SYMPOSIA

S1- DEVELOPMENT OF A VACCINE FOR PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE

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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 Aβ1-42 peptide. Nineteen percent of patients in the trial generated anti-Aβ 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 Aβ 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 Aβ40 and Aβ42, 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 Aβ42/40 is a promising indicator of Aβ plaque burden that may help discriminate Aβ PET scan positivity, and detect Aβ pathophysiology earlier than PET. Plasma p-tau217 is is an extremely promising indicator of Aβ-related tau pathophysiology that may discriminate neuropathological diagnosis of AD, inform prognosis, and detect Aβ-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 Aβ42/40 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

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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[1], N. Proctor[1], D. Airey[1], J. Sims[1], M. Devous[2], T. Iwatsubo[3] *((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 (Aβ) 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 Aβ by 5-10 years. Neuropathological research also suggests that the accumulation of tau is more closely associated than Aβ with the degree of neuronal loss, cognitive impairment and declining functions of daily living across the AD continuum. Molecular imaging of Aβ 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 Aβ 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[1], S. Walter[1], O. Langford[1], G. Jimenez-Maggiora[1] *((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 rationalee*, P.S. Aisen[1], R.A. Sperling[2], R. Raman[1], M.C. Donohue[1], O. Langford[1], G.A. Jimenez-Maggiora[1], R.A. Rissman[1], M.S. Rafii[1], S. Walter[1], T. Clanton[1], J. Cummings[3] ((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[1], O. Langford[1], T. Clanton[1], M.S. Rafii[1], E. Shaffer[1], J.D. Grill[3], G. Jimenez-Maggiora[1], R. Raman[1], R.A. Sperling[2], J. Cummings[4], P.S. Aisen[1] 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)

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[1], M. Donohue[1], G. Jimenez-Maggiora[1], R. Sperling[2], J. Cummings[3], P. Aisen[1], R. Raman[1] 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) 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)

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.aptwebstudy.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-Maggiora[1], S. Bruschi[1], R. Raman[1], O. Langford[1], M.Donohue[1], M.S. Rafii[1], R.A. Sperling[2], J.L. Cummings[3], P.S. Aisen[1] 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) 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

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[1], N. Bose[2], H. Zetterberg[3,4], S. Lovestone[5], R. Au[6] *((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. T. Goldberg[1], L. Schneider[2], K.V. Papp[3], D. Rentz[3], B. Mormino[4], R.A. Sperling[5], J.C. Stout[6], R. Fuller[7], M. Roché[7], G.T. Stebbins[8], D. Langbehn[8], C. Sampaio[7], M. Donohue[2], C.J. Edgar[9] *((1) Columbia University Medical Center - New York, USA; (2) Keck School Of Medicine - Los Angeles, USA; (3) Department Of Neurology, Brigham And Women's Hospital - Boston, USA; (4) Department Of Neurology And Neurological Sciences Stanford University - Boston, USA; (5) Brigham And Women's Hospital; Massachusetts General Hospital; Harvard Medical School - Boston, USA; (6) School Of Psychological Sciences At Monash University - Melbourne, Australia; (7) Chdi Foundation, USA; (8) Department Of Neurological Sciences, Rush Medical College, USA; (9) Cogstate Ltd., United Kingdom)*

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 β 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 Aβ-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

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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[1], R. Amariglio[1], S. Dhadda[2], M.C. Donohue[3], M.C. Irizarry[2], C. Jenkins[3], D. Jianjun Li[2], K.A. Johnson[4], L. Kramer[2], S. Krause[2], K. Papp[1], M. Rabe[2], R. Raman[3], D. Rentz[1], G. Sethuraman[3], C.J. Swanson[2], J. Zhou[2], P.S. Aisen[3] *((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-ß (Aβ) 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 Aβ 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 Aβ 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 ε4 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 Aβ 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 Aβ 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 Aβ aggregates and prevent further Aβ 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 Aβ, followed by 10 mg/kg every 4 weeks maintenance dosing through 216 weeks to prevent re-accumulation of Aβ. 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 Aβ 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.

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Background: Aducanumab (BIIB037) is a human monoclonal antibody that selectively targets aggregated forms of amyloid beta (Aβ), 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.

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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-β (Aβ), 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 (1:1:1:1) 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 ≥1.27 in the entorhinal cortex [3]). At baseline, mean (SD) core CSF biomarker values measured in a subset of 224 patients were: Aβ40, 17.6 (5.1) ng/mL; Aβ42, 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: α-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: Aβ42/Aβ40, 0.04 (0.01); t-tau/Aβ42, 0.6 (0.3); and p-tau181/Aβ42, 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. Betthauser 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.

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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 (amnestic and non-amnestic 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 Δ Z-score), correct answers on the Verbal Fluency Test increased by 2 words (+0.3 Δ Z-score) but decreased by 1 word on placebo (-0.1 Δ 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[1], K. Adamczuk[1], M. Sampat [1], H. Pham[1], J. Kost[2], M. Egan[2], C. Sur[2] *((1) Bioclinica - Newar, USA; (2) Merck - Kenilworth, USA)*

Background: Inhibition of β-amyloid precursor protein cleaving enzyme (BACE1) has been proposed as a therapeutic strategy to slow Alzheimer's disease (AD) progression by reducing Aβ 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 Aβ, 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 amnestic 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 (β=3.21, η2=0.29, P=0.0001). Synaptic density was also a significant predictor of performance in all five cognitive domains: Language (β=3.82, η2=0.25, P=0.001), Executive Function (β=3.28, η2=0.20, P=0.001), Processing Speed (β=4.03, η2=0.23, P=0.001), Visuospatial Ability (β=3.58, η2=0.22, P=0.001), verbal memory (β=1.35, η2=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 (β=2.16, η2=0.23, P=0.001), and synaptic density was a stronger predictor of cognitive performance than gray matter volume (β=0.01, η2=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. 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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[1], G. Klein[2], N. Cullen[3], N. Mattsson-Carlgren[1], S. Janelidze[1], S. Palmqvist[1], X. Teitsma[1], O. Strandberg[1], P. Coloma[2], E. Borroni[2], E. Stomrud[1], R. Smith[1], R. Ossenkoppele[1], O. Hansson[1] *((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-β (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-β 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 Aβ-positive CU, 49 MCI and 47 AD dementia (all Aβ-positive) and 90 Aβ-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 Aβ-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-flutemeramol 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 Aβ-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 Aβ-positive CU (3.13%), III/IV for Aβ-positive MCI (3.37%) and V/VI (neocortical) for AD dementia (4.94%). In Aβ-negative subjects, SUVR values increased <1% across ROIs. Regression models showed that in Aβ-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, R2=0.141). In Aβ-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, R2=0.253). Power analyses in Aβ-positive CU showed that among 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 Aβ-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 Aβ-positive CU subjects, as well as cortical increases in Aβ-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[1,2], S. Janelidze[1], J. Hertze[2], H. Zetterberg[3,4,5], K. Blennow[3,4], N. Mattsson-Carlgren[1], O. Hansson[1,2] *((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 (Aβ) 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. Aβ 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 Aβ42 were determined using xMAP technology. CSF Aβ40 and Aβ42 levels were analyzed by electrochemiluminescence technology (Meso Scale Discovery) using the MS6000 Human Abeta 3-Plex Ultra-Sensitive Kit. Aβ positivity (Aβ+) was defined as CSF Aβ42/40 <0.07 (cut-off calculated with Youden index within the cohort). **Results:** Baseline plasma NFL was not significantly different between Aβ+ and Aβ- groups (p=0.294). NFL was significantly higher in the MCI-other Aβ+ group than the stable MCI groups (Aβ-: p=0.024, Aβ+: p=0.035), but comparable to MCI-AD. GFAP at baseline was significantly different between Aβ+ and Aβ- groups (p<0.0001). The MCI-AD group had significantly higher baseline concentrations than stable MCI Aβ- and MCI-other Aβ- groups (p<0.0001 both). Higher concentrations at baseline were observed in every Aβ+ subgroup compared to Aβ- ones. Binary logistic regression models for prediction of Aβ+ status showed that plasma GFAP could predict Aβ+ 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 Aβ+ 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 Aβ+ 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 Aβ+ group (ß=0.179, p=0.037) and in the MCI-AD group compared to the stable MCI Aβ- (ß=-0.292, p=0.01). Slopes for plasma GFAP show a significant longitudinal increase (ß=2.018, p<0.0001), with a larger increase in the Aβ+ group compared to Aβ- (ß=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 Aβ- (ß=-4.078, p<0.0001) and stable MCI Aβ+ (ß=-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 Aβ 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[1], M. Irizarry[1], S. Dhadda[1], Y. Zhang[1], J. Wang[1], T. Bogoslovsky[1], L. Reyderman[1], J. Kaplow[1], H. Bradley[1], M. Rabe[1], K. Totsuka[2], L. Kramer[1], H. Hampel[1], C. Swanson[1] *((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 Aβ 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/Aβ(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: LIPIDIDIET RESULTS: 3-YEAR EVALUATION OF FORTASYN CONNECT IN INDIVIDUALS WITH PRODROMAL ALZHEIMER'S DISEASE. T. Hartmann[1,2], A. Solomon[3,4,5], P. Visser[6,7], S. Hendrix[8], K. Blennow[9,10], M. Kivipelto[11,12,5], H. Soininen[13,14] *((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 - Kupio, 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 dementia1,2. Fortasyn Connect is a multinutrient combination that has been shown in preclinical studies to reduce AD-linked brain pathology3. Benefits on memory and functional connectivity were demonstrated in patients with mild AD4,5. 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 20176. **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 multinutrient 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 AD7. 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[1], A. Samaroo[2], H.C. Chou[2], R. Buckley[1], D. Rentz[1], R. Sperling[1], R. Amariglio[1] (*(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[1], T. Ostenfeld[2], M. Pomfret[2], A. Billinton[3], I. Chessell[2], K. Tan[2], N. Brayshaw[4], K. Blennow[5], S. Persson[5], F. Natanegara[6], Y. Feng[6], J. Sims[6], J. Dage[6] *((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 IgG1λ monoclonal antibody, engineered for selective, high-affinity binding of Aβx-42 (Aβ42) peptides and for reduced effector function. **Objectives:** Neurofilament light (NfL) levels in cerebrospinal (CSF) and plasma samples, from the previously reported1 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 ρ: 0.47 at baseline and 0.74 at endpoint). **Conclusions:** MEDI1814, which shows dose-dependent suppression of CSF free Aβ42, 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 (Aβ42)-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[1], L. Reyderman[2], Y. Zhang[2], O. Takenaka[1], S. Yasuda[2], E. Schuck[2], A. Koyama[2], C.J. Swanson[2], Z. Hussein[2] *((1) Eisai Co., Ltd - Tokyo, Japan; (2) Eisai Inc. - Woodcliff Lake, USA)*

Background: BAN2401 is a humanized IgG1 monoclonal antibody thatselectively targets soluble aggregated Aβ 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 (Cmax) at the time of latest dosing before the safety assessment and average serum concentration (Cav) 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 Cmax using the log-hazard model, including attenuation factor of exposure effects and the effect of APOE4 carrier status. Correlation of ARIA-E with Cmax resulted in lower objective function compared to Cav. Thus, BAN2401 exposure in the ARIA-E model was expressed as Cmax. 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 Cmax. 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[1], S. Hennessey[1], J. Neff[2], T. Syndergaard[2], M. Earnshaw[2], S. Hendrix[1] *((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[1], C. Murchison[2], L. Silbert[1], H. Dodge[1], K. Hagen[1], J. David[1], D. Lahna[1], J. Kaye[1], J. Quinn[1], L. Shinto[1] *((1) Oregon Health &is 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 cm3 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[1], E.P. Foff[1], J. Passarell[2], D. Jaworowicz[2], M. Forman[1], J. Owen[1], S. Stankovic[1] *((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-HT2A 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 antidementia 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 (Aβ) accumulation is driving disease pathogenesis. Thus, Aβ reduction has been a target of therapeutic development in AD. Monoclonal antibodies against Aβ 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-Aβ monoclonal antibodies can be an effective treatment for AD remains controversial. **Objectives:** To determine the efficacy of anti-Aβ monoclonal antibodies class as a whole, elucidate differences between individual drugs, and try to ascertain what would be the best anti-Aβ 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)], Aβ pathology (amyloid PET SUVR, CSF Aβ1-40, CSF Aβ1-42), 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 I2statistic. 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 Aβ 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 antibodiesimproved

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 Aβ 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 Aβ1-42 increase {SMD: 0.66 [95% CI (-0.02; 1.34), I2 = 93%]} and a clear increase of CSF Aβ1-40 {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 Aβ 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 Aβ1-40 {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 Aβ 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.
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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 Aβ1-42, 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-β (Aβ) 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.
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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 ADRD trials. A Fellowship track includes current and future principal investigators and focuses on the design, conduct and analysis of ADRD clinical trials. **Objectives:** IMPACT-AD aims to train the next generation of ADRD clinical trialists. Both tracks have an emphasis on inclusion and diversifying the pipeline of ADRD 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 ADRD understanding (e.g., unique ADRD trial populations, ADRD biomarkers, etc.) to trial design and biostatistics. Important but often overlooked topics, such as ADRD-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, ADRD

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 Aβ 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 Aβ prion assemblies into non-toxic Aβ 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-Aβ-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 Aβ 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) APPswePS1dE9 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 Aβ 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.

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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.

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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 22 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[1,2], H. Zetterberg[3], J. Pegueroles[1], T. Karikari[3], M. Carmona-Iragui[1,2], N.J. Ashton[3], V. Montal[1], I. Barroeta[1], L. Videla[1,2], M. Altuna[1], B. Benejam[2], S. Fernández[2], S. Valldeneu[1], D. Alcolea[1], R. Blesa[1], K. Blennow[3], A. Lleó[1]
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Background: Alzheimer's 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-β (Aβ)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 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 Aβ42/40 (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 mechansisms 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 aquired 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 TRIALSB. 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: β-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[1,2] *((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 Aβ42/40 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 Aβ and tau biomarkers using absolute concentrations of body fluids we have introduced the Aβ misfolding as a structure biomarker. The Aß misfolding from a monomeric/unstructured to a β-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 Aβ backbone (1, 2). This vibration causes the amide I absorbance band, which in turn gives information about the secondary structure distribution of all Aβ isoforms. This initial misfolding takes place about 15-20 years before AD is clinically diagnosed followed by β-sheet oligomerization and aggregation to much larger fibrils on the nanometer scale. After several years, this Aß 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 APOEe4 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-1 indicating abnormal misfolding in diseased individuals, recently a second threshold >1646 cm-1 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-1 reflect abnormal misfolding, ≥1644 cm-1 and ≤1646 cm-1 low misfolding, and >1646 cm-1 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 APOEe4 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 APOEe4 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:**
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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 (Aβ) 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 Aβ42 (positive <735 pg/mL; negative ≥735 pg/mL), baseline MMSE, APOE ε4 status (carrier, non-carrier) as well as an interaction between treatment, visit, CSF Aβ42, 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 ≥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 (±7.2 years), 58.4% women, and 69.9% living at home. At baseline, mean MMSE score was 10.0 (±8.0), CMAI score was 62.0 (±15.8), CMAI-IPA was 38.5 (±12.2), NPI-C A+A clinician severity score was 15.8 (±10.8),

and NPI-C-IPA was 15.2 (±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[1], E.P. Foff[2], P. Tariot[3], B. Mcevoy[2], B. Coate[2], G. Demos[2], A. Berrio[2], B. Abbs[2], J.M. Youakim[2], S. Stankovic[2] *((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-HT2A 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 ≥1 and ≤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 ≥6 and ≤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 ≥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 ≥5 and ≤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[1], P. Manser[1], C. Randolph[2], K. Pickthorn[1], M. Blendstrup[1], M. Keeley[1], P. Scheltens[3], S. Sikkes[3] *((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's<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 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 (rs=0.63, p<0.001). However, the correlation was stronger amongst participants with mild AD (rs=0.56, p<0.001) than those with prodromal AD (rs=0.37, p<0.001). Both scales exhibited similar correlations with cognition as measured by the ADAS-Cog13 (A-IADL-Q: rs=-0.44, p<0.001; ADCS-ADL: rs=-0.46, p<0.001) and MMSE (A-IADL-Q: rs=0.33, p<0.001; ADCS-ADL: rs=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[1], I.A. Higgins[1], S. Shcherbinin[1], S.W. Andersen[1], D. Scott[2], K.C. Holdridge[1], R. Yaari[1], J.R. Sims[1] *((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 β and promotes its clearance from the brain. Prior evidence from the solanezumab EXPEDITION3 phase 3 trial (EXP3; NCT01900665) showed that solanzeumab 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 apolipopprotein (APOE) ε4 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 cm3, 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 (± standard deviation [SD]) age of the total cohort was 72.76 (±7.78) years and 42.8% of participants were male. At baseline, mean (± SD) WBV for the total cohort was 990.74 (±106.05) cm3 and mean (±SD) VV was 47.81 (±22.42) cm3. The APOE4 positive cohort consisted of 1835 subjects (N = 927 solanezumab, N =

908 placebo). Mean (±SD) age of the APOE4 positive cohort was 72.67 (±7.19) and 42.3% of the participants were male. Mean (±SD) WBV for the APOE4 positive cohort was 992.56 (±105.56) and mean (SD) VV was 47.60 (±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.

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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 ethnoracial 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 ethnoracial participant groups: Latinx, non-Latinx Black/African American, and non-Latinx White. We determined the overall number and ethnoracial 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 ethnoracial 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±8.0) and had a lower percentage of female participants (48%) (age: Latinx=70.9±7.4, non-Latinx Black/African American=72.0±.7.8; % female: Latinx=73%; non-Latinx Black/African American=72%). Education (years) was similar across the three ethnoracial groups (Latinx=15.9±2.6; non-Latinx Black/African American=15.8±2.5; non-Latinx White=16.5±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 ethnoracial 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 ethnoracial 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 ethnoracially 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[1], T. Howell[1], A. Ekanem[1], D. Flenniken[2], A. Happ[2], M. Ashford[2], J. Hayes[2], D. Truran[2], R.S. Mackin[1], K. Blennow[3], D. Geschwind[4], E. Halperin[4], G. Coppola[5], R. Nosheny[1], M. Weiner[1] *((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 β-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 ± 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 ± 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[1], C. Junge[2], L. Mignon[2], K. Moore[2], C. Yun[2], D. Li[2], D. Norris[2], R. Crean[2], E. Ratti[3], E. Huang[3], R. Lane[2] *((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[1], K. Baruch[1], A. Kertser[1], O. Matalon[1], O. Fursht[1], S. Braiman[1], C. David[1], E. Shochat[2], J.M. Cedarbaum[1,3] M. Schwartz[1,4] *((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 ≥20 mg/kg administered periodically (>q8 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.

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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±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±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. S. Saunders[1], C. Ritchie[1], G. Muniz-Terrera[1], S. Sheehan[1], S. Luz[1], A. Evans[2] *((1) University Of Edinburgh - Edinburgh, United Kingdom; (2) Alzheimer's Research Uk - Edinburgh, United Kingdom)*

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. S. Mattke 1, S.K. Cho[1], T. Bittner[2], J. Hlavka[1], M. Hanson[1] *((1) University Of Southern California - Los Angeles, USA; (2) Roche - Basel, Switzerland)*

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[1], N. Adluru[1], N. Vogt[1], C.A. Van Hulle[1], E. Jonaitis[1], R. Koscik[1], S.R. Kecskemeti[1], N.A. Chin[1], S. Asthana[1], G. Kollmorgen[2], C.M. Carlsson[1], S.C. Johnson[1], H. Zetterberg[3], K. Blennow[3], A.L. Alexander[1], B. Bendlin[1] *((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 vivocharacterizations 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 ε4-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®β-Amyloid (1–42) CSF, Elecsys®Phospho-Tau (181P) CSF and the β-Amyloid (1–40) robust prototype assay. Cutoff values for amyloid and pTau positivity were developed as follows: A CSF Aβ42/Aβ40cutoff (<0.046, Aβ42/Aβ40+) 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 (>= 24.8, pTau+) equals a +2SD above the mean of a reference group of 223 CSF Aβ42/Aβ40-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[1], M. Sanderson-Cimino[1], J. Elman[1], X. Tu[1], A. Gross[2], M. Bondi[1], A. Jak[1], M. Lyons[3], C. Franz[1] *((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 amnestic 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 Aβ-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 effected 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[1], J. Woodcock[1], T. Boyd[1], S. Sillau[1], C. Coughlan[1], J. O'shaughnessy[1], M. Borges[1], A. Thaker[1], B. Raj[2], V. Adame[1], K. Adamszuk[3], D. Scott[3], H. Chial[1], H. Gray[1], J. Daniels[1], M. Stocker[1] *((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/m2/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 (SUVr), 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[1], P. Manser[1], G. Kerchner[2], M. Ward[1], K. Pickthorn[1], M. Blendstrup[1], C. Lansdall[2], M. Keeley[1], F. Mcdougall[1] *((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[1], A. Aschenbrenner[1], G. Wang[1], Y. Li[1], C. Xiong[1], E. Mcdade[1], D. Clifford[1], Y. Roy[2], K. Holdridge[2], R. Bateman[1] *((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[1,2,3], C.A. Mcgibbon[4], P. Jarrett[5,6], D. Bouchard[7], G. Handrigan[8], C.C. Tranchant[9], S. Belleville[10], H. Chertkow[11], H. Feldman[12], H. Nygaard[13], M. Speechley[14] *((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.

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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 ≥ 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 Aβ42/Aβ40, 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[1] *(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 ≥ 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 SUVr, 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 ≥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[1], D. Gillen[1], J. Grill[2] *((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[1], D. Vock[2], L. Zhang[2], D. Salisbury[2], N. Nelson[3], L. Chow[2], G. Smith[4], M. Dysken[2], J. Wyman[2] *((1) Arizona State University - Phoenix, USA; (2) University Of Minnesota - Minneapolis, USA; (3) University Of St Thomas - St Paul, USA; (4) University Of Florida - Gainsville, 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 participanbts, 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 nay reduce decline in global cognition in older adults with mild-to-moderate AD dementia. In summary, exercises nay 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[1], S. Guyonnet[1,2], C. Cantet[1,2], P. De Souto Barreto[1,2], M.W. Weiner[3,4,5], D. Tosun[3,4], C. Boschat[6], J. Hudry[6], T. Bartfai[7], S. Andrieu[2,8], B. Vellas[1,2], J.A.J. Schmitt[6] *((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 ω-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, 15µg of vitamin D, 85mg of choline, 80µg of selenium, 3g of citrulline, 700mg of eicosapentaenoic acid (EPA) and 770mg of docosahexaenoic acid (DHA). Erythrocyte ω-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 ε4 genotype and to presenting low ω-3 index (≤5.69%, i.e. the lowest quartile); high homocysteine (>14µmol/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 ω-3 index (between-group differences: 2.7%, 95%CI: 2.3 to 3.0; $p < 0.0001$) and decreased homocysteine (-3.2µmol/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 (42.4mm3, 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 ε4 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 ε4 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 ω-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[1], O. Billette[1], D. Berron[2], X. Grande[1], A. Spottke[3], K. Buerger[4], R. Perneczky[4], C. Laske[5], A. Schneider[3], F. Klaus[3], S. Teipel[6], J. Wiltfang[7], M. Wagner[3], F. Jessen[8] *((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[1], F. Andersson[2], S. Janelidze[1], E. Stomrud[2], O. Hansson[1] *((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% β-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. E. Ponimaskin[1], J. Labus[1], K.F. Roehrs[1], H. Varbanov[1], R. Kaushik[2], S. Jia[2] *((1) Hanover Medical School - Hannover, Germany; (2) Dzne - Magdeburg, Germany)*

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. C. Hölscher *(Kariya Pharmaceuticals - Copenhagen, Denmark)*

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-1ß 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[1], H. Suzuki[1], E. Musiek[2], T. Ueno[1], T. Sato[1], Y. Osada[1], M. Moline[3] *((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[1,3] D. Frenke[1,2], O. Butovsky[1], H.L. Weiner[1,3] *((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 (Aβ) in the brain resulting from defects in Aβ production and clearance. Our previous studies have shown that intranasal administration of Protollin - a proteosome-based adjuvant composed of outer membrane proteins from Neisseria meningitis and LPS from Shigella flexneri - leads to reduction of insoluble, fibrillar and soluble Aβ 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 Aβ1-42. We also investigated the impact of Protollin on the phagocytic ability of human CD14+ monocytes against Aβ1-42 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 Aβ1-42 in the hippocampus were performed to assess the phagocytic ability of infiltrating monocytes. The phagocytic ability of Protollin-treated FACS-sorted human CD14+ monocytes against HiLyteTM Fluor488-labeled Aβ1-42 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 Aβ1-42 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 Aβ1-42+ monocytes in the brain was observed following stereotactic injection of HiLyteTM Fluor488-labeled Aβ1-42 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+CX3CR1+ cells into the hippocampal regions of the brain after both two and six weeks of treatment. Confocal imaging showed that infiltrating monocytes accumulated around Aβ plaques, exhibited intracellular immunoreactivity to Aβ 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+ monocytes. Confocal imaging and flow cytometry analysis of Protollin-treated human CD14+ monocytes showed an increased uptake of HiLyteTM Fluor488-labeled Aβ1-42 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+ monocytes towards a phagocytic phenotype which results in increased Aβ 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 Aβ 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 AB42/40 RATIO: COGNITIVE IMPACT AT 3 AND 5 YEARS IN A SUBGROUP ANALYSIS FROM THE RANDOMIZED CLINICAL MAPT TRIAL. J. Delrieu[1], B. Vellas[1], C. Cantet[1], R. Bateman[2], S. Andrieu[1] *((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 Aβ42/40 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 Aβ42/40. **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 Aβ42/40 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

Aβ42/40 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[1,2], S. Janelidze[1], S. Erik[1], S. Palmqvist[1], J. Dage[3], N. Mattsson-Carlgren[1], O. Hansson[1] *((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-β 42/40 (Aβ42/40), 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 Aβ42/40, 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 Aβ42/40 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[1], B. Gordon[1], C. Chen[1], G. Wang[1], G. Klein[2], R. Bateman[1], T. Benzinger[1] *((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 he 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 (β = -.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 (β = -.01, SE = .005, t = -1.579, p = .118 [benefit is pos.]) or precuneus thickness (β = .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 β= -.141; putamen β= .151), thalamus (β= -.109), pallidum (β= -.099), and anterior cingulate (rost. ant. cingulate β= -.098; caud. ant. cingulate β= -.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 β= -.063; posterior cingulate β= -.07; isthmus cingulate β= -.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 β= .004, thickness β= -.001]; caud. ant. cingulate [FDG β= -.003, thickness β= -.005]) or subcortical structures (caudate [FDG β= .001, volume β= -11.2]; putamen [FDG β= .007, volume β= -9.92]; thalamus [FDG β= .002, volume β= -32.5]; Pallidum [FDG β= .002, volume β= -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[1], K. Messer[2], R. Thomas[2], C. Evans[2], D. Jacobs[2], S. Jin[2], J. Kaye[3], A. Lacroix[2], Y. Qiu[2], D. Salmon[2], M. Sano[4], K. Schafer[2], H. Feldman[2] *((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 Medine 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[1], Z. Pei[1], K.C. Lee[1], Y. Gonzalez-Rojas[2], T. Doehner[3], J. Puente[3], P. Sciara[4], B. Beck[4], E. Lopez-Brignoni[5], B. Nikolov[5], C. Crowley[6], N. Friedmann[6], L. Burns[6] *((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 Aβ42. Altered FLNA links to the α7-nicotinic acetylcholine receptor (α7nAChR) to allow Aβ42 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 Aβ42-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 Aβ42'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 ≥ 16 and ≤ 26, age 50-85 and CSF total tau/Aβ42 ratio ≥ 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 Aβ42) 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 α7nAChR 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, Aβ42 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 α7nAChR 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 ($R2=0.5$). 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[1], S.N. Gomperts[2], P. Dautzenberg[3], A.W. Lemstra[4,5], S.E. Arnold[2], N. Prins[4,5], H.M. Chu[6], A. Gardner[1], K. Blackburn[1], C. Edgar[7], P. Maruff[8], P. Scheltens[5], J.E. Harrison[5,9] *((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 ("p38α 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 p38α 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, p38α kinase has been linked to the neurotoxicity of α-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 ≥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™, 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 ≥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® 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 p38α 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[1], M. Giroux[2], P. Boyd[1], J. Aluri[2], M. Aoyama[3], P. Sachdev[2], S. O'sullivan[2], E. Takahashi[3], R. Gordon[1], L. Reyderman[2] *((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 (Cmax and AUC). The median time to maximum E2814 concentrations in serum (tmax) 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 (Vz) of 36 L, a clearance (CL) of 0.06 L/hour, and a half-life (t1/2z) 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 Aβ 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 (≥ 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; 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 (Aβ) protein production in vitro and lower lifetime Aβ 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. Aß(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 Aβ oligomers, or reduction of synaptic binding of these oligomers may combine with overall lower Aβ 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) Aβ(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 (Kd = 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 Aβ 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.