changes, ADAD study findings might be translatable to sporadic AD, which could greatly expedite therapy development. **Disclosures:** Research of CET is supported by the European Commission (Marie Curie International Training Network, grant agreement No 860197 (MIRIADE), Innovative Medicines Initiatives 3TR (Horizon 2020, grant no 831434) EPND (IMI 2 Joint Undertaking (JU), grant No. 101034344) and JPND (bPRIDE), National MS Society (Progressive MS alliance), Alzheimer Association, Health Holland, the Dutch Research Council (ZonMW), Alzheimer Drug Discovery Foundation (2 grants as PI), The Selfridges Group Foundation, Alzheimer Netherlands. CT is recipient of ABOARD, which is a public-private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). CT is recipient of TAP-dementia, a ZonMw funded project (#10510032120003) in the context of the Dutch National Dementia Strategy. CET has a collaboration contract with ADx Neurosciences, Quanterix and Eli Lilly, performed contract research or received grants from AC-Immune, Axon Neurosciences, BioConnect, Bioorchestra, Brainstorm Therapeutics, Celgene, EIP Pharma, Eisai, Fujirebio, Grifols, Instant Nano Biosensors, Merck, Novo Nordisk, PeopleBio, Roche, Siemens, Toyama, Vivoryon. She is editor of Alzheimer Research and Therapy, and serves on editorial boards of Medidact Neurologie/Springer, and Neurology: Neuroimmunology & Neuroinflammation.

P199- LIPID DICARBONYL SCAVENGERS FOR THE PREVENTION OF ALZHEIMER'S DISEASE.

J.A. Rathmacher[1], N.N. Abumrad[2], P.A. Newhouse[2] *(1. MTI BioTech Inc - Ames (United States), 2. Vanderbilt University Medical Center - Nashville (United States))*

Background: At present, there is no preventive or curative treatments for Alzheimer's Disease (AD). This situation underscores the urgency of identifying novel preventive and therapeutic targets that will support retention of cognitive function with aging. Oxidative stress is a major pathogenic mechanism that underlies both the pre-clinical development and subsequent progression of AD. In pre-clinical and clinical AD, increased production of reactive oxygen species (ROS) occurs through multiple mechanisms such as mitochondrial dysfunction [1], inflammation, and metal redox cycling catalyzed by Aß peptides [2]. Rising ROS production accelerates formation of lipid dicarbonyls, including 4-oxo-2-nonenal, malondialdehyde (MDA) and levuglandins (LGs), all of which exert toxic effects by readily forming adducts on lysine residues to permanently alter protein function, conformation, localization, and degradation [3, 4]. The major risk factor for development of AD is aging, which is associated with increased neuroinflammation and oxidative stress, the two principal contributors to dicarbonyl formation. MDA and LG adducts

on lysine residues are significantly elevated in hippocampus of AD postmortem brains and levels of LG-lysine adducts correlate positively with both the CERAD plaque score and the Braak stage of AD [5]. It has also demonstrated an age-dependent increase in levels of LG-adducts in the well-characterized mouse model for AD, the APPSwe-PS1ΔE9 mice, and have shown that LG-adduct levels correlate with amyloid deposition and memory impairment in this model [6]. We have developed 2-hydroxybenzylamine (2-HOBA) a novel small "scavenger" molecule that specifically inactivate dicarbonyls both in vitro and in vivo. 2-HOBA prevents the formation of neurotoxic Aβ oligomers in vitro and has a neuroprotective effect in rodent studies [7]. These findings support the hypothesis that protein modification by dicarbonyls contribute to the development of AD and that preventing formation of these adducts could decrease the disease progression The overall goal of this project is to provide proof-of-concept that a dicarbonyl scavenger, 2-HOBA, can protect brain proteins from covalent modifications by products of oxidative stress in patients with mild AD. **Methods:** This is a phase II, randomized, double-blind, placebo-controlled, parallel group dose finding, biomarker study to evaluate the safety, tolerability, and efficacy of 2-HOBA, a dicarbonyl scavenger, in 48 participants with mild AD. Participants will be randomized 1:1:1:1 to receive 2-HOBA (250, 500, 750 mg 2-HOBA acetate TID) or placebo for 16 weeks. Blood and cerebrospinal fluid (CSF) will be collected at baseline and after 16-weeks of treatment. The primary endpoints will be CSF dilysyl-MDA crosslink and the lysyl-LG adducts of CSF proteins, and safety of 2-HOBA administered in dose-responsive relationship. The secondary aims are to evaluate the effect of 2-HOBA treatment on markers of disease severity, brain inflammation, and cognitive performance. **Conclusion:** Our therapeutic objective is to use 2-HOBA to prevent AD development by inhibiting proteotoxicity caused by dicarbonyls generated during conditions known to be risk factors for sporadic AD and age-related cognitive decline. This approach is novel in that it does not target a specific enzyme or receptor but rather shields brain proteins from oxidative injury, preserving their physiological structures and functions. **Key words:** Alzheimer's Disease, malondialdehyde, Isolevuglandin, 2-HOBA, Reactive Oxygen Species, Lipid Dicarbonyl. **Disclosures:** JAR is an employee of MTI BioTech and is listed as an inventor on 2-HOBA patent applications. NNA is the CEO of MTI BioTech. MTI BioTech intends to market/license 2-HOBA for commercial purposes. **References:** 1. Higgins, G. C. et al. J. Alzheimers Dis. 20 Suppl 2, S453-473, doi:5XUNG72X453WJ154 [pii] 10.3233/JAD-2010-100321 (2010). 2. Opazo, C. et al. J. Biol. Chem. 277, 40302-40308, doi:10.1074/jbc.M206428200M206428200 [pii] (2002). 3. Singh, M., Nam, D. T., Arseneault, M. & Ramassamy, C. J. Alzheimers Dis. 21, 741-756, doi:J51G3HRU854623N1 [pii]10.3233/JAD-2010-100405 (2010). 4. Sayre, L. M., Perry, G. & Smith, M. A. Chem. Res. Toxicol. 21, 172-188, doi:10.1021/tx700210j (2008). 5. Zagol-Ikapitte, I. et al. J. Neurochem. 94, 1140-1145 (2005). 6 . Woodling, N. S. et al. J Neurosci 34, 5882-5894, doi:10.1523/JNEUROSCI.0410-14.2014 (2014). 7. Davies, S. S. et al. J Alzheimers Dis 27, 49-59, doi:10.3233/JAD-2011-102118 (2011).

P200- TRANSLATION STUDIES AND CLINICAL DEVELOPMENT OF THN391, A NOVEL ANTI-FIBRIN ANTIBODY FOR THE TREATMENT OF DEMENTIA.

J. Stavenhagen[1], M. Rickert[1], K. Flanagan[1], H. Cheng[1], A. Suppahia[1], V. Salgotra[1], J.K. Ryu[2], K. Akassoglou[2] *(1. Therini Bio - San Francisco (United States), 2. Gladstone Institute - San Francisco (United States))*

Background: Fibrin is implicated in multiple neurological diseases, including Alzheimer's Disease (AD) and Multiple Sclerosis (MS). Dysregulation of the blood brain barrier (BBB) is associated with neurological diseases and allows fibrinogen to enter the brain. Persistent chronic fibrin deposition due to reduced levels of fibrinolysis is a hallmark of these neurodegenerative diseases. Fibrin deposits are increased in brains of patients with dementia and levels of detectable fibrinogen in the cerebral spinal fluid (CSF) increase with disease severity. Fibrin is generated by the proteolytic action of thrombin on fibrinogen which causes it to polymerize and create a blood clot network. Thrombin cleavage also exposes a cryptic amino acid sequence, Fibγ377-395, termed P2. Exposed P2 binding to CD11b/CD18 or CD11c on microglia, macrophages and dendritic cells activates multiple signal transduction pathways to trigger an inflammatory response. Activation of innate immune cell types is known to drive disease pathophysiology in dementia. THN391 is a humanized affinity matured monoclonal antibody (mAb) targeting the P2 epitope of fibrin. It is being developed for the treatment of dementia. **Objective:** Generation of preclinical and translational data to support the clinical development of THN391 for treatment of AD. **Methods:** Preclinical studies included plate based binding and cellular assays to evaluate functional activity of THN391. Rodent models of neuroinflammatory diseases were incorporated to assess the function of THN391 in vivo and its impact on the innate immune system. The potential for THN391 to impact hemostasis was evaluated in vitro using aPTT assays. Thromboelastography (TEG) was used to measure impact on coagulation in whole blood of human donors. Safety pharmacology assessments of THN391 were incorporated into Good Laboratory Practice (GLP)-compliant repeated-dose toxicity studies in rats and monkeys. PK and TK analysis was performed for both species. Pharmacokinetic data was used in allometric and PDPK modeling studies to determine human dose and safety margins. **Results:** The clinical candidate, THN391, is a humanized affinity matured monoclonal antibody with <1.0 nM affinity to the human fibrin P2 epitope. It harbors a modified human IgG1 heavy chain constant region containing 2 mutations in the antibody (Fc) domain (L234A/L235A) that eliminates most of its ability to mediate Fc receptor effector function, reducing the potential risk of unwanted side effects due to the removal of fibrin deposits. THN391 inhibits binding to both CD11b and CD11c in a dose-proportional manner, illustrating an ability to inhibit binding to the fibrin P2 peptide in vitro. In cell-based assays using bone marrow derived macrophages THN391 binding significantly reduced the expression of pro-inflammatory cytokines IL-12, IL-1β, and IL-6. In both acute and chronic rodent models of neuroinflammation administration of THN391 inhibited activation of innate immune cells, microglial and infiltrating macrophages. This activity blocked disease progression in a dose dependent manner. Investigation into CNS tissue showed. THN391 was colocalized to its fibrin target in a rodent model of AD. Hemostasis was evaluated for safety. THN391 did not impact fibrin polymerization or coagulation at concentrations as high as 100 ug/ml. There were no THN391-related effects observed

on the CNS in rats at IV doses of up to 100 mg/kg every 4 days, and there were no THN391-related effects observed on the cardiovascular (CV) system or respiratory systems, or in the neurological assessment in monkeys at IV weekly doses of up to 100 mg/kg. The no-observed-adverse-effect-level (NOAEL) for the rat study was 100 mg/kg every 4 days for 4 weeks and the monkey toxicology study was 100 mg/kg once weekly for 4 weeks. These data demonstrated large safety margins (333-fold on a mg/kg basis) relative to the proposed clinical starting dose of 0.3 mg/kg. Plasma PK data from rodent and monkey were used to predict human plasma PK following a single dose, every 2 weeks (Q2W), and every 4 weeks (Q4W) dosing as proposed in the first-in-human study. Consistent with the typical PK profile of mAb therapeutics, the model predicts a long plasma, CSF, and ISF terminal elimination phase in humans following single, Q2W, and Q4W dosing. **Conclusion:** THN391 specifically targets the P2 epitope on fibrin, blocking activation of innate immune cells. This activity prevents disease progression in multiple models of Neuroinflammation. These models have helped to identify potential fluid biomarkers for translation to the clinic. THN391 is safe and well tolerated in 2 tox species. High levels of THN391 do not impact hemostasis. We have initiated the first in human (FIH) study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenous (IV) infusion in healthy adults. The final cohort of this study will be used to assess safety in a small dementia patient cohort. Selection for potential responder population of dementia patients, selection criteria will include apoe4 carriers (known to have leaky BBB) and significant CSF fibrinogen levels. Inflammatory biomarkers will be evaluated as a pharmacodynamic read out. **Key words:** Fibrin, CD11b, microglia, macrophage, neuroinflammation, dementia. **Disclosures:** All authors are employees or shareholders of Therini Bio

P201- THE TEMPORAL RELATIONSHIP BETWEEN NEUROPSYCHIATRIC SYMPTOMS, PHYSICAL ACTIVITY, AND SLEEP: A THREE COHORT-STUDY. A. Noriega De La Colina[1], M. Ai[2], N. Scarmeas[3], A.F. Kramer[2], M.R. Geddes[1] *(1. Department of Neurology and Neurosurgery, The Montreal Neurological Institute-Hospital, McGill University - Montreal (Canada), 2. Center for Cognitive and Brain Health, Department of Psychology, Northeastern University - Boston (United States), 3. 1st Department of Neurology, Aeginition Hospital, National and Kapodistrian University of Athens - Athens (Greece))*

Background: Physical Inactivity, sedentarity, and decreased sleep are key modifiable lifestyle behaviours that are individually associated with lower cognitive decline [1]. Prior research suggests there may be a tridirectionally relationship among these three behaviours. Furthermore, these behaviours are affected by the presence of neuropsychiatric symptoms like depression, apathy, and anxiety. The temporal relationship among these three behaviours and neuropsychiatric symptoms is unknown. Using an Ecological Momentary Assessment (ECA) and a time series analysis we aim to understand the temporal and longitudinal relationship among these factors for the development of a behavioural therapeutic fingerprint. **Method:** We performed a 28-day lead-lag analysis using Moderate-to-Vigorous Physical Activity (MVPA), step count, and sleep as measured by a 24-hour wrist-worn accelerometer, on 30 community-dwelling older adults who participated in a behavioural study to enhance physical activity in sedentary individuals (Clinicaltrials.gov identifier: NCT04315363). Participants were included if they did not exercise more than 150 minutes of MVPA per week (International Physical Activity Questionnaire) and were sitting more than 8 hours per day (Marshall Sitting Questionnaire). We examine each variable separately for auto-correlative relationships for different time points of the same variable. The temporal dynamics are calculated from the rank order of the lead-lag coefficients. The relationships between different time points of step count, MVPA, and sleep are examined through cross-correlations. The presence of neuropsychiatric symptoms was assessed using the apathy evaluation scale (AES-S), the Geriatric Depression Scale (GDS), and the Geriatric Anxiety Inventory (GAI). The results were externally validated in the Healthy Aging Brain Study (HABS) (n=25) and the Aiginition Longitudinal Biomarker Investigation Of Neurodegeneration (ALBION) study (n=125). **Results:** Autocorrelations showed that mood presented seasonality with baseline mood positively correlated to the subsequent day's mood (r= +.571, p= .037) and negatively correlated with mood at day 7 (r= -.330, p=0.27) and day 8 (r=-.248, p=.013). The temporal dynamics identified mood (B=+.602), preceding Step count (B=+.112), MVPA time (B=-.001), and sleep time (B=-.276) (Figure 1). Furthermore, cross-correlations demonstrated that mood was positively correlated to MVPA at the same time point (r=-.605) and also that the previous day's mood predicted the next day's MVPA (r=-.629). Cross-correlations confirmed that MVPA (r=-.507) and mood (r=-.504) predicted the next day's sleep time. **Conclusion:** Improved mood precedes the increase in MVPA and sleep time in sedentary older adults. Understanding temporal dynamics between mood, sleep time, and MVPA, can help develop more personalized interventions targeting an increase in physical activity in older adults, using behavioural targets as a base.

P202- CEREBROSPINAL FLUID PROTEOMIC ANALYSIS REVEALS REVERSAL EFFECTS ON GLUCOSE DYSMETABOLISM IN ALZHEIMER'S DISEASE AFTER TREATMENT WITH ATOMOXETINE. E. Dammer[1], L. Ping[1], D. Duong[1], E. Modeste[1], N. Seyfried[1], J. Lah[1], A. Levey[1], E. Johnson[1] *(1. Emory University - Atlanta (United States))*

Background: Alzheimer's disease (AD) is currently defined at the research level by the aggregation of amyloid-β (Aβ) and tau proteins in brain. While biofluid biomarkers are available to measure Aβ and tau pathology, few biomarkers are available to measure the complex pathophysiology associated with these two cardinal neuropathologies. **Methods:** To develop biomarkers for other AD pathophysiologic processes, we performed a proteomic analysis of cerebrospinal fluid (CSF) from control (n=140) and AD (n=160) Emory research participants classified by their CSF Aβ1-42/total tau ratios. Proteomic measurements were obtained using two orthogonal technologies—tandem mass tag mass spectrometry (TMT-MS) and SomaScan. Protein abundance data were harmonized across platforms and analyzed using protein co-expression to generate an AD CSF protein co-expression network from the participants (n=300). In a separate analysis we performed the same dual proteomic platform CSF measurements in patients (n=39) with mild cognitive impairment due to AD who participated in a phase 2 clinical trial of atomoxetine (ATX)—a norepinephrine reuptake inhibitor—in which ATX treatment demonstrated beneficial effects on CSF tau and pTau levels. We leveraged the proteomic network generated from the n=300 participants to understand the broader biological effects of ATX treatment in the clinical trial population. **Results:** A total of 4576 unique proteins were measured between the two platforms after quality control. Analysis by protein co-expression revealed

34 different AD CSF network modules related to autophagy, ubiquitination, endocytosis, and glycolysis, among others. Proteomic analysis of the ATX trial population demonstrated that abnormal elevations in the glycolysis CSF module—the network module most strongly correlated to cognitive function—were reduced by ATX treatment. Individuals who had more severe glycolytic changes at baseline responded better to ATX, but the strongest individual protein predictors of ATX response were not present in the glycolytic module. Clustering of individuals based on their CSF proteomic network profiles to identify patients who would best respond to ATX revealed ten groups that did not cleanly stratify by Aβ and tau status, underscoring the heterogeneity of pathological changes not fully reflected by Aβ and tau. The best responders to ATX clustered within two out of the ten groups. **Conclusion:** AD biofluid proteomics holds promise for the development of biomarker panels that reflect diverse pathologies for use in clinical trials and precision medicine. **Key words:** proteomics, cerebrospinal fluid, atomoxetine, glucose metabolism. **Disclosures:** The authors declare no competing interests.

P203- BLOOD-BASED SMALL RNA BIOMARKERS AND THE ATN(V) FRAMEWORK: PREDICTING NEURODEGENERATION AND VASCULAR PROFILES IN THE EPAD COHORT. B. Steinkraus[1], M. Heuvelman[1], L. Lorenzini[2], J. Jehn[1], T. Sikosek[1], R. Horos[1], K. Tikk[1], J. Cummings[3], J. Manson[4], C. Ritchie[4] *(1. Hummingbird Diagnostics GmbH - Heidelberg (Germany), 2. Amsterdam University Medical Center - Amsterdam (Netherlands), 3. Department of Brain Health, Chambers-Grundy Center for Transformative Neuroscience, University of Nevada Las Vegas - Las Vegas (United States), 4. Centre for Clinical Brain Sciences, The University of Edinburgh - Edinburgh (United Kingdom))*

Background: Alzheimer's disease (AD) progression is characterized by the ATN (Amyloid, Tau, Neurodegeneration) framework, encompassing key pathological features of the disease, yet early diagnosis and predictive and prognostic forecasting remain challenging. Emerging evidence suggests that microRNAs (miRNAs) regulate key cellular processes involved in AD, and alterations in miRNA profiles may serve as valuable indicators of pathological changes and disease progression, particularly with regards to inflammatory (I) and vascular (V) phenotypes. Their biological importance, together with the observation that miRNAs are frequently secreted into the extracellular space and stable in blood and other body fluids, suggest they may be specific, robust and non-invasive biomarkers that could augment the ATN(V) framework. With funding from the Alzheimer's Drug Discovery Foundation (ADDF) Hummingbird Diagnostics (HBDx) is developing blood-based miRNA biomarkers intended to inform the diagnosis and prognosis of AD. This study aims to identify specific blood-based miRNA signatures in AD patients to enhance the predictive and prognostic capacity of the ATN framework, with a particular focus on neurodegeneration and vascular profile alterations. **Methods:** Through collaboration with the European Prevention of Alzheimer's Disease (EPAD) consortium, we analyzed 3,302 whole blood samples (PAXgene) of 1,895 patients from over 20 European sites. 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. For neurodegeneration (N), normalized hippocampal volumes from MRI data were extracted and binarized at (LHVL+LHVR)/2*PTIV < 1.5 standard deviations. 1446 participants (95%) were negative (N-) and 78 (5%) were positive (N+). The vascular (V) profile was approximated from the Fazekas deep score (correlating with small blood vessel lesions). 0/1 was considered negative (V-) and 2/3 was considered V+. 243 (15%) were V+, and 1329 (85%) V-. 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 predicting neurodegeneration and the vascular profile within the ATN/V framework. Blood cell sorting and sequencing was performed to deconvolve small RNAs into their source of origin. **Results:** We generated small RNA feature models and report a median diagnostic receiver operating area under the curve (AUC) of 0.72 (95% CI 0.66-0.79) for neurodegeneration ((LHVL+LHVR)/2*PTIV < 1.5 s.d.). We could detect vascular profiles with an AUC of 0.62 (95% CI 0.58-0.63). Deconvolving the whole blood signatures into their blood cell or plasma origin using small RNA expression data from sorted cells, revealed that 27% of features selected for the classification were found in plasma and 73 % originated from circulating immune cells. This marked a significant upregulation of 124% compared to the unselected feature expression in plasma of 12% ($p<0.001$). Thrombocytes (-78%, $p<0.001$) and basophil (-65%, $p<0.001$) contribution to the signature decreased significantly. **Conclusion:** These data suggest the potential of a small RNA-based blood test as a viable complement to the ATNV framework for the management of individuals at risk for AD. Refinement is needed to improve the AUCs and comprise the next step of our research program. **Key words:** Small RNA, microRNA, blood-based biomarker, peripheral inflammation, neurodegeneration, vascular phenotypes, EPAD. **Disclosures:** B.R.S., M.H., J.J., R.H., T.S., K.T. are employees at Hummingbird Diagnostics and hold company stock options. The remaining authors declare no competing interests.

P204- EVALUATION OF GLP-1 ANALOGUE, LIRAGLUTIDE IN THE TREATMENT OF ALZHEIMER'S DISEASE. P. Edison[1] *(1. Imperial College London - London (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 in MRI scans were evaluated using both regional volume analysis and voxel-based morphometric analysis. MRI analysis demonstrated a slower decline of temporal lobe volume and total grey matter

volume. This was associated with slower decline in cognitive function (ADAS-EXEC). 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.

LP118- AN OPEN-LABEL, PILOT STUDY OF DARATUMUMAB SC IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE (DARZAD). M.L. Gordon[1,2], E. Christen[1], L. Keehlisen[1], M. Gong[1], F. Lam[3], L. Giliberto[1,4], J.J. Gomar[1], J. Koppel[1,5] *(1. Litwin-Zucker Research Center, Feinstein Institutes for Medical Research, Northwell Health - Manhasset, New York (United States), 2. Departments of Neurology and Psychiatry, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell - Hempstead, New York (United States), 3. Feinstein Institutes for Medical Research, Northwell Health - Manhasset, New York (United States), 4. Institute for Neurology and Neurosurgery, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell - Great Neck, New York (United States), 5. Department of Psychiatry, Zucker Hillside Hospital, Northwell Health - Glen Oaks, New York (United States))*

Background: Daratumumab is a human IgG1k monoclonal antibody that targets CD38, a multi-functional enzyme that hydrolyzes nicotinamide adenine dinucleotide (NAD) and is involved in cell signaling. CD38 levels increase with age and correlate with NAD decline [1]. In CD38 knockout mice, tissue levels of NAD are significantly increased [2]. When CD38 knockout mice were crossed with APPswePS1ΔE9 transgenic mice, they showed significant reductions in amyloid-beta (Aβ) plaque load and soluble Aβ levels, and this correlated with improved spatial learning [3]. CD38 expression on CD8+ T cells, indicative of activation, is significantly increased in the blood of early AD patients as compared with age-matched controls, and activated T cells are capable of trafficking into the brain and exerting cytotoxic effects [4]. CD38 affects regulation of the amount and function of activated microglia, with important consequences for injury and repair processes in the brain [5]. Accordingly, CD38 may be a novel target for AD treatment. **Methods:** This was a single-site open-label study enrolling subjects ≥ 55 to ≤ 85 years of age with a diagnosis of probable AD dementia according to NIA-AA criteria, MMSE score ≥ 15 and ≤ 26, confirmed amyloid positive by PET scan. Eligible subjects were treated with daratumumab SC 1800 mg (daratumumab 1800 mg with rHuPH20 30,000 units) subcutaneous infusion once weekly for 8 weeks followed by daratumumab SC 1800 mg every 2 weeks for 16 weeks. A total of 16 subjects were screened, with 6 screen failures, 1 subject who withdrew consent prior to treatment, 1 subject who withdrew consent after 3 treatment visits, 1 subject withdrawn by the investigator after having missed 7 consecutive visits due to the COVID pandemic, and 1 subject withdrawn due to a possibly related adverse event, leaving 6 evaluable subjects who completed treatment. Cognitive outcome measures (ADAS-Cog/11, ADAS-Cog/12, MMSE, CDR-SB, and ADCOMS) were assessed at screening, day 85 (midpoint), day 176 (end of treatment), and day 246 (11 weeks post-treatment). Flow cytometry to measure the CD38+ proportion of CD8+CD4- T cells was performed at baseline, day 176, and day 246. **Results:** Daratumumab significantly reduced the CD38+ proportion of CD8+CD4- T cells after 24 weeks of treatment and this effect persisted 11 weeks thereafter (repeated measures ANOVA $F=8.61$, $p<0.005$). One subject had a serious adverse effect while on treatment (hospitalization for COVID-19 pneumonia). Two subjects experienced mild post-injection reactions consisting of urticaria that responded to diphenhydramine and hydrocortisone, and did not recur with subsequent injections. One subject had onset of a rash 4 days after a daratumumab injection, and a few hours after having received IV iodine contrast. There was no incidence of anemia, leukocytopenia, or thrombocytopenia. Responder analysis showed no subjects who improved with treatment on any of the cognitive outcome measures. **Conclusions:** Daratumumab showed evidence of target engagement as manifested by robust and persistent reduction in the CD38+ proportion of CD8+CD4- T cells. It was generally safe and well-tolerated in this study population. However, in this small pilot study there was no signal of clinical efficacy based on responder analysis. **Key words:** Phase 2a, daratumumab, CD38, Alzheimer's disease. **Clinical Trial Registry:** NCT04070378; https://clinicaltrials.gov. **Disclosures:** Funding for this study and study medication were provided by Janssen Scientific Affairs, LLC. Dr. Gordon has participated in Advisory Board meetings for Corium and Labcorp, and is currently a clinical trial site Principal Investigator for Alector and Novo Nordisk. Dr. Koppel is currently a clinical trial site Principal Investigator for Karuna and Otsuka. **References:** 1. Camacho-Pereira J, et al. Cell Metab 2016; 23: 1127-1139. http://doi.org/10.1016/j.cmet.2016.05.006; 2. Askoy P, et al. Biochem Biophys Res Commun 2006; 349: 353-9. http://doi.org/10.1016/j.bbrc.2006.08.066; 3. Blacher E, et al. Ann Neurol 2015; 78: 88-103. http://doi.org/10.1002/ana.24425; 4. Zhang R, et al. J Neuroimmunol 2013; 256: 38-42. http://doi.org/10.1016/j.jneuroim.2013.01.002; 5. Mayo L, et al. J Immunol 2008; 181: 92-103. https://doi.org/10.4049/jimmunol.181.1.92

LP119- ASSOCIATION OF SERUM LEPTIN WITH IN VIVO BRAIN ALZHEIMER'S DISEASE PATHOLOGIES IN COGNITIVELY NORMAL OLDER ADULTS. S. Lee[1], M.S. Byun[2,3], D. Yi[4], D. Lee[2,3,4] *(1. Department of Psychiatry, Myongji hospital, Hanyang University College of Medicine - Goyang (Korea, Republic of), 2. Department of Neuropsychiatry, Seoul National University Hospital - Seoul (Korea, Republic of), 3. Department of Psychiatry, Seoul National University College of Medicine, - Seoul (Korea, Republic of), 4. Institute of Human Behavioral Medicine, Medical Research Center Seoul National University - Seoul (Korea, Republic of))*

Background: The adipokine leptin linked to adipose tissue impacts brain physiology and the association between low plasma leptin level and an increased risk of Alzheimer disease (AD) dementia has been reported. However, the relationship between late-life leptin and longitudinal change of in-vivo AD pathology has not yet been performed. **Methods:** The study included a total of 194 cognitively normal older adults from the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), prospective longitudinal study. Plasma leptin level at baseline was measured, and the primary outcomes of this study were changes in brain Aβ and tau deposition on PET imaging over a two-year period. The relationship between plasma leptin level and the longitudinal change in AD neuropathological biomarkers was examined using linear mixed-effects (LME) models. **Results:** Baseline leptin was negatively associated with global Aβ deposition at baseline (β, -0.039; 95% CI, -0.075 to -0.003; p=.035). However, there was no significant association between baseline leptin and tau deposition of AD signature region in the baseline. baseline (β, -0.015; 95% CI, -0.073 to 0.071; p=.410) For longitudinal analyses, higher leptin level at baseline was associated with a lower increase in tau deposition in AD-signature region over 2 years (β, -0.057; 95% CI, -0.100 to -0.015; p=.009), In contrast,

leptin level was not related to two-year changes in global Aβ deposition (β, 0.003; 95% CI, 0.000 to 0.012, p = .467). In additional exploratory analysis for each sex, higher plasma leptin levels were associated with a greater decrease in tau deposition in males (β, -0.066; 95% CI, -0.140 to -0.015; p=0.020), but not in females. **Conclusion:** The findings suggest that higher levels of leptin may be related to the prevention of tau pathology over the subsequent years, as well as low deposition of Aβ in cognitively unimpaired older adults. **Key words:** leptin, Alzheimer's disease, beta-amyloid, tau, longitudinal changes. **Disclosure:** The authors declare no financial relationships with commercial interests.

LP120- MISFOLDING OF BIOMARKERS STRATIFIES PROTEINOPATHIES. K. Gerwert[1] *(1. Ruhr-University Bochum - Bochum (Germany))*

Background: The identification and validation of early-stage biomarkers is coming into the focus. In contrast to the widely studied concentration-based biomarkers in body fluids we have examined Aβ misfolding, as structure-based biomarkers to identify Alzheimer´s. 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. 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]. In an extension of the follow-up period up to 17 years, Aβ misfolding could predict disease onset with an AUC of 0.78 and in combination with GFAP levels, AUC was further increased to 0.83 [4]. 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 [5]. Besides 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 [6]. Values between both thresholds indicate low misfolding. This analysis enables the risk stratification as already proven on SCD subjects from the Amsterdam dementia cohort [6]. This approach was recently extended to misfolding of TDP-43 in ALS [7]. **Methods:** We investigated in the next step the performance of alpha-synuclein misfolding as a structure-based biomarker for Parkinson´s disease (PD) in a discovery and validation study. The initial discovery cohort consisted of 30 PD patients and 37 controls without PD diagnosis. We used the iRIS platform analogue to our Aβ analyses with an exception of the antibody. Here, we used a monoclonal antibody which extracts the whole fraction and all conformations of alpha-synuclein from CSF. **Results:** In the discovery study, misfolding of alpha-synuclein was significant higher in PD compared to controls. Using a discriminative threshold at 1637 cm-1, PD could be separated from controls with a ROC-AUC of 0.86. In a subsequent validation study, these findings were further supported. **Conclusions:** Fluid-derived biomarkers are urgently needed for diagnostic purposes in PD. We could show that misfolding of alpha-synuclein in CSF can serve as a biomarker. Structure biomarkers can stratify proteinopathies of the CNS for a personalized precision therapy. **References:**

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