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The Journal of Prevention of Alzheimer's Disease

## 13<sup>th</sup> Clinical Trials on Alzheimer's Disease (CTAD) November 4-7, 2020

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# The Journal of Prevention of Alzheimer's Disease

# JPAD

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**Supplement: 13<sup>th</sup> Conference Clinical Trials Alzheimer's Disease,  
November 4-7, 2020**

**S2** • Symposia - Oral Communications - Late Breaking News

**S55** • Posters

## SYMPOSIA

**S1- DEVELOPMENT OF A VACCINE FOR PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE.** S. Hendrix<sup>1</sup>, C. Jeffrey<sup>2</sup>, R. Eric<sup>3</sup>, M. Richard<sup>4</sup> ((1) *Pentara - Millcreek, USA*; (2) *Cns Innovations - Las Vegas; USA*; (3) *Banner Alzheimer's Institute - Phoenix, USA*; (4) *Global Alzheimer's Platform Foundation - Washington Dc, USA*)

**Presentation 1:** *Past and current vaccine and immunotherapy development in Alzheimer's disease*

Developing vaccines for the treatment of Alzheimer's disease poses unique challenges. Success for a vaccine approach aimed at endogenous targets relies on the ability to break immune tolerance and generate a humoral antibody response against the desired epitopes. AN1792 was created using a synthetic full-length A $\beta$ 1-42 peptide. Nineteen percent of patients in the trial generated anti-A $\beta$  antibody responses and showed improved memory and decreased levels of tau protein in the CSF. Postmortem pathology examination of former AN1792 patients showed that the vaccine had markedly cleared plaques from the brain. Vaccine candidates such as CAD106 and UB-311 use selective epitopes and were developed to avoid the undesirable inflammatory effects that were seen with AN1792. Studies of recent and current amyloid targeting immunotherapies (18 therapeutics) and vaccine therapeutics (8) illustrate lessons learned regarding patient selection, clinical and biomarker outcomes, dosing regimens and assessment of antibody response. A meta-analysis of 13 RCT of amyloid-based immunotherapies in AD showed statistically significant improvement in ADAS-cog ( $p < 0.01$ ) on drug. Solanezumab and AN1792 showed the largest effect sizes and safest profiles, but the rates of ARIA-E were significantly higher with monoclonal antibodies. Positive ADAS-cog effect sizes were seen for AN1792, Solanezumab EXPEDITION 3, BAN2401 and Aducanumab ENGAGE. Earlier EXPEDITION studies also included moderate disease, with substantially lower effect sizes.

Immune response can vary. Only 19% of patients achieved an immune response to AN1792. This variability may necessitate enrollment of more patients to enable assessment of therapeutic benefit in patients with adequate response. Active vaccine approaches may offer advantages over passive immunotherapy (mAbs) due to simpler dosing, greater compliance, and fewer side effects. While systemic allergic reactions are possible, rare and disease-specific side effects such as ARIA-H may be reduced, compared to mAbs. Active vaccination achieving a predictable and high antibody response in amyloid positive, early AD participants increases the likelihood of technical success. The longer duration of immune response with active immunization combined with safety advantages make the modality well suited to AD.

**Presentation 2:** *UB-311, a novel UBITH® amyloid beta peptide vaccine in development for Alzheimer's disease*

UB-311 is a mixture of two synthetic peptides having active UBITH® helper T-cell epitopes and B-cell epitope from the first 14 amino acids of the N-terminal of A $\beta$  with no epitope spreading to the C-terminal. This stimulates a Th2-biased regulatory immune response over a Th1 proinflammatory response, avoiding cross-reactivity with similar endogenous antigens responsible for autoimmune responses. Nonclinical

studies in small mammals, baboons, and macaques showed that UB-311 generated antibody responses, cleared insoluble amyloid and reduced amyloid toxicity. A Ph1 safety, tolerability, and immunogenicity trial demonstrated that UB-311 was safe, well-tolerated, and produced a specific antibody response in all participants tested. A Ph2 trial included 45 patients at four sites; participants had a 97% immunologic response rate. All secondary endpoints - including Amyloid PET burden, CDR-SB, ADCS-ADL, ADAS-Cog and MMSE - pointed directionally in favor of UB-311. The most common adverse events were injection site-related reactions and asymptomatic ARIA-H. UB-311 is being advanced to Ph3 in a randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability in participants with mild AD dementia or MCI due to AD. Eligible participants will be 60-85 years old, have MMSE of 20-26, CDR global scores of 0.5 or 1, and International Shopping List Test scores 1 standard deviation below the mean or greater, and positive amyloid imaging. The primary outcome measure is the CDR-SB difference in change from baseline in the active treatment groups vs placebo at week 73. Secondary outcomes include ADAS-Cog 13 item, Amsterdam Instrumental Activities of Daily Living Questionnaire, AD Composite Score (ADCOMS), MMSE, and safety and tolerability of UB 311. Biomarker outcomes include NfL, p-tau, tau, amyloid PET, CSF (subgroup) and plasma A $\beta$ 40 and A $\beta$ 42, and hippocampal and whole brain volume as measured by MRI. The relationship between the primary and biomarker outcomes will be assessed.

**Presentation 3:** *The promise of blood-based biomarkers in the evaluation, approval and affordability in Alzheimer's prevention therapies*

Blood-based biomarkers (BBBs) have the potential to transform Alzheimer's research, treatment and care. I will note several promising BBB's, suggest how they could inform treatment development, accelerate the evaluation and approval of vaccines and other prevention therapies, and support the affordability and widespread availability of approved drugs. Plasma A $\beta$ 42/40 is a promising indicator of A $\beta$  plaque burden that may help discriminate A $\beta$  PET scan positivity, and detect A $\beta$  pathophysiology earlier than PET. Plasma p-tau217 is an extremely promising indicator of A $\beta$ -related tau pathophysiology that may discriminate neuropathological diagnosis of AD, inform prognosis, and detect A $\beta$ -related tau pathophysiology earlier than PET. Plasma or serum NfL indicates active neuronal degeneration or injury with demonstrated theragnostic value in the evaluation of at least two other disorders and may support the evaluation of AD-modifying and prevention therapies. I propose 1) use of plasma (and/or CSF) p-tau and NfL in individuals with elevated p-tau and NfL to inform the potential efficacy of AD-modifying treatments in cost-effective early phase trials, 2) use of plasma A $\beta$ 42/40 or ptau217 to help galvanize the screening and enrollment in secondary and primary prevention therapies, 3) use of ptau217 as an inclusion criterion to support secondary prevention trials in persons most likely to show subsequent biomarker, cognitive and clinical progression, 4) use of more affordable, scalable, and rapidly repeatable blood samples and biomarkers to support the evaluation of prevention therapies in persons at biomarker and/or genetic risk, and 5) a plan to use BBBs in the clinical setting, transform patient and family care, and optimize the affordability and availability

of AD-modifying and prevention therapies. Additional work is needed to further optimize and compare different assays, characterize their technical, diagnostic, prognostic, and theragnostic value, inform the size and design of the proposed trials, and optimize their use in different research, treatment and prevention trial, and clinical settings.

## **S2- LATEST ADVANCES: BLOOD AND IMAGING BIOMARKERS OF TAU IN ALZHEIMER'S PATIENTS.**

J. Dage<sup>1</sup>, N. Proctor<sup>1</sup>, D. Airey<sup>1</sup>, J. Sims<sup>1</sup>, M. Devous<sup>2</sup>, T. Iwatsubo<sup>3</sup> (1) *Eli Lilly & Company - Cincinnati, USA*; (2) *Avid Radiopharmaceuticals - Philadelphia, USA*; (3) *University Of Tokyo - Tokyo, Japan*)

**Presentation 1:** *Phosphorylated Tau in Blood can Transform Alzheimer's Disease Research and Clinical Trials*

Recent advancements have made possible the accurate and precise measurement of phosphorylated tau in blood samples (P-tau). Recent literature has demonstrated P-tau levels are elevated many years prior to Alzheimer's disease (AD) symptom onset and in line with detection of amyloid pathology. Using blood samples collected prior to death, P-tau has good sensitivity and specificity and overall accuracy in the differential diagnosis of AD as well as the presence of neurofibrillary tangles. The availability of a blood P-tau assay has provided an opportunity to demonstrate an association with tau pathology measured in vivo with Tau PET and affords an opportunity to compare the clinical utility of molecular imaging (association with neurodegeneration and cognitive decline) with that achieved with a P-tau blood test. Given the simplicity a blood test offers, this test is being broadly explored for applicability to clinical research and within trials for new drugs. This presentation will provide evidence to support the use of P-tau in screening for inclusion through identification of subjects with AD pathology and risk of progression. Additionally, longitudinal data recently obtained through the use of stored samples from two past phase 3 clinical trials of Solanezumab will be used to evaluate P-tau for monitoring therapeutic response of a potential disease modifying treatment.

**Presentation 2:** *Tau Imaging in Alzheimer's Disease Clinical Trials and in AD research*

Most research strongly supports the role of beta amyloid plaques (A $\beta$ ) as a disease initiating event occurring years before symptom onset in Alzheimer's Disease (AD). Accumulation of appreciable tau neurofibrillary tangles (NFTs) has been thought to follow A $\beta$  by 5-10 years. Neuropathological research also suggests that the accumulation of tau is more closely associated than A $\beta$  with the degree of neuronal loss, cognitive impairment and declining functions of daily living across the AD continuum. Molecular imaging of A $\beta$  and tau have allowed researchers to explore these protein aggregates in AD in vivo. Research from such PET studies support the concept that the distribution and density of tau is indicative of the degree of neurodegeneration, synaptic dysfunction, and the character of cognitive deficits. Further, therapeutic trials now routinely employ molecular imaging of A $\beta$  and tau to screen prospective subjects as a component of enrollment criteria and to monitor response to therapy occurring at the cellular level. Cross-sectional studies indicate that visual interpretation and quantitative measures of tau tracer signal (standardized uptake value ratio, SUVR) correlate with the degree of cognitive

impairment. Similarly, both baseline and change in tau signal over time have been associated with longitudinal decline in cognitive performance. One of these tracers, flortaucipir, has been recently compared to neuropathology within a Phase 3 trial. Visual interpretation of flortaucipir PET scans was demonstrated to be associated with the detection of cortical NFTs in a large autopsy cohort study. This presentation will review recent Phase 3 trial results (NCT02016560, NCT03901105, NCT02516046, NCT03901092), the role of tau PET in clinical trials, its relationship to diagnosis, cognition and function as well as the longitudinal evolution of tau as visualized by PET imaging. Finally, tau imaging will be reviewed in the context of ATN research framework.

**Presentation 3:** *What Could Tau Biomarker Research in Alzheimer's Disease Mean for Patients?*

Alzheimer's disease (AD) is a relentless, fatal disease creating a health crisis for patients, families and nations. If we can't stop it, the cost to society will be great. In Japan, especially, we are a super-aging society that will feel the effects of an aging society before other countries. As researchers, we have made much progress scientifically, and now understand that the hallmark pathologies of AD occur 10-20 years before clinical symptoms. We have dramatically increased our understanding of the underlying biology of Alzheimer's disease and no longer argue about amyloid vs. tau, but instead believe they are both part of a common disease cascade that can trigger neuroinflammation and neuronal death. And yet, our expert scientific community and research findings are not translating into the realities of community practice and the broader patient experience. Biomarkers for amyloid, tau, and neuroinflammation are now commonly used in research, they play a critical role in risk stratification for clinical trial populations. However, a critical gap exists in communicating a clear understanding of the use of these biomarkers in clinical practice. Combined with our current knowledge of amyloid as a biomarker, this presentation will discuss how the addition of these latest tau biomarker findings can change the face of clinical practice when combined with a clinical assessment, family history, and policies supporting early detection. The ATN framework provides research guidance but may have limitations when applied in a community setting to tests with continuous measures. While there have been no positive late-stage studies of investigational medicines in the last decade, the scientific advancement and understanding of AD progression and diagnosis has shifted our knowledge of the disease significantly and led to increased drug development targeting populations in the earliest stages of disease. As researchers, we believe this evolving scientific understanding of Alzheimer's Disease and the promise that treating earlier than we do today will translate to better patient outcomes, but only if patients can be identified early in the real-world setting. This presentation will propose a potential vision for a future state of clinical practice and discuss the role that clinical trialists in AD could have in education and advocacy in conquering the translational gap of biomarkers in research to diagnostic tools in clinical practice.

**S3- TRIAL-READY COHORT FOR PRECLINICAL AND PRODROMAL ALZHEIMER'S DISEASE PLATFORM (TRC-PAD PLATFORM).** P. Aisen<sup>1</sup>, S. Walter<sup>1</sup>, O. Langford<sup>1</sup>, G. Jimenez-Maggiore<sup>1</sup> ((1) Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego (United States))

**Presentation 1:** *Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's disease Platform (TRC-PAD Platform) - Design and Scientific rationale*, P.S. Aisen<sup>1</sup>, R.A. Sperling<sup>2</sup>, R. Raman<sup>1</sup>, M.C. Donohue<sup>1</sup>, O. Langford<sup>1</sup>, G.A. Jimenez-Maggiore<sup>1</sup>, R.A. Rissman<sup>1</sup>, M.S. Rafii<sup>1</sup>, S. Walter<sup>1</sup>, T. Clanton<sup>1</sup>, J. Cummings<sup>3</sup> ((1) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA; (2) Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; (3) Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Las Vegas, Nevada; Cleveland Clinic Lou Ruvo Center for Brain Health, USA)

The Trial-Ready Cohort for Preclinical/prodromal Alzheimer's Disease (TRC-PAD) project is a collaborative effort to establish an efficient mechanism for recruiting participants into very early stage Alzheimer's disease trials. Clinically normal and mildly symptomatic individuals are followed longitudinally in a web-based component called the Alzheimer's Prevention Trial Webstudy (APT Webstudy), with quarterly assessment of cognition and subjective concerns. The Webstudy data is used to predict the likelihood of brain amyloid elevation; individuals at relatively high risk are invited for in-person assessment in the TRC screening phase, during which a cognitive battery is administered and Apolipoprotein E genotype is obtained followed by reassessment of risk of amyloid elevation. After an initial validation study, plasma amyloid peptide ratios will be included in this risk assessment. Based on this second risk calculation, individuals may have amyloid testing by PET scan or lumbar puncture, with those potentially eligible for trials followed in the TRC, while the rest are invited to remain in the APT Webstudy. To date, over 30,000 individuals have participated in the Webstudy; enrollment in the TRC is in its early stage.

**Presentation 2:** *Building the Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's Disease (TRC-PAD) - Experience from the first three years*, S. Walter<sup>1</sup>, O. Langford<sup>1</sup>, T. Clanton<sup>1</sup>, M.S. Rafii<sup>1</sup>, E. Shaffer<sup>1</sup>, J.D. Grill<sup>3</sup>, G. Jimenez-Maggiore<sup>1</sup>, R. Raman<sup>1</sup>, R.A. Sperling<sup>2</sup>, J. Cummings<sup>4</sup>, P.S. Aisen<sup>1</sup> and the TRC-PAD Investigators† ((1) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA; (2) Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; (3) Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, USA; (4) Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Las Vegas, Nevada; Cleveland Clinic Lou Ruvo Center for Brain Health, USA; † TRC-PAD investigators are listed at [www.trcpad.org](http://www.trcpad.org))

**Background:** The Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's disease (TRC-PAD) aims to accelerate enrollment for Alzheimer's disease (AD) clinical trials by remotely identifying and tracking individuals who

are at high risk for developing AD and referring them for in-person cognitive and biomarker evaluation and subsequent randomization into clinical trials. A risk algorithm using statistical modeling to predict elevated brain amyloid will be refined as TRC-PAD advances with a maturing data set. **Objectives:** To provide a summary of the steps taken to build the Trial-Ready Cohort (TRC) and share results from the first 3 years of enrollment into the program, with a focus on the recruitment strategies utilized as part of the webstudy. **Methods:** Participants are referred to the Alzheimer Prevention Trials (APT) Webstudy from existing registries comprised of individuals interested in brain health and Alzheimer's disease research, as well as through central and site recruitment efforts. The study team utilizes Urchin Tracking Modules (UTM) codes to better understand the impact of electronic recruitment methods. Eligibility for the APT Webstudy is minimal: participants are aged 50 or older, with an interest in participating in AD therapeutic trials. Participants are asked to complete brief quarterly clinical and cognitive assessments which include the Cognitive Function Instrument and Cogstate Brief Battery. An algorithm evaluates their scores and identifies participants who may be at higher risk for future decline. These participants are then referred to clinical sites for in-person screening. Trial-Ready Cohort (TRC) participants must have a study partner, stable medical condition, and elevated brain amyloid, as measured by amyloid positron emission tomography or cerebrospinal fluid analysis. Additional risk assessments include apolipoprotein E genotyping and family history. Participants in the TRC complete the Preclinical Alzheimer's Cognitive Composite (PACC), which is comprised of the Free and Cued Selective Reminding Test, the Delayed Paragraph Recall score on the Logical Memory IIa test from the Wechsler Memory Scale, the Digit-Symbol Substitution test from the Wechsler Adult Intelligence Scale-Revised, and the Mini Mental State Examination. **Results:** During the first 3 years of this program, 30,650 participants consented to the APT Webstudy, with 69.7% being referrals from online registries. Emails sent by registries to participants were the most effective means of recruitment. The Trial-Ready Cohort (TRC) has 23 sites approved for in-person screening, with 112 participants referred for in-clinic screening visits and 18 enrolled in the TRC. The majority of participants who consented to participate in the APT Webstudy have a family history of AD (62%), identify as Caucasian (92.5%), have over twelve years of formal education (85%), and are women (73%). The mean age of APT Webstudy participants is 64.5. Follow up rates for the first quarterly assessment were 38.2% with 29.5% completing the follow-up Cogstate Battery. **Conclusions:** Within a relatively short period of time, we have successfully designed and recruited a large online study that is now transitioning to in-person follow-up. The study team's priority is to improve retention to the APT Webstudy, and to engage in recruitment initiatives that will improve the racial and ethnic diversity of the cohort, towards the goal of clinical trials that better represent the US population. We also aim to continue enrollment into the TRC to our target of 2,000 while beginning the process of referring TRC participants into clinical trials.

**Presentation 3: Accelerating Participant Recruitment in Alzheimer's Disease Clinical Trials using adaptive statistical modeling.** O. Langford<sup>1</sup>, M. Donohue<sup>1</sup>, G. Jimenez-Maggiore<sup>1</sup>, R. Sperling<sup>2</sup>, J. Cummings<sup>3</sup>, P. Aisen<sup>1</sup>, R. Raman<sup>1</sup> the TRC-PAD Investigatorst (1) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA; (2) Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; (3) Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Las Vegas, Nevada; Cleveland Clinic Lou Ruvo Center for Brain Health; † TRC-PAD investigators are listed at [www.trcpad.org](http://www.trcpad.org))

**Background:** Trial Ready Cohort for Preclinical/Prodromal Alzheimer's Dementia (TRC-PAD) aims to develop a large, well-characterized, biomarker-confirmed, trial-ready cohort to facilitate rapid enrollment into Alzheimer's Disease prevention trials. Screening evaluation, which often includes amyloid PET imaging and disclosure of results, is an expensive and time-consuming process. Preclinical Alzheimer's studies to date have had more than a 2/3rd amyloid screen fail rate, resulting in prolonged and expensive recruitment. **Objectives:** One of our primary aims is to optimize an innovative, adaptive risk algorithm to efficiently identify the most appropriate trial participants. We propose algorithms using statistical modeling to predict amyloid burden (Ab) and describe their application in the TRC-PAD project. **Methods:** Enrollment is ongoing on our web-based registry <https://www.apwebstudy.org/>. It is here where participants, after consent, complete a number of online cognitive assessments. Using these data, we assess their eligibility for in-clinic assessments via a multi-stage algorithm and make predictions about their amyloid status using Machine Learning models. Once referred for an in-clinic screening visit, we collect additional data on their APOE4 status and Preclinical Alzheimer Cognitive Composite (PACC) scores. This additional information is used to update the assessment about the participant's risk of being Ab+ and whether or not they are eligible for a PET/CSF scan. **Results:** The area under the Receiver Operating Characteristic curves for these models ranges from ~0.6 for a web-based battery without APOE4, to ~0.7 for an in-person battery with APOE4. Current number needed to screen one elevated amyloid participant stands at ~2. **Conclusion:** With a simple remote unsupervised cognitive battery, we are able to have an impact on the expense of screening for Preclinical AD clinical trials and the inclusion of APOE4 status reduces this further. This talk will present details on the adaptive statistical algorithms used in this week in addition to data on the current status of the Trial Ready Cohort.

**Presentation 4: TRC-PAD: Accelerating Recruitment of AD Clinical Trials through Innovative Information Technology,** G.A. Jimenez-Maggiore<sup>1</sup>, S. Bruschi<sup>1</sup>, R. Raman<sup>1</sup>, O. Langford<sup>1</sup>, M. Donohue<sup>1</sup>, M.S. Rafii<sup>1</sup>, R.A. Sperling<sup>2</sup>, J.L. Cummings<sup>3</sup>, P.S. Aisen<sup>1</sup> and the TRC-PAD Investigatorst (1) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA; (2) Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; (3) Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Las Vegas, Nevada; Cleveland Clinic Lou Ruvo Center for Brain Health, USA; † TRC-PAD investigators are listed at [www.trcpad.org](http://www.trcpad.org)

**Background:** The Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease (TRC-PAD) program was initiated with the overarching goal of accelerating therapeutic development for pre-dementia AD through the establishment of an infrastructure to ensure timely recruitment of targeted individuals into optimally designed trials (Aisen et al., 2020, in press). The Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease (TRC-PAD) Informatics Platform (TRC-PAD IP) was developed to facilitate the efficient selection, recruitment, and assessment of study participants in support of the TRC-PAD program. **Objectives:** To describe the innovative information technology (IT) architecture, workflows, and components of the TRC-PAD IP. **Methods:** The TRC-PAD Informatics Platform (TRC-PAD IP) was conceived as a secure, scalable, multi-tiered information management platform designed to facilitate high-throughput, cost-effective selection, recruitment, and assessment of TRC-PAD study participants. The program aims called for the construction of a multi-stage process that encompassed 1) a public-facing web-based registry, the Alzheimer Prevention Trials (APT) Webstudy registry, 2) an analytics platform capable of supporting the development and implementation of risk-based referral and screening algorithms, 3) a web-based referral management system, the Site Referral System (SRS), and 4) a regulatory-compliant clinical data management system to collect data for the standing Trial Ready Cohort (TRC). TRC-PAD participants were evaluated using both web-based and in-person assessments to predict their risk of amyloid biomarker abnormalities and eligibility for preclinical and prodromal clinical trials. Participant data were integrated across multiple stages to inform the prediction of elevated brain amyloid. TRC-PAD participants were age 50 and above, with an interest in participating in Alzheimer's research. TRC-PAD participants' demographic characteristics, cognitive performance and subjective memory concerns were remotely assessed on a longitudinal basis to predict participant risk of biomarker abnormalities. Those participants determined to be at increased risk for elevated brain amyloid were invited to an in-clinic screening visit for a full battery of clinical and cognitive assessments as well as brain amyloid biomarker confirmation using positron emission tomography (PET) or lumbar puncture (LP). **Results:** The TRC-PAD IP supported growth in recruitment, screening, and enrollment of TRC-PAD participants by leveraging a secure, scalable, cost-effective cloud-based information technology architecture. As of July 6, 2020, 36,955 users had registered for an APT account. Of these registered users, 33,259 (90.0%) enrolled in the study via online consent and had completed more than 280,000 remote assessments. Participant mobile device usage

(43.0%) on the APT Webstudy was higher than anticipated. The demographic characteristics of the cohort are female (73.0%), non-Hispanic White (92.4%), with a mean age of 64.6 years (SD = 8.3). 87.7% agreed to have their contact information shared with the TRC sites. After one year of quarterly follow-up, 44.7% of participants were retained. The retention rate after two years of quarterly follow-up was 29.7%. TRC sites began in-person screening of participant referrals in August 2019. As of July 6, 2020, 27 of 35 TRC sites were activated and had received 1,675 risk-ranked participant referrals via the SRS. Of these, 246 (14.7%) participants were referred to the TRC for initial screening, 123 (50.0%) participants completed the initial screening visit, 99 (80.5%) participants were authorized for amyloid testing, 55 (55.6%) participants were biomarker-confirmed using amyloid PET or CSF assessment, 26 (47.3%) participants were found to be amyloid elevated, and 23 (88.5%) participants were enrolled into the TRC. **Conclusions:** The TRC-PAD program and its underlying information management infrastructure, TRC-PAD IP, have demonstrated feasibility in achieving the program aims. The flexible and modular design of the TRC-PAD IP will accommodate the introduction of emerging diagnostic technologies.

**S4- ACCELERATING THE DEVELOPMENT OF NOVEL BIOMARKERS FOR ALZHEIMER'S DISEASE AND RELATED DEMENTIAS: A PROGRESS REPORT FROM THE DIAGNOSTICS ACCELERATOR INITIATIVE.** H. Fillit<sup>1</sup>, N. Bose<sup>2</sup>, H. Zetterberg<sup>3,4</sup>, S. Lovestone<sup>5</sup>, R. Au<sup>6</sup> ((1) *Alzheimer's Drug Discovery Foundation, New York, NY, USA*; (2) *Gates Ventures LLC, Kirkland, WA, USA*; (3) *University of Gothenburg, Gothenburg, Sweden*; (4) *University College London, London, United Kingdom*; (5) *Janssen-Cilag, High Wycombe, United Kingdom*; (6) *Boston University Schools of Medicine, Boston, MA, USA*)

Biomarkers are critical to improving care and the development of new drugs for Alzheimer's disease. Their context of use can vary from early diagnosis and prognosis to inclusion criteria for clinical trials and as outcome measures. With recent innovation in the diversity of targets and pathways being tested in clinical trials, the need for novel biomarkers has never been greater. While neuroimaging and cerebrospinal fluid biomarkers have made significant advances in recent years, there is a great need for novel, inexpensive, less invasive biomarkers that correlate highly with the new phenotypes being described with existing neuroimaging and CSF biomarkers. Exciting advances are being made in blood biomarkers, retinal biomarkers, and digital biomarkers for Alzheimer's disease. The Diagnostics Accelerator (DxA) is a \$50MM USD partnership of leading philanthropists and investors that is dedicated to promoting innovation in these latter spheres of biomarker research. The Alzheimer's Drug Discovery Foundation and Gates Ventures are the operating entities of the fund. In this panel discussion, an update on the progress of the DxA will be presented, including descriptions of the strategy the fund is employing and its operating principles. Selected scientists representing recent DxA investments in biotechnology companies and academic institutions worldwide will discuss their progress.

## **S5- COMPOSITE COGNITIVE ENDPOINTS FOR CLINICAL TRIALS IN NEURODEGENERATIVE DISEASE.**

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**Overview:** Introduction: In recent years, several composite cognitive outcomes have been developed for use as endpoints for neurodegenerative disease trials, including as single primary endpoints for Alzheimer's disease (AD) secondary prevention trials. Many newer composites include only objective cognitive tests given limited expected decline on functional measures in early/preclinical disease stages and evidence for cognitive changes on sensitive neuropsychological tests. These have been developed using theory and statistically driven approaches, primarily to optimize sensitivity to disease progression, with the expectation that a continuous outcome will provide the greatest opportunity to detect a statistically significant treatment effect. Whether such outcomes have clinical meaningfulness/patient relevance as direct measures of treatment benefit, or whether they should be considered as intermediate or surrogate endpoints remains to be established. Methodological issues of practice effects, derivation of composites, weightings of individual outcomes, ceiling effects, cross-cultural issues, heterogeneity etc. are not fully resolved. **Objectives:** This symposium will review conceptual and methodological issues relevant to the development and validation of composites, with a focus on neuropsychological tests. Approaches to establishing clinical meaningfulness will be reviewed. The development and validation of the Alzheimer's Prevention Initiative Composite Cognitive Test (PACC), and the Huntington's disease Cognitive Assessment Battery (HD-CAB), will be reviewed as case studies. **Discussion:** Existing composite outcomes may have limitations and require iterative development and validation to improve our understanding of their conceptual basis, psychometric properties, optimal application, and relative utility. In the case of the PACC this iterative development continues to inform its clinical meaningfulness for preclinical AD trials, with ongoing and planned studies contributing important data. For the HD-CAB, different approaches to handling multiple outcome variables are under evaluation to optimize data analysis. **Conclusion:** Though of great importance for clinical trials in neurodegenerative diseases, there is no consensus or 'good practice' for the development of composite cognitive outcomes. Given the cardinal nature of cognitive decline across neurodegenerative, dementia-causing diseases, establishing a pathway for endpoint development and validation, including data analysis approaches, is an important area of focus for clinical trials methodology.



**Presentation 1:** *Conceptual and methodological issues related to composite development and validation*

**Introduction:** Composite cognitive scales are desirable for pivotal clinical trials because they, in principle, provide a single, primary outcome combining neurocognitive domains. Several composite scales, composed of multiple neurocognitive subscales, have been advanced as primary outcomes in early stage AD trials. These have used different approaches to their development and validation, including combining scores into summary outcomes. There is limited consensus regarding the optimal development and validation pathway, as well as the necessary evidentiary standards. **Objectives:** This communication will outline unresolved methodological challenges to the development and validation of novel composite outcomes from combinations of neurocognitive subscales, for early AD clinical trials. **Discussion:** Existing composite outcomes may have substantial limitations, including our understanding of their conceptual basis and clinical meaningfulness, their common derivations, inattention to basic psychometric principles, redundancy, and absence of alternate forms that might reduce practice effects. In effect, any currently used composite is undergoing validation through its use in a trial. The assumption that a composite, by its construction alone, is more likely than an individual measure to detect an effect of a drug and that the effect is more clinically relevant or valid has not been demonstrated. New data relevant to the development of composites will be presented. **Conclusion:** The increasing use of composite measures in early stage AD trials highlights important and unresolved conceptual and methodological challenges. Implicit assumptions regarding the nature of measurement constructs need to be articulated and challenged, and greater consensus achieved regarding their development and validation.

**Presentation 2:** *The PACC: Development, validation, and current-status*

**Introduction:** The Preclinical Alzheimer Cognitive Composite (PACC) combines tests that assess episodic memory, timed executive function, and global cognition and serves as the primary outcome measure for the A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer's study) secondary prevention trial. The PACC was developed using a combination of clinical and expert judgment to identify relevant cognitive domains/tests of cognition, followed by validation in multiple observational cohort studies. **Objectives:** This communication will describe the development and validation of the PACC including iterative development steps, such as including a semantic language measure to produce the PACC5, as well as considerations regarding methodological questions regarding domain and test selection, derivation of the composite score and approaches to outcome measure validation. **Discussion:** The PACC has undergone several steps of iterative development and validation leading to the current version (PACC5). These steps inform its clinical meaningfulness, including sensitivity to amyloid  $\beta$  related decline, subjective cognition complaints, and clinical progression. **Conclusion:** The current PACC5 improves upon earlier versions of the PACC to further enhance detection of early A $\beta$ -related cognitive decline and will be the primary outcome in the AHEAD 3-45 Study.

**Presentation 3:** *The HD-CAB: Data summarization approaches, and clinical meaningfulness*

**Introduction:** In premanifest Huntington's disease (HD) gene expansion carriers, subtle cognitive signs appear before motor diagnosis, initially in the absence of detectable functional impairment. As neurodegeneration progresses, motor diagnosis is made and functional impacts of HD signs become apparent. Ongoing and planned disease-modifying HD trials have adopted the HD Cognitive Assessment Battery (HD-CAB), a brief, well-tolerated battery, designed to capture the breadth of HD cognitive symptoms using six established performance-based tests. **Objectives:** This communication will consider a series of approaches to handle the six outcome variables of the HD-CAB within a single clinical trial endpoint strategy. We will describe our approach to establish clinical meaningfulness of the HD-CAB via a planned longitudinal co-validation study called FOCUS-HD, along with the FuRST 2.0, a patient-reported outcome measure of function, and a performance-based functional measure. **Discussion:** Based on input from clinical scientists, cognition experts, regulatory agencies and biostatisticians, our team will evaluate a series of approaches to handle the multiple outcome variables generated by the HD-CAB to optimize the data analysis in HD clinical trials. **Conclusion:** No roadmap exists to guide the use of cognitive outcomes for clinical trials in neurodegenerative diseases or for vetting their clinical meaningfulness. Because cognitive decline is the predominant cause of functional impairment across many neurodegenerative, dementia-causing diseases, robust measurement and data analysis approaches are urgently needed to test the effects of disease modifying treatments on cognition.

## ORAL COMMUNICATIONS

**OC1: EFFICACY AND SAFETY OF AXS-05, A NOVEL ORAL NMDA RECEPTOR ANTAGONIST WITH MULTIMODAL ACTIVITY, IN THE TREATMENT OF ALZHEIMER'S DISEASE AGITATION: RESULTS OF THE ADVANCE-1 TRIAL.** C. O Gorman<sup>1</sup>, A. Jones<sup>1</sup>, J. Cummings<sup>2</sup>, H. Tabuteau<sup>1</sup> ((1) Axsome Therapeutics Inc. - New York, USA; (2) Center For Neurodegeneration And Translational Neuroscience; Cleveland Clinic Lou Ruvo Center For Brain Health; Cleveland Clinic Lerner College Of Medicine - Las Vegas, USA)

**Background:** Worldwide, nearly 50 million people have Alzheimer's or related dementia. Alzheimer's disease (AD) afflicts an estimated 6 million adults in the US and its prevalence is expected to more than double in the next 30 years. Up to 70% of AD patients experience the neuropsychiatric symptom of agitation related to the underlying pathology of AD. Alterations in neurotransmitters, including serotonin, glutamate, sigma-1, norepinephrine, and dopamine, in AD are thought to contribute to cognitive and behavioral symptoms including agitation and aggression. AD agitation is highly distressing and is associated with decreased functioning, accelerated cognitive decline, earlier institutionalization, heightened caregiver burden, and increased mortality. With no approved pharmacotherapies for AD agitation, prescribers often resort to off-label use of medications, especially atypical antipsychotics, which are associated with adverse health sequelae such as increased occurrence of cerebrovascular events and death. There is therefore an urgent unmet need to find safe and effective medicines to treat AD agitation. AXS-05

is a novel, oral, investigational NMDA receptor antagonist with multimodal activity under development for the treatment of Alzheimer's disease agitation, major depressive disorder, and other central nervous system (CNS) disorders. The dextromethorphan component of AXS-05 is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, also known as a glutamate receptor modulator, a sigma-1 receptor agonist, an inhibitor of the serotonin and norepinephrine transporters, a nicotinic acetylcholine receptor antagonist, and an inhibitor of microglial activation. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. AXS-05 has been granted breakthrough therapy designation by the FDA for the treatment of AD agitation. **Objective:** The objective of the ADVANCE-1 trial was to evaluate the efficacy and safety of AXS-05 in the treatment of AD agitation. **Methods:** The ADVANCE-1 Phase 2/3 trial was a randomized, double-blind, controlled, multicenter, 5-week trial conducted entirely in the United States. Patients with a diagnosis of probable AD and with clinically significant agitation were randomized initially in a 1:1:1 ratio to treatment with AXS-05, bupropion or placebo. AXS-05 was dose escalated to 45 mg/105 mg twice daily over the first 2 weeks. Based on an interim analysis at approximately 30% enrollment, an independent data monitoring committee recommended no further randomization to the bupropion arm and randomization continued 1:1 to AXS-05 or placebo. The primary endpoint was the change in the Cohen Mansfield Agitation Inventory (CMAI) total score from baseline to 5 weeks for AXS-05 versus placebo. **Results:** Three hundred and sixty-six (366) subjects were randomized in the ADVANCE-1 trial: 159 to AXS-05, 158 to placebo, and 49 to bupropion. On the primary endpoint, AXS-05 treatment resulted in a statistically significant improvement in symptoms of agitation as measured by the change in the CMAI total score from baseline to week 5 as compared to placebo (-15.4 points vs. -11.5 respectively;  $p=0.010$ ). AXS-05 rapidly improved agitation demonstrated by statistically significant improvement on the CMAI total score one week after achieving the target dose of AXS-05 ( $p=0.007$ ). Component contribution was demonstrated with AXS-05 by statistically significantly improving CMAI total scores compared to bupropion (-15.4 vs. -10.0 respectively;  $p<0.001$ ) at week 5. These results with AXS-05 were clinically meaningful and statistically significant as assessed by a clinical response of 30% percent or greater improvement on the CMAI. At week 5, 73% of patients treated with AXS-05 achieved a clinical response versus 57% with placebo ( $p=0.005$ ). Superiority over placebo was also achieved with AXS-05 on the clinicians' global assessment, the modified Alzheimer's Disease Cooperative Study clinical global impression of change for agitation (mADCS-CGI agitation) ( $p=0.036$ ) at week 5, a key secondary endpoint. AXS-05 was well tolerated in this trial. The most commonly reported adverse events in the AXS-05 arm were somnolence (8.2% for AXS-05 versus 4.1% for bupropion and 3.2% for placebo), dizziness (6.3%, 10.2%, 3.2%, respectively), and diarrhea (4.4%, 6.1%, 4.4%, respectively). The rates of discontinuation due to adverse events were 1.3%, 2.0%, and 1.3% in the AXS-05, bupropion, and placebo arms, respectively. There was no evidence of cognitive decline for patients treated with AXS-05 as shown by the Mini-Mental State Examination (MMSE). Treatment with AXS-05 was not associated with sedation. **Conclusion:** AXS-05 rapidly and robustly improved symptoms of agitation in patients with AD. With no FDA-approved treatment for AD

agitation, AXS-05 represents a novel approach and potentially first-in-class treatment for this condition. Statistically significant improvements in agitation as measured by the CMAI total score also translated into statistically significantly superior rates of clinical response with AXS-05 as compared to placebo. AXS-05 was safe and well tolerated in this trial and was neither associated with cognitive impairment nor sedation.

**OC2: THE AHEAD 3-45 STUDY OF BAN2401 IN PRECLINICAL ALZHEIMER'S DISEASE: STUDY DESIGN AND INITIAL SCREENING RESULTS.** R.A. Sperling<sup>1</sup>, R. Amariglio<sup>1</sup>, S. Dhadda<sup>2</sup>, M.C. Donohue<sup>3</sup>, M.C. Irizarry<sup>2</sup>, C. Jenkins<sup>3</sup>, D. Jianjun Li<sup>2</sup>, K.A. Johnson<sup>4</sup>, L. Kramer<sup>2</sup>, S. Krause<sup>2</sup>, K. Papp<sup>1</sup>, M. Rabe<sup>2</sup>, R. Raman<sup>3</sup>, D. Rentz<sup>1</sup>, G. Sethuraman<sup>3</sup>, C.J. Swanson<sup>2</sup>, J. Zhou<sup>2</sup>, P.S. Aisen<sup>3</sup> ((1) Brigham And Women's Hospital, Massachusetts General Hospital, Harvard Medical School - Boston, Massachusetts, USA; (2) Eisai - Woodcliff Lake, New Jersey, USA; (3) University Of Southern California - San Diego, California, USA; (4) Massachusetts General Hospital, Brigham And Women's Hospital, Harvard Medical School - Boston, Massachusetts, USA)

**Background:** Amyloid- $\beta$  ( $A\beta$ ) accumulation begins more than a decade prior to the clinical stages of Alzheimer's disease (AD) and is thought to play a critical role in accelerating the spread of tauopathy and neurodegeneration during the preclinical stages of the disease. Multiple neuroimaging and biomarker observational studies demonstrate that  $A\beta$  accumulation is associated with increased risk of cognitive decline among clinically normal older individuals. BAN2401 is an IgG1 monoclonal antibody that selectively targets soluble aggregated  $A\beta$  species, with activity across oligomers, protofibrils and fibrillar deposits. In a recent Phase 2 Bayesian adaptive design trial in patients with mild cognitive impairment (MCI) due to AD or mild AD dementia (NCT01767311), BAN2401 demonstrated dose-related reduction of amyloid burden on PET imaging, with some supporting evidence of associated change in cerebrospinal fluid markers and slowing of cognitive decline in the highest dose groups. The AHEAD 3-45 Study (NCT04468659) was designed to test the efficacy and safety of BAN2401 in the preclinical stages of the AD continuum. **Objective:** To describe the study design and initial screening data for the AHEAD 3-45 study, a global multicenter clinical trial aimed at preventing pathophysiological progression and cognitive decline due to AD. **Methods:** The AHEAD 3-45 Study is designed and conducted as a Public-Private Partnership of the Alzheimer's Clinical Trial Consortium (ACTC) funded by the National Institute on Aging/National Institutes of Health (NIH) and Eisai, Inc. The AHEAD 3-45 Study consists of two sister trials (A3 Trial and A45 Trial) with tailored dosing regimens based on the screening amyloid PET level, conducted under a single protocol and screening process with a common schedule of assessments in cognitively normal (CN) individuals ages 55-80. Individuals age 55-64 must have an additional risk factor, including family history of first degree relative with AD/dementia prior to age 75, APOE  $\epsilon 4$  carrier, or previously known amyloid status, to be eligible for screening. The AHEAD 3-45 study is a global study with study sites in North America, Europe, Japan, Singapore and Australia. The Phase 2 A3 Trial aims to get closer to primary prevention of AD, through preventing early  $A\beta$  build-up in the brain. The A3 Trial will enroll CN individuals with intermediate levels of amyloid on screening PET imaging (approximately 20-40 centiloids), thought to be in the earliest preclinical stages of AD who are at risk for further  $A\beta$  accumulation and early spread of

tau pathology over four years. In the A3 Trial, approximately 400 participants will be randomized 1:1 to placebo or BAN2401 infusion—8 weeks of titration followed by 10 mg/kg every 4 weeks for 216 weeks to reduce soluble A $\beta$  aggregates and prevent further A $\beta$  accumulation. The Phase 3 A45 Trial targets the later stages of preclinical AD and aims to slow cognitive decline. The A45 Trial will enroll CN individuals with elevated amyloid on screening PET imaging (approximately >40 centiloids), who are at high risk for cognitive decline over 4 years. In the A45 trial, approximately 1000 participants will be randomized 1:1 to placebo or BAN2401 infusion—8 weeks of biweekly titration dosing, then 10 mg/kg biweekly induction dosing through 96 weeks to clear aggregated A $\beta$ , followed by 10 mg/kg every 4 weeks maintenance dosing through 216 weeks to prevent re-accumulation of A $\beta$ . The A3 and A45 Trials will utilize NAV4694 (flutafuranol) amyloid PET imaging to assess fibrillar amyloid pathology for eligibility and longitudinal outcomes, and the MK6240 tau PET tracer to assess spread of neurofibrillary tangle and tau neurite pathology longitudinally. Clinical outcomes include the Preclinical Alzheimer Cognitive Composite-5 (PACC-5) composed of the Free and Cued Selective Reminding Test, Paragraph Recall IIa, Digit-Symbol, MMSE, and Semantic Category Fluency, as well as the Cognitive Function Index (CFI), a participant- and study-partner report of cognitive function. **Results:** The primary outcome measure of the A45 Trial is the PACC-5 at 216 weeks, whereas the primary outcome of the A3 Trial is amyloid PET at 216 weeks, with tau PET accumulation as a key secondary outcome. Longitudinal cognitive, safety, amyloid and tau PET, MRI and fluid biomarker assessments will be performed. The AHEAD 3-45 Study participant screening launched on July 13, 2020, and initial patient screening data will be presented. **Conclusion:** The AHEAD 3-45 Study will evaluate the efficacy of BAN2401 in the prevention of A $\beta$  accumulation, spread of downstream tau pathology, and cognitive decline across the continuum of preclinical AD. The AHEAD 3-45 Study will utilize targeted dosing based on screening amyloid burden, aiming to delay the pathophysiological and clinical progression of AD, initiated prior to significant irreversible neurodegeneration and cognitive impairment.

**OC3: EMBARK: A PHASE 3B, OPEN-LABEL, SINGLE-ARM, SAFETY STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF ADUCANUMAB IN ELIGIBLE PARTICIPANTS WITH ALZHEIMER'S DISEASE.** C. Castrillo-Viguera<sup>1</sup>, S. Chalkias<sup>1</sup>, P. Burkett<sup>1</sup>, S. Wu<sup>1</sup>, H. Chen<sup>1</sup>, K. Harrison<sup>1</sup>, C. Yurgalevitch<sup>1</sup>, S. Budd Haeberlein<sup>1</sup> ((1) Biogen - Cambridge, USA)

**Background:** Aducanumab (BIIB037) is a human monoclonal antibody that selectively targets aggregated forms of amyloid beta (A $\beta$ ), including soluble oligomers and insoluble fibrils. Aducanumab is being investigated as a disease-modifying treatment for early Alzheimer's disease (AD). On March 21st, 2019, all ongoing clinical trials of aducanumab were terminated following a pre-specified futility interim analysis of the Phase 3 studies, EMERGE and ENGAGE. Further analyses of the Phase 3 studies were conducted post-futility announcement using data from all randomized and dosed participants collected through April 1, 2019 with data after March 20, 2019 censored for efficacy analysis. In these final analyses, EMERGE met the pre-specified primary and secondary endpoints and data demonstrated that participants treated with high dose aducanumab had a statistically significant slowing of

clinical decline when compared to placebo at 18 months. Post-hoc analyses of data from a subset of patients exposed to high dose aducanumab in ENGAGE support the findings of EMERGE. The EMBARK (NCT04241068) re-dosing study was designed following analyses of the results of the Phase 3 studies of aducanumab. **Objectives:** We describe the design of EMBARK, a Phase 3b re-dosing study of aducanumab in eligible participants with Alzheimer's disease. **Methods:** EMBARK is an open-label, single arm clinical safety study (NCT04241068) with a 24-month treatment period assessing the long-term safety and efficacy of aducanumab in participants with AD who were actively participating in the aducanumab clinical studies PRIME, EVOLVE, EMERGE, or ENGAGE at the time of their discontinuation (March 21, 2019). Eligible participants, who were previously receiving aducanumab or placebo in an aducanumab clinical study at the time of the announcement of early termination, must also have one care partner who, in the investigator's opinion, has adequate contact with the participant and is able to provide accurate information about the participant's cognitive and functional abilities. Other protocol-defined inclusion/exclusion criteria may apply. All participants will be titrated (1mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter) to receive 10 mg/kg aducanumab by intravenous (IV) infusion every 4 weeks. All participants will be assigned to the same titration schedule regardless of the dose received in the prior trial in which they took part. The study includes an approximately 8-week screening period, a 100-week treatment period and an 18-week safety and follow-up visit after the last dose. The primary objective of EMBARK is to evaluate the long-term safety and tolerability of aducanumab. The primary endpoints are number of participants with adverse events (AEs) and serious adverse events (SAEs), number of participants with AEs leading to treatment discontinuation or study withdrawal, number of participants with amyloid-related imaging abnormality-edema (ARIA-E) or amyloid-related imaging abnormality-hemorrhage or superficial siderosis (ARIA-H), and number of participants with anti-aducanumab antibodies in serum. Exploratory objectives of the study are the evaluation of long-term efficacy of aducanumab as measured by change in cognitive, neuropsychiatric, functional and quality of life assessments. In addition, long-term effect of aducanumab on pharmacokinetic endpoints will be evaluated. Exploratory biomarker endpoints include amyloid and tau positron emission tomography (substudies), morphometric magnetic resonance imaging, and fluid biomarkers (blood and cerebrospinal fluid). **Results:** The EMBARK study is currently enrolling. **Conclusions:** EMBARK is expected to be one of the largest clinical trials in AD, with a plan to enroll approximately 2400 participants. The results of EMBARK will provide further information on the long-term safety and efficacy of aducanumab.

**OC4: PHASE 2 STUDY OF TILAVONEMAB, AN ANTI-TAU ANTIBODY, IN EARLY ALZHEIMER'S DISEASE: STUDY DESIGN, BASELINE DEMOGRAPHICS, AND BIOMARKER PROFILES.** N. Fisseha<sup>1</sup>, A. Bannon<sup>1</sup>, H. Florian<sup>1</sup>, Q. Guo<sup>1</sup>, Z. Jin<sup>1</sup>, B. Rendenbach-Mueller<sup>1</sup>, D. Wang<sup>1</sup>, D. Wooten<sup>1</sup>, S. Arnold<sup>2</sup> ((1) Abbvie Inc., - North Chicago, USA; (2) Massachusetts General Hospital - Boston, USA)

**Background:** Tau and amyloid are recognized as hallmarks of Alzheimer's disease (AD). Positron emission tomography (PET) imaging of these proteins and biofluid markers like

amyloid- $\beta$  (A $\beta$ ), total tau (t-tau) and phosphorylated tau (p-tau) are key to assessing pathophysiology of AD (1, 2). Accumulating tau pathology is closely associated with cognitive decline (2); therefore, anti-tau therapies may have the potential to be efficacious, even when administered to patients who may already be showing clinical symptoms of AD. Tilavonemab is a monoclonal antibody that binds to the N terminus of human tau and is currently being developed as a treatment for early AD. **Objectives:** The purpose of this work is to present the study design and characterize the baseline demographic and preliminary biomarker profile of patients with early AD in an ongoing phase 2 study of tilavonemab. **Methods:** This is a 96-week, randomized, double-blind, placebo-controlled, global phase 2 study evaluating the efficacy and safety of tilavonemab in patients with early AD (NCT02880956). The study targeted enrollment of approximately 400 male and female patients (aged 55–85 years) who met the clinical criteria for early AD (Clinical Dementia Rating [CDR]-Global Score of 0.5, Mini-Mental State Examination [MMSE] score of 22 to 30, Repeated Battery for the Assessment of Neuropsychological Status-Delayed Memory Index [RBANS-DMI] score of 85 or lower, and had a positive amyloid PET scan). Patients were randomized (1:1:1) to 1 of the 3 doses of tilavonemab or placebo. Cerebrospinal fluid (CSF) samples are being collected in a subset of patients at screening and at weeks 12 and 96 for biomarker analysis. Blood samples are being collected at screening and at several timepoints throughout the study. A subset of patients are undergoing tau PET imaging at screening, and at weeks 44 and 96. The primary efficacy endpoint is the change from baseline to week 96 in CDR-Sum of Boxes (CDR-SB) score. Secondary efficacy outcomes include tilavonemab pharmacokinetics, and efficacy in slowing cognitive and functional impairment as measured by changes from baseline to week 96 in MMSE, RBANS, and other outcome measures. Adverse events are being recorded. For this exploratory biofluid biomarker analysis, the Roche Elecsys® immunoassay platform (Roche Group, Basel, Switzerland) was used to assess CSF biomarkers. An automated, validated image processing pipeline (AbbVie Inc., North Chicago, IL, USA) was used for Centiloid (CL) estimation of PET amyloid burden in the brain in addition to visual assessment at screening, and a standardized uptake value ratio (SUVR) was calculated in the entorhinal cortex to assess the presence of tau pathology in the brain. **Results:** The study enrolled 453 patients with a mean (standard deviation [SD]) age of 71.3 (7.0) years. Of all enrolled patients, 48% were male, 52% were female, 97% were white, 2% were black, and 1% were Asian. Baseline mean (SD) MMSE score was 24.4 (2.9), RBANS score was 71.7 (12.3), and CDR-SB score was 3.0 (1.2). All randomized patients were amyloid positive by visual read. Mean (SD) amyloid PET was 99.0 CL (31.1), and >99% of subjects (449/453) had measurements over 20 CL, a threshold used for positivity (1). For 70 patients with baseline tau PET data, 96% (67/70) were considered to have tau pathology in the brain (SUVR  $\geq$ 1.27 in the entorhinal cortex [3]). At baseline, mean (SD) core CSF biomarker values measured in a subset of 224 patients were: A $\beta$ 40, 17.6 (5.1) ng/mL; A $\beta$ 42, 615.7 (179.7) pg/mL; t-tau, 384.0 (166.6) pg/mL; and p-tau181, 38.2 (15.7) pg/mL. Other emerging CSF biomarker values measured in the same subset of 224 patients were:  $\alpha$ -synuclein, 254.5 (125.2) pg/mL; glial fibrillary acidic protein (GFAP), 12.2 (4.5) ng/mL; interleukin (IL)-6, 4.4 (7.2) pg/mL; neurogranin, 1134.9 (524.7) pg/mL; neurofilament light chain (NFL), 192.9 (130.0) pg/mL; S100B protein, 1.2 (0.4) ng/mL; soluble triggering receptor expressed on myeloid

cells 2 (sTREM2), 9.6 (3.1) ng/mL; and YKL-40, 193.9 (80.0) ng/mL. Mean (SD) biomarker ratios were: A $\beta$ 42/A $\beta$ 40, 0.04 (0.01); t-tau/A $\beta$ 42, 0.6 (0.3); and p-tau181/A $\beta$ 42, 0.06 (0.03).

**Conclusion:** Baseline demographics, disease characteristics, and biomarker profiles of patients in this phase 2 study are similar to the profiles of patients with early AD reported in the literature, including cognitive status, and tau and amyloid burden on PET [1,4,5]. At baseline, patients in this study exhibit slightly higher levels of CSF amyloid and slightly lower levels of CSF tau than patients in other studies with similar populations [4,5]. Evaluation of tilavonemab safety and efficacy in these patients remains ongoing. Future analyses will examine the effect of tilavonemab treatment on biomarker profiles in this population of patients with early AD. **References:** 1. Burnham SC, et al. *Brain Communications*. 2020;2:1-7. 2. Holtzman DM, et al. *Sci Transl Med*. 2011;3:77sr1. 3. Betthausen TJ, et al. *Brain*. 2020;143:320-335. 4. Ostrowitzki S, et al. *Alzheimers Res Ther*. 2017;9:95. 5. Timmers M, et al. *Alzheimers Res Ther*. 2018;10:85.

**OC5: KETONES IMPROVE BRAIN ENERGETICS AND COGNITIVE PERFORMANCE IN MILD COGNITIVE IMPAIRMENT: FINAL RESULTS OF THE 6-MONTH BENEFIC TRIAL IN MCI.** S. Cunnane<sup>1</sup>, M. Fortier<sup>1</sup>, A. Castellano<sup>1</sup>, V. St-Pierre<sup>1</sup>, É. Myette-Côté<sup>1</sup>, M. Roy<sup>1</sup>, M.C. Morin<sup>1</sup>, F. Langlois<sup>1</sup>, C. Delannoy<sup>2</sup>, B. Cuenoud<sup>2</sup>, C. Bocti<sup>1</sup>, T. Fulop<sup>1</sup> ((1) *Université De Sherbrooke - Sherbrooke, Canada*; (2) *Nestlé Health Science - Lausanne, Switzerland*)

**Background:** Brain glucose uptake is about 10% below normal in mild cognitive impairment (MCI) and deteriorates further in Alzheimer disease (AD). It is now clear that in contrast to glucose, uptake of the brain's main alternative fuel – ketones (acetoacetate and beta-hydroxybutyrate) – remains normal in both MCI and mild-moderate AD. Furthermore, evidence is accumulating that an endogenous or exogenous source of ketones can at least partially bypass brain glucose hypometabolism and improve brain energy metabolism in both MCI and mild-moderate AD. The key question now is whether improved brain energy metabolism also improves cognitive performance in MCI or AD. The objective of the randomized, placebo-controlled Benefic trial (NCT02551419) was to assess whether counteracting the brain glucose deficit with an oral nutritional supplement containing a ketogenic medium chain triglyceride (kMCT-ONS) could improve cognitive performance over 6 months in MCI. **Methods:** Following screening with a comprehensive cognitive battery, n=122 MCI were recruited (amnesic and non-amnesic MCI combined). An overall sample size of n=82 completers for both arms combined was required to have the necessary power to detect at least a moderate effect size on cognitive outcomes of episodic memory and executive function. Outcomes in all five main cognitive domains were assessed immediately before and at the end of the intervention. The ONS was lactose-free skim milk emulsion containing 12% kMCT providing 15 g kMCT twice/day (active arm) or an energy equivalent placebo providing 12 g non-ketogenic vegetable oil twice/day. The formulation and organoleptic properties of the ONS were identical for both active and placebo arms. Brain ketone and glucose PET were done before and at the end of the 6-month intervention on sub-groups of both arms (n=19/arm pre- and post-intervention). The plasma ketone response was assessed before and after the intervention in a different sub-group (n=10/arm pre- and post-intervention). Plasma cardiometabolic and inflammatory marker profiles were also assessed. Data were analyzed by ANCOVA using

pre-intervention cognitive score plus age, sex, education and apolipoprotein E4 status combined as covariates. **Results:** N=39 completed the active arm and n=44 completed the placebo arm. Raw scores as well as normalized Z-scores for five tests in three cognitive domains improved post-intervention on the kMCT arm only ( $p \leq 0.01$ ). Specifically, on the kMCT arm, trial 1 of the Free and Cued Recall Test showed a +1 word improvement ( $+0.5 \Delta$  Z-score), correct answers on the Verbal Fluency Test increased by 2 words ( $+0.3 \Delta$  Z-score) but decreased by 1 word on placebo ( $-0.1 \Delta$  Z-score), correct answers on the Boston Naming Test increased by 1.1, time taken on the Stroop Colour Naming Test decreased by 1 sec ( $p=0.09$ ), and errors on the Trail Making Test decreased by 0.9 on the kMCT arm but increased by 0.8 on the placebo arm ( $p=0.02$ ). Global brain ketone uptake doubled on the kMCT arm only and directly as the increase in plasma ketones ( $r = +0.87$ ,  $p < 0.01$ ). Moderate effect sizes (partial  $\eta^2 = 0.06 - 0.14$ ) were seen for several cognitive outcomes on the kMCT arm only. Free and cued recall, Trail-making, and Boston Naming test scores all correlated significantly and directly as the increase in plasma or global brain ketone uptake on kMCT ( $r = +0.23 - +0.33$ ,  $p = 0.013 - 0.042$ ). Increased uptake of ketones in multiple brain white matter fascicles was significantly positively correlated with faster processing speed on the kMCT arm ( $r = +0.47 - +0.61$ ,  $p = 0.014 - 0.047$ ;  $n=16$ ). Plasma ketone response to a single 15-gram dose of the kMCT did not change significantly at the end vs. before the 6-month intervention; ketones did not increase at all on the placebo arm. Changes in anthropometry (weight, BMI) and plasma markers of cardiometabolic health (insulin, glucose, cholesterol) were not clinically significant post-intervention on either arm. Amongst the plasma inflammatory markers, only interleukin 8 increased on the kMCT arm ( $+3$  pg/ml; interaction  $p = 0.002$  vs. post-placebo;  $n=17$ ). Average drop-out rate on both arms combined was 31%. In completers, protocol adherence was 89% over six months. **Conclusions:** The Benefic Trial was powered to assess outcomes of memory and executive function in MCI and demonstrated that this kMCT-ONS improved several cognitive outcomes that were positively correlated with the improved brain energy status achieved by the increased supply of ketones. Hence, there was a direct mechanistic link between raising brain ketones with the kMCT-ONS and improving cognitive performance in MCI. The consistent plasma ketone response suggests there was no metabolic adaptation or loss of response to an oral dose of kMCT after daily consumption over six months. These results demonstrate efficacy, safety, acceptability, and feasibility of long-term use of 15-gram twice daily dose of kMCT-ONS to improve cognitive performance in MCI. The moderate effect size of the improved cognitive scores (raw and Z-scores) indicates that the cognitive improvement observed was probably clinically meaningful, suggesting that sustainably improving brain energy supply with this kMCT-ONS could significantly reduce the risk of MCI progressing toward AD. This possibility now deserves to be prospectively assessed in a multi-center longitudinal study. **Acknowledgments:** Financial support for the Benefic Trial was provided by the Alzheimer Association USA, FRQS, Université de Sherbrooke and Nestlé Health Science. Abitec provided the kMCT (Captex 355) and placebo oil (high oleic acid sunflower oil). EMC held a postdoctoral fellowship jointly funded by the Fonds de recherche du Québec-Santé and the Alzheimer's Society of Canada. MR was funded by MITACS. The ONS for both arms was prepared under contract at INAF, Université Laval, Québec, QC, Canada. SCC has consulted for or received travel

honoraria or test products for research from Nestlé Health Science, Bulletproof, Cerecin, and Abitec. SCC is the founder and director of the consulting company, Senotec Ltd. No other conflicts to report.

**OC6: VOXEL BASED MORPHOMETRY REVEALS A DISTRIBUTED PATTERN OF GREY MATTER VOLUME CHANGES FOLLOWING VERUBECESTAT EXPOSURE IN THE EPOCH TRIAL.** D. Scott<sup>1</sup>, K. Adamczuk<sup>1</sup>, M. Sampat<sup>1</sup>, H. Pham<sup>1</sup>, J. Kost<sup>2</sup>, M. Egan<sup>2</sup>, C. Sur<sup>2</sup> ((1) Bioclinica - Newar, USA; (2) Merck - Kenilworth, USA)

**Background:** Inhibition of  $\beta$ -amyloid precursor protein cleaving enzyme (BACE1) has been proposed as a therapeutic strategy to slow Alzheimer's disease (AD) progression by reducing  $A\beta$  production. The EPOCH trial of the BACE1 inhibitor verubecestat in patients with mild-to-moderate AD failed to demonstrate slowing of disease progression over 78 weeks, despite significant reduction of brain amyloid as assessed by amyloid PET. Following 78 weeks of treatment, verubecestat was associated with greater reduction in total hippocampal volume, greater reduction in cortical thickness, and increased ventricular enlargement compared to placebo. Similar findings have been reported for other investigational treatments targeting  $A\beta$ , as well as those targeting non-amyloid mechanisms. Several hypotheses have been proposed to explain the MRI findings including increased neurodegeneration, amyloid clearance and/or inflammation, or fluid shifts. **Objective:** Here we report on additional analyses of volumetric MRI (vMRI) data from EPOCH to provide a more comprehensive assessment of vMRI changes with verubecestat. We performed whole-brain voxel based morphometric (VBM) analysis to assess the impact of verubecestat exposure on grey matter (GM) tissue density at week 13 and week 78, compared to baseline. **Methods:** MR images from 1,040 patients were assigned to placebo ( $n=355$ ), 12mg ( $n=336$ ) and 40mg ( $n=349$ ) treatment groups. SPM12 was used to segment 3D T1-weighted MR images by tissue class, after which native-space grey and white matter segments were input into the DARTEL routine. DARTEL uses non-linear deformation fields to warp GM images together while simultaneously warping white matter images, and generates an increasingly crisp average template to which the data are iteratively aligned. The population-based template was then registered to MNI template space via affine transformation, and the combined transformations are propagated to the individual flow fields generated for each exam. The final template, flow fields and native-space tissue segments are entered as input into the algorithm, which is configured to preserve the amount of tissue ("modulation"). Modulation normalizes local tissue intensities such that the regional total is preserved, thus permitting voxelwise comparison of the amount of GM in brain regions which are completely registered. Spatially-normalized, Jacobian-scaled GM tissue maps were smoothed with a 4mm isotropic FWHM kernel, and pairwise change-from-baseline maps were generated for each subject at week 13 and week 78 visits. Difference images were entered into general linear models to perform voxelwise t-tests between treatment groups. Resulting statistical maps were thresholded at family-wise error  $p < 0.05$  to correct for multiple comparisons. **Results:** Verubecestat treatment was associated with a highly significant reduction in GM tissue density at week 13 and week 78 in both dose groups, compared to placebo. Compared to the placebo group at week 13, the 12mg dose group demonstrated significantly greater GM

volume loss in left inferior frontal gyrus, left fusiform gyrus and right occipital cortex; the 40mg dose group demonstrated significantly greater volume loss in bilateral angular gyrus, bilateral occipital cortex, left fusiform gyrus, left inferior frontal gyrus, left orbitofrontal cortex, right middle temporal cortex, right supplementary motor area, and left posterior cingulate cortex. Compared to the placebo group at week 78, the 12 mg dose group demonstrated significantly greater volume loss in bilateral occipital cortex, bilateral superior parietal cortex, left fusiform gyrus, bilateral posterior cingulate cortex, left primary motor cortex, bilateral primary auditory cortex, left inferior temporal cortex, bilateral superior temporal cortex, right premotor cortex, left hippocampus, right medial prefrontal cortex, right supramarginal gyrus, right angular gyrus, left dorsal anterior cingulate cortex; the 40mg dose group demonstrated significantly greater volume loss in bilateral occipital cortex, right hippocampus, bilateral superior parietal cortex, bilateral angular gyrus, bilateral supplementary motor area, left primary sensory cortex, left fusiform gyrus, right supramarginal gyrus, and bilateral medial prefrontal cortex. **Conclusion:** These results suggest exposure to verubecestat is associated with significant alteration in GM tissue density throughout the brain. GM tissue volumes are reduced in a consistent set of brain regions for both dose groups, and the effect is apparent after 13 weeks of treatment. The pattern of GM tissue reduction is most prominent in occipital and posterior brain regions, though relevant temporal, parietal and frontal features are also observed. These findings add further evidence that BACE1 inhibition is associated with a distributed pattern of altered tissue contrast throughout the brain.

**OC7: SYNAPTIC DENSITY IS ASSOCIATED WITH COGNITIVE PERFORMANCE IN ALZHEIMER'S DISEASE: A PET IMAGING STUDY WITH [11C]UCB-J.** A. Mecca, E. Sharp, R. O'dell, E. Banks, H. Bartlett, M.K. Chen, M. Naganawa, T. Toyonaga, J. Harris, G. Ni, W. Zhao, N. Nabulsi, B. Vander Wyk, Y. Huang, A. Arnsten, R. Carson, C. Van Dyck (*Yale School Of Medicine - New Haven, USA*)

**Background:** For 30 years synapse loss has been referred to as the major pathological correlate of cognitive impairment in Alzheimer's disease (AD) (1, 2). However, this statement is based on remarkably few patients studied by autopsy or biopsy in limited brain regions, largely at the moderate to severe stages of disease. With the recent advent of synaptic positron emission tomography (PET) imaging, we have begun to evaluate synaptic alterations in vivo. Synaptic vesicle glycoprotein 2A (SV2A) is expressed in virtually all synapses and is located in synaptic vesicles at presynaptic terminals (3). [11C]UCB-J was recently developed as a PET tracer for SV2A and advanced for human studies (4). In our recent study of [11C]UCB-J PET, we observed widespread reductions of SV2A binding in medial temporal and neocortical brain regions in early AD compared to CN participants (5). However, initial attempts using PET imaging to associate synaptic density with cognitive performance have been hindered by the use of limited cognitive measures. **Objectives:** In this study we examined the relationship between synaptic density and cognitive performance in early AD using [11C]UCB-J PET and an extensive neuropsychological test battery. **Methods:** Using [11C]UCB-J binding to SV2A, synaptic density was measured in 45 amyloid positive participants with AD (17 amnesic mild cognitive impairment and 28 mild dementia) and 20 amyloid negative cognitively normal (CN) participants aged 50-85 years. Synaptic density was calculated

as the distribution volume ratio (DVR) in a composite region of interest (ROI) of AD-affected regions (prefrontal, lateral temporal, medial temporal, lateral parietal, anterior cingulate, posterior cingulate, precuneus, and lateral occipital) using cerebellum as reference region. A neuropsychological test battery was administered to assess performance in five cognitive domains: Verbal Memory (Logical Memory II, Rey Auditory Verbal Learning Test [RAVLT] total words recalled across trials 1-5, RAVLT delayed recall), Language (Boston Naming Test, Category Fluency), Executive Function (Stroop Color Word, Trails B, Letter Fluency), Processing Speed (Stroop Word, Trails A, WAIS-3 Digit Symbol Substitution), and Visuospatial Ability (Rey-Osterrieth Complex Figure, WAIS-3 Block Design, WAIS-3 Picture Completion). Neuropsychological test raw scores were converted to z-scores using the means and SDs from the pooled AD and CN sample), and cognitive domain scores were generated for each AD participant by averaging z-scores within the domain. Global cognitive scores were then generated for each participant by averaging the five domain scores. **Results:** In a multiple linear regression model controlling for age, sex, and education, synaptic density ([11C]UCB-J DVR) was a significant predictor of global cognitive performance in participants with AD ( $\beta=3.21$ ,  $\eta^2=0.29$ ,  $P=0.0001$ ). Synaptic density was also a significant predictor of performance in all five cognitive domains: Language ( $\beta=3.82$ ,  $\eta^2=0.25$ ,  $P=0.001$ ), Executive Function ( $\beta=3.28$ ,  $\eta^2=0.20$ ,  $P=0.001$ ), Processing Speed ( $\beta=4.03$ ,  $\eta^2=0.23$ ,  $P=0.001$ ), Visuospatial Ability ( $\beta=3.58$ ,  $\eta^2=0.22$ ,  $P=0.001$ ), verbal memory ( $\beta=1.35$ ,  $\eta^2=0.11$ ,  $P=0.022$ ). The relatively weak association with verbal memory may have resulted from floor effects on the measures that comprised this domain. The observed associations between synaptic density and global cognition remained significant after correction for partial volume effects ( $\beta=2.16$ ,  $\eta^2=0.23$ ,  $P=0.001$ ), and synaptic density was a stronger predictor of cognitive performance than gray matter volume ( $\beta=0.01$ ,  $\eta^2=0.17$ ,  $P=0.005$ ). **Conclusion:** These results confirm neuropathologic studies, demonstrating a significant association between synaptic density and cognitive performance, and suggest that this correlation extends to the mild and prodromal stages of AD. They further support the use of synaptic imaging as a potential surrogate biomarker outcome for therapeutic trials that is well-correlated with clinical measures. Longitudinal studies are needed to relate change in synaptic density as measured by [11C]UCB-J PET with change in cognitive performance. **References:** 1. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann Neurol.* 1991;30:572-580. 2. DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. *Ann Neurol.* 1990;27:457-464. 3. Bajjalieh SM, Peterson K, Linial M, Scheller RH. Brain contains two forms of synaptic vesicle protein 2. *Proc Natl Acad Sci U S A.* 1993;90:2150-2154. 4. Finnema SJ, Nabulsi NB, Eid T, Detyniecki K, Lin SF, Chen MK, Dhaher R, Matuskey D, Baum E, Holden D, Spencer DD, Mercier J, Hannestad J, Huang Y, Carson RE. Imaging synaptic density in the living human brain. *Sci Transl Med.* 2016;8:348ra96. 5. Mecca AP, Chen MK, O'Dell RS, Naganawa M, Toyonaga T, Godek TA, Harris JE, Bartlett HH, Zhao W, Nabulsi NB, Vander Wyk BC, Varma P, Arnsten AFT, Huang Y, Carson RE, van Dyck CH. In vivo measurement of widespread synaptic loss in Alzheimer's disease with SV2A PET. *Alzheimers Dement.* 2020;16:974-982.

**OC8: LONGITUDINAL 18F-RO948 PET AND BIOMARKER DRIVEN ENRICHMENT STRATEGIES FOR TAU PATHOLOGY IN AD CLINICAL TRIALS.** A. Leuzy<sup>1</sup>, G. Klein<sup>2</sup>, N. Cullen<sup>3</sup>, N. Mattsson-Carlgrén<sup>1</sup>, S. Janelidze<sup>1</sup>, S. Palmqvist<sup>1</sup>, X. Teitsma<sup>1</sup>, O. Strandberg<sup>1</sup>, P. Coloma<sup>2</sup>, E. Borroni<sup>2</sup>, E. Stomrud<sup>1</sup>, R. Smith<sup>1</sup>, R. Ossenkoppele<sup>1</sup>, O. Hansson<sup>1</sup> ((1) *Lund University - Lund, Sweden*; (2) *F. Hoffmann-La Roche Ltd - Basel, Switzerland*)

**Background:** Tau PET imaging has been shown to reliably detect the tau-containing paired helical filaments seen in Alzheimer's disease (AD), allowing for their visualization and quantification in vivo. Given the central role that tau pathology is thought to play in the progression and clinical manifestation of AD, tau PET carries great potential, both as a diagnostic tool and as a method to select and monitor patients in clinical trials (e.g. for patient selection, resulting in shorter trial duration and fewer persons needed; and as an indicator of target engagement). As tau PET is a relatively recent technique, there is little longitudinal data looking at change in regional uptake over time. In addition, several novel tracers characterized by improved specificity and dynamic range have recently entered the field, including 18F-RO948. Alongside measures of amyloid- $\beta$  (A) and neurodegeneration (N), tau PET (T) has been incorporated into an ATN classification system which defines AD by its underlying pathological processes. **Objectives:** To examine the spatial pattern of longitudinal change in 18F-RO948 PET SUVR across predetermined regions of interest (ROIs) in cognitively unimpaired (CU) individuals and patients with mild cognitive impairment (MCI) and AD dementia who were amyloid- $\beta$  positive. Further, we examined potential enrichment strategies using longitudinal change in 18F-RO948 SUVR as outcome and cross-sectional (baseline) measures of A, T and N as predictors. In connection with this, we also calculated sample sizes required to achieve 80% power to observe a reduction in annual change in tau PET when using different combinations of ATN biomarkers as baseline inclusion measures. **Methods:** The cohort consisted of 232 subjects from the Swedish BioFINDER-2 study. These included 46 A $\beta$ -positive CU, 49 MCI and 47 AD dementia (all A $\beta$ -positive) and 90 A $\beta$ -negative subjects (79 CU, 11 MCI). PET using 18F-RO948 was performed 70 to 90 minutes post injection. Subjects underwent follow-up scans with 18F-RO948 after approximately 18-months [mean 18.81 (4.02)]. Standardized uptake value ratio (SUVR) images were created using the inferior cerebellar cortex as the reference region. Annual change in SUVR was calculated by diagnostic group across three predefined ROIs: Braak I/II (entorhinal cortex and hippocampus), Braak III/IV (inferior/middle temporal, amygdala, parahippocampal cortex fusiform gyrus) and Braak V/VI (widespread neocortical areas). For the second aim, we selected the Braak ROIs showing the highest annual change in tau PET SUVR in A $\beta$ -positive CU and MCI. We then used linear models, with change in 18F-RO948 SUVR as outcome variable and different combinations of A (amyloid PET: neocortical 18F-flutemetamol SUVR, using pons as reference), T (18F-RO948 SUVR at baseline in the ROI that showed the highest annual change) and N (hippocampal volume) as predictors. Model fit was assessed using Akaike information criterion (AIC). As amyloid PET is, by design, only performed in CU and MCI subjects in BioFINDER-2, these analyses were performed using A $\beta$ -positive CU and MCI only. Power analyses were performed groupwise to explore the required sample size as a function of estimated treatment effect (25% reduction in annual change

in tau PET in the ROI showing the greatest annual increase). **Results:** The largest annual longitudinal changes in 18F-RO948 SUVR followed a group/Braak ROI specific pattern: Braak I/II for A $\beta$ -positive CU (3.13%), III/IV for A $\beta$ -positive MCI (3.37%) and V/VI (neocortical) for AD dementia (4.94%). In A $\beta$ -negative subjects, SUVR values increased <1% across ROIs. Regression models showed that in A $\beta$ -positive CU, the best model fit was seen when using 18F-RO948 SUVR in Braak I/II at baseline as predictor and annual change in hippocampal 18F-RO948 SUVR as outcome (AIC=-136.4, R<sup>2</sup>=0.141). In A $\beta$ -positive MCI (using annual change in 18F-RO948 SUVR in Braak III/IV as outcome), the best model fit, as assessed by AIC, was provided by 18F-RO948 SUVR at baseline in the Braak III/IV ROI (AIC=-160.5, R<sup>2</sup>=0.253). Power analyses in A $\beta$ -positive CU showed that among all the ATN biomarkers evaluated, tau PET in Braak I/II was the best screening marker as it was associated with the largest drop in sample size needed (e.g. by excluding those in the bottom 10% of 18F-RO948 SUVR values in Braak I/II at baseline, the number of required participants decreased by 11%). Tau PET at baseline was also the best performing measure in A $\beta$ -positive MCI, where excluding those in the bottom 10% of 18F-RO948 SUVR values in Braak III/IV at baseline reduced the number of participants required by 48%. Additional analyses are ongoing, including using biofluid (CSF and plasma) based measures of ATN and neuropsychological tests, as well as the validation of our findings using longitudinal 18F-flortaucipir data from a multicentre cohort (n=419). **Conclusion:** Initial results with longitudinal 18F-RO948 indicate that it is able to capture the progression of early tau pathology in A $\beta$ -positive CU subjects, as well as cortical increases in A $\beta$ -positive subjects with cognitive impairment. From a clinical trial perspective, a single baseline tau PET scan may prove suitable as an enrichment approach to capture longitudinal tau accumulation.

**OC9: PLASMA BIOMARKERS NEUROFILAMENT LIGHT AND GLIAL FIBRILLARY ACIDIC PROTEIN HIGHLIGHT DIFFERENT COMPONENTS OF ALZHEIMER'S DISEASE PROGRESSION IN A LONGITUDINAL MILD COGNITIVE IMPAIRMENT COHORT.** C. Cicognola<sup>1,2</sup>, S. Janelidze<sup>1</sup>, J. Hertze<sup>2</sup>, H. Zetterberg<sup>3,4,5</sup>, K. Blennow<sup>3,4</sup>, N. Mattsson-Carlgrén<sup>1</sup>, O. Hansson<sup>1,2</sup> ((1) *Clinical Memory Research Unit, Lund University - Lund, Sweden*; (2) *Memory Clinic, Skåne University Hospital - Malmö, Sweden*; (3) *Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At The University Of Gothenburg - Mölndal, Sweden*; (4) *Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal, Sweden*; (5) *Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square - London, United Kingdom*)

**Background:** While several studies have been done on pathognomonic Alzheimer's disease (AD) plasma biomarkers amyloid-beta (A $\beta$ ) and tau, only few have investigated other plasma biomarkers measuring processes associated to or initiated by AD pathology. Neurofilament light chain (NFL) is a protein expressed in myelinated axons that has been found increased in cerebrospinal fluid (CSF) following axonal damage in AD. NFL has been measured in plasma, where it showed that it was able to track the rate of neurodegeneration over time. A $\beta$  plaques also cause functional and morphological changes in the surrounding astrocytes; this process is defined as astrogliosis which is an early feature in the AD pathological cascade. Glial fibrillary acidic protein (GFAP) is expressed in the cytoskeleton of astrocytes and has been found significantly

increased in CSF in AD and other neurodegenerative diseases. Studies on plasma GFAP as AD biomarker are few and not longitudinal. **Objectives:** In this study, our aim was to evaluate and compare the potential of NFL and GFAP as potential plasma biomarkers of AD. **Methods:** 161 subjects with a baseline clinical MCI diagnosis were included, genotyped for APOE, followed for 4.7 years (average) and assessed for conversion to AD at follow-up. During follow-up, patients were divided into: -stable MCI, if they did not evolve to AD dementia or other dementias; -MCI-AD, if they evolved to dementia due to AD; -MCI-other, if they evolved to dementia due to other diseases (vascular dementia, progressive supranuclear palsy, Lewy body dementia, semantic dementia, normal pressure hydrocephalus). Plasma was collected at baseline and follow-up. Plasma NFL was measured with Simoa NF-light Advantage kits for SR-X (Quanterix®). Plasma GFAP was measured with Simoa GFAP Discovery kits for SR-X (Quanterix®). The levels of total tau (t-tau), tau phosphorylated at Thr181 (p-tau) and A $\beta$ 42 were determined using xMAP technology. CSF A $\beta$ 40 and A $\beta$ 42 levels were analyzed by electrochemiluminescence technology (Meso Scale Discovery) using the MS6000 Human Abeta 3-Plex Ultra-Sensitive Kit. A $\beta$  positivity (A $\beta$ +) was defined as CSF A $\beta$ 42/40 <0.07 (cut-off calculated with Youden index within the cohort). **Results:** Baseline plasma NFL was not significantly different between A $\beta$ + and A $\beta$ - groups ( $p=0.294$ ). NFL was significantly higher in the MCI-other A $\beta$ + group than the stable MCI groups (A $\beta$ -:  $p=0.024$ , A $\beta$ +:  $p=0.035$ ), but comparable to MCI-AD. GFAP at baseline was significantly different between A $\beta$ + and A $\beta$ - groups ( $p<0.0001$ ). The MCI-AD group had significantly higher baseline concentrations than stable MCI A $\beta$ - and MCI-other A $\beta$ - groups ( $p<0.0001$  both). Higher concentrations at baseline were observed in every A $\beta$ + subgroup compared to A $\beta$ - ones. Binary logistic regression models for prediction of A $\beta$ + status showed that plasma GFAP could predict A $\beta$ + status ( $p<0.0001$ , AIC=184.3). Accuracy was increased by combining plasma GFAP and APOE genotype ( $p<0.0001$ , AIC 154.7). NFL could not significantly predict A $\beta$ + status by itself or combined with age and/or APOE genotype. Plasma GFAP could also predict subsequent development of AD dementia ( $p<0.0001$ , AIC=154.4). Accuracy was improved by combining plasma GFAP with APOE genotype and age ( $p<0.0001$ , AIC 140). NFL could not predict MCI-AD status neither by itself or combined with age and/or APOE genotype. ROC curves for prediction of A $\beta$ + status showed the greatest AUC for GFAP combined with APOE genotype or APOE and age (AUC= 0.859 for both). GFAP alone had a better AUC than NFL alone (0.787 versus 0.618) or NFL combined with age or APOE (0.649 and 0.784, respectively). When predicting MCI-AD status, GFAP combined with APOE or APOE and age was the most accurate (AUC= 0.864 for both). GFAP alone had a better AUC than NFL alone (0.836 versus 0.666) or NFL combined with age, APOE or both (0.724, 0.755 and 0.791, respectively). Slopes for plasma NFL show a significant increase over time in the A $\beta$ + group ( $\beta=0.179$ ,  $p=0.037$ ) and in the MCI-AD group compared to the stable MCI A $\beta$ - ( $\beta=-0.292$ ,  $p=0.01$ ). Slopes for plasma GFAP show a significant longitudinal increase ( $\beta=2.018$ ,  $p<0.0001$ ), with a larger increase in the A $\beta$ + group compared to A $\beta$ - ( $\beta=2.06$ ,  $p=0.007$ ). When looking at slopes for different cognitive groups, plasma GFAP showed a significantly higher longitudinal increase in MCI-AD compared to stable MCI A $\beta$ - ( $\beta=-4.078$ ,  $p<0.0001$ ) and stable MCI A $\beta$ + ( $\beta=-2.48$ ,  $p=0.049$ ). **Conclusions:** Although plasma NFL is not an AD-specific biomarker, it showed a steeper increase over time in those that developed AD dementia, making it useful for monitoring the progress of

neurodegeneration in these patients. Plasma GFAP was strongly associated to A $\beta$  status and could accurately predict clinical progression to AD dementia, making it a potential candidate to add to the blood-based biomarker panel for AD.

**OC10: BASELINE CHARACTERISTICS FOR CLARITY-AD: A PHASE 3 PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL-GROUP, 18-MONTH STUDY EVALUATING BAN2401 IN EARLY ALZHEIMER'S DISEASE.** S.Y. Lynch<sup>1</sup>, M. Irizarry<sup>1</sup>, S. Dhadda<sup>1</sup>, Y. Zhang<sup>1</sup>, J. Wang<sup>1</sup>, T. Bogoslovsky<sup>1</sup>, L. Reyderman<sup>1</sup>, J. Kaplow<sup>1</sup>, H. Bradley<sup>1</sup>, M. Rabe<sup>1</sup>, K. Totsuka<sup>2</sup>, L. Kramer<sup>1</sup>, H. Hampel<sup>1</sup>, C. Swanson<sup>1</sup> ((1) Eisai Inc. - Woodcliff Lake, USA; (2) Eisai Co., Ltd. - Tokyo, Japan)

**Background:** BAN2401 is a humanized IgG1 monoclonal antibody that selectively targets soluble aggregated A $\beta$  species, with activity across oligomers, protofibrils and insoluble fibrils. A large, 18-month phase 2 proof of concept study (BAN2401-G000-201; NCT01767311) using Bayesian adaptive design was recently conducted in 856 patients with early Alzheimer's disease (AD); mild cognitive impairment (MCI) due to AD or mild AD dementia. Although the threshold for the primary Bayesian analysis at 12 months was not met, results from pre-specified 18-month frequentist analyses indicated that BAN2401 treatment reduced clinical decline and brain amyloid burden in patients with early AD at the highest dose (10 mg/kg biweekly). These reductions were accompanied by effects on CSF biomarkers of neurodegeneration. Based on the encouraging results from the phase 2 study, a phase 3 study (BAN2401-G000-301 [CLARITY AD], NCT03887455) was designed to confirm the efficacy and safety of BAN2401 in patients with early AD. **Objective:** To describe the baseline characteristics for currently enrolling subjects in the ongoing CLARITY AD study. **Methods:** CLARITY AD is an 18-month treatment (core study), multicenter, double-blind, placebo-controlled, parallel-group study with open-label extension in patients with early AD. Eligibility criteria include age 50 to 90 years old, MCI due to AD with intermediate likelihood or mild AD dementia with amyloid pathology confirmed by amyloid positron emission tomography (PET) or CSF assessment of t-tau/A $\beta$ (1-42) ratio. Patients are required to have objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII). A total of 1566 patients will be randomized in the core study across 2 treatment groups (placebo and BAN2401 10 mg/kg, biweekly) according to a fixed 1:1 (placebo: BAN2401) schedule. Randomization will be stratified according to clinical subgroup (MCI due to AD or mild AD dementia); presence or absence of ongoing approved AD treatment (eg, acetylcholinesterase inhibitors, memantine, or both); ApoE4 status (ie, carriers or non-carriers); and geographical region. Treatment in the core study will be for 18 months. During the core study, patients will have the option to participate in up to three optional sub-studies that evaluate longitudinal changes in brain amyloid burden, brain tau pathology, and CSF biomarkers of neurodegeneration. At the end of the core study, patients who qualify may participate in the open-label extension phase for up to 2 years. The primary efficacy endpoint in the core study is change in CDR-SB from baseline at 18 months. Key secondary endpoints include change from baseline at 18 months in amyloid PET standardized uptake value ratio (in patients participating in the sub-study), ADCOMS, and ADAS-Cog14. Safety will be monitored throughout the study by the sponsor and by an independent data safety monitoring committee. The open-



label extension phase will evaluate the long-term safety and tolerability of BAN2401 10 mg/kg biweekly in patients with early AD and whether the long-term effects of BAN2401 (as measured on clinical outcome measures and biomarkers) at the end of the core study is maintained over time in the extension phase. Baseline clinical and demographic data for the currently enrolled study was summarized descriptively and compared to the BAN2401 phase 2 study population. Since the study is blinded, a breakdown of baseline characteristics by treatment group will not be available until after completion of the core study. **Results:** As of a data cutoff of June 22, 2020, a total of 801 subjects were enrolled in CLARITY AD. The median age of subjects was 73 years (range: 50-89 years), with 83% of patients 65 years of age or older. Overall, 51% of subjects were female and 78% were Caucasian. Mean (SD) baseline values for clinical endpoints were 3.3 (1.3) for CDR-SB, 0.4 (0.1) for ADCOMS, 25.2 (7.2) for ADAS-Cog, 25.6 (2.2) for MMSE, and 0.6 (0.2) for Global CDR. Aggregate baseline characteristics are similar to the BAN2401 phase 2 study (median age 72 years [range: 50-90 years]; 80% 65 years of age or older; 50% female; 90% Caucasian; clinical endpoints: 3.0 [1.4] for CDR-SB, 0.4 [0.2] for ADCOMS, 22.2 [7.4] for ADAS-Cog, 25.6 [2.4] for MMSE, and 0.6 [0.2] for Global CDR). Comparisons of the study populations will be presented. **Conclusion:** Building on the encouraging findings from the BAN2401 phase 2 study, the phase 3 CLARITY AD study is designed to confirm clinical efficacy and safety of BAN2401 versus placebo in patients with early AD. Baseline characteristics after enrollment of 801 subjects are consistent with previous studies and representative of an early AD population. Enrollment is ongoing.

**OC11: LIPIDIET RESULTS: 3-YEAR EVALUATION OF FORTASYN CONNECT IN INDIVIDUALS WITH PRODROMAL ALZHEIMER'S DISEASE.** T. Hartmann<sup>1,2</sup>, A. Solomon<sup>3,4,5</sup>, P. Visser<sup>6,7</sup>, S. Hendrix<sup>8</sup>, K. Blennow<sup>9,10</sup>, M. Kivipelto<sup>11,12,5</sup>, H. Soininen<sup>13,14</sup> ((1) *Deutsches Institut Für Demenz Prävention (didp), Medical Faculty, Saarland University, Homburg, Germany - Homburg, Germany*; (2) *Department of Experimental Neurology, Saarland University - Saarbrücken, Germany*; (3) *Department Of Neurology, Institute Of Clinical Medicine, University Of Eastern Finland - Kuopio, Finland*; (4) *Department of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, - Huddinge, Sweden*; (5) *Clinical Trials Unit, Theme Aging, Karolinska University Hospital - Stockholm, Sweden*; (6) *Department Of Neurology, Alzheimer Centre, Amsterdam Neuroscience, Vu University Medical Center - Amsterdam, Netherlands*; (7) *Department of Psychiatry and Neuropsychology, Alzheimer Centre Limburg, University of Maastricht - Maastricht, Netherlands*; (8) *Pentara Corporation - Millcreek, USA*; (9) *Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At University Of Gothenburg - Mölndal, Sweden*; (10) *Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal, Sweden*; (11) *Department Of Neurology, Institute Of Clinical Medicine, University Of Eastern Finland - Kuopio, Finland*; (12) *Department of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet - Huddinge, Sweden*; (13) *Neurocentre, Department Of Neurology, Kuopio University Hospital - Kuopio, Finland*; (14) *Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland - Kuopio, Finland*)

**Background:** Lifestyle factors such as nutrition and diet are increasingly recognized as modifiable risk factors for the progression of mild cognitive impairment (MCI) to

Alzheimer's disease (AD). They may contribute to improved cognitive performance in individuals at risk of progression to dementia<sup>1,2</sup>. Fortasyn Connect is a multivitamin combination that has been shown in preclinical studies to reduce AD-linked brain pathology<sup>3</sup>. Benefits on memory and functional connectivity were demonstrated in patients with mild AD<sup>4,5</sup>. The LipiDiDiet study is designed to investigate the effects of Fortasyn Connect on cognition and related measures in individuals with prodromal AD. Initial 24-month results showed significant benefit on the secondary endpoints clinical dementia rating-sum of boxes (CDR-SB) and hippocampal and ventricular volumes, but not on the primary endpoint (neuropsychological test battery [NTB] 5-item composite) in the modified intention-to-treat population. First results of the 24-month analysis were published in Soininen et al., *Lancet Neurology* 2017<sup>6</sup>. **Objectives:** Here we report previously specified primary and secondary outcomes over 36 months of intervention. **Methods:** The LipiDiDiet trial (NTR1705) was a double-blind, parallel-group, multi-center randomized controlled clinical trial (11 sites in Finland, Germany, the Netherlands, and Sweden). Following initial 24-month intervention, participants could continue in the trial for a maximum total of 72 months of randomized, controlled, double-blind, parallel-group intervention, and another 24 months of open-label extension. Here we report analyses over a total of 36 months of intervention following the initial randomization. A total of 311 participants with prodromal AD, defined according to the International Working Group (IWG)-1 criteria, were enrolled. Participants were randomly assigned (1:1) to active product (125 mL drink containing the multivitamin combination Fortasyn Connect) or an iso-caloric placebo control drink once daily. Primary outcome was the 24-month change in an NTB 5-item cognitive function composite z-score. Secondary outcomes included CDR-SB, NTB memory, NTB executive function, and hippocampal, ventricular and whole brain atrophy based on magnetic resonance imaging. Statistical analyses were performed using a linear mixed model for repeated measures in a modified intention-to-treat population, excluding (i.e. censoring) data collected after the start of open-label medication (defined as use of active product and/or AD medication after dementia diagnosis). Further, to investigate whether qualitatively differential dropout potentially played a role in the observed treatment effects, we performed a predefined sensitivity analyses using a joint model combining longitudinal and survival data, a supportive mixed model analyses including the censored observations, as well as additional mixed model analyses to investigate potential confounder effects. **Results:** Of the 382 participants assessed for eligibility, 311 were randomized, and of those 162 participants completed 36 months of intervention, including 81 with 36-month data eligible for efficacy analysis. Over 36 months, significant reductions in decline were observed for the NTB 5-item composite (-60%; between-group difference 0.212 [95% CI 0.044 to 0.380], p=0.014), CDR-SB (-45%; -0.90 [-1.62 to -0.19], p=0.014), NTB memory (-76%; 0.274 [0.071 to 0.477], p=0.008), and brain atrophy measures; with small to medium Cohen's d effect size (0.25-0.31) similar to established clinically relevant AD dementia treatment, and larger than the standardized effect sizes for primary endpoints in clinical studies with Fortasyn Connect in mild AD<sup>7</sup>. Sensitivity joint model analyses, supportive analyses including censored data points, and analyses investigating potential confounder effects confirmed the main results. **Conclusions:** Over 36 months of

intervention with Fortasyn Connect, we observed significantly slower decline on a broad array of prespecified outcomes measuring cognition including memory, cognition and function, and brain atrophy. For the clinically relevant CDR-SB, the reduction in decline was 45% in active compared to the placebo control. Overall, intervention effects ranged between 22% (less increase in brain ventricular volume compared to placebo control) and 76% (NTB memory benefit over placebo control). In addition to clinically detectable benefits, the intervention had a good safety profile and high compliance throughout this study. The results indicate that intervention benefits increased with early use. Importantly, these long-term data show, that the benefit was sustainable for at least the 3-year treatment period and that the intervention benefit became more pronounced with long-term use. EU funding EU FP7 N°211696 LipiDiDiet; Dutch Trial Register: NTR1705. **References:** 1. Anastasiou CA, et al. *Nutrients*. 2018;10. 2. Lehtisalo J, et al. *Br J Nutr*. 2017;118:291-302. 3, van Wijk N, et al. *J Alzheimers Dis*. 2014;38:459-479. 4. Scheltens P, et al. *Alzheimers Dement*. 2010;6:1-10 e1. 5. Scheltens P, et al. *J Alzheimers Dis*. 2012;31:225-236. 6. Soininen H, et al. *Lancet Neurol*. 2017;16:965-975. 7. Cummings J, et al. *J Alzheimers Dis* 2017;55:1131-1139

**OC12: REPEATED SMARTPHONE-BASED MEMORY ASSESSMENT: THE BOSTON REMOTE ASSESSMENT FOR NEUROCOGNITIVE HEALTH (BRANCH).** K. Papp<sup>1</sup>, A. Samaroo<sup>2</sup>, H.C. Chou<sup>2</sup>, R. Buckley<sup>1</sup>, D. Rentz<sup>1</sup>, R. Sperling<sup>1</sup>, R. Amariglio<sup>1</sup> ((1) *Harvard Medical School - Boston, USA*; (2) *Massachusetts General Hospital - Boston, USA*)

**Background:** Rapid detection and tracking of the earliest cognitive changes in preclinical Alzheimer's disease (AD) is critical to the success of secondary prevention trials. Remote, smartphone-based cognitive assessments may 1) improve recruitment by screening larger numbers of individuals and 2) allow for the capture of more subtle cognitive changes such as the failure to improve on retesting (i.e., a diminished learning curve) over shorter time intervals (i.e., days). Only a few smartphone-based assessments have been designed specifically for an older preclinical AD population and validated as sound measures of cognition. **Objective:** Our aim was to develop and validate the Boston Remote Assessment of Neurocognitive Health (BRANCH), a web-based smartphone assessment that targets aspects of cognition known to decline in preclinical AD (e.g., associative and semantic memory, pattern separation), using stimuli relevant to everyday life. We aimed to determine the feasibility of BRANCH for a 1) single in-clinic assessment in older adults across the diagnostic spectrum (i.e., clinically normal (CN) and those diagnosed with early Mild Cognitive Impairment-MCI) and 2) daily remote assessment in the home environment among CN older adults. To determine the validity of BRANCH, we explored correlations between BRANCH and standardized paper and pencil measures and compared performance on these measures between diagnostic groups. **Methods:** BRANCH includes 4 tasks: 2 measures of paired associative learning (a modified Face-Name Associative Memory Exam, groceries and prices), an associative memory test with facilitated encoding (categories), and a continuous visual recognition task (street signs). A total of 78 individuals (20 MCI, 58 CN; mean age=76.58; 56% female; 75% Caucasian) completed BRANCH in-clinic. BRANCH was completed on a study-provided tablet in-clinic and later refined to be for use on an individual's own smartphone. A separate 32 CN

older adults (mean age=71.76; 63% female; 75% Caucasian) completed BRANCH daily on their own smartphone for 7 consecutive days. All participants completed in-clinic cognitive assessments including measures to compute a Preclinical Alzheimer's Cognitive Composite (PACC). A composite of accuracy across BRANCH tasks was also computed. Finally, participants completed a questionnaire about their experience completing BRANCH to better assess its acceptability/usability. **Results:** A total of 93% of participants were able to complete BRANCH either in-clinic on a tablet or at home on their own smartphone device without difficulty. A total of 14% reported technical difficulties, primarily difficulty with tapping. A total of 64% of participants found BRANCH to be at least 'somewhat' to 'highly' engaging. At a single timepoint, the correlation between the BRANCH composite and PACC was moderate ( $r=0.57$ ,  $p<0.001$ ). Individuals with MCI performed worse on BRANCH compared with CN (Cohen's  $d=0.45$ ,  $p<0.001$ ). For daily BRANCH, 80% of individuals completed all assessments in the correct order over 7 days. Participants exhibited learning effects when performing BRANCH daily, improving on memory accuracy each day. **Conclusions:** A theoretically driven digital memory assessment with ecologically-valid tasks and stimuli is feasible for CN older adults to complete independently on their own smartphones. Moderate correlations between BRANCH and traditional paper and pencil measures suggest that BRANCH is a valid measure of cognition in older adults and those with early MCI. BRANCH was able to successfully discriminate between CN and MCI participants. Further work is needed to determine the feasibility of daily BRANCH assessments in a larger population and its relationship with AD biomarkers. Capturing cognitive performance remotely on an individual's smartphone has the potential to improve the efficiency with which subtle decrements in cognition can be detected and tracked.

**OC13: MEDI1814, A BETA-AMYLOID 42-SPECIFIC ANTIBODY, LOWERED NEUROFILAMENT LIGHT PLASMA LEVELS IN PATIENTS WITH MILD-MODERATE ALZHEIMER'S DISEASE.** C. Shering<sup>1</sup>, T. Ostenfeld<sup>2</sup>, M. Pomfret<sup>2</sup>, A. Billinton<sup>3</sup>, I. Chessell<sup>2</sup>, K. Tan<sup>2</sup>, N. Brayshaw<sup>4</sup>, K. Blennow<sup>5</sup>, S. Persson<sup>5</sup>, F. Natanegara<sup>6</sup>, Y. Feng<sup>6</sup>, J. Sims<sup>6</sup>, J. Dage<sup>6</sup> ((1) *Astrazeneca, Neuroscience, Biopharmaceuticals R & D - Boston, USA*; (2) *Astrazeneca, Neuroscience, Biopharmaceuticals R & D - Cambridge, USA*; (3) *Former Astrazeneca Employee, Neuroscience, Biopharmaceuticals R & D - Cambridge, USA*; (4) *Empiridat Ltd - Deal, United Kingdom*; (5) *University Of Gothenburg, Clinical Neurochemistry Lab - Molndal, Sweden*; (6) *Eli Lilly And Company, Neuroscience - Indianapolis, USA*)

**Background:** MEDI1814 is a fully human IgG1 $\alpha$  monoclonal antibody, engineered for selective, high-affinity binding of A $\beta$ x-42 (A $\beta$ 42) peptides and for reduced effector function. **Objectives:** Neurofilament light (NfL) levels in cerebrospinal (CSF) and plasma samples, from the previously reported 1 multiple ascending dose (MAD) study of MEDI1814 in patients with mild to moderate Alzheimer's Disease, were evaluated. **Methods:** Eligibility criteria for the trial included: Age 55-85, >6 month history of probable AD according to National Institute of Aging-Alzheimer's Association criteria, and a MMSE score of 16-26 inclusive. MEDI1814 intravenous doses in the MAD study (N=6/arm) were 300, 900 and 1800 mg (every 4 weeks over 12 week duration; 3 doses). CSF and plasma samples were evaluated for NfL using ELISA and Simoa platforms,

respectively. **Results:** Following 3 monthly intravenous doses of MEDI1814 1800mg, marked reduction of plasma NfL levels (median = -20.7%, nominal p-value < 0.05) compared to baseline levels were observed. A similar trend was observed in CSF NfL levels (median ~ -50%) with significant correlation across CSF and plasma measurements (Spearman's  $\rho$ : 0.47 at baseline and 0.74 at endpoint). **Conclusions:** MEDI1814, which shows dose-dependent suppression of CSF free A $\beta$ 42, reduced NfL levels in plasma. A similar trend of reduction of NfL levels in CSF was observed. This is the first observation of NfL lowering from baseline by an amyloid targeting agent. These preliminary observations in a small sample would benefit from confirmation in further clinical studies. **References:** 1) Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MEDI1814, a Beta-Amyloid 42 (A $\beta$ 42)-specific antibody, in mild-moderate Alzheimer's disease, Ostenfeld et al., AAIC 2017

**OC14: BAN2401 AND ARIA-E IN EARLY ALZHEIMER'S DISEASE: PHARMACOKINETIC / PHARMACODYNAMIC TIME-TO-EVENT ANALYSIS FROM THE PHASE 2 STUDY IN EARLY ALZHEIMER'S DISEASE.** S. Hayato<sup>1</sup>, L. Reyderman<sup>2</sup>, Y. Zhang<sup>2</sup>, O. Takenaka<sup>1</sup>, S. Yasuda<sup>2</sup>, E. Schuck<sup>2</sup>, A. Koyama<sup>2</sup>, C.J. Swanson<sup>2</sup>, Z. Hussein<sup>2</sup> ((1) Eisai Co., Ltd - Tokyo, Japan; (2) Eisai Inc. - Woodcliff Lake, USA)

**Background:** BAN2401 is a humanized IgG1 monoclonal antibody that selectively targets soluble aggregated A $\beta$  species, with activity across oligomers, protofibrils and fibrillar deposits. A multicenter, double-blind, placebo-controlled phase 2 study (study 201) was recently conducted in 856 patients with early Alzheimer's disease (EAD). Patients were randomized to five dose regimens: 2.5 mg/kg bi-weekly, 5 mg/kg monthly, 5 mg/kg bi-weekly, 10 mg/kg monthly and 10 mg/kg bi-weekly, or placebo. BAN2401 demonstrated dose-dependent reductions in brain amyloid in the 18-month core period of study 201. BAN2401 demonstrated an acceptable tolerability profile through 18 months of study drug administration. Amyloid related imaging abnormalities – edema/effusion (ARIA-E) was the adverse event of special interest in the study. Incidence of ARIA-E was BAN2401 dose-dependent and greater in APOE4 carriers. For the 10 mg/kg biweekly dose, the incidence of ARIA-E was 14.6% in APOE4 carriers and 8.0% in non-carriers. Incidence of ARIA-E was not more than 10% in any of the treatment arms. Most cases of ARIA-E occurred within the first 3 months of treatment, were mild to moderate in radiographic severity on MRI, were asymptomatic, and typically resolved within 4 to 12 weeks. The open-label extension (OLE) of study 201 was initiated to allow patients to receive open-label BAN2401 10mg/kg-biweekly for up to 24 months. 180 subjects enrolled in the OLE, with subjects initiating treatment from 9.2 to 59.8 months (mean 25.0 months) after their last dose in the core. **Objectives:** The objectives of this analysis were (1) to develop a pharmacokinetic (PK)/pharmacodynamic (PD) model relating the time-to-event of ARIA-E to BAN2401 serum concentration with data from the core study and (2) to assess whether the PK/PD model developed based on core study 201 data predicts incidence of ARIA-E observed in the on-going study 201 OLE. **Methods:** Modelling of time-to-first ARIA-E event in the core study correlating BAN2401 exposure was performed with data from core study of study 201. Log-hazard model including BAN2401 exposure effect and attenuation factor of exposure effects was considered, based on the finding that the higher risk for developing ARIA-E was observed early

in the treatment rather than late in the treatment in study 201. BAN2401 exposures explored were maximum serum concentration (C<sub>max</sub>) at the time of latest dosing before the safety assessment and average serum concentration (C<sub>av</sub>) at the safety assessment. Predictive performance of the model for the time to first ARIA-E was evaluated using visual predictive check. In addition, ARIA-E incidence in OLE was compared to simulated rates from the core study. **Results:** Time-to-event analysis for ARIA-E by log-hazard model included 5,363 records from 851 subjects from safety MRI data of core study of study 201. Time-to-first ARIA-E event was modelled as a function of BAN2401 C<sub>max</sub> using the log-hazard model, including attenuation factor of exposure effects and the effect of APOE4 carrier status. Correlation of ARIA-E with C<sub>max</sub> resulted in lower objective function compared to C<sub>av</sub>. Thus, BAN2401 exposure in the ARIA-E model was expressed as C<sub>max</sub>. Estimated baseline hazard was 26% lower for APOE4 non-carriers than APOE4 carriers. This ARIA-E model captured observed data from the core study with constant dosing regimens. Model-predicted ARIA-E incidence rates with constant dosing regimen 10 mg/kg bi-weekly for APOE4 carriers was 13.4% and this was consistent with the observed incidence rates (12.9%) for treatment naïve APOE4 carriers initiated with 10 mg/kg bi-weekly in the OLE who were treated with placebo in the core. Conversely, the observed incidence rates (8.5%) of ARIA-E for APOE4 carriers treated with 10 mg/kg bi-weekly in the OLE after being exposed to BAN2401 treatment (any doses) in the core (with dose interruption in between) was lower than model-predicted incidence rates for constant dosing of 10 mg/kg bi-weekly (i.e. without dosing interruption). Comparisons could not be made for APOE4 non-carriers in the OLE due to the small number of subjects (1 case). **Conclusions:** The incidence of ARIA-E events was correlated with BAN2401 C<sub>max</sub>. This ARIA-E model correctly predicted the observed incidence rates for APOE4 carriers in OLE with 10 mg/kg bi-weekly for those treated with placebo in the core study.

**OC15: COMPARISON OF ADUCANUMAB, SOLANEZUMAB AND BAN2401 USING A GLOBAL STATISTICAL TEST FOR ASSESSING IMPACT ON OVERALL STRENGTH OF EVIDENCE.** S. Dickson<sup>1</sup>, S. Hennessey<sup>1</sup>, J. Neff<sup>2</sup>, T. Syndergaard<sup>2</sup>, M. Earnshaw<sup>2</sup>, S. Hendrix<sup>1</sup> ((1) Pentara Corporation - Salt Lake City, USA; (2) Brigham Young University - Provo, USA)

**Background:** Alzheimer's disease (AD) progression can be measured with cognitive, behavioral, functional and global outcomes. In the natural history of the disease, these outcomes are all driven by an underlying disease process. When symptomatic treatments are given, some symptoms may be affected while others are not. With a disease modifying treatment, all the symptoms will be affected indirectly, through an effect on the underlying disease process. Because this effect is indirect, it is expected to impact all disease symptoms proportionally to the amount that they would progress without treatment. Global Statistical Tests (GSTs) have been proposed as way of assessing the impact of treatment on the underlying disease process by triangulating several symptomatic measures to get an overall estimate of treatment benefit. This would provide a single answer to the question of whether the treatment affected the underlying disease progression, rather than potentially conflicting answers from measures of multiple

symptoms. **Objectives:** Our objective is to demonstrate that a GST approach is useful for assessing the effect of a treatment on disease progression with one overall measure of the strength of the evidence in favor of an intervention. Our current approach to AD clinical trials relies on separate measures of cognition, function and global performance. Many of the scales used, particularly the ones that are traditionally acceptable for regulatory approval, tend to be highly variable and not very well correlated with each other. This leads to results that seem inconsistent across outcome variables, but are, in reality, well within the expected variability of the scales used. Because the scales are not that highly correlated, they often provide very different results in terms of p-values, which is often interpreted as an indication that the effect is not real or is only impacting a few symptoms. The GST approach allows us to get one robust measure of effect on the underlying disease and a measure of significance, by combining symptom measures into one overall outcome. **Methods:** The standard way of calculating a global statistical test requires raw data for calculating a z-score on each of the symptomatic outcomes. These z-scores are then averaged, and that average is analyzed as an outcome variable. When summary data are available from publications, then a global statistical test can be estimated by combining the estimated means and standard deviations across each effect with an adjustment due to the correlations between them. We summarize previous results for the highest dose from Aducanumab Emerge study, Solanezumab Expedition 1, 2 and 3, and Ban-2401 using this GST statistic, combining the ADAS-cog, ADCS-ADL and CDR-sb scales. We show the totality of the evidence for a treatment effect using the GST and compare to the individual p-values for each study. **Results:** The p-value for the GST for the Solanezumab Expedition 3 Study using a combination of the ADAS-cog, CDR-sb and ADCS-ADL was 0.0011. The GST for highest dose in the BAN2401 201 study resulted in a p-value of 0.0084 when combining the ADAS-cog and the CDR-sb (no ADL data was identified for this study). The Aducanumab EMERGE study had the strongest totality of evidence with a p-value of 0.0001 when combining evidence across the ADAS-cog, ADCS-ADL and CDR-sb. **Conclusion:** This analysis of historical data demonstrates that the level of evidence in a clinical trial can be hard to assess with separate outcomes for each type of symptom. Combining this evidence into a single GST score and calculating a p-value allows us to align our analysis with the primary goal of the research which is to determine whether a potentially disease modifying treatment has slowed AD progression. This approach gives us a more robust estimate of the treatment benefit and the level of evidence achieved in a single study or across multiple studies and supports better decision making in development programs. These results also suggest that the statistical evidence in favor of passive immunization is stronger than is generally believed.

**OC16: EFFECTS OF OMEGA-3 (N-3) POLYUNSATURATED FATTY ACIDS (PUFA) ON CEREBRAL WHITE MATTER HYPERINTENSITIES, MEDIAL TEMPORAL LOBE ATROPHY AND WHITE MATTER INTEGRITY IN OLDER NON-DEMENTED ADULTS: A 3-YEAR RANDOMIZED-CONTROLLED PHASE 2 TRIAL.** G. Bowman<sup>1</sup>, C. Murchison<sup>2</sup>, L. Silbert<sup>1</sup>, H. Dodge<sup>1</sup>, K. Hagen<sup>1</sup>, J. David<sup>1</sup>, D. Lahna<sup>1</sup>, J. Kaye<sup>1</sup>, J. Quinn<sup>1</sup>, L. Shinto<sup>1</sup> ((1) Oregon Health & Science University, Department Of Neurology - Portland, USA; (2) University Of Alabama, Birmingham - Birmingham, USA)

**Background:** The n-3 PUFA may modulate risk for age-related cognitive impairment and dementia through both vascular and neurodegenerative mechanisms that govern AD pathology. MRI derived cerebral white matter hyperintensities (WMH) reflect cerebrovascular disease and atrophy of the medial temporal lobe reflects seeding of AD pathology years prior to diagnosis. The omega 3 may reduce WMH accumulation, stroke risk and delay neurodegeneration. Our primary aim was to enroll an older non-demented population and test whether omega 3 are safe and effective at slowing WMH accumulation and medial temporal lobe atrophy in those presenting with suboptimum plasma omega 3 and MRI derived WMH burden. **Methods:** The study was a double-blind, placebo-controlled trial, with participants randomly assigned to 1650 mg daily omega 3 (eicosapentaenoic acid-EPA 975 mg; docosahexaenoic acid-DHA 675 mg) or placebo for 36-months. Eligibility included non-demented (MMSE > 24), age > 74 years, WMH volume > 5.0 cc, and plasma n-3 PUFA (EPA+DHA) < 110 umol/L (or < 5.5 percent of total fatty acids). Primary endpoint was linear response differences between groups over 36-month in total WMH volume with secondary endpoints including medial temporal lobe atrophy and exploratory subgroup analysis by APOE4 genotype. Multivariate adjusted linear mixed-effects models assessed change in the outcomes. **Results:** 102 participants were randomized (mean age 81±4.4 range 75-96; MMSE 27.8±1.7; 60% female, 27.5% APOE4 positive) and a total of 78 participants completed the trial (39 each group). 90 had at least one follow up MRI constituting the modified ITT (mITT) cohort. 55 met and adhered to the protocol constituting the per-protocol analysis (PPA) cohort. Under mITT, no differences in WMH progression between groups (p=0.337), however, under PPA those that adhered to protocol active group reduced WMH progression (p=0.019). No differences were seen in medial temporal lobe, total brain or ventricular volume changes. No differences were seen in executive function Z-score. No differences in adverse events were observed. **Conclusion:** Daily soft gels yielding 1650 mg omega 3 appear safe over 36-months in older adults with cerebrovascular risk factors. 36-month WMH progression is slowed in older non-demented adults with plasma omega 3 < 110 ug/mL and total WMH ≥ 5 cm<sup>3</sup> that adhered to study protocol. Sample size calculations for a larger study powered to detect cognitive benefit were achieved, and operational insights were gained. Deep and periventricular WMH changes, further diffusion MRI, domain-specific cognitive outcomes, and detailed safety profiles are planned for presentation. **Funding:** NIH-NIA R01 AG043398; OHSU Layton Aging and Alzheimer's Disease Center; OCTRI NCATS/NIH UL1TR002369; OADC NIA P30 AG008017

**OC17: RELATIONSHIP BETWEEN PIMAVANSERIN EXPOSURE AND PSYCHOSIS RELAPSE IN PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS: CLINICAL RESULTS AND MODELING ANALYSIS FROM THE PHASE 3 HARMONY STUDY.** M. Darwish<sup>1</sup>, E.P. Foff<sup>1</sup>, J. Passarelli<sup>2</sup>, D. Jaworowicz<sup>2</sup>, M. Forman<sup>1</sup>, J. Owen<sup>1</sup>, S. Stankovic<sup>1</sup> ((1) ACADIA Pharmaceuticals, Inc. - Princeton, USA; (2) Cognigen Corporation, A Simulations Plus Company - Buffalo, USA)

**Background:** Pimavanserin is a selective serotonin inverse agonist/antagonist at 5-HT<sub>2A</sub> receptors approved in the United States for treating hallucinations and delusions associated with Parkinson's disease (PD) psychosis. The recommended dose in PD psychosis is 34 mg taken orally once daily. Pimavanserin is also being investigated for dementia-related psychosis, for which there are no FDA-approved therapies. The association between pimavanserin exposure and efficacy in preventing relapse of psychosis provides information for consideration along with safety data when determining the appropriate dose for patients with dementia-related psychosis. **Objectives:** Evaluate the relationship between exposure and time to relapse in patients with dementia-related psychosis treated with pimavanserin. **Methods:** Data were from HARMONY, a relapse-prevention study (NCT03325556) in patients with moderate-to-severe psychosis associated with Alzheimer's disease, PD, dementia with Lewy bodies, vascular dementia, or frontotemporal dementia. In the 12-week open-label (OL) period, patients received oral pimavanserin 34 mg daily, with flexible dosing (20 mg) based on tolerability up to week 4. Patients with sustained response randomized into the 26-week double-blind (DB) period where they continued pimavanserin (at final OL dose) or switched to placebo. The primary endpoint was time from randomization to dementia-related psychosis relapse. A post hoc analysis was conducted to evaluate time to relapse in only patients who completed the OL period on pimavanserin 34 mg. Daily exposure measures, including area under the concentration-time curve (AUC), were predicted for each patient based on a population-pharmacokinetic model and individual empiric Bayesian estimates. An exposure-response model was developed describing the effect of pimavanserin exposure on the time to relapse. **Results:** HARMONY enrolled 392 patients in the OL period; 41 were ongoing at the time of study closure and were excluded from analyses. Of the remaining 351, 217 patients (61.8%) randomized into the DB period of the study. The study was stopped early for superior efficacy when a prespecified interim analysis revealed >2.8-fold reduction in risk of relapse with pimavanserin compared with placebo (hazard ratio [HR]=0.353; 95% CI: 0.172, 0.727; one-sided P=0.0023) in the DB period. In the subgroup of patients who completed the OL on 34 mg pimavanserin, continuing on pimavanserin reduced the risk of relapse by >3.4-fold compared to placebo (HR=0.293, 95% CI: 0.135, 0.634; one-sided P=0.0009). The exposure-response model, using 18,640 daily records collected from 185 patients throughout the DB period, demonstrated a significant relationship whereby higher pimavanserin exposure was associated with a higher probability of being relapse free. No tested covariates (demographics, dementia subtype, baseline Scale for the Assessment of Positive Symptoms Hallucinations+Delusions score, or anticholinergic medication) had a statistically significant effect on relapse risk. Compared to placebo, the model predicted a 62% reduction in relapse risk with median AUC of 1330 ng x h/mL for the 34 mg dose and a noticeably lesser effect with lower exposures/doses

**Conclusions:** In the phase 3 HARMONY relapse-prevention study, pimavanserin treatment significantly reduced the risk of relapse compared with placebo. The efficacy of pimavanserin was more pronounced when evaluated in patients who achieved stable response on the 34 mg dose. Modeling analysis results are consistent with clinical study results and predict higher pimavanserin exposure in patients with dementia-related psychosis to be associated with a greater reduction in relapse risk. Findings from these analyses support the efficacy of 34 mg pimavanserin as a potential treatment for dementia-related psychosis.

**OC18: MONOCLONAL ANTIBODIES AGAINST AMYLOID-B IN ALZHEIMER'S DISEASE. A META-ANALYSIS OF PHASE III CLINICAL TRIALS.** K. Avgerinos, L. Ferrucci, D. Kapogiannis (National Institute On Aging, National Institutes Of Health - Baltimore, USA)

**Background:** The Amyloid Hypothesis for Alzheimer's disease (AD) posits that brain amyloid-beta (A $\beta$ ) accumulation is driving disease pathogenesis. Thus, A $\beta$  reduction has been a target of therapeutic development in AD. Monoclonal antibodies against A $\beta$  have been a popular approach to achieve this goal. However, most Randomized Controlled Trials (RCTs) have shown no efficacy, although newer studies reported some improvements. Therefore, whether anti-A $\beta$  monoclonal antibodies can be an effective treatment for AD remains controversial. **Objectives:** To determine the efficacy of anti-A $\beta$  monoclonal antibodies class as a whole, elucidate differences between individual drugs, and try to ascertain what would be the best anti-A $\beta$  monoclonal antibodies properties in order to inform future clinical trials. **Methods:** We included data from phase III RCTs to perform random-effects meta-analyses. We extracted and synthesized outcomes of cognition [ADAS-Cog, MMSE, Neuropsychological Test Battery (NTB)], mixed cognition/function (CDR-SOB), function [ADCS-ADL, Dependence Scale (DS), Disability Assessment for Dementia (DAD) ], A $\beta$  pathology (amyloid PET SUVR, CSF A $\beta$ 1-40, CSF A $\beta$ 1-42), p-tau pathology (CSF p-tau), neuroimaging (vMRI) and amyloid-related imaging abnormalities (ARIA) risk. Summary measures for continuous outcomes were expressed as Standardized Mean Differences (SMDs) [95% Confidence Interval (CI)] and for binary outcomes as Risk Ratios (RR) [95% CI]. Heterogeneity between studies was assessed with the I<sup>2</sup> statistic. Risk of bias was assessed with the "Revised Cochrane risk-of-bias tool for randomized trials". Publication bias was assessed with inspection of funnel plots, performance of Egger's statistic and imputation of potentially "missing studies" with the Duval & Tweedie's trim-and-fill procedure. We additionally performed subgroup analyses by individual drug and shared characteristics of drugs (human vs. humanized murine antibody, targeted A $\beta$  conformation(s), ARIA risk) and participant disease severity (baseline MMSE). Meta-regressions by age, apoE genotype, sex, race, AD medications at baseline, and baseline MMSE were performed to examine whether these variables affected efficacy. Finally, we performed a multivariate meta-analysis to investigate the association between Amyloid PET SUVR and ADAS-Cog effect sizes. **Results:** Our synthesis had 100% statistical power (calculated for n = 12,384 included participants, k = 15 included studies, moderate between-studies heterogeneity and any effect size). No evidence for publication or high risk of general bias was observed. Meta-analyses showed that antibodies improved

cognition on ADAS-Cog {SMD = -0.06 [95% CI (-0.10; -0.02), I2 = 0%]} and MMSE {SMD = 0.05 [95% CI (0.01; 0.09), I2 = 0%]}, and showed a trend towards improvement on the cognitive/functional measure CDR-SOB {SMD = -0.03 [95% CI (-0.07; 0.00), I2 = 11%]}. Antibodies reduced A $\beta$  PET deposition {SMD = -1.02 [95% CI (-1.70; -0.34), I2 = 95%]} and CSF p-tau {SMD = -0.87 [95% CI (-1.32; -0.43), I2 = 89%]}, but increased ARIA risk [RR = 4.30 [95% CI (2.39; 7.77), I2 = 86%]}. Multivariate meta-analysis showed that effect sizes for amyloid PET SUVR were associated with effect sizes for ADAS-Cog. The two types of effect sizes were positively correlated (Pearson's  $r = +0.67$ ,  $p = 0.02$ ). Meta-analysis of ADCS-ADL showed improvement for antibodies {SMD = 0.09 [95% CI (0.04; 0.14), I2 = 11%]}. Additional syntheses showed that treatment did not change NTB, DAD and DS scores, but there was a trend for CSF A $\beta$ 1-42 increase {SMD: 0.66 [95% CI (-0.02; 1.34), I2 = 93%]} and a clear increase of CSF A $\beta$ 1-40 {SMD: 0.51 [95% CI (0.14; 0.87), I2 = 57%]}. Finally, meta-analysis of vMRI showed that monoclonal antibodies preserved whole brain volume more than placebo {SMD: 0.10 [95% CI (0.00; 0.19), I2 = 0%]}. Regarding individual drugs, Aducanumab improved ADAS-Cog {SMD = -0.10 [95% CI (-0.17; -0.03), I2 = 0%]}, CDR-SOB {SMD = -0.08 [95% CI (-0.16; -0.01), I2 = 6%]} and A $\beta$  deposition {SMD = -2.48 [95% CI (-3.18; -1.78), I2 = 89%]}, but increased ARIA risk [RR = 3.59 [95% CI (2.85; 4.53), I2 = 0%]}. Solanezumab improved ADAS-Cog {SMD = -0.07 [95% CI (-0.13; -0.01), I2 = 0%]}, MMSE {SMD = 0.08 [95% CI (0.02; 0.15), I2 = 0%]} and increased CSF A $\beta$ 1-40 {SMD = 0.51 [95% CI (0.14; 0.87), I2 = 57%]}, but did not increase ARIA risk [RR = 0.94 [95% CI (0.21; 4.32), I2 = 0%]}. Bapineuzumab and Gantenerumab showed no efficacy, although they both decreased CSF p-tau and increased ARIA risk. Most additional subgroup analyses and meta-regressions did not reach significance. **Conclusion:** Monoclonal antibodies produced statistically significant, but clinically modest improvements on cognitive and functional measures, and robust biomarker responses. The findings support the view that A $\beta$  remains a good therapeutic target for AD drug development. Differential drug performance may inform future therapeutic development. Future research should focus on development of drugs with strong amyloid-reducing ability, as a predictor of strong clinical effects. **Acknowledgement:** This research was supported entirely by the Intramural research Program of the NIH, National institute on Aging

**OC19: PHASE 2/3 GAIN TRIAL OF COR388 (ATUZAGINSTAT), A NOVEL BACTERIAL VIRULENCE FACTOR INHIBITOR FOR THE TREATMENT OF ALZHEIMER'S DISEASE: UPDATE AND BASELINE DATA.** M. Detke (Cortexyme - South San Francisco, USA)

**Background:** Cortexyme initiated a Phase 2/3 study of COR388 (atuzaginstat) in mild-to-moderate Alzheimer's disease (AD) called the GAIN trial (GingipAIN inhibitor for treatment of Alzheimer's disease) in Q2 2019. The novel mechanism of action of atuzaginstat is based on the discovery of *Porphyromonas gingivalis* (Pg), most commonly associated with periodontal disease, in the brain of >90% of mild-to-moderate AD patients. Toxic virulence factors from the bacterium, proteases called gingipains, were identified in AD brains with levels correlating with tau and ubiquitin pathology. Oral infection of mice with Pg resulted in brain colonization, increased A $\beta$ 1-42, detrimental effects on tau and loss of hippocampal neurons, effects which are blocked by

COR388 (atuzaginstat) a lysine-gingipain inhibitor. The drug was well tolerated in phase 1 studies including a cohort of mild-to-moderate AD subjects treated for 28 days. MMSE and CANTAB measures showed numerical trends of improvement for atuzaginstat vs. placebo, and multiple measures of a computerized speech assessment showed significant superiority for atuzaginstat vs. placebo, as did two relevant biomarker readouts. The Phase 2/3 GAIN trial has targeted enrollment of 570 patients in the US and Europe with enrollment currently more than 50% complete in March. Subjects (aged 55-80; mild-mod AD with MMSE 12-24) are being randomized to one of two doses of COR388 (40mg or 80mg BID) or placebo. The co-primary endpoint is mean change in ADAS-Cog 11 and ADCS-ADL from baseline to 48 weeks. Additional endpoints include change in CDR-SB, MMSE, NPI, Winterlight Speech Assessment, CSF and oral biomarkers of infection, MRI and other measures. An interim analysis is expected by year end 2020 and top-line data are expected Q4 2021. Subjects enrolled to date were tested for baseline biomarkers relevant to diagnosis of Alzheimer's disease and infection with *P. gingivalis*. These data and baseline cognitive and demographic information will be reported, including CSF levels of amyloid- $\beta$  (A $\beta$ ) peptide ratio 42/40. Approximately 50% of GAIN trial patients are also participating in a dental sub-study, and while not selected for periodontal disease, > 90% enrolled in the study to date have moderate to severe periodontitis. **Conclusions:** Enrollment of the GAIN trial is proceeding according to planned timelines and patients enrolled to date exhibit baseline characteristics consistent with enrollment of appropriate patients that are likely to be responders to COR388 (atuzaginstat).

**OC20: IMPACT-AD: A NOVEL CLINICAL TRIALS TRAINING PROGRAM.** T. Berkness<sup>1</sup>, M.C. Carrillo<sup>2</sup>, K. Mclinden<sup>3</sup>, R. Sperling<sup>4,5</sup>, R. Petersen<sup>6</sup>, P. Aisen<sup>1</sup>, H. Snyder<sup>2</sup>, L. Ryan<sup>3</sup>, J.D. Grill<sup>7</sup>, R. Raman<sup>1</sup> ((1) Alzheimer's Therapeutic Research Institute, University Of Southern California - San Diego, USA; (2) Alzheimer's Association, Division Of Medical And Scientific Relations - Chicago, USA; (3) National Institute On Aging, Dementias Of Aging Branch - Bethesda, USA; (4) Department Of Neurology, Massachusetts General Hospital, Harvard Medical School - Boston, USA; (5) Department of Radiology, Division of Nuclear Medicine and Molecular Imaging, Massachusetts General Hospital, Harvard Medical School - Boston, USA; (6) Mayo Clinic - Rochester, USA; (7) Institute Of Memory Impairment And Neurological Disorders, Department Of Psychiatry & Human Behavior, Department Of Neurobiology & Behavior, University Of California At Irvine - Irvine, USA)

**Background:** Critical to the mission to improve available therapies and curb the public health impact of Alzheimer's Disease and Related Dementias (ADRD) will be a new generation of ADRD clinical scientists with the unique training and skills necessary to design and perform clinical trials. ADRD clinical trials require multidisciplinary expertise in medicine, biostatistics, trial design, biomarkers, ethics, and informatics. The Institute on Methods and Protocols for Advancement of Clinical Trials in ADRD (IMPACT-AD) course is a novel multidisciplinary clinical trial training program funded by the National Institute on Aging and the Alzheimer's Association with two tracks of training. A Professionals track focuses on training the ADRD clinical trials workforce who fill a broad variety of roles including clinicians, study coordinators, psychometricians, and other study professionals who wish

to further their knowledge and advance their careers in AD/DRD trials. A Fellowship track includes current and future principal investigators and focuses on the design, conduct and analysis of AD/DRD clinical trials. **Objectives:** IMPACT-AD aims to train the next generation of AD/DRD clinical trialists. Both tracks have an emphasis on inclusion and diversifying the pipeline of AD/DRD clinical trialists, including the areas of gender, race, ethnicity, geography, and scientific/professional backgrounds. **Methods:** The IMPACT-AD course provides a comprehensive review of the current state of the field. Lecture content ranges from essential AD/DRD understanding (e.g., unique AD/DRD trial populations, AD/DRD biomarkers, etc.) to trial design and biostatistics. Important but often overlooked topics, such as AD/DRD-specific ethical issues and trial recruitment and retention also receive considerable attention. Multiple active learning workshops focus on career advancement, scientific communication, and scientific literature. For the Fellowship track, additional small group workshops focus on trial protocol development skills. Application requirements for both tracks included: 1) personal statement; 2) letter of support from a supervising faculty member; and 3) NIH biosketch. For the Fellowship Track, a draft protocol was submitted using the Alzheimer's Clinical Trial Consortium (ACTC) Protocol Synopsis template. We employed a breadth of strategies to ensure our goal of a robust and diverse course applicant pool, including dissemination of a Request for Applications (RFA) through the Alzheimer's Association's International Society to Advance Alzheimer's Research and Treatment (ISTAART) mailing list (n=2100 recipients) and active research awardees list (n=540), the National Institute on Aging's (NIA) mailing list to FY 2019 grantees (n=2300 individuals), the ACTC steering committee members and investigative teams for numerous studies coordinated by ATRI (n=530 individuals) and the National Alzheimer's Coordinating Center's mailing list (n=780 individuals). Separate committees composed of 6 IMPACT-AD faculty and representatives of the Alzheimer's Association reviewed the applications for each track. Each application was scored by no less than five reviewers. **Results:** We received 104 eligible applications. Forty-eight applied for the Fellowship track and 56 for the Professionals track and 16 applicants applied to both tracks. Of the 104 applications, 67 (64%) identified as female, 39 (38%) identified as being from a diverse racial background, 10 (9.8%) identified as being of Hispanic ethnicity. Twenty-three applications (22.12%) indicated that they were the first in their family to attend college and 46 (44.23%) were from sites outside of the ACTC network. Thirty-five trainees (15 in the Fellowship track and 20 in the Professionals track) were selected resulting in a 34% acceptance rate. For the Fellowship track, 11 (73%) identified as female, eight (53%) identified as being from a racially diverse background, four (28.57%) identified as being of Hispanic ethnicity, and four (26.67%) indicated that they were the first person in their family to attend college. Five (33.33%) were not from an ACTC site. For the Professionals track, 14 (70%) identified as female, seven (35%) identified as being from a racially diverse background, two (11%) identified being of Hispanic ethnicity, and four (20%) indicated that they were the first person in their family to attend college. Eight (40%) were not from an ACTC site. **Conclusions:** IMPACT-AD was envisioned as an annual course held at the ACTC Coordinating Center in San Diego, CA. The COVID-19 pandemic caused by the novel corona virus SARS-CoV-2 has forced implementation of a virtual format for the inaugural iteration of IMPACT-AD. Despite the challenges created by

the COVID-19 pandemic, IMPACT-AD is on track to achieve its main goals in 2020. The inaugural iteration of the course exceeded the stated goals of 40% female and 33% diverse racial and ethnic background applicants. The virtual course will be held in September of 2020 with an anticipated in-person course in 2021. **Acknowledgments:** This work was supported by the IMPACT-AD National Institute on Aging (NIA) grant number U13AG067696, Alzheimer's Clinical Trials Consortium (ACTC) NIA grant number U24AG057437 and the Alzheimer's Association (grant number SG-20-693744). **Disclosure:** Drs. Carrillo and Snyder are full time employees of the Alzheimer's Association, which is a funder of the IMPACT-AD course. **Key words:** IMPACT-AD, Training, Alzheimer's Disease, Clinical Trials, Diversity, AD/DRD

#### **OC21: CLINICAL PHASE I DATA AND FIVE SUCCESSFUL POC STUDIES IN TRANSGENIC AND NON-TRANSGENIC ANIMAL MODELS OF AD FOR THE FIRST ANTI-PRIONIC DRUG CANDIDATE FOR ALZHEIMER'S DISEASE.**

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**Background:** More and more data suggest that toxic protein assemblies of A $\beta$  and many other amyloidogenic proteins behave prion-like. The presence of a replicating toxic etiologic agent in the brains of AD patients suggests important consequences for drug development programs and clinical trial designs. The most efficient way to fight a self-replicating pathogen is to apply substances that kill or destroy the pathogen directly. We followed an anti-prionic treatment strategy and developed the first anti-prionic compound RD2 that is able to disassemble A $\beta$  prion assemblies into non-toxic A $\beta$  monomers. **Objectives:** Demonstration of target engagement of RD2 in vitro and in vivo as well as its beneficial effects on cognition in transgenic and non-transgenic animal models of AD. **Methods:** We carried out self-developed QIAD and sFIDA assays for investigating target engagement of RD2. Preclinical proof-of-concept (PoC) studies have been carried out in four different laboratories. **Results:** The anti-A $\beta$ -prionic drug candidate RD2 is BBB penetrable and has demonstrated target engagement in vitro and in vivo (1, 2). RD2 was able to disassemble pre-existing A $\beta$  oligomers under clearly sub-stoichiometric conditions. Treatments in three different transgenic mouse models in three different laboratories yielded deceleration of neurodegeneration and improvement of cognition (rather than only deceleration of cognition decline) also under non-preventive treatment settings (1-4). Old aged (18 months) APP<sup>swePS1dE9</sup> mice showed complete reversal of cognitive and behavioral deficits after three months oral treatment with RD2 (4). Oral treatment of cognitively impaired old Beagle dogs led to significant improvement of cognition, which was maintained after treatment stop. This clearly suggests a truly disease-modifying effect. Here, we summarize all five preclinical proof-of-concept studies in transgenic AD models (1-4) as well as in the non-transgenic dog model of AD and the results of the phase I clinical SAD and MAD trials (5). RD2 has proven to be safe in humans. A single oral dose led to RD2 plasma levels that were measured in the highest dosed animals of the PoC studies. **Conclusion:** The A $\beta$  oligomer disassembling compound RD2 is the first anti-prionic drug candidate. It is highly and repeatedly efficient in transgenic and non-transgenic AD animal models

reproduced in four different laboratories. A clinical PoC study will be the next step for the anti-prionic treatment strategy. 1. van Groen et al., *Sci. Rep.* 7, 16275 (2017); 2. Schemmert et al., *Mol. Neurobiol.* 56, 2211 (2019); 3. Kutzsche et al., *Molecules* 22, 1693 (2017); 4. Schemmert et al., *Neurobiol. Dis.* 124, 36 (2019); 5. Kutzsche et al., *Alzheimers Dement (N Y)*. (2020). 6, 12001

**OC22: INCREASED POWER WITH AVERAGING TWO SCORES AT BASELINE AND END OF STUDY FOR TWO PRIMARY OUTCOMES: ADAS-COG AND ADCS-CGIC.** N. Knowlton<sup>1</sup>, S. Dickson<sup>1</sup>, R. Thomas<sup>2</sup>, L. Schneider<sup>3</sup>, R. Kennedy<sup>4</sup>, M. Cantillon<sup>5</sup>, S.H.E.N.D. Hendrix<sup>1</sup> ((1) *Pentara Corporation - Salt Lake City, USA*; (2) *Ucsd - La Jolla, USA*; (3) *Usc - Los Angeles, USA*; (4) *Uab - Brimingham, USA*; (5) *Robert Wood Johnson Medical School - New Brunswick, USA*)

**Background:** Clinical scales in Alzheimer's disease (AD) are inherently difficult to precisely measure due to variability within patients, within and between raters, in measurement conditions, and innate in the tests themselves. The disease itself is also highly variable separate from its measurement. In clinical trials, it is standard to measure change from baseline to the end of the study, which introduces variability from two different visits. To improve the precision of our outcomes, we propose assessing study outcomes twice within approximately one month near each important timepoint. This allows averaging of two baseline and two end of study assessments. This type of approach is more routine in other therapeutic areas such as measurements of blood pressure, but also makes sense in AD due to the high variability of patient assessment. **Objectives:** To determine the potential value, measured as an increase in power, achieved by using the average score from two visits in lieu of the raw score from a single visit for the primary outcome variable in an Alzheimer's disease clinical trial. The mechanism behind this increase in power is the reduction in variance due to increased stability from using a mean of two correlated random variables. **Methods:** We calculated improvement in precision of the estimate using averaged assessments compared to single assessments at baseline and end of study. We calculate change in precision by showing the percent reduction in the width of the confidence interval. Approximate results are shown for change from baseline in ADAS-cog and a quantitative analysis of CIBIC+, using baseline CDR-sb as a covariate. **Results:** For example, the ADAS-Cog over 12 months, assuming an optimistic test-retest correlation of 0.90, averaging baseline and end of study values gives improved precision of 4.5% as seen by the confidence interval width reduction of 4.5%, and improves power from 80% to 82%. The CIBIC+ test-retest correlation is optimistically assumed to be 0.85, resulting in an improvement in power from 80% to 83% variability that is 92.5% of the original variability, equivalent to reducing the width of the confidence interval by 7.5%. Actual correlations are often lower in practice, resulting in more improvement in precision than estimated here. It should also be noted that the CIBIC+ is originally a 7-point scale, and with averaging two visits, it becomes a 13-point scale. This increased precision of measurement in addition to the stabilizing impact of averaging, contributes to the reduced width of the confidence interval. Initially, this added precision seems to come at the cost of clinical relevance of the point changes, but less precise measurement can also result in exaggerated changes within an individual if that individual is near a category boundary. **Conclusions:** The improved precision of estimates resulting from averaging at baseline and endpoint improves the power

and the reliability of results and is particularly important for this highly variable disease. This novel method can be used to effectively enhance the quality of our signal detection in clinical trials, resulting in more accurate conclusions from AD clinical trials. This will produce more clearly successful trials when treatment effects are real, and more clearly negative trials for compounds that don't work.

**OC23: A PHASE 1B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL COHORT SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND PRELIMINARY EFFICACY STUDY OF INTRAVENOUSLY INFUSED BIIB092 IN PATIENTS WITH FOUR DIFFERENT TAUOPATHY SYNDROMES.** A. Boxer<sup>1</sup>, P. Ljubenkova<sup>1</sup>, L. Vandevrede<sup>1</sup>, J. Rojas<sup>2</sup>, R. Tsai<sup>3</sup>, M. Koestler<sup>1</sup>, L. Fisher<sup>1</sup>, H. Wiest<sup>1</sup>, C. Wang<sup>1</sup>, H. Rosen<sup>4</sup>, D. Graham<sup>5</sup>, T. Dam<sup>5</sup> ((1) *University Of California, San Francisco - San Francisco, USA*; (2) *University Of California, San Francisco - San Francisco, USA*; (3) *Denali Therapeutics - San Francisco, USA*; (4) *University Of California, San Francisco-San Francisco, USA*; (5) *Biogen Inc. - Cambridge, USA*)

**Background:** Tauopathies are neurodegenerative diseases characterized by the accumulation of insoluble tau deposits that are measurable at autopsy. The most common tauopathy is Alzheimer's disease (AD), but tau protein is also found in approximately half of frontotemporal lobar degeneration (FTLD-tau) cases as well as other disorders, including chronic traumatic encephalopathy. The tau protein isoform and three dimensional conformation of tau deposits differs in different tauopathies, but anti-tau therapies targeting tau expression or clearance, or portions of the tau molecule that are common to all forms of tau might potentially find use in multiple tauopathies. In the case of monoclonal antibodies (mAbs) that may have different affinities for different three dimensional tau epitopes, it may be difficult to predict from preclinical data which disease-associated tau species may be most avidly bound by a given mAb and therefore which clinical tauopathy syndrome might best be targeted for therapy. A "basket trial" design is an efficient approach to test a therapy on multiple diseases that have a common causative molecular alteration. We investigated BIIB092 (gosuranemab), a monoclonal antibody directed against a N-terminal tau epitope, in a basket trial enrolling patients with 4 different tauopathies, including corticobasal syndrome (CBS), non-fluent agrammatic variant primary progressive aphasia (nfvPPA), symptomatic FTLD-tau secondary to the microtubule-associated protein tau gene (MAPT) mutation carriers, and traumatic encephalopathy syndrome (TES). **Objectives:** The primary objective was to assess safety and tolerability of BIIB092. Secondary objectives were to assess the CSF pharmacokinetic (PK) and pharmacodynamic (PD) response measured by unbound N-terminal tau concentration. Exploratory objectives were to screen for effects of BIIB092 treatment on CSF, MRI and clinical measures of disease severity. **Methods:** 25 participants were randomized in a 3:1 ratio and administered monthly intravenously 2000 mg BIIB092 (N=18: 8 CBS, 4 nfvPPA, 4 MAPT, and 2 TES) or placebo (N=7: 3 CBS, 2 nfvPPA, 1 MAPT, and 1 TES) for up to 6 months during the double-blind portion of the trial; 14 participants (6 CBS, 4 nfvPPA, 3 MAPT, and 1 TES) received additional monthly open label infusions for up to 6 months. CSF, plasma, volumetric imaging, and exploratory clinical measures were collected at baseline, 12 weeks, and 24 weeks of the double-



blind portion of the trial. **Results:** The study was terminated by Biogen in December, 2019, prior to completion of the planned enrollment of 32 participants, after negative Phase 2 progressive supranuclear palsy trial results were obtained. Adverse events were more frequent in participants randomized to BIIB092 (83%) compared to participants randomized to placebo (28%), though no AEs were thought to be attributable to study drug. One unrelated serious adverse event (Guillain-Barré Syndrome) was observed in a participant randomized to BIIB092. Analyses of secondary and exploratory endpoints are underway. **Conclusion:** 6 months of BIIB092 treatment was safe and well tolerated in a small number of individuals with different tauopathy syndromes. If CSF unbound N-terminal tau concentrations after BIIB092 treatment differ substantially in different tauopathies, this might indicate different affinity of this antibody for different disease associated tau species.

**OC24: PHOSPHORYLATED TAU 181 IN PLASMA AS A BIOMARKER FOR ALZHEIMER'S DISEASE IN ADULTS WITH DOWN SYNDROME: A CROSS-SECTIONAL STUDY.** J. Fortea<sup>1,2</sup>, H. Zetterberg<sup>3</sup>, J. Pegueroles<sup>1</sup>, T. Karikari<sup>3</sup>, M. Carmona-Iragui<sup>1,2</sup>, N.J. Ashton<sup>3</sup>, V. Montal<sup>1</sup>, I. Barroeta<sup>1</sup>, L. Videla<sup>1,2</sup>, M. Altuna<sup>1</sup>, B. Benejam<sup>2</sup>, S. Fernández<sup>2</sup>, S. Valldeu<sup>1</sup>, D. Alcolea<sup>1</sup>, R. Blesa<sup>1</sup>, K. Blennow<sup>3</sup>, A. Lleó<sup>1</sup> ((1) Sant Pau Memory Unit, Hospital De La Santa Creu I Sant Pau-Biomedical Research Institute Sant Pau-Universitat Autònoma De Barcelona - Barcelona, Spain; (2) Barcelona Down Medical Center, Fundació Catalana Síndrome De Down - Barcelona, Spain; (3) Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At The University Of Gothenburg - Mölndal, Sweden)

**Background:** Alzheimer's disease is extremely prevalent in people with Down syndrome due to triplication of the APP gene. CSF and PET biomarkers can reliably detect Alzheimer's disease in this population. However, a less invasive and costly biomarker would allow a more widespread assessment of Alzheimer's disease in this population. Blood levels of tau phosphorylated at threonine 181 (p-tau 181) have been shown to predict with high accuracy Alzheimer's disease pathology in the general population. We aimed to investigate whether blood p-tau 181 could be used as a biomarker of Alzheimer's Disease in Down syndrome. **Methods:** We performed a cross-sectional study of adults with Down syndrome and euploid controls. We included in this study all participants with Down syndrome with plasma available from a large population-based health plan in Catalonia, Spain. Participants underwent neurological and neuropsychological examination and blood sampling, and a subset underwent a lumbar puncture, magnetic resonance and amyloid PET imaging. Adults with Down syndrome were classified into asymptomatic, prodromal Alzheimer's disease, or Alzheimer's disease dementia by investigators blind to biomarker data. Non-trisomic controls were a convenience sample of young (median age 56.4 years) healthy individuals from the Sant Pau Initiative on Neurodegeneration. Plasma p-tau181 concentration was measured using an in house Single molecule array (Simoa) method. Amyloid- $\beta$  (A $\beta$ )1-42/1-40, total tau (t-tau) and p-tau 181 in CSF were measured with an automated ELISA platform. Plasma neurofilament light protein (NfL) concentration was measured with a Simoa assay. Plasma biomarker concentrations were compared between controls and the Down syndrome clinical groups. Diagnostic

performance was assessed with receiver operating characteristic curve analyses between asymptomatic participants and those with prodromal Alzheimer's disease and those with Alzheimer's disease dementia. **Results:** Between Feb 1, 2013, and Dec 30, 2019, we included 373 participants with Down syndrome with plasma available (245 asymptomatic, 44 prodromal Alzheimer's disease, 84 Alzheimer's disease dementia) and 46 controls; CSF, MRI, Fluorodeoxyglucose-PET and amyloid PET data were available from 127, 121, 65 and 45 participants with Down syndrome, respectively. The mean plasma p-tau 181 levels in participants with Down syndrome and prodromal Alzheimer's disease and Alzheimer's disease dementia were increased approximately two- and three-fold, respectively, compared to asymptomatic participants and controls. Levels of p-tau in participants with Down syndrome and Alzheimer's disease dementia were higher compared to those with prodromal Alzheimer's disease (p=0.028). There were no differences in p-tau levels between asymptomatic Down syndrome participants and controls (p=0.177). P-tau levels showed a high accuracy for the diagnosis of Alzheimer's disease in Down syndrome (area under the curve [AUC] 0.80 [95% CI 0.73-0.87] for the comparison between asymptomatic individuals versus those with prodromal Alzheimer's disease and 0.92 [95% CI 0.89-0.95] for the comparison between asymptomatic individuals versus those with Alzheimer's disease dementia). The AUC was 0.88 [95% CI 0.84-0.91] for the comparison between asymptomatic individuals versus those with symptomatic Alzheimer's disease (prodromal and dementia). In the subset of participants with plasma NfL levels available (n=328) the diagnostic accuracy for the diagnosis of Alzheimer's disease was similar to p-tau (AUC 0.86 [95% CI 0.81-0.91] for the comparison between asymptomatic individuals versus those with prodromal Alzheimer's disease, 0.96 [95% CI 0.93-0.98] for the comparison between asymptomatic individuals versus those with Alzheimer's disease dementia and 0.92 [95% CI 0.90-0.95] for the comparison between asymptomatic individuals versus those with symptomatic Alzheimer's disease (prodromal and dementia). The differences between p-tau and NfL in diagnostic accuracy were not statistically significant. We also analysed the correlation between log transformed plasma p-tau 181 and fluid biomarkers. Log-transformed levels of p-tau correlated with plasma NfL ( $\rho=0.67$ ;  $p<0.0001$ , Figure 2A). In paired plasma-CSF samples there was a correlation between log-transformed plasma p-tau 181 levels and the log-transformed CSF ratio A $\beta$ 42/40 ( $\rho=-0.52$ ;  $p<0.0001$ ), log-transformed CSF levels of total tau ( $\rho=0.63$ ;  $p<0.0001$ ) and log-transformed p-tau 181 ( $\rho=0.68$ ;  $p<0.0001$ ). Levels of p-tau in plasma correlated also with areas of atrophy and hypometabolism in temporoparietal regions. These results were mainly driven by those subjects with symptomatic Alzheimer's disease. Finally, the mean plasma p-tau levels were higher in participants with Down syndrome and a positive amyloid PET compared with those with a negative study (AUC for the comparison between both groups was 0.77 (CI 0.61-0.93)). **Conclusions:** Plasma 181 p-tau levels have a good diagnostic performance to detect Alzheimer's disease in adults with Down syndrome. Our findings support the utility of plasma 181 p-tau for the early detection of Alzheimer's disease in Down syndrome in clinical practice and clinical trials.

**OC25: PLASMA FRACTIONS IN ALZHEIMER'S DISEASE: BIOMARKER ANALYSIS IN THE ALK6019-201 AND ALK6019-202 TRIALS.** S. Braithwaite, B. Szoke, J. Gulati, R. Ray, S. Lohr, J. Hannestad (*Alkahest - San Carlos, USA*)

**Background:** Alzheimer's Disease (AD) is a complex disorder involving multiple pathophysiological mechanisms. As age is the primary risk factor for development of AD, targeting biological processes of aging therefore may be more effective than targeting individual targets or disease mechanisms. Plasma has been demonstrated to affect age-related mechanisms in preclinical models, acting on multiple organ systems, including in the brain, to potentially provide a multimodal approach to modify aging biology. We have further demonstrated in preclinical studies that selected plasma fractions are more efficacious and safer therapeutic candidates than whole plasma for treating disorders of cognitive aging. Initiating the translation of this work we have performed clinical studies using the Plasma Protein Fraction GRF6019 in patients with mild-moderate and severe Alzheimer's Disease demonstrating the therapeutic is safe and well tolerated and that over the course of study patients exhibited minimal functional and cognitive decline. Assessment of biomarkers can add to our understanding of how such multimodal therapies can impact patients. **Objectives:** Study plasma proteome, CSF proteome and MRI changes in response to treatment as experimental endpoints in understanding GRF6019 action. **Methods:** Samples and images were acquired over the course of the treatment and follow-up periods from 40 and 26 subjects in trials ALK6019-201 (mild-to-moderate AD) and ALK6019-202 (severe AD), respectively. Plasma and CSF proteomic composition were analyzed using the O-Link platform measuring 1161 unique proteins, and data was processed in Python. Structural MRI images were collected in the ALK6019-201 study from 39 subjects and segmented using FreeSurfer. Hippocampal volume and cortical thickness from the temporal lobes was calculated. **Results:** Pharmacodynamic response to GRF6019 treatment was observed in the plasma proteome. Altered levels of proteins corresponding with the temporal profile of treatment administration were observed in both studies and differential behavior of multiple proteins between placebo and GRF6019 treatment in the ALK6019-202 study. Interpretation of CSF changes is limited by the small number of consenting patients, but indicated little change in the typical AD biomarkers, and possible decrease in levels of an inflammatory cytokine. Structural MRI analysis indicated no significant changes in key brain areas over the course of the 6 months of the AKST6019-201 study. **Conclusions:** Pharmacodynamic changes observed in the plasma proteome are indicative of acute downstream effects on pathways of relevance for systemic function. Although limited datasets, the lack of decline indicated by CSF biomarkers and MRI imaging correlate with the lack of decline observed in clinical endpoints. These data are supportive of continued development of Plasma Protein Fractions for AD and related disorders.

**OC26: THE METHODOLOGY AND PROBABILITY OF RECRUITMENT AND ENROLLMENT INTO PHASE 2 AND 3 ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT CLINICAL RESEARCH TRIALS.** D. Anderson, D. Nathan, R. Warraich, E. Cassar, D. Weisman (*Abington Neurological Associates - Abington, PA, USA*)

**Introduction:** The rate of diagnosis for Alzheimer's Disease (AD) has continued to grow in the world's geriatric population. Alzheimer's Disease affects not only those diagnosed with the disease, but their family members and caregivers as well. Additionally, AD significantly impacts the economy, costing billions of dollars each year, estimated to increase to two trillion by 2030. An AD diagnosis is determined by a myriad of factors, some which include the presentation of symptoms, the presence of pathologies in fluid and imaging biomarkers. The progression of the disease is believed to be characterized by two pathologies:  $\beta$ -amyloid plaque and neurofibrillary tangles of hyperphosphorylated tau. Due to the limited understanding of the disease pathology, the potential for a cure is still widely debated. As a result, the majority of the clinical research trials investigating disease modifying therapies (DMTs), aim to slow the progression of the disease in order to increase the quality of life of those diagnosed. Among the ongoing clinical trials, a standard of 31,314 participants are needed to be recruited into all MCI and AD clinical trials across all sites. We performed a data analysis using a patient population that was seen for the last 10 years at Abington Neurological Associates' (ANA) Clinical Research Center. **Methods:** Utilizing the clinical research patient population at Abington Neurological Associates, we reviewed patient medical records between the dates of January 2010 to June 2020. We started with a subject pool of 5,000 patients who were seen for Mild Cognitive Impairment (MCI) or Alzheimer's Disease (AD). Out of the 5,000 patients seen, 414 were deemed potential subjects to be screened for clinical trials. Among those, 374 patients qualified for screening, out of which 179 were enrolled in trials. From the 179 enrolled, 84 patients showed positivity for amyloid based upon a PET scan or CSF examination. **Results:** Since 2010, Abington Neurological Associates' (ANA) Clinical Research Center has participated in approximately 50 phase 2 and 3 clinical trials. Our data showed that 8.28% of patients seen for MCI or AD, were deemed potential study subjects. Out of those patients, 72.46% were screened for a trial. Among those 59.66% were enrolled in a trial. Of the patients enrolled in clinical trials, 46.92% showed positivity for amyloid on either a PET scan or CSF examination. **Discussion:** Recruiting for clinical research trials can be a timely and rigorous task. Following a trial discussion, patients may opt out of participating due to the inability to commit the time necessary to complete study visits. However, if a patient does express interest in participating in a trial, they may still not meet eligibility or screen-fail due to a variety of reasons. In reviewing our data, we can summarize the most common reasons that a patient may screen-fail. A review of a patient's medical history and current medications should always occur prior to scheduling a screening visit. Certain pre-existing medical conditions such as, cardiac issues, substance abuse, and psychiatric concerns are often listed as exclusionary criteria. Additionally, patient's who are taking prohibited medications or those who are not on stable medications at the time of screening can be excluded. Qualifying for a screening visit does not necessarily mean that the patient will be enrolled into the trial. Patient's often screen-fail due to performing too

poorly or too well on clinical and cognitive assessments. Some of these assessments used to determine a patient's eligibility for a trial include, the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), or the Clinical Dementia Rating (CDR). Additionally, clinically significant lab workup done at the screening visit can exclude a patient from participating in the trial. Once past the point of enrollment, a patient may still be excluded from the trial based on adjustment of certain chronic medications, the experience of adverse events, or the inability of the caregiver to participate in the cognitive assessment of the patient (which is always mandatory for MCI and Alzheimer's trials). At any point, a patient may also choose to withdraw their consent and discontinue their participation in the study. Additionally, it is not uncommon for trials themselves to be discontinued due to a lack of efficacy or enrollment. Alzheimer's Disease is a neurodegenerative disease with a very slow progression rate. Neurodegeneration can start very gradually and can progress for years prior to the manifestation of symptoms. It is often very hard for patients and caregivers to accept the diagnosis of MCI or AD until the disease has progressed considerably. This is why clinical trials for MCI and AD are so crucial. By finding a way to slow the progression of AD, a patient's quality of life can be preserved as long as possible.

**OC27: MISFOLDING OF AB AS PRECISE PLASMA STRUCTURE BIOMARKER FOR PRECLINICAL ALZHEIMER'S.** K. Gerwert<sup>1,2</sup> ((1) Ruhr University Bochum - Bochum, Germany; (2) Center for Protein Diagnostics - Bochum, Germany)

**Background:** Biomarkers indicating Alzheimer stages in cognitively unimpaired individuals before irreversible brain pathology is induced are essential for future therapeutic approaches. In past trials PET scan and A $\beta$ 42/40 in CSF were used as diagnostic markers to identify prodromal and MCI stages. In these stages the therapeutic antibodies seem not to conserve the cognition even they perform their intended biological function. The antibodies may have a therapeutic effect on cognition when they will be applied at earlier, less damaged stages. Complementary to the A $\beta$  and tau biomarkers using absolute concentrations of body fluids we have introduced the A $\beta$  misfolding as a structure biomarker. The A $\beta$  misfolding from a monomeric/unstructured to a  $\beta$ -sheet enriched secondary structure is one of the earliest events in AD pathogenesis. This misfolding can be monitored by the immuno-infrared-sensor measuring the frequency of the C=O stretching vibration of the A $\beta$  backbone (1, 2). This vibration causes the amide I absorbance band, which in turn gives information about the secondary structure distribution of all A $\beta$  isoforms. This initial misfolding takes place about 15-20 years before AD is clinically diagnosed followed by  $\beta$ -sheet oligomerization and aggregation to much larger fibrils on the nanometer scale. After several years, this A $\beta$  misfolding becomes visible at the macroscopic scale as deposits in large amyloid plaques. We have shown in a discovery study that the structure biomarker indicates probable Alzheimer's disease in a prospective cohort (3). We extended this to prodromal AD in the BioFINDER cohort (4). Furthermore we have shown that the structure biomarker is prognostic and predicts the conversion to clinical Alzheimer's disease in preclinical cognitively unimpaired AD subjects in the population based ESTHER cohort (4). Including APOE4 as risk factor, preclinical AD states could be identified

up to 14 years before clinically diagnosed with an AUC over 0.87 (5). The additional use of the tau misfolding as a structure biomarker increases the sensitivity to 89% and specificity up to 97% as compared to clinical diagnosis (6). Beside the general threshold <1644 cm<sup>-1</sup> indicating abnormal misfolding in diseased individuals, recently a second threshold >1646 cm<sup>-1</sup> was introduced indicating a normal Ab secondary structure distribution as observed in individuals without AD (6). Frequencies between both thresholds indicate low misfolding. A general advantage of the structure biomarker is that already at baseline the frequency read-out is directly prognostic by comparison to the already validated threshold frequencies. In contrast, the concentration biomarkers have to determine the cut off values retrospectively for each study and need a follow up. Furthermore, the cut off values measured by ELISA, SIMOA, or mass spectrometry cannot be compared directly with each other but have to be determined for each technique separately. **Objectives:** We will present a study at which the Ab misfolding is validated as prognostic plasma biomarker for future clinical conversion to mild cognitive impairment (MCI) or Alzheimer's disease (AD) of individuals with subjective cognitive decline (SCD) (7). **Methods:** Baseline plasma samples of SCD subjects were analyzed using the immuno-infrared-sensor. Read-out values <1644 cm<sup>-1</sup> reflect abnormal misfolding,  $\geq$ 1644 cm<sup>-1</sup> and  $\leq$ 1646 cm<sup>-1</sup> low misfolding, and >1646 cm<sup>-1</sup> normal Ab folding as compared to healthy individuals. We used COX proportional hazard models to quantify the Ab misfolding as prognostic biomarker. The accuracy was determined by time-dependent ROC-curve analyses (t-ROC). Statistical models were adjusted for age, sex, and APOE4 status. **Results:** All 11% converters within six years of follow up show misfolding at baseline and were correctly predicted. COX analyses revealed for conversion a hazard ratio (HR) of 19 as compared to those with normal folding. T-ROC curve analyses yielded an AUC of 0.94 for the misfolding as structure biomarker including age, sex and APOE4 status as risk factors. **Conclusion:** The plasma amyloid structure biomarker including other risk factors can precisely predict in cognitively unimpaired subjects without symptoms conversion to clinical MCI and AD. Using in addition the SIMOA technology provides an added value. Plasma biomarkers provide a noninvasive and cost effective alternative to PET and CSF biomarkers for screening in clinical studies and pharmaceutical trials to identify high risk individuals. Earlier intervention might provide better therapy response. **References:** 1. Nabers A, et al. J Biophotonics. 2016 Mar;9(3):224-34. 2. Schartner J, et al. ACS Med Chem Lett. 2017 Jun 11;8(7):710-714. 3. Nabers A, et al. Anal Chem. 2016 Mar 1;88(5):2755-62. 4. Nabers A, et al. EMBO Mol Med. 2018 May;10(5):e8763. 5. Stocker H, et al. Alzheimers Dement. 2020 Feb;16(2):283-291. 6. Nabers A, et al. Alzheimers Dement (Amst). 2019 Mar 12;11:257-263. 7. Lange J\*, Verberk IMW\*, Timmesfeld N, Denz R, Budde B, Stockmann J, Scheltens P, van der Flier WM, Nabers A, Teunissen CE, Gerwert K. submitted

## OC28: COMPLEMENTARY ANALYSES OF THE AMBAR TRIAL: PLASMA EXCHANGE TREATMENT SLOWS COGNITIVE, FUNCTIONAL AND GLOBAL DECLINE OF AMYLOID POSITIVE AND NEGATIVE INDIVIDUALS.

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**Background:** Alzheimer's disease (AD) is associated with excess amyloid beta (A $\beta$ ) in the brain, which disrupts cell function and likely contributes to AD symptoms. Despite prospective functional links to brain activity, trials depleting brain amyloid have been unsuccessful at alleviating AD-associated cognitive deficits. The Grifols Alzheimer's Management By Albumin Replacement (AMBAR) study is a multicenter randomized, blinded, and placebo-controlled phase IIb/III trial for patients with mild-to-moderate (Mini-Mental Status Examination [MMSE] 18-26) AD. AMBAR investigates the effects of plasma exchange (PE) and albumin replacement (Albutein®, Grifols) with or without intravenous immunoglobulin (Flebogamma® DIF, Grifols) on cognition (Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog]), function (Activities of Daily Living [ADCS-ADL]), global change (Clinical Dementia Rating Scale-Sum of Boxes [CDR-SB]), and Clinical Global Impression of Change scales [ADCS-CGIC]). **Objective:** Since AMBAR study participant enrollment did not exclude amyloid negative individuals according to the AD definition at the time of study initiation, in this post-hoc analysis we investigated the treatment effect in amyloid positive vs amyloid negative subjects. We also investigated the association of mild and moderate individuals at baseline within each amyloid group. **Methods:** Changes from baseline in clinical measures were analyzed using a mixed model for repeated measures (MMRM). The MMRM included the baseline score of the outcome scale, treatment (active/placebo), country, visit, age, CSF A $\beta$ 42 (positive <735 pg/mL; negative  $\geq$ 735 pg/mL), baseline MMSE, APOE  $\epsilon$ 4 status (carrier, non-carrier) as well as an interaction between treatment, visit, CSF A $\beta$ 42, and baseline MMSE status as covariates. Subject ID was included as a fixed effect. The difference in LS means between active (PE-treated) and placebo (sham PE) were compared within visit. **Results:** Clinical improvement on all four endpoints with effect sizes between 61%-82% slowing decline in active relative to placebo were observed. Significant associations were seen within each measure at 12, 14 months (end of study), or both ( $p < 0.05$ ). Furthermore, significant treatment benefits were observed across all 4 outcomes by 12 or 14 months for amyloid positive and amyloid negative subjects. Data was stratified by baseline MMSE and amyloid status for remaining analyses. Among amyloid positive individuals with moderate baseline MMSE scores, the active group was significantly improved ( $p < 0.05$ ) relative to control in all clinical measures by month 14. Similar results for ADAS-Cog, CDR-SB, and ADCS-CGIC were observed for amyloid negative individuals with a moderate baseline MMSE score.

However, a markedly reduced association was observed in amyloid negative individuals with moderate MMSE scores for ADCS-ADL. Among amyloid positive individuals with mild baseline MMSE scores, only ADCS-CGIC measurements were significantly improved by 14 months ( $p = 0.03$ ). At the same time, amyloid negative individuals with a mild baseline MMSE score show significant improvement by 14 months for CDR-SB and ADCS-CGIC. The remaining clinical measures were not significantly different, but had a range of 44-130% slowing, suggesting that the amount of change observed for these measures in the mild population may require a larger sample size to reach significance due to the slow decline in the mild control group patients. **Conclusions:** Collectively, this data demonstrates that PE treatment improves clinical measures similarly for amyloid positive and amyloid negative individuals among the primary clinical measures tested and highlights the differences in responses among individuals with differing baseline amyloid and MMSE status.

## OC29: CONSTRUCTING A MORE SENSITIVE CLINICAL TRIAL OUTCOME MEASURE FOR AGITATION IN ALZHEIMER'S DISEASE: INCORPORATING IPA AGITATION CRITERIA.

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**Introduction:** The aim of this study was to respond to the EU-US-CTAD Task Force recommendation to develop a clinician-rated global instrument to serve as a primary outcome measure in agitation clinical trials. Requirements of the instrument were to reflect the agitation criteria established by the International Psychogeriatric Association (IPA), incorporate information from both patient and caregiver, define clinically meaningful effects, demonstrate sensitivity to change, and provide the ability to power studies. Here we describe the derivation of IPA Agitation-informed measures from the Cohen Mansfield Agitation Inventory (CMAI) and the Neuropsychiatric Inventory-Clinician (NPI-C), and the validation of these derived measures in the Agitation and Aggression AD Cohort (A3C). **Methods:** In a modified Delphi process, items from the CMAI and the NPI-C related to agitation symptoms were mapped by an expert panel onto IPA agitation definition domains to generate derivative measurement instruments, the CMAI-IPA (19 items) and NPI-C-IPA (25 items). Original and derivative scales were then studied in the A3C study. A3C included the CMAI and NPI-C and thus performance of the original and derived scales could be compared with respect to minimal clinically important differences (MCID), sensitivity to change (using different indices) and predictive validity properties, with the modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC) considered as gold standard (improved (1 or 2) vs unimproved  $\geq 3$  at 1 and 3 months). Intraclass correlation analyses were conducted between original and derivative measures. **Results:** A3C enrolled 262 AD patients with clinically significant agitation, with a mean age of 82.4 years ( $\pm 7.2$  years), 58.4% women, and 69.9% living at home. At baseline, mean MMSE score was 10.0 ( $\pm 8.0$ ), CMAI score was 62.0 ( $\pm 15.8$ ), CMAI-IPA was 38.5 ( $\pm 12.2$ ), NPI-C A+A clinician severity score was 15.8 ( $\pm 10.8$ ),

and NPI-C-IPA was 15.2 ( $\pm 10.8$ ). According to the IPA agitation definition, 76.3% had excessive motor activity (n=199), 76.3% had verbal aggression (n=199), and 44.1% (n=115) had physical aggression. At 3 months, CMAI score was 52.5, NPI-C A+A clinician severity score was 9.9, and 20.9% patients (n=44) were much or very much improved on the mADCS-CGIC. Using ROC Curves, at 1 month, estimated MCID for the parent CMAI was -5 (odds-ratio (OR) = 18.87,  $p < 0.0001$ ), and for the derived CMAI-IPA MCID was -2 (OR=21.19,  $p < 0.0001$ ). For the NPI-C-A+A estimated MCID was -3 (OR= 15.53,  $p < 0.0001$ ), and for the derivative NPI-C-IPA MCID was -5 (OR= 13.47,  $p < 0.0001$ ). At 3 months, MCID of CMAI was -17 (OR= 14.90,  $p < 0.0001$ ), and for the CMAI-IPA MCID was -5 (OR= 9.25,  $p < 0.0001$ ), while MCID for NPI-C-A+A was -3 (OR= 11.90,  $p < 0.0001$ ), and for NPI-C-IPA was -5 (OR= 7.84,  $p < 0.0001$ ). Most changes in ratings occurred in the first month of the three-month observation period. During the first month AUC for CMAI, CMAI-IPA, NPI-C-A+A, and NPI-C-IPA were 0.82 (0.73-0.91), 0.82 (0.73-0.90), 0.83 (0.76-0.89), and 0.84 (0.77-0.90) respectively. At 3 months, AUC for CMAI, CMAI-IPA, NPI-C-A+A, and NPI-C-IPA were 0.84 (0.77-0.91), 0.81 (0.74-0.88), 0.77 (0.70-0.84), and 0.80 (0.73-0.86), respectively. AUCs of all four scales were similar, suggesting no scale has an advantage in predicting clinician ratings. Sensitivity to change of CMAI between baseline and 3 months was high (Effect size (ES) mean = -0.99; Standardized response mean (SRM) = -0.90). According Guyatt Response Index, the sensitivity to change of total CMAI was very high. As per the reliable change index (RCI), a 13.15 point pre-post treatment change on the CMAI from baseline to 3 months would be statistically reliable. The sensitivity to change of total NPI-C-A+A between baseline and 3 months was considered as high by Effect Size (mean = -0.81) and Standardized Response Mean (mean = -0.88) and was considered as very high by Guyatt Response Index (-1.36). As per the RCI, a 12.88 point pre-post treatment change on the NPI-C-A+A from baseline to 3 months would be statistically reliable. Sensitivity to change of CMAI, NPI-C-A+A, CMAI-IPA and NPI-C-IPA between baseline and 3 months and between baseline and 1 month according to Effect Size, Standardized response mean, Guyatt Response Index and Reliable Change Index were similar between the four scales. ICC between CMAI and CMAI-IPA at 3 months showed an excellent reliability; ICC = 0.93 (0.91-0.95). ICC between NPI-C A+A and NPI-C-IPA at 3 months showed a good reliability; ICC = 0.87 (0.83-0.89). ICC between derived scales at 3 months showed a moderate reliability; ICC = 0.70 (0.63-0.77). **Conclusion:** In a naturalistic study of AD patients in both community dwelling and nursing home settings, our results demonstrate better performance for the original NPI-C-A+A over the original CMAI. The shorter, derivative CMAI-IPA and NPI-C-IPA, designed to reflect the IPA Agitation criteria, performed as well as the original scales. We propose that future studies using the IPA agitation criteria as inclusion criteria should use the derivative scales to capture the IPA domains at baseline, and the clinical effects of treatments for agitation.

### OC30: EVALUATION OF LIRAGLUTIDE IN TREATMENT FOR ALZHEIMER'S DISEASE.

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**Background:** Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue currently approved for type 2 diabetes and obesity. 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. The primary objective of the study is to evaluate the change in cerebral glucose metabolic rate after 12 months of treatment with liraglutide in participants with Alzheimer's disease compared to those receiving placebo. **Methods/design:** ELAD is a 12-month, multi-centre, randomised, double-blind, placebo-controlled, phase IIb trial of liraglutide in participants with mild Alzheimer's dementia. A total of 204 participants were randomised to receive either liraglutide or placebo as a daily injection for a year. The primary outcome is the change in cerebral glucose metabolic rate in the cortical regions (hippocampus, medial temporal lobe, and posterior cingulate) from baseline to follow-up in the treatment group compared with the placebo group. The secondary outcomes are the change from baseline to 12 months in z scores for clinical and cognitive measures (Alzheimer's Disease Assessment Scale—Cognitive Subscale and Executive domain scores of the Neuropsychological Test Battery, Clinical Dementia Rating Sum of Boxes, and Alzheimer's Disease Cooperative Study—Activities of Daily Living) and the incidence and severity of treatment-emergent adverse events or clinically important changes in safety assessments. Other secondary outcomes are 12-month change in magnetic resonance imaging volume, diffusion tensor imaging parameters, and changes in composite scores using support machine vector analysis in the treatment group compared with the placebo group. **Results:** ELAD results will be presented at the conference **Discussion:** Alzheimer's disease is a leading cause of morbidity worldwide. As available treatments are only symptomatic, the search for disease-modifying therapies is a priority. ELAD trial will form the basis of future studies using GLP-1 analogues. GLP-1 analogues will represent an important class of compounds to be further evaluated in clinical trials for Alzheimer's treatment.

**OC31: IMPACT OF PIMAVANSERIN ON COGNITIVE MEASURES IN PATIENTS WITH NEURODEGENERATIVE DISEASE: RESULTS FROM 4 PLACEBO-CONTROLLED CLINICAL STUDIES.** C. Ballard<sup>1</sup>, E.P. Foff<sup>2</sup>, P. Tariot<sup>3</sup>, B. Mcevoy<sup>2</sup>, B. Coate<sup>2</sup>, G. Demos<sup>2</sup>, A. Berrio<sup>2</sup>, B. Abbs<sup>2</sup>, J.M. Youakim<sup>2</sup>, S. Stankovic<sup>2</sup> ((1) *University Of Exeter Medical School - Exeter, United Kingdom*; (2) *ACADIA Pharmaceuticals, Inc - Princeton, USA*; (3) *Banner Alzheimer's Institute - Phoenix, USA*)

**Background:** Neuropsychiatric symptoms (NPS), including psychosis, are common among patients with dementia and are associated with poorer clinical outcomes. There are no therapies approved by the Food and Drug Administration for the treatment of dementia-related psychosis (DRP). Off-label use of antipsychotics is common but is associated with significant adverse outcomes, including acceleration of cognitive decline. Pimavanserin is a selective 5-HT<sub>2A</sub> receptor inverse agonist/antagonist approved to treat hallucinations and delusions associated with Parkinson's disease psychosis and is currently being investigated for the potential treatment of hallucinations and delusions associated with DRP. **Objectives:** Evaluate the impact of pimavanserin treatment on cognitive measures in patients with neuropsychiatric manifestations of neurodegenerative disease. **Methods:** Cognitive function (as measured by Mini-Mental State Examination [MMSE]) was a pre-specified safety outcome evaluated in 4 placebo-controlled double-blind (DB) studies enrolling elderly patients with neuropsychiatric manifestations of neurodegenerative disease (N=697 receiving pimavanserin), including those with DRP (N=622 receiving pimavanserin). Treatment-emergent adverse events (TEAEs) associated with cognition were examined across studies using a Standardized Medical Dictionary for Regulatory Activities Query based on the High Level Group Term "Cognitive and attention disorders and disturbances," plus one other relevant Preferred Term ("confusional state"), for a total of 14 terms. Whole-population mean changes in MMSE scores over time and outlier analyses of individual patient-level data were also evaluated. Study 019 (NCT02035553) was a phase 2 study in patients with Alzheimer's disease (AD) psychosis living in care homes randomized to receive pimavanserin 34 mg or placebo for 12 weeks. Patients with MMSE scores  $\geq 1$  and  $\leq 22$  were eligible. HARMONY (NCT03325556) was a phase 3 relapse-prevention study in patients with DRP. Patients received pimavanserin during a 12-week open-label (OL) period, and those with sustained response at weeks 8 and 12 were randomized to receive pimavanserin or placebo in the 26-week DB period. Patients with MMSE scores  $\geq 6$  and  $\leq 24$  were eligible for the study. Study 046 (NCT03575052) is an ongoing randomized, DB, phase 3b study of the safety of pimavanserin 34 mg for up to 8 weeks in patients with NPS related to neurodegenerative disease. Patients with MMSE scores  $\geq 6$  were eligible. Data were available from an interim safety analysis including 288 patients. Study 032 (NCT02992132) was a DB, placebo-controlled phase 2 study evaluating safety and efficacy of pimavanserin (20 mg and 34 mg) for treatment of agitation and aggression in AD. Patients with MMSE scores  $\geq 5$  and  $\leq 26$  were eligible. **Results:** In study 019, mean baseline (standard error [SE]) MMSE values were similar for pimavanserin (10.18 [0.581]; n=87) and placebo (9.85 [0.545]; n=85). The least-squares (LS) mean (SE) change from baseline to week 12 was not significantly different for pimavanserin (-0.25 [0.42]) versus placebo (0.10 [0.41]; difference in LS means [SE]: -0.35 [0.585]; 2-sided P=0.55). Of the terms queried, only

confusional state (reported in 4 pimavanserin patients [4.4%] and 2 placebo patients [2.2%]) was reported as a TEAE. In the HARMONY OL period, the mean (SE) baseline MMSE score was 16.7 (0.24). Mean (SE) change from baseline was 1.0 (0.22) at week 12. Cognition-related TEAEs of confusional state (n=8; 2.0%) and mental impairment (n=2; 0.5%) were reported. Patients randomized to pimavanserin or placebo in the DB period had similar mean (SE) MMSE scores at DB baseline (18.3 [0.53] vs 17.9 [0.55]). During the DB period there was no decline observed in mean MMSE in pimavanserin-treated patients or difference from placebo-treated patients. Patients exposed to pimavanserin for the 9-month duration of the study (n=46) had a mean (SE) change from OL baseline of 1.2 (0.51), indicating no evidence of cognitive decline. In the DB period, only confusional state was reported in 1 pimavanserin patient (1.0%) and no placebo patients. Post hoc analyses did not reveal specific subpopulations at increased risk of large MMSE score changes. In the Study 046 interim analysis, baseline mean (SE) MMSE scores were 18.5 (0.42) in the pimavanserin group and 19.2 (0.39) in the placebo group. The LS mean (SE) change from baseline to week 8 was 1.2 (0.21) in the pimavanserin group and 0.5 (0.21) in the placebo group. The TEAE of confusional state was reported in one pimavanserin patient (0.7%). In study 032, 36 patients were randomized to pimavanserin 34 mg, and 40 were randomized to placebo. The LS mean (SE) change from baseline to week 12 was small and was similar for pimavanserin (0.0 [0.57]) and placebo (0.0 [0.55]). The TEAE of confusional state was reported in two pimavanserin patients (2.8%); no cognition-related TEAEs were reported in the placebo group. **Conclusions:** Evidence from 4 randomized, placebo-controlled clinical studies of patients with neurodegenerative disease treated with pimavanserin show that mean changes in MMSE scores were small and were similar to placebo. Cognition-related TEAEs were reported infrequently. These results demonstrate that treatment with pimavanserin did not have a negative impact on cognitive function with up to 9 months of treatment.

**OC33: THE AMSTERDAM INSTRUMENTAL ACTIVITIES OF DAILY LIVING QUESTIONNAIRE IN PRODROMAL VS. MILD ALZHEIMER'S DISEASE: ANALYSIS OF BASELINE DATA FROM THE TAURIEL STUDY.** E. Teng<sup>1</sup>, P. Manser<sup>1</sup>, C. Randolph<sup>2</sup>, K. Pickthorn<sup>1</sup>, M. Blendstrup<sup>1</sup>, M. Keeley<sup>1</sup>, P. Scheltens<sup>3</sup>, S. Sikkes<sup>3</sup> ((1) *Genentech, Inc. - South San Francisco, USA*; (2) *Medavante, Inc. - Hamilton, USA*; (3) *Amsterdam University Medical Center - Amsterdam, Netherlands*)

**Background:** The Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q) is an assessment of functional performance that includes more complex activities, such as the use of modern everyday technology (e.g., computers, internet, mobile phones), than previously established scales for activities of daily living (ADLs), which may increase its sensitivity for detecting deficits in earlier stages of neurodegenerative disease, such as mild cognitive impairment (MCI). Prior work across a diverse range of observational cohorts has validated the utility of the A-IADL-Q for identifying functional decline, both cross-sectionally and longitudinally. While those data highlight its potential for use in interventional clinical trials, the performance of the A-IADL-Q in such settings has not yet been comprehensively explored. **Objectives:** Cross-sectional analyses of baseline A-IADL-Q scores from an international, multi-center, interventional clinical trial in prodromal-to-mild Alzheimer's disease (AD). **Methods:**

We examined baseline A-IADL-Q data from the Tauriel study (GN39763; NCT03289143), which is evaluating the safety and efficacy of the anti-tau antibody semorinemab in prodromal to mild AD. Individual items on the A-IADL-Q are rated by informants/caregivers on a scale from 0 (no longer able to perform the ADL) to 4 (no difficulty performing the ADL), with higher scores indicative of better performance. Overall performance was analyzed as the average response of applicable items (e.g., informants able to assess ADL, any deficits primarily due to cognitive impairment), which was multiplied by 25 to produce a global score from 0 to 100. We compared A-IADL-Q scores between prodromal and mild AD subgroups and investigated associations between the A-IADL-Q and other baseline indices of cognition [13 item version of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13), Mini-Mental State Examination (MMSE)] and function [Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)]. **Results:** Baseline data were available from 440 participants (158 prodromal AD, 282 mild AD). The AD subgroups were similar in age (prodromal: mean=69.7, SD=7.0; mild: mean=69.4, SD=6.8) and gender distribution (prodromal: 53% women; mild: 57% women). Mean global A-IADL-Q (prodromal: mean=85.0, SD=16.7; mild: mean=63.3, SD=21.9) and total ADCS-ADL (prodromal: mean=71.7, SD=4.8; mild: mean=65.9, SD=7.9) scores were significantly higher in prodromal relative to mild AD ( $p < 0.001$ ). Receiver Operating Characteristic (ROC) analyses of both instruments for distinguishing between participants classified as prodromal versus mild AD revealed higher Area Under the Curve (AUC) values for the A-IADL-Q (0.801; 95% CI: 0.757-0.845) relative to the ADCS-ADL (0.747; 95% CI: 0.700-0.794). Across the entire study population, scores on the two scales were moderately well correlated ( $r_s = 0.63$ ,  $p < 0.001$ ). However, the correlation was stronger amongst participants with mild AD ( $r_s = 0.56$ ,  $p < 0.001$ ) than those with prodromal AD ( $r_s = 0.37$ ,  $p < 0.001$ ). Both scales exhibited similar correlations with cognition as measured by the ADAS-Cog13 (A-IADL-Q:  $r_s = -0.44$ ,  $p < 0.001$ ; ADCS-ADL:  $r_s = -0.46$ ,  $p < 0.001$ ) and MMSE (A-IADL-Q:  $r_s = 0.33$ ,  $p < 0.001$ ; ADCS-ADL:  $r_s = 0.31$ ,  $p < 0.001$ ). **Conclusions:** These analyses of baseline data from a curated clinical trial cohort are consistent with prior work with the A-IADL-Q in observational cohorts which demonstrated its utility in distinguishing between participants with MCI versus dementia. Likewise, our results replicate prior work suggesting that A-IADL-Q scores correlate with other functional measures and cognitive performance. Head-to-head comparisons between the A-IADL-Q and ADCS-ADL suggest that the A-IADL-Q may better discriminate between prodromal versus mild AD and provide additional information regarding more subtle functional deficits in prodromal AD. Further analyses of the A-IADL-Q using the previously validated Item Response Theory approach and with longitudinal data from the Tauriel trial will allow for further elucidation of the role of the A-IADL-Q in therapeutic clinical trials in early AD.

**OC34: MAGNETIC RESONANCE IMAGING MEASURES OF BRAIN ATROPHY ACROSS THE EXPEDITION TRIALS IN MILD AND MODERATE ALZHEIMER'S DISEASE DEMENTIA.** D.O. Svaldi<sup>1</sup>, I.A. Higgins<sup>1</sup>, S. Shcherbinin<sup>1</sup>, S.W. Andersen<sup>1</sup>, D. Scott<sup>2</sup>, K.C. Holdridge<sup>1</sup>, R. Yaari<sup>1</sup>, J.R. Sims<sup>1</sup> ((1) *Eli Lilly And Company - Indianapolis, Indiana, USA*; (2) *Bioclinica - Newark, California, USA*)

**Background:** Volumetric magnetic resonance imaging (vMRI) and atrophy measures are critical in the evaluation of the safety profile and efficacy of candidate treatments in clinical trials for Alzheimer's disease (AD) dementia. Solanezumab (LY2062430) is a humanized monoclonal antibody that preferentially binds to soluble amyloid  $\beta$  and promotes its clearance from the brain. Prior evidence from the solanezumab EXPEDITION3 phase 3 trial (EXP3; NCT01900665) showed that solanezumab did not statistically significantly alter brain atrophy in comparison with placebo, although patients in the solanezumab group consistently showed numerically less brain atrophy than those in the placebo group. **Objectives:** The objective of this study was to further investigate the effects of solanezumab treatment on global brain atrophy measures, quantified using vMRI. We present data from participants with mild or moderate AD dementia in the EXPEDITION (EXP; NCT00905372), EXPEDITION2 (EXP2; NCT00904683), and EXP3 trials to assess whether there was a consistent effect of low-dose solanezumab, 400 mg every 4 weeks, on atrophy in each of the three trials and in the pooled sample. **Methods:** Cohort Demographics and Baseline vMRI Characteristics: All participants included in this analysis were diagnosed with mild or moderate AD dementia; additionally, EXP3 participants demonstrated biomarker evidence of elevated amyloid. At baseline, whole brain volume (WBV, not corrected for intracranial volume) and ventricle volume (VV) were estimated using either a semiautomated method developed by Bioclinica (EXP and EXP2) or using Freesurfer 6.0 (EXP3). Because participants in EXP3 were required to have biomarker evidence of elevated cerebral amyloid, while amyloid positivity was not verified in EXP and EXP2, all analyses were repeated including only participants who carried at least one apolipoprotein (APOE)  $\epsilon 4$  allele (APOE4 positive), to make the three cohorts more homogenous. Longitudinal Assessments of Brain Atrophy: Whole brain atrophy (WBA) and ventricle enlargement (VE), measured in  $\text{cm}^3$ , were estimated at 80 weeks using either boundary shift integral (EXP and EXP2) or tensor-based morphometry (EXP3). Atrophy measures from the three trials were pooled after it was confirmed that these methods produced similar values in a sub-analysis of 113 participants from EXP2, analyzed using both methods. Analysis of covariance models were applied to each cohort individually and to the pooled sample with either WBA or VE as the dependent variable and independent terms comprising baseline WBV or VV, treatment arm, gender, and baseline age. Study was also included as an independent term in the pooled sample. **Results:** The pooled cohort used for this study consisted of participants with vMRI at baseline and week 80 timepoints totaling 2933 participants (N = 1453 placebo, N = 1480 solanezumab) across the three trials. Mean ( $\pm$  standard deviation [SD]) age of the total cohort was 72.76 ( $\pm 7.78$ ) years and 42.8% of participants were male. At baseline, mean ( $\pm$  SD) WBV for the total cohort was 990.74 ( $\pm 106.05$ )  $\text{cm}^3$  and mean ( $\pm$ SD) VV was 47.81 ( $\pm 22.42$ )  $\text{cm}^3$ . The APOE4 positive cohort consisted of 1835 subjects (N = 927 solanezumab, N =

908 placebo). Mean ( $\pm$ SD) age of the APOE4 positive cohort was 72.67 ( $\pm$ 7.19) and 42.3% of the participants were male. Mean ( $\pm$ SD) WBV for the APOE4 positive cohort was 992.56 ( $\pm$ 105.56) and mean (SD) VV was 47.60 ( $\pm$ 21.91). There were no significant differences (all  $p$  values  $>$  0.05) in any of these measures between the solanezumab arm and the placebo arm for either the total pooled cohort or the pooled APOE4 positive cohort. No significant effect (all  $p$  values  $>$  0.05) of treatment was observed in individual trials or the pooled sample in either WBA or VE. Though not significant, consistent percentage slowing of atrophy was observed for solanezumab participants versus placebo participants across the three trials and in the pooled sample for WBA (0.915% EXP, 0.439% EXP2, 3.760% EXP3, 2.481% pooled sample) and VE (2.613% EXP, 6.162% EXP2, 2.897% EXP3, 3.577% pooled sample). When only APOE4 positive participants were assessed, there was still no significant effect of treatment on WBA or VE. Slowing in WBA was observed in APOE4 positive participants in EXP (2.059%), EXP3 (2.703%), and the pooled sample (1.473%). Slowing of WBA was not observed in EXP2 (-2.973%). Slowing of VE was observed for APOE4 positive participants in EXP2 (2.144%), EXP3 (4.972%), and the pooled sample (3.413%), but not in EXP (-0.869%). **Conclusions:** Analysis of 2933 participants with mild or moderate AD dementia from baseline to 80 weeks using vMRI measures of WBA and VE suggested that low-dose solanezumab was not linked to changes in atrophy at 80 weeks. Pooled analysis of low-dose solanezumab does not demonstrate worsening of volume reduction with treatment as seen with other amyloid-based therapies. Evaluation of the effect of high-dose solanezumab in other stages of AD dementia and in other age groups remain to be conducted.

**OC35: THE ADNI DIVERSITY TASKFORCE: A CLOSER LOOK AT THE SCREENING AND ENROLLMENT OF UNDERREPRESENTED POPULATIONS IN THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI)-3.** M.T. Ashford<sup>1</sup>, R. Raman<sup>2</sup>, G. Miller<sup>2</sup>, M.C. Donohue<sup>2</sup>, O. Okonkwo<sup>3</sup>, M. River Mindt<sup>4</sup>, R.L. Nosheny<sup>5</sup>, R.C. Petersen<sup>6</sup>, P.S. Aisen<sup>2</sup>, M.W. Weiner<sup>7</sup> ((1) Northern California Institute For Research And Education (ncire), Department Of Veterans Affairs Medical Center - San Francisco, USA); (2) Alzheimer's Therapeutic Research Institute, University Of Southern California - San Diego, USA; (3) Wisconsin Alzheimer's Disease Research Center And The Department Of Medicine, University Of Wisconsin School Of Medicine And Public Health - Madison, USA; (4) Psychology & Latin American Latino Studies Institute, Fordham University, Joint Appointment In Neurology, Icahn School Of Medicine At Mount Sinai - New York, USA; (5) Department Of Psychiatry, University Of California San Francisco - San Francisco, USA; (6) Department Of Neurology, Mayo Clinic - Rochester, USA; (7) Department Of Radiology And Biomedical Imaging, University Of California San Francisco - San Francisco, USA)

**Background:** Latinx and Blacks/African Americans continue to remain underrepresented in Alzheimer's disease (AD) research. This greatly limits the generalizability of research findings. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is an ongoing, longitudinal, multicenter study whose overall aim is to develop and validate clinical, imaging, genetic, and biochemical biomarkers for the use in AD clinical trials. ADNI participants are classified as cognitively unimpaired (CU) or as having mild cognitive impairment (MCI) or dementia due to AD. Analysis of the ethnorracial composition of ADNI

participants, and the relationship between race/ethnicity and screening, enrollment, and dropout is needed to assess the generalizability of ADNI data to diverse populations, and to inform future efforts to increase diversity. **Objectives:** The objectives of this study were to describe screening (including reasons for screen fails), enrollment, and participant characteristics (e.g. demographics, genetics) in ADNI-3, with a specific focus on Latinx and Black/African American participants. **Methods:** This study focused on ADNI-3 data available by July 1st, 2020. All analyses were performed in R for three ethnorracial participant groups: Latinx, non-Latinx Black/African American, and non-Latinx White. We determined the overall number and ethnorracial breakdown of the following ADNI participation metrics: initial study visits of participants who continued in ADNI-3 from a previous ADNI phase (rollover initial visits), screening visits of new participants (non-roll over), screen fails, and enrollment characteristics. For each group, the reasons for screen fail were summarized. The characteristics of enrolled participants including age, gender, education, initial diagnosis (CU vs MCI vs AD dementia), APOE e4 status, and amyloid positivity were summarized. Multivariable logistic regression was used to analyze the association between ethnorracial group and either amyloid positivity or APOE e4 status, adjusting for age, gender, education, and diagnostic group. **Results:** A total of 1276 participants entered ADNI3, including 836 new and 440 rollover participants. Of the 836 new participants, 257 participants failed screening, 23 discontinued screening and 26 are pending a decision. Of the screen fails, 10 (3.9%) were Latinx, 9 (3.5%) were non-Latinx Black/African American, and 220(85.6%) non-Latinx White. A total of 287 screen fail reasons were reported since multiple reasons were possible. Among Latinx participants, the most common screen fail reasons were related to medical exclusion criteria (29%; N=4/14) such as MRI contraindications and depression. For non-Latinx Blacks/African Americans, the most common noted reasons were related to inclusion criteria (55%; N=6/11) such as Logical Memory II Delayed score, MMSE score, and availability of study partner. For non-Latinx Whites, the most common noted reasons were related to inclusion criteria (52%; N=127/243) such as Logical Memory II Delayed score, MMSE score, CDR score, age, willingness to undergo repeated MRIs, and other health reasons. A total of 970 participants were enrolled in ADNI-3. Across the 59 ADNI sites, the percent enrolled for Latinx participants ranged from 0%-50% of total enrollment, for non-Latinx Blacks/African Americans from 0%-39%, and for non-Latinx Whites from 38%-100%. Of all enrolled participants, 48 (4.9%) were Latinx, 54 (5.6%) were non-Latinx Black/African American, and 831 (85.7%) were non-Latinx White. Compared to the Latinx and non-Latinx Black/African American groups, the non-Latinx White group was slightly older (75.3 $\pm$ 8.0) and had a lower percentage of female participants (48%) (age: Latinx=70.9 $\pm$ 7.4, non-Latinx Black/African American=72.0 $\pm$ 7.8; % female: Latinx=73%; non-Latinx Black/African American=72%). Education (years) was similar across the three ethnorracial groups (Latinx=15.9 $\pm$ 2.6; non-Latinx Black/African American=15.8 $\pm$ 2.5; non-Latinx White=16.5 $\pm$ 2.5). In terms of initial diagnosis, Latinx and non-Latinx Blacks/African Americans had a lower percentage of participants diagnosed with AD (6% and 7% respectively) when compared to the non-Latinx White group (12%). The percentage of CU diagnosis in Latinx and non-Latinx Black/African American was 62% and 59%, respectively, which is higher compared to non-Latinx Whites (51%). Multivariable analysis showed no



statistically significant differences due to ethnorracial groups on rates of APOE e4 or amyloid positivity after adjusting for age, sex, education level, diagnosis group and APOE e4 status (for amyloid positivity). After enrollment, a total of 54 participants officially dropped-out, 2 were Latinx, 1 was non-Latinx Black/African American, and 50 were non-Latinx White. **Conclusion:** Only 12.6% of individuals screened and enrolled in ADNI-3 identified as Latinx and/or non-Latinx Black/African American, which indicates that ADNI-3 reflects the general recruitment and enrollment biases present in most AD clinical research. A limitation of this work is the small sample sizes in the ADNI3 Latinx and Black/African American samples, which suggests that interpretations of trends should be made with caution. Future analyses will extend this work (1) to include previous ADNI phases and (2) additional formal hypothesis testing regarding associations between ethnorracial groups and enrollment, study task completion, and retention. The results emphasize the need for ADNI and other cohort studies to increase enrollment of underrepresented populations. Therefore, an ADNI Diversity Taskforce was recently established to evaluate the current efforts and facilitate improved recruitment approaches to make ADNI more ethnorracially representative.

**OC36: REMOTE COLLECTION OF OVER 600 BLOOD SAMPLES FROM PARTICIPANTS ENROLLED IN AN ONLINE REGISTRY IN ONE MONTH DURING THE COVID EPIDEMIC.** J. Fockler<sup>1</sup>, T. Howell<sup>1</sup>, A. Ekanem<sup>1</sup>, D. Flenniken<sup>2</sup>, A. Happ<sup>2</sup>, M. Ashford<sup>2</sup>, J. Hayes<sup>2</sup>, D. Truran<sup>2</sup>, R.S. Mackin<sup>1</sup>, K. Blennow<sup>3</sup>, D. Geschwind<sup>4</sup>, E. Halperin<sup>4</sup>, G. Coppola<sup>5</sup>, R. Nosheny<sup>1</sup>, M. Weiner<sup>1</sup> ((1) *Ucsf - San Francisco, USA*; (2) *Ncire - San Francisco, USA*; (3) *University Of Gothenburg - Gothenburg, Sweden*; (4) *Ucla - Los Angeles, USA*; (5) *Regeneron Genetic Center - New York, USA*)

**Background:** Efficient identification of those at risk for cognitive decline and Alzheimer's disease (AD) can facilitate clinical research. Online registries can address this need by efficiently collecting longitudinal data, including subjective measures and cognitive assessments, but a limitation is the lack of remotely collected biomarker data. Recent studies suggest that plasma biomarkers of  $\beta$ -amyloid, phosphorylated tau, and neurofilament light (NfL) may help identify older adults at risk or with AD and cognitive decline, with emerging evidence for validity compared to PET scans and lumbar puncture for CSF. Additionally, polygenic risk scores (PRS) have been suggested to indicate increased risk for AD. Thus, the addition of remotely collected blood, in order to obtain plasma biomarkers and PRS, to registry data represents a novel approach. The Brain Health Registry (BHR) is an online website and registry of over 70,000 participants which facilitates recruitment, screening, assessment, and longitudinal monitoring of participants for neuroscience research. It includes a comprehensive battery of self- and study partner-report questionnaires and online cognitive tests. The overall goal of the Brain Health Registry-Biomarker Prediction Study (BHR-BPS) is to efficiently identify older adults who are at risk for developing cognitive impairment and dementia due to AD using registry information and remotely-collected blood-based biomarkers. **Objectives:** Using an existing national network of phlebotomy centers, the objective was to assess the feasibility, acceptability and scalability of remote blood sample collection in older adults enrolled in an online registry, in order to obtain plasma biomarkers of AD and neurodegeneration, and PRS from DNA. **Methods:** Leveraging the existing BHR infrastructure, participants were recruited into BHR-BPS

using the following inclusion criteria: age 55+, has completed online cognitive tests, does not have a clinical or self-reported diagnosis of any type of dementia, located in California, and has a study partner enrolled in BHR who has completed the Everyday Cognition Scale. BHR-BPS participants were invited to participate via email and consented online through their BHR account. Those who consented were provided a unique identification code, and instructions on how to schedule a visit at a Quest Diagnostic Patient Service Center of their choosing for a blood draw. The samples were centrifuged, and red cell and plasma was aliquoted and sent to a specimen bank for storage and future analysis of plasma and DNA extraction. After completing sample collection, participants were mailed a \$75 gift card and asked to complete an online feedback questionnaire about their experience. Sample collection tracking and participant communication were automated using a novel BHR Biofluid Collection Management Portal, allowing study team members to collect, store, maintain, and organize data related to remote biofluids collection. **Results:** A total of 7,150 BHR participants were invited to join BHR-BPS between February-March and May-June 2020. Of those, 864 (12.1%) consented to enroll in the study. Participants had an average age of  $66.9 \pm 7.5$ , 606 (70.1%) were female, and 744 (86.1%) were Caucasian/white. Of all enrolled participants, 629 (72.8%) completed a blood draw. Participants who completed a blood draw and had demographic information available ( $n=624$ ) had an average age of  $67.1 \pm 7.4$ , 438 (70.2%) were female, and 547 (87.7%) were Caucasian/white. All samples were collected over eight weeks with 614 samples collected in the final 33 days.: 525 (83.5%) BHR-BPS participants with a completed blood draw also completed a feedback questionnaire. Of those, 486 (92.6%) rated the difficulty of scheduling an appointment at a Quest location as 1 or 2 based on a scale of 1-5 (1 = least difficult and 5 = most difficult); 200 (38.1%) reported that it took "a lot less time" or "a little less time" than expected to complete the blood draw while 238 (45.3%) reported that the time was "about what I expected"; and 510 (97.1%) reported that they would agree to participate in a similar study. **Conclusion:** BHR-BPS demonstrated feasibility, acceptability and scalability of remote blood sample collection in a large cohort of older adults engaged in longitudinal online evaluation. The high completion rate supports the feasibility while the positive participant experience feedback shows participant acceptability. Blood draws were collected in a relatively short time frame demonstrating feasibility and scalability. Additionally, we expect higher enrollment rates in future studies as most blood draws took place during the COVID epidemic, when restrictions on in-person medical visits may have deterred participants from visiting phlebotomy centers. In the future, the samples will be processed for DNA extraction for PRS analysis, and plasma will be analyzed for Ab42, Ab40, phosphorylated tau, and NfL to advance our understanding of the separate and combined contributions of genetic factors, AD plasma biomarkers, and registry data to AD, aging, and other health conditions. This novel approach could prove to be a more cost-effective way to identify older adults who may be at risk for developing cognitive impairment and dementia due to AD or other causes.

**OC37: BASELINE CHARACTERISTICS OF THE MILD ALZHEIMER'S DISEASE PATIENT POPULATION INCLUDED IN THE ONGOING RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTIPLE ASCENDING DOSE PHASE 1B STUDY OF INTRATHECALLY ADMINISTERED TAU ANTISENSE OLIGONUCLEOTIDE (ISIS 814907; BIIB080).** C. Mummery<sup>1</sup>, C. Junge<sup>2</sup>, L. Mignon<sup>2</sup>, K. Moore<sup>2</sup>, C. Yun<sup>2</sup>, D. Li<sup>2</sup>, D. Norris<sup>2</sup>, R. Crean<sup>2</sup>, E. Ratti<sup>3</sup>, E. Huang<sup>3</sup>, R. Lane<sup>2</sup> ((1) University College London - London, United Kingdom; (2) Ionis Pharmaceuticals Inc. - Carlsbad (United States), 3Biogen Inc. - Cambridge, USA)

**Background:** ISIS 814907 (BIIB080) is an antisense oligonucleotide (ASO) that hybridizes to a complementary nucleotide sequence of the mRNA of the human microtubule-associated protein tau (MAPT) gene, causing its degradation to prevent production of tau protein. MAPT is believed to contribute to or cause several neurodegenerative diseases, including Alzheimer's disease (AD) and some forms of frontotemporal lobar degeneration (FTLD). A randomized, double-blind, placebo-controlled Phase 1b, first in human, multiple ascending dose (MAD) study evaluating safety and tolerability of ISIS 814907 in patients with mild AD is currently underway in the UK, Canada, Germany, Sweden, Netherlands and Finland (EudraCT No: 2016-002713-22; NCT03186989). **Objectives:** To describe baseline characteristics from the ongoing Phase 1b study, the first evaluation of the tau ASO in AD. **Methods:** The study is divided into 2 parts. Part 1 is the randomized, double-blind, placebo-controlled MAD part, comprising a Treatment Evaluation Period of 13 weeks, and a Post-Treatment Period of 23 weeks. Part 2, the open-label long-term extension (LTE) comprising a Treatment Evaluation Period of 48 weeks, and a Post-Treatment Period of 16 or 23 weeks. Four ascending dose level cohorts (A, B, C and D) of mild AD patients were enrolled sequentially and randomized 3:1 to receive intrathecal (IT) bolus administrations of ISIS 814907 or placebo. Male or female patients aged 50-74 years of age with mild AD at Screening were eligible for the study. Mild AD was defined as CDR Global score of 1 or CDR Global score of 0.5 with a Memory Box score of 1, Mini-Mental Status Examination (MMSE) score of 20-27 (inclusive), and as well as a cerebral spinal fluid (CSF) profile consistent with mild AD diagnosis at Screening. The diagnosis of probable AD dementia was based on National Institute of Aging-Alzheimer Association (NIA-AA) criteria. The primary study objective is the assessment of safety and tolerability of ascending dose-levels of multiple IT bolus administrations of ISIS 814907. Key safety assessments include physical and neurological exams, adverse events, concomitant medications, CSF and plasma laboratory tests, Columbia Suicide Severity Rating Scale, and safety MRI. Secondary objective is to evaluate the CSF pharmacokinetics (PK). PK endpoints include assessment of CSF and plasma PK parameters throughout the MAD and LTE. Exploratory objectives include assessment of potential target engagement, disease progression biomarkers, genotype and clinical endpoints relevant to AD. **Results:** Enrollment is now complete (N=46) and the study is ongoing. The patient population was evenly split among men and women with an average age of 66 ± 6 (SD) years. The average MMSE total score at baseline was 24 ± 2 (SD). Most patients had a CDR total score of 0.5 with a Memory Box Score of 1 at baseline (N=30) and the remaining patients had a global CDR score of 1 (N=16). **Conclusion:** The patients included in the study are reflective of a younger, mild AD population.

**OC38: TRANSLATIONAL PHARMACOLOGY OF IBC-AB002, A NOVEL FULLY HUMAN ANTI-PD-L1 ANTIBODY, FOR TREATING ALZHEIMER'S DISEASE.** E. Yoles<sup>1</sup>, K. Baruch<sup>1</sup>, A. Kertser<sup>1</sup>, O. Matalon<sup>1</sup>, O. Furst<sup>1</sup>, S. Braiman<sup>1</sup>, C. David<sup>1</sup>, E. Shochat<sup>2</sup>, J.M. Cedarbaum<sup>1,3</sup> M. Schwartz<sup>1,4</sup> ((1) Immunobrain Checkpoint Ltd. - Ness Ziona, Israel; (2) Shochat Pharma Services - Reinach Bl, Switzerland; (3) Coeruleus Clinical Sciences Llc - Woodbridge Ct, USA; (4) Weizmann Institute Of Science - Rehovot, Israel)

**Background:** Blocking the PD-1/PD-L1 immune-checkpoint inhibitory pathway has been shown to ameliorate cognitive loss and manifestations of amyloid and tau pathology in mouse models of Alzheimer disease (AD) and tauopathy. The choice of targeting PD-1/PD-L1 pathways to treat neurodegenerative disease has no connection with cancer immunotherapy; it is based on the understanding that between the brain and the immune system there is a life-long dialogue, needed for supporting brain function and repair, and is insufficient or lost in AD and age-related dementia. Accordingly, targeting PD-L1/PD-1 in AD serves as a way of reviving the immune system to help moving immune repairing cells to the brain leading to cognitive improvement and ameliorating disease pathology. Preclinical pharmacological studies in mouse models of AD and Tauopathy show that the beneficial effect of anti-PD-L1 antibody is Cmax dependent, rather than the area-under-the-curve (AUC). Furthermore, the beneficial effect of anti-PD-L1 antibody treatment in animal models revealed that there is a need for only a short exposure to the antibody, which is followed by an antibody-free period of events that lead to disease modification. Here, we describe the development a novel fully human anti-PD-L1 antibody (IBC-Ab002) with a unique pharmacokinetic property tailored to the mechanism of action that it evokes in AD, and the establishment of translational pharmacologically based PK/PD. **Objectives:** The objective of this study was to establish a translational pharmacologically based PK/PD model, for our proprietary anti-PD-L1 antibody, IBC-Ab002, to inform the design and implementation of the FIH study. **Methods:** Pharmacological studies were carried out in mice and NHP using two anti-hPD-L1 antibodies, the former of which cross reacts with mouse PD-L1 (surrogate antibody). Both antibodies had the same hIgG1 backbone and high affinity to their ligands (sub-nanomolar range). To explore the dose/exposure relationship with treatment efficacy, we created several variants of the two antibodies by introducing point mutation to their Fc backbone that affected their PK profile without affecting their binding affinity or neutralizing activity. Multi-dose pharmacokinetics (PK) pharmacodynamics (PD) and efficacy studies were carried out in several transgenic mouse models of AD and Tauopathy using the surrogate anti-PD-L1 antibody. Multi-dose PK and PD studies in non-human primates (NHP) were also carried out using the anti-hPD-L1 antibody. **Results:** Multi-dose efficacy studies comparing between the different antibody variants demonstrated that anti-PD-L1 antibody with accelerated clearance properties is similarly effective and has the same effective dose range, as the non-mutated antibody, in transgenic mouse models of amyloidosis and tauopathy. The antibody variant with the faster clearance properties showed superior safety profile in terms of inducing autoimmune diabetes. Accordingly, the antibody variant with the fastest clearance properties, IBC-Ab002, was selected for clinical development. A translational PK model of IBC-Ab002 distribution in human cognition was developed by combining non-compartmental

(NCA) with compartmental target-mediated drug disposition (TMDD), ordinary differential equations (ODEs) and population PK (popPK) analysis. The expected PK parameters for IBC-Ab002 were calculated based on allometric scaling of mice and NHP data, predicting total clearance of CL ~0.8 L/day, Volume of distribution ~2.5 L and effective half-life ~4.5 days. A battery of biomarkers was identified in mice and NHPs, including biomarkers for peripheral target engagement as well as biomarkers in blood and CFS for central engagement. The PK/PD modelling, based on the proposed mechanism of action, follows the series of events triggered by PD-L1 blockade. The events include receptor occupancy (RO) and transient increase in activated memory T cells in the periphery, resulting in a robust improvement in cognitive performance in AD mouse model as well as significant reduction in cerebral tau load. Currently, the simulations predict effective dose of  $\geq 20$  mg/kg administered periodically ( $> 8$  weeks) may achieve long term treatment efficacy. This prediction will be further explored using actual clinical data in the planned clinical trials. **Conclusions:** IBC-Ab002 antibody, a novel engineered antibody that was selected for clinical development for treating AD, has a superior safety profile in terms of immune-related adverse events. We developed a predictive model that simulates PK/PD and efficacy in human and informs our Phase 1 clinical trial design. A first-in-human study of IBC-Ab002 in AD patients is planned for the second half of 2021.

**OC39: DETECTING MEANINGFUL CHANGE IN EVERYDAY FUNCTIONING: A MIXED-METHODS APPROACH TO ESTABLISH CLINICAL MEANINGFULNESS OF CHANGES ON THE AMSTERDAM IADL QUESTIONNAIRE.** M. Dubbelman<sup>1</sup>, M. Verrijp<sup>1</sup>, R. Jutten<sup>1</sup>, C. Terwee<sup>2</sup>, L. Visser<sup>1,3</sup>, W. Van Der Flier<sup>1</sup>, P. Scheltens<sup>1</sup>, S. Sikkes<sup>1,4</sup> ((1) *Alzheimer Center Amsterdam, Department Of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam Umc - Amsterdam, Netherlands;* (2) *Department Of Epidemiology And Biostatistics, Amsterdam Umc - Amsterdam, Netherlands;* (3) *Department of Medical Psychology, Amsterdam Public Health research institute, University of Amsterdam, Amsterdam UMC - Amsterdam, Netherlands;* (4) *Faculty of Behavioural and Movement Sciences, Clinical Developmental Psychology & Clinical Neuropsychology, Vrije Universiteit Amsterdam - Amsterdam, Netherlands*)

**Background:** Alzheimer's disease (AD) causes a gradual decline in cognition and function. With many disease-modifying treatment studies focusing on the early stages of AD, the revised 2018 Food and Drug Administration guidance places an emphasis on the use of clinical outcome measures that are sensitive to subtle changes, and that are capable of showing clinically meaningful effects on relevant concepts. Performance of cognitively complex everyday activities, so-called 'instrumental activities of daily living' (IADL), is considered an important and clinically meaningful outcome as it is related to cognition, patient quality of life and caregiver burden. While many clinical trials incorporate some outcome measure of functional decline, little is currently known about the clinical meaningfulness of (changes in) scores on these measures. The Amsterdam IADL Questionnaire (A-IADL-Q) is a modern functional outcome measure that has been extensively validated and is able to capture change over time. **Objectives:** First, to qualitatively establish thresholds for mild, moderate, and severe IADL impairment. Second, to define the smallest change that is considered meaningful, known as the minimally

important change (MIC), on the A-IADL-Q. Third, to investigate how many patients showed a larger decline than the MIC, and after how much time, in an independent, quantitative validation study. **Methods:** This study consisted of three parts: (1) For the qualitative part of the study, using a novel, systematic method with stakeholder input, we invited caregivers of people with dementia to participate in focus groups in order to learn from stakeholders when problems in daily functioning should be considered mild, moderate, or severe. We used short clinical summaries (called 'vignettes') describing difficulties in daily functioning of fictional patients. The vignettes were based on responses to A-IADL-Q items at different levels of daily functioning. (2) We then included caregivers of dementia patients, recruited through Hersenonderzoek.nl, and clinicians for an online questionnaire to determine the MIC. The respondents were shown seven situations with two vignettes. In each of the seven situations, one vignette described the patient's functioning 'one year ago', and one referred to functioning 'now'. Respondents were asked to indicate whether there was a change in functioning when comparing the 'now' vignette to 'one year ago' vignette (either decline or improvement). If so, respondents were asked to indicate whether they considered the change to have an important impact on daily life. The amount of change varied with each situation. (3) In the quantitative part of this study, we applied the results from the MIC questionnaire retrospectively to a set of patients who visited the Alzheimer Center Amsterdam for dementia screening, to assess how many patients showed a clinically meaningful decline. The caregivers to these patients were invited to complete the A-IADL-Q about the patients at home every three months for a year following the baseline visit. Higher A-IADL-Q scores represent better functioning. We used multinomial logistic regressions to analyze whether baseline difficulty or amyloid status predicted clinically meaningful change. **Results:** With input from the focus group (n panelists = 6), we identified thresholds for what constitutes no, mild, moderate, and severe IADL problems. A total of 1,629 caregivers (mean age 62.4 $\pm$ 9.5 years; 77% female), as well as 13 clinicians from various memory clinics in the Netherlands, completed the MIC questionnaire. The MIC was established at a decline of 2.4 points. We validated the MIC using data from 196 patients (64.5 $\pm$ 7.7 years; 41% female; 41% with AD diagnosis), of which 86 were amyloid positive. At baseline, 27 patients (14%) had no problems, 64 (32%) had mild problems, 74 (38%) had moderate problems, and 31 (16%) had severe problems. After six months, 47% of all patients (51/108) had declined more than 2.4 points, surpassing the MIC. A similar percentage of patients declined more than the MIC up to one year (95/197, 48%). Severity of IADL problems at baseline was not associated with clinically meaningful decline (odds ratio (OR)=1.00, p=.78). Amyloid positive patients were more likely to experience a meaningful decline (50/86, 58%), than those who were amyloid negative (OR=3.05, p<.01). **Conclusion:** This is the first functional outcome measure for which an extensive, systematic, stakeholder-driven appraisal of clinical meaningfulness has been performed. Using a novel technique to determine clinically meaningful change in daily functioning, we determined thresholds for mild, moderate, and severe IADL problems, and for what constitutes a clinically meaningful change in score over time. This is crucial for evaluating possible treatment effects in clinical trials. We validated these findings in an independent observational study, and found that clinically important decline in functioning was related to amyloid status, which confirms the specificity of this decline to AD-related changes. Taken together, these findings

provide converging evidence for the clinical meaningfulness of assessing changes in everyday functioning in the context of Alzheimer's disease clinical trials.

#### **OC40: THE ELECTRONIC PERSON-SPECIFIC OUTCOME MEASURE (EPSOM) DEVELOPMENT PROGRAMME.**

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**Background:** The ePSOM development programme is a collaboration between the University of Edinburgh and Alzheimer's Research UK. Though outcome measures currently used in prodromal and preclinical Alzheimer's disease (AD) clinical trials focus primarily on cognition, they are not always sensitive enough to pick up changes which occur in those early stages of the disease continuum. These cognitive outcomes, as well as biomarker outcomes, may also be less important to patients than their own individual experiences of noticing a meaningful effect on their lives arising from the intervention. Therefore, it is important to use outcome measures for novel interventions that capture the research participants' views of effectiveness. A better understanding of earlier manifestations of Alzheimer's disease and the drive for relevant outcome measures, allied to technological advances in artificial intelligence, have mediated the electronic Person-Specific Outcome Measure (ePSOM) development programme. Our group took the view that 'maintenance of brain health' as opposed to 'avoidance of symptoms' would form the underpinning narrative in the ePSOM programme and ultimately the ePSOM app design. **Objectives:** The aim of the ePSOM programme is to better understand what outcomes matter to patients in the Alzheimer's disease population with a focus on those at the pre-dementia stages of disease. Ultimately, we aim to develop an app with robust psychometric properties to be used as a patient reported outcome measure in AD clinical trials. **Method:** There are 4 sequential stages in the ePSOM programme (the first three are completed): (1) literature review, (2) focus group study, (3) national survey, and (4) development of an app for capturing person-specific outcomes. While the literature review and focus group study results are already published, the survey data is unpublished and the focus of this presentation. During the previous stages of our work, we empirically derived five domains of importance for what matters to people when developing new treatments for AD (Everyday functioning; Sense of identity; Thinking problems; Relationships and Social connections; Enjoyable activities). We designed and ran a nationwide survey (Aug 2019 – Nov 2019) exploring these five domains of priority in more detail. The survey collected data from both, forced choice questions as well as free text responses. The survey also captured a targeted amount of clinical and demographic data to support the analysis of the free text answers which represented the primary outcome of the survey. We used natural language processing (NLP) techniques to analyse the survey data. **Results:** The survey was filled in by 5808 respondents across the UK. The majority of the respondents were female (n=4463, 76.9%) and married (n=3684, 63.4%). The mean age in women was 57.35 (SD=13.8) and 62.88 (SD=13.08) in men. 73% had supported a relative with dementia but only 18.3% had seen a doctor about their own brain health. On a 10-point scale (10 = best level of health), the mean score for self-rated brain health was 9.32 (SD=1.97). The majority of the survey respondents were retired (n=2105, 36.2%), followed by respondents in full time paid work (n=1537, 26.4%). There was

a high average self-reported rating of brain health with only 107 respondents (1.8%) rating their brain health with a score of 5/10 or under. However, 2100 respondents (36.2%) answered that they were worried about their brain health. The survey received more than 80 000 free text answers. The automated NLP analysis resulted in 184 unique clusters across the whole data set. The top clusters of importance were picked similarly across dyads (younger/older respondents; gender; higher/lower education). However, the granularity of the large data set allowed for a deeper analysis of important topics, particularly focusing on what matters to people [1] who are worried about their brain health; [2] have a neurodegenerative disease diagnosis or [3] are taking anti-dementia medications. **Conclusion:** The ePSOM data has generated strong evidence based on what matters to people when developing new treatments for Alzheimer's disease. The ePSOM survey was successful in capturing a large number of people from a population at higher risk of neurodegenerative disease and we present analysis on outcomes that matter to different groups based on clinical backgrounds and sociodemographics. The ePSOM development programme is building evidence in order to deliver the methodology for incorporating personally meaningful outcome measures in Alzheimer's disease clinical trials. The completed three stages will underpin the ePSOM app, which will be using natural language processing methodologies, and have good psychometric properties enabling the app to be used in regulatory trials.

#### **OC41: PREDICTING THE IMPACT OF BLOOD BIOMARKERS ON COST AND WAIT TIME IN DIAGNOSING TREATMENT-ELIGIBLE PATIENTS FOR ALZHEIMER'S DISEASE.**

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**Background:** Recent trial results give hope that a disease-modifying treatment (DMT) for Alzheimer's disease (AD) might become available, but concerns have been raised that the large number of patients might overwhelm the healthcare system, in particular because of limited capacity of dementia specialists. Blood based biomarker (BBBM) tests for the biologic hallmarks of the disease are a promising tool to improve triaging at the primary care level. We projected their impact on cost and wait times with a simulation model. **Methods:** We simulate the U.S. population age 50+ over 30 years combining a disease progression model (Cognitively normal to MCI due to AD or due to other causes to dementia) and a system dynamics model for capacity constraints (specialist cognitive testing and confirmatory biomarker testing with PET or CSF). We compare four scenarios for primary care evaluation (1) cognitive screening only (MMSE), (2) BBBM only, (3) MMSE followed by BBBM if positive and (4) BBBM followed by MMSE if positive. Parameter for patient pools, costs and capacity were derived from published data and assumptions. **Results:** Using either MMSE or BBBM alone would result in a number of specialist referrals that is projected to continuously exceed capacity from 2020 to 2050. Combining MMSE and BBBM in either order would eliminate wait lists after the first three years. The projected number of correctly identified cases (i.e., true positive for MCI due to AD) will increase from ~480,000 for either MMSE or BBBM alone to ~600,000 for MMSE and BBBM combined on average each year. Average total cost per year would be an estimated \$7.2 billion for MMSE alone, \$7.5 billion for BBBM alone, and \$6.8 billion for MMSE and

BBBM combined, and cost per correctly identified case will decline from ~\$15,000 for MMSE or BBBM alone to ~\$11,000 for a combination of MMSE and BBBM. **Conclusions:** Combining BBBM with MMSE is projected to increase the efficiency and value of the triage process for eligibility for a DMT at the primary care level, as the addition of a BBBM would reduce wait times for specialist visits and diagnostic yield dramatically without increasing net cost.

**OC42: NEUROIMAGING-DERIVED NEURITE DENSITY AND ORIENTATION DISPERSION ARE MORE INFORMATIVE FOR PREDICTING ALZHEIMER'S CLINICAL DIAGNOSIS THAN CSF AMYLOID AND TAU STATUS ALONE.** R.L. Gallagher<sup>1</sup>, N. Adluru<sup>1</sup>, N. Vogt<sup>1</sup>, C.A. Van Hulle<sup>1</sup>, E. Jonaitis<sup>1</sup>, R. Kosciak<sup>1</sup>, S.R. Kecskemeti<sup>1</sup>, N.A. Chin<sup>1</sup>, S. Asthana<sup>1</sup>, G. Kollmorgen<sup>2</sup>, C.M. Carlsson<sup>1</sup>, S.C. Johnson<sup>1</sup>, H. Zetterberg<sup>3</sup>, K. Blennow<sup>3</sup>, A.L. Alexander<sup>1</sup>, B. Bendlin<sup>1</sup> ((1) *University Of Wisconsin-Madison - Madison, USA*; (2) *Roche Pharmaceuticals - Basel, Switzerland*; (3) *University Of Gothenburg - Gothenburg, Sweden*)

**Background:** Within the AT(N) framework, tau tangles follow amyloid plaque deposition and closely correlate with cognitive decline; however, there are no clearly established markers for neurodegeneration. Histological studies of Alzheimer's disease (AD) indicate that the disease involves substantial loss of synaptic spines, dendrites, and axons. Diffusion weighted MRI such as the Neurite Orientation Dispersion and Density Index (NODDI) technique provides non-invasive in vivo characterizations of microscopic features. We previously identified 30 regions of interest where neuron and dendrite dispersion (the orientation dispersion index, ODI) and axonal and dendrite density (the neurite density index, NDI) values in gray and white matter (GM and WM) varied across CSF biomarker grouping (A-/T-, A+/T-, A+/T+) (post FDR correction). This study further investigates whether these NODDI metrics are associated with increased risk of clinical impairment. **Objectives:** To examine whether NODDI metrics are associated with AD-related clinical diagnosis after adjusting for CSF amyloid and tau status. **Methods:** Research participants: 303 individuals (64.3% Female/37.3% APOE  $\epsilon$ 4-positive/mean age 65.3 7.9y) from the Wisconsin Registry for Alzheimer's Prevention (WRAP) study and Wisconsin Alzheimer's Disease Research Center (ADRC) clinical core who had undergone clinical diagnosis, neuroimaging, and lumbar puncture for CSF analysis were included. Neuroimaging: All participants received a MRI scan sufficient for NODDI modeling. Harvard-Oxford and JHU atlas were used for GM and WM ROIs. AD biomarkers: CSF was collected via lumbar puncture after a minimum 4 hour fast and stored at -80°C. CSF samples were assayed at the Clinical Neurochemistry Laboratory, University of Gothenburg. Measurements with the following immunoassays were performed on cobas e analyzers: Elecsys® $\beta$ -Amyloid (1-42) CSF, Elecsys®Phospho-Tau (181P) CSF and the  $\beta$ -Amyloid (1-40) robust prototype assay. Cutoff values for amyloid and pTau positivity were developed as follows: A CSF A $\beta$ 42/A $\beta$ 40 cutoff (<0.046, A $\beta$ 42/A $\beta$ 40+) was derived using Receiver Operator Characteristic (ROC) curve analysis and Youden's J statistic, with [C-11] Pittsburgh compound B PET imaging positivity as the standard of comparison. The CSF pTau cutoff ( $\geq$  24.8, pTau+) equals a +2SD above the mean of a reference group of 223 CSF A $\beta$ 42/A $\beta$ 40-negative, unimpaired younger participants (ages 45-60 years). Clinical Diagnosis: Participants

underwent comprehensive cognitive assessment and diagnosis of cognitively unimpaired (CU) (n = 285), mild cognitive impairment (MCI) (n = 11), or dementia due to (AD) (n = 5) was determined using clinical and cognitive information in accordance with the updated 2011 National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup diagnostic criteria, without reference to biomarkers. Previously we identified 30 brain ROIs that differed in NDI (WM only) or ODI (WM and GM) between biomarker groups. No ODI GM regions differed across groups. NDI and ODI values from GM and WM ROIs with up to the five largest beta values were included in the present general logistic regression models. Models predicted clinical diagnosis in a binomial fashion (CU vs. MCI, MCI vs. AD, CU vs. AD), controlling for sex and age. ROC and Akaike Information Criteria (AIC) analysis evaluated model performance. Each clinical diagnosis grouping (CU vs. MCI, MCI vs. AD, CU vs. AD) had seven models: (1) biomarker status, (2) biomarker + WM NDI, (3) biomarker + WM ODI and (4) biomarker + GM ODI, (5) WM NDI, (6) WM ODI (7) GM ODI. The following ROIs were included: GM ODI: right angular gyrus, right middle frontal gyrus, right superior parietal lobule, left superior parietal lobule, left inferior parietal lobule. WM NDI: bilateral uncinate fasciculus. WM ODI: Splenium Corpus Callosum. **Results:** To facilitate comparisons with Model 1, we report the AIC and ROC-Area under the curve confidence interval (AUC CI) for model 1 and the model with best AIC from models 2-4. For discriminating CU vs. MCI, AUC 95% CI did overlap between models. Model 1 (Biomarker Only) had AIC = 93.1 and AUC = 0.79(95% CI: 0.5667-0.9121). Model 2 (WM NDI + AD biomarker) had the lowest AIC at 85.5, and AUC was 0.8376 (95% CI: 0.712-0.9633). For discriminating CU vs. AD, AUC 95% CI did overlap between models. Model 1 (Biomarker Only) had AIC = 40.7 and AUC = 0.95(95% CI: 0.8862-1.0). Model 2 (WM NDI + AD biomarker) had the lowest AIC at 18.3 and AUC was 0.999 (95% CI: 0.9952-1.0). For discriminating MCI vs. AD, AUC 95% CI did overlap between models. Model 1 (Biomarker Only) had AIC = 22.4 and AUC = 0.7636 (95% CI: 0.4347-1.0). Model 1 (AD Biomarker only) had the lowest AIC. **Conclusions:** NODDI metrics add predictive power for discriminating between diagnostic groups compared to relying on CSF biomarker grouping alone. NDI in WM appears to be an informative feature of discriminating disease, as supported by AIC values in the MCI vs. CU, and AD vs. CU analyses. Regional metrics of brain microstructure may serve as useful markers of N, and could be considered as measures of disease severity and treatment efficacy in clinical trials.

**OC43: ACCOUNTING FOR COGNITIVE PRACTICE EFFECTS RESULTS IN EARLIER DIAGNOSIS AND CAN SAVE MILLIONS OF DOLLARS IN A CLINICAL TRIAL.** W. Kremen<sup>1</sup>, M. Sanderson-Cimino<sup>1</sup>, J. Elman<sup>1</sup>, X. Tu<sup>1</sup>, A. Gross<sup>2</sup>, M. Bondi<sup>1</sup>, A. Jak<sup>1</sup>, M. Lyons<sup>3</sup>, C. Franz<sup>1</sup> ((1) *Uc San Diego - La Jolla, USA*; (2) *Johns Hopkins University - Baltimore, USA*; (3) *Boston University - Boston, USA*)

**Background:** Delayed detection of mild cognitive impairment (MCI) reduces opportunity for slowing Alzheimer's disease (AD) progression. Delayed detection will hinder clinical trials that focus on cognitively normal individuals (CNs) and their cognitive decline and progression to MCI. Practice effects on cognitive tests obscure decline, thereby delaying detection of MCI. In older adults, even a decrease in performance may reflect a practice effect because the score might have been even lower without prior exposure. Therefore, if practice

effects were systematically accounted for in clinical trials, it ought to mean that impairment would be detectable earlier. Consequently, a subset of individuals who would normally be diagnosed as CN at follow-up might be diagnosed as having MCI if practice effects had been taken into account. **Objectives:** We developed a novel variation of the replacement-subjects method to gauge practice effects on cognitive testing. We hypothesized that after accounting for practice effects there would be increased numbers of MCI cases at 1-year follow-up. We then assessed the validity of the practice-effect-adjusted diagnoses by examining AD biomarker concordance, predicting that it would result in a higher proportion of biomarker-positive MCI cases and a lower proportion of biomarker-positive CNs. We then performed power/sample size calculations, predicting that this increased base rate of MCI cases at follow-up would reduce the required sample size for a clinical trial. Finally, we looked at the final sample size and the number of subjects that needed to be recruited to obtain the final sample in the A4 Study. We then performed power/sample size calculations to see how many subjects would be required to detect a significant drug treatment effect if practice effects were taken into account. In addition, using numbers from the A4 Study, we estimated the cost savings that would result if practice effects were taken into account when diagnosing MCI. **Methods:** We identified 889 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants who were CN at baseline, 722 of which returned at a 1-year-follow-up (mean age=74.9±6.8). A subset of baseline participants was designated to serve as replacement participants whose baseline mean age was matched to the mean age of returnees at the returnees' 1-year follow-up. Education, birth sex, and estimated premorbid IQ were also matched. Practice effects were calculated by comparing returnee scores at follow-up to those of the demographically-matched replacements at baseline, with an additional adjustment for attrition effects. This is the replacement-subjects method. We refer to ADNI replacement subjects as pseudo-replacements because systematically adding replacement subjects was not part of the ADNI design. However, the pseudo-replacements are effectively the same as any replacement subjects. The key is that in either case, replacements are demographically matched to returnees, and the only difference is that returnees have taken the tests twice and replacements have taken the tests only once. Matching and practice effect computations were bootstrapped 5000 times. Mean-bootstrapped practice effects were subtracted from follow-up scores, with resultant scores used for classifying MCI. CSF amyloid-beta, phosphorylated tau, and total tau were measured at baseline and used for criterion validation. **Results:** Practice-effect-adjusted scores increased MCI incidence by 26% ( $p<.001$ ), 19% for amnesic MCI ( $p<.005$ ). Increased proportions of biomarker-positive MCI cases ranged from +15% to +20% and reduced proportions of biomarker-positive CNs ranged from -5% to -6% ( $p<.03$ ); proportions of A $\beta$ -positive were +20% and -6% ( $p<.007$ ). Adjustment for practice effects reduced the necessary sample size for detecting significant drug treatment effects by an average of 21%. The A4 Study did initial screening on 6763 people followed by 4486 amyloid PET scans to obtain the final sample of 1323. Our calculations showed that only 1045 would be needed if practice effects were taken into account. Using proportions from the A4 Study, this would mean 5340 initial screenings and 3543 PET scans. Reductions in sample size would be 278 for the final sample, 1423 for initial screening, and 943 for PET scans. We then estimated the cost of adding 600 replacements (200 at each of 3 potential follow-up

assessments) and of conducting 1423 fewer initial screenings and 943 fewer PET scans. At \$5,000 (U.S.) each, the savings for PET scans alone would be \$4.72 million. The final estimate was a total savings of \$7.45 million. **Conclusion:** Adjusting for practice effects results in earlier detection of MCI. Diagnoses were also more accurate based on biomarker concordance. Reluctance to include additional replacement-subject testing is understandable as it increases cost and participant burden. In the end, however, the earlier detection would substantially reduce the necessary sample size, study duration, likely attrition, subject and staff burden, and cost for clinical trials. Given the public health importance of early identification of AD pathology, it is thus strongly recommended that more attention be paid to PEs. Based on scientific, medical, and cost considerations, AD clinical trials will benefit from including matched replacement subjects as part of the original study design.

**OC44: THE INNATE IMMUNE SYSTEM MODULATOR GM-CSF/SARGRAMOSTIM IS SAFE AND POTENTIALLY EFFICACIOUS IN PARTICIPANTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE.** H. Potter<sup>1</sup>, J. Woodcock<sup>1</sup>, T. Boyd<sup>1</sup>, S. Sillau<sup>1</sup>, C. Coughlan<sup>1</sup>, J. O'shaughnessy<sup>1</sup>, M. Borges<sup>1</sup>, A. Thaker<sup>1</sup>, B. Raj<sup>2</sup>, V. Adame<sup>1</sup>, K. Adamszuk<sup>3</sup>, D. Scott<sup>3</sup>, H. Chial<sup>1</sup>, H. Gray<sup>1</sup>, J. Daniels<sup>1</sup>, M. Stocker<sup>1</sup> ((1) *University Of Colorado Anschutz Medical Campus - Aurora, USA*; (2) *University Of South Florida - Tampa, USA*; (3) *Bioclinica - Newark, USA*)

**Background:** Rheumatoid arthritis (RA) patients have a reduced risk of developing Alzheimer's disease (AD), which was originally hypothesized as being attributable to their usage of non-steroidal anti-inflammatory drugs (NSAIDs). However, clinical trials with NSAIDs were unsuccessful in both AD and Mild Cognitive Impairment (MCI) participants. We hypothesized that intrinsic factors associated with RA pathogenesis itself may underlie the AD protective effect(s), and we focused on the innate immune system. We tested several protein cytokines upregulated in RA blood and found that 20 daily subcutaneous injections of granulocyte-macrophage colony-stimulating factor (GM-CSF) reduced cerebral amyloidosis by greater than 50% and completely reversed the cognitive impairment of transgenic AD mice. Additionally, in a retrospective study, we found that short-term co-treatment with sargramostim/Leukine® (recombinant human GM CSF) and recombinant human granulocyte colony-stimulating factor (G-CSF) significantly improved the cognitive function of leukemia patients following bone marrow chemoablation/hematopoietic cell transplantation after six months compared to patients who received G-CSF alone. **Objectives:** To determine whether the innate immune system modulator, GM-CSF/sargramostim, which has been FDA approved for treating leukopenia for over 20 years, can safely halt or reduce cognitive decline and brain pathology in participants with mild-to-moderate AD. **Methods:** A randomized, placebo-controlled, double-blind, Phase II safety and efficacy trial of sargramostim in 40 mild-to-moderate AD participants with half receiving placebo and half receiving 250 mg/m<sup>2</sup>/day sargramostim by subcutaneous injection five days/week for three weeks (15 total injections) with follow-up visits at 45 and 90 days post-treatment is complete (NCT01409915). Neurological and neuropsychological assessments, pathology-related plasma biomarker measures, MRI, and amyloid-PET scans were performed to assess the safety and efficacy of sargramostim

treatment. **Results:** Analyses of the 20 participants treated with sargramostim and 20 participants treated with placebo showed no drug-related serious adverse events, including no evidence of amyloid-related imaging abnormalities (ARIAs), which, if present, would indicate micro-hemorrhage or vasogenic edema. When comparing measures at the end of treatment, the mean of the Mini-Mental State Examination (MMSE) score in the sargramostim group was improved relative to baseline ( $p=0.0074$ ) and relative to the placebo group ( $p=0.037$ ) by repeated measures mixed model analysis. The beneficial effect on MMSE of sargramostim compared to placebo was retained at the first follow-up visit at 45 days after the end of treatment ( $p=0.0272$ ). In contrast, there was a poorer mean Alzheimer's Disease Assessment Scale-Cognitive Subscale-13 (ADAS-Cog-13) score in the sargramostim group compared to the placebo group at the first follow-up visit at 45 days after the end of treatment, which may be a rebound effect of ending treatment, but the difference disappeared by the second follow-up visit at 90 days after the end of treatment. Other neuropsychological measures showed no statistically significant effects. Analyses of plasma using the Quanterix Simoa® platform showed a statistically significant reduction in two measures of neuronal damage—ubiquitin C-terminal hydrolase L1 (UCHL-1) and total Tau—at the end of GM-CSF/sargramostim treatment compared to baseline and compared to placebo. Specifically, compared to baseline, GM-CSF/sargramostim treatment was associated with a 37% decrease in UCHL-1 ( $p=0.0029$ ) and an 18% decrease in total Tau ( $p=0.021$ ) at the end of treatment. Compared to placebo at the end of treatment, GM-CSF/sargramostim treatment was associated with a 39% relative lowering of UCHL-1 ( $p=0.0035$ ) and a 25% relative lowering of total Tau ( $p=0.0125$ ). Plasma levels of glial fibrillary acidic protein (GFAP) and neurofilament light (NFL) did not change significantly following GM-CSF/sargramostim treatment. Simoa® analyses of amyloid-beta biomarker levels in plasma are currently under investigation. Comparing amyloid-PET scans available at screening and at the first follow-up visit for the last 18 participants showed no statistically significant differences in the standardized uptake value ratio (SUV<sub>r</sub>), although there was a moderate, but non-statistically significant, inverse correlation (-0.336) between changes in amyloid and changes in MMSE combining both placebo- and sargramostim-treated participant data. Volumetric brain scans are currently being analyzed. **Conclusions:** GM-CSF/sargramostim treatment was safe and tolerable in mild-to-moderate AD participants. One measure of cognition (i.e., MMSE) and two plasma measures of neuronal damage (i.e., UCHL-1 and total Tau) showed improvement after three weeks (15 injections) of GM-CSF/sargramostim treatment compared to baseline and compared to placebo. These results indicate that GM-CSF/sargramostim shows promise as a potentially safe treatment for AD and provides support for our Alzheimer's Association "Part the Cloud"-funded trial with a longer, 24-week-long treatment period.

**OC45: THE ALZHEIMER'S DISEASE EVENT INVENTORY: ANALYSIS OF BASELINE DATA FROM THE TAURIEL STUDY.** E. Teng<sup>1</sup>, P. Manser<sup>1</sup>, G. Kerchner<sup>2</sup>, M. Ward<sup>1</sup>, K. Pickthorn<sup>1</sup>, M. Blendstrup<sup>1</sup>, C. Lansdall<sup>2</sup>, M. Keeley<sup>1</sup>, F. McDougall<sup>1</sup> (1) Genentech, Inc. - South San Francisco, USA; (2) F. Hoffmann-La Roche - Basel, Switzerland)

**Background:** Amyloid Background: Alzheimer's disease (AD) progression results in deterioration in multiple clinical

domains including cognition, function, and behavior. However, disease progression between individual patients can be very heterogeneous, both within and across different stages of the disease, which can complicate the interpretation of the results of clinical trials of AD therapeutics. One approach to measuring AD progression is to identify key milestones in the patient journey [e.g., loss of independence in specific activities of daily living (ADLs), emergence of troublesome behaviors, increased caregiving and/or medication requirements] and determine the relative time course over which such milestones are experienced. We devised the Alzheimer's Disease Event Inventory (ADEI), which assesses a range of potential milestones, and have included it as an exploratory outcome measure in the ongoing Tauriel study (GN39763; NCT03289143), which is evaluating the safety and efficacy of the anti-tau antibody semorinemab in prodromal-to-mild AD, to determine its potential for time-to-event analyses of AD progression. **Objectives:** To determine the relative frequencies with which the potential AD milestones assessed by the ADEI are present at baseline in an international, multi-center, interventional clinical trial in prodromal-to-mild AD. **Methods:** The presence of individual milestones on the ADEI is reported by informants/caregivers at baseline and at 3-month intervals over the course of this 18-month study. ADLs assessed with the ADEI include employment/volunteering, chores, hobbies, finances, driving, and social interactions. Troublesome behaviors assessed include aggression/violence. Escalations of care assessed include use of symptomatic AD medications and medications for depression/apathy, agitation/aggression, and sleep. **Results:** Baseline ADEI data were available from 442 participants (159 prodromal AD, 283 mild AD). The AD subgroups were similar in age (prodromal: mean=69.7, SD=7.0; mild: mean=69.5, SD=6.8) and gender distribution (prodromal: 54% women; mild: 57% women). The proportion of participants with prodromal AD who had experienced each assessed disease milestone at baseline was numerically lower than those with mild AD, with significantly fewer prodromal AD participants: no longer working/volunteering (67% vs. 83%;  $p<0.001$ ), no longer managing finances (40% vs. 79%;  $p<0.001$ ), no longer paying restaurant bills/tipping (14% vs. 44%;  $p<0.001$ ), no longer driving (24% vs. 52%;  $p<0.001$ ), no longer using dangerous tools/firearms (87% vs. 95%;  $p=0.006$ ), decreasing their social interactions (4% vs. 11%;  $p=0.015$ ), and taking symptomatic AD medications (47% vs. 77%;  $p<0.001$ ). **Conclusions:** These cross-sectional analyses of baseline ADEI data from the Tauriel study suggest preliminary validity for some of the milestones included in the ADEI relative to clinical diagnoses, given the numerically higher rates at which they were experienced in mild versus prodromal AD participants. The wide range of different milestones present at baseline in this patient population suggest that only a subset of them are likely to have utility in detecting treatment effects in prodromal-to-mild AD over an 18-month interval. Longitudinal analyses, to be conducted after the conclusion of the blinded portion of this study, will assist in the further refinement of this measure for use in detecting individualized disease progression in AD in future studies.

## LATE BREAKING COMMUNICATIONS

**LB01: AVOID OR EMBRACE? PRACTICE EFFECTS IN AD CLINICAL TRIALS.** J. Hassenstab<sup>1</sup>, A. Aschenbrenner<sup>1</sup>, G. Wang<sup>1</sup>, Y. Li<sup>1</sup>, C. Xiong<sup>1</sup>, E. Mcdade<sup>1</sup>, D. Clifford<sup>1</sup>, Y. Roy<sup>2</sup>, K. Holdridge<sup>2</sup>, R. Bateman<sup>1</sup> ((1) *Washington University In St. Louis - St. Louis, USA*; (2) *Eli Lilly - Indianapolis, USA*)

**Background:** Alzheimer's disease (AD) prevention trials typically assess cognition at regular intervals to track cognitive change across the course of a trial. Repeated testing can produce substantial improvements in performance as participants become familiar with the tests and the testing process. These practice effects (PEs) can be a vexing issue for trial design and for analyses of cognitive endpoints. When unanticipated, PEs can reduce statistical power to detect drug effects on cognition. But when anticipated, an attenuation of PEs can represent a subtle marker of very early neurodegenerative disease. Common analytical methodology (e.g., MMRM or LMEs) do not adequately account for practice effects, which may confound analyses of cognitive endpoints. In addition, trial designs based on data from observational studies may not capture the full extent of PEs and other factors that may lead to performance gains on cognition. Therefore, it is critical to have a detailed understanding of the factors that promote or exaggerate PEs in clinical trials so that they can be properly modeled in the primary analysis. Alternative approaches that embrace practice effects may be a viable option for the next generation of AD prevention trials. **Objectives:** We evaluated the influence of testing frequency and clinical status on the presence and magnitude of practice effects in the context of the Dominantly Inherited Alzheimer Network-Trials Unit (DIAN-TU) 001 clinical trial. In our presentation, we will also describe alternative approaches to cognitive assessment that embrace practice effects. **Methods:** Practice effects were analyzed in 142 mutation carriers (MCs) and 39 mutation noncarriers (NMCs) from the DIAN-TU 001 clinical trial and a matched control sample of 123 MCs from the DIAN observational study (DIAN OBS). Participants were no more than 15 years from their expected age of symptom onset and had a Clinical Dementia Rating (CDR) of 1 (mild AD) or less at baseline, the majority of which were cognitively normal (CDR 0). DIAN-TU participants undergo cognitive assessments every 6 months. This evaluation includes several measures of episodic memory, processing speed and attention / executive function. Some measures include alternate forms. Many of the same tests are given in the DIAN OBS study but at wider time intervals (annually for symptomatic participants, every two years for asymptomatic participants). We quantified performance using the mean to standard deviation ratio (MSD) of change from the first to final visit in the study. A positive value indicated improvement (PE) and negative values indicated decline. Participants from each study were split into four groups, NMCs, asymptomatic MCs (asymMCs, CDR 0 throughout the study), converters (MCs that were CDR 0 at baseline but progressed to CDR > 0), and symptomatic MCs (symMCs, CDR > 0 at baseline). PEs were compared across these groups. **Results:** DIAN-TU NMCs exhibited improvement on all cognitive tests (MSDs ranged from 0.01 to 1.95) including those with alternate forms, and asymMCs improved on all tests with the exception of the International Shopping List (MSD = -0.06), Cogstate Detection task (MSD = -0.07) and Animal fluency (MSD = -0.01).

Importantly, when both the NMCs and asymMCs improved, the magnitude of improvement was smaller in the asymMCs, e.g., practice effects were 0.54 MSD units smaller in the asymMCs on Logical Memory and 0.50 MSD units smaller on Digit Symbol relative to NMCs. Practice effects were not present on any test for either the converters or symMC groups. Compared to DIAN OBS where assessments are less frequent, PEs on key cognitive tests were substantially larger in the DIAN-TU, despite no differences in disease stage. Specifically, for asymMCs, practice effects were 1.23 MSD units higher in the TU for Digit Symbol Substitution and 1.09 MSD units higher for Logical Memory delayed recall. Although decline was apparent in both the Obs and TU studies for converters and symMCs, the magnitude was smaller in the TU for both Digit Symbol and Logical Memory. The average decline in TU converters was nearly half that of OBS converters. **Conclusion:** Practice effects in AD trials may be larger than in observational studies. Factors that increase PEs likely include more frequent exposure to cognitive testing and trial expectancy effects. Alternate forms attenuate, but do not eliminate PEs, suggesting that PEs involve more than memory for specific test stimuli. There are many methods that can reduce the impact of PEs, and we will describe these and alternative strategies that embrace PEs using analytical methods, unique trial designs, and novel assessment paradigms.

**LB02: SYNCHRONIZING EXERCISES, REMEDIES IN GAIT AND COGNITION AT HOME: FEASIBILITY OF A HOME-BASED DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL TO IMPROVE GAIT AND COGNITION IN INDIVIDUALS AT RISK FOR DEMENTIA.** M. Montero-Odasso<sup>1,2,3</sup>, C.A. McGibbon<sup>4</sup>, P. Jarrett<sup>5,6</sup>, D. Bouchard<sup>7</sup>, G. Handrigan<sup>8</sup>, C.C. Tranchant<sup>9</sup>, S. Belleville<sup>10</sup>, H. Chertkow<sup>11</sup>, H. Feldman<sup>12</sup>, H. Nygaard<sup>13</sup>, M. Speechley<sup>14</sup> ((1) *Schulich School Of Medicine & Dentistry, University Of Western Ontario - London, Ontario, Canada*; (2) *Department of Medicine (Geriatrics), University of Western Ontario - London, Ontario, Canada*; (3) *Department of Epidemiology and Biostatistics, University of Western Ontario - London, Ontario, Canada*; (4) *Faculty Of Kinesiology And Institute Of Biomedical Engineering, University Of New Brunswick - Fredericton, New Brunswick, Canada*; (5) *Department Of Geriatric Medicine, Horizon Health Network - Saint John, New Brunswick, Canada*; (6) *Division of Geriatric Medicine, Department of Medicine, Dalhousie University - Halifax, Nova Scotia, Canada*; (7) *Faculty Of Kinesiology, University Of New Brunswick - Fredericton, New Brunswick, Canada*; (8) *School Of Kinesiology And Recreation, Faculty Of Health Sciences And Community Services, Université De Moncton - Moncton, New Brunswick, Canada*; (9) *School Of Food Science, Nutrition And Family Studies, Faculty Of Health Sciences And Community Services, Université De Moncton - Moncton, New Brunswick, Canada*; (10) *Department Of Psychology Université De Montréal - Montreal, Quebec, Canada*; (11) *Baycrest And Rotman Research Institute - Toronto, Ontario, Canada*; (12) *Department Of Neurosciences, University Of California - San Diego, California, USA*; (13) *Division Of Neurology, University Of British Columbia - Vancouver, British Columbia, Canada*; (14) *Department Of Epidemiology And Biostatistics, Schulich School Of Medicine & Dentistry, University Of Western Ontario - London, Ontario, Canada*)

**Background:** Nearly half a million Canadians live with Alzheimer's Disease and Related Dementias (ADRDs), and approximately one third of those cases could have been prevented with early lifestyle interventions (Livingston et al.,



2017). Lifestyle early interventions are best applied in pre-dementia states such as in individuals with mild cognitive impairment (MCI) and those at risk for developing dementia. Physical exercise and cognitive training are emerging interventions that have the potential to enhance cognitive function and mobility in older adults with MCI. The SYNERGIC trial (SYNchronizing Exercises, Remedies in Gait and Cognition), a large multi-site randomized control trial, showed promising preliminary data that individuals in an active exercise intervention condition (EX) combining aerobic exercise with progressive resistance training and in a cognitive training (CT) program had better cognitive outcomes than a balance and toning control (BAT) intervention (Montero-Odasso et al., 2018). While these interventions were provided face to face in a research facility, little is known about the feasibility of delivering these multi-domain interventions at home in older adults at risk for developing ADRDs. **Objectives:** 1-to establish the feasibility of the home-based approach to deliver physical exercise combined with online cognitive training. 2-to assess the effect of the interventions on cognition, mobility, sleep, diet, psychological well-being, and cardiovascular functioning. **Methods:** The SYNERGIC@Home trial is a pilot randomized control trial (RCT) with a 2 x 2 factorial design, consisting of a 16-week home-based intervention program of combined physical exercises with cognitive training. Sixty-four participants will be randomized in blocks of four to one of the following four arms: 1) combined exercise intervention (EX) + cognitive training (CT); 2) combined exercise intervention (EX) + control cognitive training; 3) BAT control exercise + cognitive training; and 4) BAT control exercise + control cognitive training. SYNERGIC@Home will be implemented entirely virtually through video and phone conferencing. Baseline, immediate post-intervention follow-up, and 6-month post-intervention follow-up assessments will include measures of cognition, mobility, sleep, diet, psychological health, and cardiovascular functioning. To successfully establish feasibility of implementing this trial virtually, we will obtain measures of recruitment and retention rates. We will also conduct a series of secondary analytic outcomes examining the potential effect of the individual and combined interventions on cognition, mobility, sleep, diet, psychological well-being and cardiovascular function at all three time points. **Results:** The SYNERGIC@Home trial will establish the feasibility of a combined multimodal intervention program delivered at home in older adults. Based on recruitment success and positive preliminary results of the original SYNERGIC I trial (which was administered across 5 sites in Canada on a face-to-face basis), it is expected that the SYNERGIC@Home trial will follow suit and also yield high recruitment and retention rates. Furthermore, the SYNERGIC@Home trial has eliminated any of the natural inconveniences of in-person testing and optimizes participants' comfort. We also expect to observe a signal of efficacy in the secondary outcomes including cognitive, mobility, diet, sleep, psychological and cardiovascular outcomes such that individuals in the intervention arms outperform those in control conditions. The SYNERGIC@Home trial will inform future larger scale studies on the feasibility and success of implementing home-based interventions for individuals at risk for ADRDs. Insights gained from this pilot will be instrumental in developing various other at-home, remote, and virtual intervention programs for community-dwelling older adults. **Conclusion:** In today's technological age, it is becoming more possible than ever to conduct impactful

research with participants virtually. A home-based intervention program for older adults at risk for ADRDs has the advantages of allowing participants the freedom, flexibility and comfort to participate from their home—and may potentially lead to enhanced recruitment and retention, and reduce social isolation. In addition to the convenience of participating in research from the comfort of one's home, there are critical health considerations that uniquely justify the home-based nature of the SYNERGIC@Home pilot study. In light of the COVID-19 pandemic of 2020 and the associated risks of exposure for older populations, SYNERGIC@Home allows for safe administration of interventions in older individuals at risk for ADRDs. To ensure the safety of our participants, we are planning to administer all interventions (including exercise and cognitive training) using a home-based protocol. This home-based approach will allow participants to connect with us using video conferencing platforms (Zoom Healthcare®). This feat will not only address the feasibility goals of SYNERGIC@Home, but it will also give older individuals an opportunity to connect with others. This is particularly important at a time during which physical distancing measures may have contributed significantly to isolation, loneliness, and depression in older populations. **References:** Livingston G, Sommerlad A, Orgeta V, et al. (2017). Dementia prevention, intervention, and care. *Lancet*, 390(10113):2673-2734. Montero-Odasso M, Almedia Q, Camicioli R, et al. (2018). Preliminary results from the SYNERGIC trial: A multimodal intervention for mild cognitive impairment. *Innovation in Aging*, 2(Suppl 1):439-440.

**LB03: GV-971 (OLIGOMMANATE) BACKGROUND, DEVELOPMENT, AND GLOBAL PHASE 3 STUDY.** J. Cummings (Cleveland Clinic Lou Ruvo Center For Brain Health - Las Vegas, USA)

**Background:** Alzheimer's disease (AD) represents one of the greatest public health challenges as well as an area of urgent unmet need for treatment. GV-971 (sodium Oligomannate) is a mixture of linear, acidic oligosaccharides with a degree of polymerization ranging from dimers to decamers, originally derived from seaweed. Laboratory studies involving transgenic mice indicate that the mechanism of action of GV-971 is to normalize the gut microbiome, reduce peripheral inflammation, and decrease brain inflammation. Effects on amyloid, tau, and brain inflammation as well as microbiome effects have been observed in experimental animals treated with the agent. GV-971 has shown good tolerability in Phase 1 studies and a trend toward dose-related efficacy and good tolerability and safety in a Phase 2 trial. In a Phase 3 trial conducted in China, participants administered 900 mg/day of GV-971 exhibited rapid initial gains on the AD Assessment Scale -cognitive subscale (ADAS-cog) with sustained improvement in cognition over the 36-week study period. The improvement in cognition was supported by positive trends in global function as measured by the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus). Patients with more severe cognitive changes appeared to benefit most from treatment. GV -971 was approved by National Medical Products Agency (NMPA; Chinese equivalent of FDA) in 2019 to improve cognitive function in patients with mild to moderate AD. **Objective:** Green Valley Pharmaceuticals is conducting a global Phase 3 study --- Green Memory --- to evaluate the efficacy and safety of GV 971 in treatment of mild to moderate AD (ClinicalTrials.gov Identifier: NCT04520412). **Methods:** The

primary objective of the global study is to assess the efficacy of GV-971 compared with placebo on cognition and global function. Secondary objectives are: to assess the effects of GV 971 compared with placebo on behavioral symptoms, cognitive impairment, activities of daily living (ADL), and resource use; and to assess the safety and tolerability of GV 971. The effects of GV-971 on biomarkers of neurodegeneration, inflammation, gut metabolites, and gut microbiome will be assessed. A population pharmacokinetic (PK) evaluation will be conducted. Green Memory is a 52-week, multi-center, randomized, double-blind, 2-arm, parallel-group, placebo controlled, monotherapy Phase 3 study to be conducted in 2046 participants with mild to moderate AD dementia (MMSE score 11 to 24; with regional stratification and at least 75% of participants with MMSE scores <20). Eligible participants will have medial temporal atrophy of  $\geq$  grade 2 and Fazekas scale for white matter lesions grade < 3. Patients must not have received other AD medications (cholinesterase inhibitors, memantine) for at least 4 weeks prior to randomization and these drugs will not be allowed in the course of the study. Participants who meet all inclusion/exclusion criteria will be randomized in a 1:1 ratio to 900 mg/day GV 971 or placebo. Participants who successfully complete the double-blind treatment period may continue in the 26-week open-label extension period. The co-primary efficacy endpoints are change from baseline to end of double blind period on ADAS-cog/ 11 and ADCS-CGIC scale total scores. The primary efficacy endpoints will be analyzed for the full analysis set (FAS) population. The analysis of the change from baseline in ADAS cog/11 and the ADCS-CGIC will be performed using a Mixed Model for Repeated Measures (MMRM) with treatment group and visit as fixed effects and baseline score as a covariate. Baseline MMSE, APOE4 carrier status, and age at baseline and other factors will be included in the model. Baseline will be defined as an average of the screening and baseline scores and final score will be the average of the last two scores on treatment; this approach is taken to minimize variability in the baseline and of study scores. Other efficacy measurements include NPI, MMSE, ADCS-ADL23, A-IADL, ZBI, and RUD. Blood samples will be taken for measurements of GV-971 blood concentrations and PK studies. The effects of GV-971 on biomarkers including blood A $\beta$ 42/A $\beta$ 40, p-tau, inflammatory cells, and gut metabolites and gut microbiome changes in fecal samples will be measured. Volumetric MRI changes will be assessed. Green Memory will be conducted at approximately 200 clinical sites in North America, Europe, and the Asia-Pacific region. It is anticipated that first subject will be enrolled in Q4 2020. **Results:** GV-971 is approved in China for treatment of mild to moderate AD. A global Phase 3 clinical trial --- Green Memory --- studying GV 971 for treatment of patients with mild to moderate AD is being initiated in approximately 200 clinical centers worldwide. **Conclusions:** The Green Memory trial builds on a foundation of basic science indicating an effect on the microbiome and on successful Phase 1-3 trials in China. Clinical outcomes of Green Memory will determine the efficacy and safety of GV-971 in a global population; biomarker outcomes will provide insight into the mechanism(s) of action.

#### **LB04: DEVELOPMENT OF A DISEASE PROGRESSION MODEL FOR ALZHEIMER'S DISEASE INFORMED BY MULTIPLE CLINICAL TRIALS AND ADNI TO PREDICT LONGITUDINAL TRAJECTORY OF CDR-SOB SCORE.**

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**Background:** Different investigators have developed disease progression models for Alzheimer's disease (AD) using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset (1). These models focused on describing the trajectory of scores, such as the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-COG) or Clinical Dementia Rating Scale - Sum of Boxes (CDR-SOB), using the mixed-effect modeling approach. Earlier models assumed linear disease progression. More recent models assume a logistic shape for disease progression, to account for variation in rate of change of the score as the disease advances. In these models, a disease progression trajectory can be obtained for each subject by estimating a disease onset time prior to the start of the clinical trial. Finally, to describe slow and fast progressors within patients with mild cognitive impairment (MCI) in the ADNI dataset, mixture models have been explored (2). Here we build upon the previous work on disease modeling for AD to characterize progression of CDR-SOB using data from multiple interventional clinical trials in AD and ADNI, spanning a range of disease severity. **Objectives:** We aim to develop a disease model for AD progression, categorizing the CDR-SOB score. We estimate a disease onset time for each subject to obtain the longitudinal trajectory of the score, using data spanning different stages of the disease from prodromal to mild to moderate AD. The focus of this abstract is on model development for the placebo group and identification of covariates that influence progression of CDR-SOB score. **Methods:** We used nonlinear mixed-effect population modeling to describe progression of CDR-SOB score for placebo patients from several Roche/Genentech clinical trials and ADNI. Placebo arms from ABBY (NCT01343966; crenezumab), BLAZE (NCT01397578; crenezumab), SCarlet RoAD (NCT01224106; gantenerumab), and Marguerite RoAD (NCT02051608; gantenerumab), as well as ADNI (n=1112), were used for model building. Placebo data from CREAD I (NCT02670083; crenezumab) and CREAD II (NCT03114657; crenezumab) were used for external validation of the model (n=809). The length of clinical trials is generally up to two years, and we used data up to four years from ADNI. We included amyloid-positive patients from ADNI, which is an inclusion criterion in more recent AD clinical trials. Subjects with baseline diagnosis of late MCI or AD were included from ADNI as they were closest to the population from our clinical trials. The change in CDR-SOB score was described via a differential equation. In addition to disease onset time (DOT), the change in CDR-SOB was further described by a population disease progression rate (RATE) and an individual change in disease progression rate (ALPHA). Interindividual variability was implemented on DOT and ALPHA. Significant covariates in explaining the between-patient variability were identified and retained in the final model. Internal visual predictive check (VPC) was conducted to assess the predictive performance of the model. External validation with the placebo arm from the CREAD trials was also conducted by VPC. **Results:** We were able to capture progression of CDR-SOB score for the entire population by

including baseline CDR-SOB as a covariate on DOT and RATE. Including the baseline MMSE score as a covariate on DOT and ALPHA was also significant in explaining between-subject variability. The direction of the estimated covariate effects was in line with our expectation based on the nature of these scores. All parameters were very well estimated. Disease onset time was estimated 3.3 years before entering the trial (or start of study for ADNI) (relative standard error 1.5%). The estimated interindividual variability on ALPHA was large (84.7% [9%]). Population progression rate (RATE) was estimated at 0.305 (/y) [5%]. Overall, these estimates agreed well with the estimates from the model implemented by Delor et al; the estimated rate in our model fell between the slow and fast progression rates estimated by the mixture model (2). The model captured the disease progression in the CREAD trials very well. **Conclusion:** We developed a disease progression model for AD, building upon previous modeling efforts in this space using the nonlinear mixed-effect population modeling approach. The model was developed using data from the placebo arm of four clinical trials and ADNI, and validated using the placebo arm of the CREAD Phase 3 trials. The model captured the trajectory of CDR-SOB over time for patients in various stages of the disease. We identified baseline CDR-SOB as a significant covariate on disease onset time and disease progression rate. In the next step, this model will be used to benchmark the placebo progression of TAURIEL (NCT03289143; semorinemab). Furthermore, the model enables us to predict the change in CDR-SOB (a measure frequently used as an endpoint in trials) in the absence of active treatment for each patient, for comparison with on-treatment observed values in the same patients from upcoming trials and to aid in assessing a treatment effect. **References:** 1. Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). 2. Delor, I et al. CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e78

**LB05: THE AZELIRAGON ELEVAGE STUDY: STUDY UPDATE AND PRELIMINARY DATA ON BASELINE CHARACTERISTICS OF PARTICIPANTS WITH MILD ALZHEIMER'S DISEASE AND TYPE 2 DIABETES RANDOMIZED IN PART 1.** A. Gooch, L. Kirby, L. Humphries, I. Dunn, C. Valcarce, A. Burstein<sup>1</sup>(*Vtv Therapeutics - High Point, USA*)

**Background:** Azeliragon, an oral antagonist of the receptor for advanced glycation endproducts (RAGE), was evaluated in an 18-month Phase 3 study as a treatment for patients with mild Alzheimer's disease (AD) (the STEADFAST Study). Post-hoc analyses were performed in a subgroup of individuals with Type 2 diabetes (T2D, HbA1c  $\geq$  6.5%) as a group with presumed increased RAGE expression. In the T2D subgroup, azeliragon-treated subjects exhibited less cognitive decline when compared with placebo-treated subjects. The change from baseline in ADAS-cog11 between treatment groups (azeliragon minus placebo) was -5.5 points at 18 months (nominal  $p=0.006$ ) with clinically relevant separation (azeliragon minus placebo) of -4.9 points as early as 6 months (nominal  $p<0.001$ ). In the T2D subgroup, azeliragon-treated subjects also exhibited less whole brain atrophy, a trend to lower decreases in brain FDG-PET SUV<sub>r</sub>, and reduced plasma inflammatory cytokine concentrations compared to subjects treated with placebo. The objective of Part 1 of the Elevage study is to replicate the T2D subgroup results on cognition. **Objectives:** The Elevage study (NCT03980730) is a two-part study operationally conducted

under one protocol. Part 1 is an ongoing Phase 2 multicenter randomized double-blind placebo-controlled parallel group clinical trial designed to evaluate the impact of 6-months of treatment with azeliragon on cognitive performance in subjects with mild AD and T2D. The results of Part 1 are intended to serve as replication of post-hoc subgroup analyses from the STEADFAST study prior to advancing into Part 2, the Phase 3 registration trial portion of the Elevage study. **Methods:** Part 1 of the Elevage study is enrolling subjects aged 50-85 years with probable mild AD (Screening MMSE 21-26, CDR global 0.5-1, ADAScog 14  $\geq$ 10) and T2D (HbA1c 6.5%-9.5%) receiving stable acetylcholinesterase inhibitors and/or memantine. Subjects receiving treatment for diabetes are required to be on a stable dose and insulin use is exclusionary. Subjects are randomized 1:1 to azeliragon 5 mg/day or placebo. The primary endpoint is change from baseline in the ADAS-cog 14 at Month 6. Secondary endpoints include change from Baseline in Clinical Dementia Rating Scale – Sum of Boxes (CDR-sb), Functional Activities Questionnaire (FAQ), and Amsterdam Instrumental Activities of Daily Living (A-IADL) at Month 6. **Results / Conclusions:** Baseline characteristics of the blinded Elevage study population will be presented and descriptively compared with the baseline characteristics of the hypothesis-generating T2D subgroup from the STEADFAST Study.

**LB06: SPOUSAL VS. NON-SPOUSAL DYADS: A FLEXIBLE APPROACH TO QUANTIFYING VARIABILITY OF COGNITIVE AND FUNCTIONAL ASSESSMENTS TO BETTER INFORM FUTURE MCI AND AD TRIALS.** N. Hakhu<sup>1</sup>, D. Gillen<sup>1</sup>, J. Grill<sup>2</sup> ((1) *Department Of Statistics, University Of California, Irvine - Irvine, USA*; (2) *Departments Of Psychiatry & Human Behavior And Neurobiology & Behavior, University Of California, Irvine - Irvine, USA*)

**Background:** In Alzheimer's disease (AD) trials, as in all clinical trials, we seek to minimize bias and variance to maintain trial integrity and reliably answer the pre-specified primary question of interest. Greater than expected variability in outcome measures decreases precision of intervention estimates and leads to less efficient designs, including lower power to detect a treatment effect. In AD trials, participants must enroll with a study partner who completes informant-based assessments on the participant's cognition and function forming a dyad. We hypothesized that heterogeneity in the variability of outcome measures is associated with dyad type (e.g., spousal vs. non-spousal). The analysis of variance (ANOVA) F test is a common method to compare whether variances between two independent groups at a single time point are different. Since many cognitive and functional assessments have bounded scales, the resulting distributions can be skewed and non-normal. In such settings, the normality assumption for the ANOVA F test is violated and valid inference may not be obtained. We observed this with the AD Cooperative Study (ADCS) Donepezil/Vitamin E trial—a multi-center randomized placebo-controlled trial that enrolled participants with mild cognitive impairment (MCI) who were required to have a study partner at baseline—data for activities of daily living (ADCS-ADL-MCI ranging from 0-53, higher score indicating less impairment). **Objectives:** Obtaining reliable estimates of cross-sectional and longitudinal variability, including uncertainty estimates, will better inform AD investigators about possible heterogeneity between subpopulations to aid in designing future MCI and AD trials. We propose using the bootstrap as

a flexible method to quantify cross-sectional and longitudinal estimands that account for the correlation structure of the data. **Methods:** We considered three estimands for comparing two subpopulations (spousal vs. non-spousal dyads): (1) difference in a single post-baseline variance, (2) difference in the change from baseline variance, and (3) linear trend of differences in variances over time. Our methods were empirically evaluated via simulation and applied to the ADCS Donepezil/Vitamin E trial data. We focused on the ADCS ADLs as the outcome measure and dyad type at baseline (spousal vs. non-spousal) as the predictor of interest. Furthermore, we restricted attention to completers (the 451 out of the 790 randomized participants who had valid ADL scores at all scheduled visits: baseline and months 6, 12, 18, 24, 30, and 36) to avoid having missing data. Since no reference distribution is assumed under the null hypothesis (no difference) when using the bootstrap, no p-value can be computed. Instead, statistical significance was achieved if the 95% confidence interval (CI) excluded zero. We conducted simulations to examine finite sample properties (bias and confidence interval (CI) coverage probabilities) of estimators corresponding to the estimands under different scenarios. **Results:** Based on our proof-of-concept simulated scenarios for the three estimands, we obtained approximately unbiased estimates and CIs with coverage near the nominal level for N=100 per group. Among Donepezil/Vitamin E trial completers, there were 350 (78%) spousal vs. 101 (22%) non-spousal dyads at baseline. For Estimand 1 we estimated the variance in month 36 ADLs for a subpopulation of completers with a spousal dyad to be 34.8 squared units lower than the variance in month 36 ADLs for a subpopulation of completers with a non-spousal dyad (95% CI: -102.0, 28.1). For Estimand 2 we estimated the variance in the change from BL to month 36 ADLs for a subpopulation of completers with a spousal dyad to be 31.9 squared units lower than the variance in the change from BL to month 36 ADLs for a subpopulation of completers with a non-spousal dyad (95% CI: -91.2, 23.7). For Estimand 3 we estimated the first-order approximation to the trend in variances over time for a subpopulation of completers with a spousal dyad to be 26.1 squared units lower than the variances over time for a subpopulation of completers with a non-spousal dyad (95% CI: -71.0, 18.5). **Conclusion:** Overall, we demonstrated the bootstrap is a flexible method that requires minimal assumptions (large enough sample sizes) to yield reliable estimates of cross-sectional and longitudinal variability to aid in designing future AD, including MCI, trials. Applying the bootstrap procedure to the Donepezil/Vitamin E MCI trial data, we did not find evidence of a statistically significant difference in the variability of ADLs between spousal and non-spousal dyads. From simulations assuming equal N, we estimated power between 33-43% for N=100, 61-75% for N=250, and 88-96% for N=500. Hence, the observed lower proportion of non-spousal dyads (N=101 vs. 350) is one source that constrained power. Nevertheless, we provided a single best estimate of each estimand along with a corresponding 95% CI to quantify the uncertainty in our estimate; this information can be used to inform future MCI and AD trials.

**LB07: A PILOT RANDOMIZED CONTROLLED TRIAL OF THE COGNITIVE EFFECTS OF AEROBIC EXERCISE IN ALZHEIMER'S DISEASE.** F. Yu<sup>1</sup>, D. Vock<sup>2</sup>, L. Zhang<sup>2</sup>, D. Salisbury<sup>2</sup>, N. Nelson<sup>3</sup>, L. Chow<sup>2</sup>, G. Smith<sup>4</sup>, M. Dysken<sup>2</sup>, J. Wyman<sup>2</sup> ((1) *Arizona State University - Phoenix, USA*; (2) *University Of Minnesota - Minneapolis, USA*; (3) *University Of St Thomas - St Paul, USA*; (4) *University Of Florida - Gainesville, USA*)

**Background:** Aerobic exercise is well supported to be disease-modifying for Alzheimer's disease (AD) in basic science; however, it has shown inconsistent cognitive effects in randomized controlled trials (RCTs) among older adults with AD dementia. The inconsistent findings are attributable to methodological factors, for example, the AD clinical phase studied (mild cognitive impairment [MCI] vs. AD dementia) and exercise doses (variations in exercise frequency, duration, and intensity). Overall, meta-analyses suggest that aerobic exercise has modest-to-moderate cognitive effects across the AD spectrum. Recent evidence further supports an emerging dose-response relationship between aerobic exercise doses and cognitive outcomes in MCI and AD dementia. **Objectives:** The objective of this pilot RCT to investigate the immediate and long-term effects of a 6-month, supervised moderate-intensity cycling intervention on cognition in community-dwelling older adults with clinically defined probable mild-to-moderate AD dementia. Given the pilot nature, this trial was not powered to detect between-group differences. Instead, it was powered on the priori hypothesis that cycling participants will have a smaller within-group increase in global cognition as measured by the AD Assessment Scale-Cognition (ADAS-Cog) at six months than the natural, expected 3.2±6.3-point increase demonstrated by placebo participants in AD drug RCTs. We further examined the differences in the trajectory of changes in ADAS-Cog, episodic memory, executive function, attention, processing speed, and language over 12 months within and between the two groups. **Methods:** This pilot RCT used a 2-parallel group design to randomize participants across three age strata (66-75, 76-85, and 85+ years of age) using random permuted blocks of 3 and 6 to 6-month supervised cycling or stretching on a 2:1 allocation ratio. Allocation was concealed from all investigators and data collectors, except for the statistician who generated the randomization sequence. We followed the participants for another six months. This trial was approved by the university's Institutional Review Board (IRB: #1306M35661). The inclusion criteria were mild-to-moderate AD dementia, community-dwelling, age 66+ years, English-speaking, stable on AD drugs, verified exercise safety. The exclusion criteria were resting heart rate >100 or <50 beats/minute, neurologic/psychiatric/substance disorders, exercise contraindications, new/abnormal conditions. Among the 96 enrolled participants, 64 were randomized to cycling and 32 to stretching. The intervention was supervised, individualized moderate-intensity cycling for 20-50 minutes, 3 times a week for six months. The control exercise was light-intensity stretching. Cognition was assessed at baseline, 3, 6, 9, and 12 months. Discrete cognitive domains were measured using AD Uniform Data Set battery. **Results:** The participants were 77.4±6.8 years old and had 15.6±2.9 years of education. About 55% of the participants were male. The 6-month change in the ADAS-Cog was 1.0±4.6 for the cycling group and 0.1±4.1 for the stretching group, which were both significantly less than the natural 3.2±6.3-point increase over 6 months. Its 12-month change in the

ADAS-Cog was 2.4±5.2 for the cycling group and 2.2±5.7 for the stretching group. The ADAS-Cog did not differ between groups at 6 (p=0.386) and 12 months (p=0.856). There are no differences in the 12-month rate of change in the ADAS-Cog (0.192 vs. 0.197, p=0.967), executive function (-0.020 vs. -0.012, p=0.383), attention (-0.035 vs. -0.033, p=0.908), memory (-0.012 vs. -0.019, p=0.373), and language (-0.028 vs. -0.026, p=0.756). **Conclusion:** Our primary finding that a 6-month aerobic exercise intervention significantly reduced the decline in global cognition in comparison to its natural course is consistent with the results from other RCTs which showed that aerobic exercise improved or stabilized global cognition over time in the intervention group in older adults with dementia. Our findings on the lack of significant between-group differences are also consistent with recently completed RCTs such as the Danish ADEX trial and a U.S. trial. However, the lack of statistically significant between-group differences should not be interpreted as if aerobic exercise were not effective because our trial was not powered to detect group differences. We have learned several lessons to inform trial designs in the future. A non-exercise control is likely more appropriate to reduce Hawthorne and social interaction effects such as waitlist, usual care, or non-exercise controls because some of our stretching participants were self-motivated to engage in aerobic exercise on their own. Recruitment materials need to be designed neutrally to reduce cross-contamination from the control group by de-emphasizing aerobic exercise. Exercise makeup sessions should be offered to all participants including those who reached the lowest threshold per-protocol doses but not yet achieving 100% of the prescribed doses. Flexibility in intervention duration determination is needed to overcome the limitations imposed by calendar months when extended absences due to illnesses, medical clearance, and vacations are prevalent in older adults with AD dementia. Exercise may reduce decline in global cognition in older adults with mild-to-moderate AD dementia. In summary, exercises may reduce decline in global cognition in older adults with mild-to-moderate AD dementia. The superiority of aerobic exercise over stretching remains to be determined.

**LB08: A 1-YEAR RANDOMIZED CONTROLLED TRIAL OF A NUTRITIONAL BLEND TO PREVENT COGNITIVE DECLINE AMONG COMMUNITY-DWELLING OLDER ADULTS: THE NOLAN STUDY.** K.V. Giudici<sup>1</sup>, S. Guyonnet<sup>1,2</sup>, C. Cantet<sup>1,2</sup>, P. De Souto Barreto<sup>1,2</sup>, M.W. Weiner<sup>3,4,5</sup>, D. Tosun<sup>3,4</sup>, C. Boschat<sup>6</sup>, J. Hudry<sup>6</sup>, T. Bartfai<sup>7</sup>, S. Andrieu<sup>2,8</sup>, B. Vellas<sup>1,2</sup>, J.A.J. Schmitt<sup>6</sup> ((1) *Gerontopole Of Toulouse, Institute Of Ageing, Toulouse University Hospital (chu Toulouse) - Toulouse, France*; (2) *UPS/Inserm UMR1027, University of Toulouse III - Toulouse, France*; (3) *Department Of Veterans Affairs Medical Center - San Francisco, USA*; (4) *Department of Radiology and Biomedical Imaging, University of California - San Francisco, USA*; (5) *Department of Medicine, Department of Psychiatry, Department of Neurology, University of California - San Francisco, USA*; (6) *Société Des Produits Nestlé Sa, Nestlé Research - Lausanne, Switzerland*; (7) *Department Of Neurochemistry, Stockholm University - Stockholm, Sweden*; (8) *Department Of Epidemiology And Public Health, Toulouse University Hospital (chu Toulouse) - Toulouse, France*)

**Background:** Preclinical and epidemiological evidence in favor of individual nutritional factors protecting cognitive function has suggested nutrition as a possible intervention pathway to prevent Alzheimer's disease (AD) and cognitive

decline. Several nutrients have been linked to cognitive function through multiple mechanisms (anti-inflammatory and antioxidant properties, modulation of neuronal membrane fluidity, neuroplasticity stimulation, vasodilation and ability to decrease homocysteine). However, trials supplementing individual nutritional components have yielded controversial results on protecting cognitive function. Acknowledging multifactorial mechanisms involved in aging, more recent evidence on human and animal studies, on the other hand, have suggested that the combinations of nutrients may be a more promising strategy to prevent cognitive decline. **Objectives:** This study aimed to test the effectiveness of a nutritional blend on levels of erythrocyte  $\omega$ -3 polyunsaturated fatty acids (PUFA) index and plasma homocysteine (two nutritional biomarkers presumed to underlie an attenuation of cognitive decline during aging), as well as on subjective and objective measures of cognitive function and on neuroimaging markers among community-dwelling older adults without dementia, but with subjective memory complaints. **Methods:** This randomized, double-blind, multicenter, placebo-controlled trial (NCT03080675) was conducted in France with 362 adults older than 70 years receiving a daily nutritional blend or placebo for one year. The daily dose of the nutritional blend (composed by two soft gel capsules and one powdered sachet of approximately 15g to be consumed mixed in 120mL of cold water) provided 50mg of thiamin (vitamin B1), 15mg of riboflavin (vitamin B2), 25mg of niacin (vitamin B3), 23mg of pantothenic acid (vitamin B5), 18mg of pyridoxine (vitamin B6), 0.15mg of biotin (vitamin B7), 0.4mg of folic acid (vitamin B9), 0.5mg of cobalamin (vitamin B12), 82.6mg of vitamin E, 500mg of vitamin C, 15 $\mu$ g of vitamin D, 85mg of choline, 80 $\mu$ g of selenium, 3g of citrulline, 700mg of eicosapentaenoic acid (EPA) and 770mg of docosahexaenoic acid (DHA). Erythrocyte  $\omega$ -3 index and homocysteine concentrations were primary outcomes; other outcomes included the Patient-Reported Outcomes Measurement Information System (PROMIS) Applied Cognition-Abilities, a composite cognitive score (CCS) based on four tests, the Cognitive Function Instrument (CFI) self-assessment, the CFI study partner, hippocampal volume and AD signature cortical thickness (CT). These two last outcomes were obtained by magnetic resonance imaging (MRI) performed on a voluntary basis among a subgroup of subjects at baseline (n = 284) and one year (n = 183). Analyses were also performed according to ApoE  $\epsilon$ 4 genotype and to presenting low  $\omega$ -3 index ( $\leq$ 5.69%, i.e. the lowest quartile); high homocysteine ( $>$ 14 $\mu$ mol/L), low 25 hydroxyvitamin D concentrations ( $<$ 20ng/mL) or combined nutritional deficits at baseline. **Results:** Out of 362 randomized subjects (58.6% female, mean age 78.3 years, SD = 4.8), 305 completed the follow-up (154 intervention and 151 control). After 1 year, supplementation increased  $\omega$ -3 index (between-group differences: 2.7%, 95%CI: 2.3 to 3.0; p < 0.0001) and decreased homocysteine (-3.2 $\mu$ mol/L, 95%CI: -4.0 to -2.4; p < 0.0001). Intervention did not show an effect in CCS, CFI self-assessment, hippocampal volume and CT. A negative effect of intervention was observed for PROMIS T-score at one month (-1.17, 95%CI: -2.20 to -0.14; p = 0.026). A marginal significance was observed in between-group difference in the left hippocampal volume (42.4mm<sup>3</sup>, 95%CI: -0.1 to 84.8; p = 0.051) and in AD signature CT (0.02mm, 95% CI: 0.0 - 0.04; p = 0.088), suggesting higher annual rate of atrophy and thinning in the placebo group. Intervention showed a positive effect on the exploratory CFI study partner (-0.48, 95%CI: -0.95 to -0.01; p = 0.044). Analyses according to ApoE  $\epsilon$ 4 genotype and to

nutritional deficits provided, in general, similar finding as the main analyses (positive effect of intervention on biomarkers and no effect on the composite cognitive score and the CFI self-assessment score). Positive effect of intervention on the CFI study partner was only observed in the subgroup with high homocysteine. The unexpected finding with the PROMIS T-score in the main analysis was only observed among ApoE  $\epsilon 4$  non-carriers, those with normal vitamin D and those with only one or no nutritional deficit. No difference was observed in effect of treatment between the subgroups. **Conclusions:** Although improving nutritional biomarkers, this trial with a multinutrient novel approach was not able to show effects on cognitive outcomes among older adults after one year. Given the evidence on the ability of high homocysteine and low  $\omega$ -3 index in predicting impairments in cognitive function, enhancing both biomarkers in a 1-year range can be possibly considered an initial step on protecting cognition over aging. Findings of this study may help setting nutritional strategies for optimizing brain health and preventing or slowing cognitive decline, as also identifying individuals in the general population to whom specific nutrient supplementation may be more effective. Further investigations are needed, especially trials with longer follow-ups.

**LB09: REMOTE SMARTPHONE-BASED AND SUPERVISED NEUROPSYCHOLOGICAL ASSESSMENTS OF EPISODIC MEMORY RECALL ARE HIGHLY CORRELATED.** E. Duzel<sup>1</sup>, O. Billette<sup>1</sup>, D. Berron<sup>2</sup>, X. Grande<sup>1</sup>, A. Spottke<sup>3</sup>, K. Buerger<sup>4</sup>, R. Perneczky<sup>4</sup>, C. Laske<sup>5</sup>, A. Schneider<sup>3</sup>, F. Klaus<sup>3</sup>, S. Teipel<sup>6</sup>, J. Wiltfang<sup>7</sup>, M. Wagner<sup>3</sup>, F. Jessen<sup>8</sup> ((1) Dzne - Magdeburg, Germany; (2) Lund Univ. - Lund, Sweden; (3) Dzne - Bonn, Germany; (4) Dzne - Munich, Germany; (5) Dzne - Tubingen, Germany; (6) Dzne - Rostock, Germany; (7) Dzne - Goettingen, Germany; (8) Dzne - Bonn/cologne, Germany)

**Introduction:** Mobile app-based unsupervised monitoring of cognition holds the promise to facilitate case-finding in clinical care and the individual detection of cognitive change in clinical and scientific settings. Implementation of unsupervised mobile assessment is particularly challenging for episodic long-term recall. **Objectives:** We assessed whether an unsupervised mobile test of episodic long-term recall correlates with a detailed on-site (memory clinic-based) neuropsychological supervised assessment of episodic memory recall. **Methods** We used the object-scene pattern completion test of the neotiv platform. In this test, participants are presented with computer-generated rooms, in which two 3D-rendered objects are placed. Participants recall which object was placed at a specific location in an immediate recall test. This serves to ensure successful encoding. After a delay of 30 minutes, the key memory measure is obtained. Here, participants are presented with the empty room and a choice of three objects. In the room, a circle highlights the position of the target object which the participant must choose. Participants of the longitudinal observational DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) classified as healthy (cognitively unimpaired), cognitively unimpaired first-degree relatives of AD patients, subjective cognitive decline and mild cognitive impairment used the neotiv app to complete unsupervised tests of pattern completion on their own smartphone device at home. We assessed the relationships of performance acquired through the mobile app and on-site measures of the Free and Cued Selective Reminding Test (FCSRT, total free recall) and the

Preclinical Alzheimer Cognitive Composite (PACC) conducted by trained neuropsychologists in a memory-clinic. **Results:** A sample of 58 participants completed a single session and 44 performed at least two sessions of the pattern completion test. Correct recall performance in the pattern completion test from both a single and from two assessments was highly correlated ( $R=.63$ ,  $p<0.001$  and  $R=.53$ ,  $p<0.001$ ) with FCSRT total free recall scores. We also observed a strong correlation with the PACC (Preclinical Alzheimer Cognitive Composite) score ( $R=.61$ ,  $p<0.001$ ). **Conclusion:** Our results indicate that unsupervised mobile assessments of pattern completion-based memory recall, using the implementation in the neotiv platform, provides a valid measure of episodic memory. Thus, it is feasible to complement neuropsychological assessment of episodic memory with unsupervised, remote assessments on mobile devices. This paves the way for implementing remote episodic memory assessment in large research trials and clinical care.

**LB10: RESCUING AD CLINICAL TRIALS IMPACTED BY COVID-19 USING MACHINE LEARNING AND EXISTING PLACEBO DATA TO RECOVER TRIAL POWER.** J. Walsh, A. Schuler, D. Bertolini, D. Hall, Y. Pouliot, A. Smith, C. Fisher (Unlearn.ai - San Francisco, USA)

**Background:** Clinical trials are susceptible to enrollment challenges, timeline delays and high failure rates. Alzheimer's Disease (AD) trials can be especially sensitive to regional or global events such as COVID-19 that can amplify these barriers. The risks can be managed retrospectively or prospectively by utilizing machine learning methods and existing placebo data from AD trials to recover power in statistical analyses. **Objective:** Demonstrate how digital twins can mitigate risk and recover/maintain power in AD trials negatively impacted by COVID-19. **Methods:** Digital twins are comprehensive, longitudinal, patient-level placebo records with baseline characteristics and treatment duration matched to those of actual subjects randomized into a study. Digital twins can be generated by a machine learning model trained on placebo subject records from historical AD clinical trials as well as data from observational studies of AD. Because they predict outcomes for individual subjects, digital twins may be used as adjustment covariates to add power in a risk-free way that preserves type I error rate control, unlike many other methods of historical borrowing. We used digital twins to re-analyze a past AD clinical trial of docosahexaenoic acid (DHA) (1) to estimate their ability to restore power when the target sample size cannot be achieved. The 18-months study originally enrolled 402 subjects with mild to moderate AD randomized 3:2 to active and placebo groups; the co-primary endpoints were the 11-component Alzheimer's Disease Assessment Scale (ADAS-Cog11) and the Clinical Dementia Rating Sum-of-Boxes (CDR-SB). No statistically significant results were obtained on any of the endpoints. A disruptive event like COVID-19 was modeled in two ways. In the first approach, 50% of the latter half of subjects enrolled were randomly removed from the study. In the second approach, 25% of all visits after the midpoint of the study were randomly removed. In each scenario these changes were made in addition to the 32% observed drop-out rate which was in agreement with the rate assumed in the original study design, and in both truncated scenarios only 50% of enrolled subjects completed the study. For each enrolled subject, digital twin data was created using that subject's baseline data. The predicted outcomes of these digital twins were averaged for

each subject for both primary endpoints to compute values for adjustment covariates. These adjustment variates were integrated into a repeated measures analysis of treatment effects following the statistical analysis plan of the original study. The truncated scenario analyses were repeated multiple times and results were averaged. **Results:** With the use of digital twins, the confidence interval widths for the co-primary endpoints were maintained at nearly the same values in the truncated vs. the original trial. The two scenarios considered achieved nearly the same minimum detectable effects at 80% power for both co-primary endpoints, suggesting a robustness to missed visits in the repeated measures analysis with digital twins. These effects were 3.03 (reduced enrollment) and 3.01 (reduced visits) vs. 2.95 (original study) for ADAS-Cog11 and 0.99 (reduced enrollment) and 0.98 (reduced visits) vs. 0.93 (original study) for CDR-SB. These indicate that even in these scenarios with significant impact, the ability of the study to measure meaningful results is maintained. **Conclusions:** Our retrospective analyses indicate that the use of digital twins can recover or maintain power and mitigate the impact of stopping an AD trial before enrollment target was reached. Pairing an innovative use of machine learning with proven statistical methods, digital twins can be easily integrated into protocols. Digital twins are a ready-for-use solution for AD trials impacted by COVID-19, either to mitigate risk for ongoing studies or as a precautionary measure for planned studies to maximize power. Reference: 1. Docosahexaenoic Acid Supplementation and Cognitive Decline in Alzheimer Disease; Quinn et al, JAMA. 2010 Nov 3; 304(17): 1903–1911.

**LB11: REMOTE MOBILE APP-BASED MEMORY ASSESSMENTS REFLECT TRADITIONAL MEMORY MEASURES AND ARE SENSITIVE TO MEASURES OF TAU PATHOLOGY.** D. Berron<sup>1</sup>, F. Andersson<sup>2</sup>, S. Janelidze<sup>1</sup>, E. Stomrud<sup>2</sup>, O. Hansson<sup>1</sup> ((1) *Clinical Memory Research Unit, Department Of Clinical Sciences Malmö, Lund University - Lund, Sweden*; (2) *Memory Clinic, Skåne University Hospital - Malmö, Sweden*)

**Objectives:** The medial temporal lobe is particularly affected by AD pathology. One of the earliest anatomical sites where tau pathology can be detected is the transentorhinal region which has been associated with mnemonic discrimination of similar objects. Recent studies showed that object mnemonic discrimination was associated with fluid and imaging measures of tau pathology. Here we set out to evaluate the relationship of an adaptation of this memory task for mobile devices in an unsupervised setting with neuropsychological measures and biomarkers of tau pathology. **Methods:** 59 non-demented individuals of the Swedish BioFINDER study (34%  $\beta$ -amyloid positive, mean age 62yrs, 59% female) participated in on-site memory assessments and underwent MRI and [18F]RO948 tau-PET scans. In addition, participants completed up to 12 remote memory tests using their own mobile devices. Here we report memory performance as a mean estimate across the first two remote sessions. **Results:** Remote memory assessments correlated with computerized on-site assessments using a similar task for object-and-scene memory (Berron et al., 2018) ( $r=0.72$ ,  $p<.001$ ) as well as with delayed word recall performance ( $r=-0.57$ ,  $p<.001$ ). Remote object but not scene memory showed a significant relationship with tau-PET SUVR in the transentorhinal region ( $\beta=-0.11$ ,  $SE=0.05$ ,  $p=.039$ ) and plasma pTau217 levels ( $\beta=-0.04$ ,  $SE=0.017$ ,  $p=.047$ ).

Finally, remote object memory was lower in individuals with thinner cortex in the transentorhinal region ( $\beta=0.31$ ,  $SE=0.11$ ,  $p=.009$ ). **Conclusions:** Our results demonstrate that remote and unsupervised memory assessments via mobile devices are (i) comparable to supervised computerized on-site testing, (ii) show a relationship with traditional neuropsychological measures for memory, and (iii) are sensitive to underlying tau pathology.

**LB12: DEMENTIAS PLATFORM UK CLINICAL STUDIES AND GREAT MINDS REGISTER: A TARGETED BRAIN HEALTH VOLUNTEER RE-CONTACT PLATFORM.** I. Koychev, S. Young, M. Ben Yehuda, J. Gallacher (*University Of Oxford - Oxford, United Kingdom*)

**Background:** The case for de-risking neurodegenerative research and development through highly informative experimental medicine studies early in the disease process is strong. Such studies depend on the availability of genetic as well as high-granularity, longitudinal, phenotypic data in healthy aging individuals who can be recruited into early phase trials on the basis of their perceived dementia risk. Until now the creation of such research infrastructure has been hampered by the lack of expense and time required to gather the rich longitudinal data needed for adequate risk stratification. Dementias Platform UK (DPUK) is a public-private partnership that brings together data from over 40 cohorts in a standardised framework, which represents an until now unavailable opportunity to create such a resource through a streamlined brain health re-contact platform based on existing cohorts, as well as prospectively collected data. **Objectives:** To develop a brain health volunteer recruitment resource allowing targeted recruitment into studies on the basis of genotypic and longitudinal phenotypic information. **Methods:** The DPUK re-contact platform consists of an opt-in (Great Minds, GM) and an opt-out component (Clinical Studies register, CSR). GM requires invited DPUK cohort participants to consent to targeted re-contact at the GM website and then to provide self-reported demographic and medical history information relevant to recruitment into clinical studies. Participants complete prospective browser- and smartphone-based cognitive tests and are given the option for remote genetic and actigraphy testing. The GM data is linked to the retrospective DPUK cohort dataset, including genotypic and longitudinal phenotypic data. The CSR is a solution for cohorts explicitly allowing targeted re-contact. Approved studies provide pre-screening criteria on the basis of the CSR/GM dataset, and individuals meeting these criteria are offered participation directly (GM) or through the parent DPUK cohort (CSR). Descriptive statistics will be used to summarise the outcomes relevant to the number of participants engaged with the register. Its sample size is not defined but is limited by the size of the DPUK parent cohorts. **Results:** The register was launched in January 2018 and in September 2020 its GM and CSR membership stands at 3,516 and 53,245 individuals respectively. For the CSR, 31561 individuals have longitudinal cognitive data and 20,419 have had GWAS phenotyping. The presentation will provide an overview of the current demographics of both registers as well as a live demonstration of the GM study feasibility tool. **Conclusion:** Stratified recruitment into early phase experimental medicine studies is key to de-risking and increasing investment in neuroscience research and development. The DPUK re-contact platform described provides a novel opportunity to accelerate

research into novel dementia treatment through the linkage of highly characterised individuals with researchers.

**LB13: SEROTONIN RECEPTOR 7 (5-HT7R) AS A NOVEL TARGET FOR TREATMENT OF ALZHEIMER'S DISEASE.**

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**Background:** Multiple neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, as well as amyotrophic lateral sclerosis are characterized by the formation and deposition of protein aggregates, either inside or outside of neurons, within certain brain areas. In particular, aggregation of the microtubule-associated protein, Tau, leads to the development of so-called tauopathies. Tauopathies are generally characterized by the deposition of hyperphosphorylated, aggregated Tau protein within neurons. The most prominent members in this class of diseases are Alzheimer's disease and frontotemporal lobar degeneration, which cause the majority of dementia cases worldwide. Pathological changes in serotonergic signaling have been associated with tauopathy etiology, but the underlying mechanisms remain poorly understood. **Objectives:** In the present study we investigated a potential role of the serotonin receptor 5-HT7 (5-HT7R) in Tau-related pathology. **Methods:** We analyzed how 5-HT7R modulates Tau hyperphosphorylation, Tau aggregation, and the formation of highly bundled Tau structures (HBTS) in neuroblastoma cells and in primary neuronal cultures. To this end, 5-HT7R was co-expressed with the human Tau[R406W] mutant associated with inherited forms of frontotemporal dementia. We also studied the role of the 5-HT7R in mouse models of tauopathy using biochemical, microscopic, electrophysiological and behavioral approaches. **Results:** We showed that the constitutive 5-HT7R activity is required for Tau hyperphosphorylation and formation of highly bundled Tau structures (HBTS) through G-protein-independent, CDK5-dependent mechanism. We also showed that 5-HT7R physically interacts with CDK5. At the systemic level, 5-HT7R-mediated CDK5 activation induces HBTS leading to neuronal death, reduced long-term potentiation (LTP), and impaired memory in mice. Specific blockade of constitutive 5-HT7R activity with an inverse agonist SB-269970 in neurons that overexpressed Tau[R406W] prevents Tau hyperphosphorylation, aggregation, and neurotoxicity. Moreover, 5-HT7R knockdown in the prefrontal cortex fully abrogates Tau[R406W]-induced LTP deficits and memory impairments. Because SB-269970 is not clinically approved, we screened several FDA-approved drugs with a chemical structure similar to SB-269970. Using different approaches, including pharmacokinetic analysis, high-throughput in vitro screening for Tau aggregation, biochemical assays, and behavioral analysis in a mouse model of tauopathy we identified two anti-psychotic drugs as most promising repurposing drug candidates. Supporting evidence was also provided by our meta-analysis of a comprehensive German health insurance database that revealed lower occurrence of dementia in patients treated with one of anti-psychotics being inverse agonist of 5-HT7R in comparison to patients treated with anti-psychotic drugs without 5-HT7R inverse agonism. **Conclusion:** In the present study, we demonstrated that the constitutive activity of 5-HT7R induced Tau hyperphosphorylation and formation of HBTS through a G-protein-independent, CDK5-dependent mechanism. This

receptor-mediated CDK5 activation resulted in increased neurotoxicity, attenuated LTP, and impaired memory – hallmarks of multiple tauopathies. Blockade of the constitutive 5-HT7R activity ameliorated the pathological consequences of Tau hyperphosphorylation and aggregation. These findings highlighted 5-HT7R as a previously unrecognized therapeutic target for tauopathy treatments. Our results also demonstrate that repurposing drugs with inverse agonistic properties towards the 5-HT7R represents a highly promising strategy in the treatment of tauopathy, including Alzheimer's disease and frontotemporal dementia.

**LB14: THE DUAL GLP-1/GIP RECEPTOR AGONIST DA4-JC SHOWS SUPERIOR PROTECTIVE PROPERTIES COMPARED TO LIRAGLUTIDE IN THE APP/PS1 MOUSE MODEL OF ALZHEIMER'S DISEASE.**

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**Introduction:** The dual GLP-1/GIP receptor agonist DA4-JC shows superior protective properties compared to liraglutide in the APP/PS1 mouse model of Alzheimer's disease. Mark Maskerya, Elizabeth Mary Gouldingb, Simon Genglerb, Josefine Ulrikke MelchiorSend, Mette M. Rosenkilded, Paul Edisone, Christian Hölscherb,c. a) Lancaster Medical School, Lancaster University and Department of Neurology, Royal Preston Hospital, UK. b) Neurology department, Shanxi Medical University, Taiyuan, Shanxi province, China. c) Research and Experimental Center, Henan University of Chinese Medicine, Zhengzhou, Henan province, China. d) Dept. of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark. e) Department of Medicine, Imperial College London, London, UK. **Background:** Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which there is no cure. Type II diabetes is a risk factor for developing AD, and several drugs have been developed to treat diabetes. In previous studies, analogues of glucagon-like peptide-1 (GLP-1) that are on the market as treatments for type 2 diabetes have shown good neuroprotective effects in animal models of AD. We have tested liraglutide, an analogue of glucagon-like peptide 1 (GLP-1) in patients with MCI/Alzheimer's disease and present the results at this meeting (oral presentation by Dr. Paul Edison). The drug has shown good protective effects in key markers of AD. In addition, Glucose-dependent insulinotropic polypeptide (GIP) analogues have shown good effects in animal models of AD. Novel dual GLP-1/GIP receptor agonists have been developed by us that can activate both receptors and that can enter the brain at a higher rate than drugs that had been developed to treat diabetes (Hölscher, 2020; Salameh et al., 2020). Here, we tested the protective effects of DA4-JC in direct comparison with liraglutide in the APP/PS1 mouse model of AD. **Methods:** We tested the activity of the dual GLP-1/GIP agonist DA4-JC that has a cell penetrating sequence added to enhance blood-brain barrier penetration (Salameh et al., 2020). We tested the receptor activation properties of DA4-JC on receptors in COS-7 cells transfected with GLP-1, GLP-2, GIP and glucagon receptors to measure cAMP levels. Then, we estimated the optimal dose in a dose-response test in the APP/PS1 mouse model of AD. Doses of 0.1, 1, or 10nmol/kg bw ip. once-daily for six weeks were tested to analyse the effect on amyloid plaque load in the brain and chronic inflammation as measured by quantification of astrocyte and microglia activation. We then tested liraglutide and DA4-JC head-to-head in the APP/PS1 transgenic mouse model of AD. Memory formation in the water maze, synaptic



plasticity (LTP) in area CA1 of the hippocampus using in vivo electrophysiology techniques, amyloid plaque load, and chronic inflammation was evaluated using histological and western blot techniques. **Results:** We show in a receptor activation study that when measuring cAMP levels, DA4-JC has balanced activity on both GLP-1 and GIP receptors but does not activate GLP-2 or Glucagon receptors. A dose-response study in the APP/PS1 mouse model of AD showed a dose-dependent drug effect on both the chronic inflammation response (activated astroglia and microglia) and the reduction of amyloid plaques in the brain. The most effective dose was 10nmol/kg bw ip. once-daily for 6 weeks. When comparing DA4-JC with the GLP-1 analogue liraglutide at equal doses of 10nmol/kg bw ip. once-daily for 8 weeks in the APP/PS1 mouse model of AD, DA4-JC was more effective in reversing memory loss in the water maze task, was superior in enhancing synaptic plasticity (LTP) in the hippocampus, in reducing amyloid plaque load in the cortex, and in lowering pro-inflammatory cytokine levels of TNF-alpha and IL-1 $\beta$  in the brain compared to liraglutide. **Conclusion:** The results show good neuroprotective effects of liraglutide and DA4-JC in reducing key pathological processes linked to AD, and demonstrate that the dual GLP-1/GIP receptor agonist DA4-JC is more effective in treating AD than a single GLP-1 receptor agonist. Funded in part by the Alzheimer Society UK. **References:** Hölscher C (2020) Brain insulin resistance: role in neurodegenerative disease and potential for targeting. Expert opinion on investigational drugs, 29:333-348. Open Access review; Salameh TS, Rhea EM, Talbot K, Banks WA (2020) Brain uptake pharmacokinetics of incretin receptor agonists showing promise as Alzheimer's and Parkinson's disease therapeutics. *Biochemical Pharmacology*, 180:114187. DOI:10.1016/j.bcp.2020.114187

**LB15: IRREGULAR SLEEP-WAKE RHYTHM DISORDER IN ALZHEIMER'S DISEASE: SAMP8 MOUSE STRAIN AS AN ANIMAL MODEL AND EFFICACY OF THE DUAL OREXIN (HYPOCRETIN) RECEPTOR ANTAGONIST LEMBOREXANT.** C. Beuckmann<sup>1</sup>, H. Suzuki<sup>1</sup>, E. Musiek<sup>2</sup>, T. Ueno<sup>1</sup>, T. Sato<sup>1</sup>, Y. Osada<sup>1</sup>, M. Moline<sup>3</sup> ((1) Eisai Co., Ltd., Tsukuba - Ibaraki, Japan; (2) Washington University School Of Medicine - St. Louis, USA; (3) Eisai Inc. - Woodcliff Lake, USA)

**Background:** Irregular sleep-wake rhythm disorder (ISWRD), a circadian rhythm sleep disorder associated with Alzheimer's disease (AD), is characterized by fragmented sleep at night, involuntary sleep bouts during the day, and a general irregularity of circadian pattern. The prominence of daytime symptoms and the irregularity of the sleep-wake rhythms distinguish ISWRD from insomnia. There are no preclinical animal models or approved drug treatments for ISWRD, or clear evidence of the pathophysiology. There is some evidence however, that elevated CSF levels of orexin-A, a wake-promoting neuropeptide, could be one of the causes for sleep disturbances in AD. Lemborexant, a dual orexin receptor antagonist approved for the treatment of insomnia disorder, is currently under development for treating ISWRD in patients with AD. **Objectives:** Senescence-accelerated mouse prone-8 (SAMP8) mice are a model of rapid aging and AD. Here we test them as a model for ISWRD in AD and assess the effect of lemborexant on sleep-wake and circadian rhythm behaviors. **Methods:** Male SAMP8 and control senescence-accelerated mouse resistant-1 (SAMR1) mice at around 21-22 weeks of age were kept under a 12:12 light:dark cycle. Mice

were administered vehicle or lemborexant orally at light onset; plasma lemborexant and circadian cerebrospinal fluid (CSF) orexin-A concentrations were assessed over 24 hours. Sleep-wake behavior and running wheel activity were evaluated under baseline and vehicle- (n=8) as well as lemborexant-dosed (3 and 30 mg/kg, n=8 each) conditions. **Results:** Plasma lemborexant concentrations were approximately similar between strains. Peak and nadir timing of CSF orexin-A concentrations was approximately opposite between strains, with SAMP8 mice showing peak CSF orexin-A concentrations during lights-on, which is unusual for nocturnal animals. During lights-on, the habitual resting phase for mice, SAMP8 mice showed less non-rapid eye movement (REM) and REM sleep than SAMR1 mice, corresponding to sleep disturbances in ISWRD patients at night. Lemborexant treatment normalized wakefulness and non-REM sleep in SAMP8 mice similar to the level of vehicle-treated SAMR1 mice. During lights-off (the equivalent of daytime in humans), lemborexant-treated SAMR1 mice showed increased non-REM sleep, while in contrast, lemborexant-treated SAMP8 mice displayed increased wakefulness time through consolidation, one of the first indications that an orexin receptor antagonist can increase wakefulness during the active phase, one of the desired clinical outcomes in ISWRD patients. SAMP8 mice also showed distinct differences in electroencephalogram architecture versus SAMR1 mice, most notably a tendency to increased slow wave intensity (delta power) during wakefulness, on which lemborexant however had no influence. SAMP8 mice also exhibited increased wheel running during lights-on, concordant with the reduced sleep results. Lemborexant treatment reduced activity during lights-on and increased activity in the latter half of lights-off, demonstrating a corrective effect on overall diurnal rhythm. Lemborexant also delayed acrophase of wakefulness in both strains by roughly an hour within the lights-off period, presumably by consolidating wakefulness during the habitual active time of the day. **Conclusion:** These findings suggest that SAMP8 mice are a suitable model for preclinically studying ISWRD in AD, and indicate the potential of lemborexant to correct some of the ISWRD-like aberrances. The results therefore provide preclinical rationale for evaluation of lemborexant in patients with AD and ISWRD.

**LB16: INDUCTION OF PHAGOCYtic MONOCYTES BY A PROTEOSOME-BASED ADJUVANT (PROTOLLIN) FOR THE TREATMENT ALZHEIMER'S DISEASE.** P. Kolypetri<sup>1,3</sup>, D. Frenke<sup>1,2</sup>, O. Butovsky<sup>1</sup>, H.L. Weiner<sup>1,3</sup> ((1) Department of Neurology, Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; (2) Department of Neurobiology George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel; (3) Evergrande Center for Immunologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA)

**Background:** The primary initiating event in Alzheimer's disease (AD) pathogenesis is considered to be the accumulation of amyloid beta (A $\beta$ ) in the brain resulting from defects in A $\beta$  production and clearance. Our previous studies have shown that intranasal administration of Protollin - a proteosome-based adjuvant composed of outer membrane proteins from *Neisseria meningitidis* and LPS from *Shigella flexneri* - leads to reduction of insoluble, fibrillar and soluble A $\beta$  accumulation in the brain by activation of CD11b+ myeloid cells in young and old AD mice (1-4). **Objectives:** We investigated the effects

of nasal Protollin on activation and recruitment of peripheral monocytes in the brains of WT and AD mice as well as on their phagocytic ability against A $\beta$ 1-42. We also investigated the impact of Protollin on the phagocytic ability of human CD14<sup>+</sup> monocytes against A $\beta$ 1-42 in vitro. **Methods:** C57BL/6 and transgenic (Tg) AD-CX3CR1GFP bone marrow (BM) chimera mice were intranasally treated for two and six weeks with Protollin. Phenotypic and functional analysis of splenic monocytes was performed by flow cytometry, Nanostring nCounter Technology and a phagocytosis assay ex vivo. In the brain, quantification of infiltrating monocytes was performed by flow cytometry and confocal imaging. Stereotactic injections of HiLyteTM Fluor488-labeled A $\beta$ 1-42 in the hippocampus were performed to assess the phagocytic ability of infiltrating monocytes. The phagocytic ability of Protollin-treated FACS-sorted human CD14<sup>+</sup> monocytes against HiLyteTM Fluor488-labeled A $\beta$ 1-42 was performed using confocal imaging and flow cytometry. **Results:** Nasal Protollin administration in WT mice for two weeks increased the frequency and absolute numbers of Ly6Chigh monocytes within the spleen. Splenic Ly6Chigh monocytes expressed higher levels of SCARA-1, TLR2 and TLR4 and acquired a distinctive mRNA activation signature as defined by the Nanostring nCounter technology. Functionally, Protollin-treated splenic Ly6Chigh monocytes had a higher phagocytic ability against the HiLyteTM Fluor488-labeled A $\beta$ 1-42 peptide. In WT animals, the frequency and absolute numbers of brain infiltrating monocytes were significantly increased after two weeks of Protollin treatment. An increased number of A $\beta$ 1-42<sup>+</sup> monocytes in the brain was observed following stereotactic injection of HiLyteTM Fluor488-labeled A $\beta$ 1-42 into the hippocampus of Protollin-treated animals compared to controls. We further investigated the recruitment of peripheral monocytes into the brains of Protollin-treated Tg-AD-CX3CR1GFP BM chimera mice upon nasal treatment. Protollin-treated chimera mice had higher numbers of infiltrating CD11b<sup>+</sup>CX3CR1<sup>+</sup> cells into the hippocampal regions of the brain after both two and six weeks of treatment. Confocal imaging showed that infiltrating monocytes accumulated around A $\beta$  plaques, exhibited intracellular immunoreactivity to A $\beta$  and lead to a significant reduction in the number of plaques at both two and six weeks post treatment. Finally, we addressed the effect of in vitro Protollin treatment of human CD14<sup>+</sup> monocytes. Confocal imaging and flow cytometry analysis of Protollin-treated human CD14<sup>+</sup> monocytes showed an increased uptake of HiLyteTM Fluor488-labeled A $\beta$ 1-42 in the Protollin-treated group compared to controls. **Conclusion:** Our data demonstrates that 1) nasal Protollin induces the activation and recruitment of phagocytic monocytes to the brains of both WT and AD mice and 2) Protollin reprograms human CD14<sup>+</sup> monocytes towards a phagocytic phenotype which results in increased A $\beta$  uptake in vitro. Protollin has been given safely to human subjects as part of vaccination programs. Given its safety profile and effect on both animal models of AD and human monocytes, a phase 1 single ascending dose trial of nasal Protollin in early AD is planned. Protollin represents a novel immunologic approach to clear A $\beta$  in AD. **References:** 1. D. Frenkel, R. Maron, D. S. Burt, H. L. Weiner, Nasal vaccination with a proteosome-based adjuvant and glatiramer acetate clears beta-amyloid in a mouse model of Alzheimer disease. *Journal of Clinical Investigation* 115, 2423-2433 (2005). 2.D. Frenkel et al., A nasal proteosome adjuvant activates microglia and prevents amyloid deposition. *Ann. Neurol.* 63, 591-601 (2008). 3. D. Frenkel et al., Scara1 deficiency impairs clearance of soluble

amyloid-beta by mononuclear phagocytes and accelerates Alzheimer's-like disease progression. *Nat Commun* 4, 2030 (2013). 4. V. Lifshitz et al., Immunotherapy of cerebrovascular amyloidosis in a transgenic mouse model. *Neurobiol. Aging* 33, 432 e431-432 e413 (2012).

**LB17: MULTIDOMAIN INTERVENTION AND/OR OMEGA 3 IN NON-DEMENTED SUBJECTS ACCORDING TO PLASMA A $\beta$ 42/40 RATIO: COGNITIVE IMPACT AT 3 AND 5 YEARS IN A SUBGROUP ANALYSIS FROM THE RANDOMIZED CLINICAL MAPT TRIAL.** J. Delrieu<sup>1</sup>, B. Vellas<sup>1</sup>, C. Cantet<sup>1</sup>, R. Bateman<sup>2</sup>, S. Andrieu<sup>1</sup> ((1) *Toulouse University Hospital And Inserm Umr 1027 - Toulouse, France;* (2) *Knight Alzheimer Disease Research Center, Washington University School Of Medicine, St. Louis, Mo - Washington, USA*)

**Background:** The MAPT (Multidomain Alzheimer Prevention Trial) study has tested cognitive effect of omega 3 polyunsaturated fatty acid supplementation (omega 3) and multidomain intervention (MI) in non-demented subjects with memory complaint. In the total population, MI and omega 3 had no significant effect on cognitive decline over 3 years (1). However, MI alone or combined with omega 3, showed in MAPT cognitive effect in subjects with positive amyloid PET (2). Screening of non-demented subjects by amyloid PET is difficult to generalize in real-world settings given its cost and limited access to radioligands. Blood-based biomarkers are less invasive and cost-effective options for identification of at-risk subjects eligible for these interventions. Multiple groups have demonstrated that the ratio of plasma A $\beta$ 42/40 assays using both mass spectrometry and immunoassay methods provides a sensitive and reliable measure of amyloid status that predicts future conversion to positive amyloid PET and correlates with CSF A $\beta$ 42/40. **Objectives:** The objectives were to assess the cognitive impact of MAPT interventions at 36 and 60 months - after 2-year interruption of these interventions - in non-demented subjects according to amyloid blood status. **Methods:** MAPT was a multicenter, randomized, placebo-controlled study involving 14 sites in France. MAPT and MAPT-PLUS studies assessed the efficacy of omega 3 and MI on cognition respectively at 36 and 60 months. In a subgroup analysis from these studies, amyloid status was defined by plasma A $\beta$ 42/40 ratio < 0.0107. The analysis was conducted in the intention-to-treat (ITT, n = 483) and per-protocol populations (n = 457). All subjects included in the present analysis were non-demented, had memory complaints, limitation in one instrumental activity of daily living, or slow gait, and amyloid status defined by blood-based biomarkers (mass spectrometry). Participants were randomly assigned (1 : 1 : 1 : 1) to the combined intervention, MI, omega 3, or placebo only groups. The MI consisted of group sessions focusing on cognitive stimulation, physical activity, and nutrition advices. The primary outcome was a change from baseline in 36 and 60 months measured with a cognitive composite Z score. **Results:** The ITT population included 483 subjects (161 positive and 322 negative amyloid subjects defined by based-blood biomarkers). In the positive amyloid ITT sample, 128 (79.5%) and 84 (52.2%) subjects respectively completed 36 and 60-month visits. In the negative amyloid ITT sample, 273 (84.8%) and 215 (66.8%) subjects completed 36 and 60-month visits. In the positive amyloid ITT population, the four groups differed in total SPPB (p = .0117) but did not differ in the cognitive composite score (p = .4467). In the subjects with negative amyloid status, the four groups differed in plasma

A $\beta$ 42/40 ratio ( $p = .0322$ ) and DHA ( $p = .0310$ ) but did not differ in terms of cognitive composite score ( $p = .6723$ ). No effect was observed in the negative amyloid group ( $n = 322$ ) at 36 and 60-month visits. In the ITT positive amyloid group ( $n = 161$ ), we observed a non-significant difference of 0.2818 ( $p = .0690$ , 95% CI = [0.0190 to 0.5446]) in the change of composite score between the MI plus omega 3 and placebo groups at 36 months. In the per-protocol positive amyloid population ( $n = 154$ ), we showed a significant difference between the combined interventions and the placebo at 36 months ( $p = .0195$ , 0.3747, 95% CI = [0.1055 to 0.6439]). **Conclusion:** These MAPT findings suggest a cognitive benefit of MI plus omega 3 at 36 months in positive amyloid subjects but not at 60 months after 2 years of discontinuing non-pharmacological program. Amyloid blood biomarkers could offer opportunities to screen non-demented subject in future dementia prevention programs and also widespread brain amyloidosis identification of subjects with memory complaint in primary care. This promising trend needs to be confirmed before using blood biomarkers in practice and screening non-demented subjects in preventive trials. **Trial registration:** ClinicalTrials.gov Identifier: NCT01513252. **References:** 1. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol.* 2017 May;16(5):377–89. 2. Delrieu J, Payoux P, Carrié I, Cantet C, Weiner M, Vellas B, et al. Multidomain intervention and/or omega-3 in nondemented elderly subjects according to amyloid status. *Alzheimers Dement J Alzheimers Assoc.* 2019 Sep 23.

**LB18: PLASMA P-TAU217 PREDICTS LONGITUDINAL AMYLOID ACCUMULATION, TAU BURDEN, BRAIN ATROPHY AND COGNITIVE DECLINE IN EARLY ALZHEIMER'S DISEASE.** J. Pereira<sup>1,2</sup>, S. Janelidze<sup>1</sup>, S. Erik<sup>1</sup>, S. Palmqvist<sup>1</sup>, J. Dage<sup>3</sup>, N. Mattsson-Carlgrén<sup>1</sup>, O. Hansson<sup>1</sup> ((1) *Lund University - Lund, Sweden*; (2) *Karolinska Institute - Stockholm, Sweden*; (3) *Eli Lilly And Company - Indianapolis, USA*)

**Background:** New evidence shows that plasma biomarkers can potentially be used for the diagnosis of Alzheimer's disease (AD). However, it is currently unclear whether they can also be applied as prognostic tools to determine the progression of longitudinal changes associated with AD. **Objectives:** Here we address this question by examining plasma amyloid- $\beta$  42/40 (A $\beta$ 42/40), phosphorylated-tau 181 (P-tau181), phosphorylated-tau 217 (P-tau217) and neurofilament light (NfL) in non-demented individuals who underwent longitudinal amyloid and tau positron emission tomography (PET), magnetic resonance imaging (MRI) and cognitive testing. **Methods:** Blood was collected at baseline from all participants to determine the levels of A $\beta$ 42/40, P-tau181, P-tau217 and NfL. In addition, all subjects underwent longitudinal 18F-RO948 PET, structural MRI and cognitive assessment, and a subsample also had longitudinal 18F-flutemetamol PET scans. Linear mixed effects models and voxel-wise analyses were applied to assess the relationship between plasma biomarkers and longitudinal changes in brain imaging measures and cognition. In addition, to compare the goodness of fit between the different models, we used an analysis of variance and the Bayesian Information Criterion (BIC). **Results:** Our results show that plasma P-tau217 predicts increases in amyloid ( $t = 2.458$ ,  $p = 0.017$ ) and tau

PET signals ( $t = 2.981$ ,  $p = 0.004$ ), medial temporal atrophy (temporal cortical thinning:  $t = -4.433$ ,  $p < 0.001$ ; hippocampal atrophy:  $t = -4.112$ ,  $p < 0.001$ ) and global cognitive decline ( $t = -2.871$ ,  $p = 0.005$ ). The results for the other plasma markers were more variable, with plasma A $\beta$ 42/40 predicting amyloid ( $t = -3.222$ ,  $p = 0.002$ ) and tau PET signal increases ( $t = -2.997$ ,  $p = 0.003$ ) as well as cognition ( $t = 2.354$ ,  $p = 0.020$ ), whereas P-tau181 predicted hippocampal atrophy ( $t = -2.711$ ,  $p = 0.008$ ) and cognitive decline ( $t = -2.995$ ,  $p = 0.003$ ), and finally NfL predicted brain atrophy (temporal cortical thinning:  $t = -2.373$ ,  $p = 0.019$ ; hippocampal atrophy:  $t = -4.153$ ,  $p < 0.001$ ) and tau PET increases ( $t = 2.365$ ,  $p = 0.020$ ). The comparison between the significant models showed that the ones that included P-tau217 as a predictor had a significantly better fit to the data ( $p < 0.001$ ) reflected by lower BIC values compared to the other models. **Conclusion:** Altogether, these findings suggest that plasma P-tau217 could be useful in clinical trials to determine whether an individual is on the pathophysiological pathway of AD.

**LB19: REGIONAL EFFECTS OF GANTENERUMAB ON NEUROIMAGING BIOMARKERS IN THE DOMINANTLY INHERITED ALZHEIMER NETWORK TRIALS UNIT (DIAN-TU).** A. Mccullough<sup>1</sup>, B. Gordon<sup>1</sup>, C. Chen<sup>1</sup>, G. Wang<sup>1</sup>, G. Klein<sup>2</sup>, R. Bateman<sup>1</sup>, T. Benzinger<sup>1</sup> ((1) *Washington University School Of Medicine - Saint Louis, USA*; (2) *Roche - Basel, Switzerland*)

**Background:** The Dominantly Inherited Alzheimer Network (DIAN) is an international research effort to study Alzheimer's Disease caused by mutations in PSEN1, PSEN2, APP genes which lead to an overproduction of beta-amyloid. This rare form of the disease leads to dementia while individuals are relatively young, typically their 30's to 50's. The DIAN trials unit (DIAN-TU) is the clinical research arm of DIAN designed to evaluate disease modifying treatments in this unique population. The readout of the first two drug arms (Gantenerumab and Solanezumab) occurred in the Spring of 2020. The top line results showed that Gantenerumab successfully altered levels of beta-amyloid as measured by both cerebrospinal fluid and positron emission tomography (PET) imaging. **Objectives:** The longitudinal neuroimaging data collected from DIAN-TU participants provide a rich multimodal picture of pathology evolution over a 48-month treatment period. The current analyses investigate the neuroimaging outcome variables from longitudinal [11C] Pittsburgh Compound B (PiB) PET, [18F] fluorodeoxyglucose (FDG) PET, and structural MRI, and examine key regional variability of estimated drug effects. **Methods:** Participants carrying ADAD mutations were randomized into drug ( $n=52$ ) or placebo arms ( $n=40$ ) and received up to 48 months of drug treatment with assessments at baseline, 12, 24, and 48 months. T1-weighted structural images were processed using FreeSurfer 5.3 to generate cortical and subcortical regions of interest. The PET Unified Pipeline (PUP) was used to generate standardized uptake value ratios (SUVRs) relative to cerebellar cortex. Beta-amyloid was measured using the 40-70 min post-injection window of [11C]-PiB PET. Brain metabolism was measured with [18F]-FDG PET with data from 30-60 min post-injection window. Linear mixed effects models were implemented to determine the significance of the drug \* time interaction model component while accounting for sex and clinical status at baseline. Clinical status at each visit was determined using the Clinical Dementia Rating scale. **Results:** Solanezumab did not demonstrate any significant effect

on mean cortical levels of beta-amyloid. As such no further analyses of other modalities or regions are reported. Treatment with Gantenerumab significantly reduced the longitudinal increase of mean cortical PiB PET signal ( $\beta = -.06$ ,  $SE = .01$ ,  $t = -5.83$ ,  $p < .0001$  [benefit is neg.]), but did not affect the additional trial imaging endpoints, which were reduced longitudinal decrease in precuneus FDG ( $\beta = -.01$ ,  $SE = .005$ ,  $t = -1.579$ ,  $p = .118$  [benefit is pos.]) or precuneus thickness ( $\beta = .003$ ,  $SE = .007$ ,  $t = 0.388$ ,  $p = .69$  [benefit is pos.]). When examining individual regions, the strength of the drug effect on longitudinal PiB PET values varied considerably with the most significant drug effects seen in the dorsal striatum (caudate  $\beta = -.141$ ; putamen  $\beta = .151$ ), thalamus ( $\beta = -.109$ ), pallidum ( $\beta = -.099$ ), and anterior cingulate (rost. ant. cingulate  $\beta = -.098$ ; caud. ant. cingulate  $\beta = -.088$ ) regions. When this spatial pattern of effect was compared with regional mean baseline PiB PET levels, subcortical structures and anterior cingulate regions also displayed large levels of baseline PiB PET signal. However, more posterior cortical structures displaying equally large baseline PiB PET signal showed noticeably smaller estimated drug effects (precuneus  $\beta = -.063$ ; posterior cingulate  $\beta = -.07$ ; isthmus cingulate  $\beta = -.051$ ). Regions that displayed the highest estimated drug effects in PiB PET were investigated as potential candidates for displaying effects in FDG or MRI outcomes. No statistically significant effects were found in cortical (rost. ant. cingulate [FDG  $\beta = .004$ , thickness  $\beta = -.001$ ]; caud. ant. cingulate [FDG  $\beta = -.003$ , thickness  $\beta = -.005$ ]) or subcortical structures (caudate [FDG  $\beta = .001$ , volume  $\beta = -11.2$ ]; putamen [FDG  $\beta = .007$ , volume  $\beta = -9.92$ ]; thalamus [FDG  $\beta = .002$ , volume  $\beta = -32.5$ ]; Pallidum [FDG  $\beta = .002$ , volume  $\beta = -5.5$ ]). **Conclusion:** Gantenerumab successfully lowered levels of beta-amyloid as indexed by PiB PET. The greatest effect was seen in the basal ganglia and medial frontal regions of the brain with more modest, albeit significant, effects in posterior parietal regions. High amounts of baseline PiB PET signal yet relatively smaller estimated effects in the posterior parietal regions suggests that drug effects are not solely proportional to baseline levels of pathology. These results could be driven by variability in blood brain barrier permeability across the brain leading to differential local drug concentrations, or by Gantenerumab having a differential impact on diffuse versus dense core beta-amyloid plaques. As Gantenerumab is specifically expected to impact beta-amyloid levels and potentially impact neurodegeneration in a downstream manner, the 48-month duration of the study may have not captured a long enough period of disease progression to detect measurable downstream pathology changes. Although PiB PET levels were significantly attenuated in the trial, these levels remained elevated relative to mutation negative individuals. This raises the additional possibility that a longer duration on treatment, or at a higher dose, are needed before significant changes can be seen using MRI and FDG PET.

**LB20: MODIFICATIONS IN RESPONSE TO DISRUPTION FROM COVID-19 IN ALZHEIMER'S TRIALS.** L. Schneider<sup>1</sup>, K. Messer<sup>2</sup>, R. Thomas<sup>2</sup>, C. Evans<sup>2</sup>, D. Jacobs<sup>2</sup>, S. Jin<sup>2</sup>, J. Kaye<sup>3</sup>, A. Lacroix<sup>2</sup>, Y. Qiu<sup>2</sup>, D. Salmon<sup>2</sup>, M. Sano<sup>4</sup>, K. Schafer<sup>2</sup>, H. Feldman<sup>2</sup> ((1) Keck School Of Medicine Of Usc - Los Angeles, USA; (2) Ucsd - San Diego, USA; (3) Oregon Health Sciences University - Portland, USA; (4) Icahn School Of Medicine At Mt. Sinai - New York, USA)

**Background:** The COVID-19 pandemic disrupted Alzheimer clinical trials forcing investigators to make changes in the

conduct of trials while endeavoring to maintain their validity. Changing ongoing trials carries risks, potential biases, and threats to validity. To understand the effects of exigent modifications due to COVID-19 we examined several scenarios of changes in symptomatic and disease modification trials that could be made. **Objectives:** To show the effects of specific approaches that might be taken in reaction to disruptions from the response to COVID-19 on a trial's conduct, efficiency, potential for biases, and validity. **Methods:** We identified Alzheimer trials affected by the pandemic by searching clinicaltrials.gov for trials active on March 19, 2020, the date of California's «stay at home» order. We also identified subsequent updates and changes to the studies made by sponsors. Many trials were shorter-term symptomatic or longer-term disease modification trials. We then modeled 3 scenarios for each of the two types of trials, symptomatic and disease-modification, using existing trial databases and adjusting enrollment dates, follow-ups, and dropouts to examine the effects of potential COVID-19-related changes. Trial construct 1 was considered a phase II mild to moderate AD symptomatic trial, requiring daily medication for 12 months. For Scenario 1, the base condition, the trial was truncated on March 19. This trial was analyzed with 360 randomized to drug or placebo, 97.5% having completed 3 months, 67% completed 6 months, 45% completed 9 months, and 22% the 12-month endpoint. For Scenario 2, medications were continued until the endpoint at 12 months without providing an extension. This created a condition in which about half who completed month 9 were not included in the month 12 outcomes determination; about 25% missed a month 9 outcome but could have a month 12 assessment; and about 30% missed other outcomes. For Scenario 3 the trial continued with extended medication use beyond 12-months, most often within a 3-month window, so that outcomes would be completed after clinics were reopened. Trial construct 2 was a phase II/III disease modification trial for early AD requiring in-clinic monthly drug infusions with planned outcomes at 18 months. The sample size was 280 participants randomized to either drug or placebo. At the «stay-at-home» date, 50% of participants had completed month 6, 25% month 12, 12% month 18, 24% discontinued, and 64% were unable to receive medication due to COVID-19. For Scenario 1, the trial was truncated on the «stay-at-home» date; for Scenario 2, treatment infusions were stopped for 6 months, during which time outcomes were assessed remotely, after which infusions and in-clinic outcomes assessments were continued. Scenario 3 had infusions interrupted for 6 months as well but without outcomes assessments during the pause. Infusions and in-clinic assessment resumed after 6 months. Simulations were performed for each scenario using resampling methods. The simulations accounted for completion (scenarios described above) and dropout patterns using linear mixed effects models. Two mixed models were assessed: one modeling time as continuous and linear, and one modeling time or follow-up visits as categorical. The statistical power of the scenarios was determined. **Results:** Trial construct 1, symptomatic trial. The planned trial was given a 0.82 statistical power to detect a 2.0-point ADAS-cog difference. As expected, Scenario 1 (truncation) was under-powered at 0.49 and 0.32 for the categorical and continuous time mixed models, respectively. Scenario 2 showed 0.64 and 0.44 power, and Scenario 3 showed 0.77 and 0.50 power for the models, respectively. Trial construct 2, disease modification trial. The planned trial was designed for 0.80 statistical power to detect a 1.85-point ADAS-cog difference, Scenario 1 (truncation) was under-powered at 0.41 and 0.38

using categorical and continuous time models respectively. Scenario 3 showed 0.79 power using either categorical or linear models. Scenario 2 with a categorical model gave 0.81 power, while with a linear model was more efficient showing 0.85 power to detect a 1.85-point difference between treatments. **Conclusions:** These analyses support the idea that disrupted trials under common scenarios can be continued and extended as needed even in the face of dropouts, medication disruptions, missing outcomes, and other exigencies, and that adaptations can be made that maintain the trials validity. Under the scenarios we tested, continuing a trial is substantially better than simply truncating it and analyzing data that were collected. We suggest methods to do this in both symptomatic and disease modification trials although some methods may still be underpowered to detect the originally expected outcomes. These analyses in response to the COVID-19 pandemic provide insight and opportunity to better plan future trials that are resilient to environmental disruptions and changes to the medical, social, and political milieu. **Acknowledgements:** UCSD ADCS U19 AG010483, UCSD P30 AG062429, OHSU P30 AG066518, USC P30 AG066530, USC R01 AG057684, USC R01 AG051346.

**LB21: SUMIFILAM (PTI-125) SIGNIFICANTLY IMPROVES ELEVEN CSF BIOMARKERS IN A RANDOMIZED, PLACEBO-CONTROLLED, ONE-MONTH CLINICAL TRIAL IN ALZHEIMER'S DISEASE PATIENTS.** H.Y. Wang<sup>1</sup>, Z. Pei<sup>1</sup>, K.C. Lee<sup>1</sup>, Y. Gonzalez-Rojas<sup>2</sup>, T. Doehner<sup>3</sup>, J. Puente<sup>3</sup>, P. Sciarra<sup>4</sup>, B. Beck<sup>4</sup>, E. Lopez-Brignoni<sup>5</sup>, B. Nikolov<sup>5</sup>, C. Crowley<sup>6</sup>, N. Friedmann<sup>6</sup>, L. Burns<sup>6</sup> ((1) City University Of New York School Of Medicine - New York, USA; (2) Optimus U Corp - Miami, USA; (3) Cognitive Clinical Trials - Omaha, USA; (4) Cognitive Clinical Trials - Phoenix, USA; (5) Imic Research - Palmetto Bay, USA, (6) Cassava Sciences, Inc. - Austin, USA)

**Background:** Sumifilam (formerly PTI-125) is a novel small molecule drug candidate that binds and reverses a proteopathy in Alzheimer's disease (AD). The proteopathy, an altered conformation of the scaffolding protein filamin A (FLNA), is critical to the toxicity of soluble A $\beta$ 42. Altered FLNA links to the  $\alpha$ 7-nicotinic acetylcholine receptor ( $\alpha$ 7nAChR) to allow A $\beta$ 42 to bind with femtomolar affinity and signal through this receptor to hyperphosphorylate tau. Altered FLNA also links to toll-like receptor 4 (TLR4) to enable A $\beta$ 42-induced persistent TLR4 activation and inflammatory cytokine release. By restoring the native shape of FLNA, sumifilam disrupts FLNA's aberrant receptor linkages and markedly reduces A $\beta$ 42's binding affinity for these sites. This dual mechanism through a single target allows sumifilam to reduce both tau hyperphosphorylation and neuroinflammation. An open-label clinical study of sumifilam previously demonstrated significant improvements in biomarkers of disease in AD patients and no safety issues. **Objectives:** To assess safety and improvements in biomarkers and cognition in a well-controlled clinical trial of sumifilam in mild-to-moderate AD. To replicate earlier clinical results with sumifilam. **Methods:** In this Phase 2b trial conducted at 9 sites in the US, 64 patients with mild-to-moderate AD were randomized (1:1:1) to receive placebo, 50 or 100 mg sumifilam oral tablets b.i.d. for 28 days. Key inclusion criteria were MMSE  $\geq$  16 and  $\leq$  26, age 50-85 and CSF total tau/A $\beta$ 42 ratio  $\geq$  0.28. Safety was assessed by ECGs, clinical labs, adverse event monitoring and physical examinations. CSF and blood samples for biomarker analyses were collected at screening or Day 1 and again on Day 28. All biomarkers were

analyzed by an outside lab blind to treatment and timepoint. Commercial ELISA kits and an automated plate reader were used to measure i) core AD biomarkers (p-tau181, total tau and A $\beta$ 42) ii) biomarkers of neurodegeneration (neurofilament light chain [NfL] and neurogranin) and iii) and biomarkers of neuroinflammation (YKL-40, IL-6, soluble Triggering Receptor Expressed on Myeloid cells 2 [sTREM2] and High Mobility Group Box 1 [HMGB1]). Screening and Day 28 samples for each patient were analyzed in triplicate in the same ELISA plate for each biomarker. Values were adjusted to regression analyses on standards with R2 values ranging from 0.83 to 0.97. Blood-brain barrier (BBB) integrity was assessed by levels of blood proteins albumin and IgG in CSF, determined by immunoblotting. Target engagement was assessed by measuring FLNA linkages to  $\alpha$ 7nAChR and TLR4 in lymphocytes. Cognition was assessed by the Paired Associates Learning (PAL) and Spatial Working Memory tests of the Cambridge Neurological Automated Battery (CANTAB). Endpoints for each were total errors, with errors imputed for more difficult levels not reached. A lower score is better. **Results:** Sumifilam was safe and well-tolerated. Sumifilam 50 mg and 100 mg both significantly improved validated CSF biomarkers of AD pathology, neurodegeneration and neuroinflammation. For 50 mg and 100 mg dose groups respectively, A $\beta$ 42 increased 17% and 14%; total tau decreased 15% and 18%; and p-tau181 decreased 8% and 11% ( $p \leq 0.001$  vs. placebo for all). Reduced neurodegeneration was shown by NfL decreasing 28% and 34% and neurogranin decreasing 36% and 43% for 50 and 100 mg groups, respectively ( $p < 0.05$  for NfL in the 50 mg group;  $p \leq 0.001$  for all others). Indicating reduced neuroinflammation, both YKL-40 and IL-6 decreased 10% and 11%, and sTREM2 decreased 43% and 46% in respective dose groups. Levels of HMGB1, a stress and neuroinflammation marker that activates TLR4 and RAGE, decreased 33% and 32% for respective dose groups ( $p < 0.01$  vs. placebo for all inflammatory markers). Improved BBB integrity was shown by CSF albumin decreasing 15% ( $p = 0.059$ ) and 29% ( $p = 0.0002$ ) for respective dose groups, and by CSF IgG decreasing 30% (both doses,  $p = 0.02$  for each). Target engagement was evidenced for both doses by  $>30\%$  reductions in FLNA linkages to  $\alpha$ 7nAChR and TLR4 in lymphocytes ( $p = 0.01$ ). All but one patient responded across biomarkers. Patients on sumifilam 50 and 100 mg showed evidence of improvement on the PAL test of episodic memory, with effect sizes of 37% and 23% vs. placebo, after removing the most and least impaired subjects by baseline score. Episodic memory improvements correlated best with decreases in p-tau181 ( $R^2 = 0.5$ ). Patients also showed improvements on spatial working memory, with effect sizes of 17% and 46% vs. placebo for 50 and 100 mg dose groups, respectively. **Conclusions:** In a randomized, placebo-controlled Phase 2b trial in mild-to-moderate AD, sumifilam 50 mg or 100 mg b.i.d. for 28 days significantly improved validated biomarkers of AD pathology, neurodegeneration and neuroinflammation. Sumifilam also significantly improved BBB integrity. Drug response rate was 98%. Sumifilam appeared to improve cognition. These promising treatment effects replicate prior clinical results and validate sumifilam's potential as a disease-modifying treatment for AD. This work was funded by NIA grant AG060878.

**LB22: THE P38A KINASE INHIBITOR NEFLAMAPIMOD SIGNIFICANTLY IMPROVES COGNITION IN PATIENTS WITH MILD-TO-MODERATE DEMENTIA WITH LEWY BODIES (DLB).** J.J. Alam<sup>1</sup>, S.N. Gomperts<sup>2</sup>, P. Dautzenberg<sup>3</sup>, A.W. Lemstra<sup>4,5</sup>, S.E. Arnold<sup>2</sup>, N. Prins<sup>4,5</sup>, H.M. Chu<sup>6</sup>, A. Gardner<sup>1</sup>, K. Blackburn<sup>1</sup>, C. Edgar<sup>7</sup>, P. Maruff<sup>8</sup>, P. Scheltens<sup>5</sup>, J.E. Harrison<sup>5,9</sup> ((1) *E I P Pharma, Inc - Boston, USA*; (2) *Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital - Charlestown MA, USA*; (3) *Brain Research Center - Den Bosch, Netherlands*; (4) *Brain Research Center - Amsterdam, Netherlands*; (5) *Amsterdam UMC - Amsterdam, Netherlands*; (6) *Anoixis Corporation - Natick MA, USA*; (7) *Cogstate Ltd - London, United Kingdom*; (8) *Cogstate Ltd - Melbourne, Australia*; (9) *Metis Cognition Ltd - Kilmington, United Kingdom*)

**Background:** Neflamapimod, an oral specific inhibitor of the alpha isoform of p38 mitogen-activated-protein kinase ("p38 $\alpha$  kinase"), is in phase 2 clinical development in multiple CNS indications. Phase 2 results in Alzheimer's disease (AD) presented at CTAD 2019 demonstrated target engagement, with significant reduction relative to placebo in CSF p-tau and tau; and suggested that cognition was improved in the patients with the highest tertile of trough plasma drug concentration. The current study was undertaken because the blockade of the effect of neuroinflammation by p38 $\alpha$  kinase inhibition may also benefit patients with DLB. Moreover, in the TS2 transgenic mouse neflamapimod rescues basal forebrain cholinergic neurodegeneration, which is considered a major driver of dementia in DLB. In addition, p38 $\alpha$  kinase has been linked to the neurotoxicity of  $\alpha$ -synuclein. **Objectives:** This was a phase 2, double-blind placebo-controlled clinical study designed to evaluate the effects on cognition of the oral p38 alpha kinase inhibitor neflamapimod in mild-to-moderate patients with dementia with Lewy bodies who are receiving cholinesterase inhibitor therapy. **Methods:** 22 centers in the US and 2 centers in the Netherlands. Patients: Aged  $\geq 55$  years with mild-to-moderate (MMSE 15-28) probable DLB by consensus criteria (McKeith et al, *Neurology*, 2017; 89:88-100), including a positive DaTscan<sup>TM</sup>, and currently receiving cholinesterase inhibitor therapy (> 3 months and stable dose > 6 weeks). Treatment: 40 mg neflamapimod capsules or matching placebo capsules (randomized 1:1) administered with food for 16 weeks; dosing regimen was based on weight: subjects weighing <80 kg received capsules twice-daily (BID) and those weighing  $\geq 80$  kg received capsules three-times-a-day (TID). Endpoints: Primary objective was to evaluate the effect of neflamapimod on cognition as assessed in a study-specific Neuropsychological Test Battery (NTB) designed to primarily evaluate attention and executive function. NTB comprised of four computerized tests from Cogstate<sup>®</sup> battery (Detection, Identification, One Card Learning, One Back) and two tests recorded on paper (Letter Fluency, Category Fluency); analyzed as a composite after conversion of test results to z-scores, with individual tests equally weighted. Secondary endpoints included additional composites built from a subset of tests in the NTB, CDR-SB, Neuropsychiatric Inventory (NPI) and Timed Up and Go (TUG) test. Statistics: With no prior experience in DLB with neflamapimod to estimate the treatment effect, no formal sample size calculation was performed. However, based on prior experience with NTB, 40 study participants per treatment arm was considered adequate to provide evidence of whether neflamapimod improves cognition in patients with DLB. The primary endpoint was analyzed by linear mixed

effects model of repeated measures (MMRM). **Results:** A total of 91 patients were enrolled and received >1 dose of study drug; 45 randomized to placebo and 46 to neflamapimod. The two groups were balanced for baseline disease and demographic parameters. At baseline: mean age=72.6 (SD=6.5), mean CDR-SB=5.2 (2.5), mean MMSE=22.8 (3.5). For the Cogstate tests, baseline results ranged from -1.13 SD below age-adjusted norm in One Card Learning to -2.56 SD in One Back test. As of September 17, 2020, topline results were available. A positive effect on the primary endpoint was observed, with patients receiving neflamapimod TID demonstrating significant improvement on the NTB compared to those who received either placebo or neflamapimod BID [ $p=0.015$ ; effect size (Cohen's d) = 0.52]. The positive effect on the NTB was evident at week 4 and maintained through the 16-week study period. Multiple sensitivity analyses (with or without imputation of any missing data) support the primary analysis, as they also demonstrated significantly improved outcome on the NTB in the neflamapimod TID patients compared to placebo. Analysis of the results from individual tests and alternative composites derived from the individual tests (e.g. attention composite, executive function composite) indicate that the positive effect on the primary endpoint was driven primarily by the effects of neflamapimod on attention. Analyses of other secondary endpoints are ongoing and will be presented. With respect to safety, neflamapimod was well tolerated. A total of 10 patients discontinued early: 6 in neflamapimod (3 for adverse event, AE) and 4 in placebo (2 for AE). All events in which the AE led to discontinuation were considered unrelated to treatment. Seven SAEs reported (4 in placebo, 3 in neflamapimod), all considered unrelated. There were no SAEs reported, or early treatment discontinuations among neflamapimod TID patients. **Conclusion:** In a 16-week, double-blind placebo-controlled clinical study, neflamapimod 40 mg TID improved cognition in patients with DLB receiving stable dose cholinesterase inhibitor therapy. The results for the first time demonstrate clinical proof-of-concept for p38 $\alpha$  kinase inhibition in a neurodegenerative disease indication, and support advancing neflamapimod to late-stage development as a treatment for DLB. As the BID-to-TID differential is consistent with the trough drug-concentration relationship seen in AD, and as scientific rationale overlaps for these disease indications, the results also positively inform on the potential of neflamapimod as a treatment for AD.

**LB23: A PHASE 1, FIRST-IN-HUMAN (FIH), SINGLE ASCENDING DOSE (SAD) STUDY OF THE NOVEL ANTI-TAU THERAPEUTIC ANTIBODY E2814 IN HEALTHY VOLUNTEERS.** P. Aceves<sup>1</sup>, M. Giroux<sup>2</sup>, P. Boyd<sup>1</sup>, J. Aluri<sup>2</sup>, M. Aoyama<sup>3</sup>, P. Sachdev<sup>2</sup>, S. O'sullivan<sup>2</sup>, E. Takahashi<sup>3</sup>, R. Gordon<sup>1</sup>, L. Reyderman<sup>2</sup> ((1) *Eisai Co., Ltd - Hatfield, United Kingdom*; (2) *Eisai Inc. - Woodcliff Lake, USA*; (3) *Eisai Co., Ltd - Tsukuba, Japan*)

**Background:** E2814 is a novel, humanized, high affinity, anti-tau therapeutic monoclonal antibody (mAb) that inhibits tau aggregation in vitro by recognizing epitopes in 4R and 3R tau isoforms in the tau microtubule binding region (MTBR). MTBR forms the core of the neuropathological filaments identified in Alzheimer's disease (AD) brain and is thought to be critical to the propagation or "seeding" of tau pathology. E2814 binding to MTBR tau in human brain extracellular fluid is expected to increase tau clearance (e.g. by microglial uptake), thereby

inhibiting tau spread and positioning E2814 as a potential AD disease-modifying therapy. **Objectives:** The main objectives of this Phase 1 FIH SAD study of E2814 are to evaluate the safety and tolerability of a single intravenous infusion in healthy adults, to investigate serum and cerebrospinal fluid (CSF) pharmacokinetics (PK) and the immunogenicity (production of serum anti-E2814 antibody) of E2814. An exploratory objective is to evaluate target engagement (TE) of E2814 on MTBR-tau species in CSF. **Methods:** This is a multicenter, randomized, double-blind, placebo-controlled, SAD study in healthy male and female subjects aged 18-55 years. The study consists of 3 dose cohorts each with 8 subjects (N = 24); randomized to receive a single 1-hour intravenous infusion dose of E2814 or E2814-matched placebo (3:1 ratio). Subjects remained at the study site for 7 days following dosing and returned to the clinic at predefined outpatient visits up to End-of-Study visit on Day 113. Safety was evaluated before each dose escalation through a review of adverse event, physical examinations, clinical laboratory test results, vital signs, and electrocardiogram (ECG) results. Serial blood and CSF samples via 24 hour indwelling catheter for measurement of serum and CSF E2814 concentrations measured by a validated electrochemiluminescence (ECL) assay were obtained at prespecified time-points. The serum and CSF PK parameters were estimated using non-compartmental analysis. Anti-E2814 antibodies in serum were measured by a validated ECL assay. TE was explored by measuring E2814 bound and free MTBR-tau concentrations in CSF with a validated highly sensitive LC-MS assay (lower limit of quantification of 0.1 ng/ml) able to quantify low concentrations of MTBR-tau fragments. **Results:** Initial results (Cohorts 1 to 3) demonstrate that E2814 has an adequate safety and tolerability profile as shown by the absence of clinically significant drug-related laboratory, ECG or examination safety findings or dose limiting adverse events (AE) across the evaluated cohorts. There were no treatment emergent serious adverse events or severe AEs. Two AEs, skin rash and headache, both mild in severity, were deemed by investigator to be related to study drug. Of note one subject in cohort 3 had an elevated C-Reactive Protein compared to baseline notable on day 2 and 3 that was asymptomatic and resolved without treatment. PK results indicate there was a dose-related increase in serum and CSF E2814 exposures (C<sub>max</sub> and AUC). The median time to maximum E2814 concentrations in serum (t<sub>max</sub>) was 1.5 to 2 h. Secondary peaks were observed in the individual PK profiles, particularly during the terminal disposition phase. E2814 presented a large volume of distribution (V<sub>z</sub>) of 36 L, a clearance (CL) of 0.06 L/hour, and a half-life (t<sub>1/2z</sub>) of 20 days. CSF E2814 concentrations remained elevated from 24 hours up the last time-point of 672 hours (Day 29). The serum-to-CSF concentration ratio ranged between 0.1 to 0.3%. Preliminary E2814-bound and free MTBR-Tau TE analysis suggests a dose-related increase in TE with sustained TE upto Day 29. On ADA, only 2 out of 24 subjects had transient low level titers by the last study Day 113. **Conclusion:** E2814 was well tolerated with PK and CSF penetration comparable to that for other mAbs. The TE data demonstrated dose-related increases and sustained TE levels up to Day 29. These data supports the evaluation of four-weekly dosing in a multiple ascending dose clinical study.

#### **LB24: PRELIMINARY ANALYSIS OF BAN2401 EFFECTS ON BRAIN AMYLOID AND ARIA-E FINDINGS OVER 12 MONTHS OF TREATMENT IN THE OPEN-LABEL EXTENSION OF THE PHASE2B STUDY BAN2401-G000-201 IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE.**

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**Objectives:** BAN2401 is a humanized IgG1 monoclonal antibody that preferentially binds A $\beta$  protofibrils. Previous baseline results from the open label extension (OLE) from the BAN2401 phase 2b study in subjects with early Alzheimer's disease (EAD) indicated that brain amyloid reduction persists for up to 2 years following BAN2401 discontinuation, while the treatment differences noted for clinical outcomes at the end of the Core study period appeared to be maintained following BAN2401 discontinuation modelled to 2 years. The objective of the present analysis is to evaluate the preliminary longitudinal amyloid positron emission tomography (PET) and ARIA-E findings for 10 mg/kg biweekly (IV) BAN2401 in the ongoing OLE. **Methods:** An OLE was initiated following analysis of the Core phase 2b Study (BAN2401-G000-201). The gap period, defined as the period between the end of treatment for a subject in the Core study and the OLE baseline for that subject, ranged from 9 months to 59 months (mean range 24-27 months and median range 20-24 months across Core placebo, 10 monthly BAN2401, and 10 mg/kg biweekly BAN2401 groups). All subjects who fulfilled OLE inclusion/exclusion criteria and entered the OLE received 10 mg/kg biweekly during the OLE period. All subjects were required to be amyloid positive at baseline in the Core study. Subjects consenting to the longitudinal amyloid sub-study were allocated to one of two cohorts according to imaging time points (Cohort 1: baseline, 3 months, and 12 months; Cohort 2: baseline, 6 months, and 12 months). Magnetic resonance imaging (MRI) was conducted to monitor for amyloid related imaging abnormalities of edema/effusion (ARIA-E) at 9 weeks, 3 months, 6 months, and 12 months over the first 12 months of 10 mg/kg biweekly BAN201 treatment in the OLE. Regression analyses were conducted on amyloid PET standard uptake value ratio (SUVR) imaging data over 12 months during the OLE longitudinal period. ARIA-E data were summarized according to observed events in the longitudinal OLE period. **Results:** A total of 180 subjects have been dosed in the OLE, where 143 subjects contributed to the current OLE longitudinal amyloid PET imaging dataset (Core allocation: placebo:45; 10 mg/kg monthly:60; 10 mg/kg biweekly:38). Preliminary OLE longitudinal PET sub-study data pooled across both cohorts indicate reduction that is dependent on Core treatment, with Core placebo-treated subjects showing model estimated reduction on PET SUVR of -0.08, -0.17, and -0.33 at 3, 6, and 12 months, respectively. Point estimate reductions for Core BAN2401 treated subjects were lower over the 12-month OLE time course, dependent on starting OLE baseline PET SUVR values. In the OLE, 14/180 (7.8%) dosed subjects across all Core treatment assignments have had ARIA-E to date. Of note, four subjects treated with Placebo in the Core study had ARIA-E in the OLE (4 of 45 total; overall incidence of 8.9%). All four of these ARIA-E cases occurred in ApoE4+ subjects, yielding an incidence of 13% (4 of 31 total ApoE4 carriers; 13%) in Core placebo-treated ApoE4 carrier subjects. **Conclusions:** In this preliminary analysis, 10 mg/kg biweekly BAN2401 rapidly

reduced brain amyloid in Core placebo-treated subjects as early as 3 months, with continued reduction over 12 months of treatment in the OLE. Effects on brain amyloid reduction were dependent on Core treatment assignment and associated brain amyloid levels at OLE Baseline. The incidence of observed ARIA-E cases in the OLE is consistent with the incidence observed at 10 mg/kg biweekly treatment in the Core study. These findings suggest that 10 mg/kg biweekly BAN2401 can be initiated at the onset of treatment to elicit rapid reduction of brain amyloid with relatively low incidence of ARIA-E.

**LB25: ANAVEX®2-73 (BLARCAMESINE) CURRENTLY IN PHASE 2B/3 EARLY ALZHEIMER'S DISEASE (AD): ANALYSIS OF COGNITIVE OUTCOME MEASURES RELEVANT IN AD OF DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED PHASE 2 CLINICAL TRIAL IN 132 PATIENTS WITH PARKINSON'S DISEASE DEMENTIA.**

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**Background:** The ANAVEX®2-73-PDD-001 study was an international, double-blind, multicenter, placebo-controlled Phase 2 clinical study. 132 patients with PDD ( $\geq 50$  years, MoCA score 13-23) were randomized equally to target doses of 30mg, 50mg ANAVEX®2-73 (blarcamesine) or placebo, respectively. In addition to safety and cognitive efficacy, sleep function was assessed during the study at week 8 and week 14. **Objectives:** As previously presented at CTAD (2017, 2018, 2019) the phase 2a ANAVEX®2-73 (blarcamesine) in patients with mild to moderate Alzheimer's disease demonstrated lower rates of cognitive (MMSE) and functional (ADCS-ADL) decline in those participants with higher ANAVEX®2-73 (blarcamesine) plasma concentration or the cohort carrying the common SIGMAR1 wild type (WT) gene variant (80-84% of worldwide population) (1). Here we report the effects of ANAVEX®2-73 (blarcamesine) on cognition in patients with Parkinson's disease dementia (PDD) as well as the efficacy outcome measures of the pre-specified cohort carrying the common SIGMAR1 wild type (WT) gene variant. **Methods:** ANAVEX®2-73 (blarcamesine): a novel, oral, investigational sigma-1 receptor agonist with multimodal activity was assessed with Cognitive Drug Research computerized assessment (CDR) system, which is an automated test battery validated for use in AD, PDD and other dementias (2). **Results:** Observed results for the pre-specified cohort carrying the common SIGMAR1 wild type (WT) gene variant: Broad and statistically significant improvements in Memory (Episodic Memory) and Attention [Choice Reaction Time ( $p = 0.039$ ) and Vigilance ( $p = 0.008$ )], representing complex cognitive tasks with impact on quality of life such as making a choice between similar objects and remembering daily personal experiences, which are mostly impaired in AD and PD (3). Statistically significant dose-dependent ( $p = 0.025$ ) improvement of Episodic Memory, which has been shown to be highly correlated with the Alzheimer's Disease Assessment Scale-Cognitive score (ADAS-Cog;  $r = 0.7$ ) (4). **Conclusions:** ANAVEX®2-73 (blarcamesine) was generally safe, well tolerated, with improved safety profile compared to currently marketed dementia drugs, which are associated with typical CNS adverse effects. Potentially first dementia drug that might not impair sleep and has a positive effect on REM sleep. These results support continued development in PDD / PD as well as ongoing clinical studies with ANAVEX®2-73

(blarcamesine) in AD, especially within the Precision Medicine framework, evidenced by pre-specified analysis of the cohort carrying the common SIGMAR1 wild type (WT) gene variant (5). **References:** 1. Excluding the cohort carrying the SIGMAR1 rs1800866 gene variant (16%-20%): [https://www.ncbi.nlm.nih.gov/projects/SNP/snp\\_ref.cgi?rs=rs1800866](https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=rs1800866); 2. Simpson PM, Surmon DJ, Wesnes KA, Wilcock GR. The cognitive drug research computerised assessment system for demented subjects: a validation study. *Int J Geriatr Psychiatr* 1991;6:95-102.3. Mahurin, R. K., & Pirozzolo, F. J. (1993). Application of Hick's law of response speed in Alzheimer and Parkinson diseases. *Perceptual and Motor Skills*, 77(1), 107-113; 4. Wesnes K, Edgar C, Andreasen N, Annas P, Basun H, Lannfelt L, et al. Computerized cognition assessment during acetylcholinesterase inhibitor treatment in Alzheimer's disease. *Acta Neurol Scand* 2010; 122:270-7; 5. ClinicalTrials.gov Identifiers: NCT03790709, NCT02756858

**LB26: ALZHEIMER'S PROTECTION EFFECT OF A673T MUTATION MAY BE DRIVEN BY LOWER AB OLIGOMER BINDING AFFINITY.**

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**Background:** Carriers of the Icelandic mutation of APP (A673T) are four times less likely to get AD compared to noncarriers. This mutation results in reduced amyloid beta ( $A\beta$ ) protein production in vitro and lower lifetime  $A\beta$  concentration in carriers. Better understanding of the protective mechanisms of the mutation may provide important insights into AD pathophysiology and identify productive therapeutic intervention strategies for disease modification.  $A\beta(1-42)$  protein forms oligomers that bind saturably to a single receptor site on neuronal synapses, initiating the downstream toxicities observed in AD. Decreased formation, toxicity, or stability of soluble  $A\beta$  oligomers, or reduction of synaptic binding of these oligomers may combine with overall lower  $A\beta$  concentration to underlie A673T's disease protecting mechanism. **Methods:** To investigate these possibilities, we compared the formation rate of soluble oligomers made from Icelandic A673T mutant and wild type (wt)  $A\beta(1-42)$  synthetic protein, the amount and intensity of oligomer bound to mature primary rat hippocampal/cortical neuronal synapses, and the potency of bound oligomers to impact trafficking rate in neurons in vitro using a physiologically relevant anhydrous DMSO oligomer preparation method. **Results:** At equal protein concentrations, mutant protein forms approximately 50% or fewer oligomers of high molecular weight ( $>50$  kDa) compared to wt protein. Mutant oligomers are twice as potent at altering the cellular vesicle trafficking rate as wt at equivalent concentrations, however, mutant oligomers have a  $>4$ -fold lower binding affinity to synaptic receptors ( $K_d = 1,950$  vs 442 nM). The net effect of these differences is a lower overall toxicity at a given concentration. **Conclusions:** This study demonstrates for the first time that mutant A673T  $A\beta$  oligomers prepared with this method have fundamentally different assembly characteristics and biological impact from wt protein and indicates that its disease protecting mechanism may result primarily from the mutant protein's much lower binding affinity to synaptic receptors. This suggests that therapeutics that effectively reduce oligomer binding to synapses in the brain may be beneficial in AD.



## POSTERS

### Theme 1: CLINICAL TRIALS: METHODOLOGY

**P002: COMPARING THE DOWN SYNDROME COMMUNITY EXPERIENCE WITH SPORADIC AD PARTICIPANT INSIGHTS: OVERCOMING BARRIERS TO CLINICAL TRIAL RECRUITMENT.** J. Hendrix<sup>1</sup>, P. Ferrell<sup>2</sup>, M. Chevrette<sup>1</sup>, H. Barce<sup>2</sup>, T. Batdorf<sup>2</sup>, H. Hillerstrom<sup>1</sup> ((1) *Lumind Idsc - Burlington, USA*; (2) *Eli Lilly & Company - Indianapolis, USA*)

**Background:** With improved healthcare, the Down syndrome (DS) population is both growing and aging rapidly with a life expectancy of >55 years of age compared to just 25 year of age in the 1980's. It is estimated that there are 210 K people with DS in the USA and 40% are over the age of 30 years old (1). However, with longevity comes a very high risk of Alzheimer's disease (AD). It is estimated that by age 55–60 years at least 70% will develop Alzheimer's dementia (2, 3). Despite the Alzheimer's crisis facing the DS population, very few people with DS have participated in clinical trials. **Objectives:** The challenges in clinical trial recruiting for sporadic AD participants have been widely explored in academic and commercial site settings, including discussions at scientific conference and in scientific publications. And while many of those presentations focus on operational challenges, success in meeting enrollment goals is not simply about advertising and outreach (4). The DS population has unique needs, which are unlikely to be the same as needs of participants with sporadic AD. However, in the case of older adults with AD, familial guardians may have more similar beliefs and needs of spousal caregivers of those with early AD. **Method:** LuMind IDSC has partnered with Eli Lilly & Company to collect qualitative data from potential participants with DS and their guardians regarding their beliefs about clinical trial participation and experiences with the US medical system. The data will look holistically at lifestyle and be segmented by parental (and potential participant) age, with an attempt to collect data from a variety of residential situations to compare with experiences and beliefs of participants and caregivers in sporadic AD studies. **Results:** This talk, given by the lead author, will explore common barriers to the recruitment of AD studies, with a comparison of the special needs and potential solutions for adults with DS. DS organizations, such as LuMind IDSC, continuously work to gain the trust of participants and their families in ethical research which is a key component for successful recruitment. Lilly and LuMind will share data that support the development of strategies and tools to engage, support and educate adults with DS and their caregivers about clinical trials, and improve their experience at clinical trial sites. **Conclusion:** Unique recruitment strategies are needed for successful enrollment of adults with DS in AD trials. Existing Alzheimer's disease clinical trial sites will need new strategies and tools and need to modify their recruitment techniques from sporadic AD when they study patients with DS. Some of these new solutions may have spillover benefit into recruiting for sporadic AD clinical trials. **References:** 1. de Graaf, G.; Buckley, F.; Skotko, B. January 28, 2019 | <https://dsuri.net/us-population-factsheet>; 2. Lemere, et.al. *Neurobiol Dis*, 1996, 3(1):16-32.; 3. Hartley, et.al. *Alzheimer's Dementia*, 2015, 11(6):700-9; 4. Grill, J. & Karlawish, J. *Alzheimer's Research & Therapy*, 2010, 2(34): <https://doi.org/10.1186/alzrt58>.

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### P003: KEY BASELINE CHARACTERISTICS OF PARTICIPANTS ENROLLED USING TAU PET SCREENING IN TWO PHASE 2 TRIALS.

S. Shcherbinin, S. Andersen, W. You, C. Evans, L. Munsie, A. Lo, J. Sims (*Eli Lilly And Company - Indianapolis, USA*)

**Background:** One major challenge in Alzheimer's disease (AD) clinical trial design is addressing the heterogeneity of the disorder. Inclusion of participants with varying genotypes, phenotypes, baseline performance, compensatory strategies, clinical courses, and comorbidities may result in variable trial outcomes and accordingly affect the efficacy of disease modifying therapies (e.g., Ballard et al, *Alzheimer's and Dementia*, 2019, 5, 164-174). To enroll a more homogeneous population with more uniform cognitive decline and increased power, biomarker-driven screening criteria can be integrated with cognitive, diagnostic, functional, and demographic information. In this regard, amyloid positron emission tomography (PET) is being widely used to enroll participants with confirmed amyloid pathology and higher likelihood of clinical progression. Preliminary data suggest (Pontecorvo et al, *Brain*, 2019, 142, 1723-1735) that owing to its established correlation with disease progression and clinical course, tau PET can play an even more important role as a selection or stratifying variable in clinical trials than amyloid PET. It is hypothesized (Qian et al, *JAMA Neurology*, 2017, 74, 540-548) that stratification by tau PET may dramatically reduce the heterogeneity of participants and improve power. **Objectives:** Our goal was to characterize populations enrolled in two phase 2 therapeutic trials where flortaucipir PET was utilized as a key eligibility criterion for identifying the tau pathological stage. **Methods:** TRAILBLAZER-ALZ phase 2 therapeutic trial with anti-N3pG antibody donanemab (LY3002813; NCT03367403) and PERISCOPE-ALZ phase 2 therapeutic trial with anti-tau antibody zagotenemab (LY3303560; NCT03518073) implemented National Institute on Aging and Alzheimer's Association (NIA-AA) guidelines for AD classification based on biomarker-defined pathological stage (Jack et al, *Alzheimer's and Dementia*, 2018, 14, 535-562) with a focus on identifying an early symptomatic AD population. Flortaucipir PET imaging (central read) served as a key eligibility instrument. Specifically, only a subgroup with an intermediate tau burden was selected based on both visual reads and quantitative thresholds. Subpopulations with minimal tau burden (expected to have slower progression in both aggregated tau deposition and cognitive measurements) and high tau burden (expected to have the most rapid progression and less likely to benefit from treatment) were excluded. Cognitive (Mini-Mental Status Examination [MMSE] score of 20-28 inclusive) and age (60-85 years) restrictions were key eligibility criteria preceding a screening flortaucipir PET scan. In TRAILBLAZER-ALZ, a screening florbetapir PET scan was performed for participants who met tau eligibility criteria. We assessed homogeneity of the enrolled populations using both standard deviation (SD) and interquartile range (IQR). In particular, such cognitive and functional characteristics as MMSE, 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog13), instrumental subscale of the Alzheimer's Disease Cooperative Study (ADCS-iADL) and Integrated AD Rating Scale (iADRS; Wessels et al, *JPAD*, 2015, 2, 227-241) were examined. As a reference, we used a population enrolled in NAVIGATE-AD (NCT02791191), a phase 2 trial with BACE inhibitor using stricter diagnostic (mild AD dementia

only) and cognitive (MMSE of 20-26 inclusive) scores and more flexible pathologic (demonstration of only amyloid pathology by florbetapir PET) and age (55-85 years) restrictions. **Results:** Average characteristics (mean±SD) for populations enrolled in TRAILBLAZER-ALZ and PERISCOPE-ALZ trials were very close to each other confirming a successful and consistent implementation of our novel screening procedure based on the PET-based tau level. Comparing with NAVIGATE-AD, TRAILBLAZER-ALZ and PERISCOPE-ALZ participants had, as expected, lower tau pathology with less variable flortaucipir PET score. Specifically, composite standardized uptake value ratio (tau SUVR, Southekal et al, JNM, 2018, 59, 944-951) for baseline flortaucipir images was 1.22±0.12, 1.23±0.11, and 1.38±0.31, in TRAILBLAZER-ALZ, PERISCOPE-ALZ, and NAVIGATE-AD trials, respectively. Moreover, populations enrolled using the novel tau-based screening procedure had less variable ADAS-Cog13 baseline scores. Both SD and IQR values in TRAILBLAZER-ALZ (7.58 and 11) and PERISCOPE-ALZ (7.76 and 11) were lower than in NAVIGATE-AD (9.05 and 13) despite more flexible diagnostic and cognitive eligibility criteria. At the same time, we observed higher MMSE SDs in TRAILBLAZER-ALZ (3.12) and PERISCOPE-ALZ (2.82) than in NAVIGATE-AD (1.93). In all three trials, more women than men were enrolled. However, TRAILBLAZER-ALZ (53.31% female) and PERISCOPE-ALZ (52.78% female) were more balanced than NAVIGATE-AD population (60.76% female). No substantial difference was observed between these three trials in ADCS-iADL and iADRS. **Conclusions:** Our findings provide initial insight on using tau PET-quantification to address AD clinical trial population pathologic and clinical heterogeneity.

**P004: FIRST IN HUMAN STUDY WITH ALZ-101, A UNIQUE AND HIGHLY SPECIFIC THERAPEUTIC VACCINE AGAINST THE NEUROTOXIC OLIGOMERIC FORM OF A $\beta$  1-42.** A. Sandberg<sup>1</sup>, I. Nylander<sup>1</sup>, M. Sheinin<sup>2,3</sup>, J. Rinne<sup>2,4,5</sup>, Z. Lovro<sup>2</sup>, K. Torfgård<sup>1</sup>, A. Bylock<sup>1</sup> ((1) *Alzinova Ab - Gothenburg, Sweden*; (2) *Crst - Turku, Finland*; (3) *University of Turku, Institute of Biomedicine - Turku, Finland*; (4) *Turku PET centre, University of Turku - Turku, Finland*; (5) *Division of Clinical Neurosciences, Turku University Hospital - Turku, Finland*).

**Background:** Alzinova AB is a Swedish innovative biopharma company specialized in the development of disease-modifying treatments for Alzheimer's disease (AD). Alzinova's lead candidate, ALZ-101, is a unique and highly specific therapeutic vaccine generated using proprietary A $\beta$ CC peptide™ technology. ALZ-101 is an A $\beta$  1-42 oligomer mimic, and its use as an active immunotherapy agent is intended to elicit a strong immune reaction against the neurotoxic oligomeric form of A $\beta$  1-42. Targeting only oligomeric A $\beta$  1-42 also reduces the risk of cross-reactivity with generic epitopes which could induce unwanted inflammation. ALZ-101 was well tolerated in non-clinical toxicity studies. Efficacy data obtained from studies in transgenic mice and on human brain extracts (assessed in neuronal cell cultures and zebrafish embryos) are all showing promising results. Alzinova and Clinical Research Services Turku (CRST) in Finland have designed a First-in-Human (FiH) study to evaluate the safety and immunogenicity of ALZ-101. Exploratory endpoints are biomarkers in cerebrospinal fluid (CSF), and serum and preliminary efficacy is measured with a package of psychometric tests. Subject recruitment is planned to start in December 2020. **Objectives:** To present and discuss the design features of a FiH study with

a therapeutic vaccine in early Alzheimer's Disease. The primary objective of the FiH study to evaluate the safety and tolerability of ALZ-101, given at 4 occasions, compared to placebo. The secondary objective is to evaluate the immunologic response after injections with ALZ-101. **Methods:** The study is a phase I, placebo-controlled, double-blind, randomized, multiple dose immunization study of ALZ-101 in patients with Minimal Cognitive Impairment (MCI) due to AD or mild AD, performed at a single centre. The subjects will be randomized into one of the ALZ-101 dose-groups or to the placebo group. ALZ-101 will be administered as intramuscular (i.m.) injections. During the treatment period, the study subjects will receive four doses of study drug (ALZ-101 or placebo) at weeks 0, 4, 8 and 16. Placebo has been included in the study to allow for a comparator in the safety evaluation. The ALZ-101 doses chosen for the study have been selected based on all available non-clinical information on the ALZ-101. Appropriate safety precautions will be employed to ensure the safety of the subjects. An independent Data and Safety Monitoring Board (DSMB) will review the safety data regularly. Safety Magnetic Resonance Imaging (MRI) scans of the brain will be performed once during the screening period, 3 times during the treatment period and once during the follow-up period. The results of each MRI evaluation must be available and reviewed before each subsequent dosing. Before each immunization, a set of safety assessments will be performed, and the results evaluated. CSF samples will be taken twice, once in the screening period (to assess eligibility and to establish baseline results) and at week 20, i.e. 4 weeks after the 4th dose. Additional CSF samples will be obtained if warranted for safety reasons. All subjects starting the treatment period will receive their first immunization at Turku University Hospital. After the first dosing, subjects will be hospitalized for 24 h for observation of possible acute adverse reactions. There will be minimum intervals of 48 h between the subjects receiving their first dose. Safety follow-up will be continued on the scheduled visits at the study site with clinical and laboratory assessments, brain MRI scans and collection of Adverse Events (AEs). In addition, the Columbia Suicide Severity Rating Scale (C-SSRS) and the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC) will be used to capture any unexpected deterioration of the clinical condition. Remote visits (telephone contacts) will be performed to assess possible AEs and IREs at pre-specified time points. The potential of ALZ-101 to induce antibodies will be evaluated at 8 occasions during the study. Endpoints will be A $\beta$ -specific antibody titre, number of titre-based responders and area under serum A $\beta$ -specific antibody titre curve (AUC) from Week 0 to Week 20. **Results:** Results from the FiH study are expected in December 2022. **Conclusion:** In a FiH study, safety and tolerability are the most important parameters to evaluate for further clinical product development. Risks for subjects included in a FiH study must be minimal. Alzinova and CRST have designed a study with adequate safety precautions. At the same time, the strength and duration of the immunologic response to multiple doses of ALZ-101 will be evaluated in participants representing the target population of the novel agent.

**P005: SALVAGING COVID-19 INTERRUPTED ALZHEIMER CLINICAL TRIALS USING VIRTUAL PATIENT SIMULATIONS.** P. Van Der Graaf<sup>1</sup>, G. Hugo<sup>2</sup> ((1) *Certara - Canterbury, United Kingdom*; (2) *Certara - Berwyn, USA*)

**Objectives:** The COVID-19 pandemic has halted many ongoing CNS clinical trials, especially in Alzheimer's disease with some of the long duration trials, re-starting at different points along the trial time-line with substantial protocol amendments. In order to align the outcomes of these protocol amendments with the original trial design at the individual patient level, we propose to use Physiology-Based Pharmacokinetic (PBPK) and Quantitative Systems Pharmacology (QSP) Modeling by "correcting" the impact of the protocol amendments on the cognitive trajectory in a mirror virtual patient population with identical co-medications, genotypes, amyloid and tau status. **Methods:** The Virtual Twin approach creates a PBPK computer-simulated model of each patient with a virtual twin QSP model of trial subjects, with the same co-medications, common genotype variants affecting metabolism and cognitive outcome;  $\beta$ -amyloid and tau biomarkers. The QSP platform is a previously ADAS-Cog calibrated model of key neuronal circuits involved in cognition, allowing to model the effects of CNS active co-medications based on their pharmacology and genotypes based on imaging studies. In this Virtual Twin approach, the platform will be blindly validated against the actual clinical data from the completer set and the fragmented outcomes of the restarters with their individual protocol amendments, before "renormalizing" the cognitive trajectory to the original trial design for those subjects whose trial was interrupted. **Results:** We simulate a number of different scenarios with a three month interruption in a 24-month AD study of a bi-weekly amyloid antibody infusion and with an increased use of anxiolytics and anti-depressants after restart. The impact of these protocol amendments is highly dependent upon the genotype combination with the 5-HTTLPR rs 23351 driving most of the observed differences, followed by APOE and COMTVal158Met with different effect size (up to 3 points in ADAS-cog) in placebo and active treatment. The introduction of anti-depressants also differentially affects the cognitive trajectory in placebo versus active treatment. Using a virtual patient trial with 1200 subjects, we illustrate how to reconstruct the cognitive trajectory of 600 subjects at different time points affected by the interruption. **Discussion:** Integrating knowledge about the biology using QSP with PBPK modeling and extensive validation with the fragmented clinical data available, in principle allows to reconstruct to a certain degree the original cognitive trajectory in these patients affected by the COVID-19 interruption. In this way, the original trial design and statistical analysis plan can be applied to achieve a fair evaluation of the clinical effect of the investigative new drug.

**P006: PREDICTING CDR-SB PROGRESSION USING DATA FROM 6 INTERVENTIONAL CLINICAL TRIALS AND ADNI.** B. Toth<sup>1</sup>, V. Steffen<sup>1</sup>, Y. Chen<sup>1</sup>, C. Rabe<sup>1</sup>, M. Friesenhahn<sup>1</sup>, T. Bittner<sup>2</sup> ((1) *Genentech - South San Francisco, USA*; (2) *Roche - Basel, Switzerland*)

**Background:** Using prognostic covariates as adjustment factors in the primary efficacy assessment results in a more precise estimate of the treatment effect in AD trials. Although several studies predict conversion from CN to MCI and/or

MCI to AD, these are not commonly used endpoints in recent early AD trials. Instead, we focus on predicting a widely used primary endpoint in these studies, the change in CDR-SB score. **Objectives:** We trained and validated a model, prognostic for change in CDR-SB using baseline measures that is transferable between studies across the spectrum of early AD. The key factors identified by the model can be used as adjustment covariates in the primary efficacy analysis of an investigational trial, to improve the precision of the treatment effect estimate by reducing conditional bias. The model can also serve to identify progressors, who potentially play an important role in the successful testing of drug efficacy. **Methods:** The dataset contained 6 interventional studies (ABBY NCT01343966, BLAZE NCT01397578, SCarlet RoAD NCT01224106, Marguerite RoAD NCT02051608, CREAD NCT02670083, CREAD II NCT03114657) and subjects from the observational cohort, ADNI. Patients must have had evidence of amyloid pathology confirmed by either PET or CSF, an MMSE  $\geq 20$ , a minimum of 1 year follow up and a diagnosis of either prodromal or mild AD at baseline. Subjects from the first 4 investigational studies and ADNI were randomly split, ~60% to the training (n=1158) and ~40% to the test (n=865) subgroups. The independent validation (n=1316) cohort consists of the last 2 interventional studies (CREAD NCT02670083, CREAD II NCT03114657). For each individual subject, CDR-SB progression was calculated, using all available data up to 2 years. 10 pre-specified features (age, sex, BMI, education, ApoE4, diagnosis, MMSE, CDR-SB, ADL or FAQ and ADAS-Cog 12) formulated the benchmark model and we evaluated non-linear effects and interactions. Backward elimination and LASSO identified a simplified model with the most important features, while not compromising the bias-corrected calibration and the bootstrapped R2. An extended feature set (CDR-SB and ADAS-Cog subscores in addition to the 10 pre-specified) was evaluated with an elastic net, a random forest and XGboost regression. These machine learning techniques used 10-fold cross validation (CV) within the training set to do hyper/parameter tuning and minimize RMSE. The model performance was assessed by their calibration and R2 (CV R2 in the training cohort). The effective sample size increase (ESSI =  $1/(1-R2)$ ) measures the additional sample size needed, to achieve the same power in an unadjusted statistical analysis. **Results:** The R2 of the pre-specified 10 feature linear model was 15% 95% CI [12%, 20%], 19% [14%, 24%] and 12% [8%, 15%], which translates into a 18%, 23%, and 13% ESSI, in the training, the test and the validation cohorts, respectively. The models with non-linear effects and interactions, did not outperform the linear model. A simplified model with only 2 features (ADAS-Cog 12 and ADL or FAQ) achieved an R2 of 19% [14%, 24%] in the test cohort and 12% [8%, 15%] in the validation cohort without compromising calibration. The elastic net model had a 21% [19%, 24%] and 15% [13%, 16%] R2 in the test and the validation cohorts respectively, and identified "word recall" and the "spoken language ability" subscores from the ADAS-Cog test as the most important features predicting progression. The discrimination of random forest was R2=21% [18%, 24%] and R2=14% [12%, 15%] in the test and the validation subgroups respectively, and in addition to the previous 2, it selected the total MMSE, ADAS-Cog 12 and ADL or FAQ scores as the five most important features. Word recall and the 3 total scores were also the top picks in the XGBoost approach, which yielded an R2=14% [12%, 17%] in the test cohort and R2=7% [6%, 8%] in the validation set. **Conclusion:** A pre-specified model with 10 features to predict

progression of CDR-SB is well calibrated, and robust across various studies in early AD. A simplified version with only 2 features performs similarly. Although they yield a modest discriminative power, given their simplicity, they can be easily implemented as an adjustment factor in the efficacy analysis of clinical trials. Using subscores, and machine learning techniques for feature selection did not increase the model performance substantially. Nevertheless, the identified key features measure the clinical manifestation of the disease, namely memory and language being affected early on.

**P007: CAN PHARMACODYNAMIC INTERACTION WITH GENOTYPES AND COMEDICATIONS EXPLAIN VARIABILITY IN CLINICAL TRIALS? A QUANTITATIVE SYSTEMS ANALYSIS.** H. Geerts<sup>1</sup>, A. Spiros<sup>2</sup> ((1) Certara - Berwyn, USA; (2) In Silico Biosciences - Portland, USA)

**Objectives:** While currently pharmacokinetic (PK) interactions between a novel investigative drug and comedications/genotypes can be addressed, pharmacodynamic (PD) interactions between comedications, genotypes and disease state at the level of neuronal circuits are far less appreciated. **Methods:** We present computer-based Quantitative Systems Pharmacology (QSP) Virtual Patient simulations of cognitive ADAS-Cog readouts to identify relevant PD-PD interactions in clinical trials between comedications, common genotype variants, disease state and amyloid modulating agents. This platform is based on an advanced computer model of biophysically realistic neuronal cortical microcircuit with 35 CNS targets implemented that is calibrated for ADAS-Cog. A similar Virtual Patient model of Parkinsonian motor side-effects showed good alignment with RWE data in clinical practice. **Results:** Virtual patient simulations using the actual pharmacodynamic effect of APOE, COMTVal158Met and 5-HTTLPR rs23351 genotype derived from human imaging studies show a substantial variability of more than 6 points at 52 weeks and 3 points at 104 weeks with the same amyloid-lowering interventions in the presence or absence of standard-of-care medication. The model generates a biological hypothesis for the difference between the ENGAGE and EMERGE clinical trial outcome with aducanumab. Further interaction with benzodiazepines, antipsychotics and antidepressants leads to an additional difference of 4.5 points between the best and worse outcome. The sheer number of possible combinations (around 9 million simulated) largely exceeds the number of available subjects and precludes the use of data-driven approaches such as machine learning or artificial intelligence. **Conclusions:** QSP is a hypothesis-generating engine based on actual quantitative integration of pharmacological and biological data. Simulations suggest that knowledge and subsequent mitigation of the PD-PD interactions between a novel investigative drug and comedications/genotypes can reduce patient variability and increase the probability of success.

**P008: FINDING TREATMENT EFFECTS IN ALZHEIMER'S TRIALS IN THE FACE OF HETEROGENEITY IN DISEASE PROGRESSION.** R. Jutten, S. Sikkes, W. Van Der Flier, P. Scheltens, P.J. Visser, B. Tijms (*Amsterdam Umc, Vumc - Amsterdam, Netherlands*)

**Background:** Individuals with early Alzheimer's disease (AD) show considerable heterogeneity in their rates of cognitive

decline, even when matched on disease severity at the start of the study. This implies that randomization at the start of a clinical trial does not necessarily equalizes rates of cognitive decline for the placebo and treatment groups. As a consequence, placebo versus treatment differences may depend on variation in sampling of slow versus fast decliners on cognitive outcome measures. To date, it remains unclear how such random variation in sampling would influence (potential) treatment effects. **Objectives:** To investigate the influence of heterogeneity in disease progression for detecting treatment effects in early Alzheimer's disease (AD) trials, using a simulation study. **Methods:** Individuals with an abnormal amyloid PET scan, a clinical diagnosis of MCI or dementia, baseline MMSE  $\geq 24$  and global CDR of 0.5, and  $\geq 1$  follow-up cognitive assessment were selected from the ADNI database (N=302, age  $73\pm 6.7$ ; 44% female;  $16.1\pm 2.7$  years of education; 69% APOE-e4 carrier). We simulated a clinical trial by randomly assigning individuals to a 'placebo' and 'treatment' group and subsequently computed group differences on commonly-used cognitive outcome measures (i.e. the CDR-SB, ADAS-Cog-13 and MMSE) at 18 months follow-up. We repeated this simulation 10.000 times to determine the 95% range of possible effect-sizes, and we compared this range to placebo vs. treatment group differences that have been reported for recent anti-amyloid trials in prodromal to mild AD. To investigate the influence of sample-size on the variability in effect-sizes, we repeated our simulation procedure with simulated datasets including n=1000, n=2000, n=5000 and n=10.000 individuals with 18 month data based on the aforementioned LMM. We further studied whether effects of heterogeneity on cognitive outcomes would decrease if groups were stratified on known risk factors for AD progression, i.e. age (cut-off of 65 years), sex, education (high vs. low), CSF tau levels (normal vs. abnormal), and APOE e4 status (carrier vs. non-carrier). **Results:** Individual trajectories on all cognitive outcome measures were highly variable, and the 95% ranges of observed effect-sizes at 18 months were broad, i.e. ranging from 0.40 points improvement to 0.40 points decline on the CDR-SB; from -1.45 to +1.45 points on the ADAS-Cog; and from -0.45 to +0.45 points on the MMSE. Results of recent anti-amyloid trials mostly fell within these 95% ranges of effect-sizes, suggesting that the possibility cannot be excluded that those differences were actually a chance finding due to oversampling of fast decliners in the placebo group or oversampling of slow decliners in the treated group. We further found that by increasing sample-size the 95% range effect-sizes narrows systematically (e.g. range -0.25 to +0.25 in n=1000; range -0.18 to +0.18 in n=2000; range -0.18 to +0.18 in n=5000; and range -0.10 to +0.10 in n=10.000 for the CDR-SB). Finally, when stratifying risk factors associated with disease progression, we found that a positive APOE e4 status and baseline abnormal total tau levels were associated with steeper cognitive decline at a group level, but also with greater within-group variability. Greater within-group variability was associated with broader ranges of 95% effect-sizes for all outcome measures (e.g. range -0.80 to +0.80 for the CDR-SB in individuals with baseline abnormal tau), suggesting that stratification on risk factor actually makes it more difficult to capture a treatment effect on group level. **Conclusions:** Our study highlights the importance of understanding heterogeneity in AD progression in the context of clinical trials, by providing more insight on how this heterogeneity, if unaccounted for, could potentially impact trial outcomes, and possibly explain recent anti-amyloid trial failures and tentative successes. Furthermore, we show that the issue of

heterogeneity in disease progression cannot simply be overcome by means of risk-stratification. Altogether, our findings shine more light on how to detect (actual) treatment effects in early AD, and could thereby advance the success of future clinical trials.

**P009: ANALYTICAL VALIDATION OF APTUS-AB ASSAY: AN ACCURATE, REPRODUCIBLE AND PRECISE LC-MS/MS ASSAY FOR QUANTIFYING PLASMA AMYLOID BETA 40 AND 42.** K. Kirmess, M. Holubasch, S. Knapik, M. Meyer, J. Contois, Y. Hu, P. Verghese, E. Smith, S. Harpstrite, T. West, I. Fogelman, J. Braunstein, K. Yarasheski (*C2n Diagnostics - St Louis, USA*)

**Background:** The development of disease-modifying therapeutics for Alzheimer's disease (AD) has long been hindered by the difficulty of obtaining timely and accurate diagnosis of the disease, which contributes up to 80% screen failure rate in AD clinical trials. Despite of the availability of amyloid PET and CSF biomarker assays in identifying brain amyloid pathology, there remains a major unmet need for a radiation-free, non-invasive, cost-effective and more rapid diagnostic method to facilitate clinical trial enrollment as well as to aid in routine clinical diagnosis. Recently, C2N Diagnostics has developed a liquid chromatography mass spectrometry-(LC-MS) based assay (APTUSTM-A $\beta$ ) that can simultaneously quantify amyloid beta (A $\beta$ ) isoforms in blood samples. C2N has previously reported that the ratio of A $\beta$ 42 and A $\beta$ 40 accurately predicts brain amyloidosis, especially when combined with plasma ApoE isoform identification. **Objectives:** To comprehensively evaluate the analytical performance of APTUSTM-A $\beta$  according to CLSI guidelines. **Methods:** A known amount of stable isotope labeled A $\beta$  proteins are added as internal standards into each plasma sample. A $\beta$  isoforms are immunoprecipitated and digested into smaller C-terminal peptides. The peptides are re-suspended, separated on an analytical column, detected and analyzed using a high-resolution mass spectrometer. Peak areas for several precursor and product ions specific for each A $\beta$  isoform and the corresponding internal standard peptides are quantified and compared to those generated by known amounts of unlabeled A $\beta$  isoforms present in the calibrators, allowing for the calculation of absolute quantities of A $\beta$ 40 and A $\beta$ 42 isoforms (pg/mL) in the original plasma samples. **Results:** Precision was assessed by preparing and analyzing five plasma test samples over a wide concentration range and three quality control (QC) samples over 10 days, with two runs per day, and two replicates of each sample per run. Total imprecision (within-lab) for A $\beta$ 40 varied from 2.7% to 7.7%. Total imprecision (within-lab) for A $\beta$ 42 varied from 3.1% to 9.5%. Within-Day imprecision (Repeatability) varied from 1.5% to 3.0% for A $\beta$ 40 and from 2.5% to 8.4% for A $\beta$ 42. Greatest variability was seen at very low concentrations. Accuracy, assessed by recovery of recombinant A $\beta$ 40 and A $\beta$ 42 spiked into artificial plasma at concentrations as low as 50 pg/mL and 7.5 pg/mL, respectively, was within 10% of the expected value. Limit of quantitation (LoQ) values for A $\beta$ 40 and A $\beta$ 42 were calculated as the lowest concentration within the pre-specified precision range (20%) and were found to be 11 pg/mL and 2 pg/mL, respectively. Linearity was demonstrated throughout the entire measuring range for A $\beta$ 40: 10–1780 pg/mL and for A $\beta$ 42: 2–254 pg/mL. No interference was observed with all tested endogenous interferents and common drugs up to the concentrations tested, except for

bilirubin, hemolysate, and human anti-mouse antibody. Acceptable concentrations for these interferents were 2 mg/dL, 487 mg/dL, and 1:347 titer, respectively. Carryover was  $\leq$  0.2% for both analytes and is not considered clinically significant. **Conclusion:** These results demonstrate that APTUSTM-A $\beta$  is an accurate, reproducible and precise clinical LC-MS assay that is suitable for clinical trials and diagnostic testing.

**P010: REDUCING SAMPLE SIZE REQUIREMENTS FOR RANDOMIZED CONTROL TRIALS USING HIGH-FREQUENCY MARKERS.** D. Taylor-Rodriguez<sup>1</sup>, D. Lovitz<sup>1</sup>, N. Mattek<sup>2</sup>, C.Y. Wu<sup>2</sup>, J. Kaye<sup>2</sup>, H. Dodge<sup>2</sup>, B. Jedynek<sup>1</sup> ((1) *Portland State University - Portland, USA*; (2) *Ohsu - Portland, USA*)

**Background:** Reducing sample size requirements for randomized control trials (RCTs) would lower costs and time required to evaluate the efficacy of new treatments. The use of High-Frequency Markers (HFMs) can potentially reduce the sample size requirements for RCTs by helping identify pattern changes which could lead to early detection of disease onset. The Oregon Center for Aging and Technology (ORCATECH) at OHSU has developed unobtrusive data collection technologies to gather high-frequency measurements of a variety of motor and functional metrics, including measurements of walking speed, computer usage time, and sleeping patterns. In spite of the huge potential of these data in aiding early detection of Alzheimer's disease, the methods predominantly used in the literature to analyze longitudinal data fail to exploit these data's full potential, and as such must be further developed to take advantage of the valuable resources generated by these new technologies. **Objectives:** Our methodology aims to use HFMs to detect differences between the treatment and control groups in an RCT. Current statistical analyses including linear mixed effect models with random intercept detect changes in the mean trajectory but fail to detect changes in the covariance structure. Using data from ORCATECH, we examined whether more careful modeling could reduce the sample size and trial length for an RCT. **Methods:** We present a novel statistical methodology for assessing the outcome of an RCT using Gaussian process modeling, the Fisher Kernel, and the Hotelling test. Specifically, we use longitudinal historical data of healthy aging adults to fit a Gaussian process model with a linear slope and a 5 parameters covariance operator. This model allows us to compute the Fisher vector: a vector of dimension 6, associated with each subject's trajectory. We compute the Fisher vector for healthy aging subjects (HC group) as well as for subjects that are healthy at baseline but who eventually become cognitively impaired (mild cognitive impairment, MCI group). This transformation, a.k.a.. the Fisher transform, has the effect of mapping longitudinal data to the Euclidean space of dimension 6 endowed with the common Euclidean metric. In a hypothetical 2-arm RCT with n subjects per arm, each arm would provide a cluster of n Fisher vectors. The success of the trial would be assessed by comparing these two clusters. The Hotelling test is the standard test in this case. A permutation test (or an F test) is used to compute the p-value of the test. The non-central F distribution is used to compute the power and hence the sample size. **Results:** We demonstrate our approach using computer usage data from ORCATECH. Daily computer usage was collected from commercial software installed on the participant's desktop. The HC group had 86 subjects. The MCI group had 11 subjects. We used cross-validation to ensure that

the training and testing subjects were disjoint. We consider a hypothetical 50 week RCT with standard parameters:  $\alpha=5\%$ ,  $\text{power}=80\%$ , and the efficacy of the treatment is  $\rho=40\%$ . Effectively, the untreated group is simulated using our MCI group. We assume that the effect of the treatment is to translate the mean Fisher vector of the treated subjects toward the mean Fisher vector of the HC group. Specifically, covering  $\rho=40\%$  of the distance between these two means. We find that 92 subjects per arm are needed for a 100 weeks clinical trial which compares favorably with the linear mixed effect model applied to the same data, which is the traditional approach. **Conclusion:** Even if there is mounting evidence that HFMs are useful to track the progression of subjects from HC to MCI, designing statistically valid and efficient statistical procedures for using HFMs as outcomes of RCTs remains a challenge. With this work, we provide a framework for the case where observed sequences carry information not only in their trends but also in their covariance structure. We apply this framework to daily computer usage data from a prospectively followed cohort. We show that smaller sample size is achieved while maintaining the statistical validity of the procedure compared to the standard mixed-effect regression approach.

**P011: DISPARITIES IN ALZHEIMER'S DISEASE CLINICAL TRIAL ENROLLMENT IN THE UNITED STATES AND CANADA: AN INDIGENOUS PERSPECTIVE.** N. Olson, B. Albeni (*St Boniface Hospital Research - Winnipeg, Canada*)

Employing Randomized Clinical Trials (RCT) require labor-intensive and highly regulated enrollment methods. In addition, to be inclusive, it is imperative RCTs enroll those populations who would most benefit from the outcomes under investigation. Alzheimer's Disease (AD) is most detrimental to the ageing population, and its clinical manifestation is greatly influenced by socio-economic factors, such as race, poverty, poor education, stress, location, and chronic co-morbidities. Indigenous populations in the United States and Canada are among the minority populations most influenced by poor socio-economic conditions and are prone to the ravages of AD, with Indigenous women carrying the added burden of exposure to violence, caregiving stresses and increased risk by virtue of their sex. Race- and sex-based disparities in RCT enrollment has occurred for decades, with Indigenous men and women very poorly represented. In this poster, we examined literature from the last twenty years that highlight these disparities and provide concrete suggestions to increase the enrollment numbers in AD RCTs amongst this vulnerable and poorly represented sub-population. Biographies (1 for poster/oral communications & 4 for the symposium) / 200 words per bio; Dr. Benedict C. Albeni, PhD, BCMAS, CRQM is a professor of Pharmacology and Therapeutics at the Max Rady College of Medicine at the Univ. of Manitoba and the Everett Research Chair for Alzheimer's Disease at St. Boniface Hospital Research. He is the PI of a current RCT on AD. His research involves both clinical trials and animal models of AD where a large focus is on brain inflammation, brain metabolism, memory impairment, and novel treatment targets.

**P012: THE IMPACT OF PROTOCOL DESIGN ON DATA QUALITY FINDINGS IN DEMENTIA CLINICAL TRIALS.** D. Miller<sup>1</sup>, X. Wang<sup>1</sup>, A. Kott<sup>2</sup> ((1) *Signant Health - Blue Bell, USA*; (2) *Signant Health - Prague, Czech Republic*)

**Background:** Coupling Mini-Mental State Examination (MMSE) eCOA with a review of the audio recording of its administration presents a unique opportunity to identify errors in both MMSE administration and scoring. The presence of either of these types of errors has the potential to lead to incorrect MMSE scores and therefore may result in the inclusion of subjects who do not meet the inclusion criteria and/or a biased assessment of change post-randomization. **Objectives:** In the current analysis, we explore the effect of protocol design (i.e. – whether MMSE inclusion criteria need to be met at screening alone or at both screening and baseline) on the presence of MMSE scoring and/or administration errors at screening and baseline visits. **Methods:** Screening and baseline data were pooled from 2 types of protocols in early dementia – Type A where MMSE related inclusion criteria were required to be met only at screening and type B where the MMSE inclusion criteria were required to be met both at both screening and baseline. All assessments were audio recorded and reviewed by independent, calibrated clinicians for the presence of administration and scoring errors. For each of the MMSE domains, a scoring and/or administration error could be identified. Logistic regression was used to explore the effect of visit type (baseline vs screening) and protocol design on the presence of scoring and/or administration errors. For the purposes of the analyses we only included errors with the frequency of at least 1% in the combined dataset (“eligible errors”). All tests were performed at the alpha level set to 5%. Given the exploratory nature of the analyses we did not correct for multiplicity. **Results:** Our dataset consisted of 16,208 MMSE assessments. MMSE administration or scoring errors affected a total of 3,778 (23.3%) visits; 3,115 (24.6%) at screening and 663 (18.8%) at baseline. In type A protocols a significant reduction of odds of eligible administration errors at baseline compared to screening was observed for Orientation to place (OR = 0.66), Registration (OR = 0.57) and Attention and Calculation (OR = 0.62). In type B protocols a significant reduction of odds of eligible administration errors at baseline compared to screening was observed for Orientation to place (OR = 0.60), and Attention and Calculation (OR = 0.64). In type A protocols a significant reduction of odds of eligible scoring errors at baseline compared to screening was observed for Orientation to time (OR=0.57), Orientation to place (OR = 0.71), Registration (OR = 0.11) and Attention and Calculation (OR = 0.23). In type B protocols a significant reduction of odds of eligible scoring errors at baseline compared to screening was observed for Orientation to place (OR = 0.71), and Repetition (OR = 0.54). A significant difference in odds ratios between protocols was observed for the scoring errors in Attention and Calculation (p value = 0.0011). **Conclusion:** In the current retrospective analysis we assessed the impact of protocol design and visit type (baseline vs screening) on the presence of either MMSE administration and/or scoring errors. A comparable reduction of administration errors between screening and baseline was observed for both protocol types, indicating the reduction most likely resulted from the beneficial effect of the remediation provided to raters who recorded an administration error at screening. For scoring errors, however we see a difference in the error reduction from screening to baseline between the protocol types, with a

larger number and bigger reduction of scoring errors seen in protocols where inclusion criteria are required to be met only at screening. A possible explanation for this difference is that raters intentionally score the MMSE in a manner that would enable potential subjects to meet eligibility at both the screen and baseline visits and therefore be randomizable. We plan to replicate and expand on these results as more data become available.

**P013: RECRUITMENT AND RETENTION IN TWO DECADES OF NIH-FUNDED ALZHEIMER'S DISEASE CLINICAL TRIALS.** M. Ritchie<sup>1,2</sup>, D. Gillen<sup>2,3</sup>, J. Grill<sup>1,2,4</sup>  
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**Background:** Timely recruitment and adequate retention are key factors for whether Alzheimer's disease (AD) clinical trials successfully answer the scientific questions under study. Studies in other fields have observed that, over time, recruitment to trials has become increasingly reliant on larger numbers of sites, with declines in the average recruitment rate (Elkins et al., 2006). Here, we examine trends over a 20-year period in recruitment and retention in NIH-funded AD clinical trials conducted by the Alzheimer's Disease Cooperative Study (ADCS), a largely consistent network of sites devoted to dementia research. **Objective:** The objective of this study is to examine trends in recruitment and retention in AD clinical trials over the last two decades. **Methods:** We conducted retrospective analyses of 8 ADCS randomized clinical trials. This included one trial of vitamin E/donepezil to delay clinical progression from mild cognitive impairment to AD which began enrollment in 1999 and completed in 2004 and had a planned total sample size of n=720. Seven trials tested interventions in populations with AD dementia including simvastatin (2002-2007, n=400); high dose B vitamin supplements (2003-2007, n=400); huperzine A (2004-2007, n=210); valproate (2003-2009, n=300); docosahexaenoic acid (DHA, 2007-2009, n=400); intravenous immunoglobulin (IVIg, 2009-2013, n=385); and resveratrol (2012-2014, n=120). Of these, the valproate trial included moderate AD dementia; all others enrolled mild-to-moderate severity patients. We first assessed trial recruitment planning by calculating the expected site recruitment for each trial, defined as the planned number of participants to be randomized per site. We next examined the actual trial recruitment rates of trials, defined as the number of participants enrolled per site per month. Lastly, we assessed the overall retention rates, reported as the proportion of randomized participants who completed the study, as well as the percentage of participants randomized to placebo groups who completed the study. **Results:** The planned site enrollments for the eight trials in chronological order were as follows: vitamin E/donepezil (10.43 participants per site), simvastatin (8.89 participants per site), high dose B vitamin supplements (10.00 participants per site), huperzine A (6.56 participants per site), valproate (6.52 participants per site), DHA (7.84 participants per site), IVIg (8.56 participants per site), resveratrol (4.62 participants per site). Actual recruitment rates for the eight trials were: vitamin E/donepezil=0.50 participants per site per month; simvastatin=0.25 participants per site per month; high dose B vitamin supplements=0.43

participants per site per month; huperzine A=0.23 participants per site per month; valproate=0.21 participants per site per month; DHA=1.36 participants per site per month; IVIg=0.58 participants per site per month, and resveratrol=0.57 participants per site per month. The overall retention rates ranged from 48% to 87% with valproate (48%) having the lowest retention rate, followed by vitamin E/donepezil (60%), DHA (73%), IVIg (79%), simvastatin (80%) and high dose B vitamin supplements (84%). The highest retention rate was observed in the resveratrol trial (87%). Retention rates for the placebo groups among the trials including mild to moderate AD participants were: simvastatin=77%; high dose B vitamin supplements=83%; huperzine A=90%; valproate=43%; DHA=76%; IVIg=80% and resveratrol=87%. **Conclusion:** Recruitment is consistently challenging in AD trials. These results may suggest that those designing clinical trials anticipated fewer participants enrolled per site over time. Actual recruitment rates ranged from 0.21 to 1.36 subjects/site/month and appeared to depend more on trial specific factors (disease severity, intervention under study) than effects of time. Among the subset of trials most easily compared (those in mild-to-moderate AD), recruitment rates were higher in trials completed later in time. Only one trial, a double-blind, randomized placebo-controlled trial of the oral supplement DHA in mild-to-moderate AD, enrolled more than 1 subject/site/month. We observed widely varying overall retention rates. Four trials achieved 80% completion (simvastatin, high dose B vitamin supplements, huperzine A, and resveratrol). Retention rates among trial placebo groups similarly ranged widely (43% to 90%). Retention was lowest in the trial enrolling participants with more severe disease (valproate). Future analyses will examine additional potential predictors of recruitment and retention rates, including subject-level data. Analyses such as these may guide decisions regarding future practices, including whether specific protocol elements should be selectively implemented (or removed) to optimize trial recruitment and retention.

**P014: USING DIGITAL TWINS TO DECREASE ENROLLMENT AND INCREASE STATISTICAL POWER IN ALZHEIMER'S DISEASE CLINICAL TRIALS.** D. Hall, A. Schuler, Y. Pouliot, D. Bertolini, A. Smith, C. Fisher, J. Walsh (Unlearn.ai - San Francisco, USA)

**Background:** Drug development for Alzheimer's disease (AD) is increasingly expensive and time-consuming. To decrease the high failure rate of these trials, it will be necessary to improve clinical trial design by reducing total trial size and/or recruitment time. Randomized controlled trials (RCTs) have long been the gold-standard among clinical trial designs, even though they can be very inefficient. The volume of clinical trials provides an opportunity to improve the efficiency of AD trials, which has been highlighted by the FDA in a number of communications. With data collected from the control groups of many prior AD trials and state-of-the-art statistical methods, we have developed machine learning (ML) technology to comprehensively model the progression of control subjects. Our model can generate digital twins, which are digital subject records generated from the baseline data of actual subjects in a trial. These digital twins show the potential outcomes of individual subjects had they received a placebo. **Objective:** Describe a statistical framework for including digital twins in the analysis and interpretation of AD clinical trials. Validate the effectiveness of digital twins under this

framework to add power to trials and to allow reduced control arm enrollment through retrospective studies. **Methods:** We created an ML model that generates digital twins for control arms of AD clinical trials. This is a statistical model that captures the relationships between clinical variables relevant to AD (including key endpoints) as they change over time in an individual. Digital twins are clinical records generated from the model that predict follow-up data from baseline data of subjects. When building this model, we thoroughly validated its performance in generating digital twins that accurately model subject outcomes in a test dataset. Digital twins can be included in the analysis of a clinical trial in a number of ways, either to add additional power to both primary and secondary analyses, or to allow a reduction in the number of enrolled control subjects while maintaining power across analyses. We have developed a statistical framework to include digital twins that uses the predicted outcomes from the digital twins to reduce variability in treatment effect estimates while allowing for various levels of control over type I error. This differs from traditional methods for historical borrowing or synthetic controls and allows for a broad range of applications depending on the design and needs of a trial. To validate this approach, we reanalyzed data from past AD clinical trials in two ways. First, we added digital twins to the analysis of both primary and secondary endpoints and measured the decrease in uncertainty obtained relative to the original analyses. Second, we removed a random subset of the control arm subjects and added digital twins for all remaining subjects, measuring the average size of the control arm reduction that achieves the same uncertainty as the original analyses. This allowed us to directly measure the effectiveness of digital twins in these directions. We compared these results to results obtained when validating the model's performance to better quantify the expected gains in statistical power or efficiency when using digital twins in an AD trial. **Results:** By adding digital twins, we were able to show that this decreased uncertainty of outcome measurements in the retrospective study for both primary and secondary analyses and allowed for additional subgroup explorations. This implies that digital twins may be used in a supplemental fashion to increase the power of trials. We showed that digital twins could reduce the number of control subjects required in the analysis to achieve equivalent results to an analysis of the actual subjects. This implies that digital twins may be used in an augmenting fashion to design studies with a smaller control arm that achieves a design power. **Conclusions:** We have developed statistical frameworks to use digital twins in the analysis of clinical trials to increase confidence in results by adding power or to reduce the number of enrolled control arm subjects required to obtain a design power. We have validated the gains in power and efficiency through retrospective analyses of AD trials and plan to further validate these methods through prospective studies.

**P015: VALIDATION OF A NOVEL TECHNOLOGY FOR NON-INVASIVE PROGNOSIS OF AMNESTIC MCI IN CLINICS AND CLINICAL TRIALS.** K. Vejdani<sup>1</sup>, E. Khosravi<sup>2</sup>, T. Liebmann<sup>3</sup>, P. Krishnamurthy<sup>4</sup>, P. Kamali-Zare<sup>5</sup> ((1) *Chief Medical & Technology Officer - San Francisco, USA;* (2) *Head Of Innovations - San Francisco, USA;* (3) *Chief Scientific Officer - San Francisco, USA;* (4) *Head Of Operations - San Francisco, USA;* (5) *Chief Executive Officer - San Francisco, USA*)

**Background:** Objective, accurate, and reliable prediction of progression from mild cognitive impairment (MCI) to Alzheimer's dementia (AD) is a critical need in the evaluation and management of cognitive impairments, both in the clinical setting and for clinical trials. Neurocognitive assessments such as MMSE, MOCA, and CDR are routinely used for diagnosis at the time of clinical evaluation, but are relatively poor predictors of prognosis. For 5-year prognosis, the positive predictive value (PPV) is ~35% if the neurocog-based baseline diagnosis is MCI, ~50% if the diagnosis is amnesic MCI (aMCI), and ~70% if aMCI is also amyloid positive. As a result, nearly 30-50% of the selected amyloid-positive aMCI patients will not convert to dementia during the clinical trial period, making it extremely difficult to detect a statistically significant drug effect, if any. Darmiyan Inc. has developed a novel technology, BrainSee, for objective, accurate, and reliable prediction of progression from aMCI to AD based on basic cognitive screening and standard, clinical brain MRI. The novelty of BrainSee lies in 1) subvoxel analysis of brain tissue to quantify deviation of microstructural parameters from their physiologic range, and 2) use of machine learning and AI to find disease-specific patterns of abnormality in the whole brain. **Objectives:** The main objectives of this study were to evaluate: 1. The performance accuracy of BrainSee for 5-year prognosis of aMCI on blind samples coming from the real-world clinical setting; 2. The robustness of BrainSee to standard routine clinical-grade data; 3. Test-retest reliability of BrainSee; 4. The clinical utility and usability of the output report of BrainSee, including the quantitative whole brain maps. **Methods:** Data for third party validation were provided by the Knight ADRC (Washington University) Huntington medical research institutes (HMRI), Centre for aging and brain health innovation (CABHI), Baycrest Institute, University Health Network (UHN), and GERAS Hamilton Health Sciences (HHS). Subjects with amnesic MCI and without clinical depression or other significant medical, neurologic, or psychiatric disorders were selected for blind testing and validation of BrainSee, including performance accuracy and test-retest reliability. Patients with active use of substances, alcohol or anticholinergics were excluded. De-identified data including basic patient demographics (age, sex, education), MMSE, CDRSB, and MRI (T1, T2, DWI or DTI) were provided for analysis. BrainSee's algorithm was blind to the distribution and clinical outcomes of all patients. BrainSee processed each data point and generated a prognostic prediction of conversion to dementia within 5 years on a 4-point DarmiGrade scale, where grades 1 and 2 predict non-conversion and grades 3 and 4 predict conversion. Darmiyan's prognostic prediction was evaluated against the ground truth of a clinician's judgement of clinical outcome, i.e. the presence or absence of dementia at 5-year clinical follow-up. Progression to dementia at any point within 5 years was considered conversion. For non-conversion, absence of dementia for at least 5 years was required. To account for class size imbalance, balanced accuracy (BA) was calculated as the arithmetic mean of sensitivity and specificity,



i.e  $BA = (\text{sensitivity} + \text{specificity}) / 2$ . To account for class prevalence discordance between the sample and population, prevalence-corrected positive and negative predictive values (PPV<sub>pc</sub>, NPV<sub>pc</sub>) were calculated based on an assumed prevalence of 50% (based on known aMCI to AD conversion rate of 10-15% per year). To eliminate the bias effect of multiple time points for a single subject, a subject weighting strategy was used. For test-retest reliability, coefficient of variation was calculated for each subject and averaged over all subjects. In each subject, repeated clinical-grade or research-grade brain MRI scans were performed on the same day. **Results:** For prognosis prediction testing, a total of 101 independent clinical time points (76 converter, 25 non-converter) from 95 subjects (74 converter, 21 non-converter) were provided by 3rd party investigators to Darmiyan for prognostic analysis. Subject ages ranged from 51 to 95 years, and male to female ratio was 1.175. For test-retest variability evaluation, sixty (60) subjects (78 scan sessions) were provided. The performance analysis results were reported as follows: Balanced accuracy (BA) of prognostic prediction = 91.0 %; Sensitivity = 89.2 %, Specificity = 92.9 %; PPV<sub>pc</sub> = 92.6 %, NPV<sub>pc</sub> = 89.6 %; Test-retest coefficient of variation = 4.6%; These performance analysis results confirm the robustness of BrainSee to the variability in quality and resolution of research-grade and clinical-grade neuroimaging data. Clinicians also indicated that BrainSee's report and grading system were easy to understand and interpret. BrainSee's whole-brain maps were consistent with the predicted prognostic grades. These maps demonstrated quantitative regional differences between converter and non-converter aMCI patients. **Conclusions:** Darmiyan's technology had a 91.0 % performance accuracy on blind clinical-grade brain imaging data from aMCI patients, and showed high test-retest reliability confirmed by third party investigators. Darmiyan's BrainSee technology is therefore an accurate, non-invasive and reliable tool to be used for prognostication of cognitive impairments in clinics and clinical trials.

**LP01: FACTORS AFFECTING WILLINGNESS TO PARTICIPATE IN AN FMT STUDY FOR ALZHEIMER'S DISEASE.** J. Thorstenson<sup>1</sup>, M. Heston<sup>1,2</sup>, N. Vogt<sup>1</sup>, S. Harding<sup>1</sup>, M. Beilfuss<sup>1</sup>, R. Aune<sup>1</sup>, J. Langfus<sup>3</sup>, N. Davenport-Sis<sup>1</sup>, N. Chin<sup>1</sup>, F. Rey<sup>2</sup>, B. Bendlin<sup>1,4</sup> ((1) *Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin School Of Medicine And Public Health - Madison, USA;* (2) *University Of Wisconsin-Madison, USA;* (3) *Department Of Psychology And Neuroscience, University Of North Carolina At Chapel Hill - Chapel Hill, USA;* (4) *Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health - Madison, USA*)

**Background:** Fecal microbiota transplant (FMT) is efficacious in treating *C. difficile* infections, but it remains unknown whether it has beneficial effects in neurodegenerative diseases, including Alzheimer's disease (AD). Given that prior studies suggest that gut microbiome composition is altered in AD, and FMT improves cognitive function in mouse models of AD, safety and efficacy studies of FMT are warranted. However, individuals may be hesitant to engage in an experimental therapy with a human-derived biologic. To effectively recruit participants, it is necessary to determine the factors that may influence a person's willingness to engage in an FMT study. **Objectives:** The primary objective of this study was to identify factors that affect the decision to participate in an FMT study for AD (experimental willingness). We

hypothesized that experimental willingness may associate with greater willingness to consider FMT for disease treatment (treatment willingness). Therefore, our secondary objective was to identify factors influencing one's decision to use FMT therapy. **Methods:** 211 participants were recruited from the Wisconsin Alzheimer's Disease Research Center clinical core and the Wisconsin Registry for Alzheimer's Prevention (WRAP) studies (cognitively unimpaired, N=199; AD dementia, N=6; other cognitive impairment or no diagnosis, N=6). Participants enrolled in the Microbiome in Alzheimer's Risk Study (MARS), wherein they answered a questionnaire reporting opinions toward FMT for disease treatment and study. Outcomes from the questionnaire included experimental willingness (primary outcome, binary) and treatment willingness (secondary outcome, ordinal). Covariates included: a) Previous knowledge of FMT, b) AD impact: whether a participant self-reports AD diagnosis, c) FMT consideration for AD: whether a participant would consider FMT to treat AD if they were at increased risk for AD, d) Disease type: whether a participant's decision to undergo FMT would depend on the disease treated, e) Anonymous donor: whether a participant would consider receiving an FMT from an anonymous donor, f) Parental history of AD, g) APOE ε4 carrier status, h) Demographic covariates: participant age, sex, education. Binary logistic regression was performed to determine whether treatment willingness predicted experimental willingness, adjusting for previous knowledge of FMT, AD impact, FMT consideration for AD, and demographic covariates. Exhaustive subset selection was used to identify the best predictive model with the fewest variables. Ordinal logistic regression was performed to determine the extent to which previous knowledge of FMT, disease type, anonymous donor, FMT consideration for AD, and AD impact altered treatment willingness, adjusting for demographic covariates. Binomial logistic regression and mosaic plots were used to identify diseases that participants considered more acceptable for FMT treatment. **Results:** Higher treatment willingness was associated with greater experimental willingness. Individuals who had likely treatment willingness were 1.80 times more likely to engage in an FMT study for AD than those with very unlikely, unlikely or indifferent treatment willingness (p<.001), and people with very high treatment willingness had 1.50 times greater experimental willingness than the previous four groups (p=.002). Previous knowledge of FMT, FMT consideration for AD, and AD diagnosis did not significantly associate with experimental willingness, but they contributed meaningfully to the model based on best subsets selection. Treatment willingness was positively associated with previous knowledge of FMT (p=.028, unadjusted). When adjusting for covariates, previous FMT knowledge no longer contributed significantly. Disease type associated with decreased treatment willingness (p=.036), while anonymous donor and FMT consideration for AD was associated with increased treatment willingness (ps<.001, .005). In identifying perceived disease acceptability for FMT treatment, we found that Alzheimer's disease, *C. diff* infection, Parkinson's disease (ps<.001), autoimmune conditions, Crohn's disease, irritable bowel syndrome, ulcerative colitis (ps<.01), colitis and stroke (ps<.05) were significantly associated with higher acceptability (higher log-odds of a yes answer). Additionally, people with high treatment willingness were significantly more likely to agree to FMT therapy for any given disease (p<.001). **Conclusion:** In this study, we observed that FMT treatment willingness was the best predictor of willingness to engage in

an FMT study (experimental willingness) in the context of AD. Factors that associated with increased treatment willingness included previous knowledge of FMT, use of stool from an anonymous donor, and whether a participant would consider FMT if they were at increased risk for AD (FMT consideration for AD). Disease type— whether a participant’s decision would depend on the disease treated—associated with lower willingness to undergo FMT. Gastrointestinal disorders and several neurological diseases were gauged most acceptable for FMT treatment. These factors may guide study design, recruitment, and education of participants in future FMT clinical trials.

**LP02: USE OF PREDICTIVE ALGORITHMS FOR THE SELECTION OF PATIENTS IN CLINICAL TRIALS: AN ENRICHMENT STRATEGIES COMPARISON.** A. Movschin<sup>1</sup>, C. Longo Dos Santos<sup>1</sup>, A. Mascia<sup>1</sup>, J. Samper-González<sup>1</sup>, U. Thoprakarn<sup>1</sup>, P. Tran<sup>1,2</sup>, J.B. Martini<sup>1</sup>, E. Cavedo<sup>1</sup> ((1) *Qynapse Sas - Paris, France*; (2) *Equipe-projet ARAMIS, ICM, CNRS UMR 7225, Inserm U1117, Sorbonne Université UMR\_S 1127, Centre Inria de Paris, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Faculté de Médecine Sorbonne Université - Paris, France*)

**Backgrounds:** Although the implementation of biological markers for the diagnosis of Alzheimer’s Disease (AD) has largely increased our understanding in the AD pathophysiological processes, we are still unable to predict whether and when a patient with Mild Cognitive Impairment (MCI) will develop AD. This limitation impacts the drug development process for AD (Yiannopoulou KG et al., 2019). Clinical trials of disease-modifying drugs in patients with MCI could benefit from enrichment strategies that use predictive algorithms to select patients who are more likely to decline cognitively. **Objectives:** To compare various strategies for patient enrichment in terms of trial success probability and screening failure rate via a clinical trial simulation procedure; to evaluate the benefit of using a predictive tool to refine patient selection. **Methods:** We selected two groups of MCI patients from the ADNI database : those who underwent cognitive decline (ADNI decliners) two years from baseline, defined as a change > 0 at the Clinical Dementia Rating Sum Of Boxes (CDRSOB) (N= 288), and those who did not (ADNI non-decliners) (N= 360). For both groups (ADNI decliners and ADNI non-decliners), we derived the distribution of the CDRSOB at baseline, as well as the distribution of the CDRSOB annual percent change (CDRSOB APC). We later refer to these as the ADNI decliners and ADNI non-decliners progression distributions. Then, we defined two different patient selection strategies. The first strategy was considered as the «reference» with the following inclusion criteria: age = 55 - 90, MMSE = 24 - 30, CDR = 0.5 and amyloid positivity (PET or CSF). The second strategy included the «reference» plus a criterion based on the results of a predictive tool, QyPredict, using an adjustable threshold. This tool computes a cognitive decline risk score based on a CDRSOB change two years from baseline. We then computed the screening failure rate and the percentage of decliners obtained using the different selection strategies on ADNI MCI patients. For each strategy, we used this percentage of decliners combined with the progression distributions for ADNI decliners and ADNI non-decliners groups to simulate a 1000 subjects cohort. Therefore, the simulated cohort has the same percentage of decliners/non-decliners and progression distributions as the selected patients using the same strategy on

ADNI MCI patients. Next, we randomly split each simulated patient cohort into a placebo and a treatment arm. We then applied a correction in the treatment arm to account for a pre-specified treatment effect of 25% reduction in CDRSOB APC by the end of the trial (24 months). Then, we computed the CDRSOB APC in the placebo and the treatment arms and calculated the corresponding effect size with Cohen’s d formula. For each strategy, this simulation was run 1000 times, so we could effectively compute the success probability. The success rate was defined as the ratio of experiments for which the effect size was larger than the minimum detectable effect size with a two-tailed Student’s t-test with 5% significance and 80% power. **Results:** We found that the use of a predictive tool, such as QyPredict, improves the trial success probability at the cost of an increase in the screening failure rate. For example, while the reference strategy led to a 6% success probability with a 75% failure rate, the use of an additional inclusion criteria based on a 50% cut-off value on the QyPredict output increased the success probability to a value of 50%, at the cost of an increase of the screening failure rate to a value of 88%. **Conclusion:** We proposed a simulation framework to evaluate the success probability and screening failure rate of various patient selection strategies for a clinical trial. Such a framework could also be used to derive the cost and the duration of a trial, depending on the patient selection strategy. We used this framework to evaluate the benefit of using QyPredict to enrich the patient selection strategy. Such a tool can improve the success probability of a trial, at the cost of an increase in the screening failure rate. To maximize the potential of such an approach, a relevant trade-off should be searched for, taking into account the trial’s objectives in terms of success likelihood, cost and duration. **References:** Yiannopoulou KG et al., *Biomedicines*. 2019

**LP03: APPLYING FEEDBACK FROM AN ADVISORY BOARD OF RESEARCH PARTICIPANTS TO IMPROVE CLINICAL TRIALS IN ALZHEIMER’S DISEASE AND RELATED DEMENTIAS.** S. Walter<sup>1</sup>, E. Shaffer<sup>1</sup>, J. Ziolkowski<sup>2</sup>, N. Chan<sup>3</sup>, R.C.H. Hummel<sup>4</sup>, R. Heyde<sup>4</sup>, N. Meserve<sup>4</sup>, N. Childs<sup>4</sup>, P. Aisen<sup>1</sup> for the Alzheimer’s Clinical Trials Consortium ((1) *Alzheimer’s Therapeutic Research Institute, University of Southern California, San Diego, CA, USA*; (2) *University of Michigan, MI, USA*; (3) *Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA*; (4) *Member, ACTC Research Participant Advisory Board*)

**Background:** As a consortium funded by the National Institute on Aging (NIA), National Institutes of Health (NIH), the Alzheimer’s Clinical Trials Consortium (ACTC) has the mission to provide an optimal infrastructure, utilizing centralized resources and shared expertise, to accelerate the development of effective interventions for Alzheimer’s disease and related disorders (ADRD). The perspective of research participants is critical to improving development and effectiveness of clinical trials. **Objectives:** To share the ACTC experience in forming an advisory board of research participants with the following aims: (1) to provide guidance on study design for clinical trials in ADRD and (2) provide feedback on network conduct. To summarize feedback that led to changes in study design and implementation. **Methods:** A task force was assembled of ACTC consortium members with the aim of creating a proposal and supporting materials for the board. Experience, best practices, and sample support

materials were provided by organizations that have successfully established similar boards, including the Dominantly Inherited Alzheimer Network (DIAN) and the Alzheimer's Association Early Stage Advisory Group. Members were nominated by Site members of the ACTC Steering Committee, and were interviewed by either phone or video-conference prior to selection. Quarterly meetings were scheduled up front, with the first meeting in person in San Diego, February 7, 2020. Feedback was obtained from members after both the first in-person meeting and first remote meeting, resulting in adjustments to meeting structure and preparatory materials. **Results:** Fourteen members were selected in January 2020, including individuals with a diagnosis of mild Alzheimer's disease (AD), individuals with elevated risk for AD, and care partners of individuals with dementia. Four members are non-Caucasian. Members live in both urban and rural setting across the United States. All members have some experience in either interventional or non-interventional studies of AD. The first meeting of the board focused on general feedback on AD research studies and recruitment methods. The second was a detailed review of the draft informed consent form for the upcoming AHEAD study, and the third meeting focused on providing feedback on recruitment strategies for the same study. Research participant advisory board feedback was presented to the full ACTC Steering Committee as well as study leadership. A number of changes were implemented, including adding the option for participants to receive the results of APOE testing, separate compensation to study partners, increased flexibility for in-person visit attendance of study partners, and refining the language being used in the materials describing the AHEAD study to potential participants. **Conclusion:** We have demonstrated the feasibility of assembling a board of research participants and care partners to provide ongoing feedback. The feedback received so far has resulted in changes that may improve recruitment and retention for ACTC studies. Moving forward, we will ensure feedback is obtained as early as possible in the process of study design and implementation. We also aim to improve the diversity of the board, towards the ultimate goal of recruiting individuals that better represent the US population in research studies for AD.

## Theme 2: CLINICAL TRIALS: RESULTS

**P016: NEW HORIZONS IN ALZHEIMER RESEARCH FROM AMYLOID AND BEYOND.** J. Apter<sup>1,2</sup>, R. Iqbal<sup>3</sup>, O. Aung<sup>3</sup>  
(1) *President Of Global Clinical Trials - Princeton, USA;*  
(2) *Research Collaborator at Princeton, NJ - Princeton, USA;*  
(3) *Princeton Medical Institute - Princeton, USA*

The Amyloid and Tau Hypotheses of Alzheimer's disease, once thought to be a key component of clinical trials research in the field, have shown marginal results. However, the hypotheses have been bolstered by the recent revival of the Aducanumab study and some positive data on some anti-Tau drugs. This project examines approaches targeting Amyloid and Tau proteins in the brain, as well as those not directly involving Amyloid and Tau, including Epigenetic approaches, a low dose of an anti-epileptic drug, an antibiotic against *P. gingivalis* and other new approaches. Other newer approaches were also presented at CTAD 2019. We examined the results of clinical trials testing these mechanisms in order to assess the effectiveness in treating Alzheimer's Disease.

**P017: ADMINISTERING TRICAPRILIN AFTER A MEAL OPTIMISES BIOAVAILABILITY AND MINIMISES ADVERSE EVENTS.** J. Walker<sup>1</sup>, L. Nelleman<sup>1</sup>, L. Chow<sup>1</sup>, B. Morimoto<sup>2</sup> ((1) *Cerecin - Singapore, Singapore;* (2) *Cerecin - Denver, USA*)

**Background:** Cerebral glucose hypometabolism in posterior cingulate, parietal, temporal, and prefrontal cortex is an early feature of Alzheimer's disease. These regions exhibit declines in glucose metabolism, but have been shown to preserve the ability to metabolise ketones. Therefore, Cerecin is developing tricaprillin as treatment for Alzheimer's. Multiple formulations of tricaprillin, an 8-carbon chain triglyceride ketogenic therapy, were developed and tested in vitro, in vivo and in human studies to assess pharmacokinetics, safety and tolerability. **Objective:** To understand how food ingestion affects PK, safety and tolerability of a new formulation of tricaprillin in healthy young men of Caucasian and Chinese descent. **Method:** This food effect clinical study (Study AC-18-016) was conducted in healthy human Caucasian and Asian volunteers and in a variety of food conditions to better understand the influence of food ingestion on PK and on tolerability. It employed a 2-part, 4-way and 2-way cross-over design. (NCT03551769). **Result:** This novel formulation of tricaprillin showed desirable PK characteristics, leading to generation of ketones and excellent safety and tolerability, when administered in doses of 20g after a meal, in both Caucasians and Chinese. **Conclusion:** In future clinical studies, tricaprillin will be administered 30' after completion of a meal to optimise bioavailability and minimise any GI adverse events.

**P018: NOVEL FORMULATION AC-SD-03 OF TRICAPRILIN LEADS TO EXCELLENT PK AND SAFETY IN DOSES OF UP TO 30G BID.** L. Chow<sup>1</sup>, L. Nelleman<sup>1</sup>, B. Morimoto<sup>2</sup>, J. Walker<sup>1</sup> ((1) *Cerecin - Singapore, Singapore;* (2) *Cerecin - Denver, USA*)

**Background:** Cerecin is developing ketogenic therapies for Alzheimer's disease (AD). Ketones are an excellent source of fuel for cells in the posterior cingulate, parietal, temporal, and prefrontal cortex which have reduced ability to metabolise glucose whilst preserving the ability to metabolise ketones. Earlier studies have shown that ketone therapy can improve cognition in AD. AC-SD-03 is the latest formulation to be developed for use in a Phase 3 study in mild to moderate AD. **Objective:** To assess the pharmacokinetics, safety and tolerability of Cerecin's newest proprietary formulation of tricaprillin, AC-SD-03, in healthy young male Caucasian and Asian volunteers. To assess the ketogenic properties of a placebo to AC-SD-03 prior to moving to Phase 3 clinical studies. To assess the properties of a prototype slow-release formulation of tricaprillin. (Studies AC-19-017 Parts 1 and Parts 2). To ensure tolerability of the dose and titration regime to be used in a phase 3 study, in a healthy older population. (Study AC 20-021). **Method:** Study AC-19-017 was a 2-part study conducted in healthy young male volunteers and tested AC-SD-03 ; a prototype, slow release formulation of tricaprillin; an earlier formulation of tricaprillin; and a placebo to AC-SD-03. (NCT03971123). Study AC-20-021 was a multiple ascending dose study conducted in 12 healthy older (50 years +) subjects over 24 days, with doses of tricaprillin increasing from 5 g once a day to 30g twice a day. (NCT04268953). **Result:** AC-SD-03 showed expected bioavailability and excellent safety and tolerability, when administered in single doses of 20g

after a meal, in both Caucasians and Asians. AC-SD-03 was well tolerated in a healthy older population when titrated to a dose of 30g of tricapriline BID. At this dose, desirable PK characteristics, leading to generation of ketones and excellent safety and tolerability, were seen. **Conclusion:** Formulation AC-SD-03 has demonstrated excellent PK, safety and tolerability in young males and in an older healthy population, in doses of up to 30g BID, and will be moved forward into a Phase 3 study in mild to moderate AD.

**P019: AN EVIDENCE-BASED RISK-MITIGATION APPROACH TO STUDY DESIGN IN APOE4(-) MILD TO MODERATE AD.** J. Walker<sup>1</sup>, L. Nelleman<sup>1</sup>, B. Morimoto<sup>2</sup>, L. Chow<sup>1</sup> ((1) *Cerecin - Singapore, Singapore*; (2) *Cerecin - Denver, USA*)

**Background:** AC-SD-03 is a proprietary formulation of tricapriline, a ketogenic therapy for Alzheimer's disease (AD). Building on the known mechanism of action of ketones which act as an alternative source of fuel to brain cells which cannot metabolise glucose efficiently, on the data from Cerecin's studies, and on data from ketogenic diets, Cerecin optimised the PK and safety profile for AC-SD-03. PK-PD modelling was undertaken to understand the doses required to optimise clinical effect. In addition, a food effect and an ascending dose study were conducted in healthy older subjects. These activities were conducted in preparation for a Phase 3 AD study to start shortly, the ALTER-AD trial (NCT04187547). **Objective:** To use an evidence-based risk mitigation strategy to design a phase 3 study to increase probability of success. **Method:** The ALTER-AD trial has been designed to study the efficacy and safety of AC-SD-03 in APOE4(-) subjects with mild to moderate AD. **Result:** ALTER-AD design is a randomised placebo-controlled add-on to standard of care study of AC-SD-03 vs placebo, in APOE4(-) patients with mild to moderate AD. Key elements of the study design and how they have been informed by incremental accumulation of knowledge over 20+ years of development with a goal of mitigating risk will be presented. **Conclusion:** This Phase 3 study of AC-SD-03 in APOE4(-) patients with mild to moderate AD has been designed to mitigate risk and ensure success and builds on a firm understanding of the disease in an important subset of patients of AD.

**P020: TRICAPRILIN SHOWS SIMILAR PK, SAFETY AND TOLERABILITY IN CAUCASIANS AND ASIANS.** B. Morimoto<sup>1</sup>, L. Nelleman<sup>2</sup>, L. Chow<sup>2</sup>, J. Walker<sup>2</sup> ((1) *Cerecin - Singapore, Singapore*; (2) *Cerecin - Denver, USA*)

**Background:** Cerecin is developing ketogenic therapies for Alzheimer's disease (AD) based on earlier studies showing that ketone therapy can improve cognition in AD. AC-SD-03 is the latest formulation to be developed for use in a Phase 3 study in mild to moderate AD which will be conducted globally in Asia Pacific, United States and Europe. The pharmacokinetics of tricapriline have been well-characterized by a series of clinical pharmacology studies. **Objective:** To assess the pharmacokinetics, safety and tolerability of Cerecin's newest proprietary formulation of tricapriline, AC-SD-03, in healthy young male Caucasian and Asian volunteers. To understand differences between the two populations and any ethnic sensitivities. **Method:** In this analysis, data from several studies were included, including Cerecin's studies AC-18-

016, AC-19-017 Part 1 and AC-19-017 Part 2. Study AC-18-016 was a food effect study of the AC-SD-01 formulation of tricapriline, conducted in healthy young males (NCT03551769). Study AC-19-017 was a 2-part study conducted in healthy young male volunteers and tested AC-SD-03; a prototype, slow release formulation of tricapriline; an earlier formulation of tricapriline; and a placebo to AC-SD-03. (NCT03971123). Both of these studies included Caucasian and Asian (Chinese) subjects and several analyses were conducted to compare the effects in Caucasians vs Chinese. To explore whether ethnicity affects total ketone body exposure after tricapriline administration, the pharmacokinetic parameters AUC<sub>0-t</sub> and C<sub>max</sub> from the AC-19-017 study were examined and grouped by an individual's ethnicity (Chinese or Caucasian). **Result:** Differences between ethnicities in each study were minor and were less apparent when corrected for weight. When data from the 2 parts of study AC-19-017 were combined, the mean C<sub>max</sub> for total ketones in Chinese participants was 965 mM and 1000 mM for Caucasian participants (p=0.78) and the mean total ketone AUC<sub>0-t</sub> for Chinese participants was 3011 h\*mM; whereas, for Caucasian participants, the AUC<sub>0-t</sub> was 2953 h\*mM. (p=0.89). No differences were seen in AE profile between Asian and Caucasian subjects. **Conclusion:** Exposure to total ketones, the active species after tricapriline administration was no different for healthy ethnic Chinese participants compared to healthy Caucasians. There does not appear to be any ethnic difference in absorption or metabolism of tricapriline to produce ketone bodies, or in their safety and tolerability profile.

**P021: FREQUENCY OF ANTIPSYCHOTIC-ASSOCIATED ADVERSE EVENTS WITH PIMAVANSERIN TREATMENT IN PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.** G. Demos<sup>1</sup>, E.P. Foff<sup>1</sup>, D. Weintraub<sup>2</sup>, B. Mcevoy<sup>1</sup>, S. Stankovic<sup>1</sup> ((1) *ACADIA Pharmaceuticals, Inc. - Princeton, USA*; (2) *University Of Pennsylvania School Of Medicine - Philadelphia, USA*)

**Background:** Pharmacologic action of antipsychotics with effects at multiple receptors often results in dose-limiting side effects, such as extrapyramidal symptoms, orthostatic hypotension, hematologic and metabolic abnormalities, gastrointestinal symptoms, and sedation, in elderly patients with dementia-related psychosis (DRP). Pimavanserin is a selective serotonin (5HT<sub>2A</sub>) inverse agonist/antagonist with no appreciable affinity for non-serotonergic receptors, and is being investigated as a possible treatment for hallucinations and delusions associated with DRP. **Objectives:** Examine the incidence in the HARMONY study of adverse events (AEs) that are associated with antipsychotics that bind to multiple neurotransmitter receptors. **Methods:** HARMONY was a phase 3, double-blind (DB), placebo-controlled, relapse-prevention study in which patients received pimavanserin (n=392) during a 12-week open-label (OL) phase, with patients demonstrating sustained response to pimavanserin then randomized into the DB phase for treatment up to 26 weeks. Approximately 62% of eligible patients (217/351) achieved stable response of psychosis over the OL period and were randomized into the DB phase. Treatment-emergent adverse events (TEAEs) were assessed at each study visit. The incidence of the following TEAEs during OL and DB phase were investigated: sedation; falls; cerebrovascular events; thromboembolic events; neuroleptic malignant syndrome (NMS); metabolic disorders (diabetes, dyslipidemia); hyperprolactinemia; seizures; blood dyscrasias; orthostatic hypotension; extrapyramidal symptoms,

and cognitive events. Motor dysfunction was assessed using the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A). Cognition was assessed using the Mini-Mental State Examination (MMSE). **Results:** The median duration of exposure in the OL phase was 12 weeks; median exposure duration during the DB phase was higher in the pimavanserin group (17.7 weeks, N=105) than in the placebo group (10.9 weeks, N=112) due to higher rates of attrition in the placebo group secondary to relapse of psychosis or withdrawals. No AEs of cerebrovascular events, thromboembolic events, NMS, diabetes, dyslipidemia, hyperprolactinemia, or seizure were reported in the OL phase. The observed incidence of falls (n=7, 1.8%), somnolence (n=6, 1.5%), confusional state/mental status change (n=9, 2.3%), orthostatic hypotension (n=2, 0.5%), parkinsonism (n=2, 0.5%), and akathisia, tremor, sleep disorder, anemia, and ataxia (n=1 each, 0.3%) in the OL phase was low. Events in the DB phase were generally single reports and were similar to placebo. The only adverse reactions occurring in  $\geq 3\%$  of patients who remained on pimavanserin and at a higher rate than placebo were headache (9.5% vs. 4.5% placebo) and urinary tract infection (6.7% vs. 3.6% placebo). Measures of motor dysfunction (ESRS-A) and cognition (MMSE) did not show evidence of worsening from OL baseline through the DB phase. **Conclusions:** Adverse events commonly associated with antipsychotics impacting dopaminergic, muscarinic, cholinergic, and histaminergic receptor activity were infrequently reported in pimavanserin-exposed patients with DRP in the HARMONY study. **Disclosures:** This study was funded by ACADIA Pharmaceuticals Inc. GD, EPF, and BM are all employees of ACADIA Pharmaceuticals Inc. Dr. Weintraub has received research funding or support from the Michael J. Fox Foundation for Parkinson's Research, Alzheimer's Therapeutic Research Initiative (ATRI), Alzheimer's Disease Cooperative Study (ADCS), the International Parkinson and Movement Disorder Society (IPMDS), and National Institute on Aging (NIA); honoraria for consultancy from ACADIA, CHDI Foundation, Clintrex LLC (Aptinyx, Avanir, Otsuka), Eisai, Janssen, Sage, Signant Health, and Sunovion; and license fee payments from the University of Pennsylvania for the QUIP and QUIP-RS.

**P022: THE ALZHEIMER'S DISEASE THERAPY WITH NEUROAID (ATHENE) STUDY: ASSESSING THE SAFETY AND EFFICACY OF NEUROAID II (MLC901) IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE STABLE ON CHOLINESTERASE INHIBITORS OR MEMANTINE: A 6-MONTH RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL WITH A 6-MONTH OPEN LABEL EXTENSION: RESULTS.** C.L. Chen<sup>1</sup>, B.Y. Tan<sup>2</sup>, L. Qingshu<sup>3</sup>, N. Venketasubramanian<sup>4</sup> ((1) National University Of Singapore - Singapore; (2) St Luke's Hospital - Singapore; (3) Singapore Clinical Research Institute - Singapore; (4) Raffles Neuroscience Centre - Singapore)

**Background:** Alzheimer's disease (AD) urgently requires innovative, effective and safe treatments. MLC901 is a simplified form of MLC601 which was originally derived from traditional Chinese medicine. MLC901 has shown to have neuroprotective and neuroproliferative properties in cellular and animal models of brain injury. MLC601 has been shown to modulate amyloid precursor protein (APP) processing, and increase the levels of soluble APP $\alpha$ . Additionally, MLC901 has been shown to reduce tau phosphorylation in-vitro. Hence, MLC901 may have a disease modifying effect in AD. **Objectives:** To

investigate the safety and efficacy of MLC901 as add-on therapy to standard treatment in mild to moderate AD subjects stable on standard treatment and to evaluate if MLC901 has a disease modifying effect in AD. **Methods:** ATHENE is a 6-month randomized, double-blind, placebo-controlled trial in mild to moderate AD of MLC 901 followed by an open label extension study for another 6 months. The NINCDS-ADRDA criteria was used for defining AD. The primary outcome was the proportion of subjects experiencing serious adverse events (SAEs) within the first 6 months after randomisation. There were secondary safety and efficacy endpoints. For safety evaluation, the proportions of subjects who experienced an SAE or an AE, or discontinued medication due to AE/SAE were compared between the MLC901 and placebo groups at 6 months and 1 year, whereas for efficacy the change in clinical outcome scores from baseline were compared between the groups. Secondary clinical outcomes included the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog), Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC), Alzheimer's Disease Cooperative Study - Activities of Daily Living 23 items (ADCS-ADL23), Neuropsychiatric Inventory (NPI), and Mini Mental State Examination (MMSE). An independent data safety monitoring board (DSMB) assessed safety and monitored the progress of the study. **Results:** ATHENE was conducted at a single centre in Singapore and 125 subjects were recruited into the trial. The mean age was 78.6 ( $\pm$  6.67) years, with 87 (69.6%) female of mainly Chinese ethnicity (88.8%). 90 (72.0%) subjects had hypertension, 87 (69.6%) hyperlipidaemia, 45 (36.0%) diabetes mellitus, and 23 (18.4%) a previous stroke. Baseline characteristics were balanced between the MLC901 and placebo groups except that the placebo group had a higher educational level (p=0.003, tertiary education 23.8% vs 3.2%). Most (95%) subjects received Acetylcholinesterase inhibitors (AChEI) as standard treatment for AD. Primary Outcome: The proportions of subjects having SAE at 6 months (M) were not significantly different : 22.6% in the MLC901 and 27.0% in the placebo group with a difference of -4.4% (90% CI: -16.9 to 8.3%) and an upper limit of the 90% CI of 8.3% which falls below the pre-specified non-inferiority margin of 10%. Secondary Outcomes (Safety): There was no difference in the proportion of subjects experiencing SAE between groups at 12M: 33.9% in MLC901 and 39.7% in placebo (difference = -5.8%, 90% CI: -19.6 to 8.3%). The proportions of subjects experiencing AE were comparable between MLC901 and Placebo at 6M (61.3% vs 60.3%) and 12M (75.8% vs 74.6%). There were 5 deaths at 6M (2 in MLC901 and 3 in placebo), 2 additional deaths were observed at 12M in the placebo group. None of the SAEs were deemed related to MLC901. Secondary Outcomes (Clinical): There was no significant difference in the mean (SD) ADAS-Cog scores in the MLC901 and placebo groups: 31.1 (11.87) and 29.3 (9.46) at baseline, respectively. The difference in the mean change from baseline in ADAS-Cog scores between the two groups was statistically significant at 9M in favour of MLC901 (-3.36, 95% CI: -5.64 to -1.09; p=0.004) but did not reach significance at 6M and 12M. Sensitivity analysis in the per-protocol population (PP), showed statistical significance at 9M and 12M with a mean difference of -3.66, (95% CI: -6.42 to -0.89, p=0.010) at 9M and -4.75 (95% CI: -8.92 to -0.59, p=0.026) at 12M. ADCS-CGIC was significantly better in MLC901 than in the placebo group at 3M only (p = 0.044). No significance was observed with the other efficacy endpoints. **Conclusion:** ATHENE is the first study to assess the safety and efficacy of MLC901 in

mild to moderate AD subjects receiving standard therapy. The results show that MLC901 holds promise as a safe add-on therapy to standard AD treatments. These results also support that MLC901 may have a disease-modifying effect by delaying disease progression. Further, larger clinical trials in AD with MLC901 are recommended.

**P023: A MULTIPLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF THE ANTI-PHOSPHO-TAU ANTIBODY JNJ-63733657.** W. Galpern<sup>1</sup>, K. Haeverans<sup>2</sup>, L. Janssens<sup>2</sup>, G. Triana-Baltzer<sup>3</sup>, H. Kolb<sup>3</sup>, L. Li<sup>1</sup>, P. Nandy<sup>4</sup>, M. Mercken<sup>2</sup>, K. Van Kolen<sup>2</sup>, H. Sun<sup>1</sup>, L. Van Nueten<sup>2</sup> ((1) *Janssen Research & Development - Titusville, USA*; (2) *Janssen Research & Development - Beerse, Belgium*; (3) *Janssen Research & Development - La Jolla, USA*; (4) *Janssen Research & Development - Raritan, USA*)

**Background:** Alzheimer's disease (AD) is characterized neuropathologically by extracellular amyloid beta (plaques) and intracellular hyperphosphorylated tau (neurofibrillary tangles). There is evidence for prion-like spread of tau pathology in AD, and anti-tau antibodies are under clinical investigation for disease modification by binding to extracellular tau seeds in the interstitial fluid (ISF). JNJ-63733657 is a humanized IgG1 monoclonal antibody with high affinity for phosphorylated tau (p217+). This antibody depletes toxic tau species in in vitro seeding assays and reduces tau spreading in in vivo models. A sensitive assay has been developed to measure p217+tau fragments in the cerebrospinal fluid (CSF), and changes in CSF levels of p217+tau may serve as an indicator for changes in the levels of extracellular tau seed in the ISF following antibody administration. A single ascending dose study in healthy subjects has been completed previously, and JNJ-63733657 was found to be generally safe and well tolerated and exhibited linear PK as well as dose dependent reductions in CSF p217+tau. **Objectives:** Evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple doses of JNJ-63733657 in healthy subjects and in subjects with AD. **Methods:** A randomized, double blind, placebo controlled multiple ascending dose (MAD) study has been conducted in healthy subjects and subjects with AD aged 55-80 years. Four cohorts of up to 8 subjects each were administered placebo or multiple doses of JNJ-63733657 intravenously monthly for 3 months. Subjects were followed for 148 days, and serum, plasma, and CSF samples were collected. Safety, tolerability, PK (serum and CSF), and the effect of JNJ-63733657 on CSF and plasma levels of p217+tau fragments (PD response) were evaluated. **Results:** Following multiple dose administration, JNJ-63733657 was generally safe and well-tolerated and demonstrated linear PK in serum. Dose-dependent increases in exposures were observed, and there were dose dependent reductions in p217+tau in CSF of healthy subjects and subjects with AD following antibody administration. The PK and PD profiles were similar in the healthy subjects and subjects with AD. **Conclusions:** JNJ-63733657 to date shows a favorable clinical profile and biomarker response following multiple dose administration. A phase 2 study of JNJ-63733657 in subjects with early AD is planned.

**P024: THE CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) – PRE-COMPETITIVE DATA SHARING AND GENERATION OF INNOVATIVE HIGH-IMPACT QUANTITATIVE TOOLS TO SUPPORT ALZHEIMER'S DISEASE DRUG DEVELOPMENT.** S. Sivakumaran<sup>1</sup>, K. Romero<sup>1</sup>, N. Hanan<sup>1</sup>, Y. Karten<sup>1</sup>, V. Sinh<sup>2</sup>, S. Budd Haerberlein<sup>3</sup>, N. Rabbee<sup>4</sup> ((1) *Critical Path Institute - Tucson, USA*; (2) *Merck & Co. - Kenilworth, USA*; (3) *Biogen - Cambridge, USA*; (4) *Eisai - Woodcliff Lake, USA*)

**Background:** The Critical Path Institute's (C-Path) Critical Path for Alzheimer's Disease (CPAD) consortium's primary objective is to promote, support, and manage pre-competitive data sharing from Alzheimer disease (AD) clinical trials to allow quantification of disease progression across the AD continuum. A quantitative understanding of disease dynamics can accelerate drug development, based on integrated and standardized primary clinical trial data. This will provide solutions to optimize the design of clinical trials of AD drugs intended for regulatory review in support of marketing approval. CPAD (<https://c-path.org/programs/cpad/>) convenes diverse stakeholders from academia, advocacy groups, industry, and regulators. **Method:** As of June 2020, CPAD's database ([www.codr.c-path.org](http://www.codr.c-path.org)) contains data from 40 studies, representing 20,589 individual records and more than 420,000 data points, standardized to the AD CDISC (Clinical Data Interchange Standards Consortium) standards. CPAD's objective is to collaborate with industry and regulators to leverage their wealth of drug development knowledge by enabling pre-competitive data sharing from clinical trials in AD. Analysis of datasets (at meta-data and patient levels) will enable generation of tools involving comprehensive disease progression models across the AD continuum, to optimize and accelerate drug development. **Result:** CPAD will continue ongoing efforts towards expansion of the CPAD database with contemporary datasets containing patient-level data from both control and active arms of clinical trials in AD. By aggregating such datasets into our rich clinical trial repository, CPAD will fill existing gaps in our models and generate of quantitative solutions for drug development in AD, in collaboration with C-Path's Quantitative Medicine (QuantMed) Program. Key focus of CPAD in 2020 includes acquisition of contemporary industry clinical trial datasets and generation of a comprehensive disease progression model across the AD continuum. This effort will be based on an evolving workflow initiating with dataset exploration at the level of meta-data and patient level data and determination of model specifications, resulting in model validation, simulations and regulatory submissions. **Conclusion:** Pre-competitive sharing of contemporary clinical trial data will allow us to develop a comprehensive understanding of the disease continuum in AD, enable a fully informed trial design and advance effective drug development in AD.

**P025: SENSORY GAMMA STIMULATION THERAPY REDUCES SLEEP DISRUPTIONS IN ALZHEIMER'S SUBJECTS AS ASSESSED BY CONTINUOUS ACTIGRAPHY RECORDINGS.** A. Cimenser, E. Hempel, T. Travers, M. Williams, M. Hajos, Z. Malchano (*Cognito Therapeutics, Inc - Cambridge, USA*)

**Background:** Sleep-related problems are reported in up to 25% of patients with mild to moderate AD and in up to 50% of

patients with moderate to severe AD. Common complaints in this patient population include excessive nocturnal awakening, napping greater than 1 hour per day, early morning awakening, and excessive daytime sleepiness. Sleep disturbances are known to increase the risk for both development and accelerated progression of AD. Polysomnography, the gold standard for sleep monitoring is challenging to use in AD patients. Wrist-worn actigraphy monitoring, which continuously records movement via an accelerometer, is easier to implement, can enable long term monitoring, and has been shown to be more accurate in the assessment of sleep disturbances than patient self-report. **Objectives:** Here, we assess the effect of long-term gamma sensory stimulation (GammaSense Stimulation System, Cognito Therapeutics, Inc, Cambridge MA) on sleep disturbance in a mild-to-moderate AD population. **Methods:** The Overture study (NCT03556280) is a Phase I/II randomized, controlled, single-blind multi-center clinical trial using the GammaSense Stimulation (GSS) device to study safety, adherence rates and efficacy in patients with mild to moderate Alzheimer's disease (MMSE 14-26, inclusive). The six-month trial included treatment and sham groups receiving daily, one-hour sensory stimulation using GammaSense Stimulation System (GSS), but only participants in the treatment group were exposed to 40-Hz auditory and visual stimulation. Throughout the study, participants' activity levels were monitored continuously with a wrist-worn actigraphy watch (ActiGraph GT9X). In this interim report, we present results on the first 13 participants (N=7 for the treatment group, N=6 for the sham group) who completed the six-month study. For each participant, night-time total sleep periods, rest and active periods within each night-time sleep were estimated from actigraphy. Sleep fragmentation, a form of sleep disturbance, was estimated as the proportion of the active periods within a total night-time sleep. Changes in sleep fragmentation and differences between treatment and sham groups were studied throughout the six-month study period. **Results:** An average of 125 days of actigraphy measurements were successfully recorded for each participant, resulting in a total of approximately 39,000 hours of sleep and daytime analyzed activity data. Sleep fragmentation, as assessed from continuous actigraphy recordings over the six-month study period, was significantly reduced in the treatment group ( $p < .001$ ). In contrast, sleep fragmentation increased in the sham group ( $p < .001$ ). **Conclusion:** These findings demonstrate a means to quantify sleep fragmentation and treatment-related changes via continuous actigraphy recording with Alzheimer's patients. Gamma sensory stimulation resulted in a reduction in sleep fragmentation, as quantified by a decrease in nighttime active durations of the 6-month treatment period. In participants who received sham stimulation, increases in sleep fragmentation were measured over the same time period.

**LP04: APPLYING MACHINE LEARNING ALGORITHMS TO PREDICT AMYLOID RISK IN JAPANESE TRIAL-READY COHORT WEBSTUDY.** K. Sato<sup>1</sup>, R. Ihara<sup>2</sup>, K. Suzuki<sup>3</sup>, Y. Niimi<sup>4</sup>, A. Iwata<sup>2</sup>, T. Iwatsubo<sup>5</sup> ((1) Department Of Neurology, University Of Tokyo - Bunkyo City, Japan; (2) Department Of Neurology, Tokyo Metropolitan Geriatric Medical Center Hospital - Itabashi City, Japan; (3) Division Of Neurology, National Defence Medical College - Tokorozawa, Japan; (4) Unit For Early And Exploratory Clinical Development, University Of Tokyo - Bunkyo City, Japan; (5) Department Of Neuropathology, University Of Tokyo - Bunkyo City, Japan)

**Background:** Identifying "preclinical" Alzheimer's disease (AD) individuals, defined as cognitively normal individuals with positive amyloid deposition in brain, is critical to the success of clinical trials of disease-modifying therapy (DMT) to prevent AD. Recently, a number of global clinical study projects had launched to build cohorts of preclinical AD candidates eligible for clinical trials of DMTs for AD. We have recently started the Japanese Trial-Ready Cohort (J-TRC) study for prevention of AD study, in which we adopted basic framework of Trial-Ready Cohort for Preclinical/Prodromal AD (TRC-PAD) in the United States that is innovative in its two-layered structure of web-based registry and the successive in-person study. In the J-TRC study that launched in October 2019, cognitive normal elderly volunteers are at first invited to register to the J-TRC webstudy that are completed by themselves at home by providing basic demographics, and being monitored for their web-based cognitive performance every 3 months. Among the J-TRC webstudy population, those who are expected to have a higher probability for amyloid deposition in brain are further referred to the in-person, J-TRC on-site study for detailed assessments including cognitive, biomarker, and amyloid PET examinations. J-TRC study aims to build a large cohort of asymptomatic and amyloid-positive individuals ready for DMT trials in Japan. **Objectives:** As of 2020 summer, more than 3,000 elderly volunteers have eligibly registered to the J-TRC webstudy within the first 9 months since its launch. However, when considering to recruit eligible individuals from the J-TRC webstudy to the onsite study, effective algorithms that can predict amyloid risks from basic clinical and cognitive data available in the J-TRC webstudy (without e.g., PACC or APOE genotype) are yet to be established. Here we aimed to build machine learning models to predict the standard uptake value ratio (SUVR) of amyloid PET in our ongoing Japanese Trial-Ready Cohort (J-TRC) for preclinical and prodromal AD study using the clinical and cognitive variables available in the J-TRC webstudy. Because currently we do not have the true answer of amyloid status of J-TRC participants yet, we used A4 screening data as a reference to fit to the models. **Methods:** Using the screening data of non-Asian cognitive normal participants ( $n = 4,277$ ) from the A4 study and six different machine learning algorithms, we built models consisting of age, sex, education years, family history of dementia, and online cognitive scores (Cognitive Function Instrument (CFI) and CogState), and initially evaluated its performance in the Asian subgroup ( $n = 169$ , including up to 100 Japanese) of the A4 study. We then applied the models to the J-TRC webstudy participants registered within the initial 9 months ( $n = 3,081$ ) of launch to obtain predicted SUVR in each participant. **Results:** Models based on the A4 non-Asian subgroup had a weak (correlation  $\sim 0.3$  at most) predictive performance on A4 Asian subgroup, regardless of

the types of algorithms. The performance slightly improved when incorporating CFI into the models. In the derived models, age, family history, CFI-study participant, and CogState score were the important variables. When applying the models into the J-TRC webstudy data, in a subgroup of J-TRC webstudy participants who self-reported their prior amyloid test results conducted elsewhere (n = 37), the predicted SUVR showed a good correspondence with the self-reported amyloid test results (AUC = 0.806). **Conclusion:** Although J-TRC onsite study is still in its preliminary phase, our A4 data-based prediction algorithms of brain amyloid status may be usable for automatic prioritization of candidate participants with higher amyloid risks to be preferentially recruited from the J-TRC webstudy population to the in-person, J-TRC on-site study, and maximize the efficiency for the identification of preclinical AD participants. We need to continue to update the predicting models along with the progress of the identification of amyloid-positive individuals in the J-TRC onsite study, to confirm and secure the validity of this approach in the Japanese population. This study is a collaboration with the members of the US TRC-PAD (Jimenez-Maggiore G, Langford O, Donohue MC, Raman R, Aisen PS and Sperling RA).

### **Theme 3: CLINICAL TRIALS: IMAGING**

**P027: MOLECULAR IMAGING OF TAU PATHOLOGY IN MYOTONIC DYSTROPHY TYPE 1 AND ALZHEIMER'S DISEASE: IMPLICATIONS FOR UNDERLYING MECHANISMS.** E. Poulin<sup>1</sup>, C. Dallaire-Théroux<sup>1,3</sup>, A.M. Cayer<sup>1,2</sup>, D. Bédard-Tremblay<sup>1,2</sup>, T. Rouleau-Bonenfant<sup>1,2</sup>, F. St-Onge<sup>4</sup>, J.M. Beauregard<sup>5</sup>, N. Sergeant<sup>6</sup>, J. Puymirat<sup>5</sup>, R. Jr. Laforce<sup>2,3</sup> ((1) *Clinique Interdisciplinaire De Mémoire, Département Des Sciences Neurologiques, Chu De Québec - Québec, Canada*; (2) *Université Laval, Faculté De Médecine - Québec, Canada*; (3) *Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec - Québec, Canada*; (4) *Douglas Health Institute - Montréal (Canada), 5Centre De Recherche Du Chu De Québec - Québec, Canada*; (6) *Université De Lille, Chru, Inserm, Umrs 1172, Equipe Alzheimer & Tauopathies - Lille, France*)

**Background:** Myotonic dystrophy type 1 (DM1) is a chronic, multisystemic, neurological disease characterized by muscle weakness as well as central nervous system changes. Recent pathological reports suggest that DM1 may be a tauopathy where tau pathology accumulates in a topographic distribution similar to Alzheimer's disease (AD). **Objectives:** We performed molecular imaging to visualize in vivo tau pathology in DM1 and AD, and to study the relationship between tau accumulation and severity of cognitive impairment. In addition, we aimed to explore possible similarities in tau accumulation patterns in DM1 and AD. **Methods:** We recruited 19 patients with a genetic diagnosis of DM1 and 2 patients with AD. Both AD patients and seven DM1 patients completed the neuroimaging sub-study which included cognitive screening (Dépistage Cognitif de Québec [DCQ] and Montreal Cognitive Assessment [MoCA]), structural brain magnetic resonance imaging and positron emission tomography (PET) imaging using [18F]-AV-1451, a PET tracer that selectively binds to tau neurofibrillary tangle pathology. Standardized uptake value ratios (SUVR) images were generated using cerebellar grey matter as the reference region. Average SUVR values were calculated in key regions of interest. **Results:** Three (3/7) DM1

patients were cognitively impaired (CI+), as evidenced by lower average scores on the DCQ (79/100 vs. 90/100) and MoCA (23.3/30 vs. 29/30). DM1 CI+ patients were older than DM1 unimpaired (CI-) patients (53 vs. 46 years on average) but did not differ in years of education. Two (2/7) DM1 patients presented with increased tau PET signal: one patient (age 45) who was mildly CI+ (DCQ=82,5/100; MoCA=30/30) showed focal right temporal tau PET signal (e.g. medial right anterior temporal gyrus, SUVR=1.39); the other patient (age 69) was the most severely CI+ of the 7 DM1 patients (DCQ=61,5/100; MoCA=17/30) and showed increased tau PET signal bilaterally in the temporal lobes (e.g. average of right and left SUVRs in amygdala=1.87; parahippocampal gyrus=1.42; medial anterior temporal gyrus, SUVR=1.38). The two AD patients displayed a typical AD-like pattern (high retention across frontal, parietal, and temporal cortices and the hippocampus; e.g. SUVR<sup>3</sup>1.5 across ROIs corresponding to Braak stages I-V). **Conclusions:** To our knowledge, this is the first study to explore tau pathology in vivo in DM1. Two DM1 patients presented with increased tau PET signal in the temporal lobes; however, the magnitude and extent of tau PET signal was lower than typically seen in AD patients, and the remaining five DM1 patients did not show notable increased signal relative to the reference region. The patient with the most severe cognitive impairment also showed the most elevated tau PET signal. Whether this PET signal is related to DM1 tau pathology or concomitant AD remains unknown. Lack of post-mortem studies confirming ligand sensitivity to DM1 pathology further limits interpretation. This work is a critical step towards better understanding of the mechanisms underlying cognitive deficits in DM1. Furthermore, studying various tauopathies using tau PET may help elucidate the pathological mechanisms of tau pathology and help provide valuable biomarkers to support future therapies and clinical trials. Grant Support AFM Telethon.

**P028: A MULTI-INPUT, MULTI-MODAL DEEP LEARNING MODEL TO PREDICT TIME TO CONVERSION TO ALZHEIMER'S DISEASE.** D. Hibar, B. Toth, C. Rabe, D. Clayton (*Genentech, Inc - South San Francisco, USA*)

**Background:** Identifying presymptomatic and early MCI fast progressors is a crucial component for designing the next generation of clinical trials in AD. Innovations in deep learning (DL) in imaging have been hypothesized to improve power to detect patterns of disease pathophysiology compared to current volumetric summary statistics commonly measured in images in clinical trial settings. While DL may be promising for AD, considerable hurdles still exist for identifying and stratifying early-disease patients including: limited sample sizes, short follow up times, and limited modeling approaches for multi-modal 3D medical imaging. **Objectives:** Here we propose a new modeling strategy as a proof-of-concept to address these limitations with a novel multi-input, multi-modal deep learning (DL) model and data augmentation strategy applied to T1 MRI and Abeta PET scans. We evaluate the added value of this new framework for predicting time to conversion in patients with mild cognitive impairment (MCI) compared to models composed of traditional image-derived features currently used in clinical trials. **Methods:** Patients from the ADNI study with available Abeta (AV-45) PET and T1 MRI scans were selected for this study (n=1016). T1 MRI and Abeta PET scans were recentered/clipped to remove whitespace around the skull and resampled. The final T1 MRI and Abeta



PET scan input uses 23 equally spaced coronal slices from each image type with a final grid size of 224x224x46. We first focus on building a DL classifier that discriminates between AD and Control based on the T1 MRI and Abeta PET input. Patients with an AD (n=162) or Control (n=351) diagnosis at the time of scanning were selected and further split into Training (90%) and Holdout (10%). We used 5-fold CV within the Training set to do hyper/parameter tuning. Our DL model uses a time-distributed Long Short Term Memory (LSTM) and Convolutional Neural Network (CNN) modeling approach. We utilized a data augmentation strategy for model training including probabilistic combinations of resampling, resizing, rotations and Gaussian noise applied to each input image in 3D space. Our baseline comparison model was comprised of three commonly measured features derived from T1 MRI (i.e. average hippocampal and ventricular volumes) and from Abeta PET (i.e. SUVR normalized by whole cerebellum uptake) to predict AD or Control status with a generalized linear model. We used the same Training and Holdout splits as described in the DL modeling strategy. Performance of the DL and baseline model were evaluated in the 10% Holdout set (n=51). We applied our DL model and baseline model to MCI patients not previously used for model training (n=492). Patients were stratified by quartiles for their predicted risk for both models and evaluated by the hazard ratio of the time to conversion to AD in the highest (>75 percentile; Q4) and lowest risk (<25 percentile; Q1) groups. In addition, we evaluated the conversion rate at a 2 year landmark in order to understand model performance in a time period commonly used for AD clinical trials. **Results:** We found similar performance in discriminating AD and Control patients in both the DL (Accuracy=0.922) and baseline (Accuracy=0.941) models in the holdout sample. The difference in accuracy is explained by misclassifying 4 patients in the DL versus 3 in the baseline model. When stratifying independent MCI samples by risk, we found that the baseline model had superior performance (Q4 vs Q1; Cox HR=22.94;  $P < 2e-16$ ) to the DL model (HR=10.70;  $P < 2e-16$ ). In the DL model, 29.1% of patients in the highest risk quartile had converted to AD at the 2 year landmark (in the lowest risk group it was 5.1%). In the baseline model, 35.0% of patients in the highest risk quartile had converted to AD at the 2 year landmark (in the lowest risk group it was 0.9%). For comparison, 12.6% of patients are estimated to have converted from MCI to AD at the 2 year landmark in the full dataset (i.e. without stratifying on predicted risk). **Conclusion:** We built a proof-of-concept multi-input, multi-modal DL model to discriminate AD vs Control based on raw T1 MRI and Abeta PET scans with comparable performance to a baseline model composed of traditional features. In addition, our DL model successfully stratified MCI patients by conversion rate and identified a high-risk cohort with a considerably higher AD conversion rate than without stratifying by risk (29.1% vs. 12.6%). Compared to the baseline model, our model had slightly worse performance stratifying MCI patients, this illustrates the challenges of training a DL model from scratch (i.e. without prior knowledge) on limited sample sizes. In future, we plan to expand our proof-of-concept to additional datasets to build a more robust DL model incorporating different patient populations, disease stages, and endpoints.

**P029: PERCEPTIONS OF AMYLOID IMAGING AMONG COGNITIVELY NORMAL OLDER ADULTS WITH ELEVATED AND NOT ELEVATED AMYLOID.** M. Ryan<sup>1,2</sup>, D. Gillen<sup>1,2</sup>, J. Grill<sup>1,3,4</sup> ((1) *Institute For Memory Impairments And Neurological Disorders, University Of California, Irvine - Irvine, USA*; (2) *Department Of Statistics, University Of California, Irvine - Irvine, USA*; (3) *Department of Psychiatry and Human Behavior, University of California, Irvine - Irvine, USA*; (4) *Department of Neurobiology and Behavior, University of California, Irvine - Irvine, USA*)

**Background:** The Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (A4) Study is an ongoing preclinical Alzheimer's disease (AD) clinical trial. Cognitively normal older adults were screened to see if they met criteria for preclinical AD, defined as elevated brain amyloid on positron emission tomography (PET) imaging, and disclosed their individual biomarker result. The A4 Study incorporated the Views and Perceptions of Amyloid Imaging questionnaire before and after amyloid PET during screening. Knowledge of why participants are willing to undergo amyloid imaging could help researchers develop targeted recruitment strategies and improve biomarker disclosure processes for future studies. **Objectives:** We sought to determine if participants with "elevated" and "not elevated" amyloid differed in their Views and Perceptions of Amyloid Imaging. We hypothesized that, prior to knowing their biomarker status, those with "elevated" amyloid would score higher than those with "not elevated" amyloid due to the increased risk of subtle clinical symptoms that are associated with higher brain amyloid levels. We further hypothesized that this association would manifest, at least in part, via participant responses to the Cognitive Function Instrument (CFI). Finally, we sought to quantify how responses to the questionnaire changed after participants were told their amyloid result. We hypothesized that those with "elevated" amyloid would have more positive levels of score change than those with "not elevated" amyloid. **Methods:** We assessed data from 4,468 individuals in the A4 Study who completed the Views and Perceptions of Amyloid Imaging questionnaire at screening visit 1 and again after amyloid result disclosure. In this scale, participants score how strongly they identify with each of 9 reasons for undergoing amyloid imaging on a five-point Likert scale. We a priori grouped items into four thematic categories: Perceived Risk (Items 2, 7; Range: 2-10), Altruism/Contribute to Research (Items 4, 5; Range: 2-10), Plan/Prepare (Items 1, 6, 8; Range: 3-15), and Curiosity (Items 3, 9; Range: 2-10). Item scores in each category were summed to create total category scores. Differences in scores were calculated by subtracting the score at screening visit 1 from the score after amyloid result disclosure. Participants with PET standard uptake value ratios (SUVR) greater than 1.15 were categorized as "elevated amyloid." Participants with PET SUVR less than 1.10 were categorized as "not elevated amyloid." Participants with PET SUVR between 1.10 and 1.15 required an additional visual read to determine amyloid eligibility in A4. Since these data are not publicly available, we categorized these participants as "possibly elevated amyloid" for this analysis. We used linear regression models to assess the relationship between category scores and amyloid status. Participant age, years of education, sex, ethnorracial group, and study partner spousal status were adjusted for in all models as potential confounding variables. CFI scores were adjusted for in follow-up models as a potential mediator. We used similar linear regression models to assess the

relationship between changes in category scores and amyloid status, additionally controlling for the score at the first visit. **Results:** Participants who had “elevated” amyloid scored 0.20 points higher in the Perceived Risk category, on average, than those who had “not elevated” amyloid (95% CI: [0.06, 0.34]) prior to imaging and disclosure. Those with “elevated” amyloid did not score significantly differently than those with “not elevated” amyloid in any other category. When CFI scores were added as a potential mediator, the significant effect in Perceived Risk attenuated towards zero. Instead, when CFI was included in the model, those with “elevated” amyloid scored an average of 0.13 points lower for the curiosity category compared to those with “not elevated” amyloid (95% CI: [-0.26, -0.01]). After participants were told their amyloid status, those with “elevated” amyloid demonstrated a lower within subject change in score in the Perceived Risk category, on average, than those with similar visit 1 scores who had “not elevated” amyloid (-0.32; 95% CI: [-0.43, -0.20]). Participants with “elevated” amyloid also demonstrated greater changes in the Altruism/Contribute to Research (0.13; 95% CI: [0.05, 0.22]) and Plan/Prepare (0.23; 95% CI: [0.05, 0.41]) categories, compared to those with similar visit 1 scores who had “not elevated” amyloid. **Conclusions:** Compared to participants with “not elevated” amyloid, participants in the A4 Study with “elevated” amyloid more strongly identified learning AD risk as reasons for undergoing amyloid imaging before biomarker disclosure. This difference was likely due to their perceived cognitive concerns. After disclosure of amyloid status, participants with “elevated” amyloid more strongly endorsed feelings of Altruism/Contribution and Planning/Preparation, compared to their “not elevated” counterparts, while having lower change in their attitudes toward the relative importance of learning AD risk.

**P030: NEUROIMAGING RESULTS OF THE AMBAR STUDY, A RANDOMIZED, CONTROLLED CLINICAL TRIAL OF PLASMA EXCHANGE WITH ALBUMIN REPLACEMENT FOR ALZHEIMER’S DISEASE.** G. Cuberas-Borrós<sup>1</sup>, E. Franquet<sup>2</sup>, I. Roca<sup>2</sup>, J. Castell-Conesa<sup>2</sup>, L. Nuñez<sup>3</sup>, M. Boada<sup>4,5</sup>, O.L. López<sup>6</sup>, C. Grifols<sup>3</sup>, M. Barceló<sup>3</sup>, A. Páez<sup>3</sup> ((1) *Research & Innovation Unit, Althaia Xarxa Assistencial Universitària De Manresa - Manresa, Spain;* (2) *Department Of Nuclear Medicine, Hospital Universitari Vall D’hebrón, Universitat Autònoma De Barcelona - Barcelona, Spain;* (3) *Alzheimer’s Research Group, Grifols - Barcelona, Spain;* (4) *Research Center And Memory Clinic, Fundació Ace, Institut Català De Neurociències Aplicades-Universitat Internacional De Catalunya - Barcelona, Spain;* (5) *Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III, - Madrid, Spain;* (6) *Departments Of Neurology And Psychiatry, University Of Pittsburgh School Of Medicine - Pittsburgh, Pennsylvania, USA*)

**Background:** Positron emission tomography (PET) is a non-invasive imaging technique that allows the measurement of metabolic activity in organs within the body including the brain. PET scanning detects the gamma photons released by radiopharmaceuticals injected into the body using a ring of detectors. Magnetic resonance imaging (MRI) is another non-invasive imaging technique that uses a magnetic field to provide high resolution images of organs and tissues. MRI has been shown to detect structural changes in the brain associated with AD including cerebral atrophy and enlargement of the ventricles and sulci. Previous pilot and phase II studies

showed that plasma exchange (PE) with therapeutic albumin replacement (PE-A) favored the stabilization of brain perfusion in mild-moderate AD patients whereas untreated patients showed the expected progression of the disease. This effect was associated with changes in plasma-CSF A $\beta$  flux balance, and with improvement in cognitive and behavioral test scores. **Objectives:** To detect structural and functional brain changes in mild to moderate AD patients treated with PE-A, as part of the AMBAR phase 2b/3 clinical trial. **Methods:** Out of 496 mild to moderate AD patients enrolled, 347 were randomized into 4 arms (1:1:1:1): three receiving PE-A treatment with different doses of albumin (Albutein®, Grifols, Barcelona, Spain) and IVIG (Flebogamma® DIF, Grifols) replacement, and placebo (sham PE-A). All arms underwent a weekly conventional PE for 6 weeks followed by a 12-month period of monthly low-volume PE. Neuroimaging variables assessed were: i) structural changes in hippocampal volume, posterior cingulate volume, and other areas of interest as shown by MRI (at months 0, 2, 6, 9, 12, and 14); and ii) functional changes in the brain as detected by positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) (at months 0, 2, 9, and 14). FDG-PET acquisitions were normalized by cerebellum intensity and then compared with a database of normal subjects creating an individual defect pattern. Additionally, a voxel-based analysis with SPM (Statistical Parametric Mapping) was performed. FDG-PET resulting patterns took into account only those voxels inside gray matter mask. Statistical comparisons were performed by ANOVA (treatment groups) or Student t test for paired data (time points). **Results:** A total of 213 patients completed all sessions without any issue in image processing. MRI volumetric analyses of subcortical structures (left/right: thalamus, caudate, putamen, pallidum brain stem 4th ventricle, hippocampus, amygdala, accumbens) showed that the high dose albumin + IVIG group was the treatment with fewer changes ( $p < 0.05$  in 3 structures vs. 4 to 9 in other groups) from baseline to final visit. SPM FDG-PET analyses showed a significant decline of cerebral glucose metabolism (from baseline to final visit) in the specific areas affected in AD (posterior cingulate, precuneus, and parieto-temporal regions). The extension of brain areas in this pattern of loss of metabolism (k-extent) was lower in the high-dose albumin + IVIG group compared to other groups. When stratified by disease severity, the lower brain metabolic decline was observed in moderate AD patients compared to placebo whereas mild AD patients showed no decline in all groups. **Conclusion:** PE-A in mild-moderate AD patients was associated with less metabolic decline than the typical of the progression of the disease. This effect was more evident in the group treated with high dose albumin + IVIG group and in the moderate AD sub population.

**P031: GREATER SLEEP DISTURBANCE IS ASSOCIATED WITH LOWER MYELIN CONTENT IN THE CINGULUM IN A COHORT ENRICHED FOR ALZHEIMER'S DISEASE RISK.** K.L. Yang<sup>1</sup>, D.C. Dean<sup>2,3,4</sup>, J.M. Oh<sup>1</sup>, N. Davenport-Sis<sup>1</sup>, D.T. Plante<sup>5</sup>, B.A. Riedner<sup>5</sup>, S. Asthana<sup>1,6,7</sup>, S.C. Johnson<sup>1,6,7</sup>, A. Alexander<sup>3,4</sup>, B.B. Bendlin<sup>1,6,7</sup> ((1) *Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin - Madison, USA*; (2) *Department Of Pediatrics, University Of Wisconsin - Madison, USA*; (3) *Department Of Medical Physics, University Of Wisconsin - Madison, USA*; (4) *Waisman Center, University of Wisconsin - Madison, USA*; (5) *Wisconsin Institute For Sleep And Consciousness, University Of Wisconsin - Madison, USA*; (6) *Wisconsin Alzheimer's Institute, University Of Wisconsin - Madison, USA*; (7) *Geriatric Research Education and Clinical Center, William S. Middleton Veterans Hospital - Madison, USA*)

**Background:** Sleep abnormalities have been linked to Alzheimer's disease (AD) and greater risk for dementia (Peter-Derex et al, 2015). We have previously shown that poor self-reported sleep was associated with increased amyloid deposition in the brain (Sprecher et al, 2015) as well as CSF biomarkers of amyloid, tau, and neurodegeneration (Sprecher et al, 2017). Animal studies suggest that sleep abnormalities may also play a role in myelin degeneration (Bellesi et al, 2013 & 2018). Myelin-producing oligodendrocyte precursor cells (OPC) are integral to remyelination, as they generate new oligodendrocytes that are able to remyelinate in the mature central nervous system (Franklin, 2014). Damage to these cells can be detrimental for myelin-related processes. In mice, OPC density is higher after sleep versus sleep deprivation (Bellesi et al, 2013) and chronic sleep loss reduces myelin sheath thickness (Bellesi et al, 2018), suggesting that myelin-related cell functions are sensitive to changes in sleep. The association between sleep and myelin has been studied in children (e.g., LeBourgeois et al, 2019) but has not been well-studied in adults, thus, the current study tested the extent to which sleep quality is associated with myelin content. **Objectives:** Here, we examined the association between self-reported sleep quality and myelin content in a well-characterized cohort enriched with risk factors for developing AD dementia. We hypothesized that lower self-reported sleep quality would be associated with lower myelin content in regions affected in AD pathology. **Methods:** 151 participants were recruited into the Longitudinal Early Alzheimer Detection (LEAD) study from two parent cohorts, the Wisconsin Registry for Alzheimer's Prevention and the Wisconsin Alzheimer's Disease Research Center clinical core. A final sample of 114 cognitively-unimpaired (MMSE: median = 30, range = 27-30) participants were included in this analysis on the basis of one completed Medical Outcomes Study Sleep Survey (MOS-sleep) and one multicomponent relaxometry scan (mcDESPOT; Deoni et al, 2008). mcDESPOT myelin water fraction (MWF) maps, sensitive to myelin content, were computed and normalized to MNI space for use in this analysis. MWF values were extracted from 5 white matter tracts that are sensitive to AD pathology (e.g., Gold et al, 2012): uncinate fasciculus, cingulum bundle, inferior longitudinal fasciculus, superior longitudinal fasciculus, and forceps minor. Six sleep domains of interest were assessed with MOS-sleep: sleep disturbance, snoring, awaken short of breath or with headache, sleep quantity, sleep adequacy, and somnolence. Responses to all items were converted from the original Likert scale to a 0-100 scale based on instructions from the MOS-sleep User's Manual (Spritzer & Hays, 2003) and then averaged across different

items to derive scores for each domain. Higher scores indicated a greater likelihood of the domain being measured (e.g., score of 90 means greater sleep disturbance). Linear regression was used to examine the associations between sleep and MWF. Mean MWF in each white matter tract was the outcome with each sleep domain examined as predictors of interest in separate models. All models were fitted in R version 3.6.0 using the `lm()` function and adjusted for age (mean-centered) at time of MRI acquisition, sex, and years between MRI and sleep data acquisition. Models were considered significant at unadjusted  $p < .05$ . **Results:** Participants were middle-aged (mean  $\pm$  SD = 63.51  $\pm$  6.17) and enriched for AD risk; 36% (n=41) carried at least one apolipoprotein E  $\epsilon$ 4 (APOE4) allele and 68% (n=78) had one parent with AD. In addition, participants were mostly female (61%), primarily white (96%), and highly educated (mean  $\pm$  SD = 16.40  $\pm$  2.42). Sleep disturbance was significantly associated with myelin content in the cingulum region projecting into the hippocampus ( $b = -0.00052$ ,  $p = .043$ ) such that greater sleep disturbance was associated with lower myelin content. Sleep disturbance showed a similar association in the forceps minor ( $b = -0.00047$ ,  $p = .06$ ), though this relationship did not reach the significance threshold. No other sleep domains were associated with myelin content in other regions. **Conclusion:** This analysis is the first to show, within a human cohort enriched for AD risk, that self-reported sleep disturbance is associated with myelin content alterations as measured with quantitative imaging and supports our hypothesis that self-reported sleep quality is associated with myelin content in AD-affected brain regions. The cingulum bundle is a major white matter tract that relays information between brain regions affected early in AD, including the posterior cingulate and hippocampus, and both sleep duration (Khalsa et al, 2017) and sleep apnea (Macey et al, 2008) have previously been shown to be associated with altered cingulum microstructure. The current findings add to a growing literature linking sleep to myelin alterations, suggesting that future clinical trials testing sleep interventions for dementia should consider myelin measures as potential outcomes.

**P032: CEREBELLAR ATROPHY CAN PREDICT CONVERSION OF AMNESTIC MILD COGNITIVE IMPAIRMENT TO DEMENTIA IN PATIENT WITH AMYLOID NEGATIVE.** H.J. Kim, S. Lee, S. Jo, J.H. Lee (*Department Of Neurology, Asan Medical Center - Seoul, Republic of Korea*)

**Background:** Around 15–20% of patients with clinically probable Alzheimer's disease have been found to have no significant Alzheimer's pathology on amyloid PET. A previous study shows that conversion to dementia from amyloid-negative MCI was observed in up to 11% of patients in this subpopulation drawing attention to this condition. However, few studies had been conducted this population in terms of clinical progression. **Objective:** In this study, we used SUIT-VBM (spatially unbiased infratentorial template, voxel-based morphometry) to perform an analysis of the pattern of cerebellar gray matter atrophy in amyloid-negative amnesic MCI in converter compared to non-converter, in order to follow the changes of no-motor features of cerebellar degeneration through disease progression. **Methods:** This study was a single-institutional, retrospective cohort study of patients over the age 50 with amyloid-negative amnesic MCI who visited the memory clinic of Asan Medical Center with at least more

than 36 months of follow-up period. All subjects underwent detailed neuropsychologic test, 3 tesla brain magnetic resonance imaging (MRI) including 3-dimensional T1 image, and fluorine-18[F18]-florbetaben amyloid PET scans. SUIT-VBM was used to analyze the cerebellar gray matter volume. **Results:** In this amyloid-negative amnesic MCI cohort study, we identified the cerebellar gray matter atrophy patterns in terms of conversion to dementia. Between the 2 groups, the converter group was more likely to have volume loss in vermis and curs I, II. In terms of neuropsychologic test, no statistically significant association was found between cerebellar gray matter atrophy and neuropsychologic test results. **Conclusion:** These findings therefore emphasize the potential value of cerebellar gray matter atrophy patterns as biomarkers, which could predict the conversion to dementia from amnesic MCI in amyloid-negative patients.

**P033: EARLY IMPAIRMENT IN THE VENTRAL VISUAL PATHWAY CAN PREDICT CONVERSION TO DEMENTIA IN PATIENTS WITH AMYLOID-NEGATIVE AMNESIC MILD COGNITIVE IMPAIRMENT.** H.J. Kim<sup>1</sup>, E.N. Cheong<sup>1</sup>, S. Jo<sup>1</sup>, S. Lee<sup>1</sup>, W.H. Shim<sup>3</sup>, J.H. Lee<sup>1</sup> ((1) Department Of Neurology, Asan Medical Center, University Of Ulsan College Of Medicine - Songpa-Gu, Seoul, Republic of Korea; (2) Department Of Medical Science And Asan Medical Institute Of Convergence Science And Technology, Asan Medical Center, University Of Ulsan College Of Medicine - Songpa-Gu, Seoul, Republic of Korea; (3) Health Innovation Big Data Center, Asan Institute For Life Sciences, Department Of Radiology And Research Institute Of Radiology, Asan Medical Center, University Of Ulsan College Of Medicine - Songpa-Gu, Seoul, Republic of Korea)

**Background:** With amyloid PET scan demonstrating fibrillar amyloid  $\beta$  in vivo, it has become possible to distinguish true AD and AD-mimicking condition. Around 15–20% of patients with clinically probable Alzheimer's disease have been found to have no significant Alzheimer's pathology on amyloid PET. A previous study shows that conversion to dementia from amyloid-negative MCI was observed in up to 11% of patients in this subpopulation drawing attention to this condition. However, few studies had been conducted this population in terms of clinical progression. **Objective:** We gathered the detailed neuropsychological and neuroimaging data of this population to elucidate factors for conversion to dementia from amyloid-negative amnesic MCI. **Methods:** This study was a single-institutional, retrospective cohort study of patients over the age 50 with amyloid-negative amnesic MCI who visited the memory clinic of Asan Medical Center with at least more than 36 months of follow-up period. All subjects underwent detailed neuropsychologic test, 3 tesla brain magnetic resonance imaging (MRI) including 3-dimensional T1 image, and fluorine-18[F18]-florbetaben amyloid PET scans. **Results:** During 36 months of follow-up, 39 of 107 patients converted to dementia from amnesic MCI. 4 patients were excluded from dataset, because of segmentation error. The converter group had more severe impairment in all visual memory tasks. Hippocampal volumetry revealed that the converter group had significantly reduced total hippocampal volume on the right side. The converter group also had reduced gray matter volume in the right lateral temporal, lingual gyri, and occipital pole. **Conclusion:** Our study showed that the reduced gray matter volume related to visual memory processing may predict the clinical progression in this amyloid-negative MCI population.

**P034: PROGNOSIS OF MILD COGNITIVE IMPAIRMENT OF UNCERTAIN ETIOLOGY: ASSESSMENT AND ANALYSIS OF CONCORDANT CASES FROM THE IDEAS STUDY.** D. Weidman, V. Ghisays, H. Protas, Y. Chen, V. Devadas, G. Sidarous, Y. Su (Banner Alzheimer's Institute - Phoenix, USA)

**Background:** Banner dementia specialists participated in the Imaging Dementia--Evidence for Amyloid Scanning (IDEAS) study, which has examined the impact of amyloid-PET imaging on clinical decision-making in diagnostically uncertain cases of mild cognitive impairment (MCI) and early dementia. A prior primary aim presented in 20191 was to determine a concordance rate, or agreement level between the visual (binary) florbetapir-PET results reported to clinicians and a quantitative assessment of cerebral cortical Amyloid-beta deposition, and analyze discordant cases, visually. The primary objective of this follow-up study was to compare the likelihood of conversion to dementia, between amyloid-PET concordant-negative and concordant-positive MCI patients, the IDEAS study being completed more than two years ago. **Methods:** The approved binary result (visually positive or negative florbetapir-PET scan) and a quantification of amyloid burden, (employing a recommended standardized uptake value ratio, suvr), were tabulated. Chart review was carried out in 2020, to determine the most recent clinical diagnosis, and date of that evaluation. Demographic data including age, gender and years of education was collected, for future analyses. **Results:** 11 of 100 cases (11%) were discordant (89% agreement), using a threshold of amyloid burden accurate for moderate to frequent amyloid neuritic plaque (meeting a criterion for pathological Alzheimer's disease) and 7 cases were discordant (93% agreement), using a lower cutoff threshold proposed for any identifiable cerebral amyloid. There were 21 florbetapir-PET negative-concordant cases with a pre-PET diagnosis of MCI, uncertain primary etiology, and 38 positive-concordant cases. 3 of the 21 PET-negative cases were lost to clinical follow-up. 16 of the remaining 18 patients did not convert to dementia; two converted to dementia: one case of vascular dementia, the other primary etiology remained uncertain, over 24 and 33 months, respectively. Mean duration of follow-up post-negative PET: range 1-37 months, mean 13-14 months. Of the 38 florbetapir-PET positive-concordant MCI cases, 4 of the 38 were lost to follow-up or clinical data was not accessible. 23 of the remaining 34 patients converted to dementia; in 18/23, a diagnosis of Alzheimer's disease was made. Other diagnoses were: Mean duration post-positive PET: range 3-40 months, mean of 28 months. Amyloid-PET concordant positivity was significantly associated with conversion to dementia ( $c2 = 15.07$ ,  $p = 0.000104$ ). Clinical data for 1 of the 4 patients showing intermediate amyloid burden (suvr 1.07-1.17) was not accessible. The most recent clinical diagnoses in the remaining 3 cases were: vascular dementia, dementia with Lewy bodies, and MCI due to AD. **Conclusions:** Florbetapir-PET positivity, visually and quantitatively, was significantly associated with conversion to dementia in the MCI patients participating in the IDEAS study. An important limitation in this study is that conversion to dementia in some cases of very mild dysfunction relied on best clinical judgment of the dementia specialist, who was not always the same clinician as the one participating in the IDEAS study. And in some cases was not inability to access follow-up clinical data for some patients referred from dementia specialists outside of Banner memory centers.

**P035: THE EFFECT OF CEREBRAL AMYLOID ANGIOPATHY ON REGIONAL CORTICAL ATROPHY, INDEPENDENT OF CORTICAL AMYLOID PATHOLOGY.**

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**Background:** Cerebral amyloid angiopathy (CAA) is characterized by the accumulation of amyloid beta within small or medium sized blood vessels of the brain. CAA is commonly found in neuropathological finding of patients with Alzheimer's disease. The effect of CAA on cortical volume have been studied, but most studies did not adjust for the effect of cortical amyloid deposition on cortical atrophy. **Objectives:** We aimed to evaluate the relationship between CAA and cortical volumes, independent of cortical amyloid pathology using voxel-based morphometry. **Methods:** We retrospectively investigated 35 patients diagnosed with probable CAA according to Boston criteria, all of whom showed cortical amyloid deposition on amyloid PET. Patients with Alzheimer's disease, who showed cortical amyloid deposition on amyloid PET were matched with patients with CAA by age, sex, and clinical deteriorating scale. We conducted voxel-based morphometry to examine the association between CAA and cortical volume. **Results:** Mean age of study population was 72.3 (7.2), and 57.1% were female. Age, sex, and clinical deteriorating scale were not significantly different between two groups. Ideomotor apraxia was more frequently found in patients with CAA than patients with Alzheimer's disease. Patients with CAA showed significantly lower gray matter volume in bilateral frontal and right temporal lobes than patients with Alzheimer's disease (family-wise error corrected  $p < 0.05$ ). **Conclusion:** CAA is related to regional cortical atrophy in bilateral frontal and right temporal area, independent of cortical amyloid pathology.

**P037: EFFECT OF MULTIDOMAIN INTERVENTIONS ON BRAIN FUNCTIONAL CONNECTIVITY OF ELDERLY PEOPLE WITH SPONTANEOUS MEMORY COMPLAINT.**

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**Backgrounds:** Interest for prevention of cognitive decline on elderly population has increased in the last few years. The Multidomain Alzheimer Preventive Trial (MAPT) (1) aims to test the efficacy of multiple interventions based on omega 3 polyunsaturated fatty acid supplementation (O3) and multidomain intervention (physical activity, cognitive training, and nutritional advice ; MI), combined (O3+MI) or separated, versus placebo intake (PI). While the effect of these interventions were studied on cognitive clinical endpoint scores (2), few studies were done on distinct biomarkers, such as MRI biomarkers, and no study assessed the effect of interventions on brain functional connectivity. **Objectives:** This study aims to evaluate the impact of multidomain intervention and

omega 3 supplementation on brain functional connectivity of elderly people ( $\geq 70$  years-old) with spontaneous memory complaint, independently or in consideration of specific risk factors for cognitive decline. **Methods:** On the sample of 129 participants scanned at Montpellier hospital center, with MRI scans (1.5T Siemens AVANTO) at baseline and three-years after intervention, 100 were included in the analysis after quality control (O3+MI : 27 ; O3 : 24 ; MI : 24 ; PI : 25). All participants underwent intervention during three-years and were evaluated with cardiovascular and cognitive scores at both timepoints (CAIDE, MMSE, Composite score). Resting-state fMRI data was pre-processed and connectivity scores were computed using respectively SPM and Conn Toolbox (3). Intra and inter networks connectivity scores were computed using networks well studied for normal aging and cognitive decline: the Default-Mode Network (DMN), the Salient Network (SN) and the Executive Control Network (ECN). Group differences between intervention and placebo were analyzed on the whole population and in specific subgroups of participants with risk factors, and in a second time adjusted with the following covariates : age, sex, level of education, APOE  $\epsilon 4$  status (carriers vs non-carriers), time between the beginning of the intervention and the MRI scan. **Results:** No effect of any intervention compared to placebo was found on brain functional connectivity of the whole population. Subgroups of participants with high risk of dementia (CAIDE score  $\geq 6$ ) or with MMSE score  $< 30$  had decreased inter-DMN-SN connectivity three-years after the intervention if they underwent multidomain intervention. Participants with favorable cognitive status (based on the CDR score) and supplemented with omega 3 had decreased inter-network connectivity between the DMN, SN and ECN, three-years after the intervention. Executive function network was also strengthened for these participants between baseline and three-years. It is hypothesized that there is less functional network segregation with aging (4), these results show that interventions could prevent this natural aging process. **Conclusion:** Multidomain intervention and omega 3 supplementation did not affect brain functional connectivity of elderly people with spontaneous memory complaint. However elderly people presenting specific clinical factors may be more sensitive to these interventions and targeting these specific populations may lead to therapeutic intervention based on comprehensive intervention. 1. B. Vellas et al., « MAPT study: A Multidomain approach for preventing Alzheimer's disease: Design and baseline data », *J Prev Alzheimers Dis*, vol. 1, no 1, p. 13 22, juin 2014; 2. S. Andrieu et al., « Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial », *The Lancet Neurology*, vol. 16, no 5, p. 377 389, mai 2017, doi: 10.1016/S1474-4422(17)30040-6; 3. S. Whitfield-Gabrieli et A. Nieto-Castanon, « Conn : A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks », *Brain Connectivity*, vol. 2, no 3, p. 125 141, juin 2012, doi: 10.1089/brain.2012.0073; 4. E. Varangis, C. G. Habeck, Q. R. Razlighi, et Y. Stern, « The Effect of Aging on Resting State Connectivity of Predefined Networks in the Brain », *Front. Aging Neurosci.*, vol. 11, p. 234, sept. 2019, doi: 10.3389/fnagi.2019.00234.

**LP05: REGIONAL RETINAL AMYLOID IMAGING IN A COHORT OF PATIENTS WITH MILD COGNITIVE IMPAIRMENT.** M. Koronyo-Hamaoui<sup>1,2</sup>, T. Torbati<sup>1,3</sup>, J. Sheyn<sup>1</sup>, P.D. Lyden<sup>4</sup>, A. Sherzai<sup>5</sup>, D. Sherzai<sup>5</sup>, D. Sherman<sup>6</sup>, S. Frautschy<sup>7,8</sup>, A.D. Czeszynski<sup>9</sup>, S. Verdooner<sup>9</sup>, K.L. Black<sup>1</sup>, Y. Koronyo<sup>1</sup>, O. Dumitrascu<sup>4</sup> ((1) Department Of Neurosurgery, Maxine Dunitz Neurosurgical Institute, Cedars-Sinai Medical Center - Los Angeles, USA; (2) Department of Biomedical Sciences, Cedars-Sinai Medical Center - Los Angeles, USA; (3) Western University Of Health Sciences, College Of Osteopathic Medicine Of The Pacific - Pomona, USA; (4) Department Of Neurology, Cedars-Sinai Medical Center - Los Angeles, USA; (5) Department Of Neurology, Loma Linda University - Loma Linda, USA; (6) Department Of Neuropsychology, Cedars-Sinai Medical Center - Los Angeles, USA; (7) Department Of Neurology, University Of California, Los Angeles - Los Angeles, USA; (8) Geriatric Research Education and Clinical Center, Veterans Administration - Los Angeles, USA; (9) Neurovision Imaging Inc. - Sacramento, USA)

We previously identified increased amyloid beta-protein (A $\beta$ ) deposits, the pathological hallmarks of Alzheimer's disease (AD), in the retina of mild cognitively impaired (MCI) and AD patients. Given the retina's distinctiveness as the sole CNS organ with the advantage of enhanced accessibility for direct noninvasive visualization, imaging retinal amyloidosis is progressively gaining acceptance as a potential detection and monitoring tool for AD. Despite such advances, however, a quantitative and topographical investigation of retinal A $\beta$  burden in patients with cognitive decline was never reported. Here, we used the specific amyloid-binding fluorophore curcumin and laser ophthalmoscopy to examine retinal amyloid imaging (RAI) in 34 patients with mostly amnesic MCI (aMCI). We quantified retinal amyloid count (RAC) and area (RA) in the supero-temporal quadrant in addition to conducting correlation analyses with demographic and brain volumetric parameters. The total RAC was significantly increased in patients with higher Clinical Dementia Rating (CDR) ( $p=0.02$ ). Notably, total RAC significantly correlated with hippocampal volume (HV;  $r=-0.39$ ,  $p=0.04$ ) and CDR ( $r=0.38$ ,  $p=0.02$ ). On subregion analysis, the proximal mid-periphery (PMP) RAC and RA were significantly higher in subjects with worse dementia, as indicated by Montreal Cognitive Assessment (MOCA) lower than 26 ( $p=0.01$ ; Cohen's  $d = 0.83$  and  $0.81$ , respectively). PMP showed significantly more RAC and area in subjects with amnesic MCI and Alzheimer's disease (AD) compared to cognitively normal patients ( $p=0.04$ ; Cohen's  $d = 0.83$ ). Further analyses revealed that increased PMP amyloid count significantly correlated with reduced HV ( $r=-0.41$ ,  $p=0.03$ ) and higher CDR score ( $r=0.37$ ,  $p=0.02$ ). Overall, our study suggests that PMP retinal A $\beta$  count may predict HV and cognitive decline, supporting the use of retinal amyloid burden as an effective measure to predict AD progression. Future larger studies are warranted to validate these findings and to determine the pragmatic utility of RAI in a behavioral neurology clinic as a biomarker of early AD.

**LP06: THE EFFECTS OF HOME-BASED, ROBOT COGNITIVE INTERVENTION ON THE FUNCTIONAL BRAIN NETWORK IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT.** G.H. Kim<sup>1</sup>, B.R. Kim<sup>1</sup>, K. Yoo<sup>2</sup>, M.Y. Chun<sup>1</sup>, K.D. Park<sup>1</sup>, J. Jee Hyang<sup>3</sup> ((1) Ewha Womans University Mokdong Hospital - Seoul, Republic of Korea; (2) Department Of Psychology Yale University - New Haven, Ct, USA; (3) Ewha Womans University Seoul Hospital - Seoul, Republic of Korea)

**Background and Purpose:** Previous studies suggest that cognitive intervention can mitigate the development of dementia in patients with mild cognitive impairment (MCI). However, the previous cognitive intervention was mostly provided as a group session, with patients with MCI having difficulty in regularly attending sessions or being reluctant to participate in group-based classes. Additionally, experienced instructors for traditional cognitive intervention may be unavailable in some chronic care facilities or community centers. Considering these reasons, we have developed 20 programs for home-based cognitive intervention with a personal robot for patients with MCI. This study aimed to demonstrate the effects of our newly developed home-based cognitive intervention with robots on functional brain network in patients with MCI. **Methods:** A single-blinded randomized controlled trial was conducted in 113 patients with MCI. Participants were randomized into three groups: the robot cognitive intervention (robot) ( $n=41$ ) group, conventional training (conventional) group ( $n=43$ ), and waitlist group without cognitive intervention (control) ( $n=42$ ) groups. The primary outcome was the change in functional brain network while the secondary outcome was the cognitive function measured using the Cambridge Neuropsychological Test Automated Battery. **Results:** There were no baseline demographic and clinical differences between the three groups. After a 12-week training, the conventional intervention group showed less decreased functional activity compared to those in the control group. The robot intervention group showed significantly increased functional brain network connectivity whereas the control group showed decreased functional connectivity. The robot group showed more increased functional connectivity than the conventional group, although there were no statistical differences. In addition, the robot group improved memory, attention, and frontal executive function than the control or conventional group. **Conclusions:** Our home-based 12-week cognitive training with a personal robot improved the functional brain network as well as cognitive function in patients with MCI.

**LP07: UPDATE ON IDEAS AND NEW IDEAS STUDIES.**

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**Background:** The Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study is a single-arm, U.S.-wide longitudinal study to evaluate the association between amyloid PET and health outcomes in cognitively impaired patients, conducted under a Centers for Medicare & Medicaid Services (CMS) Coverage with Evidence Development program. **Objectives:** To review the primary outcomes of the original IDEAS study, and introduce the design and objectives of New IDEAS, a follow-up study launching in late 2020. **Methods:** IDEAS enrolled patients with MCI or atypical dementia meeting Appropriate Use Criteria for amyloid PET. Participants were evaluated by dementia specialists and underwent PET with an FDA-approved beta-amyloid ligand (18F-florbetapir, 18F-florbetaben or 18F-flutemetamol). Scans were interpreted by local radiologists as "positive" or "negative" based on tracer-specific criteria. Patient diagnosis and management plans were recorded by the dementia specialist prior to PET (pre-PET visit), and again at 90±30 days following PET (post-PET visit). Outcomes assessed from Medicare claims covering 12 months were compared to outcomes from a matched control group of Medicare beneficiaries with MCI/dementia who did not receive amyloid PET. The primary Aims were (1) to determine if amyloid PET is associated with a ≥30% change in a composite patient management endpoint between the pre-PET and post-PET visit, separately in MCI and dementia; and (2) to determine if amyloid PET is associated with a ≥10% reduction in 12-month claims-derived hospital admissions and emergency department (ED) visits in study patients vs. controls. **Results:** 18,295 participants completed amyloid PET scans between February 2016 and January 2018. Median age was 75 (range: 65-105), 51% were female, 87% were White, 60.4% had MCI, 39.6%

had dementia and 61% were amyloid-PET positive. The Aim 1 analysis included 11,409 IDEAS participants. The composite management endpoint changed in 60.2% of patients with MCI [95% CI, 59.1%-61.4%] and 63.5% [62.1%-64.9%] of patients with dementia, significantly exceeding the target of ≥ 30% change in each group (p<0.001, 1-sided). The most common change involved the use of AD-specific drugs (43.6% in MCI, 44.9% in dementia). Diagnosis changed from AD to a non-AD condition in 25.1% of patients, and from non-AD to AD in 10.5%. Of the 12,748 IDEAS participants eligible for the Aim 2 (claims-based) analysis, matched controls were identified for 12,684 (99.5%). 12-month hospitalization rates were 23.98% in IDEAS compared to 25.12% in controls (absolute difference -1.14% [-2.19% - -0.08%]; relative difference -4.52% [-8.55% - -0.30%]), falling short of the goal of ≥10% relative reduction. Differences in hospitalizations were higher in patients with dementia (absolute difference -2.03%; relative difference -7.01%) than in patients with MCI (absolute difference -0.65%, relative difference -2.82%). There were no differences in rates of ED visits between IDEAS participants (44.79%) vs. controls (44.84%) overall (absolute difference -0.05% [-1.27% - +1.18%]; relative difference -0.11% [-2.80% - +2.66%]) or when stratified by MCI versus dementia. Logistic regression revealed that amyloid-positive IDEAS participants had a lower risk of 12-month hospitalizations than amyloid-negative patients after adjusting for relevant demographic and health variables (OR 0.78 [0.71 - 0.87]). Similar results were observed when stratifying by MCI (OR 0.78 [0.70 - 0.88]) and dementia (OR 0.77 [0.66 - 0.89]). Amyloid-positive patients with dementia also had a lower risk of 12-month ED visits compared to amyloid-negative dementia patients (OR 0.85 [0.75 - 0.96]) while no differences were found in MCI (OR 0.95 [0.86 - 1.03]). The New IDEAS study, approved by CMS in April 2020, plans to launch in November 2020. New IDEAS will recruit 7,000 Medicare beneficiaries with MCI and dementia, including a minimum of 2,000 Blacks/African-Americans and 2,000 Latinx/Hispanics. The primary Aims of New IDEAS are (1) to compare 12-month claims-derived health outcomes in amyloid PET-positive versus amyloid PET-negative individuals presenting with MCI and dementia in the entire study cohort of diverse Medicare beneficiaries; (2) to describe the association of amyloid PET findings with changes in patient management and 12-month claims-derived health outcomes among Blacks/African Americans, LatinX/Hispanics and Whites/Caucasians presenting with MCI and dementia; and (3) to describe the association of amyloid PET findings with changes in management and 12-month claims-derived health outcomes in individuals presenting with typical (progressive amnesic) versus atypical clinical presentations of MCI and AD dementia. Additional objectives include (1) establishing a PET image repository and; (2) establishing a biorepository that will bank DNA and plasma from ~5,000 study participants. **Conclusions:** The first IDEAS study found that amyloid PET was associated with frequent changes in patient management and a modest reduction in 12-months hospitalizations. New IDEAS will build on these findings in a more diverse cohort of Medicare beneficiaries. Data from both studies will be shared via the Global Alzheimer's Association Interactive Network (GAAIN), and biosamples from New IDEAS will be housed at the Alzheimer's Therapeutic Research Institute. IDEAS and New IDEAS provide insights into real-world memory care and will inform the implementation of amyloid PET and other AD biomarkers into clinical practice.

## **Theme 4: CLINICAL TRIALS: BIOMARKERS INCLUDING PLASMA**

**P040: BIO-HERMES: A BIOMARKER STUDY INITIATED BY THE GLOBAL ALZHEIMER'S PLATFORM FOUNDATION® TO COMPARE SELECT DIGITAL AND BLOOD-BASED BIOMARKERS WITH CLINICAL DIAGNOSIS AND AMYLOID-B PET IMAGES.** J. Dwyer, S. Walsh, D. Beauregard, E. Gorman, J. Bork, K. Smith, S. Hollingshead, R. Mohs (*Global Alzheimer's Platform Foundation - Washington, USA*)

**Background:** A time-consuming challenge in Alzheimer's disease (AD) clinical trials is finding qualified participants. Cerebrospinal fluid sampling has been used to quantify tau and amyloid- $\beta$  (A $\beta$ ) proteins in patients suspected to have AD. Numerous clinical trials have also employed Positron Emission Tomography (PET) scans to detect tau and A $\beta$  proteins. These procedures are expensive, take time to analyze, and result in high-cost screen fails. Furthermore, participation in clinical trials by minority populations remains low despite efforts to increase minority representation in clinical trials. The Global Alzheimer's Platform Foundation® (GAP) is developing a program intended to pre-identify large numbers of potentially qualified participants based on demographics, medical history, cognitive status, and the use of select blood-based biomarkers. Because African Americans are at increased risk of developing AD and race-associated differences in CSF tau markers may lead to misdiagnosis in African Americans, GAP will also explore if racial differences related to specificity and sensitivity of blood-based biomarkers exist. Consistent with GAP's mission, broad access to deidentified data on patient characteristics, biological specimens, and biomarker data will enhance the field's ability to reduce the duration, cost, and variability of AD clinical trials. **Objectives:** The objectives of the GAP Bio-Hermes Program are as follows: Develop a cost-effective and more accurate prescreening process using blood-based biomarkers to generate substantially large numbers of participants qualified and willing to participate in AD therapeutic clinical trials. Investigate if racial variability exists in the utilization of these blood-based biomarkers in identifying appropriate trial candidates. **Methods:** GAP will obtain a common set of cognitive tests, clinical diagnostic information, and selective blood-based biomarkers from each study participant. A cognitive battery will be used to assess cognitive profiles relative to biomarker status and will consist of Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Rey Auditory Verbal Learning Test (RAVLT), and Digital Voice Analysis. Biospecimens will be collected to determine blood-based biomarker levels of A $\beta$ , phospho-tau (p-tau), and neurofilament light (NfL). The individual biomarker results will be compared with centrally read and quantitated amyloid PET scans, all encompassed within the biomarker clinical trial (Bio-Hermes). 1000 participants will be enrolled across 10 sites in GAP's network of leading clinical trial sites (GAP-Net). A minimum of 200 participants will be individuals self-identifying as African American or Latino. The trial will endeavor to recruit participants that fall into 3 clinical diagnostic classifications: Cognitively Normal, Mild Cognitive Impairment, and Mild Alzheimer's Disease. The trial consists of 3 visits (screening/biospecimen collection, imaging, and A $\beta$  PET disclosure) in a 90-day period. The trial-ready cohort of participants developed during the Bio-Hermes trial will be available to GAP-Net sites

participating in the program. Biological samples collected during the course of the trial will be deidentified and stored for future research. **Results:** Enrollment in Bio-Hermes is expected to begin in 2020, and last patient visit is planned for April 2021. The financial impact of utilizing blood biomarkers rather than PET imaging to select qualified participants for AD clinical trials will be evaluated. **Conclusions:** GAP's Bio-Hermes Program may provide several benefits. Well-characterized samples and data that will facilitate the testing of blood-based and digital biomarkers as indicators of AD pathology, thereby enhancing screening of potential participants for AD clinical trials. The trial's commitment to enroll a substantial group (minimum of 200 of 1000) of historically underrepresented minority populations will further enrich the data provided by Bio-Hermes. A trial-ready and trial-willing cohort of potential therapeutic trial participants may lower screen fail rates and accelerate enrollment.

**P041: DOWN SYNDROME ASSOCIATED ALZHEIMER'S DISEASE: EARLY DATA FROM THE LONGITUDINAL INVESTIGATION FOR ENHANCING DOWN SYNDROME RESEARCH (LIFE-DSR) STUDY.** J. Hendrix<sup>1</sup>, H. Hillerstrom<sup>1</sup>, D. Airey<sup>2</sup>, A. Britton<sup>1</sup>, R. Chavez<sup>3</sup>, J. Dage<sup>2</sup>, K. Faber<sup>4</sup>, T. Foroud<sup>4</sup>, D. Ladesma<sup>3</sup>, C. Revta<sup>3</sup>, K. Schafer<sup>3</sup>, K. Wilmes<sup>4</sup>, J. Zimmer<sup>2</sup>, H. Feldman<sup>3</sup>, W. Mobley<sup>5</sup> ((1) *Lumind Idsc - Burlington, USA*; (2) *Eli Lilly And Co. - Indianapolis, USA*; (3) *Department Of Neurosciences, Alzheimer's Disease Cooperative Study, University Of California San Diego - San Diego, USA*; (4) *National Centralized Repository For Alzheimer's Disease And Related Dementias (ncrad), Indiana University School Of Medicine - Indianapolis, USA*; (5) *Department Of Neurosciences, University Of California, San Diego - San Diego, USA*)

**Background:** With improved healthcare, the Down syndrome (DS) population is both growing and aging rapidly with a life expectancy of >55 years of age compared to just 25 year of age in the 1980's. It is estimated that there are 210,000 people with DS in the USA and 40% are over the age of 30 years. However, with longevity comes a very high risk of Alzheimer's disease (AD). It is estimated that by age 55–60 years at least 70% will develop Alzheimer's dementia. Furthermore, by their 40's virtually all adults with DS develop neuropathology consistent with AD. The LIFE-DSR study is a longitudinal natural history study recruiting 270 adults with DS over the age of 25. The study is designed to characterize trajectories of change in DS-associated AD (DS-AD) via 3 annual visits that include physical exam, medical history, neuropsychiatric evaluation, and a blood draw for biomarker and genetic analyses. The use of Phosphorylated tau (P-tau) biomarkers in plasma is relatively new but may be associated with AD progression and the onset of dementia symptoms. Neurofilament light (NfL) levels which are a general marker of axonal injury and neurodegeneration, have demonstrated a strong association with progression in DS-AD and are a primary biomarker of interest in this study investigation. **Objectives:** The LIFE-DSR study has been designed to better understand the factors that underlie symptoms and age of clinical presentation of DS-AD. During the pause in LIFE-DSR recruitment caused by COVID-19, the first 90 plasma samples banked will be analyzed for AD and neurodegenerative biomarkers P-tau181, P-tau217 and NfL. The biomarker data will be combined with clinical data from the baseline visit (detailed below). **Methods:** Plasma P-tau biomarkers will be measured using previously



published methods and NfL will be measured using the Quanterix NfL assay. The clinical data includes demographics and medical history as well as a series of neuropsychiatric exams of cognition, function, and behavior. The cognitive measures include the Severe Impairment Battery (SIB) with the Shobox test and, optionally, the Down Syndrome Mental Status Examination (DS-MSE). The Vineland-3 is used to assess function while the Dementia Questionnaire for Persons with Learning Disabilities (DLD) and the Neuropsychiatric Inventory (NPI) is used to measure behavior. Biomarker distributions will be described and compared to historical data in non-DS populations. In addition, statistical associations between clinical measures, demographic characteristics, and biomarkers will be evaluated. **Results:** Biomarker and clinical data at baseline will be presented on a subset of LIFE-DSR participants. **Conclusion:** The biomarker data contributes to understanding of disease onset and progression and clinical profiles of DS-AD and will be applied to the full LIFE-DSR longitudinal study.

**P042: STUDIES ON THE PRACTICAL PERFORMANCE OF A PLASMA AMYLOID B MEASUREMENT SYSTEM BY IMMUNOPRECIPITATION COMBINED WITH MALDI-TOF MASS SPECTROMETRY.** N. Kaneko<sup>1</sup>, Y. Hioki<sup>1,2</sup>, R. Yoda<sup>1</sup>, A. Korenaga<sup>1</sup>, Y. Ohashi<sup>3</sup>, M. Honda<sup>3</sup>, S. Sekiya<sup>1</sup>, S. Iwamoto<sup>1</sup>, K. Tsujino<sup>3</sup>, K. Tanaka<sup>1</sup> ((1) *Koichi Tanaka Mass Spectrometry Research Laboratory, Shimadzu Corporation - Kyoto, Japan;* (2) *Shimadzu Scientific Instruments - Frederick, Md, USA;* (3) *Shimadzu Techno-Research - Kyoto, Japan*)

**Background:** The measurement of plasma amyloid  $\beta$  recently attracts much attention as a biomarker of Alzheimer's disease. We previously developed a highly sensitive method for simultaneous detection of a plurality of amyloid  $\beta$  peptides in human plasma by using immunoprecipitation combined with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (IP-MALDI-MS). In this study, we examined the interference effect of contaminants such as drugs and anticoagulants in human plasma to reinforce the performance and practicability of this approach. **Methods:** Anticoagulants, Alzheimer's disease agents, and protein drugs which have similar structures with amyloid  $\beta$  were tested as possible interfering substances. Each compound was dissolved in PBS and spiked to human plasma. PBS without the compound was used as a control. Thirteen plasma samples including the control plasma were measured in triplicate by IP-MALDI-MS. **Results:** Three normalized intensities ( $A\beta 1-40$ ,  $A\beta 1-42$  and APP669-711) and two biomarker values ( $A\beta 1-40/A\beta 1-42$  and APP669-711/ $A\beta 1-42$ ) of the interfering substances doped plasma were compared to those of control plasma. The results showed that the addition of any of those compounds had only a slight effect on the measured values, and the changes of the plasma biomarkers were within  $100 \pm 12\%$  relative to the control. **Conclusion:** The analysis of plasma amyloid  $\beta$  biomarkers by IP-MALDI-MS is a unique method for the simultaneous detection of multiple amyloid  $\beta$  peptides requiring only one kind of antibody. This study showed that addition of twelve kinds of contaminants to the human plasma had limited effects on the analytical performance of the system.

**P043: IDENTIFICATION OF ADAMTS4 AS AN AMYLOID PRECURSOR PROTEIN CLEAVING ENZYME AT 669 SITE IN APP669-711 PRODUCTION PATHWAY.** T. Tomita<sup>1</sup>, M. Matsuzaki<sup>1</sup>, N. Kaneko<sup>2</sup>, M. Yokoyama<sup>1</sup>, Y. Yoshizawa<sup>1</sup>, Y. Hioki<sup>2,3</sup>, S. Iwamoto<sup>2</sup>, K. Tanaka<sup>2</sup> ((1) *Laboratory Of Neuropathology And Neuroscience, Graduate School Of Pharmaceutical Sciences, The University Of Tokyo - Tokyo, Japan;* (2) *Koichi Tanaka Mass Spectrometry Research Laboratory, Shimadzu Corporation - Kyoto, Japan;* (3) *Shimadzu Scientific Instruments - Frederick, Md, USA*)

**Background:** Amyloid- $\beta$  peptide ( $A\beta$ ) is deposited in the brains of Alzheimer disease (AD) patients, and proteolytically derived from its precursor protein, APP. APP669-711 (a.k.a.  $A\beta(1-40)$ ) is a novel APP-derived peptide detected in the plasma using immunoprecipitation combined with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (IP-MALDI-MS). We have reported that the composite plasma biomarker, which is combination of APP669-711/ $A\beta 1-42$  ratio and  $A\beta 1-40/A\beta 1-42$  ratio, surrogates the accumulation of  $A\beta$  in brain (Kaneko et al., Proc Jpn Acad Ser B Phys Biol Sci. 2014; Nakamura et al., Nature 2018). However, the mechanism of APP669-711 production is largely unclear. **Methods:** We analyzed the effects of several inhibitors and genetic knockouts on the production of APP699-711 in cultured cells. **Results:** Endogenous APP669-711 was detected in the conditioned medium of BE2-(C), Neuro2a and A549 cells by IP-MALDI-MS. Pharmacological experiments revealed that APP669-711 is generated by sequential cleavages by GM6001-sensitive metalloprotease at 669 site and  $\gamma$ -secretase. Based on the preferences of the substrate sequence, we focused on ADAMTS4, which is the secreted metalloprotease with thrombospondin motif. Overexpression of ADAMTS4 resulted in the overproduction of APP669-711. Furthermore, endogenous APP669-711 production was decreased in ADAMTS4 knockout cells. **Conclusion:** These results suggest that ADAMTS4 is involved in the production pathway of APP669-711, a novel plasma biomarker for  $A\beta$  deposition in the brain.

**P044: IDENTIFICATION OF PROGNOSTIC PROTEIN BIOMARKERS FOR COGNITIVE DYSFUNCTION IN THE ORIGIN TRIAL.** T. Cukierman-Yaffe<sup>1,2,3</sup>, S.-F. Lee<sup>3</sup>, S. Hess<sup>4</sup>, H.C. Gerstein<sup>3,5</sup> ((1) *Endocrinology Institute, Gertner Institute Sheba Medical Center, Ramat-Gan, Israel;* (2) *Epidemiology Department, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel;* (3) *Population Health Research Institute, Hamilton Health Sciences and McMaster University, USA;* (4) *Sanofi Aventis Deutschland GmbH, R&D, TMED-BCB, Frankfurt, Germany;* (5) *Department of Medicine, McMaster University, Hamilton, Ontario, Canada*)

**Background:** Diabetes and cardiovascular (CV) disease both increase the risk of incident cognitive dysfunction. Identification of novel biochemical markers for cognitive dysfunction may help to identify people with Dysglycemia who are at the highest risk while yielding insights regarding the pathophysiology of cognitive dysfunction in people with type 2 diabetes. **Methods:** We studied 8365 participants in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial with stored baseline serum. Each participants serum was analyzed for 238 cardio-metabolic protein biomarkers using the Luminex technology (Myriad RBM Inc, Austin/TX) and who completed a baseline Mini Mental State Examination (MMSE). Cox regression models accounting for

clinical risk factors, the baseline MMSE and the competing risk of death were used to identify biomarkers that independently predicted incident cognitive dysfunction. **Results:** During a median follow-up period of 6.2 years 939 individuals developed cognitive dysfunction. After accounting for 17 clinical variables and the baseline MMSE,  $\alpha$ -2 Macroglobulin (HR 1.19; 95%CI 1.12, 1.27), Macrophage Inflammatory Protein 1 $\alpha$  (HR 1.11; 95%CI 1.06, 1.16), and Growth Hormone (HR 0.91; 95%CI 0.778, 0.96) independently predicted incident cognitive dysfunction ( $P < 0.0002$ ). Addition of these biomarkers to a model that included clinical risk factors, however, did not provide a substantive improvement in the ability of the model to predict cognitive dysfunction. **Conclusions:** The addition of several biomarkers to routinely measured clinical risk factors independently predicted cognitive dysfunction in people with dysglycemia. The Origin trial was funded by Sanofi.

**P045: DEEP PROTEOMIC PROFILING OF AD CSF FOR UNBIASED BIOMARKER DISCOVERY AND SUBJECT STRATIFICATION.** Y. Feng, R. Bruderer, D. Heinzmann, L. Reiter (*Biognosys - Schlieren, Switzerland*)

**Background:** Cerebrospinal fluid (CSF) is established as a key matrix that enables interrogation of biological processes within the central nervous system. CSF biomarkers may support development of new therapies through patient stratification, determining prognosis or disease aggressiveness, and response monitoring. However, the need for better biomarkers and biological understanding is evidenced by the lack of success of disease modifying drugs in late-stage clinical trials. Here, we seek to address this unmet need by applying an optimized workflow, based on data-independent acquisition mass spectrometry (DIA-MS), to deeply characterize the proteomes of CSF from subjects with Alzheimers' Disease (AD). **Materials and Methods:** CSF samples were obtained from subjects with LOAD ( $n = 16$ ) and age-matched normal controls (CO;  $n = 8$ ). The samples were prepared using in solution digestion. A sample specific library was generated by first pooling of all samples, then by fractionation using high-pH reverse phase fractionation. Subsequently, the fractions were separated using 2h gradients and recorded by data-dependent acquisition on a Thermo Scientific Q Exactive HF-X mass spectrometer. Quantification was performed with DIA-MS on the same LC-MS setup using 2h gradients. Data analysis of DIA was conducted using Spectronaut<sup>TM</sup> (Biognosys). Peptide and protein false discovery rate was set to 1%. **Results:** A CSF library was generated covering 4,390 proteins. Across all samples 1,924 proteins were identified and quantified in single shot acquisitions. The pool of quantified proteins comprises well characterized species associated with AD and other neurological disorders such as BACE1, APP, MAPT (Tau), SNCA, TREM2, YKL-40, and NEUG. Moreover, the depth and breadth of protein quantification covers numerous pathological mechanism (e.g. AB and Tau pathology, synaptic dysfunction, iron toxicity and inflammation). Differential expression analysis identified 41 proteins that are significantly dysregulated between AD and CO groups (Q-value  $< 0.05$  and Log<sub>2</sub> FC  $> 0.58$ ). We observed several classes of proteins both up/down-regulated in AD samples including apolipoproteins (APO-A/B-100/L1), components of the complement system (C4BPA/B), regulators of synaptic functions (RGMA, LGI1 and CLSTN1) as well as markers for oxidative stress (SOD1 and PRDX2). Interestingly, based on a panel of protein signatures, we could identify two distinct subpopulations among the 16 AD

subjects. **Conclusions:** DIA-MS platform enables simultaneous quantitative characterization of close to 2,000 proteins, covering  $>90\%$  of developmental markers, from CSF with a workflow that is scalable to 100s of samples.

**P046: ANTIBODY FREE, MASS SPECTROMETRIC PROCEDURE FOR THE DETERMINATION OF AB40 AND AB42 IN HUMAN PLASMA.** L. Sarasa, P. Pesini, M. Sarasa, J.A. Allué (*Araclon Biotech - Zaragoza, Spain*)

**Background:** With the potential development of new  $\beta$ -amyloid targeted treatments for AD, screening tests that can be widely and inexpensively deployed to identify among cognitively normal people those presenting A $\beta$  pathological change, are urgently needed. The assessment of A $\beta$ 42/A $\beta$ 40 plasma ratio by different immunoassays have shown satisfactory clinical performance as surrogate biomarkers of cerebral amyloid burden as determined by A $\beta$ -PET or CSF A $\beta$ 42 analysis. However, robustness and reliability of immunoassays seem to be still hampered by the largely unknown interactions between the biochemical properties of A $\beta$  peptides and the complex composition of the plasma matrix. Mass Spectrometric (MS) procedures have become a real alternative to immunoassays due to their high specificity and sensitivity. However, most of the currently available MS procedures still rely on a preliminary immunoprecipitation step, which could be subject to plasma matrix interactions, particularly in samples from people treated with anti-beta-amyloid monoclonal antibodies, and on the other hand, increases their cost substantially. **Objectives:** We aimed to develop an antibody-free MS assay for the determination of intact A $\beta$ 40 and A $\beta$ 42 in human plasma (ABtestMS) that reduces drastically sample preparation time. In addition, as no analyte digestion is carried out, intact A $\beta$  species are quantified. **Methods:** Calibration curves and quality control samples were prepared in human plasma, after spiking with 15N-A $\beta$ 40 and 15N-A $\beta$ 42. Deuterated analogues 2H-A $\beta$ 40 and 2H-A $\beta$ 42 were used as internal standards for quantitation. Analytes are extracted from plasma without any immunoprecipitation procedure and no subsequent enzymatic digestion is carried out. A $\beta$  species are separated in a Micro-LC system and analyzed in a hybrid Triple Quadrupole-Linear Ion Trap mass spectrometer (ABSciex 6500+ Q-TRAP) fitted with a DMS interface (SelexIon). A comprehensive analytical validation including precision, accuracy, sensitivity, selectivity and linearity was performed following FDA recommendations. Clinical performance of ABtestMS was tested by ROC analysis to discriminate A $\beta$ -PET+ve versus A $\beta$ -PET-ve individuals in a pilot study using a subset of 36 samples from the AB255 study. **Results:** ABtestMS allowed quantification of intact A $\beta$ 40 and A $\beta$ 42 species in human plasma samples in the ranges of 50-1000 and 10-200 pg/ml respectively, without preliminary immunoprecipitation nor enzymatic digestion. Intra-assay precision and accuracy, expressed as coefficient of variation (CV in %) and %Error respectively, ranged from 1.9 to 9% and -8.9 to 5.8% for 15N-A $\beta$ 40. For 15N-A $\beta$ 42, %CV and %Error ranged from 3.6 to 13.2% and -5.5 to 5.6% respectively. Inter-assay precision and accuracy, ranged from 6.2 to 7.0% and -0.6 to 0.3% for 15N-A $\beta$ 40. For 15N-A $\beta$ 42, %CV and %Error ranged from 6.1 to 11.0% and -1.5 to 1.3% respectively. The unadjusted A $\beta$ 42/A $\beta$ 40 ratio, as determined by ABtestMS, allowed the identification of A $\beta$ -PET+ve subjects with an AUC of 0.84 in the AB255 study. **Conclusions:** ABtestMS allows the robust and reliable quantification of A $\beta$ 42/A $\beta$ 40 ratio in plasma without requiring preliminary immunoprecipitation

nor enzymatic digestion of the sample. The A $\beta$ 42/A $\beta$ 40 ratio in plasma as determined by ABtestMS, could be useful for the identification of cognitive normal people with cerebral  $\beta$ -amyloid preclinical Alzheimer's pathologic change.

**P047: CHOLESTEROL AND TRIGLYCERIDE LEVELS IN ALZHEIMER'S DISEASE PATIENTS UNDERGOING THERAPEUTIC PLASMA EXCHANGE WITH ALBUMIN REPLACEMENT.** A.M. Ortiz<sup>1</sup>, C. Minguet<sup>1</sup>, L. Nuñez<sup>1</sup>, A. Ruiz<sup>2,3</sup>, O.L. Lopez<sup>4</sup>, M. Boada<sup>2,3</sup>, A. Páez<sup>1</sup>, M. Costa<sup>1</sup> ((1) Alzheimer's Research Group, Grifols - Barcelona, Spain; (2) Research Center And Memory Clinic, Fundació Ace, Institut Català De Neurociències Aplicades-Universitat Internacional De Catalunya - Barcelona, Spain; (3) Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III - Madrid, Spain; (4) Departments Of Neurology And Psychiatry, University Of Pittsburgh School Of Medicine - Pittsburgh, Pennsylvania, USA)

**Background:** Some studies suggest a link between dyslipidemia biomarkers (high total cholesterol and triglyceride levels) and Alzheimer's disease (AD). The association between cholesterol levels and the disease seems stronger than for triglyceride levels. The AMBAR (Alzheimer Management By Albumin Replacement) phase 2b/3 trial is a new therapeutic approach for mild-moderate AD patients (MMSE:18-26) based on a 14-month program of plasma exchange (PE) with albumin replacement to remove neurotoxic A $\beta$  and other pathological substances from plasma to slow AD progression. **Objectives:** to assess the effect of PE on dyslipidemia biomarkers such as total cholesterol and triglyceride levels across the AMBAR study. **Methods:** We measured total cholesterol and triglyceride levels using standard techniques in serum samples of the AMBAR trial patients (n=321; PE-treated: n=243; Controls [sham-PE]: n=78) collected across the study: at baseline visit, before and after every PE session, at intermediate visit (after the 6-week period of conventional therapeutic PE [TPE] in which 1 plasma volume [2500-3000 mL] is processed; 1 TPE/week); and at final visit (after the 12-month period of low volume PE [LVPE] in which 1/3 plasma volume approximately [690-880 mL] is processed; 1 LVPE/month). Cutoff values of normal reference range were <200 mg/dL for total cholesterol and <150 mg/dL for triglyceride. PE-treated patients vs. controls were compared using the parametric or non-parametric tests depending on the nature of the comparison. **Results:** Median (IQR) total cholesterol and triglyceride baseline levels were 215 (186-242) mg/dL and 126 (94-180) mg/dL, respectively (61% and 37% of the patients above the value of normality). Women, patients younger than 65 years old, and Apo $\epsilon$ 4 carriers had higher baseline total cholesterol levels than men (p<0.01), older patients (p<0.05), and Apo $\epsilon$ 4 non-carriers (p<0.01), respectively. Patients recruited in the US had higher baseline triglyceride levels than patients in Spain (p<0.0001). Across treatment, a reduction of both total cholesterol and triglyceride levels was observed after each PE, but not in the control group, with a statistically significant effect associated with time, treatment group, and time-treatment group combined (p values ranged p<0.0001 to p=0.0019). The reduction was more marked after the TPE period than after the LVPE period: -148 mg/dL vs. -60 mg/dL in median total cholesterol level, respectively (<-19 mg/dL in controls), and -60 mg/dL vs. -20 mg/dL in median triglyceride level, respectively (-4 mg/dL in controls). Interestingly, those patients with high total cholesterol levels at baseline (>200

mg/dL) kept their values within the normal reference range (<200 mg/dL) during the entire treatment period. Regarding those with high baseline triglyceride levels (>150 mg/dL), normal values were kept only during the TPE period, but close to normal reference range (<150 mg/dL) during the LVPE period. **Conclusion:** PE with albumin replacement had a positive but transient effect in lowering both total cholesterol and triglyceride levels in mild-moderate AD patients.

**P048: PK/PD MODEL OF THE EFFECTS OF THE ANTI-SORTILIN ANTIBODY AL001 IN HUMANS.** M. Ward<sup>1</sup>, R. Paul<sup>1</sup>, F. Yeh<sup>1</sup>, H. Long<sup>1</sup>, O. Siddiqui<sup>1</sup>, M. Hagey<sup>1</sup>, I. Siah<sup>1</sup>, T. Schwabe<sup>1</sup>, S. Kathman<sup>2</sup>, C. Hines<sup>2</sup> ((1) Alector - South San Francisc, Ca, USA; (2) Ppd - Wilmington, Nc, USA)

**Background:** Frontotemporal dementia (FTD) is a rare, early-onset form of dementia that presents with marked changes in personality, speech, executive function and movement. Carriers of progranulin gene (GRN) mutations have a greater than 50% reduction in progranulin (PGRN) levels which is causative of FTD (FTD-GRN). The Sortilin receptor, expressed on neurons and microglia, is a key regulator of PGRN levels. AL001 is a human monoclonal IgG1 antibody that downregulates the Sortilin receptor, and is being developed by Alector for the treatment of FTD-GRN. AL001 normalizes the levels of PGRN in the CNS of GRN mutation carriers. Restoring PGRN levels may be an effective therapeutic approach, potentially reducing the rate of neurodegeneration and clinical decline in these individuals. AL001 is currently being evaluated in a Phase 2 and a pivotal Phase 3 study. **Objectives:** The objective was to develop a semi-mechanistic exposure-response model using data from the AL001 first-in-human Phase 1 study. The model was then used to identify an intravenous (IV) regimen for Phase 2 and Phase 3 studies that is predicted to restore PGRN in cerebrospinal fluid (CSF) of GRN mutation carriers to normal level for the entire treatment period. **Methods:** Study AL001-1 is a multi-site, first-in-human, Phase 1 study in healthy volunteers and asymptomatic and symptomatic carriers of GRN mutations that was designed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single-dose (SD) and multiple-dose (MD) intravenously administered AL001. Data from this study was used to build and refine an exposure-response model that combined the population PK model for AL001 in serum and CSF with a population PD model for Sortilin expressed on white blood cells (WBCs) and PGRN in plasma as well as PGRN in CSF. The population PK model for AL001 in serum was a two-compartment model with a linear and nonlinear clearance term in the central compartment. A third compartment was added to the model to capture the concentration of AL001 in the CSF. Sortilin expressed on WBCs and PGRN levels in plasma were modeled utilizing turnover models with zero-order synthesis and first-order elimination rates. The first-order elimination rate of Sortilin was modeled as a function of the serum concentration of AL001. Sortilin was then related to the first order elimination rate of PGRN. PGRN levels in CSF were also modeled utilizing a turnover model with zero-order synthesis and first-order elimination rates. The first-order elimination rate of PGRN in CSF was modeled as a function of the CSF concentration of AL001. Demographic covariates (e.g. age, weight) were considered for the model parameters. The model was developed using Bayesian methods in NONMEM. **Results:** Results from diagnostic plots suggest that the model fit the Phase 1 data well for concentrations

of AL001 in serum and CSF, Sortilin expression on WBCs, and PGRN levels in plasma and CSF. Weight was added as a covariate on the linear clearance term and the volume of the central distribution. The model shows that increasing doses lead to increasing serum concentrations of AL001, which lead to decreasing Sortilin on WBCs, which then leads to increasing PGRN levels in plasma. The increasing serum concentrations of AL001 also lead to increasing CSF concentrations of AL001, which lead to increasing PGRN levels in CSF. Higher AL001 doses lead to prolonged durations of increased PGRN levels in the CSF. The relationships for PGRN were modeled with Emax models, suggesting that there is a limit to the magnitude of the effect. Based on simulation results from the model, dosing AL001 every 4 weeks (q4w) with 45 mg/kg or 60 mg/kg led to increased levels of PGRN in CSF that persist throughout the entire dosing interval. The peak levels achieved are expected to be similar for 30, 45, and 60 mg/kg with the higher doses having the highest probability of prolonged effects. Dosing AL001 less frequently is expected to lead to most subjects' CSF PGRN levels returning to baseline before receiving the next dose. Because it is anticipated that prolonged increases in PGRN levels in CSF will be predictive of clinical benefit, Phase 2 and Phase 3 dosing regimens should be based, in part, on model-based simulations of CSF PGRN levels. **Conclusion:** A semi-mechanistic exposure-response model of AL001 was developed using Phase 1 first-in-human study data. Diagnostic plots, including visual predictive checks, show the model was predictive of the effect of AL001 on Sortilin expression on WBCs and PGRN levels in plasma and in CSF. Simulations were run for various regimens to inform dosing choice in clinical trials aimed at determining the efficacy of AL001 in patients with FTD-GRN. The model was used to select a dose level and dosing frequency for Phase 2 and Phase 3 trials, and will continue to be refined as more data become available.

**P049: PLATELET-MIRNAS AS BIOMARKERS FOR DEMENTIA WITH LEWY BODIES.** A. Gamez-Valero<sup>1</sup>, D. Vilas<sup>2</sup>, L. Ispuerto<sup>2</sup>, F. Borrás<sup>1</sup>, R. Alvarez<sup>1</sup>, K. Beyer<sup>1</sup> ((1) *Research Institute Germans Trias I Pujol, Spain;* (2) *University Hospital Germans Trias I Pujol, Spain*)

**Background:** Dementia with Lewy bodies (DLB) is the second most frequent degenerative dementia after Alzheimer's disease (AD). It is characterized by the neuropathological overlap with AD leading also to a clinical overlap. Although important advances are improving clinical characterization, still up to 80% of DLB cases are misdiagnosed, usually as AD, and patients receive treatments that can trigger severe adverse reaction. Platelets are abundant blood components, and are anucleate cells which contain endoplasmic reticulum, ribosomes, and complete mitochondrial and apoptotic systems. Platelets are able to modify their proteome in response to different environmental changes and stimuli by the translation of functional mRNAs after platelet activation. Platelets also contain an almost complete and functional miRNA pathway and their miRNA content has been repeatedly studied. In addition to their role in haemostasis and thrombosis, platelets are involved in apoptosis, immune response, and tissue remodelling. They also show an enzymatic pathway similar to dopaminergic neurons and can store and release neurotransmitters; they contain  $\alpha$ -synuclein and circulating amyloid precursor protein, and express neuronal receptors and inflammatory-signalling molecules. Recently, platelets have been proposed to represent

the missing link between blood and brain. **Objectives:** MAIN – identification of a platelet-based biomarker for differential DLB diagnosis. SPECIFIC – (1) to examine the complete platelet miRNA content in DLB compared to healthy individuals, (2) to identify expression changes and validate miRNA expression in independent cohorts, (3) to determine if these profiles were disease-specific, (4) to assess the utility of the identified miRNAs as diagnostic biomarker. **Methods:** The current study was conducted between 2015 and 2019. A total of 162 individuals were recruited from two Barcelona hospitals and divided into four cohorts: 59 DLB patients fulfilling criteria for probable DLB, 28 AD patients fulfilling criteria for probable AD, 24 Parkinson's disease (PD) patients fulfilling UK PD Society Brain Bank criteria, and 51 age-matched control individuals. The study consisted of three independent phases: (1) 2017 – 21 DLB patients, 21 controls, (2) 2018 – 22 DLB, 15 AD patients, 16 controls, (3) 2019 – 16 DLB, 13 AD, 24 PD patients, 14 controls. Platelet-rich pellet was obtained from peripheral blood and analyzed for purity by flow cytometry. Small RNAs were purified by the mirVana Paris Kit (Invitrogen). DISCOVERY PHASE: miRNA sequencing and sequencing data analysis was performed for 7 DLB and 7 control samples after library preparation, quality analysis and clustering on an Illumina Sequencer obtaining 200,000 reads per sample. VALIDATION PHASE: Reverse transcription was carried out with MiRCURY LNATM Universal cDNA Synthesis Kit II, and quantitative real-time PCR with miRNA LNA technology based Pick&Mix PCR pre-designed panels (Exiqon). Statistical analysis was performed using the following tests: the ddCt method, Wilcoxon-Mann-Whitney test, two-tailed unpaired T-test; multiple comparisons were performed with the Kruskal-Wallis non-parametric test and multiple corrections with Dunn's test. The diagnostic potential was assessed by ROC curve calculation and the Wilson/Brown method using SPSS Statistics. **Results:** NGS-libraries were constructed for small RNA and miRNA, and NGS generated a mean of 1,349,701 reads/sample, mapping to 1,279 known mature miRNAs. Of 534 miRNAs fulfilling expression criteria, 430 corresponded to different miRNA-precursors and 22 miRNAs were differentially expressed between DLB and controls. These miRNAs were validated by qPCR in three independent studies. In study I (2017), ten of the 22 miRNAs were diminished in DLB compared to controls. In study II (2018), miRNAs hsa-miR-128-3p, hsa-miR-139-5p, hsa-miR-150-5p, hsa-miR-25-3p, were significantly down-regulated in DLB compared to controls confirming the initial results. Additionally, 9 of the 10 miRNAs were significantly down-regulated in DLB compared with AD. In study III (2019), in addition to newly included cases, all samples were analyzed together after corresponding data normalization. Four miRNA-based molecular signatures were identified: (1) two miRNAs (hsa-miR-142-3p, hsa-miR-150-5p) were significantly diminished in DLB compared with controls, (2) seven miRNAs (hsa-let-7d-5p, hsa-miR-142-3p, hsa-miR-132-5p, hsa-miR-150-5p, hsa-miR-26b-5p, hsa-miR-146a-5p, hsa-miR-25-3p,) were significantly diminished in DLB compared to AD, (3) two miRNAs (hsa-miR-150-5p and hsa-miR-26b-5p) were down-regulated in DLB compared to PD, (4) four miRNAs (hsa-miR-132-5p, hsa-miR-146a-5p, hsa-miR-25-3p, hsa-miR-6747-3p) were over-expressed in AD vs CTRLs. ROC curve analysis revealed that the 7 differentially expressed miRNAs between DLB and AD distinguish DLB from AD patients with specificity and sensitivity of 100% (AUC=1). The ROC curve for hsa-miR-142-3p and hsa-miR-150-5p, differentially expressed between DLB and CTRLs, yielded an

AUC=0.85 (82% sensitivity, 70% specificity). Comparison of AD and CTRLs, miRNAs hsa-miR-132-5p, hsa-miR-146a-5p, hsa-miR-25-3p, and hsa-miR-6747-3p resulted in AUC=0.94 (89% sensitivity, 80% specificity); and AUC=0.81 (84% sensitivity, 76% specificity) was obtained for hsa-miR-128-3p and hsa-miR-139-5p comparing PD and CTRLs. **Conclusion:** The platelet-based 7-miRNA bio-signature meets characteristics of a biomarker for the differential diagnosis of DLB versus AD. This biomarker could be used: (1) in the clinical practice to provide patients a reliable diagnosis and assure adequate disease management, and (2) for patient stratification previous inclusion in clinical trials for either AD or DLB.

**P050: ELECSYS CSF ASSAYS ACCURATELY DISTINGUISH AD FROM FRONTOTEMPORAL LOBAR DEGENERATION.** M. Ortner<sup>1</sup>, O. Goldhardt<sup>1</sup>, J.P. Weinberger<sup>2</sup>, F. Müller-Sarnowski<sup>1</sup>, J. Diehl-Schmid<sup>1</sup>, H. Förstl<sup>1</sup>, I. Yakushev<sup>3</sup>, T. Grimmer<sup>1</sup> ((1) Department Of Psychiatry And Psychotherapy, Klinikum Rechts Der Isar, Technical University Of Munich, School Of Medicine - Munich, Germany; (2) Roche Diagnostics Gmbh - Penzberg, Germany; (3) Department Of Nuclear Medicine, Klinikum Rechts Der Isar, Technical University Of Munich - Munich, Germany)

**Background:** Fully automated Elecsys® cerebrospinal fluid (CSF) immunoassays allow accurate detection of amyloid positivity in patients with subject cognitive decline (SCD) or mild cognitive impairment (MCI) due to Alzheimer's disease (AD), using pTau181/Aβ42 (A+/T+) and tTau/Aβ42 (A+/N+) biomarker ratios. However, the diagnostic differentiation between AD and other amyloid negative diseases, using such biomarkers, particularly frontotemporal lobar degeneration (FTLD) is less well studied. Differential diagnosis typically requires patients to undergo a battery of neuropsychological tests, neurological assessments and laboratory tests. Research criteria for FTLD subtypes propose imaging biomarkers to increase diagnostic certainty, e.g FDG-PET imaging, but not CSF analyses. **Objectives:** To further inform on the potential role of CSF biomarkers in differential diagnosis, we investigated whether levels of Aβ42, Aβ40, pTau181 and tTau, and the ratios pTau181/Aβ42, tTau181/Aβ42 and Aβ42/Aβ40, measured in CSF could be used to differentiate patients with AD from those with FTLD. **Methods:** Patients with cognitive impairment (n=130) in the Center for Cognitive Disorders of the Klinikum Rechts der Isar, Technical University of Munich, School of Medicine, (Munich, Germany) were retrospectively recruited to participate in the study. AD and FTLD were diagnosed using standard diagnostic criteria, global score of clinical dementia rating scale (CDR) and typical metabolic pattern of 18F-FDG-PET examination using visual assessment (by a board certified nuclear medicine specialist). CSF was measured using Roche Elecsys AD biomarker assays. Collection and storage of CSF was performed according to a modified pre-analytical procedure similar to that described by the assay manufacturer. ROC analysis was performed and AUC's were calculated to assess biomarker performance for differentiation between AD and FTLD. Sensitivity and specificity were calculated to determine performance of CSF biomarker-based pre-specified cutoffs for amyloid positivity in MCI/SCD patients (Aβ42<1000 pg/ml, pTau181/Aβ42>0.024, and tTau/Aβ42>0.28) and optimized cutoffs based on Youden Index on clinical AD diagnosis. **Results:** Based on clinical diagnosis and FDG metabolic pattern 44 patients with FTLD (27 with behavioral variant [bvFTD],

11 with semantic variant of primary progressive aphasia [svPPA]; 6 with non-fluent variant of primary progressive aphasia [nfvPPA]), and 86 patients with AD. Of those with AD, 32 were at the stage of mild dementia (CDR global = 1.0) and 54 at the stage of MCI (CDR global = 0.5) were identified. AUC-based performance was highest for pTau/Aβ42 ratio [AUC=0.841(95%CI: 0.759-0.923)] followed by Aβ42/40 [0.829 (0.746-0.912)], tTau/Aβ42 [0.822 (0.736-0.908)] and Aβ42 [0.812 (0.722-0.908)]. Highest qualitative performance was observed using the pTau/Aβ42 ratio: pre-specified and optimized (=0.022) cutoff (for both: sensitivity=0.892, specificity=0.773); sensitivity and specificity of Aβ42/40 was 0.867/0.773 (optimized cutoff=0.055), of tTau/Aβ42 0.892/0.750 (for both pre-specified and optimized cutoff of 0.28), of Aβ42 0.856/0.750 for optimized (=825) and 0.916/0.545 for pre-specified cutoff. Interestingly, in the small group of nfvPPA, diagnosed based on clinical criteria and FDG PET, CSF biomarker pattern was comparable to the AD pattern. A post-hoc analysis excluding nfvPPA from the FTLD group resulted in higher AUC values: pTau/Aβ42 ratio [AUC=0.875 (95%CI: 0.792-0.958)], Aβ42/40 [0.867 (0.787-0.946)], tTau/Aβ42 [0.854 (0.768-0.941)] and Aβ42 [0.829 (0.738-0.921)]. **Conclusion:** Our results suggest that CSF biomarkers may potentially be used to help distinguish FTLD from AD. The CSF biomarker pattern of the nfvPPA group might be explained by misclassified individuals with a non-amnesic language presentation of AD. While additional studies are needed to verify or improve on the cutoff determined in our study, our results suggest that measuring CSF biomarkers may be considered in the diagnosis of FTLD in order to exclude patients with amyloid positivity indicative of underlying AD pathology.

**P051: USING CORTICAL DIFFUSIVITY ANALYSIS TO PREDICT PROGRESSION IN EARLY ALZHEIMER'S DISEASE.** M. Torso<sup>1</sup>, I. Hardingham<sup>1</sup>, M. Jenkinson<sup>2</sup>, S. Chance<sup>1</sup> ((1) Oxford Brain Diagnostics - Oxford, United Kingdom; (2) University Of Oxford - Oxford, United Kingdom)

**Background:** Alzheimer's Disease (AD) is characterized pathologically by important neural architecture changes. Diffusion Tensor Imaging (DTI) has provided promising results for the investigation of microstructural changes of white matter, but there is also potential to use it in grey matter. In the present study, we investigated the performance of novel cortical diffusivity measurements [McKavanagh et al. 2019] for classifying patients with AD, healthy elderly subjects (HS), patients with mild cognitive impairment (MCI) who progress to probable-AD (MCI-converter, "MCI-C"), and those with MCI who do not progress to probable-AD (MCI-stable, "MCI-S"). **Objectives:** The aim here was to test the classification power of these novel cortical diffusion measurements and to test their correspondence with the standard hallmarks of AD pathology measured in CSF (total-tau, phosphorylated-tau and amyloid beta). MCI patients were classified according to the recently proposed Alzheimer's classification framework based on the patients' biomarker profiles (Jack et al. 2018). In this "ATN" framework ("A" for amyloid deposition, "T" for tau levels and "N" for neurodegeneration) AD forms a continuum in which the extreme points are represented by A-T-N- cognitively unimpaired subjects, and A+T+N+ subjects with dementia. The present study focused on change in the underlying neural architecture that forms the structural foundation for cognitive function as a potential "N" biomarker. **Method:** DTI and

T1 structural scans of 454 subjects (respectively 310 HS, 48 MCI-S, 45 MCI-C and 51 AD) from the National-Alzheimer's-Coordinating-Center (NACC) were used. Three novel whole brain cortical diffusivity measures (AngleR, PerpPD, and PariPD) [McKavanagh et al. 2019], and three standard measures (mean diffusivity [MD], cortical grey matter volume, and bilateral hippocampal volume) were calculated for each subject. CSF Amyloid and Tau were used to classify the MCI participants according to ATN framework. Receiver Operating Characteristics (ROC) curve analysis and the Area Under the Curve (AUC) were used to assess the group discrimination capability of our method. **Results:** The results showed that the new DTI-derived measures detected altered quality of cortical grey matter in AD patients, distinguishing them from HS with an AUC of 97.5, and distinguishing between MCI-C and MCI-S with an AUC of 87.8%. All the cortical diffusivity measures were significantly correlated with CSF values (total-tau, phosphorylated-tau and amyloid beta). The ATN classification showed that the cortical diffusion values can significantly improve the prediction value. **Conclusion:** The findings support the use of cortical diffusivity measurements as a surrogate of cortical microstructure quality for detection of the early stages of AD. These changes were consistent with a CSF signature in which B amyloid was sensitive in the early stages and tau was elevated in the late stages (MCI-C and AD). Cortical microstructure quality measured by novel cortical diffusivity analysis provides a measure of Neurodegeneration (N) that appears to be sensitive at an earlier stage than other traditional measures of N. Further development may aid early diagnosis, patient cohort selection, and quantification of the microstructural changes in response to therapies in clinical trials. **Reference:** McKavanagh R, Torso M, Jenkinson M, Kolasinski J, Stagg CJ, Esiri MM, McNab JA, Johansen-Berg H, Miller KL, Chance SA. 2019. Relating diffusion tensor imaging measurements to microstructural quantities in the cerebral cortex in multiple sclerosis. *Human Brain Mapping* 40(15), 4417-4431. 10.1002/hbm.24711.

**P052: LEVEL OF NEURODEGENERATION-INDUCING MEMORY CD8 T CELLS PREDICTS ALZHEIMER'S DISEASE AND ALZHEIMER'S-RELATED MCI, AND CORRELATES WITH COGNITIVE DECLINE IN BANKED BLOOD SAMPLES FROM MULTIPLE COHORTS.** W. Christopher<sup>1</sup>, D. Van Dam<sup>2</sup>, Y. Vermeiren<sup>2</sup>, H. De Reu<sup>2</sup>, V. Van Tendeloo<sup>2</sup>, P.P. De Deyn<sup>3</sup>, K. Trujillo<sup>1</sup> ((1) *T-Neuro Pharma, Inc. - Albuquerque, USA*; (2) *University Of Antwerp - Antwerp, Belgium*; (3) *University Of Antwerp, University Center Groningen - Groningen, Netherlands*)

We recently developed a mouse model that recapitulates definitive hallmarks of Alzheimer's disease (AD), including robust neuronal loss and neurofibrillary tangle-like structures accompanied by Ab deposition and plaques with progressive cognitive decline, from a single physiological induction. This induction increased levels of an Amyloid Precursor Protein (APP)-reactive CD8 T cell subset with an age-related memory phenotype in blood ("hiT cells") – a unique characteristic shared with aging humans - and promoted hiT cell accumulation in brain, a property shared with human AD. These levels were found to be further altered in AD and related conditions. T-Neuro Pharma developed the T-Track blood test, a flow cytometry-based assay that measures the proportion of human hiT cell analogues in blood using a single 1ml collection sample.

T-Neuro Pharma analyzed over 220 blinded samples from 2 different biobank cohorts for preliminary validation of the test, comparing T cell levels against Alzheimer's disease (AD), Mild Cognitive Impairment (MCI), and A $\beta$  and Tau within CSF (AD CSF biomarkers). hiT cell analogue levels were significantly diminished in AD and AD CSF biomarker-positive MCI cohorts ( $p < 0.0005$  and  $< 0.001$ , respectively), but were less dramatically altered in AD CSF biomarker-negative MCI ( $p < 0.05$ ) compared to normal aging controls. Intriguingly, hiT cell levels were also significantly altered prior to clinical cognitive loss, while their decrease correlated significantly ( $p = 0.003$ ) with decreasing score on the Montreal Cognitive Assessment test (MoCA) in an MCI cohort. Using receiver operator characteristic curves (ROC) to assess diagnostic performance of the test, area under the curve (AUC) ranged from 0.84 and 0.89 for AD and AD CSF biomarker-positive MCI, and 0.74-0.76 for AD CSF biomarker-negative MCI. Cohorts obtained from different institutions yielded similar diagnostic thresholds, suggesting reproducibility and reliability of the test conducted on samples from diverse sources. In conclusion, the T-Track blood test appears to accurately predict AD and MCI-AD biomarker-positive conditions, quantitatively reflects poor cognitive performance in MCI, and has potential to screen for neurodegenerative risk on the AD continuum both before and after clinical cognitive decline.

**P053: TRANSCRANIAL ELECTROMAGNETIC TREATMENT (TEMT) NORMALIZES PLASMA CYTOKINE LEVELS IN ALZHEIMER'S PATIENTS: BOTH IMMEDIATE AND LONG-TERM IMMUNOREGULATION.** H. Abulaban<sup>1</sup>, R. Baranowski<sup>2</sup>, X. Lin<sup>3</sup>, E. Goodwin<sup>4</sup>, B. Gordon<sup>4</sup>, A. Gary<sup>4</sup>, C. Cao<sup>1</sup> ((1) *Axiom Clinical Research Of Florida - Tampa, USA*; (2) *Left Coast Engineering - Escondido, USA*; (3) *University Of South Florida Taneja College Of Pharmacy - Tampa, USA*; (4) *Neuroem Therapeutics, Inc - Phoenix, USA*)

**Background:** There is a general consensus that the immune system plays an important role in AD pathogenesis. However, there is disagreement as to whether progression of AD involves an over-activation (high blood cytokine levels) or an under-activation (low blood cytokine levels) of the immune system. As such, both therapeutics that suppress or increase blood cytokine levels are being therapeutically evaluated against AD. In either over-activated or under-activated scenarios, the blood cytokine levels in the peripheral immune system are abnormal and to date no current AD therapeutic has demonstrated an ability to regulate the full array of plasma cytokines back to or near their normal levels. A therapeutic demonstrating such an immunoregulatory ability could be contributory to any resultant cognitive improvement seen in the same AD subjects. In that context, we have recently published a Pilot study [J. Alz. Dis. 71:57-82, 2019] showing that Transcranial Electromagnetic Treatment (TEMT), given in-home twice daily for 2-months, was completely safe and resulted in: 1) reversal of cognitive impairment (ADAS-cog and Rey AVLT), 2) predicted changes in both blood and CSF AD markers, and 3) beneficial changes in FDG-PET and fMRI brain imaging. Mechanistically, we have established that TEMT disaggregates both Ab and tau oligomers inside neurons, as well as enhances neuronal mitochondrial function, all of which could be contributory to the cognitive benefits of TEMT in AD subjects. **Objectives:** To determine if TEMT administration to AD subjects in the aforementioned 2-month Pilot study had effects on blood cytokine levels and

if such immune responses were linked to the initial cognitive status (ADAS-cog) of these AD subjects. **Methods:** Eight mild/moderate AD patients were treated with TEMT in-home by their caregivers for two months in an open-label Pilot study, utilizing NeuroEM's first-in-class MemorEMTM head devices. The device provides full brain TEMT via eight specialized emitters embedded within a head cap, with emitters activated sequentially at 217 Hz/second. When active, any given emitter projects EMF (radiofrequency) fields into the brain at 915 MHz and 1.6 W/kg average power. TEMT was given for 1-hour twice a day for the length of the study (120 treatments total). At baseline, after the initial 1-hour treatment, and following 2-months of twice-daily 1-hour treatments, plasma was collected for later analysis of the following eight cytokines: G-CSF, GM-CSF, VEGF, PDGF, IL-10, IL-15, IL-17a, and IL-18. Baseline plasma cytokine levels for all eight AD subjects were evaluated in the context of their baseline ADAS-cog scores. As we have reported [J. Alz. Disease 71:57-82, 2019], seven of these eight subjects collectively responded to 2-months of TEMT with ADAS-cog13 scores that were improved overall by 4.1 points compared to baseline (ES=1.21;  $p < 0.02$ ). **Results:** For all eight cytokines, AD subjects with the worst ADAS-cog performance (higher scores) always had much lower baseline plasma cytokine levels compared to the AD subjects with better performance (lower scores). Therefore, the effect of TEMT administration on cytokine levels was appropriately evaluated in relation to baseline ADAS-cog scores (range 24-62), with subjects divided into two groups - poorer cognitive performance/lower plasma cytokines and better cognitive performance/higher plasma cytokines. For all eight plasma cytokines, AD subjects with lower baseline levels of a given cytokine in plasma always showed increases in that cytokine as a result of treatment, whereas those AD subjects with higher baseline levels of a given cytokine showed treatment-induced decreases for all eight cytokines. Graphing of each individual's baseline and post-treatment cytokine levels generally showed a gravitation to reported normal cytokine levels of aged, unimpaired individuals. This ability of TEMT to regulate plasma cytokine levels to a normal or near normal range was even present after the initial 1-hour of TEMT, with lower baseline cytokine levels at baseline becoming higher after this single TEMT and just the opposite occurring if baseline levels were higher. Mechanistically, TEMT most likely is providing this immunoregulatory effect by affecting blood cells within the brain's dense vascular system that are involved with cytokine regulation. In addition, the brain's microglia and astrocytes are known to secrete cytokines (e.g., G-CSF) and thus may have been impacted by TEMT as well. **Conclusion:** Immune dysfunction/dysregulation is increasingly being considered as a significant component of AD pathogenesis and resultant cognitive impairment. Results from this study clearly indicate that TEMT can exert an immunoregulatory function - one that seeks to achieve immunologic "homeostasis" by returning high or low plasma cytokine levels in AD subjects to the normal or near normal levels of unimpaired aged adults. The most important aspect of these results is that TEMT is re-activating/jump-starting a hypo-active immune system in AD subjects with lower baseline cytokine levels - AD subjects who exhibited the poorest ADAS-cog performance prior to TEMT administration. Thus immunoregulation can be added to the three aforementioned mechanisms of TEMT action against AD, collectively providing a safe, neuromodulatory therapeutic that may be providing an unparalleled, multi-targeted attack against AD.

**LP08: THE ANALYTICAL ASSESSMENT OF THREE RESEARCH SIMOA ASSAYS FOR PLASMA MEASUREMENT OF PHOSPHORYLATED TAU (PT181, PT217, PT231).** J. Vanbrabant<sup>1</sup>, E. Stoops<sup>1</sup>, K. Blennow<sup>2,3</sup>, E. Vanmechelen<sup>1</sup> ((1) *Adx Neurosciences Nv - Ghent, Belgium*; (2) *Department Of Psychiatry And Neurochemistry, The Sahlgrenska Academy At The University Of Gothenburg - Mölndal, Sweden*; (3) *Clinical Neurochemistry Laboratory - Mölndal, Sweden*)

**Background:** Recently, plasma phosphorylated Tau (P-Tau) has been shown a promising biomarker for early detection of Alzheimer's Disease (AD). Plasma Tau phosphorylated at threonine181 (pT181) is reported to distinguish AD from healthy controls (HC) and from other neurodegenerative diseases (AUC > 90%) and to correlate with pT181 in CSF and with Amyloid and Tau PET imaging scores (Janelidze et al., 2020; Thijssen et al., 2020), based on a pT181 MSD assay. A recently published plasma pT181 Simoa assay confirmed these findings in four cohorts (Karikari et al., 2020). While some post-translational modifications are associated with tau molecular diversity contributing to clinical heterogeneity (Dujardin et al., 2020) and cis-phosphorylation prolongs stability of tau (Lim et al. 2008), it is worthwhile to explore additional phospho-tau sites for plasma testing. Our work reports the exploratory performance testing on the Quanterix Single Molecule Array (Simoa) platform for phosphorylated tau at T181, T217 and T231 into plasma using monoclonal based antibody pairs. **Objectives:** The aim of this study was the technological assessment of measuring pTau181, pTau217 and pTau231 in plasma using the ultrasensitive Simoa technology. Based on performance characteristics with focus on sensitivity and reproducibility, three antibody pairs (1 pair for each biomarker) were ranked for their use as a robust phospho-tau blood based biomarker. In parallel the intention is to test an exploratory clinical sample set (controls/AD). **Methods:** Three plasma research Simoa assays were developed for P-Tau residues (pTau181; pTau217 & pTau231) using pTau specific capture monoclonal antibodies on magnetic beads (respectively ADx252 and ADx253 for pTau181 and pTau231 and a pT217 tau specific monoclonal from undisclosed source for pTau217). In contrast to AT270, which recognizes both pT175 and pT181 (Vanmechelen et al., 2000), ADx252 is a pT181 specific antibody with absence of pT175 cross reactivity, while ADx253 shows some cis-specificity for pT231 and is not affected by pT235 phosphorylation. All three pTau specific beads are combined with an N-terminal Tau specific monoclonal antibody ADx204 as biotinylated detector. The minimal required dilution was assessed and samples were measured using a 5 fold dilution factor in a two-step assay. Calibrators for these assays consisted of synthetic peptides covering the epitope regions of the respective monoclonal antibodies. All three assays were characterized in terms of analytical performance like sensitivity, reproducibility, specificity and accuracy by using a plasma sample set of healthy controls (HC). Clinical utility of the three assays will be compared using an exploratory clinical set of HC (N=20) and AD (N=20). **Results:** P-Tau specific antibodies were conjugated on Agilent High-Bind beads and applied with 50% helper beads in the assay to increase sensitivity. ADx204 was biotinylated with different linker types at increasing molar excess and the most sensitive condition was chosen for each respective analyte. Sample and calibrator diluent were optimized to maximize the signal-to-noise ratio (S/N). Duplicate measurements using 25  $\mu$ L beads, 20  $\mu$ L detector and 100  $\mu$ L calibrator or diluted sample were performed of 8 plasma

samples (HC) in three independent runs to assess repeatability, reproducibility and indicated the pTau231 assay to be the most robust for inter-test variability (CV% < 15%). Both the pTau181 and pTau217 assays had lower robustness (CV% < 25%). Sensitivity of the assays was the highest for the pTau231 assay (S/N of 3 at 0.32 pg/mL of respective peptide calibrator) whereas sensitivity for the pTau181 and pTau217 assay was significantly lower (S/N of 3 at 1.6 pg/mL of respective peptide calibrator). In the clinical study the discriminatory power of the three P-Tau assays will be compared and correlation of the pTau values in both HC and AD patients will be assessed. Additionally, tau plasma levels will be determined using in-house Simoa assays, to gain more insight of plasma tau/P-Tau ratios in HC and AD patients. **Conclusions:** Three antibody pairs specific for phosphorylated tau (pT181, pT217 and pT231) were used to test the robustness of P-Tau as AD biomarker in human EDTA plasma. All three analytes could be measured in a 8 plasma member panel originating from healthy donors with varying sensitivity (S/N ratio) and reproducibility. Irrespective of the clinical performance, and based upon the tested variables, the pTau231 assay (ADx253 combined with ADx204) allows for the most robust determination of P-Tau levels in plasma. **References:** Dujardin S. et al., *Nat Med.* 2020; <https://doi.org/10.1038/s41591-020-0938-9>; Janelidze S. et al., *Nat Med.* 2020;26(3):379-386; Karikari, T.K. et al., *The Lancet Neurology.* 2020;19(5): 422-433; Lim et al., *J. Clin. Invest.* 2008;118(5):1877-1889; Thijssen E.H. et al., *Nat Med.* 2020;26(3):387-397; Vanmechelen E. et al., *Neurosci. Lett.* 2000;285(1):49-52

**LP09: BLOOD-BASED DETECTION OF EARLY-STAGE ALZHEIMER'S USING MULTIOMICS AND MACHINE LEARNING.** B. Souchet<sup>1</sup>, A. Michail<sup>1</sup>, B. Billoir<sup>1</sup>, F. Mouton-Ligier<sup>2,3,4</sup>, J. Fortea<sup>5,6,7</sup>, A. Lleo<sup>6,7</sup>, C. Paquet<sup>2,3,4</sup>, J. Braudeau<sup>1</sup> ((1) *Agent - Paris, France*; (2) *Universite De Paris - Paris, France*; (3) *Centre de Neurologie Cognitive Hopital LARIBOISIÈRE Paris APHP - Paris, France*; (4) *INSERM U1144 - Paris, France*; (5) *Barcelona Down Medical Center, Fundació Catalana De Síndrome De Down - Barcelona, Spain*; (6) *Sant Pau Memory Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau, Universitat Autònoma de Barcelona - Barcelona, Spain*; (7) *Center of Biomedical Investigation Network for Neurodegenerative Diseases - Madrid, Spain*)

**Background:** Currently, the diagnosis of Alzheimer's disease (AD) is based on clinical symptoms (including cognitive testing) and CSF analysis, but there is no non-invasive easy method to detect AD patients from pre-dementia phase. A blood test capable of detecting patients with AD, at a prodromal or even pre-symptomatic stage, will optimize an effective clinical management. **Objectives:** The objective of this study was to assess the performance of a multiomic blood test in retrospectively collected plasma samples using Machine Learning by combining metabolomic and proteomic biomarkers, previously identified in a novel/brand-new rat model. **Methods:** We developed the first gene transfer-based (non-transgenic) animal model capable of successfully reproducing the continuum of Alzheimer's disease progression (Audrain et al. (2018), *Cereb Cortex*). We then sampled the blood of the rats at key stages of the pathology and confirmed the molecular stage of the disease by post-mortem cerebral biochemical analysis. The plasma samples were analyzed by global mass spectrometry: for each sample 2,400 blood constituents were quantified (proteins, metabolites, lipids). We identified by

Artificial Intelligence (pipeline of state-of-the-art Machine Learning algorithms: random forest, support vector machines, artificial neural networks, gradient boosting, etc) the 105 most informative biomarkers in the simplified and controlled rat model. Then we challenged these biomarkers in humans. We included sporadic form of Alzheimer's (prodromal (n=45) and demented patients (n=30)) and a genetic form of Alzheimer's (Down syndrome individuals sampled at asymptomatic (n=34), prodromal (n=10) and dementia phase (n=10)). The control group consisted of cognitively healthy individuals (n=50) but also patients suffering from other neurodegenerative diseases (n=53). The plasma of these 232 individuals was analyzed by global mass spectrometry: for each sample the 105 pre-identified biomarkers were quantified (proteins, metabolites). Using AI techniques, we identified the 25 first-in-class biomarkers in humans. Using these 25 biomarkers we developed a neural network (multilayer perceptron) to diagnose the complex human disease with a high level of accuracy. **Results:** The neural network based on 25 plasma biomarkers achieved 100% sensitivity and 99% specificity on a 5-fold cross validation. Interestingly the misclassified sample is a sample from a patient suffering from another neurodegenerative disorder. It should be noted that we didn't include MMSE score, age, gender, or APOE genotype in the model. Among these 25 biomarkers, 13 are proteins and 12 are metabolites, mainly expressed in the periphery. This combination increases the performance of the test by taking into account independent but complementary biological pathways. By clustering these 25 biomarkers regarding their trajectory, we characterized 5 trajectories describing the global behavior of our biomarkers. All the trajectories are non-linear confirming the hypothesis of a dynamic progression of the biomarker blood concentration in AD. We finally benchmarked the neural network against both CSF A $\beta$ 42 and P-Tau181 performances. We concluded that the accuracy of the neural network overperformed that of the CSF biomarkers. The main reason is that the algorithm can identify Alzheimer's status even if the CSF AD biomarkers negative. **Conclusion:** A multiomics approach that combines proteins and metabolites in plasma can be used for the early detection of AD.

**LP10: PLASMA AB RATIO MEASURED ON A FULLY AUTOMATED IMMUNOASSAY PREDICTS AMYLOID POSITIVITY DEFINED BY AMYLOID PET CENTILOID.** K. Yamashita<sup>1</sup>, S. Watanabe<sup>1</sup>, K. Matsumoto<sup>1</sup>, M. Miura<sup>1</sup>, T. Iino<sup>1</sup>, T. Watanabe<sup>2</sup>, S. Iwanaga<sup>1</sup>, D. Verbel<sup>3</sup>, M. Kanekiyo<sup>3</sup>, S. Dhadda<sup>3</sup>, M. Ino<sup>4</sup>, A. Koyama<sup>3</sup>, T. Yoshida<sup>1</sup> ((1) *Systemex Corporation - Kobe, Japan*; (2) *Systemex R&D Center Americas, Inc. - Mundelein, USA*; (3) *Eisai Inc. - Woodcliff Lake, USA*; (4) *Eisai Co., Ltd. - Tsukuba, Japan*)

**Background:** Alzheimer's disease (AD) is the most common type of dementia that has a significant impact on global public health. A key hallmark of AD is an accumulation of amyloid beta (A $\beta$ ) in the brain. The accumulation starts about 20 years before the onset of cognitive symptoms. Therefore, early detection of amyloid pathology in the brain is important for diagnosis and facilitates recruitment of patients into AD clinical trials. Amyloid positron emission tomography (PET) is used to confirm amyloid pathology, but its use may be limited by cost and accessibility. Recently, we reported the development of plasma A $\beta$ 1-40 and A $\beta$ 1-42 immunoassays on a fully automated system (HISCLTM series), which is a simple and



cost-effective method. A $\beta$  values from our immunoassays had a significant correlation with those from in-house immunoaffinity enrichment and LC-MS/MS (IA-MS) assays. In addition, plasma A $\beta$ 1-42/A $\beta$ 1-40 ratio measured on HISCLTM series showed a potential to predict amyloid pathology in the brain. In the previous analysis, we examined the capability of our assay system to predict positivity in amyloid PET images by visual read. Here, we report the performance of our plasma immunoassay to distinguish between amyloid positive and negative subjects determined using centiloids. **Objectives:** To assess the performance of our plasma immunoassay in distinguishing amyloid PET positive from amyloid negative subjects based on centiloids vis-à-vis visual reads, using screening plasma samples from the Eisai Elenbecestat Phase 3 program. **Methods:** We used our fully automated immunoassay system to measure plasma A $\beta$ 1-40 and A $\beta$ 1-42. Samples were sourced from clinical trial subjects in screening, who had a clinical diagnosis of MCI and mild AD and also underwent amyloid PET to confirm amyloid status for enrollment. Amyloid positivity was determined by visual read of a subject's PET scan. Centiloids were also derived from subject's mean composite SUVr with whole cerebellum as reference region. A centiloid cut point was determined based on visual read of all three amyloid tracer data, Florbetaben, Florbetapir and Flutemetamol (N=3257). A cohort of 149 subjects was selected for this study. The mean (SD) age of the cohort was 73.3 (6.08) years; 93.3% of subjects were White and 50.3% were Male. APOE4 status was positive in 39.6% of subjects. Florbetaben was used as the PET probe in 94.6% of subjects and Florbetapir was used in the remaining 5.4% of subjects. 82.6% of subjects were considered as having MCI due to AD; 11.4% were diagnosed as having mild AD dementia. To evaluate the overall performance of our plasma immunoassay, area under the curve (AUC) was obtained by performing receiver operating characteristic (ROC) analysis using logistic regression. Correlation between plasma A $\beta$ 1-42/A $\beta$ 1-40 ratio and centiloids was also assessed. **Results:** The centiloid cut point of 32.20 determined by predicting amyloid positivity defined by visual read and maximizing the Youden Index. Irrespective of the method used to determine amyloid positivity (centiloids or visual read), the mean plasma A $\beta$ 1-42/A $\beta$ 1-40 ratios of amyloid positive samples were statistically significantly lower than those of amyloid negative samples (p-value < 0.0001 using both methods). The plasma A $\beta$ 1-42/A $\beta$ 1-40 ratio predicted A $\beta$  PET positivity determined by visual read with an AUC of 0.74, and the sensitivity and specificity were 72% and 71%, respectively, using a cut-off of 0.097 (determined using the Youden Index). However, the performance was higher when using centiloids to determine amyloid positivity with an AUC of 0.82, and sensitivity and specificity equal to 78% for both measures. The plasma A $\beta$ 1-42/A $\beta$ 1-40 ratio was also found to correlate with centiloids values (Spearman rank correlation coefficient = -0.57, p-value < 0.0001). **Conclusion:** We have observed that plasma A $\beta$ 1-42/A $\beta$ 1-40 ratio measured on our fully automated immunoassay can predict amyloid pathology in the brain. The AUC using centiloids was higher than that of visual read to define amyloid positivity. Mismatches between plasma A $\beta$ 1-42/A $\beta$ 1-40 ratio and centiloids results were mostly observed as false-positives (A $\beta$  ratio (+) / centiloids (-)). Similar false positive mismatches have been also reported from other groups that such A $\beta$  ratio (+) / PET (-) subjects had an increased risk of conversion to PET (+) compared to A $\beta$  ratio (-) subjects. This indicated that the false positive outcomes of our blood test may actually be

a reflection of early A $\beta$  pathology that is as yet undetectable by PET imaging. To further assess clinical utility of our assay system, additional sample sets will be evaluated.

**LP11: BIOMARKERS OF RESPONSE TO NABILONE IN AGITATED PATIENTS WITH MODERATE-TO-SEVERE ALZHEIMER'S DISEASE PATIENTS.** M. Ruthirakuhan<sup>1</sup>, N. Herrmann<sup>1</sup>, A.C. Andreazza<sup>2</sup>, N.P.L.G. Verhoeff<sup>3</sup>, D. Gallagher<sup>1</sup>, S.E. Black<sup>1</sup>, K.L. Lanctot<sup>1</sup> ((1) Sunnybrook Research Institute - Toronto, Canada; (2) University Of Toronto - Toronto (Canada), 3Baycrest Health Sciences - Toronto, Canada)

**Background:** Brain cholesterol metabolism, neuroinflammation, and oxidative stress are not only altered during Alzheimer's disease (AD), but may also impeded endocannabinoid signalling and worsen agitation. We assessed which combination of markers (24S-hydroxycholesterol (24S-HOC), inflammatory cytokines, and lipid peroxidation markers) were associated with response to nabilone, a synthetic cannabinoid, in AD patients with clinically significant agitation. **Methods:** Serum to measure 24S-HOC, cytokines (tumor necrosis factor (TNF), interleukin (IL)-2, IL-1 $\beta$ , IL-6, IL-8, and IL-10), and early-stage (lipid hydroperoxides (LPH)), and late-stage lipid peroxidation markers (8-isoprostane (8-iso), 4-hydroxynonenal (4-HNE), and thiobarbituric acid reactive substances (TBARS)), was collected at baseline from AD patients enrolled in a 14-week, double-blind cross-over trial comparing 6 weeks of nabilone to placebo (NCT02351882). Agitation was assessed using the Cohen Mansfield Agitation Inventory (CMAI). Binary logistic regressions were used to select 6 markers that predicted treatment response based on CMAI improvement in nabilone > placebo. These 6 markers were entered as variables into a principal component analysis (PCA) with varimax rotation. A factor loading score was computed using markers which contributed significantly to each principal component (>17%). Principal component (PC) scores were entered together in a binary logistic regression to determine which PC predicted response to nabilone based on improvement on CMAI total and subscores. **Results:** In 38 participants (mean +/-SD age= 97 +/-10, 77% male, CMAI=68 +/-19, MMSE=6.3 +/-6.3), 24S-HOC, TNF, IL-1 $\beta$ , LPH, 4-HNE, and TBARS predicted response to nabilone. Three PCs, accounting for 74% of the cumulative variance were identified (PC1: cytokines (TNF and IL-1 $\beta$ ); PC2: 24S-HOC, 4-HNE and TBARS; PC3: LPH only). PC1 predicted response on CMAI verbal non-aggression (odds ratio (OR)=0.74, 95%CI 0.56-0.98, p=.04). PC3 predicted response on CMAI physical aggression (OR=1.74, 95%CI 1.11-2.71, p=.02) and physical non-aggression (OR=0.72, 95% CI 0.52-0.99, p=.04). PC2 did not predict treatment responders on the CMAI total or subscores. **Conclusion:** Our findings suggest that cytokines predict response to nabilone based on verbal agitation symptoms, while LPH predicts response based on physical agitation symptoms. As there are no validated biomarkers of agitation, identifying markers of agitation and response would assist in identifying patients who may benefit from treatment with nabilone.

## LP12: PRE-ANALYTICAL EFFECTS OF CAP CONTACT, TEMPERATURE, AND MIXING ON CSF A $\beta$ 1-42 CONCENTRATIONS WHEN MEASURED ON AN AUTOMATED CHEMILUMINESCENT PLATFORM.

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**Background:** Cerebrospinal fluid (CSF) biomarker concentrations are valuable in the diagnosis of Alzheimer's Disease (AD). CSF  $\beta$ -amyloid1-42 (A $\beta$ 42) is a core biomarker of AD. While analytic variability has been reduced with the advent of automated assays, pre-analytical variability drives the need for standardization to provide more clinical use. **Objectives:** The main purpose of this study was to evaluate the effect of laboratory specific pre-analytical variables (post-collection storage temperature, extended sample storage stability, sub-aliquoting, sample fill volume and mixing, and extended sample cap contact) on A $\beta$ 42 concentrations from freshly collected CSF samples. These real-world pre-analytical variables could impact practical utility of CSF A $\beta$ 42 in the clinic and research. **Methods:** Freshly collected CSF samples obtained in Sarstedt 62.610.018 low-bind polypropylene tubes from patients at the Johns Hopkins Center for CSF Disorders were subjected to laboratory specific protocols. A $\beta$ 42 concentrations were measured using Lumipulse G1200 (Fujirebio Diagnostics Inc., Malvern, PA). CSF was analyzed post centrifugation (2000 g, 10 minutes, 5  $\pm$  3°C). **Results:** Impact of making multiple aliquots from an initial collection tube was examined. Aliquots of 1.2 mL of CSF sample were transferred into six Sarstedt #72.703.600 tubes. Fresh CSF samples could be aliquoted up to 6 times from the same collection tube without significant impact on A $\beta$ 42 concentration. Each aliquot had an average percent difference from the initial collection tube of  $\leq$ 6%. Multiple tube types were examined to study the effect of fill volume on A $\beta$ 42 concentration (Sarstedt Cat#'s: 63.614.699, 72.664, 72.694.416, 72.694.600, 72.703, 72.703.600, and 62.610.018). The minimum fill volume required for sample testing, a 50% fill volume and an 80% fill volume of CSF was used to fill tubes and A $\beta$ 42 concentration was measured in fresh CSF. Fill volume did not significantly impact A $\beta$ 42 concentration in tube types 72.703.600, and 62.610.018. Then, samples were kept frozen at  $\leq$ -60°C. Mixing samples after thawing by vortexing for at least 10 seconds, roller mixing, or inverting 10x is critical. Unmixed samples had a percent difference ranging from 4% to 56% with a mean difference from initial measurement to post-storage of 26%. There was no statistically significant difference between mixing methods. However, roller mixing had the highest recovery rate. Tube and cap type did impact whether extended cap contact effected A $\beta$ 42 concentration. Samples in varying tube types were stored upright at 4°C, or upside down or horizontally at 4°C, RT, or -80°C for 48 hours. In collection tube type 62.610.018 and storage tube type 72.703.600 cap contact did not significantly impact A $\beta$ 42 concentration. However, extended cap contact did affect A $\beta$ 42 concentration in specific conditions in collection tube type 72.664, especially when samples were tested after storage upside down or horizontal at -80°C where mean difference in initial and post-storage concentrations were 15% and 13% respectively. Tube type 72.694.600 had a percent difference in initial concentration up to 25% for horizontal storage and 12% when stored upside down.

However, mean values for horizontal and inverted storage were within acceptable limits. Samples were stable up to 2 weeks at 4°C, -20°C and -80°C in tubes 72.703.600, and 62.610.018. After 48 hours at RT a decline in A $\beta$ 42 concentration is observed from an average percent difference of 0% or -3% to an average of -9% and -8% in tube types 62.620.018 and 72.703.600 respectively. **Conclusion:** Our data suggests that the pre-analytical variables tested here do not have significant effects on concentrations of A $\beta$ 1-42 if: CSF is tested from a minimum fill volume up to an 80% fill volume in the tested polypropylene tubes other than 72.703 and 72.694.600 which needed to be at least 50% filled. Directly testing fresh CSF from up to 6 subsequent aliquots from the initial collection tube. CSF comes in contact with the cap in tube type 62.610.018 and 72.703.600. CSF is stored at 4°C, -20°C and -80°C up to two weeks. However, pre-analytical variables that negatively impact concentrations of A $\beta$ 1-42 include: Samples unmixed after thawing. Mixing samples after thawing is critical. Storing samples at RT  $>$ 48 hours. If CSF is collected in tube 72.664 or tube 72.694.600, it is recommended that CSF does not contact the cap before measuring concentrations and is stored in an upright position.

## Theme 5: CLINICAL TRIALS: COGNITIVE AND FUNCTIONAL ENDPOINTS

**P054: THE EFFECT OF MULTI-TASKING EXERCISE INTERVENTION ON COGNITIVE FUNCTION IN ELDERLY AND COGNITIVE IMPAIRMENT PATIENTS: A PILOT MULTICENTER STUDY.** K.W. Park<sup>1</sup>, H.J. Lee<sup>2</sup>, H. Park<sup>3</sup>  
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**Background and Purpose:** The purpose of this study was to investigate the effects of multi-tasking exercise on cognitive and motor function in patients with mild cognitive impairment (MCI) and cognitive normal elderly (CNE). **Methods:** A total of 144 subjects were recruited from 14 regional dementia centers in Busan Metropolitan City, but except for 77 subjects who were not suitable for the study, 67 subjects participated in the intervention. Subjects were recruited to perform a multi-tasking exercise for 8 weeks once a week. Korean version of MMSE for Dementia Screening (MMSE-DS), Subject Memory Complain Questionnaire (SMCQ) and Korean version of Short-Form Geriatric Depression Scale (SGDS-K) were used to determine changes in cognitive function and depressive symptoms pre-post intervention. To observe changes in motor function, 5-chair sit to stand and 5-meter walking speed on lower body strength and walking ability was measured. **Results:** As a result, both groups appeared meaningful improvement, but the MCI group (n=33) showed a statistically more meaningful improvement than the CNE group (n=32). For the MCI group, changes in cognitive and depressive symptoms on the tasks of MMSE-DS (p=.006), SMCQ (p=.000), SGDS-K (p=.000) and the result of motor function analysis on the items of 5-chair sit to stand (p=.000), normal speed (p=.004) and maximal speed (p=.002) of 5-meter walking speed (p<.005). In the CNE group, all the items except MMSE-DS (p=.068) and SGDS-K (p=.095) showed statistically significant improvement. **Conclusions:** A multi-tasking exercise intervention with exercise and cognitive tasks is effective in improving cognitive and motor function of MCI,

and is an effective intervention for the CNE to practice dementia prevention.

**P056: EXERCISE AND CARBOHYDRATE-RESTRICTED DIET ASSOCIATES WITH IMPROVED INSULIN RESISTANCE AND COGNITIVE PERFORMANCE.**

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**Background:** Type 2 diabetes in midlife and related features such as insulin resistance (IR) are associated with increased risk for dementia. However, it is unknown whether reversing midlife IR may improve cognitive function. The Blood Flow Improvement Trial (BFiT, clinicaltrials.gov NCT03117829), tested an exercise and carbohydrate-restricted diet (CRD) intervention to determine the extent to which improving IR resulted in higher cognitive function, and test whether changes were present six months after the intervention. **Objectives:** We examined the extent to which exercise and a CRD improves a fasting measure of IR, and whether the intervention is associated with improved cognitive performance. We also studied intervention effects on related blood and anthropomorphic assessments, and we tested whether changes across all markers persist six months post-intervention. **Methods:** Twenty-nine pre-diabetic, cognitively unimpaired participants were recruited in four phases (ns = 9, 7, 5, 8, respectively) into a stepped wedge cluster randomized trial. Participants were recruited from the Wisconsin Alzheimer's Disease Research Center and engaged in a 12-week intervention of supervised moderate intensity aerobic exercise for 50 minutes three times weekly, unsupervised exercise twice weekly, and behavioral change classes once weekly to promote program adherence. At the end of the intervention, participants were instructed to maintain the regimen for an additional six months. At baseline (T1), 12 weeks (T2), and six months post-intervention (T3), blood samples analyzed for glucose homeostasis and cholesterol, anthropomorphic measures using a Tanita DC-430U body composition analyzer, and neuropsychological data were acquired to assess markers of IR and cognitive performance. All IR measurements were taken after ten or more hours of fasting. Additionally, throughout the duration of the study, participants were encouraged to perform daily self-monitoring of blood glucose levels, aiming to achieve and maintain a fasting level of <100 mg/dL, and a two-hour post-prandial level of <140 mg/dL. On each measurement occasion (i.e., T1, T2, T3), glucose readings were aggregated to calculate average glucose. a. Blood measures: glycated hemoglobin (HbA1c), fasting glucose, fasting insulin, total cholesterol, triglycerides, high- and low-density lipoprotein (HDL, LDL), total non-HDL; b. Anthropomorphic calculations: body mass index (BMI), fat and water mass as percentages of total body mass, bone mass, basal metabolic rate (calculated using muscle mass),

visceral fat rating, maximum heart rate during 6-minute walking test; c. Cognitive measures: California Verbal Learning Test (CVLT) Total score and Learning Slope, Delis-Kaplan Executive Function System (D-KEFS) Trail-Making Test (TMT) Condition 4 (C4; Number-Letter switching), D-KEFS Color-Word Interference Test (CWIT) Condition 4 (C4; Inhibition/Switching). Intervention effects on the outcomes were tested by comparing the difference between the three visits using random intercept three-level mixed models, with visits nested within participants, and participants nested within groups. Age and sex were adjusted as covariates for each outcome, and education was additionally adjusted for cognitive performance. Natural log transformation was applied on the outcomes that had heavy tailed distribution to reduce non-normality. Model residuals were checked for each outcome. If an outlier was identified, the model was re-tested upon the outlier removal. The difference between each pair of visits was tested, and Tukey-Kramer adjustment was applied to control for the inflation of type I error rate associated with multiple comparison. **Results:** Of the 29 participants enrolled in the intervention study, 23 (79%) completed the intervention, and 22 (76%) completed all three measurements occasions. Participants were 65% female, mean age at baseline was 57.9 ± 5.05 years, and 26 participants had completed college education (Associate's degree or higher). For blood and anthropomorphic measures, from T1 to T2, significant reduction was observed for HbA1C, glucose, and bone mass (ps < .01), insulin, triglycerides, BMI, fat mass/percentage, visceral fat rating, and basal metabolic rate (ps < .001), whereas significant increase was observed for HDL (p < .05). Similar changes were generally observed from T1 to T3, and no significant changes were observed between T2 and T3. For cognitive performance, CVLT total score was increased (p < .001 for T1 vs. T2 and T1 vs. T3), whereas CVLT learning slope decreased over the visits (p < .01 for T1 vs. T3 and T2 vs. T3). Average time to completion was reduced over the visits for TMT-C4, CW-C3, and CW-C4 (ps < .001, .01, .05 for T1 vs. T3, respectively). **Conclusion:** In a cognitively unimpaired cohort, an exercise and carbohydrate-restricting intervention significantly improved IR and glucose homeostasis, and changes were observed beyond the intervention period. Additionally, executive function and verbal memory improved over the duration of the study. This suggests that, in people with impaired glucose regulation, a combined regimen of CRD and exercise may improve insulin resistance and cognitive function, with the changes enduring over a sustained period. Ongoing analysis of trial data will determine the extent to which cerebral blood flow is impacted by midlife CRD and exercise, and will test whether improved cerebral blood flow and cardiorespiratory fitness mediate observed enhancements in cognitive performance.

**P057: REAL-TIME CAPTURE OF GAIT AND ACTIGRAPHY USING INDUSTRY-GRADE WEARABLE DEVICES IN OLDER ADULTS WITH AND WITHOUT SUBJECTIVE COGNITIVE DECLINE: PRELIMINARY COMPLIANCE, SENSITIVITY, AND CORRELATIONS WITH COGNITION.**

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**Background:** Integration of wearable devices into regulated clinical trials for the assessment of cognition and function continues to be a topic of growing interest. If appropriately implemented, measurements from validated wearable

technologies have the potential to revolutionize the conduct of clinical trials by facilitating development of site-less clinical trial designs. In order to be truly informative, however, endpoints collected by these devices must undergo the same clinical and technological validation process required by other currently accepted tools. **Objectives:** We report preliminary findings from an ongoing study designed to assess compliance, ease of use, reliability and sensitivity of two industry-grade wearable devices for the real-time capture of gait and actigraphy measures in 100 older adults with and without subjective cognitive decline. **Methods:** Participants currently include 38 older adults (age 55 or greater), including 26 healthy controls (HC) and 12 individuals with subjective cognitive decline (SCD). Individuals with SCD were categorized as such based on total scores of  $\geq 4$  on the Cognitive Functional Instrument (CFI). During Visit 1, participants were fitted with (1) the Empatica E2 wrist-worn device that offers continuous measurement of motor activity (i.e., actigraphy), galvanic skin response, and sleep, and (2) a pair of fitted Moticon wireless shoe insoles for the collection of gait data. Participants completed four standard lab-based mobility tests, including the timed 25 foot walk, a dual task timed 25 foot walk, Timed Up and Go (TUG), and 500 foot walk. Cognition and functioning were assessed using the Brief Assessment of Cognition (BAC), the MMSE, and the Virtual Reality Functional Capacity Assessment Test (VRFCAT), respectively. At the completion of the Visit 1, subjects were sent home with the Moticon insoles and Empatica wrist worn device. After 1 week of continuous at-home data collection, subjects returned for a second visit during which they repeated assessments of mobility and function. **Results:** Participants with SCD performed significantly worse on the BAC ( $p < .05$  for tests of episodic verbal memory, working memory, processing speed, executive functions and verbal fluency) and VRFCAT ( $p < .05$  for both completion time and errors), indicating objective impairments in the SCD sample. Regarding the Moticon insoles, 2 participants were deemed ineligible to wear these based on a foot exam by a study clinician, 1 participant had feet too large for the largest size insoles, and device malfunction resulted in incomplete data for 5 participants. Within the remaining participants, those with SCD exhibited impaired gait parameters, including significantly prolonged mean stance duration and double support time, longer cycle time, and slower cadence on most laboratory-based assessments of mobility. In the combined sample, several gait measures significantly correlated with functional capacity, such that reduced gait efficiency was associated with lower performance on the VRFCAT: Double support time (i.e. time spent with weight on both legs during walking) was correlated positively with VRFCAT completion time ( $r = .45$ ,  $p < .05$ ), as was length and variability in single leg stance duration during walking (correlations ranging from .47 - .54,  $p < .05$  for all). Similar correlations were present for BAC, with correlations in the range of .44 to .53,  $p < .05$  for all. For the wrist-worn Empatica device, compliance rates during the at home portion of the study were significantly lower for individuals with SCD (average of 13.65 hours of usable data/day) than HCs (20.16 hours/day,  $t(37) = -2.87$ ,  $p = .01$ ). Eight of 12 individuals with SCD and 25 of 26 HCs met our predefined compliance requirement by wearing the devices a minimum of 10 hours on 3 or more days. Although there were no group differences in Empatica-assessed actigraphy during lab-based assessments, there were strong positive correlations between performance-based cognition and function and measures of daily activity/movement collected

between study visits: Average waking activity level was positively correlated with BAC verbal fluency ( $r = .61$ ,  $p < .001$ ), verbal list learning ( $r = .44$ ,  $p < .05$ ), symbol coding ( $r = .45$ ,  $p < .05$ ), MMSE ( $r = .38$ ,  $p < .05$ ), and VRFCAT completion time ( $r = .42$ ,  $p < .05$ ). **Conclusion:** Preliminary findings suggest that, with proper support and maintenance, assessment of actigraphy and gait using the selected wearable devices is feasible. Challenges to integration in large-scale trials include ongoing support for users who may struggle with compliance due to cognitive impairment and lack of familiarity with wearable devices. In addition, use of Moticon insoles is reserved for participants with adequate balance and foot-health, a limitation that may limit use in more diverse samples. We continue to enroll subjects into this study. As the sample size expands, we will evaluate the robustness of these initial findings.

## **Theme 6: COGNITIVE ASSESSMENT AND CLINICAL TRIALS**

### **P058: USING SPEECH MEASURES AS PROGNOSTIC MARKERS OF RAPID COGNITIVE DECLINE: APPLICATIONS TO CLINICAL TRIAL ENRICHMENT.**

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**Background:** Alzheimer's disease (AD) is rapidly approaching a public health crisis, and there is an urgent need to detect the disease at prodromal stages in order to identify those participants who are most at risk of cognitive decline for clinical trials. In addition to amyloid, tau and neurodegeneration markers of disease progression, sensitive measures of cognitive change are needed for strategic selection of participants for high powered clinical trials. Cognitive composite scores such as the Preclinical Alzheimer's Cognitive Composite (PACC) have been shown to capture both early and late cognitive decline during stages of biomarker-defined AD, but completion of the tests that comprise the PACC typically require time and resource-intensive in-person visits. Speech and language analytics using digital recordings have shown linear associations with severity of cognitive impairment, and offer a cost-effective, low-burden, and quick assessment of the multiple cognitive and motor processes required for speech production. As such, speech analytics have the potential to reach a larger and more representative demographic, while at the same time can provide multiple metrics that may identify participants who are showing subtle yet rapid preclinical declines in cognition. **Objective:** Our primary objectives were: 1) to determine if cognitive-linguistic speech measures might help identify those participants who are declining most rapidly on the PACC, and 2) to investigate power/sample size implications for designs with varying proportions of fast decliners. **Methods:** Participants for this study were enrolled in the Wisconsin Registry for Alzheimer's Prevention (WRAP), a longitudinal, natural-history cohort study enriched with participants with a parental history of AD. Participants engage in approximately bi-annual assessments that include medical exams, lifestyle assessments, and comprehensive neuropsychological testing; since 2012, participants have provided speech samples via picture description of "Cookie Theft" from the Boston Diagnostic Aphasia Examination during the testing. Speech

samples are transcribed by trained speech-language pathology graduate students. Participants were included in this study if they had two or more connected speech-language assessments, had data for WRAP's version of the PACC, and had slopes on the PACC that were below -0.1 per year ("fast decliners") or above 0 per year ("non-decliner"); participants whose slopes were between -0.1 and 0 were excluded from these analyses. We employed forward selection random forests on a set of pre-defined speech and language measures using 10-fold cross validation to predict whether an individual was classified as a fast decliner or non-fast decliner. The selected linguistic measures of "moving average type-token ratio (MATTR)," a measure of lexical diversity, and "pronoun-to-noun ratio," a measure of semantic content, are supported by previous literature, including from our group.<sup>7</sup> Classification models included 1) a base model using the binary PACC variable as the outcome, and baseline PACC, sex, education, WRAT-3 reading scores, baseline age, and APOE risk score as predictors; and 2) the base model plus either baseline MATTR or pronoun-noun ratio as the linguistic predictor of interest. We compared the area under the curve of the base model to the full model to test the hypothesis that linguistic variables would improve prediction of fast vs. non-fast decliners on the PACC. We then performed preliminary power analysis to determine if linguistic variables increase the power to detect an effect in a study. The power analysis was based on a model where the treatment group includes a proportion of fast decliners and non-fast decliners, where the fast decliners exhibit a drug effect size of 0.5, relative to the non-fast decliners. **Results:** Sample characteristics include: n=499; mean(sd) baseline age=61.66(6.28); n(%) female=351(70%); mean (sd) education years = 15.91(2.23); n(%) APOEε4 carriers = 182(36.5%); median baseline Mini-Mental Status Examination = 30. 136 participants (27%) were classified as "fast decliners" on the PACC. The base model yielded an AUC of .64 [CI: .59, .69], while the full model including the MATTR and pronoun-noun ratio AUC was 0.70 [CI: .65, .75]. This directly translates to an improvement in power. A random sampling of the participants for inclusion in the treatment group would have yielded a proportion of 27% fast-decliners in the sample. The base model increases this proportion to 51% and the model with language parameters to 59%. Assuming a treatment effect size of Cohen's d=0.5, and designs that include recruitment proportions of 27, 51, or 59% fast decliners, sample required to reach a power of 0.9 are 1,150, 375, and 280 respectively. **Conclusion:** Our data showed a potential 25% reduction in sample size needs after including speech analytics at time of study screening. Connected speech and language is quick to collect, presents low burden to participants, and lends itself well to remote and frequent collection via a variety of communication modes (smartphone, phone, tablet, computer), thus offering potentially wider reach to those participants who are most likely to show clinical benefit in intervention trials.

**P059: GENERATION OF AN OPTIMIZED NEUROPSYCHOLOGICAL FEATURE SET FOR THE QUICK SCREENING OF MILD COGNITIVE IMPAIRMENT IN CLINICAL SETTINGS.** M.J. Kleiman, J. Galvin (*University Of Miami Miller School Of Medicine - Miami, Fl, USA*)

**Backgrounds:** The Clinical Dementia Rating (CDR) scale is commonly used as a gold standard for the staging of mild cognitive impairment (MCI) and Alzheimer's disease and

related dementias (ADRD) yet proper determination of CDR scoring is considerably more time consuming than many other measures; in particular, staging the mildest forms of cognitive impairment requires careful attention. In this study we examine the use of brief self-report patient and informant questionnaires, which approximate the information collected during semi-structured interviews used to generate a CDR, and individual cognitive performance tests collected during the Alzheimer's Disease Neuroimaging Initiative (ADNI), along with feature selection and machine learning techniques to assist in detecting borderline cases of cognitive impairment. Machine learning (ML) often benefits from a reduction in complexity, whether that is in the model itself or the selection of fewer input variables (features). Carefully choosing the most useful features and excluding those that are least helpful can significantly improve model performance, particularly in challenging clinical contexts. Furthermore, an optimized feature set is considerably more efficient and simpler to administer to patients than a broader set that, while objectively more useful for clinical diagnosis, may be time-consuming and require expertise and training not available at all clinical sites, leading to potentially fewer detections of subtle presentations of MCI and ADRD. **Objective:** This study aims to improve the detection of MCI and mild ADRD in diagnostically challenging cases using random forests, an ensemble-based ML technique, and optimized feature sets. Because CDR staging is based on time-intensive semi-structured interviews with a patient and an informant, an automated method that bases a recommendation of ADRD staging on only optimal data points can significantly reduce the time costs of physicians and researchers and enable them to better allocate their resources. **Methods:** Using data provided by ADNI including various cognitive exams (e.g. MOCA, MMSE), neuropsychological tests (e.g. trail making, logical memory), and self-report patient and informant questionnaires including the Everyday Cognition Scale (ECog) and Functional Activity Questionnaire (FAQ), we tested measures that are best able to detect CDRs of 0.5 (questionable or very mild dementia) versus CDR 0 (no impairment) separately from features that detect CDRs of greater than 1 (mild to severe dementia) vs combined CDR 0.5 and 0. We used only baseline measurements from ADNI, leaving us with 707 subjects with a CDR of 0, 766 with a CDR of 0.5, and 92 with a CDR of 1 or greater. Because of class imbalance we performed 3X augmentation on the CDR 1 class using SMOTE, being careful to separately augment the training and testing datasets to minimize the effects of data leakage. Optimal feature sets for both models are identified using a combination of Boruta feature selection and recursive feature elimination, two wrapper algorithms that also utilize machine learning to select the most useful features for each classification task. The two resulting feature sets are then analyzed using a series of binary random forest classifiers, allowing for fine-tuned models and groups of features to optimally identify CDRs of 0, 0.5, or 1+. This is contrasted with the more common technique of developing a single model to perform multiclass classification, which requires the same feature set for all levels of impairment. **Results:** Feature selection produced two datasets tuned to detect either CDR 0.5 vs CDR 0 or CDR 1+ vs CDR 0/0.5. The resulting multimodal random forest model produced a combined area under the ROC curve (AUC) of 0.978, sensitivity of 92.70%, and specificity of 94.21%. The feature set found to most optimally detect CDR 0.5 contained the immediate recall of the logical memory test, trail making tests A and B, immediate

and delayed word recall from ADAS-Cog questions 1 and 4, the tax record question from the FAQ and the attention, language, and memory questions from the ECog. The CDR 1+ feature set contained these features plus eight other questions from the FAQ and all other domains from the informant's version of the ECog. The random forest model tuned to detect a CDR 0.5 had a sensitivity of 92.48%, a specificity of 84.69%, and an AUC of 0.955, while the model tuned to detect CDR 1+ produced sensitivity of 93.09%, specificity of 99.22%, and AUC of 0.997. **Conclusion:** The optimized feature set discovered in this study can be easily administered in 5-10 minutes to complete the questionnaires and brief neuropsychological battery (immediate paragraph recall, immediate and delayed word recall, and trail-making tests). Positive identification could then prompt more in-depth evaluation, as necessary. Ultimately, these findings improve the ability to flag potentially at-risk individuals for further screening of MCI and mild dementia compared to other cognitive assessments including the MOCA (AUC = 0.89) and MMSE (AUC = 0.85).

**P060: CONGRUENCE OF CLINICAL ASSESSMENT INSTRUMENTS WITH ONLINE NARRATIVES OVER SOCIAL MEDIA BY PATIENTS WITH ALZHEIMER'S DISEASE AND CAREGIVERS.** A. Tahami<sup>1</sup>, Y. Stern<sup>2</sup>, S. Doogan<sup>3</sup>, Q. Zhang<sup>1</sup> ((1) Eisai, Inc. - Woodcliff Lake, USA; (2) Columbia University - New York, USA; (3) Real Life Sciences, Inc. - New York, USA)

**Background:** Alzheimer's is a chronic, neurodegenerative, and debilitating disease that impacts millions of people and the number of patients continue to grow in the US. Patients living with Alzheimer's disease (AD) experience increasing cognitive deterioration and declining ability to perform activities of daily functions with aging. In addition, patients may suffer from emotional disturbance, psychiatric comorbidities, social stigmatization, increased risk of unemployment and financial difficulties. **Objective:** This study aimed to better understand disease burden by capturing online patient and caregiver narratives over social media and mapping them to clinical assessment instruments commonly used in AD research and clinical trials for patient screening, diagnosis and treatment monitoring. **Methods:** Patients and caregivers were identified based on online narratives posted between January 1998 and December 2019 across 84 social media sources. The RLYtics Natural Language Processing (NLP) platform was used in combination with manual curation to codify verbatim reports of symptoms and impairments against standard medical taxonomies such as WHO-ICF and MedDRA, and further into the following categorizations: Social, Physical, Emotional, Cognitive, and Role Activity (SPEC-R). For comparison, these SPEC-R categorizations were mapped to 5 clinical instruments: ADCOMS, ADAS-COG, CDR-SB, MMSE and the NPI-Q. Items and domains from the clinical instruments were compared to concepts and sub-concepts extracted from patient and caregiver narratives. **Results:** 112,464 narratives from patients and caregivers were qualified into the final analytic samples. There were 692 patients clinically diagnosed with mild cognitive impairment due to AD (MCI-AD) (n=333) or mild AD (M-AD) (n=359) No narratives from individuals suffering from moderate or severe AD (MS-AD) were captured across the social media sources. There were also 10,174 caregivers, who were grouped according to the patient AD severity stages: MCI (n=971), M-AD (n=3,776), and MS-AD (n=5,427). For each AD stage, patient and caregiver narratives were combined, with

79.7% classified into the Cognitive domain, 84.1% Emotional, 76.1% Physical, 50.1% Role Activity and 34.5% Social domains. Some of the most frequently reported Cognitive concepts such as memory impairments (78.4%), hallucinations (61.4%) and disturbance in attention (42.5%) mapped onto items in standard instruments including ADAS-COG, NPI-Q and MMSE. The most commonly reported Emotional concepts such as anxiety (82.3%) and depression (79.9%) mapped onto items in the NPI-Q. Frequently reported Emotional concepts such as frustration (70.3%) and stress (68.6%) were not captured by any of the five selected instruments. Among Physical concepts, the most frequently reported issues such as Agitation (72.5%) were included in the NPI-Q but several commonly reported issues such as erythema, fatigue and insomnia were not captured by any of the five instruments. The CDR-SB and ADCOMS captured the most frequently reported Role Activity concept, i.e. impaired activities of daily living (48.9%). However, several key concepts such as impaired work ability (40.4%) and loss of employment (36.3%) were not contained in any instruments. In addition, specific activities commonly reported on social media such as driving impairments (24.7%) were not included by any of the five instruments; nonetheless, it was routinely captured in instruments assessing activities of daily living for Alzheimer's. For Social concepts, many of the most frequently reported issues such as social avoidant behavior (38.2%) and relationship issues (12.9%) were not captured by any of the instruments. **Conclusion:** This study identified 112,464 patient and caregiver narratives over 84 public social media sites, which were grouped according to stages of Alzheimer's disease and then mapped to five selected clinical instruments of ADCOMS, ADAS-Cog, CDR-SB, NPI-Q and MMSE. Cognitive deficiencies were well captured. However, patient burden with Emotional, Physical, Social and Role Activity challenges was only partially represented in the selected instruments and several reported challenges were unrepresented. Alzheimer's research and trials may need to employ multiple clinical instruments to properly capture key domains of disease impact on patients with various stages of severity. The study has also identified additional areas of disease burden that are not currently represented in clinical research and practice, pointing to the need for further development of clinical instruments in order to assess the full impact of AD on patients and caregivers. **Biographies:** (1 for poster/oral communications & 4 for the symposium) / 200

**P061: REMOTE ASSESSMENT OF SPEECH AND LANGUAGE CHANGES IN PRIMARY PROGRESSIVE APHASIA (PPA) AND BEHAVIORAL VARIANT FTD.** J. Robin<sup>1</sup>, M. Xu<sup>1</sup>, L. Kaufman<sup>1</sup>, M. Hagey<sup>2</sup>, R. Paul<sup>2</sup>, O. Siddiqui<sup>2</sup>, M. Ward<sup>2</sup>, W. Simpson<sup>1,3</sup> ((1) Winterlight Labs - Toronto, Canada; (2) Alector, Inc. - South San Francisco, USA; (3) McMaster University - Hamilton, Canada-)

**Background:** Changes to speech and language occur across FTD subtypes, including impairments in naming, agrammatism and increased word finding difficulty (1-5). Assessing language abilities may help to characterize disease severity and progression in FTD, and detect effects of treatment. Mobile devices and advances in natural language processing (NLP) enable objective, detailed, remote assessment of language, offering potential advantages over current clinical tools. In order to determine the feasibility of remote language assessment and the aspects of speech affected in behavioral and language variant FTD, we collected speech samples over

a one year period using a remote, digital speech assessment tool. **Objectives:** Our first objective in this study was to test the feasibility of remote speech assessments in individuals with FTD variants. Our second objective was to use natural language processing to analyze the speech samples collected and characterize the acoustic and linguistic aspects of speech that are altered in FTD, and those that change over the course of one year. **Methods:** Thirty-five individuals with variants of FTD were recruited (20 males, 15 females; mean age at recruitment = 61.2 years). FTD diagnoses were confirmed by each individual's physician and included behavioral (n = 20), semantic (n = 6), non-fluent (n = 1), logopenic (n = 4) and unspecified (n = 4) variants. With caregiver assistance, each participant completed a tablet-based speech assessment at months 1, 2, 3, 6, 9 and 12. Tasks included picture description, phonemic and semantic fluency tests, object naming and paragraph reading and recall. Verbal responses were recorded, transcribed and analyzed using NLP, producing >500 speech and language markers. We analyzed changes in selected speech and language markers over time, and compared performance with a group of healthy control participants recruited as part of a separate research study. **Results:** Overall study adherence was high, with most participants reporting no problems completing the assessment with caregiver assistance and few participant withdrawals (n = 4, reasons given include no longer being able to participate due to declines in function and due to COVID-19). Notably, this study continued during the COVID-19 pandemic, since assessments were completed at home with caregiver assistance and no clinical visits were required. Three participants who lived separately from their caregivers had to skip assessments due to restrictions on visitors during COVID-19 outbreaks, but the majority were still able to complete the study as scheduled. FTD participants had lower performance than healthy controls on standard language tests including object naming and phonemic and semantic fluency, as expected. Although there was heterogeneity across participants and by FTD variant, FTD participants had decreases in speech rate, duration of speech, vocabulary richness, and information content, and increased number of pauses compared to a healthy control group. Over the 12 month study, FTD participants showed declines in the number of words, information content and coherence of picture descriptions, and an increase in the number of pauses. **Conclusion:** This study demonstrates that remote language assessments are feasible, with caregiver assistance, in FTD populations. Remote assessments allow for frequent patient monitoring without the need for clinical visits, reducing the burden on patients and their caregivers. Our results replicate standard findings of reduced naming and fluency in FTD, and indicate that language features reflecting the amount, rate and information content of speech are affected in FTD and decline over a 12-month period. Remote language assessments represent an innovative tool for characterizing language changes and disease progression in FTD. **References:** 1. Poole, M. L., Brodtmann, A., Darby, D. & Vogel, A. P. Motor Speech Phenotypes of Frontotemporal Dementia, Primary Progressive Aphasia, and Progressive Apraxia of Speech. *J. Speech Lang. Hear. Res.* 60, 897–911 (2017). 2. Yunusova, Y. et al. Profiling Speech and Pausing in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). *PLOS ONE* 11, e0147573 (2016). 3. Hardy, C. J. D. et al. The Language Profile of Behavioral Variant Frontotemporal Dementia. *J. Alzheimers Dis.* 50, 359–371 (2015). 4. Ash, S. et al. Trying to tell a tale: Discourse impairments in progressive aphasia and

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**P063: COGNITIVE PROFILES OF COMMON NEUROLOGICAL CO-MORBIDITIES: A REVIEW OF SYSTEMATIC REVIEWS.** C. Ganzer<sup>1</sup>, A. Seifan<sup>2</sup> ((1) *Hunter College School Of Nursing - New York, USA;* (2) *The Neuro Well Free Corporation - Miami Beach, USA*)

In busy clinical settings, recognizing subtle cognitive changes in patients at risk of age-related brain diseases is challenging because patients usually present with more than one co-morbidity that can influence cognition. For more timely and accurate detection of prodromal neurodegenerative disease, a better understanding of the relative influence on cognition of the most common Neurological and Psychological co-morbidities is needed. The objective of this study was to review the existing literature that has quantified the significant cognitive differences, compared to healthy controls, in groups of patients with common Neurological and Psychological co-morbidities. This study was a literature review of prior systematic reviews that quantify cognitive performance differences among patients with common Neurological and Psychological co-morbidities published in PubMed over the last 20 years. Only English language, systematic review studies, in human, adult, populations were included. The search combined terms/synonyms for neuropsychological testing with terms/synonyms for effect size and terms/synonyms for the specific co-morbidity. A total of 648 citations of meta-analysis or systematic reviews, dating over the past 20 years, regarding cognition in patients with neurological and psychological co-morbidities were identified, of which 56 met inclusion criteria for this review. Migraine, epilepsy, small vessel cerebrovascular disease, chronic pain, concussion/TBI, Parkinson's disease, obstructive sleep apnea, ADHD, autism, and specific reading disorder are associated with significant differences in cognitive domains including attention, executive function, processing speed, social cognition, language and visuospatial function. Co-morbid neurological and psychological diagnoses are associated with distinct cognitive differences. Accounting for all of a patient's co-morbidities that may influence cognition may facilitate earlier detection of cognitive changes associated with neurodegenerative disease.

**P064: INSULIN RESISTANCE AND LONGITUDINAL COGNITION IN MIDDLE-AGED AND OLDER ADULTS.** G. Ennis, E. Jonaitis, R. Kosciak, L. Clark, S. Bouges, T. James, N. Chin, C. Engelman, R. Anderson, S. Asthana, S. Johnson, B. Bendlin (*University Of Wisconsin-Madison - Madison, USA*)

**Background:** Insulin resistance (IR) has been shown to be related to an increased risk in dementia due to Alzheimer's disease, yet longitudinal studies describing the relationship between IR and cognition are lacking. Such studies would provide insight into how IR is associated with aging-related and learning-associated change in cognitive domains known to be affected by aging and Alzheimer's disease. **Objectives:** We tested whether baseline IR was related to worse age-associated and less practice (i.e., learning) associated change in processing speed, executive function, and episodic memory in a sample of middle-aged and older adults who were non-demented at baseline IR. **Methods:** Middle-aged and older adult participants

(Mage = 59.25 years, SD = 7.18) from the Wisconsin Registry for Alzheimer's Prevention (WRAP; n=1,305) and the Wisconsin Alzheimer's Disease Research Center (ADRC) Clinical Core (n=257) were tested. The majority of participants were white (93.4%) and female (70%). Participants were selected if they were non-demented at baseline IR, were not being treated with insulin (a confound for determining IR), and had APOE4 genotyping and fasted blood for insulin and glucose. IR was measured using the homeostatic model assessment of insulin resistance (HOMA-IR) which was calculated using the first fasting insulin and glucose collected as part of an individual's participation in their study cohort. Cognitive assessments on and after the first HOMA-IR observation were used in this analysis. Processing speed and executive function were assessed using the Trail Making Test (TMT) parts A and B, respectively. Episodic memory was measured using the Rey Auditory Verbal Learning Test (RAVLT): immediate, and short- and long-delayed recall. Cognitive ability was tested every 1-2 years over an average interval of 6.2 years (SD = 3.2). Practice was assessed as the number of times a participant had completed a test during past visits. We examined aging-associated cognitive change controlling for longitudinal practice and practice-associated cognitive change controlling for longitudinal age. Baseline IR was tested as a moderator of aging- and practice-associated cognitive change in separate linear mixed effects models. Age, practice, education, sex, APOE4 carrier status, cohort, and measures of baseline health, specifically systolic blood pressure, diabetes, and cognitive impairment (MCI or cognitively impaired, not MCI) were adjusted for in all models. Higher TMT parts A and B values indicated worse performance; both TMT results were log-transformed due to skewness. Statistical significance was set at  $p < .05$ . **Results:** The majority (60.4%) of the sample had a mean baseline HOMA-IR of 1.0 which approximates normal insulin sensitivity. Baseline IR was a significant moderator of aging- and practice-associated change in RAVLT immediate recall (Age X IR:  $\gamma = -.06$ ,  $p = .004$ ; Practice X IR:  $\gamma = -.16$ ,  $p = .009$ ). Participants with higher IR experienced worse aging-related decline in immediate recall and benefited less over time from practice. Baseline IR was a weakly significant moderator of aging related change in TMT part B (Age X IR:  $\gamma = .0007$ ,  $p = .03$ ) with worse decline in participants with higher baseline IR. IR was not a significant moderator of practice associated change in TMT part B (Practice X IR:  $\gamma = .0002$ ,  $p = .06$ ). IR did not significantly moderate aging- or practice-associated change in TMT part A, and RAVLT short- and long-delayed recall. **Conclusion:** IR was related to a modest worsening of aging-related decline in immediate recall and executive function and less practice-based improvement over time in immediate recall. Results should be interpreted in the context of sample characteristics. That IR may contribute to cognitive aging and depress learning bolsters support for clinical interventions aimed at treating IR to slow cognitive decline.

**P065: POLYGENIC RISK FOR ALZHEIMER'S DISEASE PREDICTS MMSE DECLINE IN AMYLOID POSITIVE OLDER ADULTS.** A. Moore<sup>1</sup>, J. Cara<sup>1</sup>, L. Schneider<sup>2</sup>, A. Torkamani<sup>3</sup>, C. Cruchaga<sup>4</sup>, J. Collens<sup>1</sup> ((1) *Vivid Genomics - San Diego, USA*; (2) *Departments Of Neurology, Psychiatry And Behavioral Sciences, Keck School Of Medicine, University Of Southern California - Los Angeles, USA*; (3) *Scripps Research Translational Institute - La Jolla, USA*; (4) *Knight Alzheimer's Disease Research Center, Washington University School Of Medicine - St. Louis, USA*)

**Background:** A limiting factor in the optimal balance of clinical trial arms for Alzheimer's disease (AD) is the significant heterogeneity in the progression of cognitive impairment associated with AD. Polygenic risk scores (PRS) may enhance the ability to predict cognitive decline in individuals at risk for AD. **Objective:** We set out to show that a PRS which explains genetic heterogeneity and risk for cognitive decline outside of APOE4 can improve predictive power for MMSE performance decline in amyloid positive individuals. **Methods:** A PRS was calculated using genome-wide association study (GWAS) summary statistics for clinical AD diagnosis (Jansen et al, 2019; N=455,258). PRS derived from this GWAS study were computed for participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI). All non-APOE SNPs (<1Mb) that were significant at the  $p=0.001$  level in the parent GWAS study were included in the respective PRS calculation. Participants with a baseline cerebrospinal fluid (CSF) amyloid measurement equal to or below 800pg/mL, or Flortbetapir standardized uptake value ratio equal to or above 1.1 were considered amyloid positive and selected for this study (N=622). A Gaussian Mixture Model was used to classify MMSE decline, using the overall slope of decline for each participant. Logistic regression models assessed the association between PRS and Mini Mental State Exam (MMSE) decline covarying for age, sex, years of education, and APOE- $\epsilon 4$  status. Additional logistic regression models which included baseline MMSE performance as a covariate were also tested, in addition to assessment of these models in a subsample of participants with a baseline MMSE score of 25-30 (inclusive, N=475). Age, sex and APOE4 interactions with PRS were also assessed. **Results:** The PRS was a significant predictor of MMSE decline in the overall amyloid positive sample ( $p=0.006$ , Odds Ratio (OR)=1.27) and outperformed a base model which included age, sex and education but excluded genetic predictors (base model, AUC=0.56; PRS model, AUC=0.62). The PRS was also a significant predictor of MMSE decline in a subsample of participants with a baseline MMSE score 25-30 ( $p=0.005$ , OR=1.32). The PRS remained a significant predictor of MMSE decline in the amyloid positive sample and in the population with baseline MMSE 25-30 in models controlling for baseline MMSE performance. There were no interactions between the PRS and age ( $p=0.6$ ), sex ( $p=0.9$ ), or APOE4 status ( $p=0.9$ ). **Conclusion:** The proposed PRS model explains heterogeneity in cognitive decline above and beyond the APOE4 allele, as APOE and its surrounding region were excluded from the computation of the PRS. The PRS model showed robust predictive power in the early stages of cognitive decline (baseline MMSE 30-25) in amyloid positive participants. Utilization of additional genomic factors beyond APOE using PRS models could enhance clinical trial recruitment and stratification strategies for trial analyses, such that APOE4 carriers are selected for probable cognitive decline, in addition to APOE3 carriers that are also high on polygenic risk.



**P066: TOWARD DISCRIMINATING ALZHEIMER'S DISEASE FROM OTHER DEMENTING DISORDERS WITH MODELED COGNITIVE PROCESSES.** J.R. Bock<sup>1</sup>, M.D. Lee<sup>2</sup>, W.R. Shankle<sup>1,2,3</sup>, J. Hara<sup>1,3</sup>, D. Fortier<sup>1</sup>, T. Mangrola<sup>1</sup> ((1) *Medical Care Corporation - Newport Beach, USA*; (2) *Dept. Of Cognitive Sciences, University Of California At Irvine - Irvine, USA*; (3) *Pickup Family Neuroscience Institute, Hoag Memorial Hospital - Newport Beach, USA*)

**Background:** Hierarchical Bayesian Cognitive Processing (HBCP) models measure unobservable (latent) cognitive processes that underlie learning and recall of information, such as measured by cognitive tests. These processes, representing encoding, storage, or retrieval of the list items in wordlist memory tasks, after accounting for individual differences, are able to characterize individuals and the groups that they comprise. In previous work with one HBCP model, a multinomial processing tree model that captures patterns of retrieval for an item over a sequence of immediate and delayed free recall tasks, we characterized and distinguished clinical sample subjects based on dementia severity, as measured by the Functional Assessment Staging Test (FAST). In developing this model, we applied a latent-mixture structure that identified two subgroups in moderately demented (FAST 5) subjects, with a minority of such subjects presenting significantly better memory than the majority. We proposed as interpretation that the minority group represents subjects with non-amnesic functional deficits, resulting in FAST 5 classification due to disorders other than Alzheimer's disease. This suggests that patterns of cognitive processing parameters, as described by our HBCP model, may be able to differentiate diagnoses in demented patients. **Objective:** To explore the potential for diagnostic differentiation based on latent-mixture modeling with the HBCP model, through evaluation and comparison of the sample and its subgroups, using demographic information, clinician diagnoses, and apolipoprotein-E (ApoE) genotyping. **Methods:** Subjects (n = 430) were patients of a cognitive disorders clinic, with assessments (n = 1,313) performed between the years 2002 and 2019. As part of their assessments, patients were given the MCI Screen (MCIS), a battery of cognitive tasks, including multi-trial free recall of a wordlist, with three immediate and one delayed free recall tasks. Separately, a trained neurologist diagnosed subjects and determined severity of cognitive functional decline with the FAST. An HBCP latent-mixture model was used to evaluate subjects with moderate dementia (FAST 5), with a model assumption that each of two possible subgroups has a distinct mode for each cognitive processing parameter, but each with the same variance. The model estimated each subject as belonging to one of the two subgroups, via a binary indicator parameter  $z$ , drawn from a base-rate  $\phi$ . Bayes factor assessment of  $\phi$  ( $BF > 1000$ ) indicated that there were separate groups, and subjects were assigned to one or the other group by the mode of their posterior latent class parameter samples. This resulted in 66 (15%) subjects in the minority subgroup and 364 (85%) in the majority. We examined cognitive processing parameter posterior samples to characterize patterns in cognitive performance. Patients in the minority subgroup demonstrated significantly better memory, particularly through the parameters of immediate and delayed retrieval from durable storage. Sample characteristics were examined, comparing subgroups by demographic information, clinician diagnoses, and ApoE genotype. Independent samples t-tests and Fisher's

exact tests were used for continuous and categorical factors, respectively. **Results:** Despite similarity of cognitive functional impairment severity, numerous significant differences were identified between latent-mixture model-identified subgroups. Alzheimer's disease was less prevalent in the minority subgroup than in the majority subgroup ( $p < .001$ ). Additionally, there were small but significant differences in demographics, and more of the majority subgroup had one or two  $\epsilon 4$  ApoE alleles than the minority subgroup. **Discussion:** This preliminary exploration of sample characteristics in latent-mixture HBCP model-derived subgroups of moderately demented subjects validates previous findings and represents a proof of concept for application of the HBCP model as a diagnostic tool. Identification of group differences, particularly with regards to relative prevalence of Alzheimer's disease, supports the hypothesis that the model can distinguish between amnesic and non-amnesic dementing disorders in patients with at least moderately severe dementia. This requires further validation as a predictive model, particularly with imaging studies, demonstrating that subjects predicted to be non-amnesic are absent hallmark biomarkers of Alzheimer's disease (e.g., beta amyloid and pathologic tau). Furthermore, the results identify specific cognitive processes that are differentially impaired due to different disorders, which may benefit studies evaluating targeted dementia treatment.

**P067: CLINICAL CORRELATES OF TYPES OF MEMORY COMPLAINTS IN SUBJECTIVE COGNITIVE DECLINE AND AMNESIC MILD COGNITIVE IMPAIRMENT.** S.Y. Ryu, S.B. Lee, T.J. Lee, Y.J. Jung (*The Catholic University Of Korea, Daejeon St. Mary's Hospital - Daejeon (Republic of Korea)*)

**Background:** Memory complaints are a frequent phenomenon in elderly people. Those memory complaints may reflect various aspects of the cognitive symptoms, but clinical significance for different types of memory complaints are not fully understood. **Objectives:** The aim of this study was to examine whether there are the differences of the clinical correlates due to different aspects of memory complaints (i.e. prospective memory (PM) versus retrospective memory (RM) complaints) in individuals with subjective cognitive decline (SCD) and amnesic mild cognitive impairment (aMCI). **Methods:** The study included a total of 194 participants (mean age:  $69.42 \pm 838$  years) with SCD (n = 95) and aMCI (n = 99). Memory complaints were assessed using the Prospective and Retrospective Memory Questionnaire (PRMQ) consisting of 16 items which describe everyday memory failure of both PM and RM. All participants underwent clinical assessment and completed detailed neuropsychological tests. Participants were divided into more PM complaints (PM > RM) and more RM complaints (PM < RM) groups according to the PM and RM subscores of PRMQ. Group comparisons between more PM and more RM complaints for individual cognitive performances and correlation between PM-RM discrepancy scores (i.e., PRMQ-PM minus PRMQ-RM subscores) and cognitive performances were assessed in total participants and each group. **Results:** Verbal memory performances (Seoul Verbal Learning Test [SVLT] delayed recall and recognition) of more RM complaints group were worse compared to more PM complaints group in the total study participants and in the aMCI group but not in SCD group. PM-RM discrepancy scores positively correlated with SVLT immediate recall, delayed recall and recognition in the total participants and in the aMCI group. **Conclusions:**

RM complaints among subjective memory complaints are more associated with decreased verbal memory performance in the total group and aMCI group, but no association was found in SCD subjects. These results could provide diagnostic approaches for the clinical evaluation of memory complaints in individuals with MCI.

**LP13: PREDICTIVE MODEL INCORPORATING POLYGENIC RISK SCORE FOR ALZHEIMER'S DISEASE PREDICTS MMSE DECLINE IN APOE4 CARRIERS AND NONCARRIERS.** A. Moore<sup>1</sup>, J. Cara<sup>1</sup>, A. Torkamani<sup>2</sup>, L. Schneider<sup>3</sup>, J. Collens<sup>1</sup> ((1) *Vivid Genomics - San Diego, USA*; (2) *Scripps Research Translational Institute - La Jolla, USA*; (3) *Keck School Of Medicine Of The University Of Southern California - Los Angeles, USA*)

**Backgrounds:** Heterogeneity in the progression of cognitive impairment, which is common in sporadic Alzheimer's disease (AD) trials, is especially challenging to predict in pre-symptomatic populations, and has a negative impact on clinical trial power. AD is highly heritable, and this heritability extends beyond the APOE genotype, with multiple common genetic variants identified in large genome wide association studies (GWAS) comparing AD dementia cases with older normal controls. Incorporating APOE has improved models predicting cognitive decline; incorporating additional common genetic variants into models has the potential to further improve the prediction of disease progression. **Objective:** A major factor limiting the detection of drug response in AD clinical trials is the significant heterogeneity in the progression of cognitive impairment associated with AD, and the identification of individuals who are at early or pre-symptomatic stages of disease and who will progress over the duration of a clinical trial. Specifically, prescreening or identifying individuals who are non-decliners before testing for Amyloid status will increase the statistical power of AD clinical trials and may identify high-risk progressors, thus accelerating recruitment and time to efficacy readout. Including polygenic risk scores (PRS), among other factors, may increase accuracy over traditional methods to predict cognitive decline in individuals at risk for AD. Here we present validation data comparing prediction for decline among APOE4 carriers and non-carriers within a population relevant for Alzheimer's clinical trials and identify APOE4 non-carriers of equivalent risk to carriers who historically would have been excluded from pre-symptomatic studies. **Methods:** A PRS was calculated using genome-wide association study (GWAS) summary statistics for clinical AD diagnosis (Jansen et al, 2019; N=455,258). PRS derived from this GWAS study were computed for participants drawn from two aging studies, the National Alzheimer's Coordinating Center (NACC) and the Alzheimer's Disease Neuroimaging Initiative (ADNI). All non-APOE SNPs (<1Mb) that were significant at the p=0.5 level in the parent GWAS study were included in the respective PRS calculation. Logistic regression models assessed the association between PRS and Mini Mental State Exam (MMSE) decline covarying for age, sex, education, APOE-ε4, and baseline MMSE score. Age and sex interactions with PRS were also assessed. **Results:** Participants in the training and test set showed similar baseline ages, years of education and baseline MMSE scores in the whole sample and after stratification by APOE4 carrier status. The test cohort had a lower percentage of females compared to the training set (training, 52% female; testing, 43% female). The PRS model was a significant predictor of MMSE decline (p=8x10-

5), as well as in APOE4 carrier and noncarrier populations (carriers p<0.001; noncarriers p=0.02). The PRS model showed the highest classification accuracy in APOE4 noncarriers in both the training and test sets (81% and 80%, respectively). Compared to a base model for MMSE decline, which included age, sex, and education as predictors, the PRS model increased the area under the receiver-operator curve by 2% in the test cohort (base model, AUC=0.83; PRS model, AUC=0.85). The sample was narrowed to participants with a baseline MMSE of 30-25 to represent early phase of disease, and in the overall test sample the PRS model showed a 3% increase in area under the receiver-operator curve compared to the base model described above which did not consider genetics (base model, AUC=0.77; PRS model, AUC=0.80). Importantly, we were able to identify 25% of APOE4 non-carriers with equivalent risk to APOE4 carriers. There were no age or sex interactions with the PRS on MMSE decline. **Conclusion:** The proposed model including PRS explains heterogeneity in cognitive decline above and beyond the APOE4 allele, as APOE and its surrounding region were excluded from the computation of the PRS. PRS models appear to have predictive power in the early stages of cognitive decline (baseline MMSE 30-25). Utilization of additional genomic factors beyond APOE in PRS models could enhance clinical trial recruitment and stratification strategies for trial analyses, such that APOE4 carriers are selected for probable cognitive decline, in addition to APOE3 carriers that are also high on polygenic risk.

## **Theme 8: HEALTH ECONOMICS AND CLINICAL TRIALS**

**P069: MORTALITY RISK AND USE OF LONG-TERM CUSTODIAL CARE FOR PATIENTS WITH DEMENTIA AND PSYCHOSIS VERSUS PATIENTS WITH DEMENTIA ONLY: A LONGITUDINAL, MATCHED COHORT ANALYSIS OF MEDICARE CLAIMS DATA.** N. Rashid<sup>1</sup>, J. Wetmore<sup>2,3</sup>, M. Irfan<sup>4</sup>, V. Abler<sup>1</sup> ((1) *ACADIA Pharmaceuticals, Inc. - San Diego, USA*; (2) *Chronic Disease Research Group - Minneapolis, USA*; (3) *Hennepin County Medical Center - Minneapolis, USA*; (4) *University Of Minnesota And Veterans Affairs Medical Center - Minneapolis, USA*)

**Background:** Neuropsychiatric symptoms (NPS) are common in patients with dementia: 79% of patients in the long-term care setting and 97% in the community setting have 1 or more NPS (1, 2). Psychosis, characterized by hallucinations and delusions, is one type of NPS that occurs commonly in patients with dementia (2, 3). Dementia-related psychosis is associated with a higher risk of cognitive and functional decline, institutionalization, and death (3, 4) and therefore can have a negative impact on patients, caregivers, and the healthcare system. Data on the patient journey and the long-term outcomes of patients with dementia who experience psychosis can provide valuable information to optimize care. **Objective:** To evaluate an association between mortality risk and the use of long-term custodial care in patients with dementia and psychosis versus patients with dementia only. **Methods:** This retrospective cohort study used a 20% Medicare random claims dataset from 2008–2016 to identify patients with dementia who had 1 dementia diagnosis code plus a prescription for dementia-related medications, or at least 2 dementia diagnosis codes at least 30

days apart. Further, patients with dementia-related psychosis were categorized as incident psychosis patients if they had 1 psychosis diagnosis code plus an antipsychotic prescription or 2 psychosis diagnosis codes at least 30 days apart. Patients with dementia-related psychosis were matched to dementia-only patients by age, sex, race, select comorbidities, and dementia index year. Patients were followed until death, admission to custodial care, the end of eligibility, or the end of the study period, whichever came first. A cox proportional hazards model was used to assess the association of mortality and the use of custodial care. **Results:** This study identified 256,408 patients with dementia: of these, 49,509 patients (19.3%) developed dementia-related psychosis and 206,899 (80.7%) did not. Patients with dementia-related psychosis were more likely to be female (71.0% versus 68.3%) and white (85.7% versus 82.0%), and had fewer comorbid medical conditions than patients with dementia only. Within 2 years of developing dementia-related psychosis, 52.0% of patients died and 16.1% entered custodial care; corresponding percentages for patients with dementia only were 30.0% and 8.4%, respectively. In the matched cohort, dementia-related psychosis was associated with a greater risk of death (HR 2.06; 95% CI, 2.02-2.10;  $P < 0.0001$ ) and the need for custodial care (HR 2.36; 95% CI, 2.29-2.44;  $P < 0.0001$ ) compared with dementia alone. **Conclusion:** Dementia-related psychosis was associated with a 2-fold increase in the risk of death and a nearly 2.5-fold increase in the risk of the need for long-term custodial care compared with dementia alone. Although causality cannot be determined from this claims-based analysis, this work is the first to our knowledge to quantify these risks using a large, nationally representative administrative database and adds to the body of literature demonstrating worse outcomes in patients with dementia-related psychosis than in patients with dementia alone. **References:** 1. Margallo-Lana M, et al. *Int J Geriatr Psychiatry*. 2001;16:39-44; 2. Jellinger KA. *J Cell Mol Med*. 2012;16:995-1012; 3. Peters ME, et al. *Am J Psychiatry*. 2015;172:460-465; 4. Scarmeas N, et al. *Arch Neurol*. 2005;62:1601-1608.

**P070: ESTIMATING PROGRESSION RATES ACROSS THE SPECTRUM OF ALZHEIMER'S DISEASE FOR AMYLOID POSITIVE INDIVIDUALS USING NATIONAL ALZHEIMER'S COORDINATING CENTER DATA.**

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**Background:** Alzheimer's disease (AD) encompasses a continuum ranging from cognitively normal individuals with biomarker evidence of AD pathology to individuals with severe AD dementia. Older models of disease progression based solely on cognitive and functional status can now be revised with the addition of biomarker data. Biomarker-informed models will aid in health care system planning and are critical to clinical trial design. Although there are several published estimates for AD progression rates, these "transition probabilities" may not accurately reflect the experience of individuals with biomarker-confirmed amyloid beta pathology ( $A\beta^+$ ). **Objectives:** Here we use the National Alzheimer's Coordinating Center (NACC) data set to estimate annual progression rates across the entire

AD continuum in individuals confirmed as  $A\beta^+$ . Progression rates are summarized as transition probabilities to support their use in predictive disease modeling. **Methods:** Patient-level longitudinal data from the NACC were used to estimate progression rates for  $A\beta^+$  individuals. The individual was considered  $A\beta^+$  using a "broad" definition, e.g., if any of the following were present within 10 years of the first study visit: abnormal amyloid PET scan, abnormal CSF  $A\beta$ , or autopsy-confirmed  $A\beta^+$  (defined using neocortical neuritic plaques and Braak staging for neurofibrillary degeneration). Other definitions of amyloid positivity were explored in sensitivity analyses to understand how they may impact the progression of disease. Progression—measured as transition probabilities between 5 clinically defined stages (asymptomatic, mild cognitive impairment due to AD [MCI-AD], mild AD, moderate AD, severe AD), demarcated by published Clinical Dementia Rating Sum of Boxes score ranges, and death—was assessed in «incident» patients who recently entered the stage ( $N = 4395$ ). This criterion was applied to ensure that the full time in a disease stage could be captured, to lessen the influence of system variations due to diagnostic timing. Transition probabilities were generated from multinomial logit regression models that predicted an individual's health state at the current visit as a function of the health state at the previous visit and adjusted for 5 clinical variables: time between initial and follow-up visits, patient age, sex, years of education, and concomitant medications. **Results:** Annual transition probabilities to more severe stages for surviving patients with known amyloid status were 41% for transitioning from asymptomatic to MCI-AD, 22% for MCI-AD to mild AD or worse, 36% for mild AD to moderate AD or worse, and 29% for moderate AD to severe AD. Transition probabilities to less severe stages were also estimated and were: 5% for reversion from MCI-AD to asymptomatic, 3% for mild AD to MCI-AD, 2% for moderate AD to mild AD, and 1% for severe AD to moderate AD. **Conclusion:** The likelihood of transitioning between stages of disease informs our understanding of progression along the AD continuum. These estimates can aid in trial design, care planning, and clinical and economic benefit assessments of AD interventions that reduce progression rates. Examining the entire continuum in 1 data set produces methodologically consistent estimates across the disease spectrum. A small but significant number of transitions to less-severe stages were observed in  $A\beta^+$  patients. These transition probabilities, including the observed low reversion rate, should be further tested in clinical settings.

**P071: COMPARATIVE EFFICACY, SAFETY, TOLERABILITY, AND EFFECTIVENESS OF ANTIPSYCHOTICS IN THE TREATMENT OF DEMENTIA RELATED PSYCHOSIS (DRP): A SYSTEMATIC LITERATURE REVIEW.**

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**Background:** Patients with dementia often experience neuropsychiatric symptoms (NPS) such as hallucinations and delusions, which is a characteristic hallmark of dementia-related psychosis (DRP). Currently, there is no FDA approved DRP treatment, however, antipsychotics (AP) are used to treat the symptoms. AP medications, specifically atypical antipsychotics (AAPs), have significant safety risks, including a boxed warning about increased risk of mortality among elderly dementia patients. While a 2019 systematic review of double-blind

randomized clinical trials (RCTs) of AAPs suggests that no single agent has a favorable trade-off between efficacy and safety in treating DRP patients (Yunusa et al, 2019), a more recent systematic review based on RCTs, case-control and cohort studies for several classes of drugs including APs suggests that APs may carry significant risk of stroke, falls, fractures, and mortality (Watt et al, 2020). However, no studies have comprehensively evaluated the comparative effects of APs on NPS, safety, tolerability, and effectiveness in DRP patients from blinded controlled trials, open-label trials, and observational studies. **Objective:** To systematically review the literature and evaluate the comparative efficacy, safety, tolerability, and effectiveness of APs for the treatment of DRP. **Methods:** We used the preferred reporting items for systematic reviews and meta-analyses guideline to conduct this review. English language articles in PubMed/MEDLINE, PsycInfo, EMBASE, Cochrane central register of controlled trials, and conference proceedings from Jan 2000 – Apr 2020, as well as reference lists from selected articles were searched using selected key search terms that followed the PICOS framework. Studies of psychosis among dementia patients (age ≥ 40, those living at home or nursing home, gender, ethnicity) with Alzheimer’s disease (AD), frontotemporal dementia, vascular dementia (VaD), dementia with Lewy bodies (DLB), and Parkinson’s disease dementia formed the population of interest. Interventions included were typical and atypical (AAPs) antipsychotics. Double-blind active-comparator or placebo-controlled RCTs, open-label trials and observational studies were included. AP efficacy was assessed as NPS improvements related to hallucinations and delusions, measured with scales such as Neuropsychiatric Inventory (NPI) and Neuropsychiatric Inventory-Nursing Home version (NPI-NH) among others. Additionally, tolerability (i.e, weight gain) and safety (i.e, somnolence, extrapyramidal symptoms (EPS) including tardive dyskinesia, cognition, cerebrovascular events, falls and mortality among others) outcomes were also reviewed. AP effectiveness was summarized from all-cause discontinuations, and discontinuations due to lack of efficacy or safety. **Results:** Of the 1277 publications screened, 198 were selected for full-text review. After full-text review, 61 publications were selected encompassing a total of 43 blinded RCTs (6 are post hoc analyses of RCT), 16 open-label trials, and 2 observational studies, with a study duration ranging from 4-52 weeks (average of 12-weeks). Of these, 23 articles were from studies in the US and the remaining 38 were multinational studies; 32 were conducted in institutionalized settings (e.g., Nursing Home (NH) or long-term care facilities) while the rest were conducted among community dwelling, outpatient settings. Fifty-nine studies included dementia patients mostly of AD type and two (2) studies had PD dementia (PDD) related psychosis as their primary inclusion criteria. Other dementias included in these studies were VaD, DLB, PDD or mixed dementia. Of the 49 parallel group studies, 26 were placebo-controlled studies and 23 had active-controls. Overall, there were 31 trials of risperidone, 16 of quetiapine, 15 of olanzapine, 3 of aripiprazole, and one study each of ziprasidone, tiapride, and brexpiprazole. The Cochrane risk of bias assessment suggests that 10% of the reviewed articles may have a high bias risk for randomization and incomplete outcomes data. The total number of patients included in these studies was 15419 (range:5 to 4499); with a patient mean age of 80 years (range:66-87 years) and approximately 67% female. Although the review showed that risperidone, olanzapine, quetiapine, and aripiprazole demonstrated modest psychotic symptom improvements

among DRP patients, only risperidone was reported to have symptom improvements consistently. Both quetiapine and aripiprazole reported mixed results and lower dose olanzapine showed greater symptom improvements than higher doses. Somnolence was the most reported adverse event (AE) for all the major antipsychotics, with weight gain and tardive dyskinesia being more commonly reported for olanzapine and risperidone, respectively. Other AEs reported for all AAPs were falls and EPS, except for brexpiprazole. Studies also show that these antipsychotics may be associated with greater cognitive declines and potentially increased mortality in patients. Compared to placebo, odds of all-cause discontinuations were lower with aripiprazole while olanzapine, quetiapine, risperidone and brexpiprazole reported no differences. While aripiprazole and olanzapine had lower discontinuation odds due to lack of efficacy, olanzapine had higher discontinuation odds due to lack of safety. **Conclusions:** This systematic literature review suggests that currently used AAPs may confer only marginal benefits in treating hallucinations and delusions while carrying a high risk of significant AEs, accelerated cognitive decline and potentially higher mortality among DRP patients. These results underscore the need for new treatment options with a favorable benefit-risk profile for the treatment of DRP. **References:** Yunusa I, Alsumali A, Garba AE, Regestein QR, Eguale T. Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-analysis. *JAMA Netw Open.* 2019;2(3):e190828. Published 2019 Mar 1. doi:10.1001/jamanetworkopen.2019.082; Watt JA, Goodarzi Z, Veroniki AA, et al. Safety of pharmacologic interventions for neuropsychiatric symptoms in dementia: a systematic review and network meta-analysis. *BMC Geriatr.* 2020;20(1):212. Published 2020 Jun 16. doi:10.1186/s12877-020-01607-7.

**P072: CAREGIVER PERSPECTIVES ON THE BURDEN AND IMPACT OF AGITATION IN CARING FOR LOVED ONES WITH DEMENTIA/ALZHEIMER’S DISEASE: A COLLABORATION WITH USAGAINSTALZHEIMER’S A-LIST®.** M. Sanon Aigbogun<sup>1</sup>, M. Cloutier<sup>2</sup>, E. Serra<sup>2</sup>, T. Frangiosa<sup>3</sup>, V. Biggar<sup>3</sup>, R. Baker<sup>1</sup>, M. Michael<sup>4</sup>, H. Gandhi<sup>1</sup>, M. Gauthier-Loiselle<sup>2</sup> ((1) *Otsuka Pharmaceutical Development & Commercialization, Inc. - Princeton, USA*; (2) *Analysis Group, Inc. - Montreal, Canada*; (3) *Usagainst Alzheimer’s - Washington, USA*; (4) *Otsuka America Pharmaceutical, Inc. - Princeton, USA*)

**Introduction:** Agitation in Alzheimer’s disease (AD)/dementia, a commonly occurring and distressing symptom, is associated with rapid decline in cognitive functioning and higher healthcare resource use. While family caregivers are typically the primary caretakers of individuals with dementia, little data is published on the impact of agitation symptoms on caregiver quality of life and burden. **Objectives:** This study aims to assess the impact of agitation on caregiver outcomes, including treatment satisfaction, burden, and work productivity impairment among those who have cared or are currently caring for individuals with dementia/AD in the United States. **Methods:** A cross-sectional survey study was implemented in two phases: 1) in-depth, semi-structured telephone interviews to ensure survey questions capture self-reported disease characteristics and caregiving burden in the target population and 2) with UsAgainstAlzheimer’s, the final

survey was administered to members of the A-LIST® online to caregivers (current and former) of individuals with AD between April 2, 2020 and April 27, 2020. Caregivers were included in the study if they were aged 18 and older, had been caring for at least one month for an individual with dementia/AD, and were able to indicate whether or not the individual under their care has/had experienced symptoms of agitation. Caregivers were asked to report on their own demographic characteristics, physical and mental health, health resource utilization, caregiver burden (measured using the short form of Burden Scale for Family Caregivers, BSFC), employment status, work productivity impairment, and the availability of additional supports as well as agitation symptoms and therapies of the care recipient. Descriptive analyses were conducted and summarized separately for caregivers of individuals with and without agitation. **Results:** A total of 395 caregivers were eligible and completed the survey. The majority of caregivers were 55 and older (90.1%). Females constituted 73.9% of caregivers in this sample. Sleep disturbances (42.0%), anxiety (41.5%) and depression (34.9%) were the three most commonly reported caregiver comorbidities overall. The majority of care recipients were aged 70 years or older (85.3%), female (62.8%) and white (93.9%). Dementia due to AD was reported by 72.7% of caregivers. Among caregivers who reported agitation symptoms for care recipients (N=297, 75.2%), resisting care was the most frequently reported symptom (69.4%) followed by pacing, rocking or restlessness (54.9%) and cursing or shouting (45.8%). More than two-thirds of caregivers of individuals with agitation reported that their care recipient received a treatment (either pharmacologic and non-pharmacologic) to manage agitation symptoms, and 40.3% reported no or limited improvements for agitation symptoms due to treatment. Less than half of caregivers were satisfied with treatments for agitation symptoms (44.3%). Among those who were not satisfied, the primary reason for dissatisfaction was a lack of change/worsening of behavioral symptoms (48.1%). Among both caregivers of individuals with and without agitation, the majority (84.6%) had been providing care for 3 or more years. Personal assistance was the most frequently reported type of support caregivers provided to their care recipient (98.7% caregivers of individuals with agitation and 92.9% of those of individuals with no agitation). A higher proportion of caregivers of individuals with agitation reported providing support with activities of daily living (86.5%) in comparison to those without agitation (73.5%). Caregivers of individuals with agitation reported higher mean levels of burden (BSFC-s score: 18.5), than those without agitation (BSFC-s score:14.6). Approximately 70.4% of caregivers of individuals with agitation symptoms reported having severe to very severe burden (BSFC-s greater than or equal to 15) compared to 56.1% of those caring for a patient with no agitation. A higher percentage of caregivers of individuals with agitation symptoms reported making job-related decisions due to caregiving (51.9%) compared to those without agitation (39.8%). Among current caregivers (N=226, 57.2%), higher levels of work productivity impairment were also reported among caregivers of individuals with agitation (35.7%) versus without agitation (24.2%). **Conclusion:** The results of this study indicate that there is a substantial burden experienced by caregivers including negative impacts on their own health outcomes, especially when symptoms of agitation are present. These findings underscore an unmet need for interventions to manage agitation symptoms that preserve quality of life for patients and caregivers alike.

## **Theme 9: EPIDEMIOLOGY AND CLINICAL TRIALS**

**P074: COMPARING ALZHEIMER'S DISEASE (AD) PROGRESSION IN ALZHEIMER'S DISEASE NEUROIMAGING INSTITUTE (ADNI) SUBJECTS WITH MILD COGNITIVE IMPAIRMENT (MCI) TO PROGRESSION OBSERVED IN THE SCARLET ROAD CLINICAL TRIAL.** S. Yiu<sup>1</sup>, F. Model<sup>2</sup>, L. Butler<sup>2</sup>, C. Gower-Page<sup>1</sup>, X. Teitsma<sup>2</sup>, P. Delmar<sup>2</sup> ((1) Roche Products Limited - Welwyn Garden City, United Kingdom; (2) F. Hoffmann-La Roche Ltd - Basel, Switzerland)

**Background:** Alzheimer's Disease Neuroimaging Institute (ADNI) is a longitudinal multicenter study designed to develop clinical, imaging, biologic, and genetic biomarkers that will enable earlier identification and monitoring of people across the Alzheimer's disease (AD) continuum (1). It has been an invaluable resource which has been used extensively, alongside other data sources, to guide the design of a large number of clinical trials. In addition, it is of growing interest to the AD clinical trial research community to better understand whether data collected from observational research cohorts, like ADNI, can be used to contextualize or serve as an external comparator for clinical trial data. Important differences exist between a research cohort and clinical trial populations that could affect these parameters. There is currently limited published literature that formally compare ADNI and clinical trial populations. **Objectives:** We aimed to quantitatively compare disease progression in subjects with MCI from ADNI, with progression in subjects with prodromal AD in the placebo arm of the Phase III Scarlet RoAD (SR; NCT01224106) trial (2). **Methods:** We used subject-level data from 266 amyloid beta-positive subjects with prodromal AD from the SR placebo arm and compared four different approaches of creating an external comparator from 915 ADNI subjects with MCI. These approaches consisted of: 1) complete-case analysis (CCA, i.e. no imputation); 2) mixed-model for repeated measures (MMRM) to impute missing outcome data; 3) CCA with propensity score (PS) weighting using baseline characteristics; and 4) MMRM to impute missing outcome data with PS weighting. The clinical outcomes of interest: change from baseline at year 1 and 2 of follow-up in Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), Alzheimer Disease Assessment Scale-Cognition (ADAS-Cog13) and Mini Mental State Exam (MMSE) scores, were then compared between ADNI and the SR placebo arm. **Results:** The simple filtering approach without the application of PS weighting (i.e., Approaches 1 and 2) resulted in a subset of ADNI subjects that did not resemble the SR placebo arm in terms of baseline characteristic distributions. Consequently, these approaches had the poorest performance in terms of replicating the decline observed in SR for all clinical outcomes. While Approach 3 was able to create a subset of ADNI subjects who had similar baseline characteristic distributions to those in SR, the approach of excluding subjects with missing outcome data led to study subjects who, during follow-up, were not representative of the target population at baseline. Therefore, Approach 3 only offered a slight improvement over Approaches 1 and 2. In contrast Approach 4, which alleviates the limitation of Approach 3 by imputing missing outcomes, provided the best match between the ADNI data and the decline observed in the SR placebo group for all clinical outcomes. **Conclusion:** Our

results demonstrate that the publicly available ADNI data, if used carefully, can adequately represent the disease progression trajectory of subjects with prodromal AD in the SR placebo arm. Further research is needed to confirm whether these results apply to other clinical trials, and other disease stages. While these results are encouraging, there are important differences between research cohort and clinical trial settings (e.g., different baseline characteristic distributions, visit schedules, patterns of attrition, and types and amount of missing data across the studies) that need to be carefully evaluated when considering using a research cohort to inform study design, or to replace or augment a placebo arm. **References:** 1. <http://adni.loni.usc.edu/>. 2. Ostrowitzki et al. *Alzheimers Res Ther.* 2017;9:95.

**LP14: ALZHEIMER'S ASSOCIATION INTERNATIONAL COHORT STUDY OF CHRONIC NEUROPSYCHIATRIC SEQUELAE OF SARS-COV-2 (CNS-SARS-COV-2).**

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The Scientific leaders, including the Alzheimer's Association and representatives from more than 25 countries, are working together with technical guidance from the World Health Organization (WHO) to track the long-term impact of SARS-CoV-2 (also known as novel coronavirus, COVID-19) on the sequelae of psychiatric, behavioural and cognition outcomes. Although little is known about the long-term consequences of SARS-CoV-2 infection, there are several research studies to suggest that COVID-19 is associated with neurological complications. The downstream impact of COVID-19 on the brain is not well understood. There are many unanswered questions regarding the long-term consequences of infection. To coordinate an increased understanding, we established a global consortium to study a longitudinal representative cohort of individuals, to characterize neurological and neuropsychiatric sequelae from direct viral, immune-, vascular- or accelerated neurodegenerative injury to the central nervous system (CNS). Through this network of study teams, we propose to characterize the neurobehavioral phenomenology associated with SARS-CoV-2 in a large, multinational, longitudinal cohort of post Covid-19 infection patients following three sampling strategies: 1. Opportunity sample of patients discharged after hospital admission for Covid-19 related symptoms; 2. A stratified random sample from Covid-19 testing registries (including asymptomatic and negative participants) 3. Ascertaining Covid-19 exposure (based on symptom recall, antigen and antibody test) status in ongoing longitudinal, community-based cohort studies that are already collecting biosamples, cognitive, behavioral and neuroimaging data. In all samples, we will obtain core data within 6 months of discharge or testing. Core characterization will include interviews with the Schedules of Clinical Assessment in Neuropsychiatry (SCAN), neurological exams, emotional reactivity scales and a neurocognitive assessment. When feasible, we will also collect neuroimaging, blood, CSF, saliva biosamples and genetic data. Longitudinal follow up will be conducted at 9 and 18 months of the initial evaluation. A mHealth keeping-in-toch process will be set up

to minimize attrition rates. The population cohorts provide a large, unbiased, normative and validation sample, albeit with more heterogenous outcome ascertainment. They also permit examination of pre- and post-COVID trends in symptoms and biomarkers. The international scope permits examination of interaction with environmental, social, behavioral and health system factors. We will also collect genome-wide genotypes from our cohort individuals to address the role of ancestry and genetic variation on susceptibility to neuropsychiatric sequelae. High rates of mutation in Covid-19 strongly suggest that viral infectivity, including neurotropism, may not be uniform across countries impacted. Our consortium is in a unique position to address the interaction between genetics (including ancestral DNA), and viral strain variation on CNS sequelae of SARS-CoV-2. ALZ CNS SARS-CoV-2 Consortium includes the authors as well as the following teams: Prof. Ignacio Brusco; Dr. Claudia Perandones; Dean Rudy Grether; Hernán Zamponi; Dr. Perminder Sachdev; Prof. Kaarin Anstey; Dr. Reinhold Schmidt; Prof. Guillermo Rivera; Dr. Ricardo Nitrini; Dr. Carmela Tartaglia; Dr. Tomas Paus; Prof. Juan Matias Santos; Dr. Agustín Ibanez; Dr. Andrea Slachevsky; Dr. Cecilia Albala; Dr. Ramiro Javier Zepeda Iriarte; Dr. Catterina Ferrecio; Dr. Pablo Toro; Prof. Huang Yueqin; Prof. Diana Lucia Matallana; Dr. Francisco Lopera Restrepo; Dr. Antonio Caballero; Prof. Ole Mors; Prof. Per Fink; Dr. Daisy Acosta; Prof. Terry Brugha; Prof. Elizabeta Mukaetova; Prof. Golo Kronenberg; Dr. Zoe Morgan; Prof. Nandini Chakraborty; Dr. Paul Edison; Prof. Rachel Jenkins; Dr. Mohammad Zia Katshu; Dr. Akram Hosseini; Prof. Ekkehart Staufenberg; Prof. Carol Brayne; Prof. Mika Kivimaki; Dr. Solomon Teferra Abebe; Dr. Veikko Salomaa; Dr. Archana Singh-Manoux; Dr. Karen Ritchie; Dr. Carole Dufoil; Dr. Isabelle Pellegrin; Dr. Stephani Debette; Dr. Alfredo Ramirez; Dr. Hans Grabe; Dr. Michael Wagner; Dr. Monique Breteler; Prof. Venos Mavreas; Pascal Felix; Dr. Heike Hesse; Dr. Vilmundur Gudnason; Prof. Rajesh Sagar; Prof. Vasantha Padma; Prof. Kameshwar Prasad; Dr. Abdul Majid; Prof. Vijayalakshmi Ravindranath; Dr. Rajesh Raman; Dr. Murali Krishna; Dr. Weinstein Galit; Prof. Charles Newton; Dr. Ana Luisa Sosa-Ortiz; Dr. Fokko Nienhuis; Dr. Sebastian Köhler; Dr. Charlotte Teunissen; Dr. Mohammad Arfan Ikram; Dr. Hieab Adams; Dr. M.I. Mirjam Geerlings; Prof. Rufus Olusola Akinyemi; Dr. Carla Gallo; Dr. Nilton Custodio; Dr. Yuri Cutipe; Dr. Jacqueline Dominguez; Dr. Owais Wadoo; Dr. Ian Deary; Prof. Dan Stein; Dr. Merce Boada; Prof. Ingmar Skoog; Prof. Kaj Blennow; Dr. Krister Hakansson; Kristal Morales Perez; Prof. Sylvia Kaaya; Dr. Dickens Akena; Dr. Sriram Iyengar; Dr. Andrew Murtishaw; Dr. Daniel Chasman; Dr. David Bennett; Dr. Charles DeCarli; Dr. Mary Cushman; Dr. Elizabeth Oelsner; Dr. Jennifer Manly; Dr. Joshua Bis; Dr. W.T. Longstreth, Jr.; Dr. Bruce Psaty; Prof. Lisa Yanek; Dr. Paul Nyquist; Dr. Hugh Henrie; Dr. Sophia Wang; Dr. Hector Gonzales; Dr. Myriam Fornage; Dr. Norrina Allen; Dr. Thomas Mosley; Dr. Mary Hann; Prof. Timothy Hughes; Dr. Emily Levitan; Dr. Virginia Howard; Dr. Sonali Sarkar; Dr. Dallas Anderson; Dr. Mary Ganguli; Dr. Timothy Girard; Dr. Mindy Katz; Dr. Richard Lipton; Dr. Debby W. Tsuang; Dr. Alberto Salmoiraghi; Dr. Paul Mullins; Dr. Giovanni D'Avossa

## Theme 11: NEW THERAPIES AND CLINICAL TRIALS

**P075: IMPACT OF PIMAVANSERIN TREATMENT ON MOTOR FUNCTION IN PATIENTS WITH NEURODEGENERATIVE DISEASE: RESULTS FROM 3 CLINICAL STUDIES.** D. Weintraub<sup>1</sup>, E.P. Foff<sup>2</sup>, C. Ballard<sup>3</sup>, B. Mcevoy<sup>2</sup>, B. Coate<sup>2</sup>, G. Demos<sup>2</sup>, A. Berrio<sup>2</sup>, B. Abbs<sup>2</sup>, J.M. Youakim<sup>2</sup>, S. Stankovic<sup>2</sup> ((1) *Departments Of Psychiatry And Neurology, Perelman School Of Medicine At The University Of Pennsylvania - Philadelphia, USA*; (2) *ACADIA Pharmaceuticals, Inc - Princeton, USA*; (3) *University Of Exeter Medical School, Exeter - Exeter, United Kingdom*)

**Background:** Patients with dementia commonly experience hallucinations and delusions, called dementia-related psychosis (DRP), but no treatments are approved by the Food and Drug Administration for this condition. Commonly-used off-label antipsychotics have substantial safety concerns, including worsening motor function, and extrapyramidal symptoms (EPS), primarily due to brain dopamine receptor antagonism. Pimavanserin is a 5-HT<sub>2A</sub> receptor inverse agonist/antagonist without appreciable dopaminergic activity in vitro and is currently approved to treat hallucinations and delusions associated with Parkinson's disease psychosis (PDP). In clinical studies of patients with PDP, pimavanserin did not show an impact on motor dysfunction. **Objectives:** Evaluate changes in motor function during pimavanserin treatment in patients with neuropsychiatric manifestations of neurodegenerative disease. **Methods:** Motor function was evaluated in 3 independent studies of patients with neuropsychiatric manifestations of neurodegenerative disease (N=626 receiving pimavanserin), including patients with DRP (N=562 receiving pimavanserin). Treatment-emergent adverse events (TEAEs) related to motor function were examined across studies using a Standardized Medical Dictionary for Regulatory Activities Query for Extrapyramidal syndrome. Motor function was directly measured using validated scales. Study 019 (NCT02035553) was a phase 2 study in patients with Alzheimer's disease psychosis randomized to receive pimavanserin 34 mg or placebo for 12 weeks. Motor function was physician assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS III) administered at baseline and each subsequent visit. HARMONY (NCT03325556) was a phase 3 relapse-prevention study in patients with dementia-related psychosis. Enrolled patients received pimavanserin during a 12-week open-label (OL) period. Patients with a sustained psychosis response at weeks 8 and 12 were randomized to receive pimavanserin or placebo in the 26-week double-blind (DB) period. The Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) was used to monitor for EPS at baseline and week 12 of the OL period and at regular intervals throughout the DB period. Change from OL baseline was analyzed using descriptive statistics and change from DB baseline was analyzed using a mixed model repeated measures approach. Study 046 (NCT03575052) is an ongoing randomized, DB, phase 3b study of the safety of pimavanserin 34 mg for up to 8 weeks in patients with neuropsychiatric symptoms (NPS) related to neurodegenerative disease. ESRS-A was assessed at baseline and weeks 1, 2, 4, 6, and 8. Mean change in ESRS-A from baseline to week 8 was estimated using a mixed-effects model repeated measure analysis. Data were available from an interim safety analysis

including 288 patients. **Results:** In study 019, the mean (standard error [SE]) UPDRS III score at baseline was similar for the 74 patients on pimavanserin (12.5 [1.08]) and the 65 patients on placebo (11.8 [1.00]). Mean (SE) change from baseline to week 12 was similar for the pimavanserin (-1.0 [0.96]) and placebo (-0.5 [1.20]) groups. TEAEs related to motor function included dyskinesia, musculoskeletal stiffness (1 placebo [1.1%], 0 pimavanserin, each), tremor (0 placebo, 1 pimavanserin [1.1%]), gait disturbance (0 placebo, 2 pimavanserin [2.2%]), mobility decreased (3 placebo [3.3%], 2 pimavanserin [2.2%]), and restlessness (1 placebo [1.1%], 2 pimavanserin [2.2%]). In the HARMONY OL period, the mean ESRS-A score at baseline was 6.7 (0.60; N=392); the mean (SE) change from baseline to week 12 was minimal (-0.7 [0.17]; n=244) with a trend toward improved (rather than worsened) motor function. Motor TEAEs were infrequent; psychomotor hyperactivity was reported by 3 patients (0.8%), parkinsonism was reported by 2 patients (0.5%), and akathisia, dysphonia, mobility decreased and tremor were reported by 1 patient each (0.3%). During the DB period, there were no changes in mean ESRS-A score in pimavanserin-treated patients or difference over time for pimavanserin vs placebo. For TEAEs, musculoskeletal stiffness and restlessness were reported in 1 patient each (1.0%) in the pimavanserin group and were not reported in the placebo group; akathisia, dyskinesia, dystonia, and tremor were reported in 1 patient (1.0%) each in the placebo group and were not reported in the pimavanserin group. In the study 046 interim analysis, mean (SE) baseline ESRS-A scores were similar for patients randomized to pimavanserin (7.9 [1.01]; n=144) or placebo (6.7 [0.88]; n=144). Least-squares mean change from baseline to week 8 was similar for pimavanserin (-0.3 [0.37]; n=132) and placebo (-0.6 [0.37]; n=130). TEAEs related to motor function included propulsive gait (1 pimavanserin [0.7%], 0 placebo), muscle rigidity (1 pimavanserin [0.7%], 0 placebo), tremor (3 pimavanserin [2.1%], 1 placebo [0.7%]), akathisia (2 pimavanserin [1.4%], 0 placebo), and dyskinesia (1 pimavanserin [0.7%], 0 placebo). **Conclusions:** Mean changes in motor function were minimal in pimavanserin-treated patients and were similar to placebo across three randomized placebo-controlled studies in patients with neuropsychiatric manifestations of neurodegenerative disease. In pimavanserin-treated patients, TEAEs related to motor dysfunction were reported infrequently and at similar rates to placebo. Pimavanserin did not have a negative impact on motor function in this aggregated dataset of frail, vulnerable patients with a range of neurodegenerative diseases.

**P076: A PHASE 2A, OPEN-LABEL MULTICENTER STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF REPEATED INTRATHECAL ADMINISTRATION OF NUROWN® (AUTOLOGOUS MESENCHYMAL STEM CELLS SECRETING NEUROTROPHIC FACTORS) IN PATIENTS WITH PRODROMAL TO MILD ALZHEIMER'S DISEASE.** B. Dubois<sup>1</sup>, R. Kern<sup>2</sup>, S. Ward<sup>2</sup>, S. Lindborg<sup>2</sup>, C. Lebovits<sup>2</sup>, P. Scheltens<sup>3</sup> ((1) *Salpêtrière University Hospital - Paris, France*; (2) *Brainstorm Cell Therapeutics - New York, USA*; (3) *Amsterdam Umc - Amsterdam, Netherlands*)

**Backgrounds:** Alzheimer's disease (AD) is the most common cause of dementia, affecting up to 50 million people worldwide. AD is a progressive neurodegenerative brain disorder that causes gradually increasing neuronal loss and disruption of synaptic function that is essential for cognition and behavior. The main pathological mechanisms of AD are neuroitic

plaques in the brain that contain amyloid beta (A $\beta$ ) protein (an early event) and neurofibrillary tangles within neurons that are composed of phosphorylated tau (p-tau) protein. The accumulation of Alzheimer's specific pathology is accompanied by activation of innate immunity, astrocyte dysfunction and loss of neurotrophic support (NTFs), as well as oxidative stress and mitochondrial dysfunction. Due to the complexity and multifactorial pathophysiology of AD, a multi-target approach that can attenuate, modify or repair neurodegenerative and neuroinflammatory processes is much needed. Brainstorm has developed a proprietary process based on autologous bone marrow-derived Mesenchymal Stem Cells (MSC), which are induced to differentiate into neurotrophic factor (NTF) secreting cells, designated as MSC-NTF cells (NurOwn®). NTFs are potent survival factors for embryonic, neonatal, and adult neurons that have neuroprotective effects against oxidative stress and neurotoxic insults and have demonstrated potential benefits in preclinical AD models. In addition, MSC-NTF cells may modulate aberrant immune activation in AD that is known to be associated with disease progression. Thus, MSC-NTF cell-based therapy offers a promising therapy by simultaneously addressing multiple disease pathways. The safety and efficacy of intrathecal administration of MSC-NTF cells have been evaluated in 3 clinical trials (phases 1/2, 2a and 2) with Amyotrophic Lateral Sclerosis patients (ALS) and in a phase 2 trial in progressive MS. **Objectives:** The Phase 2a, open-label, multicenter study is designed to evaluate the safety and tolerability of three intrathecal injections of NurOwn® cells, administered every two months in patients with prodromal to mild AD. Secondary objectives include cognitive and clinical outcome measures and changes in the levels of Cerebrospinal (CSF) and blood-derived biomarkers, including a focus on neurotrophic factors, neurodegenerative, and inflammatory biomarkers, as well as A $\beta$ 42/40 and phosphorylated tau/total tau. **Methods:** The study will include 40 participants with prodromal to mild AD, as defined by a clinical diagnosis using IWG-2 or NIA-AAA criteria at least 6 months prior to enrollment. Combined with this, patients should have a Mini-Mental State Examination of 20-30, inclusive and Clinical dementia rating-global score of 0.5 or 1.0; and A $\beta$ 42 concentration of <1000 pg/ml and p-tau >19 pg/ml or ratio of p-tau/ A $\beta$  > 0.024 in the CSF. Eligible subjects will undergo a bone marrow aspiration and following a 10-week screening period 3 intrathecally of NurOwn® cells will be administered at 8-week intervals. A 26-week follow-up period to assess safety and clinical disease progression will be conducted. Blood and CSF samples will be collected prior to each intrathecal administration of NurOwn cells and assessed for levels of disease and other relevant biomarkers. Safety will be evaluated by the changes in vital signs and physical examination findings, hematology, blood chemistry, urinalysis, and changes in concomitant medications, as well as deterioration in cognition and Columbia Suicide Severity Rating Scale scores. Adverse events will be reported and monitored. Efficacy assessments will be based cognitive and clinical outcome measures (Clinical Dementia Rating Scaled CDR-SB, Free and Cued Selective Reminding Test, Neuropsychological Test Battery (NTB) and Delis-Kaplan Executive Function System subtests, and A-IADL-Q-SV to measure efficacy and safety, as well as MMSE). Levels of disease and other relevant biomarkers, such as neurotrophic, neurodegenerative and inflammatory factors. In addition, markers associated with amyloid deposition, A $\beta$ 42 and A $\beta$ 40 ratio, p-tau and total tau, will be measured from

the blood and CSF samples. **Results:** Study enrollment is expected to begin in Q4 2020. **Conclusion:** This phase 2 open-label study was designed to provide preliminary clinical and biomarker outcomes to understand the safety and efficacy of repeated intrathecal dosing of autologous MSC-NTF cells in prodromal to mild AD patients, providing data that will support the design of a subsequent Phase 3 trial. Based on the documented mechanisms of action of MSC-NTF cells (NurOwn®) of enhanced delivery of NTF's, neuroprotection and immunomodulation, this study holds promise to introduce a new therapeutic approach that addresses the multiple disease pathways in AD.

#### **P077: THE EPIGENETIC BET PROTEIN INHIBITOR APABETALONE COUNTERS BRAIN ENDOTHELIAL ACTIVATION AND MONOCYTE ADHESION.**

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**Background:** Peripheral inflammation stimulates brain microvascular endothelial cells to secrete apical cytokines that promote monocyte recruitment and transmigration across the blood brain barrier (BBB), while basolateral cytokine secretion causes pro-inflammatory activation of brain-resident cells. This increased immune cell activity in the brain can initiate or exacerbate neuroinflammation, impairing the integrity of the BBB. With aging, tissue nonspecific alkaline phosphatase (TNAP; gene symbol ALPL) abundance increases in the cerebrovasculature, reducing transcytosis of plasma proteins across the BBB. Bromodomain and extraterminal domain (BET) proteins are histone and transcription factor acetylation readers that activate cytokine-dependent transcription in monocytes and endothelial cells in chronic vascular inflammation models. Targeting BETs with epigenetic therapies may reduce monocyte and brain endothelial activation during neuroinflammation, and reduce TNAP associated decreases in plasma protein transcytosis during aging. **Objectives:** To investigate the impact of apabetalone, a clinical stage BET inhibitor, on inflammatory activation of human brain microvascular endothelial cells and monocytes. To assess apabetalone regulation of brain microvascular endothelial cell ALPL transcription. **Methods:** Brain microvascular endothelial hCMEC/D3 monolayers, a simple BBB model, were grown on plastic or suspended inserts. Unstimulated monolayers (treated with solvent alone [DMSO]) or monolayers receiving inflammatory stimuli (TNF $\alpha$ +IFN $\gamma$ ) were co-treated with apabetalone, the BET protein degrading compound MZ-1 or DMSO for 4-24h. Cytokine abundance in the apical and basolateral supernatant was measured via multiplex ELISAs. Surface cell adhesion protein abundance was assessed by FACS on similarly treated primary human brain microvascular endothelial cells (HBMVECs) and unstimulated THP-1 monocytes treated with apabetalone. Gene expression was measured by real time PCR. THP-1 adhesion to HBMVECs was measured in laminar flow conditions. **Results:** hCMEC/D3 cells grown on suspended filters displayed polarized cytokine secretion and low dextran permeability, an indication of monolayer impermeability. During TNF $\alpha$ +IFN $\gamma$  stimulation of hCMEC/D3 cells, apabetalone treatment bilaterally reduced protein secretion of key proinflammatory cytokines and chemokines, including MCP-3, CX3CL1, GM-CSF, MCP-1, IL-6,



IL-8, IP-10 and RANTES (-40% to -90%). Transcription of these genes was BET-dependent, as BRD2, BRD3 and BRD4 inhibition with apabetalone or knockdown with MZ-1 prevented their expression. In TNF $\alpha$ +IFN $\gamma$  stimulated HBMVECs, apabetalone reduced the surface abundance of VCAM-1 (-80%) and E-selectin (-50%), cell adhesion proteins that are involved in monocyte capture and firm adhesion. Consequently, apabetalone treatment of cytokine activated HBMVECs countered THP-1 adhesion in laminar flow assays. Unstimulated THP-1 monocytes treated with apabetalone also had lower surface abundance of the MCP-3 and RANTES receptor CCR1, the MCP-1 receptor CCR2 and the CX3CL1 receptor CX3CR1, which is expected to lower interactions between monocytes and endothelial cells. Apabetalone treatment of HBMVECs decreased ALPL gene expression in a dose dependent manner by up to 70%. **Conclusions:** Apabetalone decreases endothelial chemokine secretion, monocyte chemokine receptor expression and endothelium-monocyte adhesion in a BBB model. These effects may reduce immune cell transmigration into the brain during neurovascular inflammation and neurodegeneration. Apabetalone also decreases the expression of ALPL by brain endothelial cells, potentially restoring physiological plasma protein transcytosis known to decline with aging. The findings provide mechanistic insights to the beneficial effects of apabetalone on cognition that were recently demonstrated in a phase 3 clinical trial (BETonMACE): diabetic coronary artery disease patients with a baseline MoCA scores <22 experienced a significant 1.8 unit improvement in MoCA scores following apabetalone treatment versus placebo (p=0.02).

**P078: ACD856, A NOVEL COGNITIVE ENHANCER TARGETING NEUROTROPHIN SIGNALING FOR THE TREATMENT OF ALZHEIMER'S DISEASE.** P. Forsell<sup>1</sup>, G. Nordvall<sup>1</sup>, M. Halldin<sup>1</sup>, M. Dahlström<sup>1</sup>, N. Madjid<sup>1</sup>, M. Rother<sup>1</sup>, A. Van Es Johansson<sup>1</sup>, J. Lundkvist<sup>1</sup>, M. Eriksdotter<sup>2,3</sup>, M. Jönsson<sup>1</sup>, B. Winblad<sup>2,3</sup>, J. Sandin<sup>1</sup> ((1) Alzecure Pharma Ab - Huddinge, Sweden; (2) Dept Of Neurobiology, Care Sciences And Society, Karolinska Institutet - Stockholm, Sweden; (3) Dept Geriatric Medicine, Karolinska University Hospital - Huddinge, Sweden)

**Background:** Neurotrophins are growth factors involved in key mechanisms for memory formation such as hippocampal long-term potentiation, and also in the development and survival of neurons. The neurotrophins, including nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and neurotrophin (NT) 3 and NT-4/5, bind to the tropomyosin-related kinase (Trk) family of receptor tyrosine kinases (TrkA, TrkB and TrkC). Neurotrophic signaling, and in particular BDNF signaling, plays a pivotal role in hippocampal neurogenesis, synaptogenesis and synaptic plasticity. Several studies have shown a decrease in BDNF in the hippocampus and in CSF in disease states with cognitive decline, including Alzheimer's disease (AD). This suggests that decreased BDNF signalling may contribute to the progression of hippocampal dysfunction. Clinical studies have shown that a polymorphism in the BDNF gene, Val66Met, which leads to a reduction of BDNF signaling, affects the anatomy of hippocampus and prefrontal cortex in normal individuals. It also moderates episodic memory, hippocampal function and hippocampal volume in patients with either sporadic or familial AD. Moreover, a large body of pathological and mechanistic evidence also suggests that loss of NGF signaling

contributes significantly to the dysfunction of basal forebrain cholinergic neurons during the course of AD. Impairments in formation and retrieval of episodic memory observed in AD patients have been reported to be partly due to this cholinergic dysfunction. Thus, existing data strongly support and validate the development of stimulators of neurotrophin signaling as novel and promising therapeutic strategies for AD. ACD856 is a novel in vivo active positive modulator of neurotrophin signaling developed by AlzeCure Pharma and has demonstrated clear effects on the neurotrophin system in different in vitro and in vivo models. Considering the role of neurotrophins it may also have an additional upside to achieve disease-modifying effects in neurodegenerative disorders like AD. **Objective:** Based on the extensive amount of supporting data for the role of neurotrophins in synaptic plasticity and cognitive function, the objective of this project is to develop ACD856, a positive modulator of neurotrophin signaling, as a novel symptomatic therapy for cognitive disorders such as AD. **Methods:** Through a high throughput screen and an extensive lead optimization effort, AlzeCure Pharma have identified several chemical series as positive modulators of NGF/TrkA- and BDNF/TrkB-signaling. Representative compounds in each series were characterized in recombinant cell-based assays, biochemical assays, native systems and functional assays e.g. ERK phosphorylation in primary cortical neurons. Based on these results, ACD856 was selected for further investigation in different in vivo models, i.e. scopolamine, MK-801 or age induced memory impairment in contextual fear conditioning. Subsequently, ACD856 was tested in non-clinical regulatory safety studies before proceeding to clinical stage. A clinical microdose study was recently conducted with ACD856 in healthy volunteers with the primary aim to assess the pharmacokinetic properties of the compound in man. **Results:** ACD856 was discovered as a potent enhancer of NGF and BDNF signaling through positive modulation of the signaling of TrkA and TrkB receptors in recombinant cell lines. The modulatory effect of ACD856 was confirmed in in vitro experiments showing that the compound was able to increase phosphorylation of ERK1/2 in mouse primary cortical neurons stimulated with low concentrations of BDNF. ACD856 has been tested in vivo and shown consistent effects in preclinical models of learning and memory, including reversing scopolamine or MK-801 induced memory impairment. Interestingly, ACD856 also showed additive effects to that of an acetylcholine esterase inhibitor. Moreover, in a model of age-induced impairment in 18-month-old mice, ACD856 was able to fully reverse the cognitive impairment in long-term associative memory. The candidate compound also induced an increase of the levels of 5-HT, noradrenalin and dopamine in the hippocampus, a key area involved in cognitive function and which is affected early on in Alzheimer's disease. Results from the non-clinical safety studies conducted support further development of ACD856 for the treatment of AD. The first clinical study with ACD856, which was focused on assessing the pharmacokinetic properties of the compound in man showed a suitable pharmacokinetic profile for further clinical development. **Conclusion:** ACD856 is a potent enhancer of NGF and BDNF signaling, systems involved in synaptic plasticity and cognitive function. The consistent positive preclinical effects of ACD856 on cognition, the observation that it acts in an additive manner to physostigmine, the effects exerted on neurotransmitters in the hippocampus, as well as the scientific evidence supporting a key role of neurotrophins in synaptic plasticity and cognitive

function, indicate a broad applicability of ACD856 for cognitive disorders. Further development is supported by the recently conducted clinical microdose study and preparations are currently ongoing to initiate further clinical trials, with a planned start by the end of 2020.

**P079: THERAPEUTIC EFFICACY OF A SMALL MOLECULE INHIBITOR TARGETING TAU SELF-ASSOCIATION IN MOUSE MODELS OF TAUOPATHY.** J. Moe<sup>1</sup>, P. Lopez<sup>1</sup>, H. Jimenez-Bravar<sup>2</sup>, L. Adrien<sup>2</sup>, J. Eun<sup>2</sup>, A. Wolin<sup>2</sup>, J. Koppel<sup>2</sup>, P. Davies<sup>2</sup>, E. Davidowitz<sup>1</sup> ((1) *Oligomerix, Inc. - White Plains, USA*; (2) *The Litwin-Zucker Research Center For The Study Of Alzheimer's Disease, The Feinstein Institute For Medical Research, Northwell Health - Manhasset, USA*)

**Background:** The premise of this program is that tau oligomers are the acutely toxic species of tau and that their reduction will modify the course of AD. We have shown that tau oligomers cause disruption of neuronal signaling and inhibit the formation of memory in mice (Fá et al., *Sci Rep.* 2016 Jan 20;6:19393), and that certain forms of tau oligomers are toxic when applied to cultured neurons (Tian et al., *Int J Cell Biol.* 2013;2013:260787). The discovery of small molecule inhibitors was performed with assays targeting tau self-association, the initial step in the tau aggregation cascade. This program is highly differentiated in that it targets full-length, non-mutated tau, whereas other tau aggregation inhibitor programs have largely focused on inhibiting formation and or dissociating large and relatively inert fibrils which could generate toxic tau oligomers. Preventive efficacy studies were performed in htau (Davidowitz et al., *J Alzheimers Dis.* 2020, 73:147-161) and JNPL3 mice that demonstrated that the lead compound reduced self-association of soluble tau and inhibited formation of insoluble tau aggregates. **Objectives:** The overall goal of this program is to discover and develop small molecule therapeutics targeting tau self-association for the treatment of AD and ADRD. Here, we present studies conducted to determine the therapeutic efficacy of the lead compound in the htau and JNPL3 mouse models of tauopathy. Measurements of therapeutic efficacy include reduction of insoluble and hyperphosphorylated tau that has already accumulated and inhibition of the continued progression of tau pathology, as well as amelioration of behavioral deficits. **Methods:** Therapeutic studies were independently performed in male htau and female JNPL3 transgenic mice. Mice were aged to 7 months (baseline) and treated for 4 months. Each study had 4 groups including baseline (n=20), vehicle (n=25), and two treatment groups (n=25, each) that were administered 40 or 80 mg/kg dose of lead compound formulated in feed. The htau baseline group was tested for working memory performance with the Barnes maze and the JNPL3 baseline group had open field behavior and Rotarod performance testing prior to sacrifice at 7 months; the vehicle and treatment groups had behavioral testing performed at 7 and 12 months. Samples of brain were taken for biochemical analysis of levels of tau and phosphorylated tau, as well as levels and phosphorylation of insoluble, aggregated tau. Immunocytochemical examination was performed with 4 tau antibodies (MC1, PHF1, CP13 and RZ3), as well as with Iba1 and GFAP for microgliosis and astrogliosis, respectively, as time permitted under restricted access related to the pandemic. **Results:** The behavioral studies were completed; biochemical analyses of specimens are in progress and results will be presented. **Conclusion:** The results of the therapeutic studies

build upon the successful preventive efficacy studies that were previously presented and will help in the design of Phase 1b clinical studies.

**P080: DEVELOPMENT OF A DUAL AB-TAU VACCINE FOR THE PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE.** R. Barbour, F. Bard, A. Elmaarouf, H. Prill, K. Thomas, G. Kinney, W. Zago (*Prothena Biosciences Inc - South San Francisco, USA*)

**Background:** Alzheimer's disease (AD) is characterized by two main pathological hallmarks, amyloid beta (A $\beta$ ) plaques and neurofibrillary tangles composed of tau proteins. Multiple therapeutics targeting A $\beta$  are being developed and one such molecule currently under FDA review, aducanumab, showed signs of slowing of disease progression in late-stage clinical development. Additionally, several therapeutics targeting various tau epitopes that aim to inhibit the cell-to-cell transmission and spread of pathological tau are in earlier stages of clinical development. A small number of vaccines (active immunization) targeting either A $\beta$  or tau are also being evaluated. The vast majority of vaccines and passive therapies target only one of the pathological AD features; however, there is strong evidence from preclinical models that A $\beta$  and tau may act synergistically in the development of disease. Therefore, a vaccine concomitantly targeting A $\beta$  and tau may lead to a more efficacious therapeutic for the prevention and treatment of AD. **Objectives:** To develop a single-agent, dual-immunogen vaccine (active immunization) that targets both A $\beta$  and tau, and investigate its ability to induce an optimal immune response to both targets in guinea pigs, and to characterize the quality of the resultant antibody response in functional assays. **Methods:** A variety of immunogens were developed by combining in a single linear immunogen, amino acid sequences of A $\beta$  and tau, and cleavage sites for optimal dendritic cell presentation. A $\beta$  and tau epitopes were selected based on the ability to raise antibodies with potential to clear A $\beta$  plaques, neutralize A $\beta$  oligomer activity, and block tau transmission, but unable to induce cytotoxic and potentially harmful T-cell responses. Guinea pigs were immunized with immunogens and adjuvant QS21 intramuscularly. Test bleeds were taken 1 week after each injection. Guinea pig serum titer levels were determined against soluble and fibrillar A $\beta$  and full-length tau. Sections of fresh frozen human AD or control brain sections were stained with sera from immunized and control animals. The effect of sera on soluble Ab oligomer binding in primary rat hippocampal neurons was also assessed. Studies evaluating the potential for sera to inhibit oligomeric tau binding to neurons are ongoing. **Results:** A subset of vaccine constructs provided balanced immunogenic responses against both A $\beta$  and tau proteins and for those, we subsequently demonstrated the presence of antibodies able to avidly bind to pathological A $\beta$  plaques and tau tangles in Alzheimer's brain sections at concentrations expected to cross the blood-brain barrier in humans. Similarly, immunized guinea pig serum inhibited the binding of soluble, oligomeric A $\beta$  to rat hippocampal neurons in a concentration dependent manner. **Conclusion:** We developed dual-epitope vaccine constructs able to concomitantly raise optimal and balanced titers to A $\beta$  and tau in guinea pigs. The antibodies generated by the immunizations were immunoreactive with both plaques and neurofibrillary tangles in Alzheimer's brains and blocked the binding of A $\beta$  oligomers to neurons. These results support the development of a single-agent, dual-

immunogen vaccine with the ability to target the pathogenic forms of both A $\beta$  and tau. This approach may result in a more convenient and accessible alternative to antibody infusion therapies for the potential prevention and treatment of AD.

**P081: NOVEL AMYLOID BETA MONOCLONAL ANTIBODIES WITH SUPERIOR BINDING PROPERTIES: POTENTIAL FOR MORE CONVENIENT DOSING AND GREATER PATIENT ACCESS IN ALZHEIMER'S DISEASE.** M. Skov, R. Barbour, P. Dolan, A. Elmaarouf, E. Goldbach, M. Holden, L. Li, T. Nijjar, H. Prill, J. Salmans, K. Thomas, S. Tam, C. Tourino, F. Bard, G. Kinney, W. Zago (*Prothena Biosciences Inc - South San Francisco, USA*)

**Background:** Monoclonal antibodies (mAbs) targeting the N-terminus of amyloid beta (A $\beta$ ) have been demonstrated clinically to reduce amyloid plaque burden and one such antibody currently under FDA review, aducanumab, showed that significant reduction in plaque burden was associated with slowing of cognitive decline in Alzheimer's disease (AD). Preclinical studies have also indicated that N-terminal mAbs elicit an antibody-dependent microglial-mediated A $\beta$ -plaque clearance and neutralization of soluble toxic A $\beta$  oligomers both in vitro and in vivo. It is hypothesized that administration of N-terminal A $\beta$  targeting mAbs slows disease progression via clearance of Ab plaques and neutralization of soluble Ab aggregates in patients with AD. **Objectives:** Several novel humanized N-terminal targeting A $\beta$  (Prothena antibodies, PRO) mAbs were generated with greater binding strength (affinity and avidity) for pathologic fibrillar A $\beta$  than has been reported with current experimental therapies, and with high affinity for soluble toxic forms. These PRO mAbs could enable lower and more convenient dosing strategies, which will enhance patient access. **Methods:** Antibody binding profiles to aggregated or fibrillar A $\beta$  were characterized by ELISA, surface plasmon resonance (SPR) and immunohistochemistry (IHC). The ability of these mAbs to induce phagocytic plaque clearance was quantified in an ex vivo assay using APP/PS1 transgenic (Tg) mouse brain sections with exogenous primary mouse microglia by immunoassay. Neutralization of A $\beta$  oligomer neuronal binding was assessed in rat primary hippocampal cultures. **Results:** Relative to other N-terminal A $\beta$  antibody therapies, PRO mAbs exhibited greater apparent affinity for aggregated or fibrillar A $\beta$  in competition or standard binding ELISAs. The enhanced avidity of PRO mAbs for fibrillar A $\beta$  was confirmed by SPR equilibrium binding kinetics, indicating up to 10-fold higher avidity than aducanumab due to slower off-rate kinetics of PRO mAbs. IHC dose response assessments with PRO mAbs on frozen human AD brain sections showed greater apparent affinity and plaque area binding than aducanumab, regardless of the individual AD donor tissue tested. In an ex vivo activity assay, PRO mAbs were shown to significantly facilitate A $\beta$  reduction by microglial phagocytosis in APP/PS1 mouse tissue and to block soluble A $\beta$  oligomer binding to rat primary neurons in a concentration-dependent manner. **Conclusions:** It is anticipated that enhanced A $\beta$  binding properties of PRO mAbs will enable evaluation of lower and more convenient dosing strategies in the clinic. These characteristics could lead to improved patient access, improved efficacy and/or a potential reduction in ARIA.

**P082: GAMMA-SECRETASE MODULATORS SHOW SELECTIVITY FOR GAMMA-SECRETASE-MEDIATED AMYLOID PRECURSOR PROTEIN INTRAMEMBRANE PROCESSING.** J. Lundkvist<sup>1,2</sup>, T. Weber<sup>2,3</sup>, J. Wanngren<sup>2</sup>, H. Kvarnberg<sup>4,5</sup>, P. Larssen<sup>2,6</sup>, D. Wu<sup>2,7</sup>, D. Oliveira<sup>2</sup>, J. Sandin<sup>1,2</sup>, H. Zetterberg<sup>4,5,8</sup>, K. Blennow<sup>4,5</sup>, G. Nordval<sup>11,2</sup>, B. Winblad<sup>2</sup>, E. Portelius<sup>4,5</sup>, H. Karlström<sup>2</sup> ((1) *Alzecure Pharma - Stockholm, Sweden*; (2) *Department Of Neurobiology, Care And Society, Karolinska Institutet - Solna, Sweden*; (3) *Aesculap Ag - Tuttlingen, Germany*; (4) *Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At The University Of Gothenburg - Gothenburg, Sweden*; (5) *Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal, Sweden*; (6) *Mabtech AB - Stockholm, Sweden*; (7) *Department of Obstetrics and Gynecology, First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu - Nanjing, China*; (8) *Department of Neurodegenerative Disease, UCL Institute of Neurology - London, United Kingdom*)

**Background:** The process of A $\beta$  amyloidosis plays a pivotal role in the onset of Alzheimer's disease (AD) and starts decades prior to symptomatic disease. Data generated in clinical trials during the last decade indicate that it is conceivable that an A $\beta$ -targeting drug would be most beneficial as a chronic therapy initiated during the presymptomatic or preclinical phase, i.e., at the earliest stages of A $\beta$  amyloidosis. A $\beta$  is a family of postproteolytic peptides, varying from 30 to 43 amino acids in length, and is generated as the result of  $\gamma$ -secretase-mediated intramembrane proteolysis of the amyloid precursor protein, APP. A $\beta$ 42 is particularly prone to aggregate and is also the primary A $\beta$  component of amyloid plaques, whereas shorter A $\beta$  peptides are less amyloidogenic and have also been suggested to inhibit A $\beta$ 42 amyloidosis.  $\gamma$ -Secretase modulators (GSMs) represent a promising class of A $\beta$ 42-lowering anti-amyloidogenic compounds for the treatment of AD. GSMs exhibit several key features that make them suitable for the treatment of preclinical Alzheimer: 1) they target amyloidogenic A $\beta$ 42 production while stimulating the formation of A $\beta$ 37 and 38, and 2) they modulate but do not affect total  $\gamma$ -secretase activity, a property that is of central importance from a safety perspective. As such, GSMs modulate the formation of secreted A $\beta$ , while sparing the  $\gamma$ -secretase-mediated processing event resulting in the release of the cytoplasmic APP intracellular domain. **Objectives:** In this study we have asked whether GSMs affect the intramembrane processing of E-cadherin, EphA4 and EphB2; three reported  $\gamma$ -secretase substrates which are implicated in important contexts of cell signaling. **Methods:** Expression constructs encoding N-terminally truncated EphA4, EphB2 and E-cadherin were expressed in murine blastocyst-derived cells lacking presenilin expression (BD8 cells) and in HEK293 cells. Intracellular domain (ICD) formation and secretion of A $\beta$ -like peptides were analyzed with a reporter gene assay, western blot analysis and by a combined immunoprecipitation/mass spectrometric analysis, respectively. The  $\gamma$ -secretase dependency of the different reactions studied was assessed by rescuing presenilin expression in the blastocyst derived cells and by treating the transfectants with the  $\gamma$ -secretase inhibitor L685,458. Three structurally distinct GSMs were used to explore the impact of GSMs on the intramembrane processing of EphA4, EphB2 and E-cadherin. **Results:** We demonstrate that the  $\gamma$ -secretase-dependent generation of EphA4 and EphB2 ICDs are unaffected by GSMs. We also find that  $\gamma$ -secretase processing of EphA4 and EphB2 results in the

release of several but different number and lengths of A $\beta$ -like peptides, but that only the production of A $\beta$ -like proteins from EphA4 is modulated by GSMs, albeit with an order of magnitude lower potency as compared to A $\beta$  modulation. Unexpectedly, neither the ICD formation nor the secretion of A $\beta$ -like peptides derived from E-cadherin were dependent on  $\gamma$ -secretase activity. In addition, GSM treatment did not have any effect on the processing of E-cadherin. **Conclusion:** In summary, we have characterized the intramembrane proteolysis of EphA4, EphB2 and E-cadherin. Our studies show that  $\gamma$ -secretase-mediated intramembrane processing results in the production of multiple secreted A $\beta$ -like peptides from EphA4 and EphB2. We also demonstrate that GSMs developed for targeting APP processing and A $\beta$  production show a strong selectivity for A $\beta$  modulation, and do not affect  $\gamma$ -secretase-dependent ICD formation in general and the production of A $\beta$ -like peptides from EphA4, EphB2 and E-cadherin to a lesser extent. Collectively these results suggest that GSMs are selective for  $\gamma$ -secretase-mediated A $\beta$  production and strongly support the further development of GSMs as a tolerable, chronic A $\beta$ -targeting therapy in early AD.

**P083: PREDICTING RESPONSE TO VIRTUAL REALITY THERAPY FOR TREATMENT OF BPSD IN ACUTE-CARE SETTINGS.** L. Appel<sup>1</sup>, B. Chen<sup>2</sup>, E. Kisonas<sup>3</sup>, E. Appel<sup>3</sup>, J. Rosenberg<sup>3</sup>, C. Smith<sup>3</sup> ((1) *York University - Toronto, Canada*; (2) *University Of Toronto - Toronto (Canada)*, 3Uhn - Toronto, Canada)

**Background:** As the Canadian population ages, the prevalence of dementia is expected to increase with approximately 76,000 new cases being diagnosed annually, and upwards of half of these patients will experience behavioural or psychiatric symptoms (BPSD) during the course of their illness. Currently, recommended first-line interventions for BPSD are non-pharmacologic and often require trained personnel and structured environments to administer, resulting in difficult implementation and a significant cost burden. While these measures are slowly being more broadly adopted in long-term care facilities, in acute hospital stays, BPSD are largely managed through medications such as antipsychotics. These drugs often come with unwanted side effects such as sedation, and may increase the frequency of adverse events such as delirium or falls and even death. Despite multiple guidelines recommending against the routine use of these drugs for treating BPSD, their use remains common and is often governed by individual practitioner experience or institutional practices. In the past decade, virtual reality (VR) emerged as a promising therapy for patients with dementia. Immersive VR uses a head-mounted device (HMD) to deliver three-dimensional visuals and sounds to simulate a real-world environment. VR offers unique advantages compared to other non-pharmacologic therapies for dementia because it requires minimal personnel to administer, is easily portable, and can be personalized to the patient's preferences. A pilot study performed by our group demonstrated that the use of VR for dementia patients on acute care hospital wards is both feasible and effective. Because of the symptomatic and etiologic heterogeneity of dementia, predicting response is clinically relevant, but has been unsurprisingly challenging. In this study we explore the possibility that patient's response to VR therapy can be predicted based on baseline patient characteristics. **Objective:** To quantify response to VR therapy in dementia patients and

identify patient characteristics that predict response to VR therapy. **Methods:** As part of an ongoing randomized clinical trial examining the efficacy of VR as a treatment for BPSD, demographic data for patients (N=24) aged 65 and over with a prior diagnosis of dementia that were admitted for an acute hospital stay were obtained through a short questionnaire. This questionnaire could be completed alone by the patient independently or with the assistance of a family member and included parameters such as the patient's living situation, functional status and relationship status, and was supplemented with data collected from the patient's EMR. Every 24-72 hours, a series of short VR nature scenes, up to 20 minutes in length, was administered to patients through a Samsung Oculus Go HMD. During the session, any patient vocalizations and gestures were transcribed, and patients were given a subjective rating on their engagement with the VR experience. Following the session, patients completed a semi-structured interview with a research coordinator detailing their experience. Patient demographics were compared to their VR response. **Results:** Patients living with others were more likely (P=0.037) to accept participating in VR session compared to those living alone. For patients that engaged in one or more VR sessions, those with normal neck mobility were statically more likely (P=0.043) to report willingness to participate in future VR sessions compared to those with limited neck mobility. These patients were also significantly more likely (P=0.033) to report feeling relaxed during VR therapy. No patient demographic information predicted patient's perception of enjoyment or relaxation when engaging with VR. Dementia severity did not significantly correlate to patients' willingness to participate, perception of fun or relaxation, or willingness to engage in future sessions. **Conclusions:** Patients that live with others may be more adventurous or socially conditioned to engage with VR therapy. Additionally, family members or close friends may encourage patients to engage with VR and can be an important motivator for patients. Those with limited neck mobility were likely unable to derive the full benefit of the VR device, given that they are not able to fully manipulate the headset in 3-dimensional space. This was reflected in their poor experience of relaxation, and unwillingness to use the device in future sessions. This suggests that patients with limited neck mobility may need accommodations to maximize benefit from VR therapy. Lastly, dementia severity did not affect patient experience with VR, an encouraging finding that suggests that even patients with severe dementia should still be candidates for VR therapy. Since the study is ongoing, and the data in this study is preliminary, more parameters may become statistically significant as sample size increases.

**P084: ADMINISTERING VIRTUAL REALITY THERAPY TO MANAGE BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS IN PATIENTS WITH DEMENTIA ADMITTED TO AN ACUTE-CARE HOSPITAL: RESULTS OF A PILOT STUDY.** L. Appel<sup>1</sup>, E. Kisonas<sup>2</sup>, E. Appe<sup>2</sup>, D. Bartlett<sup>3</sup>, J. Klein<sup>1</sup>, J. Rosenberg<sup>4</sup>, C. Smith<sup>4</sup> ((1) *York University - Toronto, Canada*; (2) *Uhn - Toronto, Canada*; (3) *York U - Toronto, Canada*; (4) *Mgh - Toronto, Canada*)

**Background:** Behavioural and Psychological Symptoms of Dementia (BPSD) are complex, costly and lead to poor health outcomes. For patients admitted to an acute-care inpatient unit the prevalence of having associated BPSD is up to 75%, with aggression and activity disturbance being the most

common. Family caregivers have given rich reports about how BPSD may worsen during the acute-care hospital stay. The magnitude of BPSD impact on hospital staff is evident from the number of physical assaults against care aides. Such workplace violence is a widespread problem that many health systems have struggled to manage and the need for supports in the community are ever increasing. Among current interventions to manage BPSD are pharmacological interventions (neuroleptic /sedating medications) and application of physical barriers and restraints (alarms, locks, Buxton chairs, tethers), both of which associated with harmful consequences. As VR technology become increasingly accessible and affordable, it provides a unique opportunity to expose individuals who are otherwise confined indoors (e.g. in hospitals) to a variety of simulated natural and social environments that can be both calming and engaging (e.g. peaceful beach, sunny autumn forest, live music at a restaurant). This novel therapy has been tested with various clinical populations including frail older adults, and researchers and clinicians are now eager to explore its potential to manage BPSD. The hope is that this may prove to be a less expensive, more ethically acceptable means of engaging and distracting individuals with dementia, without the negative side effects associated with current approaches (e.g. medication, physical restraints). To date, no evaluations of immersive VR-therapy have been reported for patients with dementia in acute-care hospitals. **Objectives:** Determine the feasibility (acceptance, comfort, safety) of using immersive VR-therapy for people living with dementia (mild, moderate, or advanced) during acute-care hospitalization, and explore its potential to manage BPSD. **Methods:** A prospective longitudinal pilot-study was conducted at a community teaching hospital in Toronto. Ten patients (8 female) over 65 years (average age 86.5), with dementia ranging from mild (2), moderate (1) and advanced (4), (3 were unspecified) participated in the study. The VR therapy intervention consisted of participants viewing a sequence of five short 360° video clips (one to three minutes each) depicting various nature scenes (rocky lakeshore, sunny forest, dense forest, floating icebergs, and sunny beach) displayed on Samsung Gear-VR head-mounted-display for a maximum of twenty minutes. The mixed-methods study included chart review, standardized observations during intervention, and pre- and post-intervention semi-structured interviews about the VR experience. **Results:** Presentation of BPSD during hospitalization varied greatly, with participants displaying differing frequencies of agitation, refusal of medical care, wandering, vocalizations, having symptoms of insomnia, and requiring additional falls precautions applied by staff. Twenty percent of participants displayed violent behaviour, and 30% required a sitter/Patient Care Assistant/Personal Support Worker at the bedside for monitoring purposes. Participants also had chemical restraints (40%) or physical restraints (30%) administered during their hospital stay. All recruited participants completed the study; a total of 18 VR-sessions were conducted with an average exposure of 6 minutes per viewing. The majority (7) of participants reported that they found the headset comfortable, and one found the VR headset too heavy; they also mentioned that they would like to own VR at home if a lighter model was available. No participants reported feeling pressure on their nose from the HMD. Of the 10 participants, one experienced negative side effects of self-limiting dizziness with mild nausea from the VR session. There was no report of interference between the VR equipment and medical devices worn by participants (such as hearing aids). During the majority

of sessions (78%), participants made conversation/vocalizations, and while many simply described what they were seeing, one expressed interest and desire to engage with their (virtual) surroundings. In over half of the VR-therapy sessions (56%), the researcher noted the expression of enjoyment by the participant during the VR experience, deduced from the participant's active looking around and movements that suggested they were interacting with their environment (e.g. reaching out with hands or legs, pointing, waving, and wiggling toes), as well as from laughter and verbal feedback. In almost two thirds of the sessions (61%) the researcher remarked participant relaxation from VR, perceived through deep, slow and steady breathing, relaxed grip of the caregiver's hand, and caregivers noting that the participant looks relaxed or "calmer than usual". The majority of participants (7) opted for additional VR-therapy sessions during their hospital stay. **Conclusion:** The results of this study show that it is feasible and safe to expose older adults with various degrees of dementia, admitted to an acute-care hospital, to immersive VR-therapy. Patients tolerated the VR equipment and content very well, with rare side effects. These findings support conducting a large-scale RCT to investigate immersive VR therapy as a non-pharmacological intervention to manage BPSD in acute-care hospitals.

**P085: INTRODUCING VIRTUAL REALITY THERAPY FOR INPATIENTS WITH DEMENTIA ADMITTED TO AN ACUTE-CARE HOSPITAL: LEARNINGS FROM A PILOT TO PAVE THE WAY TO A RANDOMIZED CONTROLLED TRIAL.** L. Appel<sup>1</sup>, E. Kisonas<sup>2</sup>, E. Appel<sup>2</sup>, J. Klein<sup>3</sup>, D. Bartlett<sup>3</sup>, J. Rosenberg<sup>4</sup>, C. Smith<sup>4</sup> ((1) York University - Toronto, Canada; (2) Uhn - Toronto, Canada; (3) York U - Toronto, Canada; (4) Mgh - Toronto, Canada)

**Background:** As Virtual Reality (VR) technology becomes increasingly accessible and affordable there is growing interest among clinicians to evaluate VR-therapy to manage Behavioural and Psychological Symptoms of Dementia (BPSD) in hospitalized patients, as an alternative to administering antipsychotics/sedatives or using physical restraints, both of which are associated with negative side-effects. Given the growing interest in therapeutic VR, there is a consensus among leaders in the field that standardized evaluation methodology and implementation guidelines are sorely needed. A recent article, published by the Virtual Reality Committee of Outcomes Research Experts (VR-CORE) international working group, recommends that VR trials in health care follow a 3-phase framework similar to the Food and Drug Administration phased pharmacotherapy model: VR1 studies focus on content development by working with end-users and applying principles of human-centered design; VR2 trials conduct early testing with a focus on feasibility, acceptability, tolerability, and initial clinical efficacy; and VR3 trials are RCTs that evaluate clinically important outcomes versus a control condition. While the VR-CORE group brings the theoretical framework to conceptualize VR studies, gaps remain in the provisioning of detailed guidelines to aid with designing and conducting these studies. Our study aims to fill some gaps by documenting the process, identifying challenges and making recommendations for conducting VR studies with people with dementia admitted to acute care hospitals. **Objectives:** Validate and refine the proposed research protocol for a randomized controlled trial (RCT) that evaluates the impact of VR-therapy on managing BPSD and improving quality

of life in acute-care hospitals. Gather and document details, and make recommendations on the processes of introducing VR-therapy as a non-pharmacological intervention in acute-care hospitals. **Methods:** Ten patients 65 years or older (mean = 87) previously diagnosed with dementia, admitted to an acute-care hospital, were recruited over a three-month period into a prospective longitudinal pilot study. The intervention consisted of viewing up to twenty minutes of immersive 360°-VR using a head-mounted-display. Baseline and outcomes data were collected from the hospital electronic medical records, pre/post mood-state questionnaires, Neuropsychiatric Inventory (NPI) score, and standardized qualitative observations. A comprehensive record of the research process was captured, including task sequence and timing requirements for each step of the study. Qualitative observations regarding integration of study activities in the current work-flow and hospital staff availability were collected to help validate initial expectations and refine requirements. **Results:** Of 516 patients admitted during the study period, 67 met the inclusion criteria. In total 234 calls were initiated to substitute decision makers (SDM) for the consenting process; 40% could not be reached in time before patients being discharged. Ten consented participants enrolled and completed the study. The initial VR sessions averaged 53.6 minutes, largely due to the administration of the NPI (mean = 19.5 minutes). Checking the participants' current medical condition (heart rate, blood pressure, and blood glucose measurements) and daily schedule was not a timely endeavor. Certain clinical measures were infrequently recorded; only four out of ten participants had one or more validated cognitive screening tool score(s) recorded in the EMR. Four participants could consistently respond reliably to the questions in the semi-structured interviews, while five patients had difficulty answering questions about their mood before and after VR-therapy. The researcher often had to rely on caregiver input and participant body language to make educated estimations of participants' moods. Seven participants opted for additional VR-therapy sessions; of those providing feedback regarding the VR-content, they wanted more varied scenery (animals, fields of flowers, holiday themes). Few sessions (4/18) encountered technical difficulties, most difficulties were due to syncing of the phone and the HMD. The data collected was reviewed by the research team and variables affecting the study feasibility to an extent that could negatively impact the success of conducting the RCT were identified. These variables were grouped into three categories: Processes (changes in research study tasks or the means and methods by which tasks are achieved), Materials (changes to equipment or instruments, either related to the VR technology hardware (HMD), software (films), or data collection tools), and Resources (changes to the amount of time and materials required to complete tasks, personnel that need to be consulted (e.g. nurses, ward clerks), and elements of the hospital environment). Recommendations for changes to the protocol were documented. **Conclusion:** The pilot was instrumental in identifying issues and providing recommendations for the RCT. Screening, inclusion criteria, consenting, data collection, interaction with SDMs and hospital staff, were all processes requiring changes and optimizations. Overall, patients with dementia appear to tolerate immersive VR, and with suggested protocol alterations, it is feasible to evaluate VR-therapy interventions in acute-care hospitals.

**P086: NON-INVASIVE GAMMA SENSORY STIMULATION FOR THE TREATMENT OF ALZHEIMER'S DISEASE: INTERIM SAFETY AND FEASIBILITY FROM MULTIPLE PROSPECTIVE CLINICAL STUDIES EVALUATING LONG-TERM, HOME USE.** Z. Malchano, E. Hempel, A. Boasso, N. Myrthil, K. Martin, N. Strozewski, T. Travers, K. Kwan, C. Cotter, M. Williams, A. Cimenser, M. Hajos (*Cognito Therapeutics - Cambridge, USA*)

**Background:** Abnormal neuronal activity and brain network dysfunction are increasingly recognized as contributors to Alzheimer's disease (AD) pathophysiology and progression. Recent preclinical research has shown that induction of steady-state 40 Hz gamma brain oscillations on a daily basis results in beneficial effects on multiple pathological features of AD in several different transgenic mouse models. The gamma stimulation paradigm, using synchronized visual and auditory stimulation, is associated with a frequency and dose-dependent reduction in soluble and insoluble A $\beta$  production, reduction in hyperphosphorylated tau, and activation of innate microglia and phagocytosis of A $\beta$  plaques (Iaccarino et al., 2016; Martorell et al., 2019; Adaikkan et al., 2019). **Objectives:** The GammaSense Stimulation System (Cognito Therapeutics, Inc., Cambridge, MA) is a home use medical device that has been designed and developed to deliver daily non-invasive, gamma sensory stimulation consisting of synchronized auditory and visual sensory input to patients with cognitive disorders. Here we describe three prospective longitudinal clinical studies in patients with Alzheimer's disease investigating the safety, feasibility, and therapeutic effects of this wearable device for long-term, home use therapy. **Methods:** The Overture study (NCT03556280) is a multi-center, randomized, sham controlled trial of mild to moderate AD subjects receiving a one-hour daily treatment over a 6-month treatment period with the assistance of a care partner. The Etude study (NCT03661034) is a single-center, randomized, open-label dosing study with amyloid-positive mild cognitive impairment (MCI) subjects receiving either one or two one-hour treatment sessions per day over a 12-month period. The Flicker study (NCT03543878) is a single-center, randomized, delayed-start study with amyloid positive MCI subjects receiving either 8-weeks of one-hour treatment daily or 4-weeks of no treatment, followed by 4 weeks of one-hour treatment for each participant. For all studies, subjects underwent baseline clinical assessments for cognition and function, and biomarker evaluations including MR and PET amyloid imaging. Tolerability and evoked gamma response were assessed during initial in-clinic EEG evaluation to determine individual eligibility and device settings per subject. Therapy usage was monitored via device log, treatment diary, and routine assessment. Daytime and sleep activity were monitored via continuous actigraphy recording. Adverse events were assessed during clinic visits, scheduled phone assessments, and daily treatment diary. For Overture and Etude, MR imaging data was reviewed by a neuroradiology core lab, blinded to group assignments of participants for treatment-emergent changes compared to baseline. **Results:** Interim results for these three studies are reported based on available data. Of screened subjects, a patient-reported tolerable stimulation output range was determined in 98 of 103 (95%) Overture subjects, 27 of 29 (93%) Etude subjects, and 15 of 17 (88%) Flicker subjects. Neural response to auditory and visual stimulation within the patient-reported tolerated range was characterized via EEG in all participants and met pre-specified criteria in 91 of 98 (93%)

Overture subjects, 27 of 27 (100%) Etude subjects, and 10 of 10 (100%) Flicker subjects who underwent testing to determine stimulation settings. A total of 97 subjects were enrolled in the three clinical investigations: Overture (n=74), Etude (n=13), and Flicker (n=10). Daily treatment adherence rate was high from participant and care partner-report during user experience interviews; detailed adherence data will be extracted from device usage logs, daily treatment diaries and actigraphy data upon completion of all studies. For the Overture study, of the 74 participants enrolled, 53 have continued or completed the study; 21 did not complete the study due to withdrawal of consent by patient (15) or care partner (4) or due to adverse events (2). All Etude subjects have continued (3) or completed (10) the study, and all Flicker subjects (10) completed the study. With regards to safety, an adverse event (AE) was defined as any untoward medical event occurring during the treatment period but does not indicate that the event was necessarily related to the investigational treatment. The percentage of Overture participants who experienced any adverse events (AEs) is higher in the control group (78.6%) than the treatment group (60.9%). In the Etude study, 77% of participants experienced any AE, and no participants have discontinued treatment due to AEs. In the Flicker study, 70% of participants experience any AE, and no participants have discontinued treatment due to AEs. The three most common AEs reported across the Overture and Etude studies were headache, confusion, and agitation. Neuroradiological review of 131 MR imaging datasets acquired at baseline, during, and following the treatment period for the Overture and Etude studies revealed no new abnormalities arising during the treatment period and no other concerning findings. **Conclusion:** Interim results from three clinical trials demonstrate that gamma sensory stimulation is safe and well-tolerated for long-term home use in cognitive disorder patient populations including MCI and mild to moderate AD patients.

## Theme 12: PROOF OF CONCEPT/ TRANSLATIONAL RESEARCH IN AD

**P088: PHYSICAL EXERCISE PREVENT ALZHEIMER'S DISEASE BY ENHANCING HIPPOCAMPAL NEUROGENESIS.** X. Bo, Z. Xianliang (*School Of Physical Education & Health Care, East China Normal University - Shanghai, China*)

**Background:** Alzheimer's disease (AD) is an age-related neurodegenerative disease. The major pathological changes of AD include the accumulation of extracellular plaques of  $\beta$ -amyloid ( $A\beta$ ) proteins and intracellular tangles of abnormally phosphorylated tau proteins.  $A\beta$  is the main component of senile plaques, and is a 40-42 amino-acid peptide cleaved from the amyloid precursor protein by  $\beta$ -secretase and  $\gamma$ -secretase. Existing research suggests that the accumulation of  $A\beta$  is neurotoxic and that failure to clear the deposit of  $A\beta$  is an important mechanism by which leads to AD. **Objectives:** Changes in the hippocampus due to natural aging or the onset of neurodegenerative diseases can cause cognitive decline, including diminution of learning and memory. Animal studies have shown that exercise improves spatial memory by enhancing neurogenesis in mice. Furthermore, studies from transgenic models of Alzheimer's disease suggest that exercise may alleviate learning and memory decline through various

cellular mechanisms. The current study aimed to investigate the effects of exercise on hippocampal neurogenesis in male mice and analyze the molecular mechanism of exercise intervention for AD. **Methods:** A total of 24 male mice were used in this study. The mice were randomly divided into four groups: control groups 1 and 2, and running groups 1 and 2. The mice were housed individually in temperature-controlled conditions at 23°C with a 12-h light/dark cycle. All experimental procedures were approved by the Experimental Animal Care and Use Committee at East China Normal University. On the first day of the ninth week, the C1 and R1 mice were anaesthetized and hippocampal neuronal proliferation was assessed using immunohistochemistry. The mice in C2 and R2 were sacrificed to test the expression levels of Jagged-1, Notch-1, PS-1 and Hes-1 in hippocampus using RT-PCR. **Results:** We examined the number of proliferative neural cells using BrdU immunofluorescence staining. There were significantly higher BrdU-positive cells in the DG of group R1 than in the DG of group C1, suggesting that hippocampal proliferation was increased in mice housed with running wheel. In subsequent research, they divided 3-month-old mice into sedentary and running groups. Runners had unlimited access to a running wheel for 45 days. The result revealed that wheel running increased the number of BrdU-positive cells in the DG. These results indicated that voluntary wheel running could increase hippocampal proliferation, which was in accordance with our current results. After 8 weeks of exercise, the expression levels of Jagged-1, Notch-1, PS-1 and Hes-1 in hippocampus of the mice in group R2 increased significantly as compared with those of the mice in group C2. **Conclusion:** 8 weeks voluntary exercise can obviously increase BrdU+ labeled neural stem cells in hippocampal region. Voluntary exercise significantly increased Jagged-1, Notch-1, PS-1 and Hes-1 gene expression, illustrating that voluntary exercise activate the Notch signaling pathway, which impact the hippocampal neural stem cell proliferation and improve the ability of learning and memory. **References:** 1. Na Zhao, Xianliang Zhang, Chenghui Song, Youcai Yang, Biao He, Bo Xu\*. The effects of treadmill exercise on autophagy in hippocampus of APP/PS1 transgenic mice[J]. *Neuroreport*. 2018, 29(10): 819-825. 2. Jie Xia, Baixia Li, Lingyu Yin, Na Zhao, Qingwei Yan, Bo Xu\*. Treadmill exercise decreases beta-amyloid burden in APP/PS1 transgenic mice involving regulation of the unfolded protein response[J]. *Neurosci Lett*. 2019, 703: 125-131. 3. Baixia Li, Fei Liang, Xiaoyan Ding, Qingwei Yan, Yongcai Zhao, Xianliang Zhang, Yidong Bai, Tao Huang\*, Bo Xu\*. Interval and continuous exercise overcome memory deficits related to beta-Amyloid accumulation through modulating mitochondrial dynamics[J]. *Behav Brain Res*. 2019 Dec 30;376:112171. 4. Fei Liang, Tao Huang, Baixia Li, Yongcai Zhao, Xianliang Zhang, Bo Xu\*. High-intensity interval training and moderate-intensity continuous training alleviate  $\beta$ -amyloid deposition by inhibiting NLRP3 inflammasome activation in APPswe/PS1dE9 mice[J]. *Neuroreport*. 2020, 31(5): 425-432. 5. Zhao N, Yan QW, Xia J, Zhang XL, Li BX, Yin LY, Xu B\*. Treadmill exercise attenuates  $A\beta$  -induced mitochondrial dysfunction and enhances mitophagy activity in APP/PS1 transgenic mice[J]. *Neurochem Res*. 2020, 45(5):1202-1214 .

**P089: EFFECTS OF THN201, A COMBINATION OF DONEPEZIL AND LOW DOSE MEFLOQUINE, ON COGNITION AND QUANTITATIVE EEG IN HEALTHY SUBJECTS DURING A SCOPOLAMINE CHALLENGE.**

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**Background:** THN201 is a combination of donepezil (DPZ) and a low-dose of mefloquine which has been shown to improve cognitive function (learning, spatial working memory) compared to DPZ in acute and chronic animal models. It was recently demonstrated that the size of an astrocyte connexin-based network controls the activity profile of donepezil on cognition. Furthermore, mefloquine at low-doses was reported to enhance the efficacy of DPZ through the inhibition of astroglial connexins (Droguerre et al, 2020). **Objectives:** The primary objective of this study was to compare the effects of THN201 to donepezil and placebo in healthy subjects after a scopolamine challenge on cognition assessed with the Cognitive Drug Research (CDR) Battery, on quantitative EEG (qEEG) and event-related potential (P300). Safety of the combination and pharmacokinetics were secondary objectives. **Methods:** This was a randomized, double-blind, placebo-controlled, parallel group Phase 1 study in healthy male participants. Subjects were randomized in a 2:2:1 ratio to either THN201 (donepezil 5 mg/ mefloquine 10 mg) or donepezil (DZP) 5 mg or placebo and treated during 15 days. On D1, subjects in the THN201 group received an additional loading dose of 50 mg mefloquine to reach steady state faster. On D15, each subject received a subcutaneous (S.C.) injection of 0.5 mg of scopolamine approximately 2 hours after the morning drug intake. The Cognitive Drug Research (CDR) battery and EEG were recorded at D1 before first drug intake and at D15 1 hour before and 1, 3, and 7 hours (H1, H3, H7) after scopolamine injection. **Results:** 152 healthy male subjects were randomized (THN201: 62, donepezil: 60, placebo: 30), mean age 30.8 (7.1) and 147 completed the study (3 discontinued due to adverse events (AEs) and 2 withdrew participation). As expected, scopolamine induced a global decrease in cognitive performance and P300 amplitude with a maximum effect at H1 post scopolamine and a return to baseline at H7 post scopolamine. THN201 significantly enhanced the “speed of memory” composite score (sum of the speed scores from Spatial Working Memory and Numeric Working Memory tasks, Word Recognition and Picture Recognition) of the CDR battery vs placebo at H1 post scopolamine ( $p < 0.05$ ) whereas DZP was not different from placebo at H1. Results from the other composite scores did not show differences between the groups (ANCOVA, log transformed data). EEG results showed a significant increase of power in the gamma band (Fz) in the THN201 group after scopolamine compared to placebo and DZP ( $p < 0.05$ ). No consistent differences were found in the other EEG variables and P300. There were no safety issues observed during the study. The most frequently reported AEs (>20% in all groups) were dizziness, somnolence, and dry mouth, probably linked to the scopolamine injection as incidence was similar in placebo and active treatment groups. Vital signs and lab values

showed no clinically significant abnormalities. **Conclusion:** The results with THN201 demonstrate an augmentation of the fluidity of executive and memory processes as shown by the improvement of speed of memory in the CDR battery, as well as an increase of the power of the gamma band of the EEG compared to DZP alone suggesting an improvement in frontal lobe-related cognitive performance. These results corroborate the findings in animal models of cognitive impairments of the augmentation of the cognitive effects of donepezil with low-dose mefloquine. **References:** Droguerre M, Duchêne A, Picoli C, Portal B, Lejards C, Guiard BP, Meunier J, Villard V, Déglon N, Hamon M, Mouthon F, Charvériat M. Efficacy of THN201, a combination of donepezil and mefloquine, to reverse neurocognitive deficits in Alzheimer’s disease. *Front. Neurosci.* 2020, doi: 10.3389/fnins.2020.00563. **Biographies:** (1 for poster/oral communications & 4 for the symposium) / 200

**P090: REDUCED NON-FIBRILLAR AB SPECIES IN A PATIENT TREATED WITH LOW DOSES OF BACE1 INHIBITOR.**

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**Background:** We describe the neuropathological findings of a 63-year old man with Alzheimer’s disease (AD) who received treatment with a BACE-1 inhibitor (Verubecestat, MK-8931) at lower doses (12 mg/day) for 38 months. **Objectives:** Our aim was to evaluate, postmortem, the effect of the drug on different A $\beta$  species and synaptic markers in brain tissue samples. **Methods:** We also include a group of age matched sporadic AD cases (n=9). Frontal and occipital cortices were selected for the quantitative neuropathological assessment. Sections were stained for NAB61, an antibody that detects non-fibrillar A $\beta$  species, total A $\beta$  (clone 6F/3D), synaptophysin and PSD95. An automated in-house computer-based algorithm was applied to quantify pathology burden and synaptic loss. **Results:** We found low NAB61 immunoreactivity in the patient treated with verubecestat compared to the other AD cases in both frontal and occipital regions. In contrast, total A $\beta$  immunoreactivity was similar in the treated case compared with the AD group in both regions. No differences were found in synaptic markers, synaptophysin or PSD95. **Conclusion:** Our data indicate that low-dose Verubecestat may have exerted some effect on the non-fibrillar forms of A $\beta$ .



**P091: INDEPENDENT VALIDATION OF EUROPOND ALZHEIMER'S DISEASE STAGING MODEL ON REAL-WORLD CLINICAL DATA.** M.M.J. Wittens<sup>1</sup>, D.M. Sima<sup>2</sup>, A. Brys<sup>2</sup>, E. De Roeck<sup>1</sup>, H. Struyfs<sup>1</sup>, E. Niemantsverdriet<sup>1</sup>, M. Bellio<sup>3</sup>, N. Oxtoby<sup>3</sup>, D. Alexander<sup>3</sup>, A. Ribbens<sup>2</sup>, S. Engelborghs<sup>1</sup> ((1) *Dep. Of Biomedical Sciences, Institute Born-Bunge, University Of Antwerp - Antwerpen, Belgium*; (2) *Icometrix - Leuven, Belgium*; (3) *Centre For Medical Image Computing, Department Of Computer Science, U C L - London, United Kingdom*; (4) *Dep. of Neurology and Center for Neurosciences, UZ Brussel and Vrije Universiteit Brussel (VUB) - Jette, Belgium*)

**Background:** Event-based modeling (EBM) is a promising approach for establishing the most likely sequence of events in progressive processes such as neurodegenerative diseases, including uncertainty in the sequence. In the context of Alzheimer's disease (AD), EBMs built on the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset obtained characteristic biomarker orderings and demonstrated a good ability to classify cognitively normal (CN) and AD subjects (1). **Objectives:** To assess the validity of an EBM for AD staging, trained on a cross-sectional ADNI dataset and tested/deployed on an independent dataset, as a step towards using these models in multi-center trials. To establish potential differences between EBM profiles of amnesic and non-amnesic mild cognitive impairment (MCI) patients in the independent dataset. **Methods:** An EBM of AD progression was trained on a dataset of 1737 baseline records from ADNI-1/GO/2 subjects, using the EuroPOND ebm toolbox (2). The following 9 biomarkers were considered: 2 clinical scores (Mini Mental State Examination (MMSE) and Rey Auditory Verbal Learning Test (RAVLT)); 3 CSF-biomarkers (A $\beta$ -42, pTau181 and total tau); and 4 MRI biomarkers (volumes of the hippocampi, temporal cortex, parietal cortex, frontal cortex) computed with icobrain dm and normalized for head size. Each EBM stage corresponds to the accumulation of a new biomarker event, therefore, for 9 biomarkers, there are 10 EBM stages (from 0 to 9). The EBM stage 0 corresponds to no biomarker event having occurred, while stage 9 corresponds to the occurrence of all events. According to diagnosis information available from ADNI, there were 417 CN, 342 AD, 310 early MCI, 562 late MCI and 106 subjects with subjective cognitive decline (SCD) in the considered dataset. Mean age was 73.7 $\pm$ 7.2 years and mean MMSE score 27.2 $\pm$ 2.6. Clinical scores and MRIs were available in 99.4% of the cases; CSF biomarkers were available in 23% of the cases, but were missing at random across diagnostic groups, therefore the EBM software was able to deal with the missing data. An independent dataset was acquired from 119 subjects of a memory clinic-based research cohort who participated in a study at the University of Antwerp, Belgium (mean age 66.9 $\pm$ 9.8 years, mean MMSE score 26.6  $\pm$  3.7). According to clinical evaluation, this population consisted of 46 CN, 16 AD, 47 MCI and 10 SCD subjects. The MCI patients consisted of 8 non-amnesic and 39 amnesic subjects. The battery of tests included various cognitive scores, CSF biomarkers, FDG and amyloid PET, MR imaging, and clinical follow-up. Only baseline data was used, and the 9 biomarkers mentioned for the ADNI dataset were extracted. To correct for batch-to-batch variability in absolute CSF values, a global pre-processing step of rescaling the 3 CSF biomarkers using the min-max range in each cohort was applied. The subjects from the independent dataset were staged within the EBM trained on ADNI. The staging results were used to compare different diagnostic

groups. Additionally, the non-amnesic and amnesic MCI groups were compared in terms of proportions assigned to each EBM stage. **Results:** The EBM trained on cross-sectional ADNI data confirmed previous findings (1). The maximum likelihood event sequence for the 9 considered biomarkers was: CSF total tau, CSF A $\beta$ -42, CSF pTau181, MMSE, RAVLT, hippocampal volume, volumes of temporal cortex, parietal cortex and frontal cortex. In (1), cognitive scores were preceded by hippocampal atrophy rates computed in individuals using longitudinal MRI, but cross-sectional hippocampal and other brain volumes were staged after the cognitive scores, consistent with our results. Applied on the independent dataset, the model provided a plausible distribution of subjects across EBM stages: - 72% CN subjects had no abnormal biomarkers (EBM stage 0), and 26% were assigned to stages between 1 and 4 (CSF and MMSE abnormality); - all SCD subjects were assigned stages between 0 and 4; - all AD subjects had at least stage 6 (CSF+cognition+hippocampi), with 62% being assigned to stage 9; the MCI subjects were scattered across all EBM stages in an increasing fashion, with 6% in EBM stage 0 (no abnormal biomarker), 10% in stages 1-3 (CSF), 18% in stages 4-5 (+cognition), 19% in stages 6-8 (+hippocampi/temporal/parietal), and 47% in stage 9 (+frontal). Comparing the staging results of non-amnesic and amnesic MCI subjects, a clear trend towards higher staging was observed in amnesic subjects, with 54% of amnesic subjects being assigned stages 8-9 as opposed to 38% of the non-amnesic subjects. **Conclusion:** Our study showed that the event-based model for AD staging is generalizable, meaning that it can be trained on large cross-sectional historical datasets such as ADNI, and still have reliable staging results in new independent data, provided that the same biomarkers are used. This provides confidence towards using these kinds of models in multi-center trials, for instance, as a screening tool. Furthermore, we show that amnesic MCI subjects score in general higher than non-amnesic subjects, demonstrating utility for precision recruitment/screening. **References:** (1) Young et al, 2014: <https://academic.oup.com/brain/article/137/9/2564/2848155>; (2) EuroPOND ebm toolbox available from <http://europond.eu/software/>

**P093: QUANTITATIVE SYSTEMS PHARMACOLOGY MODEL OF TAU SPREADING IN AD TO ENABLE THE DEVELOPMENT OF ANTI-TAU THERAPIES.** L. Wille<sup>1</sup>, J. Grant<sup>1</sup>, S. Iadevaia<sup>2</sup>, H. Abdul<sup>1</sup>, K. Madras<sup>1</sup>, A. Simen<sup>2</sup>, A.J. Schwarz<sup>2</sup>, M. Quinton<sup>2</sup>, H. Faessel<sup>2</sup>, F. Hua<sup>1</sup>, J. Apgar<sup>1</sup>, J. Burke<sup>1</sup>, M. Vakilynejad<sup>2</sup> ((1) *Applied Biomath - Concord, USA*; (2) *Takeda - Cambridge, USA*)

**Background:** Alzheimer's Disease (AD) is a progressive neurodegenerative disease and is the cause of 60 - 80% of dementia cases. The pathological hallmarks of AD are 1) amyloid-beta (A $\beta$ ) plaques and 2) neurofibrillary tangles (NFT) composed of hyperphosphorylated tau proteins. Multiple drugs targeting the A $\beta$  pathway have recently failed in large clinical trials; however, Biogen is filing for regulatory approval of aducanumab. New drug candidates targeting the tau pathway are being developed aiming to reduce tau accumulation. **Objectives:** The aim of this study was to develop a Quantitative Systems Pharmacology (QSP) model of tau spreading in AD to examine the ability of various drug modalities to reduce NFT accumulation. **Methods:** Multiple brain regions were modeled as a series of connected compartments to simulate tau spreading and disease progression. Each brain region consists of cellular,

synaptic and interstitial fluid (ISF) compartments. Within the cellular compartment, tau is synthesized, hyperphosphorylated, oligomerized and then forms NFTs. Hyperphosphorylation of tau occurs upon introduction of a seed into the first cellular compartment of the model. Soluble tau is then transported into the synaptic and the ISF compartments, then to adjacent brain regions, resulting in pathological tau spreading. Two different therapeutic mechanisms of action, including an anti-tau mAb that binds to extracellular tau and an antisense oligonucleotide (ASO) that knocks down MAPT mRNA were implemented in the model. **Results:** The model was calibrated to match ADNI tau PET data in AD patients. In addition, the model qualitatively matches tau kinetics from preclinical mouse studies. The model was used to assess the impact of various drug design parameters on two different drug modalities and their ability to reduce NFT accumulation. We also assessed the impact of timing of drug administration relative to seeding on NFT accumulation as a function of disease stage. Results suggest that clinically-feasible doses of both mAbs and ASOs are capable of reducing tau accumulation relative to placebo but there are important differences in these therapeutic approaches with implications for likely clinical response. **Conclusions:** Our QSP model enables the efficacy of various drug modalities for reducing NFT accumulation in AD to be assessed. This model lays the foundation for model-informed drug discovery and development for various tauopathies.

**P094: INVESTIGATING THE GLOBAL PROTEOMIC IMPACT AND TRANSLATIONAL IMPLICATIONS OF TOLFENAMIC ACID TREATMENT.** J. Hill<sup>1</sup>, N. Zawia<sup>1,2,3</sup> ((1) *Department Of Biomedical And Pharmaceutical Sciences, University Of Rhode Island - Kingston, USA;* (2) *Interdisciplinary Neuroscience Program, University of Rhode Island, - Kingston, USA;* (3) *George and Anne Ryan Institute for Neuroscience, University of Rhode Island - Kingston, USA*)

**Background:** The pathological hallmarks of Alzheimer's disease (AD) are the cortical accumulation of extracellular amyloid  $\beta$  ( $A\beta$ ) plaques and intracellular neurofibrillary tau tangles (NFTs) composed of hyperphosphorylated tau. Hyperphosphorylation of tau is regulated by the upstream signaling factor: specificity protein 1 (Sp1). Sp1 is a zinc finger protein and transcription factor that regulates both tau and cyclin-dependent kinase 5 (CDK5). Increased levels of SP1 have been proven to increase CDK5 activity and tau phosphorylation. Tolfenamic Acid (TA) or Clotam® Rapid is an NSAID that is currently used in Europe for the treatment of migraine headaches. TA is a unique drug among other NSAIDs due to its ability to cross the blood-brain barrier (BBB) and interact directly with Sp1. Previous publications from our lab have shown that short-term treatment with TA resulted in a significant decrease in Sp1, total tau, APP, and other AD-related targets in human transgenic mouse models. Moreover, TA treatment increased the cognitive performance of mice compared to vehicle control-treated mice. TA is, currently, designated as an orphan drug for Progressive Supranuclear Palsy (PSP) and Frontotemporal Dementia (FTD). This project aimed to determine the off-target effects of TA, in partnership with a current clinical trial, to anticipate potential human side-effects of TA treatment using a proteomic and translational approach combined with in-depth pathway analysis. **Objectives:** (A) Determine the global proteomic impact and off-target effects of Tolfenamic acid in vitro. (B) Conduct thorough

pathway analysis using Ingenuity Pathway Analysis (IPA) to analyze and integrate the proteomic data into translational information for future animal and clinical trials. **Methods:** Human Neuroblastoma (SH-SY5Y) cells were exposed to 25  $\mu$ M lead (Pb acetate) for 48 hours. Then, cells were treated with vehicle, 5 or 25  $\mu$ M Tolfenamic acid (TA) for 48 or 72 hours. Protein was prepared by digestion of approximately 1 million cells in 5 mL Urea buffer using the Omni International Bead Rupter Elite (Omni International, Kennesaw, GA) and quantified using Pierce BCA Protein Assay Kit (Thermo Fisher Scientific, Rockford IL). Protein samples (250-500  $\mu$ g protein) were denatured with 25  $\mu$ L DTT (100 mM, Sigma, St. Louis, MO) at 35°C for 30 min in a shaking water bath (100 rpm) and alkylated in the dark with 25  $\mu$ L iodoacetamide (IAA; 200 mM, Sigma, St. Louis, MO) for 30 min at room temperature. 100  $\mu$ L of the reduced and alkylated protein sample was taken for digestion. Protein was digested using a pressure cycling technology-based method. The barocycler (Pressure Biosciences, South Easton, MA) was run at 35°C, for 90 cycles with 60 sec per pressure-cycled (50 sec high pressure, 10 sec ambient pressure, 25 kpsi). Then, 20  $\mu$ L of the sample was analyzed using SCIEX 5600 TripleTOF LC-QTOF/MS (SCIEX, Concord, Canada) for data-independent acquisition (DIA) and sequential window acquisition of all theoretical mass spectra (SWATH-MS) for the proteomic analysis. Western blot analysis was also used to confirm proteomic findings and further elucidate pathway analysis. Data were normalized and statistically analyzed using R. Pathway analysis was conducted using Ingenuity Pathway Analysis (IPA) software. **Results:** Treatment with Tolfenamic acid decreased Sp1 and total tau levels. A global proteomic shift revealed a protein signature difference between the vehicle- and TA-treated groups. **Conclusion:** Proteomic analysis, western blot, and pathway analysis data reveal that TA is a potential disease-modifying treatment with minimal side effects to patients. Furthermore, a proteomic approach to drug development may expedite drug discovery by elucidating potential side-effects and off-target effects of drugs prior to clinical trial commencement.

**P095: THE LACK OF C-ABL IMPROVES BEHAVIORAL PERFORMANCE IN AN ANIMAL MODEL OF ALZHEIMER'S DISEASE.** A. Alvarez<sup>1</sup>, R. León<sup>1</sup>, C. Riquelme<sup>1</sup>, S. Zanlungo<sup>2</sup>, A. Dulcey<sup>3</sup>, J. Marugan<sup>3</sup> ((1) *Cell Signaling Laboratory, Department Of Cell And Molecular Biology, Biological Sciences Faculty, Care-Uc, P. Universidad Catolica De Chile. - Santiago, Chile;* (2) *Gastroenterology Department, School Of Medicine, P. Universidad Catolica De Chile - Santiago, Chile;* (3) *Ncats-Nih Chemical Genomic Center - Bethesda, USA*)

c-Abl is a non-receptor tyrosine kinase involved in neuronal development, neurogenesis, neuronal migration, axonal extension, and synaptic plasticity. Growing evidence suggests that c-Abl plays a role in the pathogenesis of Alzheimer's disease (AD). Our laboratory has shown that c-Abl is activated in both in vitro and in vivo AD models, and its activation is involved in synaptic loss and long-term potentiation inhibition induced by  $A\beta$  oligomers. Also, treatment with Imatinib, a c-Abl inhibitor, reduces neuronal loss, tau phosphorylation,  $A\beta$  deposition, and cognitive impairments in transgenic AD mouse models. However, one of the limitations of using these inhibitors is that they have poor permeability of the blood-brain barrier and also target other kinases. To determine the role of c-Abl in AD, we developed a novel transgenic strain of AD that

has a brain-specific genetic deletion of c-Abl and performed cognitive tests such as Novel object recognition (NOR), Object-location memory (OLM), Barnes Maze test (BM) and Memory flexibility (MF). There were no differences between groups in the NOR test, a hippocampus-independent task. However, in the OLM test a hippocampus-dependent task, we found that mice null for c-Abl in the brain (Abl-KO and APP/PS1/Abl-KO) had an improved ability to discriminate. Also, in the BM test, another hippocampus-dependent test, the mice null for c-Abl learned faster. Similarly, in the MF test, c-Abl null mice required fewer trials to reach the criterion. These results suggest that c-Abl exerts a detrimental role in hippocampal-dependent memory formation in AD. Furthermore, we evaluated a novel specific inhibitor of c-Abl called "Abyl1" on the cognitive tests of AD mice. Similarly to the results obtained with brain c-Abl ablation, the APP/PS1 mice treated with Abyl1 required fewer trials to reach the criterion in the MF test compared to the untreated APP/PS1 mice. However, there was no differences in the NOR test and OP. These results suggest that c-Abl exerts an important role in the loss of hippocampal-dependent memory in AD. Taken together, these results indicate that c-Abl is a relevant actor in the pathology of AD and that its absence is beneficial for AD, strengthening the use of the novel therapy for AD based in the inhibition of c-Abl. This also suggests that the specific inhibition of c-Abl with Abyl1 could be a good candidate for future therapies for AD with a specific target. ANID PhD fellowship 21160057, Fondecyt 1201668, FONDEF D10E1077, Grant AFB 170005.

**LP16: PERIPHERAL INFLAMMATION, COGNITIVE IMPAIRMENT AND AD-RELATED HIPPOCAMPAL NEURODEGENERATION IN PRODROMAL AD PATIENTS.** M. Marizzoni<sup>1</sup>, C. Chevalier<sup>2</sup>, N. Lopizzo<sup>1</sup>, D. Albani<sup>3</sup>, G. Forloni<sup>3</sup>, J. Jovicich<sup>4</sup>, A. Cattaneo<sup>1</sup>, G. Frisoni<sup>2</sup> ((1) *Irccs Istituto Centro San Giovanni Di Dio Fatebenefratelli - Brescia, Italy*; (2) *University Hospitals And University Of Geneva - Geneva, Switzerland*; (3) *Irccs Istituto Di Ricerche Farmacologiche «mario Negri» - Milano, Italy*; (4) *Center For Mind/brain Sciences - Trento, Italy*)

**Background:** Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the presence of beta-amyloid (A $\beta$ 42) and phosphorylated tau (P-tau) deposits in the brain, neurodegeneration in specific brain regions, and inflammation. Mild Cognitive Impairment (MCI) is defined as the "symptomatic pre-dementia stage" on the continuum of cognitive decline and is characterized by objective impairment in cognition. **Objective:** This study aimed at investigating the association of peripheral inflammation with cognitive performance and neurodegeneration in MCI patients with or without AD pathology. **Methods:** Study population: 89 consecutive enrolled amnesic MCI patients. AD pathology definition: based on baseline CSF A $\beta$ 42/P-tau level as well as APOE genotype (positivity defined as A $\beta$ 42/P-tau ratio < 7.8 for APOE4 non-carriers, < 15.2 for carriers). Global cognition: Alzheimer's Disease Assessment Scale 13 (ADAS-cog13). Neurodegeneration: volumes of the hippocampus and its subfields were extracted from 3T T1 MRI brain images with Freesurfer (version 6). Inflammation: the cytokine expression of pro- (IL6, IL8, IL1beta, TNF-alpha, NLRP3) and anti- (IL10) inflammatory molecules were measured by Real Time PCR Assay. The human biological samples were sourced ethically and subjects provided written informed consent. **Results:**

Positive patients showed lower expression of IL-10 (p=.033) as well as higher expression of NLRP3 (p=.050) and IL-8 (p=.037). Correlation analyses revealed that i) high NLRP3 levels was associated with whole hippocampus and subfields volume reduction (whole hippocampus, r=-.33, p=.021; presubiculum, r=-.32, p=.031; CA1, r=-.30, p=.039; presubiculum, r=-.36, p=.012) and, ii) low IL10 levels was associated with worse cognition (r=-.58, p=.032) in the positive but not in the negative group. **Conclusions:** Altered expression of proinflammatory factors are associated to hippocampal neurodegeneration and worse cognitive performance in prodromal AD patients. These preliminary results suggest that non-invasive peripheral inflammatory biomarkers could represent possible biomarkers to support the early diagnosis of AD.

**LP17: CS6253 ABCA1 AGONIST TREATMENT IN CYNOMOLGUS MONKEYS REDUCES CEREBROSPINAL FLUID CONCENTRATIONS OF AB42, AB40, APP AND AP2B1 IN DOSE-RESPONSE MANNER.** J.O. Johansson<sup>1</sup>, H.N. Yassine<sup>2</sup>, D.M. Michaelson<sup>3</sup>, J.E.G. Johansson<sup>4</sup>, H. Zetterberg<sup>5</sup>, B. Winblad<sup>6</sup>, J.L. Cummings<sup>7</sup> ((1) *Artery Therapeutics, Inc. - San Ramon, Ca, USA*; (2) *Usc - Los Angeles, USA*; (3) *Tel Aviv University - Tel Aviv, Israel*; (4) *Artery Therapeutics, Inc. - San Ramon, USA*; (5) *U Of Gothenburg - Gothenburg, Sweden*; (6) *Karolinska Institutet - Stockholm, Sweden*; (7) *Unlv - Las Vegas, USA*)

**Background:** The apoE4 protein, encoded by the  $\epsilon$ 4 allele of the APOE gene, a major genetic risk factor for sporadic Alzheimer's disease (AD), has impaired interaction with astrocyte's ATP-binding cassette transporter A1 (ABCA1) resulting in: a) poor cholesterol efflux and b) build-up of residual cholesterol in lipid rafts, impeding astrocyte function (Rawat 2019) and increasing neuron cell death (Voskuhl 2018). Cynomolgus monkeys (cynos) have arginine in the critical 112 and 158 positions (like hu apoE4) but not in the 61 position, a 93% homology with human apoE, as well as lipid and amyloid metabolism similar to human. Consistent with humans, cyno CSF A $\beta$ 42 decreases with age as opposed to A $\beta$ 40. **Objectives:** In a dose-range finding toxicology study in cynos, we explored effects of CS6253 ABCA1 agonist treatment on CSF amyloid markers. **Methods:** CS6253 was administered iv at 0 (Placebo), 75 (low dose), 150 (mid dose) and 225 (high dose) mg/kg (n=2/sex/group) 5 times over 10 days to 2 year old cynos. CSF was collected before treatment and 6 hours after the 5th/last dosing. CSF A $\beta$ 42 and A $\beta$ 40 were analyzed by SIMOA, APP and amyloid protein complex2B1 (AP2B1) by mass spectrometry. **Results:** CS6253 treatment decreased CSF levels of A $\beta$ 42, A $\beta$ 40, APP and AP2B1 in dose-response fashion with no significant differences between female and male cynos. For CSF A $\beta$ 42 the change in concentrations were: placebo +187 pg/mL (+64%), low dose +18 pg/mL (+3%), mid dose +87 pg/mL (+18%) and high dose -95 pg/mL (-23%). The relative changes were of similar magnitude also for A $\beta$ 40, APP and AP2B1. The reduction in CSF A $\beta$ 42 correlated strongly with the CSF reductions in APP (R<sup>2</sup>=0.80, p<0.001) and AP2B1 (R<sup>2</sup>=0.64, p<0.001). **Conclusions:** Compared to placebo, the ABCA1 agonist CS6253 reduced CSF A $\beta$ 42, A $\beta$ 40, APP and AP2B1 in dose-response manner in the 2 year old cynos. The results are consistent with previous finding in APOE4 mice models where brain A $\beta$ 42 (and P-tau) was reduced, AD pathology prevented, and cognition improved. The results need to be corroborated in humans with and without APOE  $\epsilon$ 4 at therapeutic doses.

CS6253 holds high promise for the prevention and/or treatment of APOE ε4-associated dementias, including AD.

### **Theme 13: DIGITAL HEALTH/E-TRIALS**

**P096: EVALUATION OF SPEECH-BASED DIGITAL BIOMARKERS FOR ALZHEIMER'S DISEASE.** J. Robin<sup>1</sup>, L. Kaufman<sup>1</sup>, W. Simpson<sup>1,2</sup> ((1) *Winterlight Labs - Toronto, Canada*; (2) *McMaster University - Hamilton, Canada*)

**Backgrounds:** Non-invasive, low-cost digital biomarkers for Alzheimer's disease (AD) would represent a major advance for dementia research. Digital biomarkers could facilitate more efficient screening and treatment of disease, and provide more sensitive endpoints for research studies and clinical trials. Speech changes in AD have emerged as an exciting area of research and a promising potential biomarker. Longitudinal studies of AD have highlighted numerous changes in speech as the disease progresses, including declines in the number of unique words used and the density of ideas in speech (1–3). More recently, advances in Natural Language Processing (NLP) technology and machine-learning techniques have provided new insights into what aspects of speech may be affected by disease. Machine-learning classifiers have shown that models leveraging the acoustic and linguistic components of speech can differentiate AD cases from healthy controls with >90% accuracy (4–6). While these findings are exciting, rigorous validation is needed to better understand what speech features are affected by disease, the time course of speech changes, and how these novel measures compare to current clinical standards. **Objectives:** In this presentation we will outline a framework for clinical validation of digital biomarkers. With reference to this framework, we will provide evidence from our research studies on the development of speech-based biomarkers for detecting and monitoring AD. Our objective is to demonstrate what aspects of speech are useful for AD screening and symptom tracking, and present directions for future research and further validation. **Methods:** In a series of studies, we examine the relationship between features extracted from automated speech processing and the presence and severity of cognitive impairment in mild cognitive impairment (MCI) and AD. We evaluate the accuracy of machine-learning models to differentiate healthy controls from cases of AD. We examine the progression of speech changes over time in a sample of longitudinal cases with MCI and early AD. We compare speech measures with current clinical tools such as the Montreal Cognitive Assessment (MoCA). We test whether and when speech changes are detectable prior to AD diagnosis, and whether speech shows changes with treatment in clinical trials. **Results:** We demonstrate that machine-learning models of speech can be used to differentiate healthy controls from cases of AD with high sensitivity (82%) and specificity (91%), and examine which speech features contribute most to classification. We identify speech features that show significant decline over time in MCI and AD, including measures relating to the coherence and information content of speech. We show that speech features can be used to predict scores on current clinical measures, such as the MMSE and MoCA, within an average of 2.6 points of actual values. In a sample of individuals with multi-year longitudinal data, classification of later AD diagnosis was above chance based on speech recorded more than five years prior to diagnosis. Based on preliminary clinical

trial data, we show evidence of changes to speech following treatment for AD. **Conclusion:** Together, these studies show how speech represents an exciting potential biomarker for AD by demonstrating diagnostic specificity, change with disease progression and correlation with current clinical tools. Preliminary evidence supports prediction of disease before onset and responsiveness to treatment. Collection of speech is naturalistic, low-cost and requires little or no clinical training, making it a much more flexible tool for clinicians and researchers compared to current standards. Future work will continue to develop and refine speech-based biomarkers for identifying and tracking AD onset and progression. **References:** 1. Berisha, V., Wang, S., LaCross, A. & Liss, J. Tracking Discourse Complexity Preceding Alzheimer's Disease Diagnosis: A Case Study Comparing the Press Conferences of Presidents Ronald Reagan and George Herbert Walker Bush. *J. Alzheimers Dis.* 45, 959–963 (2015). 2. Le, X., Lancashire, I., Hirst, G. & Jokel, R. Longitudinal detection of dementia through lexical and syntactic changes in writing: a case study of three British novelists. *Lit. Linguist. Comput.* 26, 435–461 (2011). 3. Snowdon, D. A. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. *JAMA J. Am. Med. Assoc.* 275, 528–532 (1996). 4. Fraser, K. C., Meltzer, J. A. & Rudzicz, F. Linguistic Features Identify Alzheimer's Disease in Narrative Speech. *J. Alzheimers Dis.* 49, 407–422 (2015). 5. Konig, A. et al. Use of Speech Analyses within a Mobile Application for the Assessment of Cognitive Impairment in Elderly People. *Curr. Alzheimer Res.* 15, (2018). 6. Asgari, M., Kaye, J. & Dodge, H. Predicting mild cognitive impairment from spontaneous spoken utterances. *Alzheimers Dement. Transl. Res. Clin. Interv.* 3, 219–228 (2017).

**P097: DEVELOPING AND ASSESSING A DIGITALLY SUPPORTED CARE MANAGEMENT PROGRAMME FOR CAREGIVERS OF PEOPLE WITH DEMENTIA: A CLUSTER-RANDOMISED CONTROLLED TRIAL (GAIN).** O.A. Klein<sup>1</sup>, J.R. Thryian<sup>2</sup>, M. Boekholt<sup>2</sup>, D. Afrin<sup>2</sup>, C. Dornquas<sup>2</sup>, M. Lindner<sup>2</sup>, B. Michalowsky<sup>2</sup>, I. Zwingmann<sup>3</sup>, A. Dreier-Wolfgramm<sup>4</sup>, S. Teipel<sup>1</sup>, W. Hoffmann<sup>2</sup>, I. Kilimann<sup>1</sup> ((1) *German Center For Neurodegenerative Diseases - Rostock, Germany*; (2) *German Center For Neurodegenerative Diseases - Greifswald, Germany*; (3) *European University Of Applied Sciences - Rostock, Germany*; (4) *Hamburg University Of Applied Sciences - Hamburg, Germany*)

**Background:** In an ageing population, family caregivers of people with dementia are essential to the quality of life of the care recipients. Efficiently supporting dementia family caregivers and ensuring their well-being is imperative. Enabling family caregivers to provide care at home prevents early institutionalisation of the person with dementia and alleviates the economic burden of dementia in the long term. As the first point of contact, general practitioners (GPs) have a key role in identifying burden and care needs of family caregivers. However, in routine care, this opportunity is limited by time constraints and detailed information on regionally available support and healthcare services is often lacking or services are not available. Digital support systems can aid in overcoming current limitations in service provision. **Objectives:** To develop a digital care management system to detect and manage unmet healthcare needs of family caregivers of people with dementia (PwD). To assess the clinical use, effectiveness and cost-effectiveness of a digitally supported care management programme to reduce unmet care needs

of family caregivers of PwD in the primary care setting. **Methods:** The development of the digital care management system (phase 1) was embedded within a multi-site, cluster randomised, controlled trial (phase 2) comparing a digitally supported care management programme with usual care. In phase 1, using a participatory research approach, we developed and piloted a tablet PC-based care management system that identifies unmet needs in family caregivers via a self-administered baseline assessment and supports healthcare professionals in the management of the unmet needs identified. The following steps were conducted to develop the digital care management system: (i) a literature search examining the definition of an unmet need and identifying existing instruments used to assess medical, psychological, and social unmet needs, (ii) development of a baseline assessment to assess unmet needs, (iii) defining conditions that identify an unmet need in the system, (iv) matching intervention recommendations for each unmet need, (v) developing an automated outcome report of the baseline assessment, (vi) developing a success monitoring system to facilitate the management of unmet needs and (vii) piloting the system. In phase 2, five hundred family caregivers will be randomised at GP offices, specialist practices, and memory clinics, with about n=250 participants per arm. The tablet PC-based assessment will identify needs of family caregivers of PwD and will automatically generate an individual management plan. Specifically qualified study nurses in collaboration with the treating GP will carry out the management plan generated. The study nurses will support and monitor the implementation of the care plan via four monthly telephone follow-ups. All participants will receive a final follow-up assessment at six months post-randomisation. Participants in the control group will receive usual care at first and the individual management plan at the six months follow-up. Primary outcomes are the Camberwell Assessment of Need for the Elderly and the EQ-5D. Secondary outcomes include the Zarit Burden Interview, the Social Lubben Network Scale, and use of medical and non-medical services. This trial is funded by the German Federal Joint Committee (G-BA) Innovation Fund and registered in the clinical trials database under NCT04037501. **Results:** A list of already existing instruments was identified. With the help of 27 caregivers and experts including neurologists, psychologists, psychiatrists and nurses, an initial selection of questions and existing instruments was generated and piloted. The preliminary selection comprised of 63 questions. Items and response options were examined for content, clarity, interpretability, and length. Caregivers and experts commented on the content, wording and order of questions, the response options provided, the length of the instrument, and the layout of each section. Questions and response options were re-worded to minimise ambiguity. The order and layout of questions were changed based on respondents' comments. On average, it took 37 minutes (range 15-90, SD = 24) to complete the baseline assessment. Respondents stated that they lost focus towards the end of the assessment. As a result, the instrument was simplified. Based on the feedback we received, the baseline assessment was adapted and a tablet PC-based version was created, which resulted in an assessment containing 57 questions and a completion time of 18 minutes. Subsequently, assessment items were paired with care management recommendations, which are automatically triggered by the system if an item is identified as unmet need. The outcome report contains all unmet needs identified as well as information about the caregiver's health status.

A success monitoring system was developed to support the management of unmet needs. Piloting of the system is currently being finalised to examine the handling and usability in clinical practice using a participatory research approach. Results for phase 2 will be reported at a later point when preliminary results are available. **Conclusion:** The findings of this trial will be useful in informing and improving current healthcare system structures to support family dementia caregivers within routine primary care practice.

**P098: VALIDATING VIRTUAL TOOLS FOR REMOTE SAMPLING OF NEUROLOGICAL FUNCTION: COMPARING TASK-DRIVEN EEG IN THE LAB AND IN THE HOME.** B. Murphy<sup>1</sup>, F. Barbey<sup>1</sup>, A. Buick<sup>2</sup>, J. Dyer<sup>1</sup>, H. Nolan<sup>1</sup> ((1) *Brainwavebank Ltd. - Dublin; Ireland;* (2) *Brainwavebank Ltd. - Belfast, United Kingdom*)

**Background:** During the current pandemic many clinical trials have been disrupted as travel and movement is limited, and clinical staff and vulnerable populations avoid face-to-face meetings. This has accelerated the adoption, and in the process proven the feasibility, of many existing tools for remote or "virtual" trials. However to date, sampling of neurological function has required visits to larger clinics and imaging centres. Here we describe a suite of tools that allow repeated recording of resting and domain-specific neurological function, that is suited for use in small remote clinics or a patient's home. The BrainWaveBank platform consists of an easy-to-use 16 dry-sensor wireless EEG headset, engaging tablet-based cognitive assessments, and a secure cloud infrastructure that collects, preprocesses and presents remote session data for immediate review by clinical trial staff. **Objectives:** Here we present evidence from a structured series of lab and field-based validation studies, to demonstrate both the suitability of the platform for use by elderly participants, and the integrity of the data it yields. **Methods:** 1. Signal quality comparison to conventional wet EEG in-lab: the BrainWaveBank headset was used to record EEG while 8 adult participants viewed simple visual stimuli in two task variants: a visual-evoked-potential (VEP) elicited by a series of white circles presented on screen; and a steady-state VEP, elicited by a series of flickering white circle stimuli (at 14Hz). Both tasks are low-level measures of cortical engagement, less affected by cognitive confounds. The same tasks were recorded using a Biosemi ActiveTwo setup which uses state-of-the-art preamplified wet sensors. The ordering of wet/dry sessions was counterbalanced. 2. User acceptance and compliance, at-home: after an in-person familiarisation session, 90 uncompensated older adults (40-90yrs) were asked to use the EEG headset and paired behavioural tasks (resting EEG, and tasks in attention, memory and executive function) for 20 minutes a day, 5 days a week for 12 weeks. 3. Signal quality comparison recording in-lab vs at-home: 30 young adults took part in a benchmark study using a well-studied and safe psychoactive compound (intravenous racemic ketamine). During the pre-intervention period, 2 in-lab baseline recordings were taken, alongside 6 at-home baseline recordings. Passive and task-driven recordings were made. **Results:** 1. In the static VEP task condition the waveform morphology and scalp topography were similar, and the average signal spread at occipital electrodes was marginally higher (1.27 $\mu$ V) for dry sensors than for wet sensors (1.24 $\mu$ V), based on a Montecarlo based 95% confidence interval, calculated over the grand average ERP (8 participants x 2 sessions x 2

modalities). For the 14Hz steady-state VEP, the corresponding dry EEG signal spread was again marginally higher (1.28 $\mu$ V) than the wet (1.25 $\mu$ V). 2. Home-based users reported high satisfaction with the system, at 78.9 on the System Usability Scale (SUS), though it was somewhat lower for those aged 67 years or more (SUS of 68.6). The mean compliance rate over the 12 weeks of the study was 82% (i.e. 4.1 weekly sessions were submitted, of the 5 requested). Compliance was somewhat higher among older users, at 4.5 sessions per week for those aged 67 or more. An analysis of sensor contact reliability showed that at a single point in time of an average session, 14 or 15 of the 16 dry sensors were in contact and recording EEG. Grand average P300 and ERN ERPs, gathered during gamified versions of the visual 2-stimulus oddball paradigm, and the Flanker task, showed morphology and topography matching those reported in the literature. 3. Grand-average lab-based and home-based signals for three ERPs (the P300, the ERN and the MMN) all showed similar topography and morphology. The variance of home-based recordings was higher, to the extent that 19%, 46% and 22% more data would be required of it to yield equivalent statistical power to in-lab recordings. **Conclusion:** The BrainWaveBank platform is judged as easy to use by participants, and this results in very high levels of compliance for frequent repeated sampling autonomously in the home, even with older individuals. Resting and domain-specific event related potentials can be collected in supervised lab, and unsupervised home environments. In controlled settings, grand average signal quality is very similar to that from burdensome lab-systems. The additional noise associated with unsupervised data collection in uncontrolled home settings adds only modestly to the amount of data required to achieve similar statistical power – as can easily be achieved by asking patients to make multiple daily recordings. We are now conducting pilots of entirely virtual enrolment sessions. These suggest that video-conference-based familiarisation sessions are effective in place of the face-to-face modality that we have used to date. We will have new results on a direct comparison between in-person and web-based cohorts to present by the date of CTAD.

**P099: MEASUREMENT OF ALZHEIMER'S DISEASE SYMPTOMATOLOGY USING REMOTE SMARTPHONE-BASED ASSESSMENT OF VISUAL AND AUDITORY BEHAVIOR.** A. Abbas, A. Paley, I. Galatzer-Levy (*Aicure - New York, USA*)

**Background:** Measurement of Alzheimer's Disease severity and assessment of disease progression presents several key challenges during drug development research, both for patient selection and measurement of treatment response. Traditional clinical assessments can be subjective, have poor inter-rater reliability, and often require in-person evaluation, which can be burdensome for both patients, caregivers, and clinicians and pose practical and logistical difficulties. There is a need for novel evaluation tools that are able to address measurement challenges and provide objective, reliable, and scalable assessment of disease progression and treatment response. **Objectives:** Here, we propose a study paradigm that utilizes novel digital measurement tools to assess symptom severity in individuals with Alzheimer's Disease enrolled in clinical trials. Individuals with Alzheimer's Disease demonstrate a heterogeneous range of symptomatology, with cognitive impairment manifesting in key aspects of observable patient behavior. Part of this manifestation is visual and auditory

behavior such as changes in speech and language characteristics, vocal acoustic and prosodic markers, and facial expressivity and motor functioning. Given the availability of novel methods for digital measurement of all such markers, we aim to demonstrate the viability of an automated remote assessment for video and audio data capture that allows for measurement of visual and auditory markers of Alzheimer's Disease. **Methods:** Individuals enrolled in clinical trials are asked to download a smartphone application from which they can perform remote assessments at scheduled time points. The assessments engage participants in active visual and verbal interactions with the smartphone app while video and audio of their behavior is recorded. The tasks are designed to be simple and brief, taking approximately 1-2 minutes to complete. The video and audio recorded is then securely uploaded to a software backend. Once uploaded, a host of machine learning models are able to quantify specific behavioral characteristics indicative of Alzheimer's Disease severity including natural language, speech prosody, and facial activity. Natural language analysis has demonstrated several characteristics of speech indicative of Alzheimer's disease severity. This includes measures such as word repetitions, parts of speech used (e.g. fewer nouns, more pronouns, adjectives), fillers between words, lexical diversity, complex syntactic units, word entropy, and unintelligible words. The analysis of the acoustics of voice in individuals with Alzheimer's Disease has revealed strong measures of disease presence and severity. Prosodic markers such as pause characteristics, shimmer, harmonics-to-noise ratio, and amount spoken have been shown to consistently differ in patients with Alzheimer's Disease. Despite emotional experience being unaffected in Alzheimer's Disease patients, individuals with the disorder can demonstrate abnormal patterns of facial activation during general behavior and in response to valenced stimuli. **Results:** Machine learning-based measurements of visual and auditory behavior acquired through patient participation in smartphone-based assessments provide significant promise as digital endpoints, allowing for assessment of treatment efficacy with greater frequency and sensitivity than is possible with traditional clinical endpoints, as well as supporting selection of appropriate patients in trials. These measures provide additional insight beyond what is acquired through existing endpoints, allowing for a deeper understanding of how Alzheimer's Disease symptomatology is affected by the treatment compound. **Conclusion:** Traditional endpoints used in clinical research pose both practical and clinical challenges. A growing literature around facial and vocal markers associated with AD progression provides significant promise, but gaps remain with scalability needed for large-scale drug development trials. Digital measurement tools are a proposed solution that provide remote, accurate, scalable, and frequent measurement of disease severity and treatment response. Utilization of such technologies in clinical research can allow for a richer understanding of how compounds affect disease symptomatology and reduce logistical burden on clinical trial operations.

**P100: AUTOMATED ADMINISTRATION OF SERIAL SUBTRACTION IN A REMOTE DATA COLLECTION CONTEXT: NOVEL TIMING FEATURES RELATED TO TASK DIFFICULTY AND PARTICIPANT DEMOGRAPHICS.** N. Taptiklis<sup>1</sup>, B. Jennifer<sup>1,2</sup>, F. Francesca<sup>1,2</sup> ((1) *Cambridge Cognition - Cambridge, United Kingdom*; (2) *Dept. Psychiatry, University of Cambridge - Cambridge, United Kingdom*)

**Background:** Serial Subtraction is a widely used task considered to be a valid and sensitive measure of processing speed and attention (Williams et al., 1996). Variants of this task have been used in as part of neuropsychological screening tools (e.g. MoCA), and in conjunction with measures of gait and balance in the context of measurement of dual tasking, where Serial Subtraction is considered means of applying cognitive load. Despite the wide-spread utility of this task, measures derived from it have typically been limited to accuracy, or number of attempts over a given period (rate), and delivery has been restricted to in-person testing. Here, we report on the derivation of novel measures related to the timing of responses from Serial Subtraction data collected in an automated and remote context. **Objectives:** To validate the automatic administration of serial subtraction using the Neurovocalix platform. To explore fine-grained aspects of task performance derived from the timing and syntax of serial subtraction audio responses. **Methods:** From a pool of 5,742 recordings of participants aged 17-86 years, 100 were randomly selected for manual review and scoring. Participants were all fluent English speakers, and completed serial subtraction by three and seven, via a device-agnostic web-app on their own devices. We recorded participant demographics and information regarding the operating system, browser and device on which the tasks were completed. Manual transcription was completed off-line by trained raters through the Neurovocalix system. These transcripts were scored for accuracy. We derived measures of the number of responses, the rate of responses (responses / task duration) and accuracy for both subtraction by sevens and threes, as these were measures which had previously been used to characterise performance. Transcripts were also used to derive timing measures, capturing the duration of each subtraction attempt and intervening silence between attempts. From these timing data, summary measures of variability (root mean square of successive differences (RMSSD), SD and Instability) and average durations were calculated. Acceleration in responses were computed using methods previously applied to tasks of oromotor function. These capture slowing or speeding of responses as the task progresses. Automated analysis of syntax from responses was used to characterised the style of responding, and the presence and frequency of non-target responses (intrusions or self-corrections). **Results:** From the recordings selected to review, 21 were excluded, the majority for technical audio or recording difficulty (n=11) or background noise (n=5). Two participants failed to follow task instructions, and in three recordings another party was heard helping. As expected, mean response rate was significantly faster for subtraction by threes than by sevens (.41/second vs .27/second). Accuracy was also significantly higher for subtraction by threes (.91) by subtraction by sevens (.79), supporting the validity of automated data collection for this task. Non-target responses were seen more often during subtraction by seven than by three (2.06 vs 1.6). Syntactic analysis found four distinct styles of serial subtraction which differed in verbosity: 1: "two hundred and sixty three";

2: "two sixty three"; 3: "two six three" 4: "two hundred sixty three". The first style was the most common (50% of responses), and also the one associated with the longest latency. Response styles were typically consistent within participants. Both task difficulty and response style were significantly associated with response rates and response durations, which could confound comparisons across individuals. Mixed effects analysis was carried out which allowed us to control for individual styles in responding by allowing a random intercept. Significant effects of subtraction difficulty was observed on both standard performance measures, and more detailed timing measures such as variability, instability and acceleration. Gender was significantly associated with rate of responding and acceleration in responses, whereas level of education was a significant predictor for instability in responding. Age predicted both mean duration and standard deviation in response. **Conclusion:** Serial subtraction is a widely used paradigm, which we have deployed on a remote data collection platform. The results demonstrate 1) the feasibility of automated data collection of this task 2) the derivation of novel measures of timing in assessing task performance and 3) the limitations of rate or number of responses as a measures of performance, given the dependence on the individual style of responding. Future work will focus on the automation of the transcription process, and the exploration of the changes to these timing features in the context of both dual task paradigms and neurodegeneration. **Reference:** Williams, M. A., LaMarche, J. A., Alexander, R. W., Stanford, L. D., Fielstein, E. M., & Boll, T. J. (1996). Serial 7s and Alphabet Backwards as brief measures of information processing speed. *Archives of Clinical Neuropsychology*, 11(8), 651-659.

**LP18: FEASIBILITY, ACCEPTABILITY AND EFFECTS ON CLINICAL OUTCOMES OF A WEB-BASED MULTIDOMAIN LIFESTYLE INTERVENTION IN OLDER ADULTS: THE EMIND RANDOMIZED CONTROLLED TRIAL.** P. De Souto Barreto<sup>1</sup>, K. Pothier<sup>2</sup>, G. Soriano<sup>1</sup>, M. Lussier<sup>3</sup>, L. Bherer<sup>3</sup>, S. Guyonnet<sup>1</sup>, A. Piau<sup>1</sup>, P.J. Ousset<sup>1</sup>, B. Vellas<sup>1</sup> ((1) *Gerontopole Of Toulouse - Toulouse, France*; (2) *University Of Tours - Tours, France*; (3) *Université De Montréal - Montreal, Canada*)

**Background:** Multidomain lifestyle training provided through a web platform for older adults are rare. **Objectives:** To describe the feasibility and acceptability of a 6-month web-based multidomain lifestyle training intervention for community-dwelling older people and to test the effects of the intervention on both function- and lifestyle-related outcomes. **Methods:** 6-month, parallel-group, randomized controlled trial (RCT), ran in the Toulouse area, South-West, France. Participants were community-dwelling men and women,  $\geq 65$  years-old, presenting subjective memory complaint, without dementia. The web-based multidomain intervention group (MIG) received a tablet to access the multidomain platform and a wrist-worn accelerometer measuring step counts; the control group (CG) received only the wrist-worn accelerometer. The multidomain platform was composed of nutritional advices, personalized exercise training, and cognitive training. Participants should follow: both exercise and cognitive training twice a week, and nutritional advices twice a month. The main outcomes measures were the feasibility, defined as the proportion of people connecting to  $\geq 75\%$  of the prescribed sessions, and acceptability, investigated through content analysis from

recorded semi-structured interviews. Secondary outcomes included clinical (cognitive function, mobility, mood, nutritional status, health-related quality of life (HRQOL)) and lifestyle (physical activity, step count, food intake, leisure-time cognitive activities) measurements. **Results:** Among the 120 subjects (74.2 ±5.6 years-old; 57.5% women) equally randomized between groups, 109 completed the study (n=54, MIG; n=55, CG). 58 MIG subjects connected to the multidomain platform at least once; among them, adherers of ≥75% of sessions varied across multidomain components: 37 people (63.8% of 58 participants) for cognitive training, 35 (60.3%) for nutrition, and three (5.2%) for exercise; these three persons adhered to all multidomain components. Participants considered study procedures and multidomain content in a positive way; the most cited weaknesses were related to exercise: too easy, repetitive, and slow progression. Compared to controls, the intervention had a positive effect on HRQOL; no significant effects were observed across the other clinical and lifestyle outcomes. **Conclusion:** Providing multidomain lifestyle training through a web-platform is feasible and well-accepted, but the training should be challenging enough and adequately progress according to participants' capabilities to increase adherence. Trial registration. ClinicalTrials.gov; NCT03336320; available at: <https://clinicaltrials.gov/ct2/show/NCT03336320>.

## **Theme 14: TELEMEDICINE AND AD CLINICAL TRIALS**

**P101: REINVENTING ALZHEIMER'S DISEASE PRESCHOOLING: THE GLOBAL ALZHEIMER'S PLATFORM FOUNDATION® (GAP) REMOTE RECRUITMENT AND PRESCHOOLING PROGRAM.** L. Zisko, C. Cordell, J. Smith, J. Trotter, L. Thurman, J. Sipchen (*Global Alzheimer's Platform Foundation (gap) - Washington, USA*)

**Background:** Many parts of clinical trials are moving toward a remote design to reduce COVID-19 exposure and transmission. Conventional recruitment and outreach events often involve direct contact with potential participants during memory clinics, brain health check-ins, or health fairs. The traditional clinical trial prescreening process often requires a potential participant to travel to a research site for an initial appointment. For both prescreening and recruitment events, the usual challenges of getting the potential participant to the event or site due to distance, time constraints, and access to transportation have now been further compounded by increased potential for exposure to COVID-19. Potential participants in Alzheimer's disease (AD) clinical trials are especially vulnerable due to their age. Furthermore, AD trials typically require a study partner, so the potential for exposure has now been doubled. The Global Alzheimer's Platform Foundation® (GAP) is developing a comprehensive remote recruitment and prescreening program for sites in its network (GAP-Net) that protects the safety of the clinical trial community while generating interest in clinical research and enabling collection of robust prescreening data. This program is designed not solely as a contingency during the COVID-19 pandemic but as a long-term strategy to make recruitment and prescreening events more accessible to potential AD participants. **Objectives:** The objectives of the GAP Remote Recruitment and Prescreening Program are as follows: Protect the health and safety of

potential participants and clinical research personnel. Comply with the Health Insurance Portability and Accountability Act (HIPAA) and protect sensitive health information. Deliver remote recruitment and outreach processes / materials that enable sites to generate potential candidates for AD clinical research. Identify participants that are well-characterized for AD clinical trials and retain the interest of those participants. Ensure essential, user-friendly prescreening technology is available to sites and participants. Recommend a pathway for potential reimbursement of prescreening efforts under appropriate federal regulations. **Methods:** GAP's proposed multipronged strategy contains several elements designed to engage potential participants, enable prescreening, and maintain relationships with the community. All programming is customizable to address unique conditions in the community and to leverage annual observances (eg, Black History Month, Clinical Trials Awareness Week). Remote recruitment toolkits facilitate community engagement and stimulate interest in AD clinical research and brain health. Toolkits focus on telehealth options, e-communication platforms, and virtual strategies for staying connected to participants and the community. Among these are GAP-facilitated events such as GAP-Talks, which connect with potential participants on behalf of GAP-Net sites to provide education and awareness about Alzheimer's and Brain Health and engage potential study volunteers. GAP also focuses on information sharing across sites regarding what is working effectively by hosting regular webinars for GAP-Net sites to connect with one another and share ideas. GAP works with sites to develop remote workshops, educational lectures, Town Halls, brain health activities, and other virtual options to maintain a steady recruitment cadence. GAP-Net sites are also focusing on social and digital media campaigns to direct individuals to site websites, study landing pages, and online intake forms. The prescreening toolkit includes a detailed implementation roadmap for sites, a benchmarked process for conducting virtual memory screens (including cognitive assessments), and participant-facing materials explaining the prescreening journey as well as addressing any technology concerns. Technology guidance regarding HIPAA-compliant telehealth video applications is provided, as is technology (laptops, iPads) when possible, to ensure sites have the necessary telehealth equipment. Education on billing opportunities for cognitive testing based on Centers for Medicare and Medicaid Services (CMS) regulations is also available so sites can be appropriately reimbursed for their prescreening activities. **Results:** Program implementation began late 2Q2020 in different venues: Over 450 people have participated in 6 virtual talks (hosted by GAP and GAP-Net sites); more are registering for future events. Sites are seeing increased participation in webinars ranging from 40 to 130 registrants per session. GAP-Net sites recently implementing virtual prescreening programs have already seen a return to pre-pandemic prescreening rates. The Program will be further refined as additional elements are implemented and as more GAP-Net sites re-open for prescreening and screening. **Conclusions:** GAP-Net sites can effectively recruit and prescreen in a remote and virtual environment when provided information, support, and resources. Additional opportunities for more advanced programming may be included for support on specific trials, including kits to facilitate home health visits, where appropriate and approved. GAP's Remote Recruitment and Prescreening Program will provide the field with several benefits. A mechanism for remote prescreening will allow sites



to continue to prescreen while protecting the health and safety of the clinical trial community. A cohort of potential participants that are well-characterized and willing to participate in AD clinical research, which can lower screen fail rates and accelerate enrollment. The remote prescreening process will help offset

delays experienced because of the COVID-19 pandemic. Finally, the program will provide much needed liquidity to AD clinical trial sites.



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