

SYMPOSIA

S1- RECENT ADVANCES IN PLASMA BIOMARKERS TO IMPROVE PRECLINICAL AND PRODROMAL AD TRIALS.

Kaj Blennow¹, Jeffrey Dage², Randall Bateman³, Oskar Hansson⁴
(1. University Of Gothenburg - Gothenburg, Sweden, 2. Eli Lilly And Company - Indianapolis, (United states), 3. Washington University School Of Medicine - St. Louis, (United States), 4. Lund University - Lund, (Sweden))

Presentation 1: *Measuring Blood Based Biomarkers of Alzheimer's Disease for Clinical Trials*, Jeffrey L. Dage (Research Fellow; Eli Lilly and Company, Indianapolis, IN, (United States))

Alzheimer's disease is characterized by two core pathologies, amyloid plaques and tau neurofibrillary tangles. There are many molecules in clinical development targeting these pathologies and biomarkers that can identify subjects with either or both pathologies prior to dementia onset are being used to enroll and monitor for treatment effects. Recent advancements have made possible precise measurement of amyloid beta (Ab) peptides and phosphorylated tau in blood samples (P-tau). Given the simplicity a blood test offers, these tests are being broadly explored for applicability to clinical research and used within trials for new drugs. There are many choices for the measurement of each biomarker and a detailed understanding of the methodology and underlying biology is important when making decisions for implementation in clinical trials. Ab is typically evaluated as a ratio incorporating two or more measurements but these can be performed simultaneously through multiplexing technologies. P-tau is measured using isoform specific assays (181, 217, or 231) that may also differ in the location of the tau epitope in sandwich ELISA or Immunoprecipitation methods. This presentation will provide background related to the biology and assay methodology for biomarker measurement as well as recent examples of their use in clinical trials.

Presentation 2: *Blood plasma measures of A β , tau, and NfL species for screening and use in clinical trials of Alzheimer's disease*, Randall J. Bateman (Washington University School of Medicine, St. Louis, MO, (United States))

Background: Recent advances in the development of novel Alzheimer's disease (AD) measures of amyloid, tau, and neurodegeneration in blood have enabled the ability to implement fundamentally different clinical trials in AD. The discoveries of novel tau species in blood, including specific phospho-tau (p-tau) and truncated species have greatly expanded our understanding of tau biology and tau target development. The longitudinal A β , tau, and neurofilament light chain (NfL) changes previously measured in CSF are now being measured accurately in blood, enabling the ability to screen and enroll much larger and diverse populations, design secondary and primary prevention trials, measure drug effects, and speed trial completion. These advances promise to accelerate treatment and prevention development for AD. **Methods:** We analyzed blood plasma measures of A β 42/A β 40, multiple p-tau species, and NfL in sporadic AD and dominantly inherited AD cohorts and determined concordance with their respective CSF biomarkers, amyloid and tau aggregation measures by Positron Emission Tomography (PET) scans, and clinical and cognitive

measures in local and international clinical cohorts. Utilizing diagnostic and progression metrics, we determined potential ways to improve clinical trial performance. **Results:** The longitudinal results indicate that a pathophysiological cascade of events begin with altered CSF and blood plasma A β 42/A β 40, followed by increases in amyloid plaques as measured by amyloid PET, associated with increased phosphorylation of specific CSF tau species (e.g., p-tau217, p-tau181), before increases in NfL, total tau concentrations, hypometabolism, and atrophy. Utilizing these findings and properties of diagnostics of plasma tests, we developed a program for estimating the impact of implementing blood tests in clinical trial design. We found that when high accuracy tests are utilized as an initial screen, months to years and millions of dollars can be saved. **Conclusions:** These findings indicate that blood plasma A β , p-tau, and NfL measures can be highly precise biomarkers of brain amyloidosis, tauopathy, and neurodegeneration and can make much larger and diverse trials possible, and also accelerate enrollment for clinical trials.

Presentation 3: *Diagnostic and prognostic algorithms based on blood biomarkers for use in clinical trials*, Oskar Hansson (Lund University, (Sweden))

Objective: To define optimal diagnostic and prognostic algorithms that can be used to identify AD pathology as well as cognitive decline for use in clinical trials. **Methods:** We used the prospective and longitudinal BioFINDER-1, BioFINDER-2 and ADNI studies to develop and cross-validate different diagnostic and prognostic algorithms. We use data obtained from blood, CSF, cognitive testing, MRI, tau PET and amyloid PET. We focused on the following scenarios: - Preclinical AD trials: i) Identification of Ab pathology in cognitively unimpaired (CU) populations using a combination of cost-effective plasma biomarkers. ii) Defining optimal prognostic algorithm predicting change cognition (in PACC) in Ab+ CU cases. - Trials in prodromal and mild AD. i) Identification of both Ab and tau pathology in cognitively impaired (CI) populations using a combination of cost-effective plasma biomarkers. ii) Defining optimal prognostic algorithm predicting change cognition (in CDR and MMSE) in Ab+ cases with prodromal and mild AD. **Results:** First we compared the accuracy of eight of the most commonly used plasma Ab assays and found that the IP-MS methods performed better than immunoassays to detect cerebral Ab pathology. Next, we found that algorithms including several plasma biomarkers, especially Ab and P-tau, could detect Ab pathology in CU populations and thereby lower the costs of screening to identify study participants for preclinical AD trials. However, when predicting cognitive decline in cases with confirmed preclinical AD, we found that Ab PET and cognitive tests were superior to plasma biomarkers. In CI populations, we found that plasma P-tau-based algorithms were best at detecting both Ab and tau pathology. However, tau PET-based algorithms were superior at predicting cognitive decline in cases Ab+ cases with prodromal and mild AD. **Conclusions:** Different plasma-based algorithms can be used for screening of either CU or CI populations to find individuals with high probability of having AD pathology, which can then be confirmed using PET. However, PET is superior to plasma biomarkers at predicting subsequent cognitive decline.

S2- TRAILBLAZER-ALZ: THREE CLINICAL TRIALS OF DONANEMAB IN EARLY ALZHEIMER'S DISEASE.

Presentation 1: *TRAILBLAZER-ALZ studies: Plasma P-tau assays and the initial performance in clinical trials*, John R. Sims¹, Ming Lu¹, Andrew E. Schade¹, Dawn A. Brooks¹, Mark A. Mintun^{1,2} (1. Eli Lilly and Company, Indianapolis, IN, (United States), 2. Avid Radiopharmaceuticals, Philadelphia, PA, (United States))

Background: Hallmarks of Alzheimer's disease (AD) include the accumulation of amyloid- β (A β) peptide and aggregation of tau protein, leading to amyloid plaques and neurofibrillary tangles, respectively. Plasma levels of phosphorylated (P)-tau217 and P-tau181 are highly associated with AD, as they are elevated in pathologically and clinically diagnosed patients with AD. Donanemab, an antibody specific for the N-terminal pyroglutamate A β epitope that is only present in amyloid plaques, is being investigated for the treatment of AD. Donanemab has demonstrated rapid and deep clearance of amyloid and slowing of clinical decline as measured with the Integrated AD Rating Scale (iADRS) in individuals with early symptomatic AD. **Objectives:** The aim of these analyses was to assess the effect of donanemab treatment on amyloid and tau pathology in the brain, and on plasma levels of the biomarker P-tau217. Also, we explored plasma P-tau181 as a prescreening tool. **Methods:** TRAILBLAZER-ALZ (NCT03367403) was a randomized, double-blind, placebo-controlled Phase 2 study, in participants aged from 60-85 years. Participants were diagnosed with early symptomatic AD and had amyloid- and intermediate tau-positive PET scans. Patients were randomized 1:1 to receive intravenous donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo every 4 weeks for up to 72 weeks. The effect of donanemab on brain amyloid and tau pathology was assessed using the specific PET tracers florbetapir and flortaucipir, respectively. Amyloid-PET scans were collected at baseline, weeks 24, 52 and 76; tau-PET scans were collected at baseline and week 76. Plasma P-tau217 was measured with a fully automated, validated, laboratory-developed test using Quanterix Simoa HD-X technology, with the ability to target low analyte levels in small sample volumes. Plasma samples were collected at baseline, weeks 12, 24, 36, 52, 64 and 76. P-tau217 values were log10-transformed in pre-specified analyses including mixed model analyses to assess the level of change from baseline. Spearman's rank correlation analyses were performed with imaging biomarkers. TRAILBLAZER-ALZ 2 (NCT04437511) is an ongoing Phase 3 study further assessing the efficacy and safety of donanemab in a larger population with early symptomatic AD. It was a similarly designed study as above, with the exception that we also enrolled participants with high tau levels at baseline and used plasma P-tau181 as a non-invasive prescreening tool to reduce PET imaging demand. **Results:** We identified that baseline plasma P-tau217 levels were positively associated with levels at baseline of both amyloid plaque (R=0.147, p=0.026) and neurofibrillary tangles (R=0.383, p<0.0001) as measured by PET. At 76 weeks, donanemab decreased plasma levels of P-tau217 by 24% from baseline (p<0.0001), and significant differences compared to placebo were observed as early as 12 weeks of treatment (p<0.01). Participants in the placebo group had increased plasma P-tau217 with a 6% increase from baseline to the end of the study, which could reflect the progression of the disease. Moreover, we found that change in plasma P-tau217 levels positively correlated with change in amyloid plaque at 24 (R=0.349, p<0.0001) and 76 (R=0.482,

p<0.0001) weeks. Participants were divided into those who reached complete amyloid clearance at 24 weeks of donanemab treatment and those who did not. The decrease in plasma P-tau217 levels at the end of the study mirrored changes seen in neurofibrillary tangles as measured by flortaucipir. Indeed, neurofibrillary tangles tended to be fewer in participants who achieved complete amyloid clearance after 24 weeks compared to those who did not, although these differences were not statistically significant. We subsequently investigated the relationship between the plasma P-tau217 biomarker and neurofibrillary tangles as determined by tau-PET at regional levels in the brain. Again, we found a significant positive correlation between the change in plasma levels of P-tau217 and change in neurofibrillary tangles in the parietal lobe (R=0.171, p=0.031) and frontal lobe (R=0.257, p=0.0011). Finally, we applied modeled data to describe the relationship between decreased plasma P-tau217 and slowing of clinical decline as measured by the iADRS. In addition to the plasma P-tau217 data, we will present initial results of plasma P-tau181 screening in TRAILBLAZER-ALZ 2. **Conclusions:** We demonstrated that amyloid clearance results in a rapid and sustained reduction in plasma P-tau217 levels. Furthermore, change in plasma P-tau217 over the course of the study positively correlated with reduction in amyloid plaque, slowing of neurofibrillary tangle growth and, importantly, slowing of clinical progression. Our results suggest that the plasma P-tau217 blood assay may be considered as an additional biomarker for efficacy, linking the donanemab mechanism of plaque clearance with positive effects on both clinical outcomes and brain tau pathology. TRAILBLAZER-ALZ 2 (NCT04437511) provided an initial look at screening results using a blood-based P-tau assay.

Presentation 2: *TRAILBLAZER-ALZ 2: A Phase 3 Study to Assess Safety and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease*, Paul Solomon¹, Jennifer Zimmer², Cynthia D. Evans², Ming Lu², John R. Sims², Dawn A. Brooks², Mark A. Mintun^{2,3} (1. Boston Center for Memory, Boston, MA, (United States), 2. Eli Lilly and Company, Indianapolis, IN, USA, 3. Avid Radiopharmaceuticals, Philadelphia, (United States))

Background/Objective: Donanemab is an antibody that targets N3pG, a modified form of amyloid- β (A β). TRAILBLAZER-ALZ (NCT03367403) was a phase 2 study of 272 individuals with early symptomatic Alzheimer's disease (AD) with elevated amyloid plaque levels and intermediate tau levels on positron-emission tomography (PET). In TRAILBLAZER-ALZ, donanemab resulted in a 32% slowing of disease progression at 76 weeks on the Integrated Alzheimer's disease Rating Scale (iADRS, composite measure of cognition and function) with a reduction of 85 centiloids in amyloid plaque level. We present baseline characteristics of TRAILBLAZER-ALZ 2 (NCT04437511), a global phase 3 study designed to assess the treatment effects of donanemab on disease progression in individuals with early symptomatic AD. **Methods:** TRAILBLAZER-ALZ 2 is a randomized, placebo-controlled, double-blind study with a planned enrolment of ~1500 participants. The study population comprises individuals 60-85 years of age, with mild cognitive impairment or mild dementia due to AD, and the presence of both brain amyloid plaque and tau pathology (intermediate or high level). The primary analysis will test the intermediate tau pathology population. Participants were randomized 1:1 to placebo every 4 weeks (Q4W) or to donanemab 700mg IV Q4W for 3 doses and then 1400mg IV Q4W, with a potential blinded dose reduction

to placebo based on amyloid plaque clearance at 24 and 52 weeks. The primary endpoint is change from baseline to 76 weeks on the iADRS; secondary endpoints include changes in other cognitive assessments, amyloid PET, tau PET, and volumetric MRI. **Results/Conclusions:** Available enrollment and baseline findings will be presented.

Presentation 3: TRAILBLAZER-ALZ 3 Trial Design and Rationale, Pierre N. Tariot¹, Eric M. Reiman¹, Robert C. Alexander¹, Jessica B. Langbaum¹, Karen Holdridge², Margaret B Ferguson², Roy Yaari², John R Sims² (1. Banner Alzheimer's Institute, Phoenix, AZ, (United States), 2. Eli Lilly and Company, Indianapolis, IN, (United States))

Background: Genetic, biomarker and recent clinical trial evidence support the potential role of the amyloid pathway in the pathogenesis of Alzheimer's disease (AD) (1). The pathophysiological process of AD begins more than two decades before symptoms first appear (2-5). This stage, in which individuals have preserved cognitive and functional abilities but AD pathophysiology is present, is known as preclinical AD. Consensus in the field is that compounds targeting the underlying disease process may have greater benefit when started earlier in the disease continuum (2, 3, 5-8), but no treatments that target AD pathology at the preclinical AD stage are currently available. Donanemab is an antibody specific for the N-terminal pyroglutamate A β epitope that is only present in mature brain amyloid plaques (9). The efficacy of donanemab in plaque removal and slowing cognitive decline in early symptomatic AD was demonstrated in the TRAILBLAZER-ALZ study (9). Exploratory analyses by baseline tau burden also suggest that clinical efficacy following donanemab treatment may be greater when initiated at earlier stages in the neuropathological cascade (10). Thus, this study will evaluate the efficacy of donanemab, an antibody that binds to and removes deposited amyloid plaque, in preclinical AD. **Objectives:** TRAILBLAZER-ALZ 3 (NCT05026866), is a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial designed to assess the impact of donanemab versus placebo in cognitively unimpaired participants with evidence of AD pathology. **Methods:** Overview: Approximately 3300 participants who meet entry criteria will be randomized in a 1:1 ratio to either donanemab (700 mg intravenously (IV) once every 4 weeks (Q4W) for the first 3 doses, then 1400 mg IV Q4W for the next 6 doses) or placebo (IV Q4W for 9 doses). Participants will be followed until approximately 434 participants experience a primary outcome event of clinical progression (an increase at 2 consecutive visits in the Clinical Dementia Rating Global Score (CDR-GS) from CDR-GS = 0 at baseline), so the total duration of study participation will vary for each participant. This trial will use a decentralized approach with visits conducted remotely in whole or in part, with a goal of increasing the number of eligible participants, including those from under-represented groups. All clinical and cognitive assessments will be conducted remotely by central raters. Inclusion/exclusion criteria: Inclusion criteria include: • Males & females aged 55-80 years old; • Telephone interview for cognitive status – Modified (TICS-m) score of intact cognitive functioning, and • Eligible plasma P-tau217 result. Exclusion criteria include: • Mild cognitive impairment (MCI)/dementia or other neurodegenerative disease affecting cognition; • Current or previous use of prescription medications for treatment for MCI or dementia; • Current serious or unstable illnesses; • History of cancer with high risk of recurrence and preventing completion of the trial;

• History of clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions; • Prior treatment with an anti-amyloid immunotherapy; • Any clinically important abnormality at screening on MRI or clinical laboratory test; • Any contraindications for MRI, and; • A centrally read MRI demonstrating presence of ARIA-E (Amyloid-related imaging abnormalities with effusion or edema), >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage or severe white matter disease at screening. **Results:** Other Efficacy Assessments. Secondary endpoints to assess clinical progression include International Shopping List Test, Continuous Paired Associate Learning, International Daily Symbol Substitution Test-Medicines, Category Fluency, Face Name Association Test, Behavioral Pattern Separation-Object test, Cogstate Brief Battery, CDR-Sum of Boxes, Cognitive Function Index, and Montreal Cognitive Assessment. Safety Assessments: To evaluate safety and tolerability of donanemab, this study will monitor spontaneously reported adverse events (AEs), MRI (for ARIA and emergent radiological findings), infusion-related reactions, and Columbia Suicide Severity Rating Scale. Biomarkers: Serum, plasma, and whole-blood RNA samples for biomarker research will be collected at screening and throughout the study. Biomarker analysis will be performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, and variability of participant response (including safety). Plasma P-tau217 and other blood-based biomarkers will be used to further inform clinical outcomes and response to therapy. To assess the effect of donanemab on cerebral amyloid plaque burden and cerebral neurofibrillary tangle burden relative to placebo in the preclinical AD population, a subset of participants will undergo florbetapir and/or flortaucipir PET imaging. **Potential Impact/Conclusions:** TRAILBLAZER-ALZ 3 represents an innovative decentralized trial design with central raters. It includes a time-to-clinical-event model, a blood-based AD biomarker selection criterion, and potentially supportive AD biomarker endpoints. The results of this trial will help address the question of whether donanemab treatment with rapid lowering of cerebral amyloid plaque can delay or even prevent progression to the clinical stages of AD. **References:** (1) Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297(5580):353-356. (2) Bateman RJ, et al. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimers Res Ther*. 2011;3(1):1. (3) Sperling RA, et al. Testing the right target and right drug at the right stage. *Sci Transl Med*. 2011;3(111):111cm33. (4) Villemagne VL, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol*. 2013;12(4):357-367. (5) Fleisher AS, et al. Associations between biomarkers and age in the presenilin 1 E280A autosomal dominant Alzheimer disease kindred: a cross-sectional study. *JAMA Neurol*. 2015 Mar;72(3):316-24. (6) Reiman EM, et al. Alzheimer's prevention initiative: a proposal to evaluate presymptomatic treatments as quickly as possible. *Biomark Med*. 2010 Feb;4(1):3-14. (7) Schneider LS. The potential and limits for clinical trials for early Alzheimer's disease and some recommendations. *J Nutr Health Aging*. 2010;14(4):295-298. (8) Siemers ER, et al. Phase 3 solanezumab trials: secondary outcomes in mild Alzheimer's disease patients. *Alzheimers Dement*. 2016;12(2):110-120. (9) Mintun MA, et al. Donanemab in early Alzheimer's Disease. *N Engl J Med*. 2021;384(18):1691-1704. (10) Mintun MA, et al. Donanemab slows progression

of early symptomatic Alzheimer's disease in Phase 2 proof of concept trial. Presented virtually at the International Conference on Alzheimer's & Parkinson Diseases™ 2021 (AD/PD™ 2021); March 9-14.

S3- BRINGING REPURPOSED DRUGS TO MARKET: CHALLENGES AND OPPORTUNITIES FROM RESEARCH TO COMMERCIALIZATION. Howard Fillit¹, Ana Pereira², Giacomo Koch³, Michela Gallagher⁴ (1. *Alzheimer's Drug Discovery Foundation - New York, (United States)*, 2. *Icahn School Of Medicine At Mount Sinai - New York, (United States)*, 3. *Fondazione Santa Lucia - Rome, (Italy)*, 4. *Agenebio - Baltimore, (United States)*)

Repurposing drugs for a new indication offers an accelerated pathway for new treatments to patients but is also fraught with significant challenges. These risks include: 1) the continued need for expensive and risk clinical trials; 2) limited or no patent protection or patent life; and 3) commercialization and reimbursement challenges (1). Repurposing of drugs requires funding to prove that the drugs are safe and effective and creation of financial incentives to enable these drugs to reach the target patient population. The current symposium will feature presentations from three investigators who have recently reported promising results of their phase II clinical trials of repurposed drugs for Alzheimer's disease. Each researcher will provide results from these investigations followed by a discussion of commercialization strategies being planned as they advance their drug trials including: - Barriers to investment in the necessary clinical trials; - Novel approaches to getting new indications added to labels of generic drugs; - Creating innovative royalty structures to provide financial incentives to justify the cost of testing old drugs for a new disease.

Presentation 1: *Repurposing Riluzole for Mild Alzheimer's Disease*, Ana Pereira (Icahn School Of Medicine At Mount Sinai - New York, (United States))

Dysregulation of glutamatergic neural circuits is implicated in a cycle of toxicity, believed to contribute to the neurobiological underpinning of Alzheimer's disease. Preclinical studies demonstrated that the glutamate modulator riluzole, which is an FDA-approved for the treatment of amyotrophic lateral sclerosis, has potential benefits on cognition, structural and molecular markers of aging and Alzheimer's disease. Based on these data an exploratory clinical trial was conducted, using neuroimaging biomarkers, to assess the potential efficacy and safety of riluzole in patients with Alzheimer's disease as compared to placebo that was funded by the Alzheimer's Drug Discovery Foundation (ADDF) and the Dana Foundation. Measures of cerebral glucose metabolism, a well-established Alzheimer's disease biomarker and predictor of disease progression, declined significantly less in several pre-specified brain regions of interest in riluzole-treated subjects in comparison to placebo group. A positive correlation was observed between cognitive measures and regional cerebral glucose metabolism. These findings support our primary hypothesis that cerebral glucose metabolism is preserved by treatment with riluzole. Investment in larger, longer duration studies to test riluzole's efficacy as a potential novel therapeutic intervention for Alzheimer's disease are being planned to support a label claim; a commercialization strategy will be discussed.

Presentation 2: *Towards a Phase III Trial of Rotigotine in Combination with Cholinesterase Inhibitors in Patients with Alzheimer's Disease*, Giacomo Koch (Fondazione Santa Lucia - Rome, (Italy))

Impairment of synaptic plasticity represents a key pathogenic mechanism in the development of Alzheimer's disease. Dopamine (DA) is a key neuromodulator affecting several distinct steps of synaptic transmission and synaptic plasticity. In addition, DA plays an important role in the control of higher cognitive functions such as memory, learning, attention and decision-making. Thus, dysfunction of dopaminergic transmission has been hypothesized to contribute to the pathophysiology of Alzheimer's disease. In a Phase Ib study, treatment with DA agonists restored the altered mechanism of LTP-like cortical plasticity in patients with Alzheimer's disease as well as improved executive function. In a Phase II safety and efficacy study, funded by the ADDF, rotigotine as an add-on therapy to cholinesterase inhibitors in mild-moderate Alzheimer's disease, improved frontal lobe function and reduced functional decline relative to placebo. Given these promising results, we hypothesize that treatment with the dopaminergic agonist rotigotine may slow down Alzheimer's disease related decline by improving frontal lobe cognitive function and reducing the decline of functional impairment. Hence, we aim to confirm our hypothesis by testing the efficacy, safety and tolerability of rotigotine as adjunctive therapy to cholinesterase inhibitors in patients with mild-moderate Alzheimer's disease in a multi-site, randomized, double-blind, placebo-controlled Phase III study that will be funded by the ADDF. This study design and regulatory strategy was developed in consultation with the FDA that provides a path to commercialization for a new rotigotine indication.

Presentation 3: *Low-dose Levetiracetam for Treatment of Age-related Cognitive Impairment and to Delay Progression of Alzheimer's Dementia*, Michela Gallagher (Agenebio, Baltimore, MD, (United States))

There is now strong evidence from preclinical models and human patients that neuronal circuits become hyperactive in prodromal Alzheimer's disease contributing to the accumulation and spread of Alzheimer's pathology and to subsequent cognitive decline. Hippocampal hyperactivity is most pronounced in patients with amnesic MCI and amyloid pathology (i.e., MCI due to Alzheimer's disease). AgeneBio is developing therapeutics to reduce hippocampal overactivity and to test the hypothesis that such treatment will slow progression from MCI to Alzheimer's dementia. In a phase II dose-ranging study, similar to observations in preclinical studies, low-dose levetiracetam reduced hippocampal hyperactivity and improved cognition improvement in subjects with Alzheimer's disease; efficacy was not observed at higher doses used clinically to treat epilepsy. AgeneBio subsequently developed a once-a-day extended-release formulation of levetiracetam (AGB101) in order to maintain efficacious drug exposure in the low dose range. AgeneBio's Phase IIb/III candidate AGB101 is now the first and only therapeutic being investigated to target hippocampal overactivity to slow progression and delay the onset of Alzheimer's dementia (HOPE4MCI trial). The HOPE4MCI trial (NCT03486938) is now fully enrolled using FDA agreed Phase III endpoints. The challenge of developing and bringing a repurposed drug to market is foremost patent protection. AgeneBio developed a unique approach to Intellectual Property protection related

to the need for a low, consistent concentration of drug to be efficacious. Thus, AgeneBio has strong protection for AGB101 with multiple patents including the use of low-dose levetiracetam to treat age-related cognitive impairment and to delay progression of Alzheimer's dementia, the low-dose, extended-release formulation, and the relevant pharmacokinetic exposure range. 1. Shineman DW et al. Overcoming obstacles to repurposing for neurodegenerative disease. *Ann Clin Transl Neurol.* 2014; 1(7):512-8.

S4- METABOLOMICS A BIOCHEMICAL ROADMAP FOR DRUG DISCOVERY IN ALZHEIMER'S DISEASE.

Rima Kaddurah Daouk¹, Priyanka Baloni², Kamil Borkowski³
(1. *Duke University Medical Center - Durham, (United States)*,
2. *Institute For Systems Biology - Seattle, (United States)*; 3. *Univ Of California, Davis - Davis, (United States)*)

The Accelerating Medicines Partnership Alzheimer's Disease (AMP-AD) is a precompetitive partnership among government, industry, and nonprofit organizations to transform the current model for developing new diagnostics and treatments for Alzheimer's disease. AMP-AD initiative believes that developing effective therapies will require transforming the AD research and drug development process into one that is participatory, collaborative, well-integrated, and iterative. Six large consortia embedded in AMP-AD are generating big data that are used synergistically to inform about disease mechanisms and to highlight novel targets for drug design. The AD Disease Metabolomics Consortium under AMP-AD leverages powerful metabolomics and lipidomics technologies to define alterations in biochemical pathways and networks across the trajectory of disease using large cohorts including ADNI, AIBL, ROSMAP, and Rotterdam study. By connecting the genome, metabolome and clinical data we have created a first molecular atlas for AD that can help define genetic contributions to biochemical aberrances steps for accelerating drug discovery and drug development for AD. Our large NIA funded initiative "Alzheimer Gut Microbiome Project" seeks to better characterize the gut-brain biochemical axis and contributions of the gut microbiome to AD biogenesis. We will share approaches and progress to date highlighting three therapeutic areas and possibilities for drug repurposing that include: role for gut microbiome through cholesterol clearance and bile acid production; a role for lipid metabolism ceramide sphingomyelin S1P, and inflammation-related pathway endocannabinoids and eicosanoids. In the first presentation, we will provide evidence that supports a role for gut microbiome in AD pathogenesis. Bile acids (BAs) are the end products of cholesterol metabolism produced by human and gut microbiome co-metabolism. Profiling ADNI 1600 participants we show that AD compared to cognitively normal older adults have significantly lower serum concentrations of a primary BA (cholic acid [CA]) and increased levels of the bacterially produced, secondary BA, deoxycholic acid, and its glycine and taurine conjugated forms. An increased ratio of deoxycholic acid:CA, which reflects 7 α -dehydroxylation of CA by gut bacteria, strongly associated with cognitive decline, a finding replicated in serum and brain samples in the Rush Religious Orders and Memory and Aging Project. Of 23 BAs and relevant calculated ratios, three BA signatures were associated with CSF A β 1-42 («A») and three with CSF p-tau181. Furthermore, three, twelve, and fourteen BA signatures were associated with CSF t-tau, glucose metabolism, and atrophy. Analysis of 2,114 post-mortem brain transcriptomes, and 500 brain metabolomes from ROSMAP collection we confirm that bacterially produced BA are all present in brains and that most likely they were

transported from the blood into the brain. We suggest novel therapeutic approaches based on gut microbiome modulation. In the second presentation, we provide an overview of multi-omic analyses to identify potential actionable targets in the ceramide sphingolipid pathway that is implicated in AD. We analyzed post-mortem brain transcriptome data of 1000 AD and cognitively normal individuals from three independent cohorts. The transcriptome data was integrated with the brain region-specific metabolic networks to identify metabolic genes and differential reaction fluxes in this pathway in AD individuals. The genes identified from the metabolic analysis were subjected to multimodal neuroimaging analysis to identify genetic variants associated with brain atrophy and brain glucose metabolism in AD. We assessed the lipid species in SM pathway using the lipidomics data and metabolite wide association studies. The multiomic analyses provided insights into potential drug targets and we identified drug repositioning candidates that were tested in animal models. To show the power of multiomic approach in identifying metabolic readouts that can be translated to potential therapeutic interventions in AD, we analyzed the human data (blood and brain) using various in silico approaches and validated our findings in animal models. The multiomic analyses indicated an increase in ceramides and depletion of sphingosine-1-phosphate (S1P) levels that in turn disrupted the sphingolipid homeostasis in AD. From our analysis we identified S1P metabolism as potential AD drug target. We tested our hypothesis by modulating the S1P activity in amyloidogenic APP/PS1 mice model using fingolimod, an FDA-approved drug for relapsing multiple sclerosis. Fingolimod treatment alleviated cognitive deficits in APP/PS1 mice. Our multiomic approach identified potential targets in the SM pathway and suggested that modulators of S1P metabolism are potential candidates for treatment of AD. Other than Fingolimod, we have also identified other S1P receptor modulators that can be tested and repurposed for treatment of AD. In our third presentation, we discuss the lipid mediators, (i.e. endocannabinoids and oxylipins) as potential new biomarkers of cognition in AD and targets for therapeutic intervention. We analyzed two cohorts: A) cross-sectional analysis of serum from elderly subjects (n=210) with or without mild cognitive impairment (MCI); B) case-control comparison of plasma and matched CSF from AD patients (n=150) and healthy controls (n=135). Lipid mediators were measured using state-of-the-art targeted quantitative mass spectrometry. We used machine learning as a variable reduction technique, followed by stepwise regression (linear for cognitive measures and logistic for AD phenotype) to identify independent lipid mediator predictors of cognition and AD phenotype. We found associations with both cognition and AD phenotype with members of two metabolic pathways: soluble epoxide hydrolase (sEH) was negatively associated with perceptual speed and higher in AD patients; fatty acids ethanolamides, a class of endocannabinoids, manifesting positive associations with perceptual speed and lower levels in AD patients. Both pathways regulate inflammation with sEH additionally regulating vascular tone, a potential implication for blood brain barrier. Current work shows association of cognition and AD phenotype with both central and peripheral markers of inflammation and vascular regulators. This study supports the involvement of sEH and endocannabinoid metabolism in AD, yielding potential biomarkers of the disorder. The results further suggest that combined pharmacological intervention targeting both metabolic pathways, possibly by using natural exogenous cannabinoids and newly developed sEH inhibitors, may have therapeutic benefits.

S5- DIVERSITY IN ALZHEIMER'S DISEASE CLINICAL TRIALS. Holly Massett¹, Nancy Lynn², Jason Resendez³, Peggie Dilworth-Anderson⁴ (1. National Institute on Aging, U.S. National Institutes of Health, Bethesda, MD, (United States), 2. BrightFocus Foundation, Los Angeles, California, CA, (United States), 3. UsAgainstAlzheimer's Center for Brain Health Equity; Washington, DC, (United States), 4. Gillings School of Global Public Health UNC; Chapel Hill, NC, (United States))

Alzheimer's Disease (AD) is the most common cause of dementia, accounting for 60-80% of dementia cases and affecting an estimated five million Americans aged 65 or older (Alzheimers Association, 2020). By 2050, this number is expected to almost triple to 14 million (Kelley & Petersen, 2007). Race and gender disparities are first order issues in the prevalence of AD, with disproportionately higher rates among women, blacks, and Hispanics (Manly & Mayeux, 2004). The field has seen meaningful scientific advancement; however, non-scientific barriers dramatically impact researchers' ability to find an Alzheimer's treatment. The rates of trial enrollment and completion are much slower for Alzheimer's disease than other therapeutic areas (Aisen et al., 2020), and often the recruiting period is double the length of the trial treatment period itself. And while minorities in the US are more likely to be impacted by the disease, they are less likely to be included in clinical research, as over 95% of clinical trial participants are white (Olin et al., 2002). Despite the challenges, many African Americans express interest in participating in clinical research especially if it can benefit their own communities (Farmer et al., 2007). The lack of inclusiveness in clinical research further exacerbates the lack of knowledge about the progression of disease in populations of color. Faster completion of clinical trials increases our understanding of Alzheimer's and our ability to find treatments and a cure. We must do better to ensure that our scientific data from randomized clinical trials matched the burden of disease in our U.S. population as much as possible.

SYMPOSIUM RS01- CANNABINOIDS FOR NEUROPSYCHIATRIC SYMPTOMS OF ALZHEIMER'S: TRIAL DESIGNS AND OUTCOMES. Paul Rosenberg¹, Krista Lanctôt², Brent Forester³, Jacobo Mintzer⁴ (1. Johns Hopkins Hospital - Baltimore, (United States), 2. Sunnybrook Research Institute - Toronto, (Canada), 3. Mclean Hospital - Belmont, (United States), 4. Roper St. Francis Healthcare - Charleston, (United States))

Neuropsychiatric symptoms (NPS) are near-universal in Alzheimer's disease (AD) causing great distress to patients and caregivers alike. There are no FDA-approved medication treatments and for this reason new classes of medications are being explored including cannabinoids (CBs) particularly for agitation and anxiety. There are two classes of CB receptors: CB1 which appears to be associated with anxiety and other NPS, and CB2 which may mediate neuroinflammation. There are two CB receptor agonists being explored for treating agitation in AD: 1) tetrahydrocannabinol (THC) which is the major active ingredient of cannabis and mediates many of the effects popular in recreational cannabis use; 2) cannabidiol (CBD). There has been increasing use of THC and CBD to treat NPS (particularly agitation and anxiety) in AD with many anecdotal reports of improvement. In this symposium Dr. Lanctôt will present results from a randomized controlled trial (RCT) of THC (nabilone) with impressive benefit in lowering agitation and present the design of a multi-site nabilone trial currently in the field. Dr. Mintzer will present the rationale and design of LIBBY, an RCT of a THC/CBD combination for agitation in hospice eligible patients with Dementia. Dr. Forester will

present the rationale and design of an RCT of THC targeting agitation AD (THC-AD) and for an open-label trial of CBD in AD targeting anxiety. We believe that improving knowledge and understanding of the potential for cannabinoid treatment for NPS in dementia is timely and potentially of great impact for AD treatment.

Presentation 1: *Nabilone for the treatment of agitation in Alzheimer's disease*, Krista Lanctôt (Sunnybrook Research Institute - Toronto, Canada)

The high prevalence and impact of agitation in moderate to severe Alzheimer's disease (AD) makes this neuropsychiatric symptom a key determinant of quality of life. Agitation frequently necessitates use of antipsychotics, which, while well-studied, have modest efficacy and severe side effects including increased mortality. Therefore, new treatments for agitation need to be explored. This presentation will focus on the study design for NAB-IT (Nabilone for Agitation Blinded Intervention Trial). NAB-IT is an ongoing nine-week, placebo-controlled, double-blind RCT of nabilone, a synthetic form of THC. The NAB-IT protocol was based on results from our initial pilot study, which compared nabilone (1-2 mg x 6 weeks) to placebo (x 6 weeks) in a cross-over trial in 38 patients with moderate-to-severe AD. Those results showed that nabilone significantly improved agitation and other AD-related outcomes but it was limited by its sample size. NAB-IT is a multicentre trial with 5 sites across Canada, and aims to recruit 112 patients with AD and agitation. Based on our pilot trial, all patients will undergo a one-week placebo run-in. The purpose of the placebo run-in is two-fold: to minimize placebo effect, where patients experience improvements in agitation symptoms through non-specific study effects, and to monitor adherence. The primary outcome of NAB-IT will be the Cohen-Mansfield Agitation Inventory, and secondary measures will include safety, behaviour, cognitive measures, weight, nutritional status, pain and global change, which will be measured using standard, validated, stage and disease-appropriate assessments. This trial will evaluate the efficacy and safety of nabilone for agitation associated with AD.

Presentation 2: *Assessing the efficacy and safety of synthetic THC (Dronabinol) for agitation and CBD for anxiety in Alzheimer's dementia*, Brent Forester (Mclean Hospital - Belmont, MA, (United States))

Given the prevalence, morbidity and caregiver burden associated with agitation and anxiety in Alzheimer's disease (AD), and lack of approved therapies, there is a need for safer and more effective interventions for these common complicating neuropsychiatric symptoms (NPS) of AD. This presentation will summarize the rationale, aims, study design and planned study outcomes for two ongoing trials investigating endocannabinoids for the treatment of agitation and anxiety in AD. THC-AD is a three-week placebo-controlled, double-blind, RCT of dronabinol (10 mg QD) in 80 subjects with severe agitation in Alzheimer's disease (AD). Dronabinol is synthetic tetrahydrocannabinol (THC, one of the predominant biochemical constituents of cannabis). We hypothesize that, compared with placebo, dronabinol treatment will be associated with greater reduction in agitation symptoms, as measured by the Pittsburgh Agitation Scale and NPI-C Agitation/Aggression subscales, and will be well tolerated with adverse events not significantly different than placebo. The CBD-AD trial aims to reduce anxiety symptoms, affecting 25-70% of individuals with dementia, with cannabidiol (CBD), the non-intoxicating

constituent of cannabis and industrial hemp. Hemp contains <0.3% Delta-9-Tetrahydrocannabinol (THC) by weight. This study is an 8-week open-label clinical trial of 12 subjects, utilizing a full spectrum, hemp based, high-CBD/low-THC sublingual solution as a treatment for anxiety in older adults with Alzheimer's disease. We hypothesize that twice daily treatment with this product will be associated with a reduction in anxiety, as measured by the anxiety domain of the NPI-C, the GAD-7 and the Beck Anxiety Inventory). We also hypothesize that the product will be well tolerated.

Presentation 3: *Life's end Benefits of CannaBidol and TetraHydrocannabinol (LiBBY) Trial*, Jacobo Mintzer (Roper St. Francis Healthcare – Charleston, SC, (United States))

This presentation will describe a project that will be conducted in the context of the Alzheimer's Clinical Trials Consortium (ACTC). The goal is to develop safe and effective approaches for the treatment of hospice care-eligible, agitated subjects suffering from Alzheimer's Disease (AD) or other types of dementia (HAAD). Today, half of the subjects suffering from AD will use hospice care in the last days of their life. In the absence of evidence-based guidelines, HAAD is treated with a combination of antipsychotics, benzodiazepines, and opiates, which generate a variety of side effects. This ongoing project will test the efficacy of an oral combination of two cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD), for the treatment of agitation in HAAD. A combination of THC and CBD oils will be used because of the enhanced synergistic effects while maintaining a low side effect profile that the combination may provide. The will be a 12-week, phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in HAAD patients. The primary outcome will be agitation as measured by the Cohen-Mansfield Agitation Inventory. A total daily dose of 8 mg of THC and 400 mg of CBD dissolved in digestible oil will be administered 2 times per day. The study will recruit 150 HAAD subjects from 15 USA sites over a 2-year period. A 6-month, open-label extension study will be available to facilitate recruitment and retention and to monitor long-term safety of the THC/CBD combination.

SYMPOSIUM RS02- THE NEXT GENERATION OF SPEECH BIOMARKERS FOR THE EARLY DETECTION OF ALZHEIMER'S DISEASE. Emil Fristed¹, Caroline Skirrow², Jack Weston¹, Lampros Kourtis³, Nicole Bjorklund⁴, Kristina Malzbender⁵, Shobha Purushothama⁴, Howard Fillit⁴ (1. Novoic - London, (United Kingdom), 2. Novoic - Bristol, United Kingdom, 3. Tufts University Medical Center, Gates Ventures, Circadic - Boston, (United States), 4. Alzheimer's Drug Discovery Foundation - New York, (United States), 5. Gates Ventures - Kirkland, (United States))

Presentation 1: *Validation of a novel fully automated story recall task for repeated remote high-frequency administration*, Caroline, Skirrow (Novoic - Bristol, (United Kingdom))

Episodic memory tests, such as story recall tasks, show some of the earliest changes associated with Alzheimer's disease. The Automatic Story Recall Task (ASRT) consists of 36 parallel stories (18 long stories and 18 short), balanced for key linguistic and discourse metrics, and developed for self-supervised administration. The ASRT is designed to elicit naturalistic connected speech while constraining the domain of discourse, providing a natural setting for automated speech assessment. We present initial results from the AMYPRED

study (NCT04828122) in which a subset of participants (N=95; 32 with Mild Cognitive Impairment (MCI), and 63 cognitively normal (CN)) were assessed remotely over seven days using their personal smart devices. Stories were administered in triplets, with recall recorded immediately after presentation, and after a delay. Responses were automatically uploaded, auto-transcribed by an automatic speech recognition system, and auto-scored using an automated text similarity metric. Engagement with the assessment battery was high (mean 73% MCI vs 80% CN completing at least one story each day), and did not differ between groups. Lower text similarity score indicating poorer task performance was observed in participants with MCI ($p<0.001$). Correlations of task performance between individual parallel ASRT stories were moderate, as were correlations with the Wechsler Logical Memory Test (a test of verbal episodic memory administered in clinic and manually scored), indicating acceptable parallel forms reliability and concurrent validity, respectively. Despite using a generic text similarity metric to score responses, the results show that remote self-supervised administration and auto-scoring yields sensitive cognitive data in key populations, supporting the use case for longitudinal disease monitoring. New metrics targeting other changes measurable in speech data (acoustic, semantic, linguistic) in early-stage Alzheimer's disease could further leverage the information content of ASRTs, developing a new class of powerful, fully automated speech biomarkers.

Presentation 2: *How clinically informed deep learning can make better speech biomarkers*, Jack, Weston (Novoic London, (United Kingdom))

Development of speech biomarkers for Alzheimer's disease has been dominated by hand-crafted speech features, such as articulation rate and idea density, typically with clinical or at least empirical rationale. More recently, out-of-the-box deep learning approaches such as BERT have gained traction, sometimes outperforming hand-crafted features while requiring no domain expertise. Despite this, the difficulty in characterizing what patterns these 'black box' models are detecting raises concerns about their clinical viability. Whether to use deep learning or domain expertise is a false dichotomy. In this presentation, we make a case for clinically informed deep learning: exploiting domain knowledge in speech, language, cognition and disease to inform inductive biases for deep learning models. Instead of hand-crafting features, which act as narrow proxies for the true quantity of interest (such as syntactic fluency), models can be primed to detect broader classes of patterns. This is a powerful paradigm when the quantities of interest are poorly understood or difficult to describe mathematically. To illustrate this, we review a number of deep-learning-based biomarkers informed by clinical inductive biases for detecting early-stage Alzheimer's disease. One example analyses a story recall task to make a biomarker targeting episodic memory, framing it as a generalized paraphrase evaluation task. Another example exploits domain knowledge of speech and acoustic physics to learn representations of non-timbral prosody, which retains information predictive of Alzheimer's disease despite being de-identified, an important consideration for sharing data ethically and compliantly. Little progress has been made incorporating domain knowledge into deep learning models for Alzheimer's disease. We believe these methodologies will prove vital for building robust, reliable speech biomarkers that can be used in clinical care.

Presentation 3: : *A harmonized speech dataset for Alzheimer's disease biomarker development: study design of the Diagnostics Accelerator Speech Consortium Study*, Lampros Kourtis (Tufts University Medical Center, Gates Ventures, Circadic - Boston, (United States))

Translating speech biomarkers for early stage AD into the clinic will require a speech dataset with robust sample sizes in an early to middle to late stage population, multi-lingual samples, appropriate negative controls, and a uniform gold standard to validate against – all requirements that previous datasets have failed to meet. While recent studies such as the AMYPRED studies (NCT04828122, NCT04928690) are addressing some of these problems, others remain. To address this gap, the Alzheimer's Drug Discovery Foundation's Diagnostics Accelerator (DxA) has set up a Speech and Language Consortium, a global partnership between clinicians, researchers, and data scientists that aims to create and share a gold-standard dataset. The DxA Speech and Language Consortium Study is a longitudinal, observational, multi-site substudy for speech collection based on in-clinic and remote, self-administered speech and language assessments. The study intends to implement a harmonized speech collection protocol, designed by global leaders in the field, in multiple ongoing global cohort studies/sites. The study aims to recruit approximately 3000 subjects ranging from cognitively normal, through preclinical and prodromal Alzheimer's, to Alzheimer's dementia, as well as subjects with FTD, LBD, VD, and PD. Associated data will include the annual collection of neurocognitive assessments, imaging (MRI, PET), CSF and blood biomarkers. Speech collection is done annually in-clinic and remotely every 3 months, through an app-based speech task battery and a study-provided tablet. The speech task battery includes a novel fully automated story recall task, a picture description task, and open ended questions along with sleepiness, mood and vigilance assessments for quality control. The study's pilot phase will be initiated in selected centres in Q3 2021 with the main phase expected to start in Q1 2022. The DxA Speech Consortium Study will enable head-to-head comparison of existing algorithms, and facilitate the next decade of research in speech biomarkers.

SYMPOSIUM RS03- BACK TO THE FUTURE: EMERGING OPPORTUNITIES TO TREAT BASAL FOREBRAIN CHOLINERGIC NEURON (BFCN) DYSFUNCTION IN ALZHEIMER'S DISEASE (AD). Marwan Sabbagh¹, Ole Isacson^{2,3}, Ralph A Nixon^{4,5}, John J. Alam⁶ (1. *leveland Clinic Lou Ruvo Center for Brain Health - Las Vegas, NV, (United States)*, 2. *Neuroregeneration Research Institute At Mclean Hospital - Belmont, (United States)*, 3; *Harvard Medical School - Boston, (United States)*, 4. *Center For Dementia Research, Nathan S. Kline Institute for Psychiatric Research - Orangeburg, (United States)*, 5. *NYU Langone Health - New York, (United States)*, 6. *EIP Pharma, Inc - Boston, (United States)*)

Presentation 1: *The Contribution of BFCN Dysfunction and Degeneration to Disease Expression and Progression in AD*, Ole Isacson (McLean Hospital Belmont, MA, (United States))

The basal forebrain is the primary source of cholinergic innervation in the brain and plays a major role in learning, memory, and attention. Diffuse projections from basal forebrain cholinergic neurons (BFCNs) terminate notably in the hippocampus and throughout the cortex. Degeneration of the basal forebrain occurs in age-related cognitive decline and with a range of neurodegenerative diseases, including and

particularly Alzheimer's disease (AD)), with basal forebrain dysfunction preceding hippocampal dysfunction and being predictive of AD. Though the approval of cholinesterase inhibitors validated the "cholinergic hypothesis", the limited symptomatic effects and minimal effects on disease progression of these agents led the scientific community to look elsewhere for disease-modifying therapies. In retrospect, as the cholinesterase inhibitors do not address the functional deficits within BFCNs, the limited efficacy does not negate the cholinergic hypothesis. This is particularly so because recent evidence indicates that timing of acetylcholine release in hippocampus is critical, with spikes in release at specific time junctures during memory formation being beneficial, while prolonged exposures that mimic the effect of cholinesterase inhibitors being deleterious. That is, physiologic cyclical release of acetylcholine from healthy, functional BFCNs may have very different effects from prolonging the duration of the signal through inhibiting the degradation of residual acetylcholine released from dysfunctional BFCNs. Thus, therapies that reverse BFCN dysfunction, leading to physiologic release patterns, could be expected to have significantly better efficacy than the approach of compensating for BFCN dysfunction with cholinesterase inhibitors. This presentation will review the current state of the art understanding of function and dysfunction of BFCNs, and the most recent evidence supporting the role of BFCN degeneration to disease progression in AD. In addition, the evidence supporting the reversibility of BFCN dysfunction, and reversibility of the loss of cholinergic phenotype, will be presented. Finally, a perspective on the role of therapies directed at BFCNs relative to the anti-amyloid therapies, have demonstrated modest effects on disease progression, will be provided.

Presentation 2: *Mechanisms of, and Preclinical Results with Novel Approaches to Treating, BFCN Dysfunction and Degeneration* Ralph Nixon (Nathan S. Kline Institute for Psychiatric Research Orangeburg, NY and NYU Langone Health, New York, NY, (United States))

BFCN are among the earliest neuronal targets in AD and a basis for cognitive decline. Nerve growth factor (NGF) signaling, critical for their survival, declines in early AD and Down Syndrome (DS). NGF signaling is transduced by endocytosis and retrograde trafficking of a maturing Rab5- "signaling endosome" containing the NGF receptor, TrkA to initiate a transcriptional program. Rab5, a GTPase, is a master signaling molecule normally regulating endocytosis and the diverse functions of endosomes that go awry early in AD. Overactive rab5 signaling is also linked to cell survival/death, in part, via the nuclear delivery of transcription factors via rab5 endosomes. Both Rab5 hyper-activation and lowered rates of recycling from endosomes impair these processes partly due to enlargement of endosomes which slows their retrograde transport and trophic signaling and induces cholinergic atrophy deficits in DS mouse models, which recapitulate AD pathology in the basal forebrain, including endosome enlargement and cholinergic neurodegeneration. Elevating APP expression directly or inhibiting gamma secretase yield elevated levels of APP- β CTF that hyper-activate rab5 and induce rab5-dependent atrophy of cultured BFCNs. Hyperactivating rab5 directly in vivo in rab5 overexpressing transgenic mice causes BFCN degeneration and memory deficit. Cholinergic deficits in DS mouse models are rescued by raising NGF levels, through BACE1 inhibition (or through deleting one allele of BACE1 genetically), or through reducing rab5 activation with the p38alpha inhibitor neflamapimod. The relevance of these

mechanisms to late-onset AD is supported by ApoE4 having been shown to activate rab5, in part by raising APP- β CTF levels by promoting APP and BACE1 colocalization on early endosomes and by delaying endosome recycling. Moreover, many of the LOAD risk genes have roles in endocytic function that when activated in AD models activate Rab5. Thus, the pathological over-activation of neuronal rab5 by converging disease factors is central to pathogenesis of BFCN degeneration, and rab5 represents a therapeutic target for treating BFCN dysfunction in AD.

Presentation 3: *Clinical Results with Novel Approaches that Reverse BFCN Dysfunction*, John Alam (EIP Pharma Boston, MA, (United States))

The two approaches based on preclinical results (see presentation 2) best validated as approaches to target Rab5-mediated BFCN dysfunction to improve cognitive function (i.e., to act as disease-modifying symptomatic therapies) are beta-secretase (BACE) and p38 α inhibitors. In the case of BACE inhibition, clinical evidence supporting the approach to target BFCN dysfunction was provided in a combined retrospective analysis of phase 3 clinical trials conducted with verubecestat and lanabecestat, respectively, in which the effects of these BACE inhibitors on specific cognitive domains were evaluated. While both drugs worsened overall cognitive function, both improved outcomes in tests of executive function, the Letter Fluency Test (LFT) and the Category Fluency Test, impairments considered to reflect BFCN dysfunction; though, the results are confounded by a deleterious effect in the verubecestat trial on attentional/processing speed, also considered to be measure of BFCN function. In the case of p38 α inhibition, results of a phase 2, 91-patient, 16-week, placebo-controlled study ("AscenD-LB") with the specific p38 α kinase inhibitor neflamapimod (at 40mg TID) demonstrated statistically significant, clinically relevant effect size (0.5) improvement relative to placebo in a cognitive test battery assessing attention and executive function. In addition, statistically significant improvement, with a similar effect size, was demonstrated on gait (assessed by timed up and go test); while gait dysfunction in Parkinson's disease was recently reported to correlate with basal forebrain cholinergic neuronal volume. Finally, dose-dependent improvement relative to placebo was seen in hallucination severity and frequency, another outcome considered related to cholinergic dysfunction. The results of the AscenD-LB study, the totality of which indicates a substantial positive effect on BFCN function, are to be confirmed in a 160-patient phase 2b study that is planned to commence in the fourth quarter of 2021.

SYMPOSIUM RS04- INNOVATIVE APPROACHES AND TECHNOLOGIES SHAPING THE FUTURE OF ALZHEIMER'S CLINICAL TRIALS. Alejandro Schuler¹, Kathryn Papp², Steven Chance³ (1. *Unlearn.ai, Stanford University - San Francisco, (United States)*, 2. *Harvard Medical School; Brigham And Women's Hospital - Boston, (United States)*, 3. *Oxford Brain Diagnostics - Oxford, (United Kingdom)*)

Presentation 1: *Prognostic Covariate Adjustment (PROCOVA) enables smaller, more powerful trials while reducing uncertainty and maintaining control of type I error*, Alejandro Schuler (Unlearn.ai, San Francisco, CA, (United States))

Objective: Our objective is to demonstrate a method using an Alzheimer's Disease (AD) prognostic model to decrease the uncertainty in effect estimates from randomized controlled trials (RCTs) without introducing bias. **Method:** Our approach

is to train a prognostic model on historical controls (from prior trials or observational data) and then estimate the trial treatment effect while adjusting for the trial subjects' predicted outcomes. We demonstrate this approach using simulations and a reanalysis of an Alzheimer's trial dataset. **Results:** We prove that PROCOVA is more efficient (i.e. produces estimates that are more certain) than ANOVA and that the gain in efficiency is proportional to a measure of the predictive accuracy of the prognostic model. We observed up to a 63% reduction in the mean-squared error of our effect estimates in simulation. Re-analysis of data from an AD Phase III trial with PROCOVA leveraging an existing AD prognostic model delivered 16.3% smaller confidence intervals than analysis with ANOVA. In addition, we show how these gains in efficiency can be exploited to prospectively design well-powered clinical trials using a smaller number of subjects than would otherwise be required. Given existing performance metrics from our AD prognostic model, our PROCOVA-based power formula showed that the trial could have attained 80% power using 18% fewer subjects than were originally enrolled. **Conclusion:** Adjusting for a prognostic score obtained from a nonlinear prognostic model trained on a large database of historical control arm data provides near optimal treatment effect estimates in RCTs with continuous outcomes under certain conditions. Furthermore, the procedure offers practical advantages even when the assumptions that guarantee some forms of optimality are violated and in comparison to other kinds of historical borrowing methods, prognostic covariate adjustment theoretically guarantees strict type-I error rate control and confidence interval coverage in general settings. There has recently been tremendous growth in the availability and performance of technology for nonlinear regression modeling (i.e., supervised machine learning), particularly in the area of deep learning. The intersection of this technological development with the creation of large historical control databases provides an opportunity to use PROCOVATM to substantially improve the efficiency of RCTs.

Presentation 2: *Design and implementation of novel trial designs: Harnessing short-term learning curves (STLCs) to accelerate early detection and tracking in Alzheimer's disease secondary prevention trials*, Kathryn Papp (Harvard Medical School, Brigham and Women's Hospital, Boston, MA, (United States))

Background: The degree of cognitive decline observed in the preclinical stages of Alzheimer's disease (AD), currently measured using cognitive outcomes administered in-clinic over long intervals (e.g., 6-12 months), is subtle. Thus, determining the cognitive benefit of an intervention in secondary prevention currently requires long timeframes (4+ years) and large sample sizes (n=1000+). Practice effects, that is, improved performance on re-testing, have long been considered an additional obstacle that further obscures the measurement of cognitive decline. However, diminished practice effects may offer a unique cognitive signal that can be exploited to capture meaningful cognitive decrements over shorter time intervals [1, 2], particularly if assessments can be completed remotely on an individual's own device. **Objectives:** To discuss the emerging evidence suggesting specific types of diminished practice effects amongst clinically normal older adults are associated with AD biomarkers [3, 4], confer greater risk of cognitive decline, and are able to be tested remotely over short intervals (i.e., days) on an individual's own mobile device. **Methods:** We describe results from two different studies to illustrate the potential value of short term learning curves (STLCs) as a means of

capturing subtle cognitive decline over shorter intervals in individuals with preclinical AD. We use the term STLCs as a more specific type of practice effect, that is, improved memory performance when identical content is presented over multiple discrete intervals that may be reduced in individuals at risk for AD progression. The first study involves 75 clinically normal older adults from the Harvard Aging Brain Study who completed a challenging face-name associative memory (FNAME) test at-home each month (same stimuli each month) via a study-issued iPad. Participants also completed the in-clinic Preclinical Alzheimer's Cognitive Composite (PACC) at baseline and one-year follow-up and a subset underwent neuroimaging quantifying global amyloid burden. PACC decliners were defined as those who showed more than 0.10 standard deviation decline on this well-validated composite after one year [5]. The second study involves 58 community-dwelling older adults who completed seven consecutive days of memory tests using the Boston Remote Assessment for Neurocognitive Health (BRANCH). BRANCH is a web-based platform which uses associative memory tasks (including a variation of FNAME) with stimuli relevant to everyday life (e.g., groceries, faces) on a user-friendly interface that can be accessed on an individual's own device. **Results:** In the first study, diminished STLCs over 3 months for face-name memory were associated greater amyloid burden and with greater decline on PACC over one year ($r=.68$ $p<.001$), unlike baseline/Day 1 performance, which was not associated with amyloid or PACC decline. A diminished STLC on FNAME over 3 months was able to accurately predict PACC decliners over one year (AUC:86.7%, $p=0.03$) while controlling for age, sex, education, and baseline PACC performance. In the second study, 58 community dwelling older adults with no in-person contact were able to complete BRANCH for 7 consecutive days on their own devices. STLCs were able to be computed for each participant, mirroring what was previously observed over longer time intervals. By allowing participants to complete STLCs using their own electronic device, data collection exponentially increases, improving the ability for clinical trials to progress more efficiently. **Conclusions:** Capitalizing on the measurement of short-term learning curves (STLCs), a specific type of practice effect, may improve the sensitivity and rapidity with which subtle cognitive decrements can be observed. Rapid acquisition of STLCs is made feasible by remote, digital assessments such as BRANCH. We discuss how diminished STLCs may serve as clinically meaningful outcomes over short timescales as a predictor of future decline and clinical progression.

Presentation 3: *Design and implementation of novel trial approaches: New imaging markers for clinical trials*, Steven Chance, (Oxford Brain Diagnostics, Oxford, (United Kingdom))

Background: Dementia cripples aging societies and the cost of failure to meet this challenge for government will be at least as big as COVID 19, although slower. There have been over 200 unsuccessful investigational programmes looking for pharmacological solutions. Even the most significant recent advance, just announced, of the first drug to receive FDA approval as a disease altering treatment for Alzheimer's disease, was challenged by the complexity of the drug trial evidence. Possible reasons for the difficulty in AD trials include: wrong hypotheses, wrong drugs, wrong participants, wrong trial design, wrong end points. **Objectives:** To consider the possible reasons for difficulty in demonstrating efficacy in Alzheimer's drug trials, identify key areas for solutions, and focus on one or two emerging examples of new markers that

could help to improve selection of patients for inclusion and tracking of drug efficacy in clinical trials. **Methods:** A selective review of the choice of endpoints, study design, and patient selection, including example studies comparing markers of the ATN framework for defining patient groups and measuring progression. Data is drawn from retrospective analysis of small cohorts from existing datasets including ADNI and DIAN. **Results:** Recent progress in fluid biomarkers, notably blood based methods, has raised expectations for the benefits of several protein markers to track A & T in the ATN framework, particularly combinations of tau markers. New MRI brain structural markers offer insight into the spatial distribution of neuropathology and patterns differentiating sub-types of dementia. As a marker of N in the ATN framework, diffusion metrics in the grey matter provide better classification accuracy than some traditional volumetric measures. Wearables and digital data also aid passive and domestic data collection for screening, although there may be a priori limits to the sensitivity of such behavioural measures. Digital twins and other sophisticated study design methods have the potential to improve trial efficiency. **Conclusion:** Selection of patients within the ATN framework may be helpful for inclusion criteria and recent developments for all three elements of the framework should be adopted in trial design. More effective endpoints are also needed. Primary endpoints are likely to continue to be cognitive/behavioural measures that are clinically relevant, however, good ATN markers will be important endpoints to justify the biological basis of drug effects. Quantification of Neurodegeneration ('N') at the microstructural stage before volumetric atrophy provides an evidential link between the presence of pathological proteins and the effect on the brain's neural structure. With the potential addition of 'i' for inflammation these new markers will better characterise the vulnerability to pathology and potential response to treatment of patients within trials.

ROUNDTABLES

ROUNDTABLE 3- DIGITAL THERAPEUTICS FOR MILD COGNITIVE IMPAIRMENT: NEW PATHWAYS TO TREATMENT. Murali Doraiswamy¹, Jeffrey Shuren², Rhoda Au³, James R. Williams⁴ (1. Duke University - Durham, NC (United States), 2. Food & Drug Administration - Silver Spring, MD (United States), 3. Boston University - Boston, MA (United States), 4. Biogen Digital Health - Cambridge, MA (United States))

The COVID-19 pandemic has highlighted the importance of mobile health applications. Unlike wellness apps, digital therapeutics deliver treatment to patients using evidence-based, clinically evaluated software that have received regulatory clearance. Recently, prescription digital therapeutics have been cleared by the US Food and Drug Administration (FDA) for use in substance abuse and sleep disorders. Although there is a growing body of evidence, from pre-clinical, observational and RCT data, to support the utility of digital cognitive rehabilitation, no software device is specifically indicated for this purpose by regulators. This round table will discuss the latest research findings and the roadmap to advance digital therapeutics for MCI and AD.

Opening Remarks: *Digital Therapeutics for MCI: New Pathways to Treatment*, Murali Doraiswamy (Duke University School of Medicine, Durham, NC, (United States))

The Chair's opening remarks will present the latest findings on the bidirectional links between COVID-19 and

cognitive impairment (both direct viral and mitigation effects) and summarize the current landscape and unmet needs with regards to use of digital therapeutics for MCI and AD.

Presentation 1: *FDA's current thinking about digital therapeutics for Alzheimer's*, Jeffrey Shuren (Food and Drug Administration, Silver Springs, MD, (United States))

Dr. Shuren will discuss the FDA's current thinking about digital therapeutics for Alzheimer's disease. He will also address the work of the FDA's Digital Health Center of Excellence. Two of the key goals of the Center are to strategically advance science/evidence for digital health technologies that meets the needs of stakeholders and align regulatory approach to harmonize international regulatory expectations and industry standards.

Presentation 2: *Advances in Digital Biomarkers*, Rhoda Au (Boston University School of Medicine, Boston, (United States))

Digital therapeutics will depend on such biomarkers to detect disease symptoms and/or treatment efficacy. Dr. Au will discuss the latest findings from the Framingham Heart Study where she is using technologies to develop digital cognitive biomarkers as surrogate indices of fluid and imaging biomarkers. She will highlight why conceptualizing digital biomarkers in the same way as fluid biomarkers may miss the mark. She will present a definition of a fluidic digital biomarker and potential methods for validating them and employing them as a key outcome in clinical trials.

Presentation 3: *An Industry Perspective on Opportunities/Challenges in Digital Therapeutics for MCI*, James R. Williams (Biogen Digital Health, Cambridge, MA (United States))

Mr. Williams will present the perspective of an industry leader on the opportunities and challenges with regards to digital therapeutics for MCI, as well as what will be needed to scale them. In late 2021, Biogen will launch a new, multi-year, virtual research study, in collaboration with Apple, to investigate the role Apple Watch and iPhone could play in monitoring cognitive performance with a primary objective to develop digital biomarkers for mild cognitive impairment.

ROUNDTABLE 4- PHASE 2 TRIAL OF SEMORINEMAB IN MILD-TO-MODERATE ALZHEIMER'S DISEASE (LAURIET): TOPLINE RESULTS. Cecilia Monteiro¹, Balazs Toth¹, Kristin Wildsmith¹, Sandra Sanabria-Bohorquez¹, Flavia Brunstein¹, Andrew Madsen¹, Michael Dolton², Vidya Ramakrishnan¹, Dan Abramzon¹, Edmond Teng¹ (1. Genentech, Inc. - South San Francisco, (United States), 2. F. Hoffmann-La Roche Ltd. - Basel, (Switzerland))

Background: Semorinemab is a humanized anti-tau IgG4 monoclonal antibody that targets the N-terminal region of the tau protein (amino acid residues 6-23) and is in development for the treatment of Alzheimer's disease (AD). In preclinical studies with tau transgenic mice, a murine surrogate of semorinemab significantly reduced accumulation of tau pathology. However, in a subsequent Phase 2 trial in participants with prodromal-to-mild AD (Tauriel study; NCT03289143) semorinemab administered at monthly IV doses of up to 8100 mg did not demonstrate efficacy on primary or secondary clinical endpoints. **Objectives:** The Lauriet study (NCT03828747) is a Phase 2 multi-center randomized double-blind placebo-

controlled parallel-group clinical trial that is assessing the safety and efficacy of semorinemab in mild-to-moderate AD. Preliminary analyses of data from the first 12 months of the blinded portion of the study will be presented. **Methods:** Participants aged 50-85 years who fulfilled National Institute on Aging-Alzheimer's Association criteria for probable AD dementia and had Mini-Mental Status Examination (MMSE) scores of 16-21 (inclusive), global Clinical Dementia Rating (CDR) scores of 1 or 2 were randomized to receive monthly IV doses of either placebo or semorinemab (4500 mg) over 48 weeks. During the course of the study, the protocol was amended to mitigate potential COVID-19 associated disruptions by extending the blinded period of the study to 60 weeks for participants who missed at least one dose of study medication during the pandemic. Randomization was stratified by MMSE (16-18 vs. 19-21) and APOE status ($\epsilon 4+$ vs. $\epsilon 4-$). The co-primary efficacy endpoints were change from Baseline to Week 49 on the 11-item version of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog11) and on the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL). Secondary and exploratory efficacy endpoints included change from baseline on the MMSE, CDR Sum of Boxes (CDR-SB), and whole cortical grey [18F]GTP1 tau PET SUVR. Analyses incorporated a mixed-effect model of repeated measures (MMRM) using an unstructured covariance matrix. Key safety assessments included physical and neurologic examinations, clinical laboratory assessments, brain magnetic resonance imaging (MRI), and adverse event monitoring. **Results:** A total of 272 participants were randomized 1:1 in the semorinemab and placebo treatment arms. The modified intent-to-treat population (mITT; n=241) included those who received ≥ 1 dose(s) of study medication and underwent baseline and at least 1 post-baseline assessment(s). Within the mITT population, the overall distributions of age (mean=72.0, SD=8.2), gender (64.3% female), education (80.5% high school graduate or higher), and APOE status (63.1% $\epsilon 4+$) did not differ between treatment arms. At Week 49, the semorinemab arm demonstrated a 42.2% reduction (-2.89 points, SE=0.85, p=0.0008) in decline on ADAS-Cog11 relative to the placebo arm. Similar rates of clinical decline on ADCS-ADL, MMSE, and CDR-SB and similar rates of tau accumulation per whole cortical grey [18F]GTP1 tau PET SUVR were seen between treatment arms. Findings remained consistent when other analysis populations were examined, including the pre-specified analysis population (mITT*: mITT participants who missed ≤ 1 blinded study drug doses), in which the semorinemab arm demonstrated a 43.6% reduction (-2.96 points, SE=0.97, p=0.0025) in decline on ADAS-Cog11 relative to the placebo arm. Preliminary analyses of safety data indicated that the rates of adverse events, serious adverse events, deaths, and withdrawals due to adverse events were reasonably balanced between treatment arms. Serum and CSF pharmacokinetics of semorinemab were consistent with prior studies. Similar serum semorinemab exposure was observed between the mITT and mITT* populations. **Conclusion:** In the Lauriet study, participants with mild-to-moderate AD who were treated with semorinemab demonstrated a statistically significant and potentially clinically meaningful reduction in decline on co-primary cognitive endpoint (ADAS-Cog11). However, no clear treatment effects were seen with semorinemab on the co-primary functional endpoint (ADCS-ADL), the secondary clinical endpoints, or an exploratory tau PET analysis. The safety data was in line with previous data; semorinemab was well tolerated, with an acceptable safety profile and no unanticipated safety signals. Further analyses of data from both

the completed the blinded portion of the study and the ongoing open label extension are in progress.

ROUNDTABLE 5- LECANEMAB: AN ASSESSMENT OF THE CLINICAL EFFECTS, THE CORRELATION OF PLASMA A β 42/40 RATIO WITH CHANGES IN BRAIN AMYLOID PET SUVR, AND SAFETY FROM THE CORE AND OPEN LABEL EXTENSION OF THE PHASE 2 PROOF-OF-CONCEPT STUDY, BAN2401-G000-201, IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE. Chad Swanson¹, Shobha Dhadda¹, Michael Irizarry¹, Michio Kanekiyo¹, David Li¹, Akihiko Koyama¹, June Kaplow¹, Robert Gordon², Lynn Kramer¹, Christopher Van Dyck³, Randy Bateman⁴, Jeffrey Cummings⁵ (1. Eisai Inc. - Woodcliff Lake, (United States); 2. Eisai Ltd. - Hatfield, (United Kingdom); 3. Yale School Of Medicine - New Haven, (United States); 4. Washington University School Of Medicine - St Louis, (United States); 5. University Of Nevada Las Vegas - Las Vegas, (United States))

Background: Lecanemab (BAN2401), a humanized IgG1 monoclonal antibody, preferentially binds large soluble aggregated A β species (oligomers, protofibrils), with activity at insoluble fibrils. Lecanemab produced a robust brain fibrillar amyloid reduction that correlated with slowing of clinical decline in an 18-month phase 2 proof-of-concept study in early Alzheimer's disease (Swanson et al. *Alz Res Therapy* 13; 2021). An open label extension (OLE) with 10 mg/kg IV biweekly lecanemab dosing was implemented after analysis of the core study, with an intervening off-treatment period (gap period) ranging from 9-59 months (mean 24 months). **Objectives:** We report the early time course of brain fibrillar amyloid reduction and provide an updated analysis of the longitudinal clinical status (CDR-SB, ADAS-cog, ADCOMS) for subjects completing the core and 18 months of treatment in the OLE. Key safety results from the OLE are summarized. Furthermore, we report data on the longitudinal plasma A β 42/40 ratio (C2N PrecivityAD assay) and the relationship to longitudinal amyloid PET in the core study, gap period, and OLE. **Methods:** At entry into the core study, subjects were required to have early AD (amyloid positive) with global CDR of 0.5 or 1. Subjects who fulfilled OLE inclusion/exclusion criteria were eligible to resume therapy. MMRM analyses modeled clinical data across the core, variable gap period off lecanemab, and the OLE period. Analyses were conducted based on subjects who were: (1) global CDR 0.5 or 1 at OLE baseline; or (2) who had progressed beyond the early AD stage to CDR global >1 by OLE baseline. The core amyloid PET sub-study assessed baseline, 12 months, and 18 months SUVR with florbetapir, whereas the OLE amyloid PET sub-study assessments were at baseline, 3 or 6 months, and 12 months. Plasma samples were collected at the same timepoints and analyzed by mass spectrometry. Mean changes from core or OLE baseline and Pearson correlation coefficients were calculated at the group and individual levels for amyloid PET SUVR and plasma A β 42/40 ratio, accounting for repeated measures. Safety results were summarized descriptively. **Results:** In subjects with global CDR 0.5 or 1 at OLE baseline, lecanemab treatment differences relative to placebo observed after 18 months of treatment in the core were maintained on all 3 clinical assessments at a 3 month follow-up (off drug) visit and at the end of the off drug gap period (OLE baseline). Over the gap period (average gap of 24 months), the rates of progression were similar between those treated with lecanemab and placebo in the core period. In the OLE, progression on all 3 clinical endpoints appeared to plateau with lecanemab treatment among those with global CDR 0.5 or 1 at

the OLE baseline, while those with global CDR >1 continued to progress, though less than a comparative natural disease progression rate (ADNI). OLE subjects with plasma samples (N=121) were evaluated in the plasma A β 42/40 ratio analysis. Lecanemab produced dose dependent reductions in PET SUVR, with corresponding increases in plasma A β 42/40 ratio in core and OLE. In the OLE, reductions in amyloid assessed by PET SUVR occurred within 3 months of treatment and resulted in >80% conversion to amyloid negative status with 12 months of treatment. The absolute magnitude of amyloid reduction was dependent on OLE baseline SUVR. Amyloid PET changes were inversely correlated with changes in plasma A β 42/40 ratio (reduction in PET SUVR was associated with an increase in plasma A β 42/40 ratio) at both group and individual levels in the core (group: $r=-0.939$, $p=0.0056$; individual: $r=-0.49$; $p<0.0001$) and OLE (group: $r=-0.907$, $p=0.0007$). Consistent with core safety findings, lecanemab was well-tolerated with <10% incidence of ARIA-E at 10-mg/kg biweekly in the OLE. **Conclusions:** Lecanemab was well tolerated and demonstrated rapid (in as early as 3 months) and marked (>80% amyloid negative in as early as 12 months) clearance of brain amyloid (by PET SUVR) that correlated with clinical decline across several endpoints in the core study. Clinical data over an average 2-year gap period (range 9 to 59 months) off lecanemab treatment suggest potential disease modifying effects, but also indicate that subjects with early AD may need maintenance treatment with lecanemab, even after fibrillar amyloid is extensively cleared. Clinical data from the OLE suggest those with global CDR 0.5 or 1 may be more likely to benefit from treatment. In addition, reduction in brain amyloid PET SUVR correlated with increases in plasma A β 42/40 ratio, highlighting the potential to track the treatment effects of lecanemab in AD patients at the individual level. Discontinuing treatment allows plasma A β 42/40 ratio to decrease, potentially reflecting an early brain amyloid accumulation indicator which is associated with clinical decline. These findings suggest that continued treatment may be beneficial for subjects while still in the early AD Stage. These data are hypothesis generating and will be further explored in ongoing phase 3 lecanemab clinical trials in early AD and preclinical AD (Clarity AD and AHEAD 3-45, respectively). **Disclosure:** Dr Swanson is an employee of Eisai Inc.

ROUNDTABLE 7- VALUE-GENERATING EXPLORATORY TRIALS IN NEURODEGENERATIVE DEMENTIAS. Howard Fillit (*Alzheimer's Drug Discovery Foundation, New York, NY, (United States)*)

The estimated cost of developing an Alzheimer's drug is eight times more than a cancer drug and takes nearly twice as long. Regulatory Phase 2b/3 studies account for the largest portion of development costs. It is important that investigators run well-designed biomarker-based exploratory trials to deliver solid data that can inform go/no-go decision points about moving a drug forward to a larger Phase 2b/3 study. It is best for drugs that are unlikely to succeed to fail fast so resources can be devoted to more promising compounds. This roundtable will discuss guidance on best practices for conducting exploratory trials for Alzheimer's disease, frontotemporal degeneration (FTD), and other neurodegenerative dementias, based on an advisory panel convened by the Alzheimer's Drug Discovery Foundation and The Association for Frontotemporal Degeneration (paper published May 18, 2020 issue of *Neurology*®). The panel will discuss recommendations and provide evidence where

these have been used in practice. Recommendations include:

- Development of robust translational plans that include deep understanding of pharmacokinetic/pharmacodynamic relationships;
- Incorporating appropriate endpoints (both biomarkers and clinical endpoints) that reflect target engagement, drug's mechanism of action and specific study population;
- Leveraging historical data to determine appropriate outcomes that are well aligned with the disease and mechanism of action for the treatment;
- Utilization of rigorous statistical analyses/procedures in these studies and engaging with biostatisticians early in the study design;
- Considering the use of novel clinical development plans to improve the efficiency of clinical development

ORAL COMMUNICATIONS

OC01- EVOKE AND EVOKE+: TWO PHASE 3 TRIALS INVESTIGATING ORAL SEMAGLUTIDE IN PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE. Philip Scheltens¹, Alireza Atri^{2,3}, Howard H. Feldman⁴, Kristine Brown Frandsen⁵, Stephen C.i. Gough⁵, Peter Johannsen⁵, Filip Krag Knop⁶, Pernille Poulsen⁵, Lars Lau Raket⁵, Mary Sano⁷, Hilka Soininen⁸, Jeffrey Cummings⁹ (1. *Vu University Medical Center - Amsterdam (Netherlands)*, 2. *Banner Sun Health Research Institute - Sun City (United States)*, 3. *Brigham & Women's Hospital and Harvard Medical School - Boston (United States)*, 4. *Harvard Medical School, Harvard University - University Of California (United States)*, 5. *Novo Nordisk A/s - Søborg (Denmark)*, 6. *Herlev And Gentofte Hospital, University Of Copenhagen - Copenhagen (Denmark)*, 7. *Icahn School Of Medicine At Mount Sinai - New York (United States)*, 8. *University Of Eastern Finland - Kuopio (Finland)*, 9. *University Of Nevada - Las Vegas (United States)*)

Background: Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA), approved for type 2 diabetes (T2D) treatment and available as an oral, once-daily (OD) formulation in several countries, including the USA. Nonclinical research has shown that GLP-1RAs can reduce neuroinflammation, reduce phospho-tau accumulation, provide neuroprotective effects, and improve cognitive function (1–5). In humans, GLP-1RA treatment has been shown to preserve cerebral glucose metabolism (6), favorably affect cognition and cortical volume (7), and post hoc analyses of randomized clinical trials indicated reduced cognitive impairment and dementia risk in GLP-1RA-treated patients with T2D (8–10). Based on these data, the efficacy and safety of oral semaglutide versus placebo in participants with early Alzheimer's disease (AD) including mild cognitive impairment (MCI) or mild dementia, both of the Alzheimer's type, are being investigated in the phase 3 evoke and evoke+ trials. **Objectives:** Description of the evoke and evoke+ trial designs. **Methods:** evoke (NCT04777396) and evoke+ (NCT04777409) are 156-week, randomized (1:1), double-blind, placebo-controlled, multicenter, multinational trials comparing oral semaglutide 14 mg OD versus placebo, each added to standard of care in participants (age ≥ 55 – ≤ 85 years) with early AD, including MCI or mild dementia, both of the Alzheimer's type (11). The trial designs incorporated input from interviews with potential participants, conducted by an independent non-profit organization. Unlike evoke, $\geq 20\%$ of evoke+ participants will have significant small vessel pathology. Key inclusion criteria for both trials are: a Clinical Dementia Rating (CDR) global score of 1.0, or a CDR global score of 0.5 with CDR scores of ≥ 0.5 in at least one of the three

instrumental activities of daily living categories (personal care, home and hobbies, community affairs); a Mini-Mental State Examination (MMSE) score ≥ 22 ; a Repeatable Battery for the Assessment of Neuropsychological Status delayed memory index score ≤ 85 ; and amyloid positivity confirmed by either amyloid positron emission tomography or cerebrospinal fluid amyloid $\beta 1-42$. Participants may receive a stable dose of approved AD treatment ≥ 3 months before screening. Exclusion criteria for both trials include: cranial MRI or CT head scan findings suggestive of clinically significant structural central nervous system disease; strategic infarcts confirmed by central read; evidence of a relevant neurological disorder other than MCI or mild dementia of the Alzheimer's type at screening; or evidence of a clinically relevant or unstable psychiatric disorder. An additional exclusion criterion for the evoke trial is significant small-vessel pathology, defined as >1 lacunar infarct and/or age-related white matter change scale >2 (white matter >20 mm) (12). Also, diabetes prevalence in the trial should not exceed 30%. The primary endpoint of both trials is change in CDR–Sum of Boxes score from baseline to week 104. Secondary confirmatory endpoints are change in AD Cooperative Study–Activities of Daily Living–MCI score from baseline to week 104 and time to progression to dementia (CDR global score ≥ 1.0) among participants with MCI (CDR global score of 0.5) at baseline. Supportive secondary endpoints for both trials are change from baseline to week 104 in the AD Composite Score, the MMSE score, the 13-item AD Assessment Scale–Cognitive Subscale score, the Montreal Cognitive Assessment score, and the 10-item Neuropsychiatric Inventory score; time to progression in disease stage, based on global CDR score; and change in the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) proxy score. Safety is being evaluated throughout the trials, with monitoring by a Data Monitoring Committee. A subgroup of participants and their caregivers will be interviewed during the trial to provide their input and to give a patient's perspective on clinical meaningfulness. Randomization of 1,840 participants into each trial is planned, to provide 95% power to confirm a treatment effect of at least 20% assuming a 15% dropout rate. evoke and evoke+ have been designed to enable pooled analyses. **Results:** evoke and evoke+ are currently enrolling and will include sites in 40 countries. The first participants entered the trials in May 2021. **Conclusions:** evoke and evoke+ will be the first large-scale trials to investigate the potential of a GLP-1RA to treat patients with AD; their read-out is expected in the second half of 2024 (primary endpoints at 104 weeks). **References:** 1. Hansen HH et al. *Brain Res* 2016;1634:158–70; 2. Hansen HH et al. *J Alzheimers Dis* 2015;46:877–88; 3. Rakipovski G et al. *JACC Basic Transl Sci* 2018;3:844–57; 4. Brundin L et al. *Nat Med* 2018;24:900–2; 5. Yun SP et al. *Nat Med* 2018;24:931–8; 6. Gejl M et al. *Front Aging Neurosci* 2016;8:108; 7. Edison P et al. Presentation OC30 presented at CTAD 2020; 8. Ballard C et al. Poster 42909 presented at AAIC 2020; 9. Cukierman-Yaffe T et al. *Lancet Neurol* 2020;19:582–90; 10. Zhou B et al. *Alzheimers Dement* 2021;7:e12139; 11. Jack Jr CR et al. *Alzheimers Dement* 2018;14:535–62; 12. Wahlund LO et al. *Stroke* 2001;32:1318–22. **Conflict of interest:** The lead author's disclosures will be included as part of the oral presentation slides if the abstract is accepted.

OC02- PLASMA GFAP IS AN EARLY MARKER OF AB BUT NOT TAU PATHOLOGY IN ALZHEIMER'S DISEASE.

Joana Pereira¹, Shorena Janelidze², Ruben Smith², Mattsson-Carlgrén Niklas², Sebastian Palmqvist², Charlotte Teunissen³, Henrik Zetterberg⁴, Erik Stomrud², Nicholas Ashton⁴, Kaj Blennow⁴, Oskar Hansson² (1. *Ki, Lund University - Lund (Sweden)*, 2. *Lund University - Lund (Sweden)*, 3. *Amsterdam University Medical Centers - Amsterdam (Sweden)*; 4. *Sahlgrenska University Hospital - Sahlgrenska University Hospital (Sweden)*)

Background: Although recent clinical trials targeting amyloid- β (A β) in Alzheimer's disease (AD) have shown promising results, there is increasing evidence suggesting that understanding alternative disease pathways that interact with A β metabolism and amyloid pathology might be important to halt the clinical deterioration. In particular, there is evidence supporting a critical role of astroglial activation and astrocytosis in AD. However, to this date, no studies have assessed whether astrocytosis is independently related to either A β or tau pathology, respectively, in vivo. **Aim:** To address this question, we determined the levels of the astrocytic marker glial fibrillary acidic protein (GFAP) in plasma and cerebrospinal fluid (CSF) in addition to other glial markers (YKL-40, sTREM2) of 217 A β -negative cognitively unimpaired individuals, 71 A β -positive cognitively unimpaired individuals, 78 A β -positive cognitively impaired individuals, 63 A β -negative cognitively impaired individuals and 75 patients with a non-AD neurodegenerative disorder from the Swedish BioFINDER-2 study. **Methods:** Subjects underwent longitudinal A β (18F-flutemetamol) and tau (18F-RO948) positron emission tomography (PET) as well as cognitive testing. Plasma GFAP was measured using GFAP Simoa Discovery kits for HD-X (Quanterix®, Billerica, MA, USA); CSF GFAP, YKL-40 and sTREM2 were measured using Elecsys assays (NeuroToolKit robust prototype, Roche Diagnostics); and CSF A β 42 and CSF A β 40 were measured using Meso Scale Discovery immunoassays (MSD; Rockville, MD, USA). **Results:** We found that plasma GFAP concentration was significantly increased in all A β -positive groups compared with subjects without A β pathology ($p < 0.01$). In addition, there were significant associations between plasma GFAP with higher A β -PET signal in all A β -positive groups, but also in cognitively normal individuals with normal A β values ($p < 0.001$), which remained significant after controlling for tau-PET signal. Furthermore, plasma GFAP could predict A β -PET positivity with an area under the curve of 0.76, which was greater than the performance achieved by CSF GFAP (0.69) and other glial markers (CSF YKL-40: 0.64, sTREM2: 0.71). Although correlations were also observed between tau-PET and plasma GFAP, these were no longer significant after controlling for A β -PET. In contrast to plasma GFAP, CSF GFAP concentration was significantly increased in non-AD patients compared to other groups ($p < 0.05$) and correlated with A β -PET only in A β -positive cognitively impaired individuals ($p = 0.005$). Finally, plasma GFAP was associated with both longitudinal A β -PET and cognitive decline, and mediated the effect of A β -PET on tau-PET burden, suggesting that astrocytosis secondary to A β aggregation might promote tau accumulation. **Conclusion:** Altogether, these findings indicate that plasma GFAP is an early marker associated with brain A β pathology but not tau aggregation, even in cognitively normal individuals with a normal A β status. Although current models of AD have adopted a neurocentric view that starts with A β accumulation, followed by tau deposition and neurodegeneration, it is well known that neurons cannot function properly without the

proper support of glial cells such as astrocytes. Thus, our findings highlight the importance of including astroglial markers in the cascade of pathological changes occurring in AD, particularly plasma GFAP, which could potentially be used as a non-invasive tool to evaluate the effects of anti-A β drugs or anti-inflammatory treatments on astrocytosis in clinical trials.

OC03- PHASE 1 TRIAL DESIGN FOR ACU193, A MONOCLONAL ANTIBODY THAT SELECTIVELY BINDS SOLUBLE ABETA OLIGOMERS.

Eric Siemers¹, Janice Hitchcock¹, Karen Sundell¹, James Senetar¹, Robert Dean¹, Jasna Jerecic², Ericka Cline², Kent Iverson², Kathleen Powell², Jerry Moore², Deven Dandekar², Chris Edgar³, Richard Manber⁴, Niccolo Fuin⁴, Russell Barton¹ (1. *Acumen Pharmaceuticals - Carmel (United States)*, 2. *Acumen Pharmaceuticals - Charlottesville (United States)*, 3. *Cogstate Ltd. - Melbourne (Australia)*, 4. *Ixico Plc - London (United Kingdom)*)

Background: ACU193 is a monoclonal antibody with over 500-fold selectivity for A β oligomers (A β O) compared to A β monomers and limited to no binding to deposited amyloid plaques (1,2). ACU193 is in clinical development primarily as a potential disease-modifying treatment for Alzheimer's disease (AD). In addition, nonclinical studies demonstrate that acute deleterious effects of A β O-mediated inhibition of long term potentiation can be reversed by ACU193 (3), that A β O-induced calcium influx into neurons in culture can be reduced by ACU193 (4), and that behavioral deficits in AD transgenic mouse models can be reduced by ACU193 (5-7), suggesting that acute or sub-acute cognitive or biomarker effects might be observable in a Phase 1 study. **Objectives:** To design a Phase 1 first-in-humans study that primarily assesses patient safety and clinical pharmacokinetics but also allows for the possibility of detecting cognitive or biomarker effects of ACU193 in a small trial with a relatively short treatment duration. **Methods:** Trial designs were carefully reviewed for monoclonal antibodies currently or recently in development that appear to have promising results. These included trials using aducanumab, lecanemab, and donanemab. Clinical rating scales and rates of amyloid-related imaging abnormalities (ARIA) were noted, particularly for Phase 1 and 2 studies. **Results:** PET-confirmed amyloid-positive participants with mild cognitive impairment (MCI) or mild dementia due to AD will be randomized to ACU193 or placebo in either single ascending dose (SAD) or multiple ascending dose (MAD; 3 intravenous administrations) cohorts. The SAD cohorts include an initial in-patient treatment phase and a sentinel dosing scheme, while the MAD cohorts are performed with out-patients. Extensive safety reviews will occur before each dose escalation, and ARIA will be assessed throughout the study. SAD cohorts will include 8 participants (6:2 active to placebo) and MAD cohorts will include 10 participants (8:2 active to placebo), for a total of 62 participants. Assuming adequate safety and tolerability, doses for the SAD will be 2 mg/kg, 10 mg/kg, 25 mg/kg, and 60 mg/kg, and doses for the MAD will be 10 mg/kg Q4 weeks, 60 mg/kg Q4 weeks and 60 mg/kg Q2 weeks. Typical clinical assessments, including the Clinical Dementia Rating Scale-Sum of Boxes and Alzheimer's Disease Assessment Scale-cognition, will be employed; however, statistical power will be lacking given the size and duration of the study. Computerized cognitive testing, developed in collaboration with Cogstate Ltd., will be employed at multiple time points during the trial for each cohort. Tests include the International Shopping List Test (immediate and delayed recall), the Cogstate Brief Battery, the Groton Maze Learning Test, and the International Digit-Symbol

Substitution Test. The testing can be completed in about 30 minutes. Given extensive literature showing reduced cerebral blood flow (CBF) in AD, CBF will be determined using the MRI pulse sequence for arterial spin labelling (ASL) at baseline and following dosing with ACU193. Amyloid PET and CSF and blood-based biomarkers will also be assessed. **Conclusions:** A first-in-human study can be designed that ensures the safety of participants with early AD while also assessing cognition and biomarkers with sensitive new testing techniques. **References:** 1. Plotkin SS, Cashman NR. Passive immunotherapies targeting Abeta and tau in Alzheimer's disease. *Neurobiol Dis* 2020;144:105010. DOI: 10.1016/j.nbd.2020.105010. 2. Savage MJ, Kalinina J, Wolfe A, et al. A sensitive abeta oligomer assay discriminates Alzheimer's and aged control cerebrospinal fluid. *J Neurosci* 2014;34(8):2884-97. DOI: 10.1523/JNEUROSCI.1675-13.2014. 3. Cline E. VK, Klein W., Wang X., Bacskai B., Rammes G., Dodart J., Palop J., Siemers E., Jerecic J., Krafft G. Synaptic intervention in Alzheimer's disease: soluble A β oligomer directed ACU193 monoclonal antibody therapeutic for treatment of early Alzheimer's disease. *J Prevent Alzheimer's Dis* 2019;6:Supplement 1:S151. 4. Wang X, Kastanenka KV, Arbel-Ornath M, et al. An acute functional screen identifies an effective antibody targeting amyloid-beta oligomers based on calcium imaging. *Sci Rep* 2018;8(1):4634. DOI: 10.1038/s41598-018-22979-2. 5. Dodart JC, Nay S, Monbureau M, Hefti FF, Jerecic J, Shamloo M. Passive immunization with the anti-A β oligomer antibody ACU-3B3 improves behavioral deficits in hAPPSL transgenic mice. Society for Neuroscience. Washington, DC2014. 6. Khan A, Martinez-Losa MM, Ho K, Dodart J, Jerecic J, Palop JJ. Soluble A β -oligomer-selective antibody ACU-3B3 reduces amyloid pathology and improves multiple behavioral domains in a mouse model of Alzheimer's disease. Society for Neuroscience. Washington DC2014. 7. Gouré WF, Krafft GA, Jerecic J, Hefti F. Targeting the prion amyloid-beta neuronal toxins: a path forward for Alzheimer's disease immunotherapeutics. *Alzheimers Res Ther* 2014;6(4):42. DOI: 10.1186/alzrt272.

OC04- SENOLYTIC THERAPY TO MODULATE THE PROGRESSION OF ALZHEIMER'S DISEASE (STOMP-AD): METHODOLOGY FOR A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II TRIAL. Miranda E. Orr^{1,2}, Mitzi M. Gonzales³, Valentina R. Garbarino⁴, Eduardo M. Zilli³, Ronald C. Peterson⁵, James L. Kirkland⁶, Tamara Tchkonja⁶, Nicolas Musi^{4,7}, Sudha Seshadri^{3,8}, Suzanne Craft¹ (1. Wake Forest School Of Medicine, Gerontology And Geriatric Medicine, Wake Forest Alzheimer's Disease Research Center - Winston-Salem (United States), 2. W. G. (Bill) Hefner VA Medical Center - Salisbury (United States), 3. University Of Texas Health Science Center At San Antonio, Glenn Biggs Institute For Alzheimer's And Neurodegenerative Diseases, Department Of Neurology - San Antonio (United States), 4. University Of Texas Health Science Center At San Antonio, Glenn Biggs Institute For Alzheimer's And Neurodegenerative Diseases, Department Of Medicine - San Antonio (United States), 5. Mayo Clinic, Department Of Neurology, Mayo Clinic Alzheimer's Disease Research Center, The Mayo Clinic Study Of Aging - Rochester (United States), 6. Mayo Clinic, Robert And Arlene Kogod Center On Aging - Rochester (United States), 7. Barshop Institute for Longevity and Aging Studies and Geriatric Research, Education and Clinical Center - San Antonio (United States), 8. Boston University School of Medicine, Department of Neurology - Boston (United States))

Background: Preclinical studies indicate an age-associated accumulation of senescent cells across multiple organ systems.

Alzheimer's disease (AD)-associated beta-amyloid and tau protein accumulation drive brain cell senescence in rodent models. Pharmacologically clearing senescent cells, a therapy referred to as "senolytic", effectively reduced AD pathogenesis in these mice. Specifically, studies have demonstrated that senescent cell clearance reduced tau and beta-amyloid accumulation, neuroinflammation, ventricle enlargement, and behavioral deficits; preserved neuronal and synaptic density, and restored aberrant cerebral blood flow. Intermittent dosing of senolytics, dasatinib plus quercetin (D+Q), has shown an acceptable safety profile in clinical studies for other senescence-associated conditions. With these promising preclinical data, we proposed and herein describe the objectives and methods of a randomized, double-blind, placebo-controlled, multicenter phase II clinical trial of intermittent senolytic therapy in older adults with amnesic mild cognitive impairment (aMCI) and early-stage AD. **Objectives:** The objective of the Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (STOMP-AD) study is to evaluate the safety, feasibility, and efficacy of senolytic therapy in older adults with aMCI or early-stage AD. **Methods:** Forty-eight participants, ≥ 65 -years-old, with aMCI or early-stage AD (CDR = 0.5 or 1; NIA-Alzheimer's Association criteria) with elevated phosphorylated tau in cerebrospinal fluid (CSF) and/or plasma will be recruited from the Wake Forest School of Medicine Alzheimer's Disease Research Center and the University of Texas Health San Antonio. Participants will be randomized 1:1 to receive senolytics (D, 100mg, + Q, 1g) or placebo. Senolytics or placebo will be administered for two consecutive days followed by a 14-day no-drug period for completion of one cycle. Six cycles will be completed across twelve consecutive weeks. Participants will undergo assessments of cognition, functional status, mood, physical functioning, brain magnetic resonance imaging, tau positron emission tomography (PET) imaging, blood draw, and lumbar puncture at baseline and after 12-weeks of treatment and/or after an extended 9-month follow up period. **Outcome Measures:** Our primary outcome measure is safety and tolerability as assessed through adverse events between treatment arms. Secondary outcome measures include pre-versus post-treatment change in senescence biomarkers in the blood, change in disease trajectory as assessed through cognitive measures and cerebral tau burden assessed by PET. Exploratory measures include pre- and post-treatment effects on functional status, mood, physical functioning, brain structure and CSF measures of pathology and senescence. This multi-site study will begin enrollment in late summer 2021, but a smaller (N=5), open-label, preliminary study aimed at determining blood-brain barrier penetration of D+Q in participants with early-AD is underway at UT Health San Antonio. Data from this study will be presented to provide preliminary results relevant to the larger STOMP-AD trial. **Conclusion:** The STOMP-AD study will provide initial proof-of-concept data relevant to safety, feasibility, and efficacy of the use of senolytics for indication of the treatment of neurodegenerative diseases. These data will inform the development of a phase III trial, to further explore the efficacy of senolytics to modulate the progression of AD. Trial registration number and date of registration: NCT04685590 (12/28/2020). **Acknowledgments:** This work was made possible by grants through the Alzheimer's Drug Discovery Foundation GC-201908-2019443, the OAIC Collaborating Center the UTHSCSA Center for Biomedical Neuroscience, and the San Antonio Claude D. Pepper OAIC (P30AG044271).

OC05- EFFECTS OF THE ORAL P38A KINASE INHIBITOR NEFLAMAPIMOD ON MOTOR FUNCTION (GAIT) IN PATIENTS WITH MILD-TO-MODERATE DEMENTIA WITH LEWY BODIES (DLB). John Alam¹, Hui-May Chu², Kelly Blackburn¹ (1. *Eip Pharma, Inc - Boston (United States)*, 2. *Anoixis Corporation - Natick (United States)*)

Background: Neflamapimod (NFMD) targets pathogenic mechanisms considered to underlie basal forebrain cholinergic (BFC) neurodegeneration (Pensalfini et al, 2020), considered to be a major driver of dementia in DLB; and in preclinical studies neflamapimod rescues neurodegeneration in the basal forebrain (Jiang, 2019). At last year's CTAD, positive clinical results from a 91-patient, 16-week placebo-controlled phase 2 study ("AscenD-LB Study") in mild-to-moderate DLB were reported. In that study, 40mg three-times-daily (TID) NFMD demonstrated clinically meaningful, statistically significant improvement, relative to placebo, in cognition (assessed by DLB-specific Neuropsychological Test Battery) and function [as assessed by the Timed-Up-and-Go (TUG) Test]. At the time of the initial presentation, a limited set of analyses of the TUG data had been conducted, as due to limited data on the connection between BFC function and gait a positive effect on the TUG had not anticipated. However, two very recent publications provide substantially evidence for that connection. First, in a prospective longitudinal study, decline in gait function was correlated to baseline volume of the nucleus basalis of Meynert in the basal forebrain (Wilson et al, 2021). Second, analysis of cortical connectivity in PD and DLB patients undergoing deep brain stimulation revealed a major network was one between the basal forebrain and the supplementary motor area (Oswal, 2021). Given this new biological understanding, a full set of analyses of the TUG results were conducted and are reported herein. **Objectives:** To evaluate the effects of neflamapimod on motor function, specifically gait, as assessed by the Timed-Up-And-Go test, in mild-to-moderate DLB patients receiving cholinesterase inhibitor therapy. **Methods & Patients:** Mild-to-moderate (MMSE 15-28) probable DLB by consensus criteria (McKeith et al, *Neurology*, 2017; 89:88-100), including a positive DaTscan™, and currently receiving cholinesterase inhibitor therapy. Treatment: 40 mg NFMD capsules or matching placebo capsules administered with food for 16 weeks; dosing regimen was based on weight: subjects weighing <80 kg received capsules twice-daily (BID) and those weighing ≥80 kg received capsules TID. The original intent was to evaluate the neflamapimod-recipients as one combined dose group, as prior data had indicated that this weight-regimen would lead to similar plasma drug levels across weight levels. However, a fuller dataset indicated that the effect of weight would be marginal and the measured plasma drug concentrations in the current study were with 50% higher in NFMD40mg TID compared to those in NFMD40mg BID. Accordingly, we report comparisons of the placebo group to (1) the combined NFMD group, and to (2) NFMD40mg TID. The TUG is a test of mobility that uses the time that a person takes to rise from a chair, walk three meters, turn around 180 degrees, walk back to the chair, and sit down while turning 180 degrees. The TUG was evaluated at baseline, weeks 8 and 16 of the study. Due to Covid19 restrictions on access to the clinical centers, not all patients had both week 8 and week 16 assessments, though in the analysis all had an assessment at one and/or the other. **Results:** Baseline and at least one-on-treatment TUG data are available on 38 (27 at week 8, 31 at week 16) placebo, 19 (13,16) NFMD40mg BID and 20 (10,17) NFMD40mg TID recipients. At baseline, the mean(SD) time in

seconds required to complete the TUG was 13.5(6.4) in placebo, 11.9(3.5) in NFMD40mg BID, and 13.3(3.8) in NFMD40mg TID. At week 16, the mean observed changes from baseline were an increase(worsening) of 1.5(5.1) seconds in placebo and 1.3(2.7) seconds in NFMD40mg BID and a decrease(improvement) of 1.4(4.1) seconds in NFMD40mg TID. In the comparison of the combined NFMD groups vs. placebo, there was significant reduction in the time required to complete the TUG test (i.e., improvement) with neflamapimod treatment (p=0.04, difference of -1.36 sec, 95% CI -0.04 to -2.69, linear mixed effects (LME) model of repeated measures). A significant difference favoring neflamapimod treatment was also noted for the comparison of NFMD TID vs. placebo (p=0.028, difference of -2.56 sec, 95% CI -0.28 to -4.84, LME). To evaluate the impact of missing tests due to Covid19 restrictions, an endpoint analysis was conducted in which the 14 patients who had missing week 16 visits had the value for that visit imputed utilizing their week 8 result. ANOVA analysis revealed a significant improvement with neflamapimod treatment compared to placebo (p=0.03, linear trend test: placebo vs. NFMD40mg BID vs. NFMD40mg TID). **Conclusion:** Neflamapimod treatment appears to dose-dependently improve gait in patients with mild-to-moderate DLB. Further, consistent with recent scientific literature, the Timed-Up-and-Go-test may be useful to evaluate treatments that would be expected to improve basal forebrain cholinergic function. The results of the AscenD-LB study, the totality of which indicates that neflamapimod positively impacts both the cognitive and motor aspects of DLB, are to be confirmed in a 160-patient phase 2b study that is planned to commence in the fourth quarter of 2021.

OC06- ACCESS TO ALZHEIMER'S DISEASE PARTICIPANT LEVEL RESULTS DATA VIA DATA SHARING PLATFORMS. Rebecca Li^{1,2}, Murali Doraiswamy³, Ida Sim^{1,4}, Lon Schneider⁵ (1. *Vivli - Cambridge (United States)*, 2. *Harvard Medical School - Boston (United States)*, 3. *Duke University, School Of Medicine - Durham (United States)*, 4. *University of California, San Francisco - San Francisco (United States)*, 5. *Keck School Of Medicine Of The University Of Southern California - Los Angeles (United States)*)

Background: In recent years, data sharing is becoming a reality now that journal editors, funders and others have begun to promote policies to promote and encourage policies to encourage the re-use and sharing of individual participant-level clinical trial data (termed IPD data). Sharing of this "raw" data that is collected from individual participants enables researchers to combine data to drive new scientific insights and assess reproducibility in ways not possible with summary or aggregate data tables. On the contrary, a failure to exploit existing data could mean that new trials are launched unnecessarily or that they do not fully leverage the key learnings from prior trials (1). **Methods:** The number of clinical trial data sharing platforms has grown and most remain disconnected from each other unfortunately resulting in a somewhat fragmented ecosystem. We discuss the potential of data sharing platforms, its impact on researchers and also reflect on the lessons learned on the journey towards a sustainable global data sharing platform. Within the ecosystem of current data sharing repositories and platforms, there is a spectrum of approaches to execution. Some platforms and repositories deploy an "open access" or "open data" approach allowing the data is to be available via download upon signing of a legal use agreement. Other platforms offer a "managed access" or "gatekeeper" model whereby additional requirements are needed for data access

including submission of a research proposal and review through an independent panel. We discuss how the increasing prevalence of Alzheimer's disease has only magnified the necessity of these data sharing platforms and the need for data sharing. If most data are shared in a timely fashion that ideally allows for facile interoperability across datasets, this increases the probability of researchers moving towards a more unified scientific understanding of the underlying disease state. On the contrary, if datasets are not shared or platforms are not interconnected, the impact may be that society could lose an opportunity to quickly accelerate towards developing critical insights in our understanding of Alzheimer's disease and its challenges. The FAIR Data Principles are foundational and serve as guide for research data sharing. Data should be identifiable and searchable ("Findable"), accessible under ("Accessible"), able to be combined with other data in a meaningful way ("Interoperable"), and able to be re-used for multiple purposes ("Reusable"). Vivli, a global data sharing platform established 3 years ago will be presented as a case study which exemplifies a practical implementation of these FAIR data principles and currently provides clinical trial data for re-use from 34 institutional members <https://vivli.org/members/ourmembers/> including 22 from the biopharmaceutical industry and 12 academic institutions, government, non-profits (2). Currently Vivli provides access to over 6,200 trials which represents 3.6 Million trial participants from over 120 countries – included in the platform are a number of trials in Alzheimer's Disease and other dementias that may be integrated to drive "big data insights" through the combining of these multiple studies (or with data from other diseases to answer questions across diseases such as looking at the interaction of Alzheimer's Disease and Covid19) and pooling analyses to answer specific questions. Access is available to researchers through a request process. Most proposals submitted addressed either new questions surrounding treatment effectiveness or were designed to conduct participant-level meta-analysis rather than trying to confirm or reproduce prior analyses. **Results:** One recent individual patient data network meta-analysis conducted using data on Vivli assessed the comparative safety and efficacy of cognitive enhancers for Alzheimer's dementia (3). The aim of this work was to examine the comparative effectiveness and safety of cognitive enhancers for different patient characteristics. Two studies sponsored by AbbVie were obtained through the Vivli platform and compared donepezil with placebo and with no treatment. Both studies assessed the outcomes of interest: Mini-Mental State Examination (MMSE) and Serious Adverse Events (SAE). Aggregate data for 80 clinical trials (21,138 patients for which individual patient data were not available). These results showed that, overall, the cognitive enhancers that showed large treatment effects in MMSE are associated as well with a high risk of a serious adverse events. **Conclusion:** Clinical trial data sharing and data reuse has the potential to accelerate scientific progress, answer new lines of scientific inquiry, support reproducibility and prevent redundancy. In the area of Alzheimer's disease this is a fertile, and yet to be fully tapped, resource for researchers and help yield new insights and potentially novel understandings of the disease. **References:** 1. Schneider LS, Kennedy RE, Wang G, Cutter GR. Differences in Alzheimer disease clinical trial outcomes based on age of the participants. *Neurology*, 2015;84(11):1121-1127. 2. Li, R., Wood, J., Baskaran, A., Neumann, S., Graham, E., Levenstein, M., & Sim, I. (2020). Timely access to trial data in the context of a pandemic: the time is now. *BMJ open*, 10(10), e039326. 3. Veroniki AA, Ashoor H, Rios P, Seitidis G, Mavridis D, Holroyd-Leduc J, Straus S, Tricco A. Comparative

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OC07- PHASE 2/3 TRIALS OF ATH-1017, A NOVEL TREATMENT FOR MILD-TO-MODERATE ALZHEIMER'S DISEASE: UPDATES AND BASELINE DATA. Xue Hua¹, Kevin Church¹, Kai-Bin Ooi¹, Joyce Maalouf¹, William Walker¹, Charles Bernick², Sam Dickson³, Suzanne Hendrix³, Larry Ereshefsky⁴, Hans J Moebius⁵ (1. *Athira Pharma, Inc. - Bothell, Wa (United States)*, 2. *Department Of Neurology, University Of Washington - Seattle, Wa (United States)*, 3. *Pentara Corporation - Millcreek, Ut (United States)*, 4. *Follow The Molecule: Cns Consulting Llc - California (United States)*, 5. *Athira Pharma, Inc. - Bothell Wa (United States)*)

Background: Athira Pharma initiated the Phase 2/3 LIFT-AD study of ATH-1017 in mild-to-moderate Alzheimer's disease (AD) in Q3 of 2020, and the Phase 2 ACT-AD study in Q4 of 2020. ATH-1017 is a brain-penetrant, small-molecule drug with a novel mechanism of action that is designed to augment HGF/MET, a critical neurotrophic system underpowered in AD. AD brains exhibit markedly reduced neuronal MET expression, particularly in the cortex and hippocampus, which may contribute to synaptic loss, neurodegeneration, and functional decline. Enhancement of HGF/MET activity by ATH-1017 has the potential to induce pro-survival and regenerative mechanisms, stimulate spinogenesis and synaptogenesis, and improve cognition by promoting neuronal health, connectivity, and function. A wide dose range of ATH-1017 was well-tolerated in Phase 1 including cohorts of healthy elderly and AD subjects treated for 9 days; also, ERP P300 latency, a functional, objective, non-invasive, neurophysiological biomarker of cognitive performance status, significantly improved in AD patients treated with ATH-1017 compared to placebo. **Methods/design:** The LIFT-AD trial is a 26-week, randomized, double-blind, placebo-controlled, Phase 2/3 study of ATH-1017 in mild-to-moderate AD. The LIFT-AD trial has a target enrollment of 300 patients (aged 55-85, CDR 1 and 2, MMSE 14-24) in the US. Subjects are being randomized 1:1:1 to placebo or one of two doses of ATH-1017 (high and low). The primary endpoints are a Global Statistical Test (GST) and safety. The GST combines the two key secondaries: ADAS-Cog11 and ADCS-CGIC. Additional endpoints include the ADCS-ADL23, COWAT, NPI, and other measures. The concurrent ACT-AD trial is a 26-week, randomized, double-blind, placebo-controlled, Phase 2 study of ATH-1017 in mild-to-moderate AD. The ACT-AD trial has a target enrollment of 75 patients (aged 55-85, CDR 1 and 2, MMSE 14-24) in the US and Australia. Subjects are being randomized 1:1:1 to placebo or one of two doses of ATH-1017 (high and low). The primary endpoints are change in P300 latency and safety. The P300 data is intended to replicate and expand upon the Phase 1 findings in which ATH-1017 treatment significantly improved P300 latency measures in AD patients. Additional endpoints include the GST, ADAS-Cog11, ADCS-CGIC, ADCS-ADL23, COWAT, NPI, and other measures. The ACT-AD is expected to readout ahead of the LIFT-AD, enabling earlier strategic decisions for the larger trial. **Results:** The LIFT-AD and ACT-AD trials are currently enrolling. Baseline data and study updates will be presented at the conference. **Conclusions:** Enrollment of the LIFT-AD and ACT-AD trials are proceeding along expected timelines. Patients enrolled to date exhibit baseline characteristics consistent with a diagnosis

of mild-to-moderate AD likely to experience a substantial decline in cognition and function over a 26-week period in the absence of therapeutic intervention, therefore, this population is appropriate to measure the potential pro-cognitive, neurotrophic effects of ATH-1017.

OC09- BINDING PROFILES TO DIFFERENT AMYLOID-BETA SPECIES OF LECANEMAB, ADUCANUMAB AND GANTENERUMAB, THE THREE MOST DEVELOPED ANTIBODIES FOR ALZHEIMER'S DISEASE. Lars Lannfelt¹, Malin Johannesson², Patrik Nygren², Linda Söderberg², Christer Möller² (1. *Uppsala University - Uppsala (Sweden)*, 2. *Bioarctic - Stockholm (Sweden)*)

Background: Immunotherapy against amyloid β ($A\beta$) has emerged as a promising treatment option for Alzheimer's disease (AD). Although many challenges remain, late-stage clinical trial data from $A\beta$ immunotherapy suggest that disease modifying effects are possible. $A\beta$ exists as various species, including soluble monomers, soluble aggregates of increasing size, e.g., oligomers and protofibrils, and insoluble fibrils in plaques. There is strong evidence that soluble $A\beta$ aggregates are more toxic than monomers or insoluble fibrils. Eliminating these soluble $A\beta$ aggregates might represent an effective treatment approach for AD. **Objectives:** Here, we have examined the binding characteristics of lecanemab, aducanumab and gantenerumab, the three most developed antibodies for AD, to different species of $A\beta$ in vitro. Although all three antibodies showed significant amyloid plaque reduction in clinical trials, the differences in how each antibody engage with different Ab species could impact the disease modifying effect, the side-effect profile and may potentially explain varying clinical results observed for these antibodies. **Methods:** Binding strength of lecanemab, aducanumab and gantenerumab to different in vitro generated species of $A\beta$ such as monomers, oligomers, protofibrils and fibrils, were evaluated side-by-side by inhibition ELISA, immunodepletion and Surface Plasmon Resonance (SPR). Our definition of protofibrils was soluble aggregated $A\beta$ with a size of approximately 75 kDa and larger. Smaller aggregated species were defined as $A\beta$ oligomers. Antibody analogues were produced from sequences published in patents, except for lecanemab. **Results:** Inhibition ELISA: For lecanemab, aducanumab and gantenerumab, IC50 values, when using inhibition ELISA, were in the low to high μ M range for monomeric $A\beta$, reflecting the favor for aggregated soluble species over monomers for all three antibodies. Aducanumab and lecanemab both showed IC50 values above 25 μ M, which reflected very weak binding to monomers. Gantenerumab had a somewhat stronger binding with an IC50 above 925 nM for $A\beta$ monomers. Aducanumab displayed a rather weak binding to protofibrils with an IC50 above 80 nM. Gantenerumab displayed a stronger binding with an IC50 of 2.5 nM for protofibrils. The strongest binding to protofibrils was obtained with lecanemab with an IC50 of 0.8 nM. Binding profiles towards $A\beta$ oligomers were also investigated by inhibition ELISA. Aducanumab displayed no binding to oligomers, whereas both gantenerumab and lecanemab displayed binding to oligomers with an IC50 of approximately 6 nM, i.e. lower binding strength as compared to protofibrils. Immunodepletion: Binding to protofibrils in solution was further evaluated where serially diluted antibodies and a constant amount of 10 pM $A\beta$ protofibrils were allowed to interact in solution, followed by an immunodepletion step. For aducanumab, a complete depletion of protofibrils was only observed at the highest antibody concentration of 6670 pM. Gantenerumab demonstrated

complete depletion of protofibrils at a concentration of 667 pM. For lecanemab complete depletion of protofibrils was observed already at an antibody concentration of 67 pM, implying a stronger binding to protofibrils as compared with the other two antibodies. SPR: The kinetic properties that determined the binding strength of the antibodies for different $A\beta$ species were also investigated using SPR. A very weak binding to monomers were observed for all three antibodies with an affinity (KD) of 7350 nM for aducanumab, 1270 nM for gantenerumab and 2290 nM for lecanemab. The binding of aducanumab to the protofibrils differed from that of gantenerumab and lecanemab, with a non-typical sensogram resulting in an apparently low KD1, as affinity was driven by a fast association rate rather than by a slow dissociation rate. Gantenerumab bound protofibrils with a binding strength of 6.2 nM, and lecanemab was the strongest binder to protofibrils with a KD1 of 1.0 nM. Aducanumab bound fibrils with high affinity with a KD1 of 3.3 nM. Gantenerumab displayed higher affinity for fibrils as compared to monomers and protofibrils, with a KD1 of 0.7 nM. Lecanemab also had strong binding to fibrils but the binding was approximately 10-fold lower than to protofibrils. Lecanemab's relatively lower affinity for the fibrils was mainly due to a slower association rate when binding to the fibrils, consistent with that protofibrils were the preferred target for lecanemab. Lars Lannfelt is a co-founder of BioArctic AB

OC10- A POLYMORPHISM CLUSTER AT THE 2Q12 LOCUS MAY PREDICT RESPONSE TO PIROMELATINE IN PATIENTS WITH MILD ALZHEIMER'S DISEASE. Lon Schneider¹, Moshe Laudon², Tali Nir¹, Juan Caceres³, Generoso Ianniciello³, Mattia Capulli³, Nava Zisapel³ (*University Of Southern California - Department Of Psychiatry And The Behavioral Sciences, And Department Of Neurology, Keck School Of Medicine, And Leonard Davis School Of Gerontology Of The University Of Southern California, Los Angeles, Ca (United States)*, 2. *Neurim Pharmaceuticals Ltd, Tel Aviv, (Israel)*, 3. *Dante Labs, Cambridge, (United Kingdom)*)

Background: Piromelatine is a novel melatonin MT1/2/3 and serotonin 5-HT-1A/1D receptors agonist developed for mild Alzheimer's disease. Melatonin receptor agonism appears to clinically benefit mild to moderate AD patients (1). Simultaneous activation of melatonergic and 5-HT-1A receptors may synergistically promote neurogenesis (2). Piromelatine, 20 mg and 50 mg daily over 1 month enhanced sleep maintenance in a phase 2, randomized, placebo-controlled, sleep study in patients with insomnia (n=137 aged 18-80) (3); and enhanced NREM delta power and decreased beta power (4). Both effects may be beneficial in early AD and enhance $A\beta$ clearance from the brain (5). In a Phase 2, randomized, placebo-controlled, dose-ranging study (ReCognition) of piromelatine (5, 20, and 50 mg daily for 6 months) in participants with mild dementia due to Alzheimer's disease (n=352 age 60-85 years), no statistically significant differences were found between the piromelatine and placebo groups on the primary and secondary outcomes (the computerized Neuropsychological Test Battery (cNTB), Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog14) and Pittsburgh Sleep Quality Index (PSQI)), nor were there safety concerns (NCT02615002). **Objectives:** This study was aimed at identifying genetic factors predicting piromelatine treatment response (i.e., > 0.125 change from baseline in cNTB) in ReCognition study participants using a genome-wide association approach (GWAS). **Methods:** For 107 patients, genomic DNA was extracted from lymphocytes, and variant genotyping of a combined Whole Genome and Whole

Exome sequencing was performed. The general case-control allelic test was performed on piromelatine treated subjects, taking “responders” as cases and “non responders” as controls, through a Cochran-Armitage trend test. Results were cross-checked against potential confounding variables, given as a stratification test. The stratification was assessed by a complete-linkage hierarchical clustering using the pairwise population concordance as a constraint. The SNP calling was done on the aligned BAM files using DRAGEN: support.illumina.com/help/DRAGEN_Germline_OLH_100000083701/Content/Source/Informatics/Apps/DRAGENGermlineSmallVarCaller_appDRAG.htm and filter SNPs using VQSR: gatk.broadinstitute.org/hc/en-us/articles/360035531612-Variant-Quality-Score-Recalibration-VQSR. **Results:** The GWAS sample did not differ in demographics or clinical characteristics from the larger trials sample. The cNTB response to piromelatine was 41% (42% in the full sample). We did not observe any SNP p-value with enough significance in isolation to ensure the discovery of a locus associated with the drug response. However, we observed a few loci in chromosome 2q12, within the range 2:107,510,000-107,540,000 which had multiple SNPs with a p-value < 1x10⁻⁴ each (rs12328439 (T>C), rs62155556 (T>A), rs62155557 (G>T), rs62155558 (G>A), rs17033479 (A>G) and rs9789618 (T>A) as disclosed in the Genome Reference Consortium Human genome build 37 (GRCh37)). In particular, the SNPs in this locus also appear the most significant list as the best predictors of response when adjusted for covariates (apoE alleles, piromelatine dose, and group) which adds further significance to the loci. Thus far, the intergenic 2:107,510,000-107,540,000 range has not been described in relation to any disease. However, copy number variants in chromosome 2q12 region encompassing the 2:107,510,000-107,540,000 range have been associated with schizophrenia (6). Subsequent post-hoc analyses suggested that the participants carrying the 2q12 polymorphism cluster (27% of the GWAS sample) improved significantly in cNTB on piromelatine as compared to placebo; the 20 mg dose was more effective (0.44 (N=12) vs 0.04 (N=10) respectively, p=0.04). In contrast, there was a significant worsening in ADAS-Cog14 (+3.58 (N=12) vs -3.1 (N=10), respectively; p=0.01) and in PSQI (-0.17 (N=12) vs -3.80 (N=10), respectively; p=0.04). In contrast, “non-carriers” (73% of the GWAS sample) improved significantly with piromelatine on the ADAS-Cog14 and PSQI compared to placebo. The 20 mg dose was more effective in improving ADAS-Cog14 (-2.91 (N=23) vs 1.65 (N=19), respectively; p=0.03) and PSQI (-2.13 (N=23) vs -0.06 (N=19), respectively; p=0.05). Of the “non-carriers” 34.7 % improved (decreased) by ≥ 4 ADAS-Cog14 points in the piromelatine 20 mg vs. 11.8% in the placebo group. **Conclusions:** The 2q12 (2:107,510,000-107,540,000) 5-6 SNPs polymorphism cluster may serve as a predictor of cognitive worsening with piromelatine treatment in patients with mild Alzheimer’s disease. In line with previous reports on association between progressive cognitive deterioration with parallel deterioration in sleep (7). The main limitation in the study is the small sample due to the available GWAS specimens. Piromelatine may be particularly effective for mild Alzheimer’s disease patients who do not carry this 2q12 polymorphism cluster. These findings warrant further investigation in a larger, prospective clinical trial focusing on early-stage Alzheimer disease patients who do not carry the 2q12 polymorphism cluster. **Declaration of interest:** Nava Zisapel is the founder and CSO of Neurim Pharmaceuticals, the sponsor of the ReCognition study **References:** 1. Wade AG, Farmer M, Harari G, et al. Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer’s disease: a 6-month, randomized, placebo-

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OC11- IMPACT OF COCOA FLAVANOLS AND MULTIVITAMINS ON COGNITIVE FUNCTION: FINDINGS OF THE COCOA SUPPLEMENT AND MULTIVITAMIN OUTCOMES STUDY OF COGNITION (COSMOS-MIND). Laura Baker¹, Joann Manson^{2,3}, Stephen Rapp¹, Howard Sesso², Sarah Gaussoin¹, Sally Shumaker¹, Mark Espeland¹ (1. Wake Forest School Of Medicine - Winston-Salem (United States), 2. Brigham And Women’s Hospital - Boston (United States), 3. Harvard Medical School - Boston (United States))

Background: COSMOS-Mind examined whether daily treatment with cocoa flavanol extract (CF) versus placebo or standard multivitamin-multimineral (MVM; Centrum Silver) versus placebo for 3 years in adults aged ≥65 years protected cognitive function and slowed cognitive decline associated with normal and pathological aging, including Alzheimer’s disease (AD). COSMOS-Mind (NCT03035201; MPI: Baker, Espeland) is an ancillary study to the large 2x2 factorial randomized controlled trial, COcoa Supplement and Multivitamin Outcomes Study (COSMOS; NCT102422745; MPI: Manson, Sesso, Anderson) that tests the effects of these supplements on cardiovascular disease and cancer. Epidemiologic evidence suggests that higher flavonoid intake is associated with lower risk for cognitive decline and AD, and two small, controlled trials provided evidence of short-term cognition-enhancing effects of CF. Although essential nutrient deficiencies have been linked to higher risk of cognitive decline and AD, evidence to support MVM supplementation for cognitive benefit is inconsistent. The majority of trials examining MVM effects on cognition included relatively healthy cohorts (e.g., the Physicians’ Health Study) or relied on individual test scores rather than a multi-test composite to assess treatment effects. COSMOS-Mind provides an important opportunity to further examine the effects of long-term MVM and CF supplementation on a composite measure of global cognitive function in a large and diverse sample of older adults. **Objectives:** To test whether randomized assignment to daily CF (primary aim) and/or MVM (secondary aim) affects cognitive function across 3 years in non-demented adults aged ≥65 years. **Methods:** COSMOS-Mind methods are published (Baker et al., *Contemporary Clinical Trials* 2019;83:57-63). The study targeted enrollment of 2000 participants from the planned 18,000-person parent trial to provide >90% statistical power to detect mean cognitive change over 3 years of annual follow-up. Interested participants from

the parent trial were recruited into COSMOS-Mind. Participants were consented by telephone, and a 45-minute telephone-based cognitive battery was administered at baseline and annually at years 1, 2, and 3. Supplements and placebos were distributed by mail. Cognitive tests administered included the Telephone Interview of Cognitive Status-modified (TICS_m), Delayed Word Recall, Story Recall, Oral Trail-Making Test, Verbal Fluency, Number Span and Digit Ordering. Cognitive outcomes for analysis included composite scores of global cognitive function, episodic memory and executive function (all converted to z-scores). Statistical analyses (intention-to-treat) were based on mixed effects models in which constituent test scores for the composite outcome (baseline through year 3 for all participants) were included as dependent variables and linear contrasts were used to assess two-tailed differences between the average mean scores across follow-up and the baseline mean score. Interactions between treatment groups (CF, MVM) were explored, and multiple imputation was used to examine the influence of missing data. **Results:** COSMOS-Mind enrolled 2262 geographically diverse participants over 13 months (mean age=73 years [SD=5.6]; female: 60%; racial/ethnic minorities: 11%; education ≤12 years: 11%); 92% completed the baseline and at least one follow-up cognitive assessment. Those assigned to active versus placebo CF and MVM were comparably balanced, did not differ in attrition, and demonstrated excellent safety profiles. For CF, there was no significant difference between active and placebo groups in global cognitive function (p=0.28; difference: z=0.03, 95%CI: -0.02, 0.08). Likewise, CF had no effect on episodic memory (p=0.40; difference: z=0.03, 95%CI: -0.04, 0.09) or on executive function (p=0.23; difference: z=0.03, 95%CI: -0.02, 0.08). In contrast, the MVM group showed a statistically significant improvement in global cognitive function relative to the placebo group (p=0.007; difference: z=0.07, 95%CI: 0.02, 0.12). In addition, the MVM group showed statistically significant improvements relative to placebo in episodic memory (p=0.04; difference: z=0.06, 95%CI: 0.002, 0.13) and executive function (p=0.02; difference: z=0.06, 95%CI: 0.01, 0.11). There was no evidence of an interaction between CF and MVM treatment response. The results of multiple imputation were consistent with results based on observed data. **Conclusion:** COSMOS-Mind provides the first evidence from a large-scale, long-term, randomized controlled pragmatic trial in a community-based cohort to support the efficacy of daily MVM use as a safe and readily available intervention to protect cognitive function in older adults. The results of COSMOS-Mind may have important implications for standard of health care in older adults to protect brain health and possibly prevent cognitive decline associated with AD and related disorders. CF supplementation, however, did not slow cognitive decline.

OC12- RECRUITING THE INNATE IMMUNE SYSTEM TO TREAT MILD-TO-MODERATE ALZHEIMER'S DISEASE: SHORT-TERM, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II TRIAL SHOWS THAT GM-CSF/SARGRAMOSTIM TREATMENT LEADS TO IMPROVEMENTS IN MMSE AND BLOOD BIOMARKERS OF NEUROPATHOLOGY/NEURODEGENERATION (AB, TAU, AND UCH-L1). Huntington Potter¹, Jonathan Woodcock¹, Timothy Boyd², Christina Coughlan¹, John O'shaughnessy¹, Manuel Borges¹, Ashesh Thaker¹, Balaibail Raj³, Katarzyna Adamszuk⁴, David Scott⁴, Vanesa Adame¹, Paige Anton¹, Heidi Chial¹, Joseph Daniels¹, Helen Gray¹, Michelle Stocker¹, Stefan Sillau¹ (1. *University Of Colorado Alzheimer's And Cognition Center - Aurora (United States)*, 2. *Partner Therapeutics - Lexington (United States)*, 3. *University Of South Florida - Tampa (United States)*, 4*Bioclinica - Princeton (United States)*)

Background: Rheumatoid arthritis (RA) patients have a reduced risk of developing Alzheimer's disease (AD), which was originally thought to be due to their usage of non-steroidal anti-inflammatory drugs (NSAIDs). However, clinical trials with NSAIDs were unsuccessful in participants with AD or mild cognitive impairment (MCI). In an alternative approach, we focused on the innate immune system and hypothesized that intrinsic factors associated with RA pathogenesis itself may underlie the AD protective effect(s). We tested several cytokines that are upregulated in the blood of RA patients, 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 sargramostim, an innate immune system modulator that 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 is complete and published (NCT01409915; PMID: 33778150). Specifically, the study recruited 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. The safety and efficacy of sargramostim treatment were assessed by neurological and neuropsychological, pathology- and inflammation-related plasma biomarker measures, MRI, and amyloid-PET scans. **Results:** Analyses of all 40 participants showed no drug-related serious adverse events, including no evidence of micro-hemorrhage or vasogenic edema, together termed amyloid-related imaging abnormalities (ARIAs). 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 of sargramostim on MMSE 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, which may result from a rebound effect of ending treatment. This difference disappeared by the second follow-up visit at 90 days after the end of treatment. Other neuropsychological measures showed no statistically significant effects. Complete blood counts revealed that sargramostim treatment led to increases in monocytes, lymphocytes, and neutrophils, as expected. Analyses of plasma samples using the Meso Scale Discovery platform showed highly statistically significant increases in the inflammatory cytokines IL-2, IL-6, and TNF- α , and also an increase in the anti-inflammatory marker IL-10 at the end of treatment, compared to placebo. The Quanterix Simoa® platform showed that GM-CSF treatment led to a statistically significant reduction (toward normal) in two blood biomarkers of neuronal damage—ubiquitin C-terminal hydrolase L1 (UCHL-1) and total Tau—compared to baseline and compared to placebo. Specifically, at the end of treatment, compared to placebo, sargramostim treatment led to a 42% relative lowering of UCHL-1 ($p=0.0019$) and a 24% relative lowering of total Tau ($p=0.0174$). Plasma levels of Ab40 were increased (toward normal) by 10% ($p=0.0105$), compared to placebo. Plasma levels of glial fibrillary acidic protein (GFAP) and neurofilament light (NfL) did not change significantly following sargramostim treatment, although their changes were highly correlated with each other. MMSE changes were positively correlated with changes in lymphocytes, neutrophils, and ADCS-Activities of Daily Living=. 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). Volumetric brain scans and measures of plasma pTau-181 are currently being analyzed, as are comparisons of all biomarkers to similarly analyzed plasma samples from non-demented controls. **Conclusions:** Treatment with sargramostim was safe and tolerable in mild-to-moderate AD participants. One measure of cognition (MMSE), and all three Amyloid, Tau, Neurodegeneration (ATN) plasma measures of neuropathology and neurodegeneration (i.e., Ab, total Tau, and UCHL-1) improved towards normal after three weeks (15 injections) of sargramostim treatment compared to baseline and compared to placebo. These results indicate that modulating the innate immune system using the classically described proinflammatory cytokine, GM-CSF/sargramostim, shows promise as a potentially safe treatment for AD. These results also suggest that activation of inflammation and the innate immune system in AD may reflect a compensatory mechanism that sargramostim treatment can recruit further for therapeutic benefit. A second, longer Phase II trial funded by the NIH and an Alzheimer's Association "Part the Cloud" grant is underway.

OC13- TARGETED MEDICATION THERAPY MANAGEMENT CAN SUCCESSFULLY AUGMENT COGNITIVE RESERVE IN PREDEMENTIA ALZHEIMER'S DISEASE: RESULTS FROM THE INTERVENTION FOR COGNITIVE RESERVE ENHANCEMENT IN DELAYING THE ONSET OF ALZHEIMER'S SYMPTOMATIC EXPRESSION (INCREASE) STUDY. Gregory Jicha¹, Erin Abner¹, Frederick Schmitt¹, Lynne Eckmann¹, Mark Huffmyer¹, Ashley Martinez^{1,2}, Brooke Beech^{1,3}, Rosmy George¹, Riham El Khoulil¹, Doaa Ali¹, Daniela Moga¹ (1. University Of Kentucky - Lexington (United States), 2. Harvard Medical School - Boston (United States), 3. Washington State University - Pullman (United States))

Background: Cognitive reserve (CR) is a theoretical construct that explains why some individuals can remain asymptomatic in the presence of high levels of Alzheimer's disease pathology (pAD). As such, developing methods to augment CR may prove effective delaying the clinical manifestations of dementia and might further have a profound impact on the prevalence and societal burden of dementia. The INCREASE study is based on the hypothesis that targeted reductions in inappropriate medication use will bolster cognitive reserve (CR) in individuals at risk for Alzheimer's Disease (AD), thereby delaying the onset of clinical symptoms, and reducing the prevalence and duration of symptomatic disease. **Objectives:** The INCREASE study is a randomized, 12-month, parallel-arm, controlled study of a multidisciplinary medication therapy management (MTM) intervention targeting reductions in inappropriate medication use designed to bolster CR in individuals with pAD. **Methods:** Non-demented, community-dwelling participants, age >65 years, were randomized to a 12-month trial of MTM or placebo intervention, stratified by age, education, sex, diagnosis (normal vs MCI), Medication Appropriateness Index (MAI), and amyloid-PET SUVR (clustered as SUVR <1.2, 1.2-1.4, and >1.4). A CR index was developed based on a comparison of scopolamine (0.4mg transdermal) challenged vs. unchallenged cognitive test scores conducted within a four-week window at both baseline and end of study (EOS) visits. The MTM intervention included a physician-pharmacist team assessment of potentially inappropriate medication use (based on Beer's criteria) followed by a sustained 12-month intervention that attempted to optimize medication use. Primary outcome measures included pre- to post-intervention measures of 1) MAI, and 2) CR Change Score (CRCS) defined as the ratio of scopolamine-challenged vs unchallenged Trail Making Test B (TMT B) time to completion. Secondary outcome measures included CRCS for both the Montreal Cognitive Assessment (MoCA) and the California Verbal Learning Test, total learning (CVLT-TL) and long-delay free recall (CVLT-LDFR) scores. Multivariate linear regression models were used to analyze the data including assessment of amyloid SUVR*treatment group interactions (main effects). This study was funded by NIH/NIA R01 AG054130 and was registered on clinicaltrials.gov NCT NCT02849639. **Results:** Ninety community-dwelling participants were randomized into the study (N=104 screened for eligibility). Mean (SD) age at enrollment was 73.9 (6.0), with N=57 (63%) female, and N=10 (10%) non-white participants. At baseline, participants reported using a mean (SD) of 12.72 (4.87) medications, with 2.37 (1.29) potentially inappropriate (Beers 2015 criteria). The MTM intervention arm demonstrated significant reductions in MAI scores from baseline to EOS visits compared to the placebo arm after adjusting the model for age, sex, education, baseline MAI, # baseline meds, # baseline meds, SUVR ≥ 1.4 (mean change difference = 1.90 ± 0.81 ;

$p = 0.0195$; primary outcome measure). TMT B CRCS scores demonstrated a significant effect when the multivariate model included the of amyloid SUVR*treatment group interaction term for subjects with SUVR > 1.4 ($n = 29$; mean CRCS difference = -43.7 ± 18.3 ; $p = 0.017$; primary outcome measure), but not for those without pAD ($n = 61$; mean CRCS difference = 8.8 ± 11.6 ; $p = 0.45$). MoCA CRCS scores demonstrated a significant effect when the multivariate model included the of amyloid SUVR*treatment group interaction term for subjects with SUVR > 1.4 ($n = 29$; mean CRCS difference = -0.18 ± 0.08 ; $p = 0.026$; secondary outcome measure), but not for those without pAD ($n = 61$; mean CRCS difference = 0.003 ± 0.05 ; $p = 0.95$). CVLT-TL and CVLT-LDFR demonstrated no significant effects of treatment for any of the models studied (secondary outcome measure). **Conclusions:** The INCREASE study results demonstrate that a multidisciplinary MTM intervention can reduce inappropriate medication use for non-demented persons irrespective of pAD amyloid levels, but that CR benefits are only seen in those with advanced amyloid-PET SUVR levels (>1.4). The strongest impact of the MTM intervention for those with amyloid-PET SUVR > 1.4 was on executive function (TMT B CRCS) and global cognition (MoCA CRCS), with little impact seen on measures of learning (CVLT-TL CRCS) or delayed recall (CVLT-LDFR CRCS). It remains unclear if the demonstrated augmentation of CR by the MTM can truly delay the onset and or progression of dementia based on the study data, but the results are highly supportive of such a possibility. Given the importance of this question, it is clear that larger, multi-site, longer-duration studies of the MTM in pAD are warranted.

OC14- A MODEL COMBINING TAU PET, BASELINE COGNITION AND NEUROFILAMENT LIGHT OPTIMALLY PREDICTS COGNITIVE DECLINE OVER 24 MONTHS IN AMNESTIC MILD COGNITIVE IMPAIRMENT AND DEMENTIA. Ruben Smith, Nicholas Cullen, Antoine Leuzy, Shorena Janelidze, Sebastian Palmqvist, Niklas Mattsson-Carlgren, Oskar Hansson (*Lund University - Lund (Sweden)*)

Background: Biomarkers for optimal prediction of subsequent cognitive decline in patients with amnesic mild cognitive impairment (MCI) and amnesic mild dementia are needed for both clinical practice and clinical trials. **Objectives:** To assess the best combination of MRI, cognition, tau PET, as well as phosphorylated tau (pTau217), neurofilament light (NfL), and Amyloid β 42/A β 40 in plasma and cerebrospinal fluid (CSF) for predicting cognitive decline over a 24-month period using MMSE. **Methods:** Cognitively impaired participants with amnesic MCI ($n=65$) or mild amnesic dementia (baseline MMSE ≥ 22 ; $n=22$) were assessed at baseline with cognitive testing (Trailmaking test B, Animal Fluency and ADAS delayed word recall), blood and CSF sampling, MRI, and [18F]RO948 tau PET and followed longitudinally with repeated cognitive testing over 24 months in The BioFINDER-2 study. Individual slopes of change in MMSE were calculated over the follow-up period. Linear regression models were used to assess the ability of individual and combinations of biomarkers to predict cognitive decline in MMSE over two years. All biomarker models also included age, sex, education, baseline MMSE (a model with these predictors alone without biomarkers was also tested, and called the basic model). **Results:** We found that a combination of baseline temporal lobe tau PET, plasma NfL and baseline cognition provided the best model fit for predicting cognitive decline ($R^2 = 0.47$, $\Delta AIC = -35.5$ versus basic model ($R^2 = 0.15$)), where all predictors remained independently significant, but tau PET was the most significant contributor. Similar results

were obtained in sensitivity analyses using only A β positive participants ($n=59$). Tau PET, NfL and baseline cognition predicted cognitive decline ≥ 2 points in MMSE/year with an AUC of 0.83 [95% C.I. 0.71-0.94] using CSF NfL and 0.82 [95% C.I. 0.71-0.94] using plasma NfL. Further, using this biomarker model to enrich patient selection in a theoretical clinical trial led to a significantly lower required sample size with preserved statistical power. For example, selecting the 50% with the most pathological biomarkers resulted in ~60% fewer participants needed in the study. This model also enriched for A β -positive cases, 68% were A β -positive in the unselected population, and 93% in the top 50%. The prediction model has further been implemented as an online tool for individual prediction of the probability of cognitive decline over 2 years. **Conclusions:** A model combining tau PET, plasma or CSF NfL and baseline cognition provided the best prediction for change in MMSE over 2 years in patients with amnesic MCI or mild dementia. Participant selection using this model could significantly reduce the number of participants needed in clinical trials.

OC15- FLORTAUCIPIR IN THE TRAILBLAZER-ALZ TRIAL. Sergey Shcherbinin¹, Ming Lu², Amanda Morris², Ixavier Higgins¹, Cynthia Evans¹, Albert Lo¹, Emily Collins^{1,2}, John Sims¹, Dawn Brooks¹, Mark Mintun^{1,2} (1. Eli Lilly And Company - Indianapolis (United States), 2. Avid Radiopharmaceuticals - Philadelphia (United States))

Background: TRAILBLAZER-ALZ (NCT03367403), a multicenter, randomized, double-blind, placebo-controlled phase 2 trial, assessed the safety and efficacy of donanemab in early symptomatic patients with Alzheimer's disease (AD). Donanemab is a humanized antibody specific for the N-terminal pyroglutamate A β epitope that is only present in mature brain amyloid plaques (Mintun et al, NEJM, 2021). In this trial, we enrolled only participants with an intermediate tau level as determined using 18F-flortaucipir positron emission tomography (PET). We also implemented longitudinal 18F-flortaucipir scans to test if donanemab therapy affects the further progression of tau pathology. **Objectives:** Characterize patients enrolled in TRAILBLAZER-ALZ using novel 18F-flortaucipir-driven screening criteria and evaluate the pharmacodynamic effect of donanemab using longitudinal 18F-flortaucipir scans. **Methods:** Key eligibility criteria preceding a screening 18F-flortaucipir PET scan included cognitive (Mini-Mental Status Examination [MMSE] score of 20-28 inclusive) and age (60-85 years) restrictions. The 18F-flortaucipir images were first interpreted by visual examination (Fleisher et al, JAMA Neurology, 2020) and only patients having regional patterns of tracer uptake that were consistent with AD (moderate AD pattern ($\tau AD+$) or advanced AD pattern ($\tau AD++$)) were further characterized using quantitative analysis. A composite standardized uptake value ratio (SUVR) in a posterior neocortical region of interest (MUBADA, Devous et al, JNM, 2017) with respect to a reference signal intensity in white matter (PERSI, Southekal et al, JNM, 2018) was calculated. Patients with either (a) $\tau AD+$ patterns and MUBADA SUVRPERSI between 1.10 and 1.46, inclusive, or (b) $\tau AD++$ patterns and MUBADA SUVRPERSI ≤ 1.46 were deemed to have an intermediate tau level and were selected. A screening 18F-florbetapir PET scan with a cut-point equivalent to 37 centiloids was performed for patients who met these tau eligibility criteria. We implemented longitudinal 18F-flortaucipir scans to evaluate the change from baseline to 76 weeks in both tau global deposition and regional patterns after donanemab therapy. Global tau deposition was

assessed using the global tau load endpoint (TauIQ algorithm, Whittington and Gunn, JNM, 2021) and MUBADA SUVR values with respect to both PERSI and cerebellar grey matter (CGM) region as a reference. In our post hoc exploratory analyses, regional patterns were examined using predetermined cortical regions of interest (ROIs) from the Automated Anatomical Labeling (AAL, Tzourio-Mazoyer et al, Neuroimage, 2002) brain atlas. We utilized an event-based modeling concept (EBM, Young et al, Brain, 2014 and Berron D et al, Brain, 2021) to an independent cross-sectional dataset (N=442) of 18F-flortaucipir images to establish a sequence in which the AAL regions exhibit abnormally high tau burden. Analysis of covariance (ANCOVA) was used to evaluate change in 18F-flortaucipir endpoints. The ANCOVA model included the continuous, fixed covariate of baseline measure and age at baseline. **Results:** During enrollment, 30.3% of those screened did not meet 18F-flortaucipir eligibility requirements. Importantly, a small percentage (0.9%) of patients who met tau eligibility criteria did not have an elevated amyloid level with a cut-point equivalent to 37 centiloids. Therefore, the established intermediate tau level was largely linked with amyloid level notably exceeding an amyloid positivity threshold of 24.1 centiloids. Compared to NAVIGATE-AD (NCT02791191, a BACE inhibitor phase 2 trial that used only a presence of amyloid pathology as eligibility criteria), TRAILBLAZER-ALZ participants had lower and less variable MUBADA SUVRPERSI scores as well as less variable ADAS-Cog13 baseline score (Shcherbinin et al, JPAD, 2020). Comparing four phase 2 and 3 AD trials, TRAILBLAZER-ALZ trial showed the highest signal-to-noise ratio for longitudinal change in cognitive and functional parameters among placebo-treated patients. In the placebo arm, all three global measures of tau deposition (global tau load (TauIQ), MUBADA SUVRPERSI and MUBADA SUVRCGM) demonstrated increase in tau over 76 weeks with the least-squares mean changes and standard errors of 0.0986 (0.0075), 0.0548 (0.0047), and 0.1039 (0.0100), respectively. Global tau load (TauIQ algorithm) and MUBADA SUVRPERSI failed to show a significant difference between donanemab and placebo groups in terms of the change from baseline to 76 weeks with a percent difference of -3.60% and +3.67%, respectively. However, a significant ($p=0.0125$) difference of -33.98% on MUBADA SUVRCGM was observed. Directionally, regional SUVRCGM values showed more pronounced separation in regions identified later in the sequence using EBM. Specifically, difference with donanemab treatment was not significant in the earliest cortical ROIs: fusiform (-30.68%) and inferior temporal (-22.83%). Conversely, difference in all nine bilateral frontal ROIs was significant and varied between -50.86% (frontal middle) and -88.58% (medial orbitofrontal). **Conclusions:** We successfully implemented a novel 18F-flortaucipir-based pathologically-defined screening procedure in the TRAILBLAZER-ALZ phase 2 trial and reduced heterogeneity in tau and efficacy measurements of the enrolled population. When cerebellum grey matter region was used as a reference, both global and regional SUVRs suggested a slowing of tau accumulation in the donanemab arm comparing with the placebo arm. Additional analyses will be presented during the meeting.

OC16- EFFECT OF RACIAL DIFFERENCES IN ALZHEIMER DISEASE BIOMARKERS ON DESIGN AND ANALYSIS OF PREVENTION TRIALS. Chengjie Xiong, Tammie Benzinger, Suzanne Schindler, Anne Fagan, Jason Hassenstab, John Morris (Washington University (United States))

Background: Decades of biomarker studies have established the validity of an array of AD biomarkers to detect A β and neurofibrillary tangles (NFTs) in the brain as well as associated neuronal death and neurodegeneration, including the molecular imaging of cerebral fibrillar β -amyloid with positron emission tomography (PET) using the [11C] benzothiazole tracer, Pittsburgh Compound-B (PiB) and other tracers (e.g., 18F-AV45), cerebrospinal fluid (CSF) analytes, tau PET regional uptakes, and magnetic resonance imaging (MRI)-based brain structural measures. These studies further converge to demonstrate that the neuropathological course of AD begins decades prior to symptom onset, and biomarker changes follow a temporal cascade with early A β accumulation and deposition in the brain, followed by formation of NFTs, neuronal death and brain structural changes. However, most of these important findings are from predominantly Caucasian cohorts. Better understanding of cross-sectional and longitudinal racial differences in AD biomarkers is crucial for the optimal design of prevention/intervention trials to ensure that treatments benefit under-represented groups (URG). **Objectives:** To assess how the cross-sectional and longitudinal racial differences in AD biomarkers may impact design and analyses of prevention trials in AD. **Methods:** We will summarize main findings on cross-sectional and longitudinal differences in AD biomarkers between African Americans (AAs) and Whites from the Washington University Knight Alzheimer Disease Research Center (ADRC) databases. We will assess how the observed racial differences may potentially impact the design and analysis of future prevention trials in AD, especially in terms of sample sizes necessary to power the trials when the biomarkers and cognition are used as the primary efficacy endpoints. **Results:** A total of 85 AAs and 583 Whites were cognitively normal at baseline and had molecular biomarker data from either CSF or amyloid PET imaging. Longitudinal data were available from 37 AAs for CSF biomarkers, 47 AAs for amyloid PET, 330 Whites for CSF biomarkers, and 374 Whites for amyloid PET. Significant racial differences were observed between AAs and Whites. At baseline, based on the cutoffs to define amyloid and pTau181 positivity, the rate of biomarker positivity for AAs was 14.3% by CSF amyloid- β peptide 42 to 40 (A β 42/A β 40) ratio, 10.7% by CSF tau phosphorylated at position 181 (pTau181), and 10.7% by amyloid PET mean cortical uptake. The rate of positivity for Whites was significantly higher with 28.7% by CSF A β 42/A β 40 ($p=0.0055$), 29.2% by pTau181 ($p=0.0004$), and 24.7% by amyloid PET mean cortical uptake ($p=0.0209$). Longitudinally, CSF A β 42/A β 40 declined more slowly in AAs than Whites ($-0.0004/\text{year} \pm \text{standard error [SE]} 0.0002/\text{year}$ and $-0.0009/\text{year} \pm 0.0001/\text{year}$, respectively, $p=0.0390$). Amyloid PET centiloid also suggested that amyloid accumulated more slowly over time in AAs than Whites ($0.85/\text{year} \pm 0.30/\text{year}$ vs. $1.61/\text{year} \pm 0.10/\text{year}$; $p=0.0157$). The estimated annual rate of increase in CSF total tau and pTau181 for AAs was about half of that for Whites, but the differences were not statistically significant ($p=0.1715$ and 0.1395 , respectively). We assume a future prevention trial enrolls both AAs and Whites in a ratio of 1:k ($k>1$), and the randomization is 1:1 between an active treatment and a placebo that is stratified by race. We further assume participants will be followed for a total of 4 years with

annual biomarker and cognitive assessments. For a total sample size of 1000 participants in the clinical trial, the statistical power to detect a 50% effect size in CSF A β 42/A β 40 on the annual rate of change is 71.6% when k=9 (10% AAs) and 95.5% when k=3 (25% AAs). The statistical power to detect a 50% effect size in CSF pTau181 on the annual rate of change is 61.6% when k=9 and 90.2% when k=3. The statistical power to detect a 50% effect size in PET amyloid uptake on the annual rate of change is 81.9% when k=9 and 98.6% when k=3. The statistical power to detect a 50% effect size in the cognitive composite on the annual rate of change is 61.4% when k=9 and 90.1% when k=3. **Conclusions:** Our analyses provide evidence of cross-sectional and longitudinal differences in amyloid accumulation and CSF tau and pTau181 between cognitively normal AAs and Whites. Race-specific cutoffs may be necessary to allow more AAs to be enrolled in prevention trials. Adequate representations of AAs improve the statistical power to optimally design future primary and secondary prevention trials on AD.

OC17- WHY YOUR ALZHEIMER'S DISEASE STUDY IS GOING TO FAIL. Samuel Dickson, Newman Knowlton, Jessie Nicodemus Johnson, Sean Hennessey, Suzanne Hendrix (Pentara Corporation - Salt Lake City (United States))

Background: In many fields, past success lays the groundwork for future success, but in AD the many failures have led to more failures, culminating recently in a long-awaited regulatory approval greeted with more controversy and confusion than celebration. Like the many failures that preceded it, we may have more to learn from the missteps along aducanumab's path to approval than from any correct decisions Biogen may have made. One certainty that is highlighted by the low rate of approval for AD treatments is that successful AD trials require better design and higher-level execution to achieve success. **Objectives:** We aim to use the lessons learned from dozens of AD clinical trials designed and analyzed to explain what researchers and sponsors can do to improve their chances of success in AD clinical trials. **Methods:** We aggregated published results from previous clinical trials in AD and supplemented these with simulation studies to demonstrate several common errors that have been made over the years. **Results:** There are many decisions that lead to incremental decreases in power throughout the design and analysis process. Even with simple designs, the studies we examined underestimated their effect by between 10% to over 100%. This underestimation is caused by underestimating variation or failing to account for attenuation in effect resulting from the winner's curse when planning future studies. A failure to understand variability in placebo progression, which may be twice as large between studies as it is within studies, has led to unexpected failures. Even when properly accounting from effect size, studies with more arms than necessary or too frequent interim analyses have cost power that would have led to a successful outcome with simpler designs. Additionally, many studies could have succeeded with a better use of the study outcomes. We identify several studies that failed on individual outcomes but succeed when the totality of the evidence is considered. **Conclusion:** One result that people on both sides of the aducanumab controversy can appreciate better is that we may never find a single mechanism that can be addressed through treatment that will provide the dramatic slowing and even improvements for those afflicted with AD we all hope for. So far, treatments targeting amyloid have only demonstrated at best mild slowing of disease progression, but there is also evidence even in the failed studies that some

effect is present. Effective treatment may require approval of several treatments of mild effect that work together to provide more dramatic slowing. This requires thoughtful and thorough design that allows the detection of smaller effect sizes.

OC18- HOPE4MCI TRIAL: FIRST TRIAL TARGETING REDUCTION OF HIPPOCAMPAL OVERACTIVITY TO TREAT MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE WITH AGB101. Sharon Rosenzweig-Lipson¹, Russ Barton¹, Michela Gallagher^{1,2}, Richard Mohs¹ (1. Agenebio - Baltimore (United States), 2. Johns Hopkins University - Baltimore (United States))

Background: No effective therapies exist to halt or reverse Alzheimer's disease (AD). With a predicted prevalence of AD cases rising to >100 million worldwide by 2050, the need for such therapies is urgent. The prevalence of patients with AD dementia, who represent the greatest human and economic burden, could be dramatically reduced by preventing or delaying progression in early phases of the disease, such as Mild Cognitive Impairment (MCI) due to AD (prodromal AD). There is now strong evidence from preclinical models and human patients that neuronal circuits become hyperactive in prodromal AD contributing to the accumulation and spread of Alzheimer's pathology and to subsequent cognitive decline. Hippocampal hyperactivity is most pronounced in patients with amnesic MCI and deposited amyloid as determined by amyloid PET imaging (MCI due to AD). AgeneBio is developing therapeutics to reduce hippocampal overactivity and slow progression to Alzheimer's dementia. Extensive clinical and preclinical data support the hypothesis that neural overactivity is a critical driver of AD neuropathology, including the deposition of amyloid and spread of tau along connective pathways. AGB101 (low dose levetiracetam) demonstrates efficacy on a range of molecular, synaptic, electrophysiological, functional and behavioral endpoints across models (age-related memory impairment, amyloid, tau) and species (flies, mice, rats, aMCI in humans). In a Phase 2 study measuring hippocampal activity during a pattern separation memory test in patients with aMCI, AGB101 normalized hippocampal activity and improved performance on this highly specific memory assessment of hippocampal function. AgeneBio's Phase 2b/3 candidate AGB101 is the first and only therapeutic being investigated to target hippocampal overactivity to slow progression and delay the onset of Alzheimer's dementia (HOPE4MCI trial). **Objectives Clinical/Cognitive:** Primary objective: To assess the efficacy of AGB101 (low-dose levetiracetam, 220 mg, extended release tablet) compared to placebo in subjects with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) using Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores; Secondary objective: To assess the efficacy of AGB101 compared to placebo on FAQ and MMSE scores. **Objectives Biomarkers:** In addition to clinical/cognitive endpoints for efficacy, the trial includes a series of cutting-edge biomarkers to provide evidence for therapeutic efficacy in the MCI due to AD phase of disease. Longitudinal high-resolution MRI neuroimaging will provide evidence for comparison of AGB101 vs placebo on structural progression of tissue loss in the medial temporal lobe. Longitudinal tau PET imaging MK-6420 will assess the amount and spread of tau in an anatomical analysis consistent with Braak staging. Blood based biomarkers distinctive for AD will also be quantified for assessment across treatment conditions. **Methods:** This is a multicenter, randomized, double-blind, placebo-controlled, 78-week, fixed-dose study evaluating AGB101 versus placebo

as a treatment for slowing the progression of MCI due to AD. A total of 164 subjects were enrolled (82/treatment group). Inclusion criteria: Subjects must meet all the following inclusion criteria at screening: Subjects between 55 and 85 years old (inclusive) in good general health; Have MCI due to AD as defined by all the following criteria and consistent with the National Institute on Aging Alzheimer's Association criteria [MMSE scores between 24 and 30 (inclusive)]; A memory complaint reported by the subject or his/her study partner; Evidence of lower memory performance based on the delayed recall portion of the ISLT; A Clinical Dementia Rating (CDR) score of 0.5 with a memory box score of ≥ 0.5 ; Evidence of an amyloid-positive PET scan. **Results:** The HOPE4MCI trial (NCT03486938) now fully enrolled using FDA agreed Phase 3 endpoints. Baseline blinded demographic, clinical/cognitive and biomarker data for the enrolled subjects will be presented at CTAD and will demonstrate enrollment consistent with late-stage MCI due to AD. **Conclusions:** The HOPE4MCI trial (fully enrolled) is the first and only late-stage clinical trial investigating the effects of AGB101 (220 mg) vs placebo in patients with MCI due to AD to slow progression and delay the onset of Alzheimer's dementia. The HOPE4MCI trial is supported, in part, by R01AG061091 to RM and R01AG048349 to MG.

OC19- SEMA4D BLOCKING ANTIBODY, PEPINEMAB, IS A NOVEL POTENTIAL TREATMENT FOR NEURODEGENERATIVE DISEASE: CLINICAL PROOF OF CONCEPT IN HD SUPPORTS CLINICAL DEVELOPMENT IN AD. Terrence Fisher¹, Elizabeth Evans¹, Alisha Reader¹, Vikas Mishra¹, Crystal Mallow¹, Ernest Smith¹, John Leonard¹, Andrew Feigin², Eric Siemers³, Janet Wittes⁴, Maurice Zauderer¹ (1. Vaccinex - Rochester (United States), 2. For The Huntington Study Group And Signal Investigators And Coordinators - Rochester (United States), 3. Siemers Integration Llc - Indianapolis (United States), 4. For Statistics Collaborative - Washington (United States))

Background: Pepinemb (VX15/2503) is a humanized IgG4 monoclonal antibody that blocks the binding of semaphorin 4D (SEMA4D) to its plexin receptors. SEMA4D is upregulated in neurons in response to stress and triggers activation of plexin-positive astrocytes with concomitant loss of normal astrocyte functions. Drivers of glial cell activation may represent important targets to preserve normal homeostatic maintenance and modify progression of neurodegenerative pathology. Blocking antibody to SEMA4D has been shown to reduce neurodegenerative processes in preclinical models, including Huntington's disease (HD) and Alzheimer's disease (AD). SIGNAL-HD (NCT02481674) is a completed double-blind, randomized, placebo-controlled study of pepinemb in HD. SIGNAL-AD (NCT04381468) is an ongoing trial of pepinemb in AD that opened for enrollment in June 2021. **Objectives:** Present the updated safety, clinical, and biomarker data from the completed SIGNAL-HD trial. In addition, describe how neuroimaging and subgroup analysis of the clinical HD results provide further rationale for investigation in AD, and present the trial design and enrollment status for the Phase 1b/2a double-blind, randomized, placebo-controlled SIGNAL-AD trial. **Methods:** The SIGNAL-HD study included 301 subjects with late prodromal (LP) and early manifest (EM) HD at 30 sites in the US and Canada. Subjects were treated with monthly infusions of pepinemb for at least 18 months and evaluated for safety and a variety of clinical parameters including cognition (HD-CAB) and Clinical Global Impression of Change (CGIC). Imaging endpoints included structural MRI to assess brain

atrophy and FDG-PET to assess brain metabolism. Clinical parameters and imaging biomarker analysis was stratified by disease severity, comparing pre-symptomatic LP subjects with early symptomatic EM subjects and, in a post-hoc analysis, according to Total Functional Capacity (TFC) in EM subjects. **Results:** Pepinemb was well-tolerated and was shown to cross the BBB at the anticipated level of 0.1% or greater of circulating antibody. Co-primary efficacy outcome measures consisted of a two-item HD cognitive assessment family including One Touch Stockings of Cambridge (OTS) and Paced Tapping (PTAP) components of the HD-Cognitive Assessment Battery (HD-CAB), and CGIC, a global measure of clinical meaningfulness. The primary endpoints did not achieve statistical significance in this study, however, positive trends in the direction of pepinemb benefit were observed and analysis of secondary and exploratory endpoints including post-hoc subgroup analysis was, therefore, pursued. Treatment benefits reflected in clinical and imaging endpoints appeared to be restricted to the EM subjects. A treatment benefit was observed in 6/6 components of the HD-CAB cognitive assessment battery, with a significant HD-CAB composite score ($p=0.007$). In a posthoc subgroup analysis of EM subjects with somewhat more advanced disease progression (TFC 11 vs TFC 12 and 13), treatment appeared to reduce deteriorating CGIC status ($p=0.04$). Effects on cognition are further supported by prespecified exploratory imaging endpoints, demonstrating that pepinemb treatment reduced brain atrophy (volumetric MRI) and slowed or reversed decline in metabolic activity in 26/26 brain regions, with 15/26 regions showing a significant positive treatment effect ($p \leq 0.05$) in FDG-PET imaging. **Conclusions:** Pepinemb did not achieve primary efficacy outcome measures in the SIGNAL study, but favorable safety profile and positive trends in cognition and imaging endpoints encourage continued development in both HD and AD. A Phase 1b/2a study in AD (SIGNAL-AD), has been initiated with partial support from the Alzheimer's Association and the Alzheimer's Drug Discovery Foundation.

OC20- CURRENT STATUS AND QUANTITATIVE RESULTS OF THE AMYPAD PROGNOSTIC AND NATURAL HISTORY STUDY. Juan Domingo Gispert¹, Lyduine Collij², Katherine Gray¹, David Vallez-García², Fiona Heeman², Gemma Salvadó¹, Bruno Dubois⁴, Bruno Vellas⁵, Miia Kivipelto⁶, Agneta Nordberg⁶, Bernard Hansseuw⁷, Merce Boada⁸, Pablo Martnez-Lage⁹, Andrew Stephens¹⁰, Giovanni Frisoni¹¹, Craig Ritchie¹², Lisa Ford¹³, Pieter Jelle Visser², Gill Farrar¹⁴, Frederik Barkhof² (1. Barcelonabeta Brain Research Center - Barcelona (Spain), 2. Amsterdam Umc - Amsterdam (Netherlands), 3. Ixico - London (United Kingdom), 4. Aphp - Paris (France), 5. Chu Toulouse - Toulouse (France), 6. Karolinska Institutet - Solna (Sweden), 7. Uc Louvain - Ottignies-Louvain-la-Neuve (Belgium), 8. Fundacio Ace - Barcelona (Spain), 9. Cita - San Sebastian (Spain), 10. Life Mi - Berlin (Germany), 11. University Of Geneva - Geneva (Switzerland), 12. University Of Edinburgh - Edinburgh (United Kingdom), 13. Janssen - Raritan (United States), 14. Ge Healthcare - Amersham (United Kingdom))

Background: Understanding the role of amyloid imaging in the earliest stages of Alzheimer's Disease (AD) becomes increasingly relevant for secondary prevention. In this context, the AMYPAD Prognostic and Natural History Study (PNHS) is an open-label, prospective, multi-centre cohort study (<http://amypad.eu/>) to determine the value of quantitative amyloid PET imaging in determining AD dementia risk. The study recruits from several European cohorts and aims at enrolling

2000 non-demented individuals with a particular focus on those with emerging amyloid pathology. **Methods:** As of June 15th, 2021, AMYPAD PNHS had 17 actively recruiting sites across Europe, and 1027 non-demented participants (>95% cognitively unimpaired) had consented to participate in the study. Of those, 536 are from EPAD LCS, 165 from FACEHBI, 140 from ALFA+, 139 from EMIF-AD Twin 60+, 34 from FPACK, 10 from the UCL-2010-412 cohort and 3 from Microbiota. Within AMYPAD PNHS, 790 subjects have been scanned with either [18F]flutemetamol or [18F]florbetaben so far. Of them, 285 have undergone a follow-up scan within AMYPAD PNHS, while 478 already had a previous scan available. The primary outcome measure is the Centiloid (CL) quantification approach, with the whole cerebellum as reference region. This method enables quantitative comparability between the two tracers and across sites/scanners in the pan-European study. Subjects were categorized as amyloid-negative ($CL \leq 12$); as in a “gray-zone” ($12 < CL \leq 50$) or amyloid-positive ($CL > 50$) and a Gaussian Mixture Model was used to assess the population’s Centiloid distribution. In addition, PET scans have been visually assessed by local raters according to product guidelines, classifying subjects as amyloid negative or positive. In total, 417 of the 790 baseline PET scans have been quantified with IXICO’s LEAP pipeline and passed Quality Control, thus rendering valid CL values. Visual assessment had been completed in 338 of these 417 scans. In the EPAD LCS participants, MMSE, CDR Sum of Boxes, and RBANS indexes for Immediate and Delayed Recall were available. In this subset of participants, we built linear models with Age, Sex, APOE- $\epsilon 4$ carriership as independent variables and cognition scores as dependent ones. In addition, we assessed the association between age and APOE- $\epsilon 4$ carriership in CL values by means of a linear regression and a two sample t-test, respectively. **Results:** Based on visual assessment, 69/338 (20%) of the baseline scans were visually rated as positive and 269/338 (80%) as negative. Centiloid values ranged from -32.6 to 116.2 (Mean \pm SD: 19.0 \pm 28.0 CL). Quantitatively, 227/417 (54%) of scans were categorized as negative, 133/417 (32% in the gray-zone, and 57/417 (14%) as positive. Of the negative group by CL quantification, 8/179 (4%) were visually rated as positive, as compared to 20/116 (17%) of the ‘gray-zone’ group and 41/43 (95%) of the positive one. As expected, higher CL values were associated with higher age ($r = 0.366$; $p < 0.001$) and APOE- $\epsilon 4$ carriership ($t = 6.53$; $df = 288$; $p < 0.001$). Higher baseline CL value was associated with lower MMSE scores ($t = -2.73$; $p = 0.007$), CDR SOB ($t = 3.82$; $p < 0.001$), RBANS Immediate Recall ($t = -6.43$; $p < 0.001$) and RBANS Delayed Recall ($t = -5.92$; $p < 0.001$). **Conclusion:** Preliminary quantitative results indicate that AMYPAD Prognostic and Natural History Study (PNHS) is being successful in recruiting its intended target population; a cohort mostly composed of cognitively unimpaired individuals who are enriched for both early and established amyloid abnormalities. The AMYPAD PNHS cohort is therefore a highly valuable resource for future (early) secondary prevention trials, aimed at intervening amyloid accumulation in a preclinical population. **CoI:** No conflict of Interest is declared

OC21- DYADIC ENROLLMENT IN A PHASE 3 MILD COGNITIVE IMPAIRMENT CLINICAL TRIAL. Navneet Hakhu, Daniel Gillen, Josh Grill (*University Of California, Irvine - Irvine (United States)*)

Background: Dyadic enrollment of a study participant and study partner is required for all Alzheimer’s disease (AD) clinical trials. This includes trials enrolling individuals with

mild cognitive impairment (MCI), despite these individuals being functionally independent. The impact of the study partner requirement in MCI trials is less understood, compared to AD dementia trials. Hence, we examined potential relationships between dyad type and baseline participant characteristics. Such findings may better inform future trial design, including recruitment efforts and generalizability of results. **Objectives:** (1) To quantify enrollment in an MCI trial by dyad type; (2) to identify participant-level characteristics associated with study partner type at baseline; and (3) to compare baseline participant-level characteristics across dyad types. **Method:** We performed retrospective analyses using data from the phase 3 Alzheimer’s Disease Cooperative Study (ADCS) trial of donepezil and vitamin E as potential treatments for MCI. The primary outcome of our study was dyad type. We classified dyad types based on the relationship of the study partner to the participant with MCI: spouse, adult child, or other study partner. We classified daughters, daughters-in-law, sons, and sons-in-law as adult child study partners, and anyone who was neither a spouse nor an adult child (e.g., sibling, friend, paid caregiver) as other study partners. The secondary outcomes of this study were baseline participant characteristics, namely age, sex, race/ethnicity (underrepresented vs. non-Hispanic White), apolipoprotein E (APOE) $\epsilon 4$ carrier status, education, and residence type. For the primary analysis, we used multinomial regression to simultaneously model the relative odds of having an adult child vs. spouse study partner and the relative odds of having an other vs. spouse study partner. The predictors of interest were six of the baseline participant characteristics (participant age, sex, underrepresented racial/ethnic background, APOE $\epsilon 4$ carrier status, education, and residence type). We performed six tests (one for each predictor) and used a Holm-Bonferroni correction to account for multiple testing. In secondary analyses, we compared baseline participant characteristics across dyad types. We used linear regression to model the difference in means for continuous outcomes and logistic (or multinomial) regression to model the relative odds for binary (or categorical) outcomes. As these secondary analyses served to support the primary analysis findings, no formal statistical significance tests were conducted, and hence the secondary analyses did not factor into the multiple comparisons correction. **Results:** Among the 769 randomized participants included in this study, 560 (73%) enrolled with a spouse study partner, 109 (14%) enrolled with an adult child, and 100 (13%) enrolled with an other study partner. In analyses adjusting for potential confounding factors and independent risk factors, we found that participant age, female sex, underrepresented racial/ethnic background, APOE $\epsilon 4$ non-carrier status, and non-house residence type were each associated with a higher odds of having an adult child as well as an other study partner, respectively (with having a spouse study partner as the reference group in each case). For example, comparing participants with an underrepresented racial/ethnic background to those who were non-Hispanic White, we estimated the odds of having an adult child to be 4.8-fold higher (OR=4.8; 95% CI: 2.3, 10.3) and the odds of having an other study partner to be 6.2-fold higher (OR=6.2; 95% CI: 3.1, 12.5), compared to having a spouse study partner, respectively. We found that dyad type was associated with several secondary outcomes including participant age, sex, underrepresented racial/ethnic background, and APOE $\epsilon 4$ carrier status. For example, we estimated the odds of a participant having an underrepresented racial/ethnic background to be 4.3-fold higher for adult child dyads (OR=4.3; 95% CI: 2.2, 8.4) and 6.2-fold higher for other

dyads (OR=6.2; 95% CI: 3.3, 11.7), compared to spousal dyads. **Conclusions:** To our knowledge, this is among the first reports to examine the characteristics of participant dyads in MCI clinical trials. In the donepezil and vitamin E MCI trial, nearly three-quarters of participants enrolled with a spouse study partner. The proportion of non-spouse study partners was evenly split between adult child and other study partners. We found that underrepresented racial/ethnic background, age, and APOE ϵ 4 non-carrier status were associated with a higher odds of having a non-spouse study partner. Enrolling a representative sample from the target patient population is paramount for external validity of trial results. One way to improve representativeness by race/ethnicity in MCI trials is to continue efforts to identify and overcome barriers for non-spousal dyads. Our findings may have implications for MCI trial design, recruitment, and generalizability of results. In planning future trials, investigators may wish to consider the pros and cons of potential inclusion/exclusion criteria and recruitment strategies based on baseline participant characteristics and study partner type. **Conflicts of Interest:** NRH and DLG declare no conflicts of interest. JDG declares: research support from the National Institute on Aging, Biogen, Eli Lilly, Genentech, Eisai, BrightFocus Foundation, Alzheimer's Association; consulted for SiteRx, Cogniciti, and Flint Rehab.

OC22- PIONEER, A PHASE 2 STUDY TO EVALUATE TREATMENT WITH T3D-959 IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE: STUDY DESIGN AND UPDATED DESIGN AND UPDATE. John Didsbury, Warren Strittmatter, Jessica Stanek, Stanley Chamberlain, Blake Swearingen, Hoda Gabriel (*T3d Therapeutics, Inc. - Research Triangle Park (United States)*)

Background: T3D-959 is a novel (non-amyloid/non-tau-directed) new chemical entity aimed at improving dysfunctional brain glucose energy and lipid metabolism in Alzheimer's disease (AD). Dysfunctional brain metabolism in AD results from increasing resistance to insulin. Insulin resistance contributes to amyloid plaque formation by increasing secretion of A β 1-42, decreasing A β oligomer removal and increasing plaque load. Insulin resistance contributes to tau tangle formation by increasing tau phosphorylation and decreasing O-GlcNAcylation. Insulin resistance also contributes to inflammation by making normal proteins antigenic via glycation and by reducing mitochondrial ATP production, another cause of protein misfolding. T3D-959, a small molecule dual nuclear receptor agonist, acts as an insulin sensitizer to overcome insulin resistance to restore and maintain metabolic homeostasis. T3D-959 in a rat model of sporadic AD improved spatial learning and memory, reduced A β levels, altered phospho-tau levels, and decreased multiple pro-inflammatory cytokines. Phase 1 trials documented a robust safety profile. Exploratory human clinical test results in a Phase 2a study of T3D-959 in mild to moderate severity AD patients demonstrated multiple efficacy signals indicating a potential to be disease modifying, including enhanced glucose uptake in brain regions of interest, changes in systemic lipid and amino acid profiles in plasma indicating insulin sensitization, and suggested improved cognition by ADAS-Cog11 and DSST [See ClinicalTrials.gov identifier NCT02560753 and J. Alz. Dis. 73: 1085 (2020)]. **Methods:** To validate and expand upon these observed efficacy signals, a larger and longer Phase 2 clinical trial statistically powered to measure significant differences versus placebo in outcome measures of cognition and function and assessments of multiple biomarkers of disease, has been

designed. The Phase 2 randomized, placebo-controlled 'PIONEER' Study (Prospective therapy to Inhibit and Overcome Alzheimer's Disease Neurodegeneration via Brain Energetics and Metabolism Restoration) is assessing multiple T3D-959 dose strengths vs. placebo (15mg, 30mg & 45mg QD and placebo in a 1:1:1:1 ratio) to identify the most safe and effective dose or doses to use in subsequent Phase 3 testing. The multi-center trial, using 40-45 U.S. clinical trial sites, will randomize 256 mild to moderate AD patients stratified by ApoE4 genotype. Dosing will be orally delivered, once-a-day, for 24-weeks with a 4-week followup. Eligible patients are 50-90 years old, have mild to moderate AD according to National Institute on Aging-Alzheimer's Association guidelines. In addition, patients must have a CDR-Sum of Boxes score of >3.0 and MMSE score of 14-26. Co-primary outcome measures include the ADAS-Cog11 cognition and ADCS-CGIC global function measures. Secondary outcome measures include executive function as measured by DSCT and change from baseline in plasma A β 42/40 ratio. Exploratory outcome measures include the effect of T3D-959 on absolute regional and whole brain metabolic rate for glucose (CMRgl) assessed by FDG-PET, on plasma metabolomic and lipidomic biomarkers, and on plasma proteomic biomarkers including Nfl, total tau, p-tau217, and p-tau181. **Results:** Enrollment in PIONEER commenced in March 2021 and is ongoing [See ClinicalTrials.gov identifier NCT04251182]. **Conclusion:** The etiology of AD remains unknown. Significant research effort has focused on amyloid plaques and tau tangles as causation however no clinical trials of therapies directed at these pathologies have provided consistent clinically meaningful benefit to patients. Consequently, research focus has recently shifted towards inflammation as causation. Brain metabolic dysfunction as causation, however, remains underserved in AD research leaving a gap in knowledge. The PIONEER study serves to fill this gap. It supposes that aberrant glucose and lipid metabolism in AD, for one, cause protein misfolding which causes formation of plaques, tangles and promotes inflammation. While T3D-959 may have the potential to be disease-modifying, a more rapid clinical development progression path to demonstrate symptomatic improvement is being followed. The Phase 2 PIONEER Study will determine the clinical efficacy and safety profile of T3D-959 in individuals with mild to moderate AD. PIONEER is supported by the National Institute on Aging, part of the National Institutes of Health, under award number R01AG061122 and by the Alzheimer's Association's Part the Cloud Gates Partnership Grant Program.

OC23- COMPARISON OF THE FCSRT AND RBANS IN SCREENING FOR EARLY AD CLINICAL TRIALS: ENRICHMENT FOR DISEASE PROGRESSION. Edmond Teng¹, Paul Manser¹, Nan Hu¹, Monarch Shah¹, Karen Pickthorn¹, Mira Blendstrup¹, Giuliana Faccin¹, Susanne Ostrowitzki², Kaycee Sink¹ (*1. Genentech, Inc. - South San Francisco (United States), 2. F. Hoffmann-La Roche Ltd. - Basel (Switzerland)*)

Background: Assessments of episodic memory have been included in the screening procedures for treatment trials in prodromal-to-mild AD to efficiently identify potential participants that fulfill applicable clinical diagnostic criteria (including biomarker data consistent with underlying AD) and are most likely to exhibit detectable clinical progression. Prior work from our group suggests that the Free and Cued Selective Reminding Test-Immediate Recall (FCSRT-IR) and the Repeatable Battery for the Assessment of Neuropsychological

Status Delayed Memory Index (RBANS-DMI) perform similarly in enriching screening cohorts for potential participants with biomarker data consistent with underlying AD (Teng et al., CTAD 2019). Furthermore, use of the FCSRT-IR for screening appears to enrich for progression on the Clinical Dementia Rating Sum of Boxes (CDR-SB) in prodromal-to-mild AD (Sink et al., CTAD 2019). However, the relative utility of the FCSRT-IR versus RBANS-DMI for identifying participants more likely to experience clinical decline and/or exhibit treatment benefits remains uncertain. **Objectives:** We sought to compare the rates and variability of clinical progression on cognitive and functional endpoints in prodromal-to-mild AD participants across studies that included the FCSRT-IR or RBANS-DMI as part of the screening procedures and inclusion criteria. **Methods:** We analyzed clinical data from the CREAD (NCT02670083; crenezumab) and Tauriel (NCT03289143; semorinemab) trials for participants who fulfilled National Institute on Aging-Alzheimer's Association criteria for probable AD dementia or mild cognitive impairment (MCI) due to AD and had Mini-Mental Status Examination scores of 22-30, CDR Global Scores of 0.5 or 1, cerebral A β pathology per positron emission tomography or cerebrospinal fluid analyses, and significant episodic memory impairment (CREAD: FCSRT-IR free recall \leq 27, cueing index \leq 0.67; Tauriel: RBANS-DMI \leq 85). We characterized change from baseline on CDR-SB, ADAS-Cog13, and ADCS-ADL as annualized rates of decline and at Week 73 (Tauriel) or Week 77 (CREAD). All models were adjusted for APOE4 status (positive versus negative) and baseline diagnosis (prodromal AD versus mild AD). Since treatment effects were not observed with either crenezumab (CREAD) or semorinemab (Tauriel), both separate and pooled analyses were performed with the placebo and treatment arms from these studies. **Results:** Mixed-Effect Model Repeated Measure (MMRM) analyses of placebo arms from Tauriel (n=81; Week 73) and CREAD (n=278; Week 77) indicated similar rates of progression on CDR-SB (Tauriel: 2.27, SD=2.13; CREAD: 2.30, SD=2.61), ADAS-Cog13 (Tauriel: 6.43, SD=7.66; CREAD: 7.23, SD=8.66), and ADCS-ADL (Tauriel: -7.85, SD=10.53; CREAD: -7.04, SD=9.70). Likewise, similar Random Coefficient Regression Model (RCRM) annualized slopes were seen between studies on CDR-SB (Tauriel: 1.54, SD=1.87; CREAD: 1.60, SD=2.11), ADAS-Cog13 (Tauriel: 4.16, SD=6.52; CREAD: 4.87, SD=7.36), and ADCS-ADL (Tauriel: -5.47, SD=8.48, CREAD: -5.04, SD=8.07). When all treatment arms were pooled (Tauriel: n=287; CREAD: n=546), analogous results were seen using the Week 73/77 MMRM (CDR-SB [Tauriel: 2.16, SD=2.31; CREAD: 2.23, SD=2.65], ADAS-Cog13 [Tauriel: 6.69, SD=7.96; CREAD: 7.17, SD=8.53], ADCS-ADL [Tauriel: -7.79, SD=9.78; CREAD: -7.89, SD=11.22]) and RCRM annualized slope (CDR-SB [Tauriel: 1.56, SD=2.02; CREAD: 1.56, SD=2.12], ADAS-Cog13 [Tauriel: 4.51, SD=6.81; CREAD: 4.75, SD=7.14], ADCS-ADL [Tauriel: -5.51, SD=8.30; CREAD: -5.48, SD=8.93]). **Conclusion:** Screening for significant episodic memory deficits using either RBANS-DMI (Tauriel) or FCSRT-IR (CREAD) resulted in recruitment of early AD cohorts with similar rates of disease progression across multiple clinical outcomes over 18 months. Our results suggest that both of these episodic memory assessments yield comparable enrichment for participants likely to demonstrate clinical progression over this interval. The choice of specific episodic memory tests for inclusion in future early AD studies may be influenced by study design considerations beyond enrichment for participants at highest risk for subsequent cognitive decline.

OC24- DIVERGENT LONGITUDINAL PATTERNS BETWEEN PARTICIPANT AND STUDY PARTNER REPORT ON THE COGNITIVE FUNCTION INDEX IN THE HARVARD AGING BRAIN STUDY.

Rebecca Amariglio¹, Rachel Buckley², Hannah Klinger², Kathryn Papp¹, Gad Marshall¹, Catherine Munro¹, Jennifer Gatchel², Patrizia Vannini¹, Dorene Rentz¹, Keith Johnson¹, Reisa Sperling¹ (1. Brigham And Women's Hospital - Boston (United States), 2. Massachusetts General Hospital - Boston (United States))

Background: Participant (PT)-reported outcomes that assess high level cognitive functioning and subjective change in memory may be particularly useful in preclinical Alzheimer's disease (AD) prevention trials, which seek to capture clinically meaningful change that is not easily detected using standard clinical measures. However, as individuals progress towards clinical impairment, their awareness of cognitive deficits may degrade (Hanseeuw et al., 2020), potentially reducing the interpretability of PT-reported outcomes over the course of a prevention trial. Likewise, study partner (SP)-reported outcomes, which are regularly used at symptomatic stages of AD, may not be as sensitive at the preclinical stage when subtle functional changes may be challenging to observe in the participant. Thus, it remains unclear how to optimally track cognitive functioning at the preclinical stages of AD using subjective instruments. **Objectives:** To better understand the dynamic nature of subjective report in cognitive functioning at the earliest stages of AD, we examined the longitudinal trajectories of both PT- and SP-reported outcomes. We were particularly interested in examining their association with other indicators of disease risk, including baseline AD biomarkers of amyloid and tau, concurrent objective cognitive decline, and clinical progression. **Methods:** Participants (256 cognitively unimpaired (CU), 16 Mild Cognitive Impairment (MCI), 1 dementia, age=75 \pm 9.28, female=60%) were recruited from the Harvard Aging Brain Study (HABS), an ongoing community-based longitudinal observational cohort study. Participants and their study partners were administered the Cognitive Function Index (CFI) annually with 2 \pm 0.90 years of follow-up. The CFI is a 15-item questionnaire that asks participants and their study partners about change in cognitive functioning over the last year. As part of the overall HABS protocol, participants underwent PiB-PET to quantify neocortical amyloid burden (0.14 \pm 1.79 years from CFI baseline), FTP-PET to quantify regional tau in the entorhinal cortex and inferior temporal lobe (0.19 \pm 1.33 years from CFI baseline) and the Preclinical Alzheimer Cognitive Composite (PACC) to quantify multi-domain cognition annually. Linear mixed models were used to examine longitudinal trajectories of PT- and SP-reported CFI with baseline amyloid and tau, and age, sex and, education as covariates. Next, we examined associations between temporally concurrent slopes of CFI and PACC, adjusting for covariates. In exploratory analyses, we examined slopes of CFI and PACC in association with risk of progression to MCI in a subset of 238 participants who were CU at baseline using survival analyses. **Results:** Greater baseline PT-reported CFI was associated with greater global amyloid (estimate=3.57 CI: 2.33-4.80, p<0.001), entorhinal tau (estimate=3.99, CI: 1.64-6.34, p=0.001) and inferior temporal tau (estimate=5.07, CI: 2.90-7.35, p<0.001). However, there was no significant overall change in PT-reported CFI over time and no associations with amyloid and tau in longitudinal models. When looking at SP report, baseline SP-reported CFI was associated with greater global amyloid (estimate=2.61, CI: 1.41-3.82, p<0.001) and inferior temporal tau (estimate=2.90, CI: 0.59-5.21, p=0.014).

Likewise, in longitudinal models, increasing SP-reported CFI was associated with higher baseline amyloid (estimate=1.17, CI: 0.7-1.63, $p<0.001$), entorhinal tau (estimate=1.27, CI: 0.47-2.07, $p=0.002$), and inferior temporal tau signal (estimate=1.54, CI: 0.82-2.26, $p<0.001$). Increasing SP-reported CFI slopes were associated with decreasing PACC slopes (estimate=-0.85, CI: -1.32- -0.38, $p<0.001$), but no association was found with PT-reported CFI slopes. Exploratory analyses revealed that baseline PT-reported CFI (estimate= 1.38, CI: 1.10-1.73, $p=0.005$) and baseline SP-reported CFI (OR= 1.55, CI: 1.11-2.17, $p=0.011$) predicted progression to MCI ($n=10$). However, only change over time in SP-CFI (OR=2.34, CI: 1.47-3.71, $p<0.001$), predicted progression to MCI. When PACC slope was added to the model, both decreasing PACC and increasing SP-reported CFI independently predicted risk of MCI. **Conclusions:** Increasing longitudinal SP-reported CFI was associated with greater amyloid and tau and aligned with decreasing PACC. Preliminary findings also revealed change on SP-reported CFI predicted risk of MCI independently from decline in PACC. By contrast, only baseline, not longitudinal, PT-reported CFI was associated with AD risk factors. In conclusion, while PT report may be optimally useful as a screening/baseline instrument to stratify participants for AD risk, participants' awareness of their deficits may decrease longitudinally as they progress to clinical impairment. Our findings suggest that SP report may better serve as an outcome measure of clinically meaningful change in trials that span preclinical/prodromal stages.

OC25- FUNCTIONAL CONNECTIVITY BASED INDIVIDUALIZED BRAIN REGIONS TO MEASURE TAU PROPAGATION: TOWARDS APPLICATION IN CLINICAL TRIALS. Diana Svaldi¹, Ixavier Higgins¹, Shcherbinin Sergey¹, Nicolai Franzmeier², Michael Ewers², Emily Collins¹ (1. *Eli Lilly And Company - Indianapolis (United States)*, 2. *University Hospital Munich - Munich (Germany)*)

Background: Given the link between tau pathology and cognition, the quantification of changes in tau accumulation is an important biomarker in Alzheimer's disease clinical trials. Pre-determined tau positron emission tomography (PET) endpoints (global or regional) are typically used to quantify tau progression in interventional trials. However, tau propagation is known to be heterogeneous (Vogel et al., *Nature Medicine*, 2021) suggesting the potential utility of individualized tau-PET endpoints. Previously, a connectivity-based, patient-specific model for prediction of regional tau-PET changes was shown to better capture tau accumulation as compared to Braak stage-specific endpoints (Franzmeier et al., *Science Advances*, 2020). The model defined individualized tau-spreading sequences based on functional connectivity to tau epicenters (regions with earliest tau pathology) at baseline. Tau burden was quantified using tau positivity probability (TPP, Vogel et al., *Nature Communications*, 2020) which converted regional standardized uptake value ratios (SUVRs) into probability of the signal being driven by on-target binding, mitigating off-target binding in 18F-flortaucipir images. A general functional connectome, derived from an independent sample of healthy adults was used. **Objectives:** Our ultimate goal is to explore the utility of individualized tau-PET endpoints in capturing progression for clinical trials. Here, we further evaluate performance of the functional connectivity-based framework as an approach to measure individualized longitudinal change in tau. Specifically, we applied the framework to a dataset acquired in a flortaucipir F 18 PET phase 2 trial (NCT02016560) and made comparisons between predicted and observed tau progression patterns. **Methods:** Subjects were included in this

analysis if they were amyloid positive by flortaucipir F18 PET and had baseline and 18-month flortaucipir scans collected. Diagnostic breakdown included 5 cognitively-normal subjects (CN), 28 mild-cognitive-impairment subjects (MCI), and 21 Alzheimer's Disease subjects (AD). To run the connectivity-based model, mean SUVR (cerebellar crus reference region) was calculated in 200 regions of interest (ROIs) for each scan. Using images from an independent cross-sectional dataset ($N=824$, MMSE = 20-28, Age = 60-85 years), regional SUVR values were converted to TPPs. To assess heterogeneity in tau deposition and propagation, we determined "epicenter ROIs" and "observed target ROIs". For each subject, epicenter ROIs were defined as those with TPP of 0.3 or greater at baseline. Observed target ROIs were defined as non-epicenter ROIs in the highest quartile for 18-month change in TPP. We then determined "epicenter frequency" and "target frequency" for each ROI, defined as the fraction of subjects showing an epicenter or respectively observed target. To examine the ability of the model to predict individualized spread, we additionally determined "predicted target ROIs". Predicted target ROIs were defined as those in the closest quartile for connectivity-based distance to the epicenters. Agreement between observed target ROIs versus predicted target ROIs was assessed using Matthews correlation coefficient, specificity (observed target reference), and sensitivity (observed target reference). Mean, standard deviation, and correlation of change in TPP in observed targets versus predicted targets were also quantified. As an additional analysis, we evaluated how shifting the percentile of nearest non-epicenter ROIs included as target ROIs affected the 18-month change in TPP. This was repeated using Euclidean distance to define target ROIs. **Results:** 46 subjects had defined epicenters necessary to run the model (4 CN, 1 MCI, 26 AD). First, we assessed heterogeneity in tau deposition and propagation. The mean epicenter frequency was $28\pm 18.0\%$ (Mean \pm Standard Deviation). Of the 200 ROIs, only 3 ROIs were defined as epicenters in 75% of subjects or greater. These three epicenters were in the left and right temporal lobes and in the left hemisphere temporal-parietal junction, and the right hemisphere temporal pole. The mean observed target frequency ROIs was $18\pm 6\%$. The maximum observed target frequency was 37% and was in the right hemisphere lateral dorsal prefrontal cortex. We then assessed the ability of the connectivity-based model to capture tau accumulation over 18 months. Mean Matthews correlation coefficient between predicted and observed target ROIs was 0.16 ± 0.15 , sensitivity was 0.37 ± 0.11 , and specificity was 0.79 ± 0.04 . The mean 18-month change in TPP was 0.09 ± 0.13 for observed targets and 0.08 ± 0.10 for predicted targets. Strong correlation ($r=.93$) was observed in 18-month change in TPP in between predicted and observed targets. Finally, we observed that change in TPP was maximized when considering the top 8th percentile of nearest non-epicenter ROIs as targets (0.121 ± 0.187) and monotonically decreased beyond this point. For all percentiles, the change in TPP was greater for target ROIs defined by connectivity-based distance versus Euclidean distance. **Conclusions:** Using an independent dataset, we confirmed the robustness of the connectivity-based model. Results presented here continue to exemplify the heterogeneity of tau deposition and propagation across subjects, highlighting the rationale to further examine subject-specific tau endpoints. We also observed that connectivity-based models reasonably capture tau progression as measured using TPP. As future work, we seek to evaluate whether individualized endpoints better capture differences in tau progression between therapeutic arms and in clinical progression.

OC26- PRACTICE EFFECTS IN THE LETTER FLUENCY TEST. Taneisha Arora¹, Daniel Gillen², Joshua Grill², Michelle Nuño³ (1. Google - Mountain View (United States), 2. University Of California, Irvine - Irvine (United States), 3. University Of Southern California - Los Angeles (United States))

Background: A key aspect of research investigating neurological diseases is the ability to quantify cognitive change when it occurs. In Alzheimer's disease studies, this is often done by administering cognitive assessments over time. The National Institute on Aging-Alzheimer's Association working groups have also recommended the use of such assessments to aid in the diagnosis of Alzheimer's disease (1). This highlights the importance of assessments such as the letter fluency test and reinforces the need to understand changes if and when they occur. Some assessments, however, are subject to a practice effect, or an improvement in test scores due to repeated testing (2). Among participants for whom scores would typically decrease, the practice effect may instead lead to stable scores (3). In Alzheimer's disease studies, practice effects can lead to misinterpretation of results. In clinical trials, for example, the practice effect could mask cognitive decline in the control group, making it difficult to identify a treatment effect if there is one. Several strategies have been proposed to account for the practice effect, but it is important that we are aware of practice effects in commonly used assessments so that we are able to plan, at the design stage, how these will be accounted for in the trial (3). The letter fluency test is one assessment that is implemented in longitudinal observational studies with annual follow-up. The test requires participants to produce as many words as possible beginning with each of three letters; often "F", "A", and "S." The number of correct, incorrect, and repeated words are recorded for each letter. **Objectives:** Our study aimed to test whether the letter fluency test is subject to practice effects. Because of the nature of the assessment, we hypothesized that individuals randomized to receive a novel letter list would perform more poorly than those randomized to repeat a previous letter list. **Methods:** Participants from an ongoing, longitudinal, observational study at the University of California, Irvine Alzheimer's Disease Research Center (UCI ADRC) were randomized to one of two versions of the letter fluency test: the FAS version and the BHR version. The FAS version of the assessment was routinely administered to participants, and the BHR version was selected as a comparable, alternate version (4). Pre- and post-randomization scores were recorded for each participant, with all participants receiving the FAS version of the assessment prior to randomization. An analysis of covariance (ANCOVA) model was used to test for the presence of a practice effect. We compared the total number of correct words for each randomization group, adjusting for the pre-randomization total fluency score to compare within-subject differences between the two groups. As part of secondary analyses, we investigated whether the practice effect differed by diagnosis and by prior exposure to the test. **Results:** Eighty-eight participants were randomized to the FAS version and ninety-four participants to the BHR version of the of the letter fluency test. Of the 182 participants, 98 were cognitively normal, 53 had mild cognitive impairment, and 31 had dementia. Participants had an average of 5.11 prior visits with a standard deviation of 3.8. The average number and standard deviation of prior visits was 6.4 and 3.2 for cognitively unimpaired participants, 2.94 and 3.58 for participants with mild cognitive impairment, and 4.71 and 4.17 for participants with dementia, respectively. We found that, on average, participants who were randomized to

the BHR version of the assessments scored approximately 3 words lower than those with similar pre-randomization scores who were randomized to the FAS version (-2.94, 95% CI: -5.04, -0.83). Boxplots stratified by exposure demonstrated larger differences for participants with greater prior exposure to the FAS version of the letter fluency test. Among participants with more than 8 visits who were randomized to the FAS version, the median change in score was 1.5, indicating improved performance on their second assessment. For the BHR group, the median score was -3.5 indicating declined performance post-randomization. When stratified by diagnostic group, we observed the largest difference between the FAS and BHR groups among participants who were cognitively unimpaired. The median changes in scores were 2.5 and -3.5 for the FAS and BHR groups, respectively. For participants with mild cognitive impairment, the median changes in scores were -2 and -3, and for participants with dementia the median scores were -1 and -5.5 for the FAS and BHR groups, respectively. **Conclusion:** Our results show that participants who were randomized to the BHR version of the test performed worse, on average, than those who were randomized to the FAS version of the assessment, indicating the presence of a practice effect. Further, our secondary analyses suggest that the practice effect may differ by both prior exposure to the test and by diagnostic group. **Conflicts of Interest:** JDG has received research support from Biogen, Eli Lilly, Genentech, Eisai, and the National Institute on Aging and has consulted for SiteRx, Cogniciti, and Flint Rehab. The other authors do not have conflicts of interest to declare. **References:** 1. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):270-9. 2. McCaffrey RJ, Duff K, Westervelt HJ. Practitioner's guide to evaluating change with neuropsychological assessment instruments: Springer Science & Business Media; 2000. 3. Goldberg TE, Harvey PD, Wesnes KA, Snyder PJ, Schneider LS. Practice effects due to serial cognitive assessment: implications for preclinical Alzheimer's disease randomized controlled trials. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring.* 2015;1(1):103-11. 4. Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. *Neuropsychologia.* 1967;5(2):135-40.

OC27- CONCORDANCE BETWEEN THE CLINICAL DEMENTIA RATING (CDR) AND THE ELECTRONIC CDR. Yan Li¹, Taylor Howell², Krista Moulder¹, John Morris¹, Michael Weiner², Rachel Nosheny² (1. Washington University In St. Louis - St. Louis (United States), 2. University Of California, San Francisco - San Francisco (United States))

Background: As the focus for Alzheimer disease research shifts from treatment to prevention, and effective drugs for mild symptomatic disease may be available in the near future, there is a pressing need for convenient, cost-effective and scalable methods to screen older adults for clinical trials and in various healthcare settings. The Clinical Dementia Rating (CDR®) is an instrument used to detect the presence or absence and, when present, the severity of dementia symptoms. It has well established reliability, it and its derivative the CDR-SumBox are widely used in clinical trials, both as a screening measure and a primary outcome. However, the CDR requires an experienced clinician or a trained assessor to conduct semi-structured interviews with both a participant and collateral source or study partner; this limits its scalability and use as

a screening tool in the general population. To address this, we developed an electronic version of the CDR (eCDR) that can be conducted unsupervised, and a scoring algorithm that can automatically assign domain box scores and global score. The eCDR is currently being validated against the traditional, in-clinic CDR at four sites: University of California San Francisco (UCSF), Mayo Clinic, Washington University, and University of Alabama at Birmingham. This study begins to address the validity of the eCDR. **Objectives:** 1. To evaluate the concordance between the CDR and the eCDR in terms of response for each item, domain box scores and CDR global. 2. To assess the change in the characteristics of the eCDR items, refine the items or adjust the scoring algorithm accordingly. **Methods:** Baseline data from 47 participants enrolled in the eCDR project at UCSF were included in this study. Forty nine CDR items, identified as informative from a previous item response theory (IRT) analysis of the CDR, were evaluated. We excluded 4 items that were identified as informative, but could not be appropriately translated into an online format (e.g. questions that were open-response, outdated). First, for each CDR item and its equivalent eCDR item, we calculated the percentage of agreement. Then, for the eCDR, we generated domain box scores and the eCDR global using an automatic scoring algorithm we previously developed based on a bi-factor item response (IRT) model of the traditional CDR. **Results:** Among the 47 participants, 39 (83%) were rated CDR 0 and 8 (17%) were rated CDR 0.5. For the 49 items we evaluated, 35 (73%) have a concordance rate greater than 90% between the eCDR and the CDR, including 11 items that are 100% concordant. The rest of the items have a concordance rate greater than 70%, except for three items (concordance rate 52% - 58%). Of all discordant items, 39% were rated as a higher level of impairment in the CDR, and 42% were rated as a higher level of impairment in the eCDR. Items with low concordance were mainly questions in the Memory domain that require comparison between the response of the participant and the study partner to determine whether the participants' response is correct, especially those that required free text write in answers (e.g., What was the last school you attended?). As the responses from the participants and the study partners may not exactly match, it is not surprising the participants' response were more likely to be determined as "incorrect" in the eCDR than in the CDR (e.g. due to different typos, abbreviations). Other types of questions most likely to be discordant were those for which the response option format differed between the CDR and eCDR (e.g., free verbal recall in the CDR vs. multiple choice in the eCDR). The concordance rate in the domain box scores and global scores between the eCDR and the CDR is 98% for Community Affairs domain, 89% for Judgment and Problem Solving domain, 87% for Home and Hobbies domain, 74% for Memory domain, 89% for Orientation domain, 100% for Personal Care domain and 81% for global score. The Memory domain box score is slightly lower than the other domain box scores because several items in the Memory domain had low concordance rate as describe above. **Conclusion:** Majority of the items in the eCDR performed similarly to those in the CDR. A few items in the eCDR tend to be slightly more difficult (participants are more likely to answer them incorrectly) or easier than their corresponding items in the CDR. The automatic scoring algorithm works reasonable well in estimating the eCDR domain box scores and global score. If future data confirm the change in the characteristics of those items in the eCDR, the difficulty and discrimination parameters in the scoring algorithm will be adjusted accordingly, and the eCDR content may be adjusted. Even though the current sample size

is small, the available data demonstrated the eCDR is promising in serving as a fast, easily accessible and inexpensive tool for cognitive screening.

OC28- QUANTIFICATION OF COGNITIVE IMPAIRMENTS IN PRECLINICAL AND EARLY ALZHEIMER'S DISEASE: A PROOF OF CONCEPT STUDY TO INVESTIGATE THE FEASIBILITY, ADHERENCE AND PRELIMINARY CLINICAL VALIDITY OF REMOTE SMARTPHONE-BASED SELF-ASSESSMENTS OF COGNITION, FUNCTION AND BEHAVIOR. Thanneer Malai Perumal¹, Arnaud Wolfer¹, Florian Lipsmeier¹, Michael Lindemann¹, Foteini Orfaniotou¹, Simone Rey-Riek¹, Irma T Kurniawan¹, David Watson², Merce Boada³, Kirsten Taylor¹ (1. F. Hoffman La Roche Ltd - Basel (Switzerland), 2. Alzheimer's Research and Treatment Center - Wellington, FL (United States), 3. Ace Alzheimer Center Barcelona, Universitat Internacional de Catalunya - Barcelona (Spain))

Background: Clinical research and drug development in Alzheimer's disease (AD) critically rely on the accurate identification of cognitive and functional impairments, and the quantification of their progression over time. This is traditionally accomplished with clinical neuropsychological tests and questionnaires administered via trained professionals. While critical, these assessments necessarily reflect only a snapshot of cognitive behavior and functioning. On the other hand, remote smartphone-based measurements enable a more frequent and in-depth assessment of cognition and functioning at scale which is closer to the actual daily lives of patients. However, they require validation against standard clinical outcomes and relevant biomarkers. **Objectives:** To present a suite of smartphone-based digital assessments - the AD digital assessments suite (AD-DAS) - and to describe the proof of concept (POC) study to test AD-DAS feasibility and preliminary clinical validity in an ongoing multicenter prospective pilot study in participants with subjective cognitive decline (SCD), early Alzheimer's disease (eAD) and healthy controls (HC). **Methods:** The AD-DAS comprises active tasks of cognitive and motor functioning, health- and functioning-related patient-reported outcome measures, and passive monitoring of behavior in daily life measured using the smartphone sensors. The active tasks comprise three smartphone tasks developed in a collaboration between the Oxford Institute of Digital Health, Roche, and Eli Lilly (i.e., an episodic memory and object recognition task, a conceptual fluency and logical memory task, and a task of executive functioning based on principles of the Trail-Making Test (TMT) and Stroop interference test). Additional active tasks include measures of visuospatial working memory, attention, and visual scanning behavior based on the Symbol Digit Modalities Test (SDMT), a dual-task gait task, a semantic memory task, a psychomotor speed and language task, a simple motor dexterity, and reaction time task. Remote surveys queried sleep quality, sociability, mood, and orientation in time. Aspects of social cognition and functioning in daily life were further measured with an optional smartphone application on participants' own smartphones. This passive monitoring application quantifies participants' gait, life space, and sociability measured as app usage from application logs. The multicenter international POC study is running in 2 countries (USA - English, and Spain - Spanish) across 5 sites with 120 participants (30 each of HC, SCD with and without amyloid-beta, early AD). At screening and baseline visits, participants aged 65 or above, underwent amyloid Positron Emission Tomography (PET) for A β +/- classification and Magnetic Resonance Imaging (MRI) for quantification

of the brain atrophy. Further, they completed a battery of standard neuropsychological, motor, activities of daily living (ADL), and health-related assessments in-clinic. Participants performed a subset of 9 different active smartphone tasks and surveys and 4 survey questionnaires (ca. 10 minutes) daily on the preconfigured study smartphone for a period of 28 days remotely without supervision. Participant acceptability and perceived difficulty of the AD-DAS tasks were assessed using an end-of-study visit questionnaire. **Results:** Recruitment of participants is still ongoing. At the time of submission of this abstract, 76 participants (10 HC, 21 SCD A β -, 24 A β +, 21 eAD) were enrolled, of which 57 successfully completed the study, and 2 discontinued. Preliminary results suggest good feasibility (~96%) and acceptance-based on a 5-point Likert scale (0 very poor, 3 poor, 7 fair, 21 good, and 25 very good). All participants adhered well to the testing protocol (~96.4%). Rates of incomplete or invalid administrations were very low. Preliminary exploration of the data suggests a dependence of adherence on disease severity. Clinical validity will be assessed when data collection is complete. **Conclusions:** Observational and interventional AD research requires robust and ecologically valid measures of cognition and functioning, ideally as close to the daily lives of patients as possible. The AD-DAS was conceptualized and designed to address these challenges. Findings from the POC study will inform the feasibility, acceptability, and preliminary validity of remote cognitive and functional assessments in individuals on the early AD spectrum. The AD-DAS aims to support the identification of target populations and subgroups of fast progressors, to provide robust measures of disease progression, and to ultimately provide remote, clinically meaningful functional outcomes for observational and interventional drug trials in preclinical and early AD.

OC29- INTEGRATED ALZHEIMER'S DISEASE RATING SCALE (IADRS): CLINICALLY MEANINGFUL CHANGE ESTIMATES. Dorene Rentz¹, Alette Wessels², Michael Case², John Sims² (1. Harvard Medical School - Boston (United States), 2. Eli Lilly And Company - Indianapolis (United States))

Background: Clinical trials for new therapies of Alzheimer's disease (AD) are enrolling patients earlier on the disease continuum (i.e., patients with mild cognitive impairment [MCI] due to AD, or earlier) with the objectives of lengthening the duration of higher cognitive function before decline and intervening before pathological changes are severe. However, this introduces a key challenge in clinical trials of AD: identifying an instrument to assess cognition and function that is sensitive, responsive, and able to detect clinically meaningful changes in both domains across the disease continuum. While it is well accepted that changes in cognition underlie changes in function, oftentimes separate scales are used to assess these two highly related outcomes. A wide range of cognitive and functional outcome measures make it difficult to compare outcomes across clinical trial cohorts. Furthermore, clinical trials to date are much more commonly focused on statistically, rather than clinically, significant differences between patient groups. Cumulatively, these challenges highlight the need to utilize one scale that measures cognitive and functional attributes in an integrated fashion. This will allow for uniform recognition of potential treatment effects on patients with AD who are enrolled in the clinical trial. Employing a combination of theory-driven and data-driven approaches, the integrated Alzheimer's Disease Rating Scale (iADRS), a composite of two widely accepted measures, the Alzheimer's Disease Assessment

Scale – Cognitive Subscale 13-item version (ADAS-Cog13) and the Alzheimer's Disease Cooperative Study – instrumental activities of daily living scale (ADCS-iADL), was developed. The iADRS has been validated,^{1,2} its statistical properties have been described,³ and the scale has been used as a clinical outcome measure in previous phase 2 and 3 clinical trials in AD.⁴⁻⁶ Cumulatively, these data demonstrated the iADRS was effective in capturing disease progression from MCI throughout moderate AD, as well as treatment effects across the early disease spectrum.⁴⁻⁶ However, questions remain, including what magnitude of change on the iADRS represents a meaningful change for patients with AD. **Objectives:** To enhance understanding of iADRS point changes in clinical trials, the objective of this work is to establish a minimal clinically important difference (MCID) on the iADRS. **Methods:** Using data from the phase 3 EXPEDITION3 and AMARANTH, and the phase 2 TRAILBLAZER-ALZ clinical trials, MCID7 will be defined using a combination of anchor-based and distribution-based methods. The anchor-based approach will identify participants experiencing a meaningful change using established clinically relevant scales. The anchor will be used to classify participants according to level of change/severity and to derive a threshold or range of score changes that reflect a clinically meaningful change on the iADRS. Distribution-based estimates will also be derived by identifying a threshold of score changes below which the "change" most likely reflects measurement error, considering the variability of scores and the reliability of the measure. The weight of evidence from both approaches will subsequently be used to define the score change or range of score changes on the iADRS that can be considered clinically meaningful. **Results:** Anchor-based and distribution-based estimates for MCID for the iADRS are not yet available for the abstract but will be presented during the meeting. **Conclusion:** Conclusion will be provided during the meeting, after data are available. **References:** 1. Wessels AM, Andersen SW, Dowsett SA, Siemers ER. The Integrated Alzheimer's Disease Rating Scale (iADRS) Findings from the EXPEDITION3 Trial. *J Prev Alzheimers Dis.* 2018;5(2):134-136. 2. Wessels AM, Siemers ER, Yu P, et al. A combined measure of cognition and function for clinical trials: The Integrated Alzheimer's Disease Rating Scale (iADRS). *J Prev Alzheimers Dis.* 2015;2(4):227-241. 3. Liu-Seifert H, Andersen S, Case M, et al. Statistical properties of continuous composite scales and implications for drug development. *J Biopharm Stat.* 2017;27(6):1104-1114. 4. Honig LS, Vellas B, Woodward M, et al. Trial of solanezumab for mild dementia due to Alzheimer's disease. *N Engl J Med.* 2018;378(4):321-330. 5. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *N Engl J Med.* 2021;384(18):1691-1704. 6. Wessels AM, Tariot PN, Zimmer JA, et al. Efficacy and safety of lanabecestat for treatment of early and mild Alzheimer disease: The AMARANTH and DAYBREAK-ALZ randomized clinical trials. *JAMA Neurology.* 2020;77(2):199-209. 7. Andrews JS, Desai U, Kirson NY, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y).* 2019;5:354-363.

OC30- A MULTINATIONAL, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, ACTIVE COMPARATOR, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF DONEPEZIL TRANSDERMAL PATCH IN PATIENTS WITH ALZHEIMER'S DISEASE. Kee-Hyung Park¹, Won Yang Dong², Mee Young Park³, Seong Hye Choi⁴, Hyun Jeong Han⁴, Hee Jin Kim⁵, Kyung Won Park⁶, Yuan-Han Yang⁷, Suraya Yusoff⁸, Gurudev M. Kewalram⁹, Seol-Heui Han¹⁰ (1. *Gachon University Gil Medical Center - Incheon (Korea, Republic of)*, 2. *The Catholic University Of Korea, Seoul St. Mary's Hospital - Seoul (Korea, Republic of)*, 3. *Yeungnam University Hospital - Daegu (Korea, Republic of)*, 4. *Inha University Medical Center - Incheon (Korea, Republic of)*, 5. *Hanyang University Seoul Hospital - Seoul (Korea, Republic of)*, 6. *Dong-A University Hospital - Busan (Korea, Republic of)*, 7. *Kaohsiung Municipal Ta-Tung Hospital - Kaohsiung (Taiwan, Province of China)*, 8. *Hospital Sultan Ismail - Johor Bahru (Malaysia)*, 9. *Prince Charles Hospital - Brisbane (Australia)*, 10. *Konkuk University Medical Center - Seoul (Korea, Republic of)*)

Background: Although the disease modifying agent for Alzheimer disease (AD) might be feasible in near future, the cholinesterase inhibitors (ChEIs) are still the mainstay in the management of patients with AD worldwide. However, oral ChEI has its own limitations in clinical practice. Taking a pill daily can pose a challenge for both AD patients and caregivers. Moreover, the oral ChEI is associated with adverse events in the gastrointestinal system and in plasma fluctuations, therefore the development of an alternative route of administration, such as the transdermal one, is urgently needed. **Objectives:** The primary objective was to demonstrate the non-inferiority of the test drug, IPI-301 (transdermal patch) to the comparator, oral ChEI (donepezil) tablet after treatment for 24 weeks in patients with mild to moderate AD in terms of the improvement in cognitive function as assessed by the Alzheimer's Disease Assessment Scale – Cognitive (ADAS-cog). **Methods:** This trial was conducted as a prospective, randomized, double-blinded, double-dummy, active-controlled, two-arm parallel, multi-center trial. At the time of randomization, the subjects were stratified based on their previous treatment and dose of donepezil and those in each stratum were randomized to the test group and the control group at a ratio of 1:1. **Results:** The difference between the control group (oral tablet) and the test group (IPI-301) in the main evaluation set, PPS was 0.00 (Hodges-Lehmann estimation-Location Shift) (95% CI: -1.00, 1.33), of which the upper limit was less than 2.02. In the Per Protocol Set (PPS), the difference in the ADAS-cog Score at Week 24 from baseline was -0.49 ± 5.72 in the test group (IPI-301) and -0.87 ± 5.14 in the control group without significant difference between the treatment groups ($p=0.9044$). As the result of primary efficacy evaluation in the Full Analysis Set (FAS), the difference between the treatment groups was 0.34 (Hodges-Lehmann estimation-Location Shift) (95% CI: -0.66, 1.34), of which the upper limit was less than 2.02, and it was confirmed the criterion for non-inferiority was also satisfied in the FAS. In the PPS, no statistically significant differences between the two groups were observed in the means of CIBI-S score at baseline (Day 0) and CIBIC-plus score 24 weeks after treatment with the investigational product (CIBI-S p -value=0.6738; CIBIC-plus: p -value=0.9830). In the PPS, the change in ADAS-cog score at Week 12 from baseline was not different between the two groups with statistical significance (p -value=0.7633). In the PPS, the change in MMSE at Week 24 from baseline was not different between the two groups without statistical significance (p -value=0.5726). In the PPS,

the change in ADCS-ADL at Week 12 from baseline was not different between the two groups with statistical significance (p -value=0.1244). However, the change in ADCS-ADL at Week 24 from baseline was different between the two groups with statistical significance (p -value=0.0138). In the PPS, the changes in the NPI intensity and score of distress felt by the caregiver at Week 24 from baseline were not different between the treatment groups with statistical significance (Intensity: p -value=0.8487; and score of distress felt by the caregiver: p -value=0.2262). In the PPS, the changes in global CDR at Weeks 12 and 24 from baseline were not different between the two groups with statistical difference (p -value=0.7832, 0.9919). In addition, the changes in CDR-SOB at Weeks 12 and 24 from baseline were not different between the two groups with statistical significance (p -value=0.8974, 0.7835). Considering the results from the PPS and FAS comprehensively, for medication convenience (10-point VAS) at the end of treatment (Week 24), it was observed that while the satisfaction or convenience with regard to the medication of tablet was high in the test group (IPI-301) to which the placebo tablet had been administered, the satisfaction or convenience with regard to the application of patch tended to be high in the control group (donepezil tablet) to which the placebo patch had been applied. In the evaluation and analyses of the adverse events manifested, vital signs, and laboratory test outcomes including hematology, blood chemistry, and urinalysis, IPI-301, was compatible with donepezil table in terms of safety. **Conclusions:** When all the results above were integrated, IPI-301 was considered to have the efficacy of improving cognitive function as assessed by ADAS-cog in patients with mild to moderate AD, which was non-inferior to the existing oral donepezil agent, and also judged to be a satisfactory drug in terms of safety.

OC31- UPDATE ON THE PHASE 2 STUDY OF AL001 IN FRONTOTEMPORAL DEMENTIA PATIENTS CARRYING A GRANULIN MUTATION. Robert Paul, Felix Yeh, Mike Ward, Sam Jackson, Herve Rhinn, Julie Huang, Jenna Pappalardo, Yijie Liao, Hua Long (*Alector, Inc. - South San Francisco (United States)*)

Background: Frontotemporal dementia (FTD) is a rare, early-onset form of dementia and loss-of-function mutations in the progranulin gene (GRN) are a common cause of familial FTD. In the brain, progranulin (PGRN) is a key regulator of microglia activity and lysosomal function. AL001 is a human monoclonal IgG1 antibody that blocks and downregulates Sortilin, a receptor in the key degradation pathway of PGRN, and is being developed by Alector for the treatment of carriers of GRN mutations causative of FTD (FTD-GRN). Restoring PGRN levels may be an effective therapeutic approach in FTD-GRN, and AL001 was shown to chronically normalize CSF PGRN levels in GRN mutation carriers in a Phase 2 study and impact biomarkers representing key nodes of the pathophysiological disease cascade of FTD. **Objective:** INFRONT-2 is an open-label, Phase 2 study in GRN mutation carriers to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AL001 administered intravenously every four weeks. **Method:** Participants aged 18 – 85 years, must be carriers of a GRN mutation causative of FTD, have a CDR® plus NACC FTLD global score of 0.5 – 2, and have 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible bvFTD (Rascovsky 2011) or a diagnosis of PPA (Gorno-Tempini 2011). Lumbar punctures and MRI scans were performed at baseline and every 6 months. Clinical assessments including the CDR® plus NACC FTLD

sum of boxes (SB) were done every 3 months. Fluid biomarkers in plasma and CSF were analyzed using multiple platforms. **Results:** AL001 continues to be generally safe and well tolerated in FTD-GRN participants in INFRONT-2. Chronic dosing led to a sustained increase in PGRN levels to the normal range in FTD-GRN participants. Biomarker data related to key aspects of FTD-GRN pathophysiology and neurodegeneration will be presented for INFRONT-2 participants who have received AL001 for 12 months. **Conclusion:** There is a high unmet need for effective therapies in FTD. AL001 is being developed for the treatment of FTD-GRN to reduce the rate of neurodegeneration by increasing levels of PGRN and disrupting the pathophysiological disease cascade associated with FTD-GRN. INFRONT-3 is an ongoing, pivotal Phase 3 study to evaluate if AL001 can slow or stop disease progression in carriers of GRN mutations.

OC32- CENTILOID SCALES MAY REPRESENT A ROBUST CLINICAL OUTCOME FOR ANTI-AB THERAPEUTIC TRIALS ACROSS DIVERSE POPULATIONS/LOCATIONS. Samantha C Burnham¹, Timothy Cox², Pierrick Bourgeat³, Vincent Doré¹, Duygu Tosun⁴, Manu Goyal⁵, Rosita Shishegar¹, Parnesh Raniga³, Simon Laws⁶, Tenielle Porter⁶, Jurgen Fripp³, Tammie Benzinger⁷, Walter Kukull⁸, Christopher C Rowe⁹, John C Morris⁷, Mike Weiner⁴, Colin L Masters¹⁰, Victor L Villemagne¹¹ (1. *The Australian E-Health Research Centre, Csiro Health & Biosecurity - Parkville (Australia)*, 2. *The Australian E-Health Research Centre, Csiro Health & Biosecurity - Canberra (Australia)*, 3. *The Australian E-Health Research Centre, Csiro Health & Biosecurity - Herston (Australia)*, 4. *Department Of Radiology And Biomedical Imaging, University Of California-San Francisco - San Francisco (United States)*, 5. *Neuroimaging Laboratories, Mallinckrodt Institute Of Radiology, Washington University School Of Medicine - St. Louis (United States)*, 6. *Centre For Precision Health, School Of Medical And Health Sciences, Edith Cowan University - Joondalup (Australia)*, 7. *Knight Alzheimer Disease Research Center, Washington University School Of Medicine - St. Louis (United States)*, 8. *Department Of Epidemiology, University Of Washington - Seattle (United States)*, 9. *Department Of Molecular Imaging & Therapy, Austin Health - Heidelberg (Australia)*, 10. *Florey Institute Of Neuroscience And Mental Health, The University Of Melbourne - Parkville (Australia)*, 11. *Department Of Psychiatry, University Of Pittsburgh School Of Medicine - Pittsburgh (United States)*)

Background: To best understand the efficacy of different therapeutic targets and intervention studies, large clinical trials run across different populations and locations are needed. Results from diverse trials would be more generalisable, hold less bias and provide more valid and nuanced conclusions in comparison to single population/location studies. However, the disparity of the data collection, e.g. the use of different imaging tracers, neuropsychological batteries, etc., makes pooling data together a non-trivial task. The ADOPIC Project aims to harmonise data across three of the best characterised, international Alzheimer's cohort studies, namely The Adult Child Study (ACS), The Alzheimer's Disease Neuroimaging Initiative (ADNI) and The Australian Imaging, Biomarkers and Lifestyle Study of Aging (AIBL), providing increased study power and more nuanced understanding of aging as well as disease pathophysiology and phenotype. ADOPIC amyloid- β PET imaging data has been harmonised through the Centiloid harmonisation strategy (1). The Centiloid project provides linear transforms from native tracer SUVRs to a common Centiloid scale. An extension to the Centiloid transformation

applied non-negative matrix factorisation (NMF) to improve longitudinal stability by accounting for non-linear differences with changes in tracers and/or scanners (2). **Objectives:** (1) To evaluate the effectiveness of Centiloid with NMF to harmonise longitudinal amyloid- β PET imaging data across different populations and locations where different tracers and scanners are utilised, (2) To define the natural history of neocortical amyloid- β pathology expressed as Centiloids in the ADOPIC Study (3) To examine the difference in the natural history across the three different cohorts and five different tracers (PiB, NAV, FBP, FBB, FLUTE). (4) To evaluate differences in the natural history between APOE e4 carriers and non-carriers. **Methods:** 1186 ADOPIC participants (182 ACS, 478 ADNI, 526 AIBL) with a minimum of three amyloid- β PET evaluations [51.19% Female, 71.81 \pm 7.62 (mean \pm SD) years of age, 33.15% APOE e4 carriers, 5.92 \pm 2.27 years of follow-up] were included in this study. Amyloid- β PET evaluations were obtained using five different amyloid tracers across a wide variety (~30) of PET/CT scanners [674 participants were scanned repeatedly using a single tracer, 482 were scanned using two different tracers and 30 were scanned with three tracers. 518 participants were repeatedly evaluated using the same scanner, 541 were evaluated across two scanners, 122 across three scanners and 5 across four scanners.]. The Centiloid transformation¹ and NMF² were applied to all amyloid- β PET data and our phase-plane method (3,4) for constructing natural history curves was applied to this data. **Results:** The natural history modelling indicates that accumulation of neocortical amyloid- β pathology expressed in Centiloids (CL) is a long-protracted process spanning over 30 years, with the time from an abnormal level of 20CL to typical levels seen in mild Alzheimer's (100CL) taking 16.8 (CI: 13.77-19.82) years. Additional evaluations demonstrated that the natural history of neocortical amyloid- β pathology expressed in Centiloids does not differ between studies nor across tracers. Further, the rate of change of neocortical amyloid- β pathology expressed in Centiloids was essentially the same for both the APOE e4 carrier and non-carrier sub-populations. However, a shift in the age of onset (or time-lag) was seen with APOE e4 carriers accumulating abnormal levels of neocortical amyloid pathology at a mean age of 60.5 \pm 0.4 years, 10.7 years earlier than their APOE e4 non-carrier counterparts at a mean age of 71.2 \pm 0.7 years. **Conclusion:** Centiloid transformation with NMF provides a suitable harmonisation pipeline for longitudinal amyloid- β PET data acquired across different studies and locations with different tracers and scanners. Abnormal levels of neocortical amyloid- β pathology (20CL) occur ~17 years prior to mild Alzheimer's disease at an age of ~61 years in APOE e4 carriers and ~71 years in APOE e4 non-carriers. Therefore, Centiloid scores may represent an accurate way to establish the optimal time-window for anti-amyloid- β interventions and a powerful clinical outcome measure in therapeutic trials run across different populations, locations and with different tracers and scanners. **Conflicts of Interest:** The authors declare no conflicts of interest. **Acknowledgements:** The authors would like to thank the participants and their families as well as the ACS, ADNI and AIBL Study teams. **References:** 1. doi:10.1016/j.jalz.2014.07.003; 2. doi:10.1016/j.neuroimage.2020.117593; 3. doi:10.1016/S1474-4422(13)70044-9; 4. doi:10.1002/sim.7300

OC33- A MACHINE LEARNING TOOL TO ENRICH ALZHEIMER'S DISEASE CLINICAL TRIALS IN PRESYMPTOMATIC COHORTS. Angela Tam, César Laurent, Christian Dansereau (*Perceiv Research Inc - Montreal (Canada)*)

Background: Alzheimer's disease clinical trials are increasingly aiming to test treatments in cognitively normal individuals who may be at high risk of later developing dementia in order to prevent or slow cognitive decline. However, at this presymptomatic stage, it is extremely challenging to identify and recruit individuals who will decline when a substantial number of people will remain cognitively stable in a given timeframe. The inclusion of participants who will remain cognitively stable can impair a trial's ability to detect a treatment effect which increases the risk that a trial will fail to meet its endpoints. **Objectives:** We propose to use a multimodal prognostic machine learning approach to identify cognitively normal individuals who will have stable cognitive trajectories from those who will decline in a period of 48 months from a single time point at baseline. We believe that by identifying stable individuals and removing these individuals prior to randomization, we can de-risk clinical trials by ensuring that a greater prevalence of individuals who are likely to decline will be enrolled. **Methods:** We trained a machine learning prognostic pipeline to classify decliners from stable individuals over a period of 48 months on 757 cognitively normal individuals at baseline from the ADNI (adni.loni.usc.edu), NACC (nacccdata.org), and OASIS (oasis-brains.org) datasets. Decliners were defined as individuals who had increased CDR-SB scores at 48 months of follow-up compared to their baseline scores. Age, sex, APOE4 carriership, education, MMSE score, FAQ score, CDR-SB score, and volumes from anatomical brain regions extracted from MRI at baseline were used as input features. The model was trained and tested with nested 5-fold cross-validation. **Results:** 636 individuals (84% of the sample) did not actually decline on the CDR-SB at 48 months of follow-up. The whole sample had a mean (\pm std) observed change of 0.19 ± 0.78 points on the CDR-SB at 48 months compared to baseline. Using the full cohort, a power analysis showed that a clinical trial would need to enroll 2898 individuals in order to detect a 30% difference between treatment and placebo groups at 80% detection power. The predictive model identified 377 individuals as stable (50% of the sample) and 380 individuals as decliners, while it achieved a mean (\pm std) AUC of 71.87 ± 5.26 . At 48 months, the stable group had a mean observed change of 0.07 ± 0.50 on the CDR-SB compared to baseline, while the decliners experienced a change that was four times as large (mean observed change of 0.31 ± 0.97). Using the enriched cohort of decliners, 1724 individuals would be required for enrollment to detect a 30% difference between a placebo and a treatment group at 80% power. By identifying stable individuals and favouring the recruitment to only include participants who are the most likely to decline in order to improve the the quality of the sample, it is possible to reduce a clinical trial sample size by nearly 43% (from $n=2989$ to $n=1724$) compared to enrolling all eligible participants while maintaining the same study power. **Conclusion:** Our machine learning prognostic model can successfully distinguish presymptomatic individuals who are at high risk of impending cognitive impairment from those who will likely remain cognitively stable over the course of 48 months. Our tool can be used in clinical trials to precisely select participants who are more likely to exhibit cognitive decline during the trial, which can reduce trial costs by minimizing the sample size to almost half of what is originally required (when enrolling all eligible participants).

OC34- THE INTERNET-BASED CONVERSATIONAL ENGAGEMENT CLINICAL TRIAL (I-CONNECT) IN SOCIALLY ISOLATED ADULTS 75+ YEARS OLD: RANDOMIZED CONTROLLED TRIAL PROTOCOL AND COVID-19 RELATED STUDY MODIFICATIONS. Kexin Yu¹, Lisa C. Silbert², Katherine Wild², Jeffrey A. Kaye², Elena L. Alfaro³, Jacob Lindsey^{2,4}, Colon Scavone¹, Mattie McDonald^{2,5}, Hiroko H. Dodge² (1. *University Of Southern California - Los Angeles (United States)*, 2. *Oregon Health & Science University - Portland (United States)*, 3. *University Of Wisconsin-Madison - Madison (United States)*, 4. *Oregon State University - Corvallis (United States)*, 5. *Syneos Health - Portland*)

Background: It is well established that social isolation (small social network and lack of social contact) and loneliness (dissatisfaction with the frequency and quality of social contact) can lead to adverse health outcomes, including dementia. A recent report by Lancet Commissions showed that 2% of dementia cases could be prevented if we could eliminate social isolation. Therefore, increasing social interaction could be a promising intervention for improving the cognitive well-being of the socially isolated older subjects. Based on our previous pilot project, which showed promising results (1, 2), we developed a multi-site, assessor-blind, randomized controlled behavioral intervention trial (RCT) named "Internet-based conversational engagement clinical trial (I-CONNECT)" (ClinicalTrials.gov: NCT02871921; www.i-connect.org). This presentation describes the progress made so far in the I-CONNECT project. The COVID-19 pandemic related protocol modifications will also be addressed. **Objectives:** The main objective of the I-CONNECT trial is to investigate the extent to which online semi-structured conversational interactions conducted remotely can enhance cognitive functions among socially isolated or lonely older adults with normal cognition or MCI. **Methods:** I-CONNECT is a multi-site, assessor-blind, randomized controlled behavioral intervention trial (RCT). Inclusion/exclusion criteria are listed in ClinicalTrials.gov: NCT02871921. We aim to randomize 320 socially isolated adults 75+ years old (160 Caucasian and 160 African American participants, 50:50 split between those with normal cognition and mild cognitive impairment (MCI)) recruited from the community to either the Video Chat Intervention Group or the Control Group (1:1 allocation). Those in the Video Chat Group receive a computer and internet service for the duration of the study, which they use to video chat with study staff for 30 minutes/day 4x/week for 6 months (high dose), and then 2x/week for an additional 6 months (maintenance dose). Both Video Chat and control groups are having a brief (about 10 minutes) telephone check-in with study staff once per week. The primary outcome is the change in global cognitive function measured by Montreal Cognitive Assessment (MoCA) from baseline to 6 months. Secondary outcomes include changes in cognition in memory and executive function domains, emotional well-being measured by NIH Toolbox emotional battery, and daily functional abilities assessed with the Revised Observed Tasks of Daily Living (OTDL-R). To examine underlying mechanisms of our trial efficacy, we assess pre- and post- trial changes in brain structure, function, and perfusion as exploratory outcomes. Eligible participants have MRIs at Baseline and 6 months. Participants contribute saliva for genetic testing (optional consent), and all video chat and neuropsychological assessment sessions are recorded for speech and language analysis. The pandemic halted research activities and resulted in protocol modifications, including replacing in-person assessment with remote assessment, remote

deployment of study equipment, and revised targeted sample size. **Results:** As of March 10, 2021, over 29,000 subjects were contacted either by mail using voter registration lists, hospital registries (limited to those who consented to participate in research), referrals from the Area Agencies on Aging (AAA), and other service providers including Meals on Wheels food delivery services, and Facebook advertisement. Among 29,664 contacted subjects, 1,139 subjects (3.8%) successfully completed telephone screening and 394 subjects (1.3 %) met the study inclusion/exclusion criteria. One hundred eighty-six participants (0.6 % of 29,664) were randomized as of March 2021. By the time of the CTAD conference (November 2021), we will complete the baseline assessments for all randomized participants and be able to provide their baseline characteristics and the final participation rate in this trial. **Discussion:** This trial provides user-friendly hardware for the conversational-based intervention that can be easily accessed at participants' homes. A large touch screen monitor with a pop-up window has been used to show daily stimuli pictures to spark conversations, allowing even the oldest old participants with no previous experience using PC/mouse/internet or those with low motivation for participating in behavioral interventions to be easily engaged in conversational interactions. This user-friendly setting also eliminated the potential confounding effect of cognitive stimulation from learning to use a PC. Additional innovations of this trial include targeting subjects aged 75+, exploring changes in speech characteristics over time, and examining underlying biological mechanisms of social interaction on cognition. The trial aspires to use conversational materials and a related platform developed in this trial as a treatment for social isolation and resultant cognitive decline. This study also provides empirical support that recruiting racially diversified socially isolated subjects aged 75 and above to participate in behavioral intervention studies is challenging but also feasible. **References:** 1. Dodge HH, Zhu J, Mattek N, Bowman M, Ybarra O, et al., Web-enabled Conversational Interactions as a Means to Improve Cognitive Functions: Results of a 6-Week Randomized Controlled Trial. *Alzheimers Dement (N Y)* 1(1): 1-12, 2015. (PMC4507295). 2. Cerino ES, Hooker K, Goodrich E, Dodge HH. Personality Moderates Intervention Effects on Cognitive Function: A 6-Week Conversation-Based Intervention. *Gerontologist*. 2019. May 21. pii: gnz063. doi: 10.1093/geront/gnz063. (PMC7362618). **Keywords:** ADRD; Behavioral intervention; RCT; Trial methodology; Cognitive health; Social interaction; Technology-ICT; Social isolation and loneliness

OC35- DEVELOPMENT OF A NOVEL DIGITAL SPEECH COMPOSITE MEASURE FOR FRONTOTEMPORAL DEMENTIA. Jessica Robin¹, Mengdan Xu¹, Liam Kaufman¹, William Simpson¹, Michael Ward², Robert Paul² (1. *Winterlight Labs - Toronto (Canada)*, 2. *Alector, Inc. - South San Francisco (United States)*)

Background: Changes to speech and language are common symptoms across different subtypes of FTD. These changes affect the ability to communicate, impacting everyday functions important to both patients and their caregivers. Assessing these changes can help to track disease progression and detect response to treatment. Current tools to assess speech and language abilities, however, often involve specialized neuropsychological testing, which can be lengthy, costly and burdensome to patients and their caregivers. Developing tools to objectively measure speech abilities remotely could allow for more frequent assessments, with lower patient burden

and higher functional relevance to everyday life. **Objectives:** In this observational study, patients with FTD and their caregivers conducted remote digital speech assessments using the Winterlight app over a period of 12-months. Our objectives were to determine which aspects of speech showed significant change over time and to develop a novel composite measure for assessing speech and language patterns in FTD. **Methods:** 36 participants (16 female, 20 male) were enrolled in the study (mean age at enrollment = 61.3 years, standard deviation = 8.7) and 27 (75%) participants completed the 12-month assessment. Participants completed the Winterlight speech assessment remotely with the assistance of a caregiver at Months 1 (baseline), 2, 3, 6, 9 and 12. The speech assessment includes different tasks to elicit speech ranging from unstructured, open-ended tasks like picture description, to more standard clinical language assessments such as phonemic and semantic fluency tests. In each task, the participant saw and heard a set of instructions prompting them to produce a verbal response which was recorded, with responses typically ranging from a few seconds to a few minutes in duration. Speech samples were analyzed using Winterlight's natural language processing platform, generating >500 variables describing acoustic and linguistic characteristics of the speech sample. We used linear mixed models to select which speech variables demonstrated significant change over time, controlling for demographic and task-related variables. A composite measure was developed from the selected variables using principal components analysis (PCA). **Results:** The picture description task, which was the most naturalistic, open-ended task, generated the highest number of variables with significant change over the 12-month study. Nine speech variables were selected, based on their significant effects of time, controlling for effects of age, sex and stimulus, good test-retest reliability and low redundancy with one another. The nine selected variables reflected different aspects of speech and language including the ratio of words to pauses, the types of words used (e.g. the frequency of nouns, the amount of prepositions), and the information content and complexity of sentences. We developed a novel composite score based on these variables, weighting them according to the results of a principal component analysis. When compared to a sample of healthy control participants, the FTD group had lower scores at baseline on the novel composite score. The resulting composite score had a significant effect of change over time ($\beta = -0.055$, $p < 0.001$) and high test-retest reliability ($ICC = 0.76$, $p < 0.001$). This novel composite score was correlated with standard scores on the speech tasks (e.g. number of words correctly produced for phonemic and semantic fluency, number of correctly named items on the object naming test). **Conclusion:** This study demonstrated that digital speech assessments, which can be completed remotely in less than 15 minutes, have the potential to characterize speech and language abilities in FTD. We identified aspects of speech that demonstrate significant decline over the course of a year, potentially tracking disease progression. The novel composite measure developed in this study could be used to characterize speech patterns in FTD in future studies and detect change over time and response to treatment. Further validation is required by comparing this measure to biomarkers or clinical standards and replicating its ability to track disease-related changes in independent samples. Digital tools to assess patients remotely can reduce the burden of clinical research and help create novel measures sensitive to disease and relevant to everyday function.

OC36- LONGITUDINAL SAFETY, CLINICAL, AND BETA AMYLOID PET OUTCOMES OF A MULTI-CENTER CLINICAL TRIAL OF FOCUSED ULTRASOUND BLOOD BRAIN BARRIER (BBB) OPENING OF THE HIPPOCAMPUS, FRONTAL AND PARIETAL LOBES IN EARLY ALZHEIMER'S DISEASE. Ali Reza¹, Manish Ranjan¹, Mark Haut¹, Jeffrey Carpenter¹, Umer Najib¹, Rashi Mehta¹, Pierre-Francois D'haese¹, J. Levi Chazen², Zion Zibly³, Daniel Claassen⁴, Peter Konrad¹, Sally Hodder⁵, Michael Kaplitt² (1. WVU Rockefeller Neuroscience Institute - Morgantown (United States), 2. Weill Cornell Medicine - New York (United States), 3. Sheba Medical Center - Ramat Gan (Israel), 4. Vanderbilt University - Nashville (United States), 5. West Virginia Clinical And Translational Institute - Morgantown (United States))

Background: Innovative treatments for Alzheimer's disease (AD) are urgently needed. Magnetic resonance (MR)-guided low intensity focused ultrasound (FUS) has been shown to reversibly open the blood-brain barrier (BBB), reduce amyloid-beta plaque, and improved memory in preclinical AD models. We previously reported the initial safety and feasibility of FUS BBB opening of the hippocampus and entorhinal cortex (EC) [Reza et al., 2020] in mild AD patients. We now report patient outcomes of FUS treatments to frontal and parietal lobes in addition to the hippocampus, with up to 32 months follow-up. **Objective:** Assess longitudinal long-term safety, clinical outcomes, and changes in beta-amyloid plaques after FUS BBB treatment to open substantial regions of the frontal and parietal lobes as well as the hippocampus in patients with mild AD. **Methods:** In this Insightec (Haifa, Israel) sponsored open-label clinical trial (ClinicalTrials.gov Identifier: NCT03671889), patients with mild AD and positive amyloid-beta PET underwent MRI-guided FUS sonication of the hippocampus and EC (220 kHz, ExAblate Neuro Type 2 system) with concomitant IV microbubble (Definity®) administration during three separate sessions (each 2 weeks apart) targeting hippocampus, entorhinal cortex, frontal and parietal lobes (up to 40cc treatment volume). Outcome assessments included safety, BBB status (opening and closure), neurological and cognitive evaluations including mini-mental status examination (MMSE), and Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog). At one-year follow-up, cognitive function of participants was compared to an age and sex-matched cohort of patients with mild AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Standard Uptake Values (SUVr) were extracted from flurobetapen (F-18) PET images at baseline and 8 weeks follow up. SUVr was then normalized using a focal Centiloid approach [Klunk et al., 2015] for the targeted hippocampus/EC, parietal and frontal lobes. Average changes in normalized SUVr between the two-time points is reported. **Results:** Ten subjects (55-73 years old) completed 30 separate FUS treatments at two participating institutions with follow-up 3-32 months (median 17 months). The initial six participants had FUS treatment of the hippocampus/EC and the last four had additional treatment in frontal and parietal lobes. All ten subjects had immediate BBB opening demonstrated by parenchymal IV contrast enhancement followed by BBB closure within 24-48 hours. All FUS treatments were well tolerated with no procedure-related complications; post-FUS procedure MRI did not demonstrate any overt hemorrhages. No serious neurological adverse events have occurred in any participant. The mean cognitive change at one-year follow-up (n=6) compared to baseline was: MMSE score, FUS -2.4 vs. ADNI -3.8, and ADAS-Cog-11 score, FUS +5.4 vs. ADNI +5.6. There was concomitant decrease in the beta-amyloid on the PET

scan with FUS treatment at 8 weeks as compared to baseline. The average reduction of beta-amyloid PET SUVr in the treated regions was: Hippocampus: 12.8% (\pm 9%), frontal lobe 6.9% (\pm 3.1%), and parietal lobe: 13.6% (\pm 7.5%). **Conclusions:** This is the first study in early AD demonstrating safe and reversible BBB opening in large parts of the frontal and parietal lobes in addition to the hippocampus with reduction of beta amyloid plaques observed with PET imaging. Average cognitive decline was not worse in the FUS treatment group compared with the ADNI cohort at 1 year follow-up, suggesting safety of FUS treatment. Further studies are needed to determine the clinical significance of these findings. The noninvasive, on-demand feature of FUS technology and focal BBB opening offers a unique opportunity for targeted delivery of therapeutics to meaningful volumes of essential brain structures. **References:** Reza AR, Ranjan M, D'Haese PF, Haut MW, Carpenter J, Najib U, et al. Noninvasive hippocampal blood-brain barrier opening in Alzheimer's disease with focused ultrasound. Proceedings of the National Academy of Sciences of the United States of America. 2020;117:9180-2. Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous MD Sr, Jagust WJ, Johnson KA, Mathis CA, Minhas D, Pontecorvo MJ, Rowe CC, Skovronsky DM, Mintun MA. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement.* 2015 Jan;11(1):1-15

ROC01- COMPARING REMOTE VERSUS IN-CLINIC CLINICAL OUTCOME ASSESSMENTS IN THE TAURIEL STUDY OF SEMORINEMAB IN EARLY AD: THE COVID-19 EXPERIENCE. Paul Manser¹, Mira Blendstrup¹, Nia Sengupta¹, Karen Pickthorn¹, Enrique Gaspar², Winnie Leung¹, Mayumi Thompson¹, Edmond Teng¹, Rajesh Menon¹ (1. Genentech, Inc. - South San Francisco (United States), 2. Medavante-Phase - Hamilton (United States))

Background: The Tauriel study (GN39763; NCT03289143) was a global Phase 2 randomized, double-blind, placebo-controlled, parallel-group clinical trial that assessed safety and efficacy of the monoclonal anti-tau antibody semorinemab in prodromal-to-mild Alzheimer's disease (AD) conducted in 13 countries. The first dose of blinded study medication was administered on 18Oct2017 and the final assessment of the 73-week double-blind period was completed during the COVID-19 pandemic on 16Jul2020. The pandemic particularly impacted patients enrolled in AD clinical trials, who are at the highest demographic risk for COVID-19 associated morbidity and mortality. Accordingly, the Tauriel study faced critical risks to data collection over the last 4 months of the double-blind period, which overlapped with the COVID-19 pandemic, particularly for multiple clinical outcome assessments (COAs), including the primary endpoint: the Clinical Dementia Rating-Sum of Boxes (CDR-SB). Beginning in March 2020, we sought to minimize the loss of COA data related to shelter-in-place orders and site closures by implementing an option for remote (i.e., telephonic and/or video) data collection. **Objectives:** We conducted exploratory analyses to assess the consistency of remote COAs collected during the COVID-19 pandemic versus those conventionally collected in-clinic prior to the pandemic. **Methods:** Study sites were provided with standardized guidance (e.g., mode, administration, data entry, best practices) for COAs that had previously been validated as being compatible for remote administration (e.g., CDR-SB, ADCS-ADL, A-IADL-Q, C-SSRS, RUD-lite; Randolph et al., AAIC 2014). Data were collected via tablet computers and/or paper forms. Retrospective analyses compared the means and

standard deviations of differences between in-clinic assessments to differences between in-clinic and remote assessments. Pre-pandemic, CDR-SB (primary endpoint) was collected at both screening and baseline, which allowed for evaluation of in-clinic test-retest characteristics within a short interval. During the pandemic, remote CDR-SB assessments were collected and compared to participants' most recent prior in-clinic assessment to evaluate test-retest characteristics across settings. Analyses of test-retest characteristics were limited to assessments completed within 100 days of each other for both in-clinic versus in-clinic and in-clinic versus remote comparisons. **Results:** Remote COA assessments were performed for 98 participants from 43 sites in 12 countries across a wide range of circumstances. While overall feedback from study sites was positive, key challenges included availability of appropriate technological infrastructure for participants and raters and optimization of home environments to increase consistency of responses. Thirty-two participants had both in-clinic/in-clinic and in-clinic/remote test-retest CDR-SB assessments conducted within 100-day intervals. Across both conditions, similar magnitudes of interval change and variability were observed (in-clinic/in-clinic: mean change=0.06, SD=1.17; in-clinic/remote: mean change=0.28, SD=1.05). **Conclusion:** Remote COA assessments were successfully implemented for prodromal-to-mild AD participants in the Tauriel study during the COVID-19 pandemic. Available data suggest reasonable consistency between remote and in-clinic assessments. Future considerations for optimizing remote assessments include: proactive provisioning/training for technological needs, flexibility in requirements for in-clinic vs. remote data collection, audio and/or video recording (for additional centralized quality control), and adaptation (and subsequent validation) of assessments that require visual and/or physical stimuli for test administration.

ROC02- THE UTILITY OF USING VERSION 3 OF THE ALZHEIMER'S DISEASE RESEARCH CENTERS' NEUROPSYCHOLOGICAL TEST BATTERY FOR PREVENTION TRIALS. Kwun Chuen Gary Chan¹, Hiroko H. Dodge², Lisa L. Barnes³, Fan Xia⁴, Walther A. Kukull⁴, Andrew J. Saykin⁵ (1. University Of Washington-Seattle (United States) - Seattle (United States), 2. Oregon Health And Science University - Portland (United States), 3. Rush University - Chicago (United States), 4. University Of Washington - Seattle (United States), 5. Indiana University - Indianapolis (United States))

Background: The National Alzheimer's Coordinating Center (NACC) at the University of Washington has coordinated collection of the Uniform Data Set (UDS) on participants from over 30 National Institute on Aging (NIA)-funded Alzheimer's Disease Research Centers (ADRC) since 2005. The UDS data include detailed neuropsychological tests for studying cognitive decline. In 2015, version 3 of the UDS neuropsychological battery was launched to replace existing proprietary measures and add a new domain in visuospatial function. The instruments were constructed with the guidance and approval of the Clinical Task Force (CTF), a group formed by NIA to develop standardized methods for collecting longitudinal data that would encourage and support collaboration across the ADRCs. The UDS v3 neuropsychological battery includes the Montreal Cognitive Assessment (MoCA) for measuring global cognition, Number Span (Forward/Backward) for measuring attention/working memory, Craft Story 21 Recall (Immediate/Delayed) for measuring episodic memory, Multilingual Naming Test (MINT) and Category Naming (animals and vegetables)

for semantic memory/language, Trail Making Test A and B for executive function, and Benson Figure (Copy/Recall) for visuospatial function. Composite scoring for each cognitive domain has been suggested previously using factor analysis. To date, over 10,000 participants have contributed UDS v3 data, but its potential utility in prevention trials remains unclear. **Objectives:** To compare the difference in the rates of change of UDS v3 neuropsychological measures and domains between participants without cognitive impairment at baseline who progressed to MCI or AD and participants who remained cognitively normal for up to 4 years of follow-up, and to determine sample size estimates in designing prevention trials that use longitudinal change in individual measures or composite scores as the primary outcome. **Methods:** The analytical sample was extracted from the March 2021 data freeze from NACC, which includes baseline and follow-up visits from participants who were administered the English version of the UDS v3 test during in-person visits. To standardize comparisons, z-scores for each test are constructed using the baseline mean and standard deviations estimated using the normal controls. Domain composite z-scores were calculated by averaging the z-scores within each cognitive domain (attention/working memory, episodic memory, semantic memory/language, executive function, visuospatial function). The global composite z-score was calculated by averaging the five domains composite z-scores. Linear mixed effects models with random intercept and random slope were used for studying longitudinal changes, controlling for baseline age, sex, race, education and APOE-ε4 carrier status. The estimated difference in longitudinal changes in these models can be regarded as the maximal difference that a prevention trial can attain. Sample size calculation is based on established formulas for linear mixed models with random intercept and random slope, using a significance level of 5% and 80% power to detect an effect size which is a fraction (20%-40%) of the estimated maximal difference, with an equal proportion of participants randomized to the intervention and the control arm. We assume that trial participants have a baseline visit and up to four annual follow-up visits, and the dropout rate is 10% per year. **Results:** Most individual measures in the UDS v3 exhibited statistically significant faster decline among individuals who progressed from normal to MCI or AD, compared to those who remained cognitively normal, except the Number Span Forward test. Except the attention/working memory composite score, which is composed of Number Span Forward and Backward tests, all other domain z-scores and the global composite z-score showed faster decline for those who progressed from normal cognition to MCI or AD. Among individual tests from the UDS v3 battery, the Montreal Cognitive Assessment (MoCA) required the smallest sample size to detect a difference for a given effect size: Detecting a 20% reduction of the maximal difference would require 700 participants per arm, and a 40% reduction would require 175 participants per arm. For the domains, the executive function composite score required the smallest sample size for a given effect size; 745 participants per arm for a 20% reduction and 186 participants per arm for a 40% reduction. The global composite score required a much smaller sample size for detecting the same reduction of the maximal difference, compared to all individual and domain scores, requiring only 398 participants per arm in detecting a 20% reduction and 100 participants per arm for a 40% reduction. **Conclusions:** The UDS v3 neuropsychological tests consistently distinguish between baseline cognitively normal participants who progressed to MCI or AD from those who remained cognitively normal. Using a

global composite score as an outcome would result in a more than 40% reduction of sample sizes needed compared to MoCA, the single instrument that required the smallest sample size. The use of UDS v3 tests in prevention trials appears promising.

ROC03- ALLOPREGNANOLONE AS A REGENERATIVE THERAPEUTIC FOR ALZHEIMER'S: EXPLORATORY PHASE 1 NEUROIMAGING MRI OUTCOMES.

Adam C. Raikes¹, Dawn Matthews², Gerson Hernandez¹, Yonggang Shi³, Meng Law⁴, Lon Schneider⁵, Roberta Brinton¹ (1. Center For Innovation In Brain Science, University Of Arizona - Tucson (United States), 2. Adm Diagnostics, Inc - Northbrook (United States), 3. Usc Stevens Neuroimaging And Informatics Institute, University Of Southern California - Los Angeles (United States), 4. Monash University - Melbourne (Australia), 5. Keck School Of Medicine Of The University Of Southern California - Los Angeles (United States))

Background: Regenerative therapeutics hold the promise of self-renewal and repair. Prior research in preclinical Alzheimer's disease (AD) models indicated that allopregnanolone promotes neurogenesis, restores cognitive function and reduces AD pathology. Allopregnanolone (Allo) is a small molecular weight, blood brain barrier penetrant molecule that induces neurogenesis through regeneration of neural stem cells in brain and promotes the innate regenerative capacity of the brain to increase the pool of neural progenitor cells. Mechanisms of Allo-induced regeneration, IND-enabling and human safety are well-established. **Objectives:** Because Allo promoted regeneration in preclinical AD models, we sought to determine whether a regenerative response could be detected in human AD brain using MRI structural and connectivity exploratory imaging outcomes. **Methods:** A randomized, double-blinded, placebo-controlled, multiple ascending dose trial was conducted. Intravenous placebo or Allo was administered once-per-week for 12 weeks. Participants with early AD (mild cognitive impairment due to AD or mild AD), a Mini-Mental State Examination score of 20-26 inclusive, and age ≥ 55 years were randomized (6:2 to three Allo dosing cohorts or one placebo cohort). Primary endpoints were safety and tolerability. The Phase1b/2a trial was powered only for safety and not for exploratory outcomes. Exploratory endpoints included imaging biomarkers. Imaging included high-resolution structural, resting-state functional (rs-fMRI) and diffusion-weighted magnetic resonance imaging (DWI). Imaging endpoints included change from baseline of: hippocampal volume, intra-regional (regional homogeneity), inter-regional, and network-wise functional connectivity, microstructural integrity. **Results:** No evidence of ARIA was detected in either Placebo or Allo treated participants. In total, 23 of 24 MRIs (6 placebo and 17 Allo (3 doses)) were analyzed for exploratory neuroimaging outcomes. Change from baseline of left hippocampal structural volume indicated that: Placebo was associated with 0% gain-15% loss in volume whereas Allo (all doses combined) was associated with a range of outcomes from 7% gain to 10% loss. Right hippocampal structural volume: Placebo 0% gain to 7% loss in volume, Allo (all doses combined) 7% gain to 7% loss. Dose response analysis indicated that the optimal Allo dose for both left and right hippocampus was associated with a range of 7% gain to 5% loss. No dose of Allo was associated with the maximum loss observed in placebo. No sex difference in MRI imaging outcomes in response to Allo was observed. An APOE genotype difference in MRI structural change was observed with APOE4 carriers associated with greater left

and right hippocampal volume gain relative to non-carriers. Allo increased functional connectivity between multiple brain regions (all FDR corrected $p < 0.05$, all Hedges $g > 1.80$). Region-to-region changes in connectivity were reflected in increased network-wise connectivity between limbic and default mode network, somatomotor and limbic networks and somatomotor network and the cerebellum (DMN; all FDR corrected $p < 0.05$). Local functional connectivity also increased following Allo administration in areas associated with AD, including posterior cingulate, precuneus, prefrontal cortex. While these regional increases did not survive multiple comparisons correction (all FDR corrected $p < 0.122$) the effect sizes were large (Hedges $g > 0.7$) and 95% confidence intervals around the effect size estimates did not include 0, suggesting potential effects with larger samples. Allo administration was associated with increased fractional anisotropy in 690 tracts (FDR corrected $p < 0.05$) compared to placebo with less decline in quantitative anisotropy across 1477 white matter tracts (FDR corrected $p < 0.017$). For both measures, increased integrity of tracts were distributed across the corpus callosum, bilateral superior corticostriatal tracts, right posterior thalamic radiation, and left superior longitudinal fasciculus. **Conclusions:** Results of MRI imaging analyses are consistent with Allo as a regenerative therapeutic for Alzheimer's disease. As a key biomarker of AD pathology, hippocampal atrophy was slowed or potentially reversed in either the left or right hippocampus in up to 42% of the participants receiving Allo compared to none of their placebo counterparts. Genotype analyses suggest that APOE-e4 carriers may be particularly responsive to regenerative effects of Allo. Allo treatment effected intra- and inter-regional functional connectivity. In particular, functional connectivity between the limbic and default mode networks (DFM) was strengthened. These networks are comprised of regions associated with progressive neurodegeneration in AD and included the orbitofrontal cortex and temporal pole. Furthermore, intra-regional connectivity was increased in key regions of the DMN associated with cognitive performance, including prefrontal regions and precuneus. Coupled with strengthened inter-regional functional connectivity, these findings suggest that the DMN may be particularly responsive to Allo. Allo was associated with preserved microstructural integrity, particularly in the corpus callosum, corticostriatal tracts, and thalamic radiation. Preserved microstructural integrity of white matter is critical as degraded structural connectivity is a hallmark feature of progressive neurodegeneration and an underlying mechanism of decreased cognitive capability. These exploratory imaging findings suggest that Allo may exert both regenerative and neuroprotective effects on structure and connectivity in the Alzheimer's brain. **Acknowledgements:** National Institute on Aging UF1AG046148, U01AG031115, U01AG047222, ADFF to RDB; P30AG066530 Clinical core to LS.

ROC04- EARLY DETECTION OF ALZHEIMER'S DISEASE WITH BRAINSEE, THE FDA BREAKTHROUGH SOFTWARE MEDICAL DEVICE.

Thomas Liebman¹, Elham Khosravi², Pavan Krishnamurthy³, Padideh Kamali-Zare³, Kaveh Vejdani³ (1. Darmiyan, Inc. - Penzberg (Germany), 2. Darmiyan, Inc. - Berlin (Germany), 3. Darmiyan, Inc. - San Francisco (United States))

Background: Early detection of Alzheimer's disease is a critical component for success of clinical trial design. The recent announcement by the FDA of the first market clearance of a therapeutic for Alzheimer's disease (AD) in decades [1] further highlights the need for accessible and affordable early

detection tools. Targeting brain amyloid beta, aducanumab will require screening for brain amyloid. However, amyloid screening alone is insufficient because it is not specific to AD [2]. More specific, reliable, non-invasive, affordable, and globally accessible screening tools will be required. Neurocognitive assessments such as Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating (CDR) tests are routinely used to evaluate the cognitive status of an individual with cognition or memory impairment. Such tests are recommended in guidelines for diagnosis of amnesic mild cognitive impairment and later stages of dementia due to AD [3], but they are not individually highly effective for diagnosing Alzheimer's disease at early stages because of the relatively late manifestation [4]. Reports of predictive value using cognitive assessments vary wildly due to factors such as biases, data leakage, presence of converters in the study population and even insufficient sample sizes [5]. Likewise, MRI-based brain volumetry is widely demonstrated to reveal brain changes in Alzheimer's dementia, but, as with cognitive testing, brain tissue atrophy appears relatively late in the disease progression process [4] and provides nominal value as a predictor [6]. Despite any benefit of cognitive assessment or brain atrophy measures for early detection of AD, there is no FDA cleared device for such use. **Objectives:** The primary objectives of this study were to design, develop and validate a software medical device, BrainSee, that can be readily used in most clinical settings for assessing the probability of progression from amnesic MCI (aMCI) to AD dementia within 5 years using routine MRI and minimal cognitive testing. The secondary objective was to demonstrate the effectiveness and likelihood of clinical success of BrainSee to the FDA to warrant a Breakthrough Device designation. **Methods:** A software medical device called BrainSee was designed to process standard cognitive assessment scores (all boxes of CDR and MMSE total score) and routine clinical brain MRI. The device pipeline performs post-processing on the brain MRI and extracts key regional features, including but not limited to proprietary volumetric measurements. The cognitive scores and MRI features are then applied to the device's algorithm together with basic demographics of age, gender and education, for predicting the likelihood of progression from aMCI to AD dementia within 5 years. The machine learning algorithm was trained on retrospective data with a minimum of 1 MRI session and sufficient follow-up clinical assessments (5 years of continuous aMCI diagnosis or a conversion to AD dementia within 5 years). In total, 409 aMCI patients with 1462 brain MRI scan sessions were included in the training. The ages ranged between 55 and 94. The gender distribution was 168 female and 241 male. Considering the 5-year time window, 37% of subjects were stable and the remaining 63% progressed to AD dementia within the 5 years. Model validation was performed by blind testing on data from third party providers. 95 patients (44 female, 51 male) were included between the ages of 51 and 94. The test-retest coefficient of variation was calculated where same-day repeat scans were available (60 patients). **Results:** The design, testing and outline of clinical use were presented to the FDA, and BrainSee was granted a Breakthrough Device designation in May 2021. The performance of BrainSee on blind test cases was as follows: Sensitivity: 89.2 %, Specificity: 92.9 %, Balanced accuracy: 91.0 %, Test-retest coefficient of variation: 4.6%. **Conclusion:** Darmiyán's software medical device, BrainSee, is a physician-oriented, easy to use software tool for non-invasive early detection of Alzheimer's disease in individuals diagnosed with aMCI. It has been blind tested for robustness and efficacy, and through the FDA Breakthrough

Device Program, the device is being packaged for market clearance to be the first and only software medical device that is approved for clinical early detection of Alzheimer's disease in individuals diagnosed with aMCI. With high diagnostic accuracy and demonstrated robustness, this device is well suited for screening patients who are enrolling in clinical trials, those considered for treatment with the recently approved therapeutic or patients requiring other early interventions. **References:** 1. <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug>; 2. Laforce R Jr, Rabinovici GD. *Alzheimers Res Ther.* 2011;3(6):31. Published 2011 Nov 10. doi:10.1186/alzrt93; 3. McKhann GM, et al. *Alzheimers Dement.* 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005; 4. Jack CR Jr, Holtzman DM. *Neuron.* 2013;80(6):1347-1358. doi:10.1016/j.neuron.2013.12.003; 5. Belleville, S. et al. *Neuropsychol Rev* 27, 328–353 (2017). <https://doi.org/10.1007/s11065-017-9361-5>; 6. Ferrari BL, et al. *Medicine (Baltimore).* 2019;98(45):e17824. doi:10.1097/MD.00000000000017824

ROC05- EVALUATING THE CONTRIBUTION OF IMAGE-DERIVED FEATURES FOR PREDICTING RATE OF COGNITIVE DECLINE IN A LARGE COHORT (INCLUDING 6 CLINICAL TRIALS; N=3,339) OF EARLY AD PATIENTS. Derrek Hibar¹, Balazs Toth¹, Christopher Galli², Tobias Bittner², Christina Rabe¹, David Clayton¹ (1. Genentech - South San Francisco (United States), 2. Roche - Basel (Switzerland))

Background: Accurate and robust prognostic models of cognitive decline in early AD patients have the potential to transform interventional clinical trials by enabling innovative clinical trial strategies that boost statistical power and reduce trial length and sample size. Well-studied image features associated with AD as well as complex features leveraging recent advancements in artificial intelligence may provide meaningful additional information about patient prognosis not previously captured by models that include only clinical, genomic, and demographic features. **Objectives:** The goal of this study is to examine the unique contribution of features derived from 3D T1 structural MRI scans to prognostic models of cognitive decline in early AD patients. Specifically, we examine the added prognostic value of traditional AD image features (hippocampal, ventricular, and whole brain volume; temporal lobe cortical thickness) as well as complex features derived using a novel deep learning framework we developed and applied to whole-brain 3D MRI scans. **Methods:** Our focus was on early AD patients from six clinical trials (ABBY NCT01343966, BLAZE NCT01397578, Scarlet RoAD NCT01224106, Marguerite RoAD NCT02051608, CREAD NCT02670083, CREAD2 NCT03114657) and from the observational ADNI study. We defined patient eligibility as: 1) positive amyloid beta status confirmed via amyloid PET scan or CSF biomarkers; 2) MMSE \geq 20; 3) a minimum of 1 year follow up of CDR-SB; and 4) a diagnosis of prodromal or mild AD at baseline. The main outcome of interest was the individual rate of change in CDR-SB over two years from baseline. We split our data into a fully independent holdout dataset consisting of CREAD and CREAD2 patients (n=1316). Patients from the remaining four clinical trials and ADNI study were randomly split ~60/40% into training (n=1158) and testing (n=865) sets. Structural T1 MRI scans associated with the baseline clinical visits for all patients were processed using two distinct procedures: 1) a harmonized pipeline (FreeSurfer v6.0) to extract volumetric, thickness, area and global brain features; and 2) a harmonized pipeline (ANTs v2.3.3) to align

all T1 scans to a common template, normalize and remove bias, and truncate extreme voxel values to be used as input for a deep learning model. We previously showed that a 10 factor model combining clinical, genomic, and demographic features (i.e. age, sex, BMI, education, ApoE4, diagnosis, MMSE, CDR-SB, ADL or FAQ and ADAS-Cog 12) has moderate, robust performance for predicting rate of cognitive decline (Toth et al., 2020). Here we use this 10 factor model as a benchmark and compare it to models that add image-derived features. We evaluate two different models incorporating: 1) well-established structural features associated with cognitive decline including volumes of the ventricles, hippocampi, and full brain and an AD-focused temporal lobe cortical thickness ROI (defined in Jack et al., 2017); 2) complex image features derived from a novel time-distributed transfer learning (deep learning) model we developed on 3D T1 structural MRI scans to extract features associated with cognitive decline. **Results:** We found that a model combining clinical, genomic, and demographic features with traditional imaging features showed an increase in variance explained of rate of change in CDR-SB in the test set ($R^2=0.23$) and independent holdout set ($R^2=0.15$) compared to the benchmark model with clinical, genomic, and demographic features only (test set: $R^2=0.20$; holdout set: $R^2=0.11$). Similarly, the model incorporating complex image features derived from the deep learning model showed an increase over the benchmark (test set: $R^2=0.21$; holdout set: $R^2=0.13$). Follow up analyses of the imaging features show that the complex features derived from the deep learning model are highly correlated with the well-studied, AD-associated imaging features. Each of the imaging features we evaluated was significantly correlated with the rate of change in CDR-SB outcome. **Conclusion:** We present an analysis of the added prognostic value of image-derived features in one of the largest data sets of early AD patients to date. Compared to our benchmark composed of clinical, genomic, and demographic features, models that include image-derived features provide increases in variance explained in the observed rate of cognitive decline. The increases observed are modest, but they may still be clinically meaningful given the heterogeneous progression rates in early AD populations. Structural MRI scans are typically a required part of safety assessments for a clinical trial and our prognostic model incorporating clinical, genomic, demographics and imaging features could be implemented without major logistical challenges. This has important implications for the practical application of such a model in clinical practice and in randomized clinical trials. In future, we will consider more complex combinations of features from images (including from the deep learning model) as well as additional data types.

ROC06- USING A SYMMETRIC WARPFIELD IN A DEEP-LEARNING FRAMEWORK FOR JACOBIAN INTEGRATION TO ESTIMATE BRAIN ATROPHY. Marina Papoutsis^{1,2}, Bianca De Blasi¹, Richard Jules¹, Michael Reinwald¹, Robin Wolz^{1,3} (1. *Ixico Plc - London (United Kingdom)*, 2. *University College London - London (United Kingdom)*, 3. *Imperial College London - London (United Kingdom)*)

Background: Measures of local and global volume change in the brain are important markers of neurodegeneration and widely employed for efficacy assessment in clinical trials. Different approaches are available to measure volume change from magnetic resonance imaging (MRI) through semi- and fully- automated image analysis tools. One approach is to assess volumetric differences in segmentations of a region of interest (ROI) between intra-subject scans, this however,

requires to carefully control measurement noise introduced by partial volume effects and ambiguities in structural boundaries. Other widely used approaches are the boundary shift integral (BSI; Freeborough and Fox, 1997) which assesses changes in a structural boundary over time and tensor-based morphometry (TBM; Vercauteren et al., 2008) which evaluates tissue shrinkage and growth from a non-linear deformation field at the voxel level. However, the BSI measurement is only applicable to regions with well-defined boundaries, whereas available TBM implementations, which overcome these limitations, are heavily dependent on the underlying registration algorithm and implied smoothness constraints and are often computationally intensive and slow. Advancements in artificial intelligence (AI) for deformable image registration offer potential for faster computation without loss of sensitivity. **Objectives:** Here, we present a non-linear registration algorithm based on a convolutional neural network (CNNs) and a spatial transformer network (STN) to measure longitudinal brain atrophy using Jacobian integration. **Methods:** In the proposed algorithm, a CNN/STN combination is trained to estimate the deformation field between serial intra-subject T1W MR image pairs. The objective function minimizes intensity differences while preserving topology. Symmetry of the warfield is achieved by penalizing differences between 'forward' and 'backward' transformations. Compute times of a few seconds of the GPU-deployed framework enables efficient optimization of the registration in both directions to obtain 'forward' and 'backward' transformations. Voxel-wise volume change measures are obtained from integration of the Jacobian Determinants of the warp field within a specific baseline region of interest. **Results:** We evaluated our algorithm in ADNI1 (<http://adni.loni.usc.edu/>) participants (44 healthy controls (HC), 45 mild cognitive impairment (MCI), 44 Alzheimer's disease (AD) age- and gender-matched) and assessed the model's ability to measure 1-year change in the whole brain, ventricles and hippocampus, which are important biomarkers in AD. We compared performance against Freesurfer 7.1, BSI and a TBM approach employing ANTs (Avants et al., 2008). Group comparisons were performed using a Mann-Whitney U-test and to enable comparison between different methods we calculated common language effect sizes (CLES). The proposed AI approach reports anatomically plausible atrophy rates across all three regions. For the AD group mean (SD) volume change was -1.0% (0.5%), 8.2% (4.8%) and -2.9% (2.2%) for wholebrain, ventricles and hippocampus respectively. For the MCI group, mean (SD) volume change was -0.7% (0.4%), 6.3% (3.9%) and -2.2% (2.0%) for wholebrain, ventricles and hippocampus respectively. The proposed approach shows comparable (e.g. all $p < 0.001$ for HD vs AD comparisons) or improved ability to differentiate clinical groups using annual atrophy when compared to the reference methods. This is apparent in the differentiation of MCI from AD where the proposed method outperforms the alternative tools across whole brain (Freesurfer: $p=0.86$, CLES=0.48, BSI: $p=0.41$, CLES=0.55, ANTs: $p=0.009$, CLES=0.66, AI: $p=0.001$, CLES=0.70), ventricles (Freesurfer: $p=0.12$, CLES=0.60, BSI: $p=0.09$, CLES=0.60, ANTs: $p=0.03$, CLES=0.63, AI: $p=0.03$, CLES=0.64), hippocampus (Freesurfer: $p=0.78$, CLES=0.52, BSI: $p=0.17$, CLES=0.58, ANTs: $p=0.77$, CLES=0.48, AI: $p=0.07$, CLES=0.61). **Conclusion:** We have proposed an algorithm for sensitive atrophy measurement using fast non-linear registrations obtained from a CNN/STN framework. While the proposed algorithm offers significant run-time improvements (close to 'real-time' analysis in seconds as opposed to hours), the preliminary results presented also show that the measured atrophy rates were sensitive

to clinical diagnosis, and at least comparable to current standard approaches. **References:** Avants, B.B., Epstein, C.L., Grossman, M., Gee, J.C., 2008. Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. *Med. Image Anal., Special Issue on The Third International Workshop on Biomedical Image Registration – WBIR 2006* 12, 26–41. <https://doi.org/10.1016/j.media.2007.06.004>. Freeborough, P.A., Fox, N.C., 1997. The boundary shift integral: an accurate and robust measure of cerebral volume changes from registered repeat MRI. *IEEE Trans. Med. Imaging* 16, 623–629. <https://doi.org/10.1109/42.640753>. Vercauteren, T., Pennec, X., Perchant, A., Ayache, N., 2008. Symmetric Log-Domain Diffeomorphic Registration: A Demons-Based Approach, in: Metaxas, D., Axel, L., Fichtinger, G., Székely, G. (Eds.), *Medical Image Computing and Computer-Assisted Intervention – MICCAI 2008, Lecture Notes in Computer Science*. Springer, Berlin, Heidelberg, pp. 754–761. https://doi.org/10.1007/978-3-540-85988-8_90

ROC07- ASSESSING 11B-HSD1 IN VIVO OCCUPANCY BY XANAMEM® USING 11C-TARACT PET. Christopher C. Rowe¹, Victor L. Villemagne², Vincent Doré³, Lee Chong¹, Rachel Mulligan¹, Svetlana Bozinovski¹, Rodney Guzman¹, Michael Kassiou⁴, Jack Taylor⁵, Tamara Miller⁵ (1. *Austin Health - Melbourne (Australia)*, 2. *University Of Pittsburgh - Pittsburgh (United States)*, 3. *Csiro - Melbourne (Australia)*, 4. *University Of Sydney - Sydney (Australia)*, 5. *Actinogen Medical Ltd - Sydney (Australia)*)

Background: The steroid converting enzyme, 11 β -HSD1, is a potential therapeutic target in diseases characterised by dysregulated cortisol including Alzheimer's Disease (AD) and Type 2 diabetes. However, elucidating the inhibitory capacity of novel drug molecules in the brain remains challenging. **Objectives:** We tested the ability of [11C]-4-(5-(2-chlorophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-1-methyl-1H-indole (11C-TARACT), a new radiotracer developed by Merk but not previously used in human studies, that specifically and reversibly binds to 11 β -HSD1, to determine 11 β -HSD1 occupancy by Xanamem® to potentially derive an optimal dose for efficacy studies in AD. **Methods:** A group of healthy controls (CN, n=19) and Mild cognitively impaired (MCI)/AD participants (n=12) aged (aged 77.3 \pm 6.4 years, 11F/20M) underwent 11C-TARACT PET at baseline and after a 7-day regimen of an oral daily dose of either 5, 10, 20 or 30 mg of Xanamem®. Participants were injected with 370 MBq of 11C-TARACT followed by a 90-min dynamic acquisition. Blood samples (10mL) were obtained at 5, 10, 20, and 30 minutes post-injection for metabolite analysis. Ichise Multilinear Reference Tissue Model (MTRM) Binding Potentials non-displaceable (BPND) were generated using the metabolite-corrected image-derived carotid artery SUV as input function. **Results:** 11C-TARACT provided high quality brain images with binding in the cerebellar cortex > occipital, sensori-motor, superior parietal cortex > thalamus, putamen, lateral frontal cortex > anterior cingulate, gyrus rectus, insula, medial temporal lobe regions > midbrain, pons > caudate nucleus and white matter. Metabolism was relatively slow (~80% parent compound remained in plasma at 20 min). There was a dramatic and dose dependent occupancy by Xanamem®. No significant differences were observed between Xanamem® occupancy in CN and AD, and the occupancy affected all regions of the brain (except cerebellar cortex) to a very similar degree in neocortex (NCTX), mesial temporal lobe (MTL), and basal ganglia (BG), with a ~80%, ~85%, ~91%, and ~97% occupancy by 5, 10, 20, and 30

mg of Xanamem®, respectively. The cerebellar cortex (CB) displayed a lower degree of occupancy by Xanamem® with a ~46%, ~64%, ~84%, and ~93% occupancy by 5, 10, 20, and 30 mg of Xanamem®, respectively. **Conclusion:** 11C-TARACT PET studies provide a robust and non-invasive way to determine the degree of 11 β -HSD1 occupancy by Xanamem®. The data enables more targeted future clinical trials where the dose of Xanamem® can be tailored to the desired level of enzyme occupancy.

ROC08- CHARACTERISTICS OF SUBJECTS WITH DISCORDANT AMYLOID STATUS BETWEEN VISUAL READ AND CENTILOID FROM THE PHASE 2 CLINICAL STUDY OF TILAVONEMAB IN EARLY ALZHEIMER'S DISEASE. Eddie Stage¹, Dustin Wooten¹, Ziyi Jin¹, Charles Locke¹, Jacob Hesterman², John Seibyl², Hana Florian¹, Robert Comley¹, Qi Guo¹ (1. *Abbvie Inc. - North Chicago (United States)*, 2. *Inovio - New Haven (United States)*)

Background: Defining amyloid positivity is crucial for screening a target population in an Alzheimer's disease (AD) clinical trial. Amyloid screening is traditionally performed using biofluid (cerebrospinal fluid, or more recently plasma) Ab biomarkers and/or positron emission tomography (PET) using a tracer specific to amyloid. Amyloid PET screening methods are often qualitative and center around a visual read. However, the recent introduction of quantitative measures that can represent a relative amyloid load across multiple tracers, such as Centiloid (CL), makes screening on the basis of quantitative thresholds more feasible and may ultimately provide a more sensitive determination of amyloid positivity. Using a CL cutoff has the potential to reduce the high number of screen failures that come from a more conservative visual read screening approach. Screening data from the phase 2 tilavonemab trial was used to compare patients with a discordant amyloid status between qualitative and quantitative assessments to those subjects who were visually positive and randomized into the trial. **Objectives:** The purpose of this work is to directly compare the baseline demographic data between patients who were not randomized due to an amyloid negative visual read but were determined to fall above a CL positivity threshold retrospectively (discordant) and those patients who were randomized into the phase 2 tilavonemab trial. **Methods:** This work includes screening data from the 96-week, randomized, double-blind, placebo-controlled, global phase 2 study evaluating the efficacy and safety of tilavonemab in patients with early AD (NCT02880956). All subjects who received an amyloid PET scan were 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). Amyloid PET scans were then read visually and only patients with a positive read confirmed by two radiologists were randomized. Amyloid PET was then quantified for all patients on the Centiloid (CL) scale utilizing a processing pipeline developed in-house and validated using recommended procedures [1]. A CL cutoff value of ≥ 20.1 CL for amyloid-positivity [2] was used to classify patients into two categories: 1) visual-negative CL-positive, or discordant patients, and 2) visual-positive, randomized patients. Mean Age, MMSE, CDR-sum-of-boxes (CDR-SB), and CL were directly compared at screening between discordant amyloid and randomized patients using a two-sample t-test. **Results:** 650 patients received an amyloid PET scan at screening (or had

a qualified previous scan) using one of five tracers (N), [18F]Florbetapir (403), [18F]Florbetaben (223), [18F]Flutemetamol (19), [18F]NAV4694 (4), and [11C]PiB (1). Of those, 453 were visually positive and 197 were visually negative. Within the visually negative group, 97 were found to meet the CL positivity threshold, thus comprising the “discordant” cohort. Randomized patients had a mean (standard deviation, SD) age of 71.3 (7.0) years, while the discordant patients had a mean (SD) age of 71.8 (7.3), $p=0.5283$. The randomized group were 48% male vs. 40% male in discordant patients. Baseline mean (SD) MMSE score was 24.4 (2.9) and CDR-SB score was 3.0 (1.2) for randomized patients, while discordant patients had a mean (SD) MMSE and CDR-SB of 26.4 (2.2) and 2.4 (1.0), respectively. Both MMSE and CDR-SB were significantly different between the two groups at $p<0.001$ and $p=0.002$, respectively. The randomized patient mean (SD) CL value was 99.0 (31.1) with >99% of subjects (449/453) falling above the CL threshold for positivity. Discordant patients had a mean (SD) CL value of 59.2 (27.3), significantly different at $p<0.001$. **Conclusion:** Visually-negative CL-positive amyloid patients had a significantly lower mean CL value than visually-positive (randomized) patients and were significantly less impaired as measured by MMSE and CDR-SB. Using a quantitative threshold (CL) as an inclusion criterion appears to be a valid strategy but is more sensitive to lower levels of amyloid, which may result in an earlier or less impaired AD population. **References:** 1. Klunk WE, et al. *Alzheimer’s & Dementia*. 2015;11(1):1-15. 2. Amadoru S, et al. *Alz Res Therapy*. 2020; 12(22):1-8. ES, DW, ZY, CL, HF, RC and are employees of AbbVie Inc., may own stock and/or stock options. JH and JS are employees of Invicro Ltd. AbbVie Inc. participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving of this abstract for submission. All authors had access to the data; participated in the development, review, and approval of the abstract; and agreed to submit this abstract to CTAD 2021 for consideration as an oral presentation or poster. AbbVie and the authors thank the patients who participated in this clinical trial. AbbVie Inc. funded the research for this study.

ROC09- PERFORMANCE OF THE PRECIVITYAD™ BLOOD TEST IN DETECTION OF BRAIN AMYLOIDOSIS IN COGNITIVELY NORMAL AND COGNITIVELY IMPAIRED INDIVIDUALS. Suzanne Schindler¹, Kevin Yarasheski², Tim West², Matthew Meyer², Kris Kirmess², Anne Fagan¹, John Morris¹, Randall Bateman¹ (1. Washington University - St. Louis (United States), 2. C2n Diagnostics - St. Louis (United States))

Background: There is a great need for accurate plasma biomarkers of Alzheimer disease (AD), and assays of plasma A β ₄₂/A β ₄₀ have widely varying performance in detection of brain amyloidosis. C2N Diagnostic’s PrecivityAD™ test is currently the only blood test for brain amyloidosis available for use in the clinic. **Objective:** We evaluated the performance of the PrecivityAD™ test in detection of brain amyloidosis in cognitively normal and cognitively impaired individuals. **Methods:** Matched plasma and cerebrospinal fluid (CSF) samples (1,564 pairs) collected at the same session were evaluated in 883 older individuals enrolled in studies of memory and aging at the Knight Alzheimer’s Disease Research Center (ADRC). The PrecivityAD™ test is a commercially available immunoprecipitation liquid chromatography-tandem mass spectrometry assay that quantifies plasma A β ₄₂/A β ₄₀ and determines APOE genotype based on the presence/absence of plasma apolipoprotein E isoform-specific peptides. These measures and age in years are incorporated into a logistic

regression model for amyloid PET status that generates the Amyloid Probability Score (APS): a value from 0–100 that reflects the likelihood of the presence of brain amyloidosis. The PrecivityAD plasma measures and APS calculations were conducted by C2N Diagnostics (St. Louis, MO). CSF biomarkers were measured with Fujirebio Lumipulse® assays and were used as the primary reference standard, where the cut-off for brain amyloid positivity was CSF A β ₄₂/A β ₄₀<0.0673 based on a separate study. The secondary reference standard for brain amyloid status was a PiB PET scan within two years of the blood collection, which was available for a sub-cohort of 404 individuals. The established cut-off for mean cortical standardized uptake value ratio was used to determine amyloid status by PiB PET. **Results:** The average age of the cohort was 68.5 ± 9.7 years, 41% carried at least one APOE ϵ 4 allele and 24% were cognitively impaired with a Clinical Dementia Rating™ (CDR) of 0.5 or greater. The Spearman correlation between plasma and CSF A β ₄₂/A β ₄₀ was 0.64 (0.60-0.68). The ROC AUC for plasma A β ₄₂/A β ₄₀ with brain amyloid status by CSF A β ₄₂/A β ₄₀ was 0.88 (0.86-0.91); corresponding values for PiB PET status were 0.85 (0.81-0.89). When APS was used to predict brain amyloid status by CSF A β ₄₂/A β ₄₀, the ROC AUC was 0.92 (0.91-0.94); corresponding values for PiB PET status were 0.90 (0.87-0.93). Plasma A β ₄₂/A β ₄₀ and APS were similarly accurate in predicting brain amyloid status by CSF A β ₄₂/A β ₄₀ in both cognitively normal and cognitively impaired individuals. In the 672 cognitively normal individuals (CDR=0), the ROC AUC for plasma A β ₄₂/A β ₄₀ was 0.89 (0.87-0.92) and for APS was 0.92 (0.90-0.94) with brain amyloid status by CSF A β ₄₂/A β ₄₀. In the 221 cognitively impaired individuals (CDR of 0.5 or greater), the ROC AUC for plasma A β ₄₂/A β ₄₀ was 0.86 (0.80-0.92) and for APS was 0.90 (0.85-0.95) with brain amyloid status by CSF A β ₄₂/A β ₄₀. A sub-cohort of 360 individuals had longitudinal data for plasma and CSF with an average follow-up interval of 6.9 ± 3.6 years. At both the baseline and last timepoints, 227 individuals were negative by CSF and plasma A β ₄₂/A β ₄₀, and 87 individuals were positive by CSF and plasma A β ₄₂/A β ₄₀. There were 46 individuals who were brain amyloid negative by CSF A β ₄₂/A β ₄₀ at baseline but who converted to brain amyloid positive at the last timepoint: 25/46 had a negative baseline plasma A β ₄₂/A β ₄₀ value and 21/46 had a positive value. Adjusted for the time of follow-up, individuals with a negative baseline CSF A β ₄₂/A β ₄₀ were 5 times more likely to become CSF positive within 6.9±3.6 years if they had a positive baseline plasma A β ₄₂/A β ₄₀ value. **Conclusions:** The PrecivityAD test accurately detects brain amyloidosis in both cognitively normal and cognitively impaired individuals. Compared to plasma A β ₄₂/A β ₄₀ alone, the Amyloid Probability Score further improves the diagnostic accuracy of the test. At baseline, individuals with a positive plasma A β ₄₂/A β ₄₀ but negative brain amyloid status by CSF A β ₄₂/A β ₄₀ have a high likelihood of converting to brain amyloid positive, suggesting that plasma A β ₄₂/A β ₄₀ detects individuals with very early brain amyloidosis.

ROC10- PLASMA NEUROFILAMENT LIGHT CHAIN AND PHOSPHORYLATED TAU217 IN PATIENTS WITH TYPE 2 DIABETES TREATED WITH GLP-1 RECEPTOR AGONIST DULAGLUTIDE IN THE REWIND CARDIOVASCULAR OUTCOMES TRIAL. Jonathan M Wilson¹, Hui-Rong Qian¹, Courtney Irelan¹, Hannah Badger¹, Jeffrey L Dage¹, Kevin L Duffin¹, Dawn A Brooks¹, Hertz C Gerstein², M Angelyn Bethel¹ (1. Eli Lilly And Company - Indianapolis (United States), 2. Population Health Research Institute - Hamilton (Canada) - Hamilton (Canada))

Background: Type 2 diabetes (T2D) is an independent risk factor for cognitive decline. Dulaglutide, a glucagon-like peptide -1 (GLP-1) receptor agonist, provides effective glucose lowering, reduces cardiovascular (CV) risk in patients with T2D with or without prior CV disease, and is associated with reduced risk of cognitive impairment in exploratory analyses from the REWIND CV outcome trial (Cukierman-Yaffe et al., 2020). Two plasma biomarkers associated with substantive cognitive impairment (SCI) events were measured in REWIND: neurofilament light chain (NfL), and plasma phosphorylated tau at threonine 217 (P-tau217). **Objectives:** This post-hoc exploratory analysis examines change from baseline in two circulating biomarkers, NfL and P-tau217, and the association of that change with dulaglutide treatment and SCI events in patients with T2D and cardiovascular risk in the REWIND trial. **Methods:** Circulating NfL and P-tau217 were quantified in stored ethylenediaminetetraacetic acid (EDTA) plasma samples collected at baseline and 2 years by Ella (ProteinSimple, San Jose, CA) and an in-house immunoassay (Mesoscale Discovery, Rockville, MD), respectively. Analysis of Covariance (ANCOVA) modeling was applied to dulaglutide and placebo treatment groups defined by baseline NfL deciles, quartiles and median, and by baseline P-tau217 above/below a cutoff value associated with Alzheimer's disease pathology. Cox proportional hazard modeling with standardized baseline Montreal Cognitive Assessment (MoCA) and Digit Symbol Substitution Test (DSST) scores as covariates was used to calculate treatment effect on SCI events. Biomarker data were analyzed on a log scale, then represented as concentrations by transforming back to linear scale. P-values are not corrected for multiple testing. **Results:** In the REWIND trial, 9901 participants were randomly assigned to either dulaglutide (n=4949) or placebo (n=4952). During median follow-up of 5.4 (IQR 5.1–5.9) years, 8828 participants provided a baseline and one or more follow-up MoCA or DSST scores, of whom 4456 were assigned dulaglutide and 4372 were assigned placebo. NfL and P-tau217 were measured at baseline and 2-years in 3671 and 3713 dulaglutide treated subjects and 3557 and 3597 placebo treated subjects, respectively. In the overall population, the baseline adjusted 2-year NfL level was not significantly different in patients treated with dulaglutide (29.83 vs 30.13 vs pg/mL, FC= -1.01, p=0.4709). However, in the highest decile subgroup of baseline NfL concentration (>56 pg/mL), the 2-year baseline adjusted levels of NfL were decreased in the dulaglutide treatment group compared to placebo (63.83 vs 75.40, FC= -1.18, p=0.0025). There was a significant interaction between treatment and baseline NfL level (p<0.0001 treating baseline NfL as continuous variable, p=0.0003 treating baseline NfL as categorical groups of top 10% and the rest 90%). Subdividing the REWIND trial cohort by low or high baseline P-tau217 (cut point 0.25 pg/mL) provided fold change of dulaglutide vs placebo baseline adjusted 2-year NfL levels of 1.004 (p=0.8323) or -1.051 (p=0.0739), respectively. P-tau217 did not show statistically significant change in

patients treated with dulaglutide in the overall population or defined subgroups. In a post-hoc analysis, patients treated with dulaglutide had a statistically significant hazard reduction (HR=0.86, 95%CI=0.79-0.95, p=0.0018) of SCI events, as previously reported (Cukierman-Yaffe et al., 2020). This finding was enhanced in subjects with P-tau217 levels > 0.25 pg/mL with a statistically significant hazard ratio (HR=0.78, 95%CI=0.65-0.93, p=0.0064). However, the interaction between treatment and the groups defined by baseline P-tau217 was not significant (p=0.1166). Conversely, subdividing by baseline NfL levels had no effect on the SCI hazard ratio as compared to the overall population (HR=0.86 in highest decile subgroup, 95%CI=0.65-1.14, p=0.3019). There are limitations in this study. It was conducted using stored samples as an exploratory post-hoc analysis. The samples were only available at baseline and 2-years while the cognitive assessments were conducted out to 5 years. Country specific, age-appropriate normative ranges were not available for DSST or MoCA which limits comparisons with other studies or effect sizes. **Conclusions:** Patients treated for two years with dulaglutide versus placebo showed attenuated circulating plasma NfL in subjects with high baseline levels of NfL or P-tau217. However, these changes were not observed with statistical significance in the overall trial population. Plasma P-tau217 levels were unchanged in patients treated with dulaglutide. In a previous post-hoc analysis, patients with dulaglutide had lower SCI events compared to placebo in the REWIND cohort. In this study, we showed that subjects with high P-tau217 levels, but not low P-tau217 levels below 0.25 pg/mL, treated with dulaglutide had lower SCI events compared to placebo. Subdividing by baseline NfL levels did not predict lower SCI events. The previously reported exploratory cognitive outcomes in diabetic patients treated with dulaglutide are consistent with this post-hoc subpopulation biomarker analysis in the REWIND trial. **Reference:** Cukierman-Yaffe T, Gerstein HC, Colhoun HM, Diaz R, García-Pérez LE, Lakshmanan M, Bethel A, Xavier D, Probstfield J, Riddle MC, Rydén L. Effect of dulaglutide on cognitive impairment in type 2 diabetes: an exploratory analysis of the REWIND trial. *The Lancet Neurology.* 2020;19(7):582-90.

ROC11- MAXIMIZING PRECISION AND POWER IN ALZHEIMER'S DISEASE TRIALS: HOW AND WHEN TO SELECT THE MOST PROGNOSTIC BASELINE VARIABLES. Michael Rosenblum, Elizabeth Colantuoni, Melody Dehghan, Michela Gallagher, Arnold Bakker (*Johns Hopkins University - Baltimore (United States)*)

Background: Adjusting for baseline variables that are prognostic for the outcome in randomized trials evaluating novel therapeutics for Alzheimer's Disease (AD) can improve precision of estimated marginal treatment effect. Improvements in precision translate to increases in power for a fixed sample size or a reduction in the required sample size to achieve a desired power. Statistical methods for estimating the adjusted marginal treatment effect have been studied extensively; however, less guidance has been provided on how and when to select the most prognostic baseline variables to include in such analyses. **Objectives:** To compare the statistical properties of the estimated marginal treatment effect derived from the Analysis of Covariance (ANCOVA) and unadjusted estimators when baseline variables are selected while planning the trial, i.e. pre-selected, or during the analysis of the trial data, i.e. post-selected, using several variable selection procedures within the context of an on-going Alzheimer's Disease (AD). **Methods:** Simulation studies were designed and implemented that mimic

the on-going HOPE4MCI trial, the goal of which is to reduce cognitive decline in patients with amnesic mild cognitive impairment due to AD as measured by 18-month change in the Clinical Dementia Rating Scale sum of boxes score (CDR-SB score). Two curated datasets from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study, representing weakly and strongly prognostic baseline variables for the 18-month change in CDR-SB score, containing 21 pre-specified candidate baseline variables were created. The two curated ADNI datasets were used to pre- or post-select baseline variables for use in hypothetical trials to which these pre- or post-selected variables were incorporated in the statistical analyses. We consider several baseline variable selection procedures including always adjusting for the baseline CDR-SB score only, adjusting for all 21 pre-specified candidate baseline variables, and adjusting for variables selected from a lasso regression procedure. **Results:** Regardless of whether baseline variables were pre- or post-selected, the lasso regression procedure selected on average roughly 1, 12 and 14 baseline variables given no, weak and strong correlation of candidate baseline variables and the 18-month change in CDR-SB score. All of our estimators of the marginal treatment effect had similar and small bias, and the corresponding confidence intervals produced roughly 95% coverage of the marginal treatment effect. Our findings were similar regardless of when baseline variables were selected. Adjusting for prognostic baseline variables from the lasso regression procedure, as well as including all pre-specified candidate baseline variables, resulted in large reductions in the required sample size when compared to the unadjusted estimator; a roughly 15 to 30% reduction in the required sample size depending on the strength of correlation between the baseline variables and the 18-month change in CDR-SB score. Selecting baseline variables using the lasso procedure resulted in adjusted marginal treatment effects with the largest precision gains. When baseline variables are not prognostic, selecting baseline variables using the lasso procedure resulted in approximately no loss of precision. **Conclusion:** We recommend baseline variable adjustment within randomized trials where there are prognostic baseline variables. The baseline variable selection procedure should be pre-planned including when and how baseline variables are selected. Post-selecting baseline variables resulted in similar precision gains compared to pre-selecting baseline variables and protects against the possibility of different patterns of correlation among baseline variables and outcomes observed in data available while planning the trial vs. the trial data itself. Using the lasso procedure resulted in the largest precision gain when baseline variables are prognostic for the outcome and small loss of precision when baseline variables are not prognostic. Additional theoretical work is required to establish asymptotic properties of machine learning approaches, like lasso regression, for selection of baseline variables.

ROC12- BASELINE CHARACTERISTICS OF THE GRADUATE STUDIES: PHASE III RANDOMIZED, PLACEBO-CONTROLLED STUDIES INVESTIGATING SUBCUTANEOUS GANTENERUMAB IN PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE. Christopher Lane¹, Szofia Bullain², Angeliki Thanasopoulou², Paul Delmar², Alison Searle¹, Mercè Boada^{3,4}, Timo Grimmer⁵, Diana Kerwin⁶, Paulo Fontoura², Monika Baudler², Geoffrey A Kerchner², Rachele S Doody^{2,7} (1. Roche Products Ltd - Welwyn Garden City (United Kingdom), 2. F. Hoffmann-La Roche - Basel (Switzerland), 3. Fundació Ace, Barcelona Alzheimer Treatment And Research Center - Barcelona (Spain), 4. Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III - Madrid (Spain), 5. Klinikum Rechts Der Isar, Technical University Of Munich, School Of Medicine - Munich (Germany), 6. Kerwin Medical Center - Dallas (United States), 7. Genentech, Inc. - South San Francisco (United States))

Background: Gantenerumab is a fully human anti-amyloid beta ($A\beta$) monoclonal immunoglobulin G1 antibody in development for the treatment of Alzheimer's disease (AD). Gantenerumab has high affinity for aggregated $A\beta$ and promotes its removal via Fc γ receptor-mediated microglial phagocytosis (1,2). Post hoc analyses of a Phase III study of gantenerumab, SCarlet RoAD (NCT01224106), which was terminated early due to a futility analysis, suggested that higher doses of gantenerumab may result in clinically relevant effects on cognition and function. Subsequent open-label extensions (OLEs) of the SCarlet RoAD and the Phase III Marguerite RoAD (NCT02051608) trials, showed robust $A\beta$ removal with higher doses of gantenerumab over longer durations, with manageable adverse events, which promoted continued investigation of gantenerumab (3). Two multicenter, randomized, double-blind, placebo-controlled, Phase III studies, GRADUATE I (NCT03444870) and GRADUATE II (NCT03443973), were initiated and are ongoing, assessing the efficacy and safety of subcutaneous gantenerumab (1,020 mg monthly dosage) in early (prodromal-to-mild) AD. **Objectives:** To describe the baseline characteristics from the two identical, global, randomized, double-blind, placebo-controlled, parallel-group, Phase III GRADUATE studies. **Methods:** At screening, participants who were aged 50–90 years; had a clinical diagnosis of prodromal AD (mild cognitive impairment due to AD) or probable AD dementia according to the National Institute on Aging–Alzheimer's Association diagnostic criteria; demonstrated abnormal memory using the Free and Cued Selective Recall Test (FCSRT); met criteria for the Mini-Mental State Examination (MMSE; ≥ 22) and the Clinical Dementia Rating – Global Score (CDR-GS; 0.5 or 1); and showed evidence of $A\beta$ pathology confirmed by $A\beta$ positron emission tomography scan or cerebrospinal fluid analysis were eligible for enrollment. Enrolled participants were randomized 1:1 to receive subcutaneous injection of either gantenerumab or placebo. The study drug is titrated in 3 up-titration steps (120 mg, 225 mg, 510 mg monthly dosage) over a 9-month period to a target monthly dosage of 1,020 mg. All participants receive the same titration and target dose, regardless of apolipoprotein E $\epsilon 4$ status. Gantenerumab is administered subcutaneously at the study site or at home using home nursing. The primary endpoint of the GRADUATE studies is the change from baseline to Week 116 in Clinical Dementia Rating scale – Sum of Boxes (CDR-SB). Secondary efficacy measures include the MMSE, Alzheimer Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) 11, ADAS-Cog 13, Verbal Fluency Task, Coding, Functional Activities Questionnaire (FAQ), and Alzheimer

Disease Cooperative Study Group – Activities of Daily Living (ADCS-ADL) total score and instrumental score. Fluid and imaging biomarker analyses are being conducted to monitor safety and to understand pharmacokinetics/pharmacodynamic relationships, as well as the impact of gantenerumab on biomarkers of AD. Magnetic resonance imaging examinations are being conducted to monitor safety and measure brain volumetric changes, before every target dose and periodically during target dosing. Change from baseline in brain amyloid load and brain tau load are being assessed in a subset of participants. An independent data monitoring committee regularly evaluates participant safety. **Results:** Recruitment for GRADUATE I and II is complete. Participants were enrolled from 32 countries across 5 different continents: Asia, Australia, Europe, North America, and South America. Detailed baseline characteristics will be presented. **Conclusion:** Following prior evidence that the current target dose of subcutaneous gantenerumab is associated with robust brain amyloid removal, the GRADUATE trials are investigating the safety and efficacy of this gantenerumab dose compared with placebo in participants with early AD. Gantenerumab is being up-titrated to a higher single monthly target dosage of 1,020 mg for a longer duration (27 months) than previously tested in placebo-controlled studies of gantenerumab, to determine the timing and persistence of the clinical effects associated with amyloid removal. By using the FCSRT as an eligibility criterion, the population is enriched for participants with early AD who are more likely to progress during the study. Amyloid pathology can be confirmed by either CSF or PET. The subcutaneous route of administration of gantenerumab allows for administration by a healthcare professional at the participant's home. Eligible participants may enter an OLE following completion of the GRADUATE trials. **References:** 1. Ostrowitzki S, Deptula D, Thurfjell L, et al. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. *Arch Neurol.* 2012;69(2):198-207. 2. Bohrmann B, Baumann K, Benz J, et al. Gantenerumab: A novel human anti-A β antibody demonstrates sustained cerebral amyloid- β binding and elicits cell-mediated removal of human amyloid- β . *J Alzheimers Dis.* 2012;28(1):49-69. 3. Klein G, Delmar P, Kerchner G, et al. Thirty-six-month amyloid positron emission tomography results show continued reduction in amyloid burden with subcutaneous gantenerumab. *J Prev Alzheimers Dis.* 2021;8(1):3-6. **Disclosures:** Christopher Lane is a full-time employee of Roche Products Limited and is a shareholder in F.Hoffmann-La Roche Ltd.

ROC13- T2 PROTECT AD: RESULTS OF A 48-WEEK RANDOMIZED CLINICAL TRIAL OF TRORILUZOLE IN MILD-TO-MODERATE ALZHEIMER'S DISEASE.

Howard Feldman¹, Qiu Yuqi¹, Karen Messer¹, Stephen Kaplita², Ronald Thomas¹, Branko Huisa-Garate¹, James Brewer¹, Lia Donahue², Vladimir Coric², Brianna Askew¹, Gregory Jicha³, Christopher Van Dyck⁴, Mark Brody⁵, Jonathan Drake⁶, Gabriel Leger¹, Anton Porsteinsson⁷, Suzanne Hendrix⁸, Diane Jacobs¹, David Salmon¹, Irfan Qureshi² (1. University Of California San Diego - La Jolla (United States), 2. Biohaven Pharmaceuticals - New Haven (United States), 3. University Of Kentucky College Of Medicine - Lexington (United States), 4. Yale University School Of Medicine - New Haven (United States), 5. Brain Matters Research - Delray Beach (United States), 6. Alzheimer's Disease And Memory Disorders Center At Rhode Island Hospital - Providence (United States), 7. University Of Rochester School Of Medicine And Dentistry - Rochester (United States), 8. Pentara Corporation - Millcreek (United States))

Background: Glutamate dysfunction is implicated in AD symptoms and disease progression, and glutamate signaling is a clinically validated AD target. Troriluzole (Tro), a novel glutamate modulator, is thought to increase glutamate cycling and normalize synaptic glutamate by enhancing expression and function of glial excitatory amino acid transporters (EAAT2) and decreasing presynaptic glutamate release. Downstream biological effects observed in AD prevention paradigms, with Tro or its active metabolite (riluzole), support exploration of potential clinical efficacy in AD. These preclinical observations include restoring synaptic and neural network homeostasis, reducing amyloid and tau, and rescuing neurodegeneration. **Objective:** T2 Protect AD ("T2;" NCT03605667), a phase 2, proof-of-concept, randomized, placebo-controlled trial, is designed to evaluate efficacy and safety of troriluzole over 48 weeks in mild-to-moderate AD. **Methods:** T2 is coordinated by the Alzheimer's Disease Cooperative Study at 44 US AD specialty centers. Enrollment criteria: clinical diagnosis of mild or moderate AD (MMSE 20-24, 14-19), MRI findings consistent with AD, age 50-85, and stable on AD medications (potentially including AChEIs and memantine). Exclusion criteria: serious or unstable medical illness, hepatic impairment, other dementia, major depression, bipolar or schizophrenia. Participants are randomized 1:1 to 48 weeks of treatment with once-daily Tro 280 mg or placebo. An optional open-label extension is ongoing (data not reported). Co-primary efficacy outcome measures are ADAS-Cog-11 and CDR-SOB. Secondary outcome measures are QUARC hippocampal volumes, Neuropsychiatric Inventory (NPI), ADCS-ADL, and MMSE. Safety measures include adverse events (AEs), clinical safety labs, and EKGs. Exploratory measures include pharmacokinetic parameters and biomarkers including CSF (YKL 40, SNAP 25, sTREM2, neurogranin) and plasma (NfL, Abeta 42, 40, total tau, p-tau 181, GFAP) analytes. Primary efficacy analyses use the mITT population, with outcome mean change from baseline at 48 weeks compared between treatment and control arms using a mixed model with repeated measures, assessed using LS means at family wise 5% significance level using a gatekeeper procedure. **Results:** From July 2018 to December 2019, 687 participants were screened, and 350 were randomized. 75.1% completed the 48-week double-blind phase. At randomization, participants were well-balanced between arms, with 58.0% female, mean age 71.7 (SD 7.9), mean education 15.30 (SD 3.05) years, 95.4% white, 66.0% ApoE4 carriers. By severity, 56.3% were mild and 43.7% moderate. Baseline mean scores were: ADAS-Cog-11, 26.0 (SD 8.07); CDR-SOB, 6.6 (SD 2.54); NPI

total, 8.9 (SD 9.67); ADCS-ADL, 61.3 (SD 9.52) and MMSE, 19.3 (SD 3.78). Mean duration of treatment was 308.4 (SD 99.73) days (median 337 days). There were no significant differences between arms in LS means of ADAS-Cog-11, 0.0 (95% CI -1.8, 1.8), CDR-SB -0.2 (95% CI -0.8, 0.3), or by preplanned mild to moderate subgroups and ApoE4 carrier status. Because the primary outcome was not significant, secondary endpoints are presented for descriptive purposes only. Secondary outcomes did not suggest LS mean differences between treatment groups on ADCS-ADL, 1.6 (95% CI -0.8, 3.9); NPI total, 1.5 (95% CI -1.1, 4.1); MMSE, 0.4 (95% CI -0.6, 1.3); or QUARC hippocampal volume change, 0.0 (95% CI -0.6, 0.5). Biomarker and other planned exploratory analyses are currently underway. For example, a post hoc exploratory, hypothesis-generating subgroup analyses of mild, ApoE4 carriers (N=87) and mild, ApoE4 non-carriers (N=47) revealed nonsignificant numerical differences at week 48 on ADAS-Cog11 of -0.8 (95% CI -3.25, 1.61; p=0.504) and -1.3 (95% CI -5.82, 3.20; p=0.561), respectively. Safety findings included at least 1 AE in 82% of Tro treated participants vs. 67.8% for Pbo, most of mild or moderate intensity; at least 1 serious adverse event in 13.5% Tro vs. 8.2% Pbo; and withdrawals due to an AE in 9% Tro vs. 1.8% Pbo. The most common treatment emergent AEs (incidence of TEAEs \geq 5% and Tro > Pbo) were: Fall (Tro 10.7% vs. Pbo 7.0%), Urinary Incontinence (Tro 9.6% vs. Pbo 7.6%), Diarrhea (Tro 9.0% vs. Pbo 3.5%), Decreased Appetite (Tro 9.0% vs. Pbo 1.2%), Weight Decreased (Tro 9.0% vs. Pbo 1.8%), Edema Peripheral (Tro 5.6% vs. Pbo 1.2%), and Anxiety (Tro 5.1% vs. Pbo 4.1%). Incidence of liver enzyme increases, ALT >3x ULN \leq 5x ULN, 1.7% Tro vs. 0% Pbo; ALT >5x ULN, 0.6% Tro vs. 0% Pbo; AST >3x ULN \leq 5x ULN, 0.6% Tro vs. 0% Pbo; and AST >5x ULN, 0% Tro vs. 0% Pbo.

ROC14- BRAINSHUTTLE AD: A PHASE IB/IIA MULTIPLE ASCENDING DOSE STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RG6102 IN PARTICIPANTS WITH PRODROMAL OR MILD-TO-MODERATE ALZHEIMER'S DISEASE. Luka Kulic, Annamarie Vogt, Fabien Alcaraz, Philip Barrington, Maddalena Marchesi, Gregory Klein, Ruth Crony, David Agnew, João A Abrantes, Paul Jordan, Hanno Svoboda (*F. Hoffmann-La Roche Ltd - Basel (Switzerland)*)

Background: RG6102 (RO7126209) is a bispecific 2+1 monoclonal antibody (mAb) under development for the treatment of Alzheimer's disease (AD). It combines the anti-amyloid beta antibody gantenerumab with a transferrin receptor 1 (TfR1) binding "Brain Shuttle" module, enabling active receptor-mediated transport across the blood-brain barrier. In preclinical studies in nonhuman primates, RG6102 showed substantially improved exposure compared with gantenerumab (6- to 17-fold increase in the steady-state brain area under the curve), as well as a more widespread distribution in the brain. In amyloid plaque-depositing amyloid precursor protein transgenic mice, chronic treatment with a murine RG6102 surrogate led to superior target engagement and amyloid plaque clearance compared with gantenerumab. Importantly, in a recent first-in-human Phase (Ph) Ia single ascending dose study of RG6102 in healthy young male volunteers, there was a markedly increased cerebrospinal fluid (CSF)/plasma ratio for RG6102 compared with typical mAbs (0.5–1.2% vs. 0.1–0.2%). Whether increased and more widespread brain penetration of RG6102 will ultimately translate into faster and more extensive amyloid plaque clearance in the clinic, is currently under evaluation in the

ongoing Ph Ib/IIa Brainshuttle AD study (NCT04639050) in participants with prodromal or mild-to-moderate AD. **Objectives:** To describe the study design for the Brainshuttle AD study, investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of RG6102 following intravenous infusion in participants with prodromal or mild-to-moderate AD. **Methods:** This is a 28-week, randomized, global, multicenter, double-blind, placebo-controlled, parallel-group Ph Ib/IIa study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics of RG6102. Multiple-ascending intravenous doses of RG6102 are being administered once every 4 weeks to patients aged 50 to 85 years with prodromal or mild-to-moderate AD, who are amyloid positive based on amyloid positron emission tomography (PET). The study consists of a screening period (up to 12 weeks, including a one-week baseline period), a double-blind treatment period (28 weeks), and a safety follow-up period (28 weeks). The study uses a staggered parallel-group design, with participants recruited in four planned sequential dose cohorts (cohorts 1 to 4) with up to 120 participants randomized to receive either RG6102 or placebo. Sentinel dosing is being applied to each cohort. The primary objective of Brainshuttle AD is to evaluate the safety and tolerability of RG6102. Adverse events, including dose-limiting adverse events, are being recorded for up to 56 weeks. Secondary outcome measures include the change from baseline in brain amyloid load as measured by amyloid PET (time frame: baseline, week 12 [Cohorts 3 and 4 only], week 28), plasma concentration of RG6102 (time frame: up to 32 weeks), CSF concentration of RG6102 (time frame: baseline, week 25), and incidence of anti-drug antibodies to RG6102 (time frame: up to 56 weeks). Among the exploratory endpoints, Brainshuttle AD will evaluate the clinical effect of multiple doses of RG6102 on clinical outcome measures (including Clinical Dementia Rating-Sum of Boxes) as well as on various pharmacodynamic biomarkers (blood, CSF, and neuroimaging). **Results:** Recruitment for the Brainshuttle AD study launched in December 2020 and is currently ongoing. **Conclusion:** The Brainshuttle AD study will evaluate the safety and tolerability profile of RG6102, and establish whether faster and more extensive amyloid plaque clearance in participants with AD can be achieved through active TfR1 receptor-mediated transcytosis of an anti-amyloid mAb to the brain. **Disclosures:** HS is a full-time employee of and owns stock in F. Hoffman-La Roche Ltd. AV is a full-time employee of and owns stock options in F. Hoffman-La Roche Ltd. PB is a Contractor of F. Hoffman-La Roche Ltd. LK is a full-time employee and owns stock in F. Hoffman-La Roche Ltd. RC is a full-time employee of F. Hoffmann-La Roche Ltd. GK is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd. FA is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd. DA is a full-time employee of F. Hoffmann-La Roche Ltd. MM, JAA, and PJ are full time employees of F. Hoffman-La Roche Ltd and may own company stock/stock options.

ROC15- PK/PD MODELING FRAMEWORK TO INFORM THE CLINICAL DEVELOPMENT OF RG6102, AN AMYLOID-TARGETING INVESTIGATIONAL DRUG WITH ENHANCED BRAIN PENETRATION PROPERTIES. João A Abrantes, Hans Peter Grimm, Carsten Hofmann, Simon Buatois, Sébastien Jolivet, Nicolas Frey, Hanna Silber Baumann, Hanno Svoboda, Luka Kulic (*Roche Innovation Center - Basel (Switzerland)*)

Background: RG6102 (RO7126209) is a bispecific 2+1 monoclonal antibody (mAb) under development for the

treatment of Alzheimer's Disease (AD). It combines the anti-amyloid beta (A β) antibody gantenerumab with a "Brain Shuttle" module that binds to the transferrin receptor 1 (TfR1), facilitating transport across the blood-brain barrier. In a recent first-in-human Phase (Ph) Ia adaptive single ascending dose study of RG6102 in healthy young volunteers (NCT04023994), there was a markedly increased cerebrospinal fluid (CSF)/plasma ratio for RG6102 compared with typical mAbs. Currently, RG6102 is under evaluation in the ongoing Ph Ib/Ia Brainshuttle AD study (NCT04639050) in participants with prodromal or mild-to-moderate AD. Modeling and simulation techniques were applied to the early clinical development of RG6102, which was facilitated by participation in the US Food and Drug Administration (FDA) model-informed drug development (MIDD) paired meeting pilot program. The interactions with the FDA took place before and after the Ph Ia study data were available. **Objectives:** The objective of this work was to inform the early clinical development of RG6102 using a pharmacokinetic (PK)/pharmacodynamic (PD) model-based framework by: 1) combining the preclinical PK data for RG6102 with the PK/PD data for gantenerumab to inform the Ph Ia study design, and; 2) updating the modeling framework with clinical data from the Ph Ia study to inform the Ph Ib/Ia Brainshuttle AD study design. **Methods:** Modeling was used to inform the design of the clinical studies through multiple learn-confirm iterations. In the first iteration, for learning, no clinical data for RG6102 were available so a PK model was developed to characterize the concentration-time course of RG6102 and gantenerumab in plasma, CSF, and brain following a single intravenous (IV) dose in nonhuman primates (NHP; N=30). The PK parameters were translated to humans and connected to a clinical population PK/PD model of A β removal, originally built for gantenerumab. In the second iteration, for confirming, the model projections for humans were compared with emerging plasma and CSF PK data from a Ph Ia study in healthy volunteers (IV doses 0.1–7.2 mg/kg; N=26), and the PK/PD model was updated with the human data. In the third iteration, for learning, the model was used to inform the design of the Ph Ib/Ia study in patients by projecting the A β removal expected for a range of dosing regimens. Advice from the FDA MIDD pilot meeting program was integrated into the modeling framework and the process of decision-making. **Results:** The PK of RG6102 in NHP plasma was captured by a 2-compartment disposition model. The PK in CSF and various brain regions was well captured with 1-compartment models. A higher distribution of RG6102 to brain tissues compared with gantenerumab was found and quantified. Simulations were used to inform the Ph Ia study dose selection (dose range 0.1–7.2 mg/kg) by comparing the projected brain exposure of RG6102 with that of gantenerumab. Plasma exposure in cohort 1 of the Ph Ia study was lower than the model projected from the NHPs, which was likely due to the higher affinity of RG6102 to the TfR1 in humans compared with the NHPs. Therefore, the dose was increased 4-fold in the second cohort, instead of 3-fold as initially planned. Based on the totality of PK data from the Ph Ia study, a plasma PK model was developed. The estimated systemic clearance was 2.0 L/day, which was faster than the typical range of clearance for monoclonal antibodies (0.2–0.5 L/day). The randomization of the CSF sampling times to 2 subgroups per dose group in the Ph Ia study enabled the model-based characterization of the concentration-time course of RG6102 in CSF (estimated CSF/plasma area under the curve [AUC] ratio: 0.6%). It is likely that the higher CSF distribution in comparison to typical IgGs is due to the affinity of RG6102 to TfR1 as well. Predictions for

the A β standardized uptake value ratio reduction following administration of repeated doses of RG6102 in AD patients will be presented using simulations from the model updated with human PK data. These PD predictions were used to inform the design for the Ph Ib/Ia multiple ascending dose study. **Conclusion:** A PK/PD modeling framework relying on learn-confirm iterations informed the early clinical development trials of RG6102 by combining information across compounds and species. In particular, a model-based approach was valuable to guide first-in-human dosing and inform the design of the first study in healthy volunteers as well as the first study in patients with AD. **Disclosures:** Authors are full time employees of F. Hoffmann-La Roche Ltd and may own stock/stock option. L.K. owns stock in F. Hoffmann-La Roche Ltd.

ROC16- RESULTS OF A PHASE 1, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED, SINGLE-ASCENDING-DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF BIIB076 IN HEALTHY VOLUNTEERS AND SUBJECTS WITH ALZHEIMER'S DISEASE. Elena Ratti, Hua Carroll, Lin Lin, Carrie Rubel, Alexis Ang, John O'gorman, Matthew Ross, Kumar Kandadi Muralidharan, Danielle Graham, Julie Czerkowicz, Ellen Huang, Jaren Landen, Samantha Budd Haeberlein (*Biogen - Cambridge (United States)*)

Background: Amyloid and tau pathology represent pathological hallmarks of Alzheimer's disease. Tau pathology in the form of neurofibrillary tangles develops in a stereotypical and predictable spatiotemporal pattern of progression, which correlates with cognitive decline as tau pathology spreads across cortical regions. Tau-lowering therapies might be beneficial to delay or prevent progression of the disease. **Objectives:** This first in human, single ascending dose study (NCT03056729) evaluated the safety, tolerability, and pharmacokinetics (PK) of BIIB076, a human monoclonal antibody that binds to human mid-region tau, in healthy volunteers (HVs) and participants with Alzheimer's disease. **Methods:** A total of 40 HVs (age criteria 50-75) and 8 Alzheimer's disease participants (age criteria 50-80, amyloid positive, global Clinical Dementia Rating Scale (CDR) criteria 0.5-1, Mini-Mental State Examination (MMSE) criteria (18-30) were planned to receive treatment with BIIB076 or placebo administered intravenously. Five cohorts of HVs and one cohort of participants with Alzheimer's disease, were planned. Participants within each cohort were randomized to receive a single infusion of BIIB076 or placebo in a 6:2 ratio. Participants were evaluated for 20 weeks after dosing with clinical, electrocardiogram, and laboratory assessments. Incidence of adverse events (AEs) and anti-BIIB076 antibodies in serum were assessed. Serum and cerebrospinal fluid (CSF) BIIB076 concentrations were measured. Mid-region unbound tau was measured in CSF. **Results:** A total of 38 HVs (age 50–72, 21 women) and 8 Alzheimer's disease participants (age 56–76, 2 women, MMSE 19-30) received treatment with BIIB076 or placebo administered intravenously. The overall AE incidences were 59% (16/27) and 82% (9/11) in the HVs BIIB076 and placebo groups, respectively, and 83% (5/6) and 100% (2/2) for participants with Alzheimer's disease in the BIIB076 and placebo groups, respectively. The most frequently reported AEs ($\geq 5\%$ in the pooled BIIB076 group) in HVs were headache, nausea, chills, post lumbar puncture syndrome, procedural pain, diarrhea, and dizziness. Among these AEs, those which occurred in at least 5% more HVs receiving BIIB076 than placebo were chills, procedural pain, and diarrhea. The only

AEs reported in more than 1 participant with Alzheimer's disease were headache (2/6 in the BIIB076 group and 2/2 in the placebo group) and depression (1/6 in the BIIB076 group and 1/2 in the placebo group). Most AEs were mild or moderate in intensity. Three HVs experienced severe AEs of chills, headache, nausea, dizziness, and syncope. The event of syncope was also a serious adverse event (SAE). All severe AEs occurred in the highest dose tested in HVs, and all were considered related to study treatment by the Investigator. Non-serious AEs consistent with infusion related reactions were reported in 8 HVs and 3 participants with Alzheimer's disease who received BIIB076, more of which were observed in the higher BIIB076 dose groups tested in HVs and Alzheimer's disease than in the lower dose groups. No anti-BIIB076 antibodies were detected. Approximately dose-proportional increase in C_{max} and slightly less than dose-proportional increase in AUC_{inf} were observed across dose groups in serum of HVs; similar serum PK was observed in HVs and participants with Alzheimer's disease receiving the same dose, while CSF exposure observed at 7 and 28 days post dose on average appeared higher in participants with Alzheimer's disease. Reductions from baseline in unbound mid-region tau in CSF were observed in some HV cohorts and in participants with Alzheimer's disease (approximately 11 to 88% mean reduction at Day 7 and 7 to 67% mean reduction at Day 28 in HV and approximately 50% sustained mean reduction at Days 7 and 28 in Alzheimer's disease). **Conclusions:** A single dose of BIIB076 was demonstrated to be tolerated, had a dose-dependent PK profile and reduced unbound mid-region tau in CSF in HVs and Alzheimer's disease participants. **Key Words:** Alzheimer's disease; pharmacokinetics; tau; first in human clinical trial. **Conflicts of Interest:** ER is an employee of Biogen

ROC17- ACI-35.030, A NOVEL ANTI-PHOSPHO-TAU VACCINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE: INTERIM PHASE 1B/2A DATA ON SAFETY, TOLERABILITY AND IMMUNOGENICITY. Johannes Streffer^{1, 2}, Bénédicte Le¹, Olivier Sol¹, Marija Vukicevic¹, Emma Fiorini¹, Eva Gollwitzer¹, Valérie Hliva¹, Julien Mermoud¹, David Hickman¹, Julian Gray¹, Antonio Melo Dos Santos¹, Nicolas Piot¹, Julien Rongère¹, Andrea Pfeifer¹, Marie Kosco-Vilbois¹, Philip Scheltens³ (1. *Ac Immune - Lausanne (Switzerland)*, 2. *Department of biomedical sciences, University of Antwerp - Antwerpen (Belgium)*, 3. *Vumc - Amsterdam (Netherlands)*)

Background: Tau neurofibrillary tangles (NFTs) represent one of the key pathological hallmarks of Alzheimer's disease (AD). The density of NFTs correlates well with cognitive status, while changes in Tau PET are closely associated with the rate of cognitive decline. It is hypothesized that Tau spreading throughout the brain involves extracellular phosphorylated Tau (pTau) species. Immunotherapy offers the potential to interfere with the spreading of Tau neuropathology and prevent or reduce cognitive impairment. In particular, vaccination against pTau represents an attractive strategy for long-term treatment and potentially prevention of AD as well as other Tauopathies. **Objectives:** ACI-35.030 is a first-in-class liposomal anti-pTau vaccine candidate for the treatment of AD which is currently assessed in a Phase 1b/2a study (NCT04445831). We report interim results of immunogenicity as well the safety and tolerability. **Methods:** This is a currently ongoing multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability and immunogenicity of different doses of pTau vaccines including ACI-35.030, as primary study objectives in subjects with early AD. Each dose-level sub-

cohort comprises 8 subjects randomized in a 3:1 active/placebo ratio. Study population is characterized by 50-75 years old male and female subjects with a diagnosis of mild AD or MCI due to AD according to NIA-AA criteria, CSF Aβ42 levels consistent with AD pathology, a CDR global score of 0.5 or 1 and an MMSE score ≥ 22. Subjects received intramuscular injections of ACI-35.030 or placebo at weeks 0, 8, 24 and 48. **Results:** To date, 24 subjects have been randomized in the 3 dose-level sub-cohorts. ACI-35.030 was safe and well tolerated with no vaccine-relevant safety concerns observed to date. A robust polyclonal IgG antibody response consisting of high anti-pTau-specific IgG titers was observed shortly after the first injection in the serum of 100% of subjects treated with the two lowest active dose-levels. This high and specific anti-pTau IgG response showed a strong preference for pathological pTau in all actively treated early AD subjects. No immune response was observed in placebo subjects. **Conclusions:** ACI-35.030 was safe, well tolerated, and induced a potent antigen-specific antibody response with the first 2-dose levels; remarkable for a vaccine against a self-protein in an aged population. Based on these data, an expansion of the second dose level sub-cohort and dose-escalation to the 3rd dose-level sub-cohort have been initiated to generate a larger dataset of safety, tolerability and immunogenicity in order to prepare for subsequent clinical steps.

ROC18- CHARACTERIZATION OF THE DISEASE COURSE DURING TRANSITIONING FROM MCI DUE TO AD TO DEMENTIA PREDICTS FOLLOW-UP PERFORMANCE AND REVEALS POSSIBLE CONTRIBUTION OF REDUCED HIPPOCAMPAL ATROPHY ON THE INTERVENTION EFFECT IN THE LIPIDIET TRIAL. Tobias Hartmann^{1,2}, Alina Solomon^{3,4,5}, Pieter Visser^{6,7}, Floor Van Oudenhoven^{8,9,10}, Dimitris Rizopoulos^{8,9}, Suzanne Hendrix¹¹, Kaj Blennow^{12,13}, Miia Kivipelto^{3,4,5}, Hilka Soyninen^{3,14} (1. *Deutsches Institut Für Demenz Prävention (didp), Medical Faculty, Saarland University - Homburg (Germany)*, 2. *Department of Experimental Neurology, Saarland University - Saarbrücken (Germany)*, 3. *Department Of Neurology, Institute Of Clinical Medicine, University Of Eastern Finland - Kuopio (Finland)*, 4. *Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institute - Huddinge (Sweden)*, 5. *Clinical Trials Unit, Theme Aging, Karolinska University Hospital Kuopio - Huddinge (Sweden)*, 6. *Department Of Psychiatry And Neuropsychology, Alzheimer Center Limburg, University Of Maastricht - Maastricht (Netherlands)*, 7. *Department of Neurology, Alzheimer Center, VU University Medical Center - Amsterdam (Netherlands)*, 8. *Department Of Biostatistics, Erasmus Mc - Rotterdam (Netherlands)*, 9. *Department of Epidemiology, Erasmus MC - Rotterdam (Netherlands)*, 10. *Danone Nutricia Research, Utrecht - Utrecht (Netherlands)*, 11. *Pentara Corporation, Milcreek - Millcreek (United States)*, 12. *Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At University Of Gothenburg - Mölndal (Sweden)*, 13. *Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden)*, 14. *Neurocenter, Department of Neurology, Kuopio University Hospital - Kuopio (Finland)*)

Background: LipiDiDiet is a 6 year, randomized, double-blind, placebo-controlled clinical trial, followed by a 2-year open-label period, investigating the specific multinutrient combination Fortasyn Connect (Souvenaid) in prodromal Alzheimer's Disease (AD)/mild cognitive impairment (MCI). When participants started the trial, they were not taking any AD drug. Once individual participants progressed to mild

dementia, they were provided AD medication and/or open-label Souvenaid (together referred to as open-label medication) and could continue in the trial. Time to open-label medication can therefore be considered a proxy for disease progression. This is the first RCT investigation during the very transition phase from prodromal AD to AD dementia using Fortasyn Connect intervention. **Objectives:** Here we explore the patterns of change of cognitive and functional performance in the active group after switch to open-label medication. Our goals are to further examine the cognitive outcome parameters to understand the relation between the disease course during the MCI stage and the following dementia stage in the Fortasyn Connect treated and placebo control group. We also aim to statistically estimate the underlying mechanism of the intervention, and to understand how the intervention affects the time to open-label medication. To this end, we report on patterns of change in performance in the active group after switch to open-label medication, and we estimate how the intervention affects the risk of starting open-label medication use, both directly and indirectly, through the slowing of the hippocampal volume decline. **Methods:** Prodromal AD participants (n=311) were randomized to receive either active product (125ml once-a-day drink; Fortasyn Connect) or a calorie-matched placebo control drink. Main outcomes included Neuropsychological Test Battery (NTB) composites, Clinical Dementia Rating-Sum of Boxes (CDR-SB), incidence of dementia, and brain atrophy measures and predefined analyses were performed on the modified intention-to-treat (mITT) by censoring data collected after initiation of open-label medication. Additional exploratory analyses assessed the intervention effects on dementia diagnosis over time, including an analysis of the overall treatment effect on the hazard of dementia diagnosis as estimated from the joint model for CDR-SB as longitudinal outcome, and 2) a Cox regression analyses for time to dementia, corrected for baseline MMSE. Furthermore, we employed a new type of multivariate joint model in which two clinical outcomes are allowed to be associated with time to open-label medication and also to affect each other. This is used to estimate how the intervention affects the risk of starting open-label medication use, both directly and indirectly, e.g. through hippocampal volume or other measures. **Results:** 162 participants completed a 36-month intervention period. As expected, baseline performance assessed as MMSE or CDR-SB score predicted the general cognitive course for both groups and did not predict regular study drop-out. Notably, the pattern of acquired cognitive and functional benefits in the active group as observed in the mITT analysis seemed to continue following initiation of open-label medication. Total progression to dementia showed no significant between-group differences over 3 years, but there were fewer diagnoses in the active vs. control group (n=4 vs. n=11) in the third year of the trial. The latter was further supported by a reduction in the time-varying hazard ratio and pointwise 95% confidence interval from baseline to year 3 (1.28 [0.73 to 2.01] to 0.67 [0.28 to 1.23] as estimated in the joint model and a hazard ratio for time to dementia diagnosis of 0.84 (0.59 to 1.19) in the Cox regression analysis. The multivariate joint model estimated a strong intervention effect on hippocampal volume (0.071 SD [95% CI: 0.011 to 0.129]) less reduction in hippocampal volume per year in the active group than in the control group), and a strong association between hippocampal volume and the risk to start open-label medication (-0.416 [95% CI: -0.710 to -0.118]); which means an increase of one SD in the trajectory of hippocampal volume is estimated to decrease the risk of open-label medication use by 34%. **Conclusions:** This first investigation on the effects of Fortasyn

Connect during transition from MCI due to AD to dementia suggests that the relative cognitive/functional performance trajectory, apparently acquired during intervention in the prodromal stage of the disease, persists during open-label treatment in mild AD dementia. This interpretability is limited by the inherent open-label bias of the transition medication. Furthermore, our results suggest that part of the intervention effect is mediated through the reduction of hippocampal atrophy. Funded by EU FP7 211696, EU JPND EURO-FINGERS

ROC19- PHASE 2 STUDY OF TILAVONEMAB, AN ANTI-TAU ANTIBODY, IN EARLY ALZHEIMER'S DISEASE. Hana Florian, Deli Wang, Qi Guo, Ziyi Jin, Nahome Fisseha, Beatrice Rendenbach-Mueller (*Abbvie, Inc. - North Chicago (United States)*)

Background: Alzheimer's disease (AD) is pathologically defined as the accumulation of extracellular amyloid- β ($A\beta$) and intracellular tau. $A\beta$ accumulation has an early role in the pathology of AD. In contrast, tau accumulation is closely associated with cognitive decline and is generally thought to play a role at later stages of disease progression [1]. Anti tau therapies may potentially be more efficacious in slowing disease progression among patients who are already showing clinical symptoms of AD. Tilavonemab is an immunoglobulin G4 monoclonal antibody that binds to the N-terminus of human tau, targets soluble extracellular tau in the brain, and is currently being developed as a treatment for early AD. **Objectives:** To present the results of a phase 2 study investigating the efficacy of tilavonemab in slowing disease progression and long-term safety of tilavonemab in patients with early AD. **Methods:** This 96-week, randomized, double-blind, placebo-controlled, global phase 2 study evaluated the efficacy and safety of tilavonemab in patients with early AD (NCT02880956). The study enrolled male and female patients (aged 55–85 years) who met the clinical criteria for early AD and had Clinical Dementia Rating (CDR)-Global Score of 0.5, Mini-Mental State Examination (MMSE) score of 22 to 30, Repeatable Battery for the Assessment of Neuropsychological Status-Delayed Memory Index (RBANS-DMI) score of 85 or lower, and a positive amyloid PET scan. Patients were randomized (1:1:1) to receive 1 of 3 doses of tilavonemab (300 mg, 1000 mg, or 2000 mg) or placebo via intravenous infusion every 4 weeks. The primary efficacy endpoint was the change from baseline up to week 96 in CDR-Sum of Boxes (CDR-SB) score. Secondary efficacy outcomes included change from baseline in the Alzheimer Disease Assessment Scale (14 Item) Cognition portion (ADAS-Cog-14) total score, RBANS total scale score, MMSE total score, Functional Activities Questionnaire (FAQ) total score, and the 24 item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment (ADCS-MCI-ADL-24) total score. Exploratory biomarker endpoints included change from baseline in plasma concentrations of neurofilament light chain (NFL) and volumetric magnetic resonance imaging (vMRI) of the medial temporal lobe and hippocampus. Safety assessments included monitoring of adverse events (AEs) and MRIs. **Results:** The study enrolled 453 patients with a mean (SD) age of 71.3 (7.0) years; 81% were > 65 year of age, 52% were female, and 97% were White. Mean (SD) age at onset of symptoms of cognitive impairment was 67.1 (7.0) years, 320 (70.6%) patients were receiving AD medication, and 342 (75.5%) patients were carriers of the apolipoprotein E ϵ 4 allele. At baseline, the mean (SD) CDR-SB score was 3.0 (1.2), RBANS total scale score was 71.7 (12.4), ADAS Cog 14 total score was 26.5 (7.4),

MMSE total score was 24.4 (2.9), FAQ total score was 7.8 (5.4), and ADCS MCI-ADL 24 total score was 54.6 (7.4). Baseline demographics and disease characteristics were comparable across all 4 treatment groups. Of the 453 randomized patients, 337 were treated with tilavonemab (300 mg, n = 108; 1000 mg, n = 116; 2000 mg, n = 113) and 116 received placebo. Mean CDR-SB score worsened through week 96 for all treatment groups; the least squares mean change from baseline at week 96 in CDR-SB score with tilavonemab compared with placebo (300 mg, -0.07; 1000 mg, -0.05; 2000 mg, 0.16) was not significantly different for any tilavonemab dose (all $P \geq .05$). Similarly, through week 96, tilavonemab did not demonstrate significant improvement in patient cognition, as assessed by ADAS-Cog-14 total score, RBANS total scale score, and MMSE total score, or improvement in function, as assessed by FAQ total score and ADCS-MCI-ADL-24 total score. There was no evidence that tilavonemab had an effect on plasma NFL levels or medial temporal lobe volume measured by vMRI. Although there was some evidence of a favorable effect of tilavonemab on hippocampal volume with less decrease from baseline at higher dose levels, the test for trend did not reach nominal significance. A treatment emergent AE was reported for 414 (91.4%) patients, and 125 (27.6%) patients experienced an AE with a reasonable possibility of being related to study drug. The incidence of any AE was generally comparable across the tilavonemab treatment groups and the placebo group. A serious AE was reported for 84 (18.5%) patients and 20 (4.4%) patients discontinued study drug due to an AE. There were 6 deaths during the study. The most common (> 10%) AEs among patients receiving tilavonemab (any dose) were fall (18.7%), headache (12.2%), dizziness (11.0%), upper respiratory tract infection (11.0%), nasopharyngitis (10.4%), urinary tract infection (10.4%), and diarrhea (10.1%). MRI safety findings were comparable among the tilavonemab dose and placebo groups. **Conclusion:** Although generally safe and well tolerated among patients in the study, tilavonemab did not demonstrate efficacy in treating patients with early AD. **References:** 1. Holtzman DM, et al. *Sci Transl Med.* 2011;3:77sr1.

ROC20- THE EPIGENETIC MODULATOR APABETALONE DECREASES NEUROINFLAMMATION IN BLOOD BRAIN BARRIER CELL MODELS AND LPS-TREATED MICE. Sylwia Wasiak¹, Li Fu¹, Emily Daze¹, Dean Gilham¹, Brooke Rakai¹, Stephanie Stotz¹, Laura Tsujikawa¹, Christopher Sarsons¹, Ravi Jahagirdar¹, Norman Wong¹, Michael Sweeney², Jan Johansson², Ewelina Kulikowski¹ (1. *Resverlogix Corp - Calgary (Canada)*, 2. *Resverlogix Corp - San Francisco (United States)*)

Background: Vascular disease and diabetes mellitus increase the risk of developing Alzheimer's disease and vascular cognitive impairment. Pro-inflammatory signaling in brain endothelial cells contributes to blood brain barrier (BBB) breakdown allowing infiltration of the brain parenchyma by blood derived cytokines and immune cells. Increased immune activity in the brain can be detrimental especially when accompanied by chronic proinflammatory signaling. Bromodomain and extraterminal domain (BET) proteins are epigenetic readers that activate cytokine-dependent transcription in monocytes and endothelial cells in chronic vascular inflammation models. Apabetalone (RVX-208) is a clinical-stage small molecule BET inhibitor that recently showed favourable effects on cognition in cardiovascular patients with type 2 diabetes. We hypothesize that targeting BETs with apabetalone may reduce brain endothelial inflammation

that accompanies neurodegenerative disorders and cognitive dysfunction. **Objectives:** To investigate the impact of the epigenetic inhibitor apabetalone on inflammatory markers in brain endothelial cells and monocytes in vitro and in mouse brain. **Methods:** Brain microvascular endothelial hCMEC/D3 monolayers grown on plastic or suspended inserts were activated with 10 ng/mL TNF α +IFN γ and co-treated with 5-25 μ M apabetalone or vehicle for 4-24h. Cytokine secretion from apical and basolateral membranes was measured via multiplex immunoprofiling (24h). Cell surface abundance of adhesion proteins was assessed by FACS. Chemokine-induced THP-1 migration was measured in suspended filter assays. THP-1 cell adhesion to hCMEC/D3 monolayers was measured in static cell adhesion assays. C57BL/6 mice treated with 150 mg/kg apabetalone for 7 days received 10 mg lipopolysaccharide (LPS) intraperitoneally. Brain gene expression was measured on day 8 by real-time PCR. **Results:** Upon TNF α +IFN γ stimulation, filter-grown brain endothelial cell monolayers secrete vascular endothelial growth factors and pro-inflammatory molecules in a polarized manner. Apabetalone bilaterally reduced secretion of proinflammatory cytokines including MCP-3, fractalkine, GM-CSF, MCP-1, IL-6, IL-8, IP-10 and RANTES (40% to 90%, 24h). Apabetalone also downregulated the abundance of VCAM-1 (60%, 4h), an endothelial cell surface protein involved in monocyte adhesion. Consequently, apabetalone-treated hCMEC/D3 monolayers showed reduced interactions with THP-1 monocyte-like cells (60%, 4h). Conversely, a 48h pre-treatment of THP-1 cells with apabetalone lessened in vitro chemoattraction towards soluble chemokines MCP-1 (60%) and RANTES (55%) as well as THP-1 cell adhesion to cytokine-activated hCMEC/D3 monolayers (60%). This in vitro reduction in monocyte pro-inflammatory behaviour was likely due to reduced expression of chemokine receptors CCR1, CCR2, CCR5, CXCR2 and CX3CR1, and cognate endothelial adhesion receptors ITGAL and ITGA4 (30 to 75%). In a systemic inflammation mouse model, apabetalone treatment countered LPS-induced transcription of leukocyte and endothelial markers Ccr2, Ccr5, Itgal, Itga4 and Sele in the brain (40 to 95%), consistent with decreased endothelial inflammation and immune cell activity in vivo. **Conclusions:** Apabetalone decreases proinflammatory activation of the neuroendothelium and monocyte activity in vitro and in mice, potentially reducing neuroinflammation. These findings provide mechanistic insights to the beneficial effects of apabetalone on cognition that were recently demonstrated in a phase 3 clinical trial (BETonMACE): diabetic coronary artery disease patients with a baseline MoCA scores <22 experienced a significant 1.8 unit improvement in MoCA scores following apabetalone treatment versus placebo (p=0.02).

ROC21- EFFECT OF PLASMA EXCHANGE WITH ALBUMIN REPLACEMENT IN ALZHEIMER'S TREATMENT ON ABILITY TO PERFORM ACTIVITIES OF DAILY LIVING (ADL). Richard B Lipton¹, Walter F Stewart², Lauren Podger³, David Gomez-Ulloa⁴, M Chris Runken⁵, Miquel Barcelo⁴, Carlota Grifols⁴, Daniel Serrano⁶ (1. *Albert Einstein College Of Medicine - New York, Ny (United States)*, 2. *Medcurio Inc - Oakland, Ca (United States)*, 3. *Open Health Group - Marlow (United Kingdom)*, 4. *Grifols - Sant Cugat Del Vallès (Spain)*, 5. *Grifols Sna - Research Triangle Park, Nc (United States)*, 6. *Open Health Group - Bethesda, Md (United States)*)

Background: Alzheimer's Management By Albumin Replacement (AMBAR) is a multicenter, randomized, blinded and placebo-controlled, Phase 2b/3 clinical trial, previously

reported elsewhere (Boada et al., 2020). Change in the ability to perform activities of daily living (ADLs) was a co-primary endpoint, measured by the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) scale. Functional impairment, a key diagnostic criterion of Alzheimer's disease (AD), encompasses the ability to perform daily instrumental activities such as meal preparation, household chores, shopping, or driving, which are typically impaired during the transition from late mild cognitive impairment (MCI) to mild AD as well as basic activities such as dressing, bathing, and toileting, or eating, which are typically impaired in the moderate-to-severe stages of AD. Increased functional impairment is associated with higher rates of institutionalization and hospitalization, and increased risk and severity of apathy, anxiety, and depression and other like conditions (Hope et al., 1998; Ballard et al., 2001). **Objectives:** To assess the impact of plasma exchange with albumin replacement on performance of ADLs in people with AD. To explore differences in the magnitude of AMBAR efficacy on ADLs by AD severity. **Methods:** ADCS-ADL efficacy was compared between two analysis populations within AMBAR: 1) the full analysis set (FAS); 2) patients with mild-to-moderate-spectrum AD based on pre-defined thresholds for both Clinical Dementia Rating-Sum of Boxes (CDR-SB 4 < CDR-SB ≤ 15.5) and Mini Mental State Examination (MMSE < 20). Change from baseline to final visit (month 14) in total ADCS-ADL scores for placebo and pooled treatment groups was modelled using a Mixed Model for Repeated Measures (MMRM). Baseline age, ADCS-ADL, and MMSE scores were included as covariates. **Results:** The FAS included 80 patients in the placebo arm and 242 in the pooled treatment arm at baseline while the mild-to-moderate-spectrum AD subgroup included 13 patients in the placebo arm (16% of FAS) and 47 in the pooled treatment arm (19% of FAS) at baseline. Within the FAS, change from baseline to final visit marginal mean was -6.5 for placebo and -3.2 for pooled treatment (difference: 3.3, P=0.0439). Within the mild-to-moderate-spectrum subgroup, change from baseline to final visit marginal mean was -19.4 for placebo and -6.7 for pooled treatment (difference: 12.8, P=0.027). There was greater separation between placebo and pooled treatment at the final visit for the mild-to-moderate-spectrum AD subgroup compared with the FAS. **Conclusion:** In comparison with placebo, plasma exchange followed by albumin replacement therapy is associated with significantly less decline in ADLs as measured by the ADCS-ADL score. The magnitude of this effect is greater in mild-to-moderate-spectrum AD relative to FAS; indicating that the benefit of treatment on function is most evident in this subpopulation. **References:** Boada M, López OL, Olazarán J, et al. A randomized, controlled clinical trial of plasma exchange with albumin replacement for Alzheimer's disease: Primary results of the AMBAR Study. *Alzheimers Dement.* 2020 Oct;16(10):1412-1425; Ballard C, O'Brien J, James I, et al. Quality of life for people with dementia living in residential and nursing home care: the impact of performance on activities of daily living, behavioral and psychological symptoms, language skills, and psychotropic drugs. *International Psychogeriatrics.* 2001 Mar 1;13(1):93; Hope T, Keene J, Gedling K, et al. Predictors of institutionalization for people with dementia living at home with a carer. *International journal of geriatric psychiatry.* 1998 Oct;13(10):682-90.

ROC22- BASELINE CHARACTERISTICS FOR CLARITY-AD: A PHASE 3 PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL-GROUP, 18-MONTH STUDY EVALUATING LECANEMAB (BAN2401) IN EARLY ALZHEIMER'S DISEASE. Shau Yu Lynch¹, Michelle Gee², Michio Kanekiyo¹, Tanya Bogoslovsky¹, June Kaplow¹, Shobha Dhadda¹, Michael Irizarry¹, David Li¹, Vicki Taylor², Mark Hodgkinson¹, Masaki Nakagawa³, Chad Swanson¹ (1. Eisai Inc - Woodcliff Lake (United States), 2. Eisai Ltd - Hatfield (United Kingdom), 3. Eisai Co., Ltd - Tokyo (Japan))

Background: According to the World Health Organization, approximately 50 million people suffer from dementia worldwide, and 60-70% of these cases are attributed to Alzheimer's disease (AD). The accumulation of soluble and insoluble aggregated A β peptides (oligomers, protofibrils, and fibrils) may initiate or potentiate AD pathology. Lecanemab (BAN2401) is a humanized IgG1 monoclonal antibody that preferentially targets soluble aggregated A β species (oligomers, protofibrils), with activity at insoluble fibrils. Recently, a large, 18-month phase 2 proof-of-concept (POC) study (BAN2401-G000-201; NCT01767311) using Bayesian adaptive design was conducted in 856 patients with mild cognitive impairment (MCI) due to AD and mild AD dementia (collectively defined as early AD patients [EAD]). Although the threshold for the primary Bayesian analysis at 12 months was not met, results from pre-specified 18-month frequentist analyses indicated that lecanemab treatment showed a consistent and clinically meaningful reduction in clinical decline and brain amyloid burden in patients with EAD at the highest dose (10 mg/kg biweekly). Based on the encouraging results from the phase 2 study, a phase 3 study (BAN2401-G000-301 [CLARITY AD], NCT03887455) was initiated to confirm the efficacy and safety of lecanemab in patients with EAD. **Objective:** To describe the baseline characteristics for currently randomized 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 EAD. Eligibility criteria include age 50 to 90 years old, MCI due to AD, or mild AD dementia with amyloid pathology confirmed by amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF). All patients are required to have objective impairment in episodic memory as indicated by at least 1 standard deviation below the age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (subscale) II. Eligible patients are randomized across 2 treatment groups (placebo and lecanemab 10 mg/kg biweekly) according to a fixed 1:1 schedule. Randomization is 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. During the core study, patients have the option to participate in one or more of the 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 of the study. The original randomization target was 1566 patients; however, to mitigate the loss of data associated with the COVID-19 pandemic, the target study sample size has been increased to 1766. The primary efficacy endpoint in the core study is change in the Clinical Dementia Rating-Sum-of-Boxes (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), AD Composite Score (ADCOMS) and AD Assessment Scale-Cognitive Subscale 14 (ADAS-Cog14). Safety is monitored throughout the study in a blinded manner by the sponsor and in an unblinded manner by an independent data safety monitoring committee. The open-label extension phase evaluates the long-term safety and tolerability of lecanemab 10 mg/kg biweekly in patients with early AD, including whether the long-term effects of lecanemab (as measured on clinical outcome measures and biomarkers) at the end of the core study is maintained over time in the extension phase. For this presentation, baseline clinical and demographic data for the currently randomized study are summarized descriptively. **Results:** As of a data cutoff of 08-Mar-2021, a total of 1795 subjects were randomized in CLARITY AD. The median age of subjects was 72 years (range: 50-90 years), with 80% of patients 65 years of age or older. Overall, 52% of subjects were female and 77% were Caucasian. Comparisons of the baseline characteristics of the study populations for the CLARITY AD study and the phase 2 POC study will be presented. **Conclusion:** Building on the findings from the lecanemab phase 2 study, the phase 3 CLARITY AD study is designed to confirm the clinical efficacy and safety of lecanemab versus placebo in patients with early AD. Baseline characteristics after randomization of 1795 subjects are consistent with previous studies and representative of an early AD population. **Conflict of Interest Statement:** All authors are employees of Eisai.

ROC23- A STEPWISE TIER-BASED APPROACH FOR DETERMINING PATIENT ELIGIBILITY IN CLARITY AD: A PHASE 3 PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO CONFIRM THE SAFETY AND EFFICACY OF LECANEMAB (BAN2401) 10 MG/KG BIWEEKLY IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE. Shau Yu Lynch¹, Michelle Gee², Michio Kanekiyo¹, Michael Smith³, Tanya Bogoslovsky¹, June Kaplow¹, Shobha Dhadda¹, Michael Irizarry¹, Vicki Taylor², Mark Hodgkinson¹, Masaki Nakagawa⁴, Chad Swanson¹ (1. Eisai Inc - Woodcliff Lake (United States), 2. Eisai Ltd - Hatfield (United Kingdom), 3. Worldwide Clinical Trials - Research Triangle (United States), 4. Eisai Co., Ltd - Tokyo (Japan))

Background: Identifying eligible patients is one of the biggest challenges of amyloid-modifying clinical trials in early Alzheimer's disease (EAD). Factors such as evidence of amyloid burden, clinical disease stage, medical comorbidities, concurrent medications, and study partner availability are the major contributors of low recruitment rates observed across AD clinical trials. An efficient screening method that excludes ineligible patients early during the screening process would therefore greatly reduce burden on both clinical sites and trial patients and allow the allocation of trial resources to eligible patients. Lecanemab (BAN2401) is a humanized IgG1 monoclonal antibody that preferentially targets soluble aggregated A β species (oligomers, protofibrils), with activity at insoluble fibrils. Results from a recent large 18-month phase 2 proof-of-concept (POC) study (BAN2401-G000-201; NCT01767311) indicated that treatment with lecanemab 10 mg/kg biweekly showed clinically meaningful reduction in cognitive decline and brain amyloid burden in patients with mild cognitive impairment (MCI) and mild AD (collectively defined as EAD). CLARITY AD (BAN2401-G000-301; NCT03887455) is a phase 3 placebo-controlled, double-blind study that evaluates the safety and efficacy of lecanemab

10 mg/kg biweekly in patients with EAD. The core study consists of a 60-day pre-randomization phase, an 18-month randomization phase, and a 3-month follow-up phase. The purpose of the 60-day pre-randomization phase is to establish patient eligibility using a stepwise tier-based approach. Using this approach, assessments that are less time-consuming and invasive occur at the beginning of the screening process such that patients who do not meet these criteria will be screen failed early. **Objective:** To evaluate the efficiency of the stepwise tier-based screening method utilized in the CLARITY AD study. **Methods:** To be eligible for the CLARITY AD study, patients must be 50 to 90 years old and diagnosed with MCI due to AD with intermediate likelihood or mild AD dementia based on NIA-AA criteria and confirmed with amyloid pathology (as determined by amyloid positron emission tomography [PET] or cerebrospinal fluid [CSF]). All patients are required to have objective impairment in episodic memory as indicated by at least 1 standard deviation below the age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (subscale) II. During the pre-randomization phase, eligibility assessments are organized into 5 progressive screening tiers and patients must meet all criteria within each tier before progressing to the following tier. The early screening tiers (Tiers 1 and 2) consist of psychometric measures (MMSE, WMS LMI and II, and CDR) and assessments of past and concurrent medical conditions and medications. MRI, baseline cognitive and safety measures, and confirmation of amyloid pathology by amyloid PET and/or CSF are placed in later screening tiers (Tiers 3-5). Patients who meet all eligibility criteria in the 5 screening tiers will be randomized in a 1:1 randomization schedule to receive either placebo or lecanemab 10mg/kg biweekly. Approximately 1766 patients will be randomized. **Results:** As of March 8, 2021, 6237 patients were screened, and 1795 patients were randomized. Data cleaning is currently ongoing. The overall screen failure rate was 71%, with approximately 50% of the screen failures at Tiers 1 and 2. Approximately only 20% of the screened subjects failed in the last three tiers of the screening period. The highest contributor to screen failure during the initial two screening tiers was the WMS LMII (>20% of the overall screening population). During Tiers 3-5, the highest screen failure rate occurred during the assessment of amyloid pathology by amyloid PET and/or CSF. Of the patients who underwent assessments for amyloid pathology, 30% of the patients were determined to be amyloid negative (representing approximately 10% of the overall screening population). A higher proportion of APOE4 carriers (82%) were amyloid positive compared with noncarriers (55%). These results are consistent with those observed in the phase 2 POC study as well as the elenbecestat phase 3 MissionAD studies. **Conclusion:** The stepwise tier-based approach utilized in the CLARITY AD study reduced trial burden on both clinical sites and patients by disqualifying approximately 70% of non-eligible patients early in the screening process. This approach eliminates unnecessary, time-consuming, and invasive procedures in these patients, allowing for sites to focus their resources and attention on potentially qualified patients for the trials. Such an approach substantially reduces overall recruitment time and costs. **Conflict of Interest Statement:** All authors are employees of Eisai.

LATE BREAKING

LB01- PLASMA PTAU231 AS AN EARLY MARKER OF AMYLOID-B PATHOLOGY FOR PRECLINICAL ALZHEIMER'S DISEASE TRIAL SELECTION.

Nicholas Ashton¹, Marta Milà-Alomà², Andrea Benedet¹, Thomas Karikari¹, José Luis Molinuevo², Eugene Vanmechelen³, Henrik Zetterberg¹, Marc Suárez-Calvet², Kaj Blennow¹ (1. Gothenburg University - Göteborg (Sweden), 2. Barcelona Beta - Barcelona (Spain), 3. Adx Neuroscience - Ghent (Belgium))

Background: Blood biomarkers that accurately indicate Alzheimer's disease (AD) pathophysiology now offer a realistic, cost-effective and non-invasive assessment that will aid the diagnostic process in primary and secondary care. In some instances, the performance of plasma p-tau biomarkers is comparable or only marginally inferior to established cerebrospinal fluid (CSF) or positron emission tomography (PET) examinations of amyloid- β (A β) and tau pathologies, but with the advantage of greater availability and tolerability for both clinicians and patients. The preclinical indication of AD pathology is also critically important, where cerebral A β deposition is occurring but cognitive symptoms have not yet manifested. However, it is not yet clear how blood biomarkers will inform on the preclinical evaluation of AD and if a temporal ordering of such biomarkers can be detected. As anti-A β therapeutic trials, already approved for symptomatic AD, move toward the assessments in the preclinical phase of the disease, a cost-effective tool is needed to reduce the budget for molecular imaging in the recruitment process. **Methods:** In this study, we leverage the unique characteristics of the ALFA+ cohort, composed of 384 cognitively unimpaired middle-aged individuals (61.1 years + 4.68); A β -positive (135 [35.2%] defined with CSF A β 42/40, and 26 [8%] defined with A β PET and hence fall into the preclinical AD. Blood biomarkers (p-tau181, p-tau231, GFAP, NfL) were analyzed on the single molecule array (Simoa) platform. **Results:** Plasma pTau231 was significantly increased in individuals who were A β -positive (A+, as defined by decreased CSF A β 42/40) but tau-negative (T-, as defined by increased CSF pTau181) ($P < 0.0001$; Cohen's $d [d] = 1.12$). The other plasma biomarkers were also increased but had lower effect sizes. Plasma pTau231 was also increased in those individuals who had abnormal CSF A β 42/40 levels but an A β PET < 30 Centiloids ($P < 0.0001$; Cohen's $d [d] = 1.01$). Again, other plasma biomarkers were also increased but not to the same magnitude. We next examined which of the plasma biomarkers had the highest accuracy to detect established A β pathology, as measured by an A β PET burden >30 Centiloids. While plasma pTau231 had the highest area under the curve (AUC = 0.835 [CI95% = 0.756 - 0.914]), it was not superior to plasma pTau181 or GFAP in this analysis. When assessing A β burden based on CSF A β 42/40, which changes earlier than A β PET, plasma pTau231 significantly ($P < 0.001$) outperformed the other biomarkers (AUC = 0.814 [CI95% = 0.767 - 0.861]). The performance of plasma p-tau231 was similar to CSF p-tau231 in the same patients (DeLong test, $P = 0.53$). The combination of plasma pTau231 with any other plasma biomarker (either pTau181, GFAP or NfL), together with age, sex and APOE- $\epsilon 4$ status, did not significantly improve the AUC of pTau231 alone. **Conclusion:** In summary, we present data supporting that plasma pTau231 reaches significant high levels in preclinical AD and has the highest AUC (compared with plasma GFAP, pTau181 and NfL) to discriminate between A β -positive and A β -negative cognitively unimpaired individuals (as defined by decreased CSF A β 42/40). Remarkably, the AUC for plasma

pTau231 is similar to that of its CSF biomarker counterpart. Both plasma pTau231 and GFAP are equally adequate to detect established A β pathology (as measured by A β PET, a stage biomarker). However, pTau231 better reflects changes in CSF A β 42/40 (a state marker), which is known to become abnormal before A β plaque load reaches the amount that can be detected by PET. Amid the recent developments in anti-A β therapies and the increasing awareness of treating AD as early as possible, the use of plasma pTau231 will facilitate the recruitment of participants in clinical trials at this early stage of the disease.

LB02- ASSOCIATION OF EMERGING BETA-AMYLOID AND TAU PATHOLOGY WITH EARLY COGNITIVE CHANGES IN CLINICALLY NORMAL OLDER ADULTS.

Michelle Farrell¹, Kathryn Papp², Rachel Buckley², Heidi Jacobs¹, Aaron Schultz¹, Michael Properzi¹, Patrizia Vannini², Bernard Hanseeuw¹, Dorene Rentz², Keith Johnson², Reisa Sperling² (1. Massachusetts General Hospital - Boston (United States), 2. Massachusetts General Hospital, Brigham & Women's Hospital - Boston (United States))

Background: Alzheimer's disease (AD) clinical trials are moving earlier in the disease process, with secondary prevention trials currently underway in clinically normal older adults with elevated beta-amyloid (A β) and tau pathology. However, moving closer to primary prevention by intervening at the first signs of emerging A β , before extensive tau proliferation, may be optimal. Cognitive measures sensitive to the earliest stages of AD pathogenesis may not be the same as those sensitive to high A β and spreading neocortical tau pathology, including specific declines in delayed recall and composites such as the Preclinical Alzheimer's Cognitive Composite (PACC). If early intervention is necessary to successfully slow AD progression, it is critical to find the right test at the right time to optimize cognitive outcome measures for clinical trials. **Objective:** To identify cognitive measures associated with the earliest detectable signs of emerging beta-amyloid (A β) and tau pathology with PET imaging. **Methods:** 112 clinically normal adults with longitudinal PIB-PET, FTP-PET and cognitive data for 7+ years were included from the Harvard Aging Brain Study (HABS). As is currently being implemented in secondary prevention trials such as the A3 trial (aheadstudy.org), two cutoffs were selected to identify those who were initially classified as PIB- ($<$ Centiloid (CL) 20), and those who were initially PIB+ but with relatively low A β up to CL 40, the approximate threshold associated with the onset of rapid neocortical tau proliferation. Separate linear mixed effects models assessed the effects of emerging global A β (PIB slope) and tau (baseline FTP level and FTP slope) in the entorhinal (ERC) and inferior temporal (IT) cortices on multiple cognitive measures over time. A total of 8 cognitive tasks (with 11 measures) were included assessing learning/memory retrieval, delayed recall/memory consolidation, processing speed, executive function and language. A composite of tasks associated with rising PIB slopes was computed as a potentially optimal tool for detecting the earliest A β -related cognitive changes and compared with the Preclinical Alzheimer's Cognitive Composite (PACC), which is often used in clinical trials as it is known to be sensitive to high levels of A β . **Results:** Faster rates of A β accumulation, indicated by higher PIB slopes, were associated with declining processing speed (DSST, Trails A) in those initially PIB- ($<$ CL20) and expanded to include learning/memory retrieval (FCSRT-FR, SRT-tr, LM-immed) when including those initially PIB+ individuals with low A β in the $<$ CL40 group. A composite measure of processing speed

and memory retrieval tasks provided the strongest prediction of early A β -related cognitive decline under CL40, while PACC remained optimal at high levels of A β (>CL40). Under CL20, rising right IT FTP slope contributed to declining FCSRT-FR and SRT-tr learning/memory retrieval (FCSRT-FR, SRT-tr) but PIB slope also remained a significant contributor. However, when expanded to the <CL 40 group, FTP baseline level and/or slope were related to declines across all tasks, and PIB slope effects on memory retrieval were reduced. In contrast, DSST declines remained strongly associated with rising PIB slope. **Conclusion:** Early, A β -mediated cognitive slowing was detected for measures of processing speed, while early declines in memory retrieval were associated with emerging A β but primarily driven by spreading tau pathology. Composites including measures of processing speed and memory retrieval may be optimal to determine whether anti-A β or anti-tau therapies administered at the first signs of pathology might preserve cognitive function, while composites such as the PACC remain ideal in those with established and elevated pathology. **Conflict of interest:** M.E. Farrell has no disclosures; K.V. Papp has served as an advisor to Biogen Idec and Digital Cognition Technologies; R.F. Buckley has no disclosures; H.I.L. Jacobs has no disclosures; A.P. Schultz has been a paid consultant for Janssen Pharmaceuticals and Biogen; M.J. Properzi has no disclosures; P. Vannini has no disclosures; B.J. Hanseeuw has no disclosures; D.M. Rentz has served as a consultant for Eli Lilly, Biogen Idec, Digital Cognition Technologies, and serves as a member of the Scientific Advisory Board for Neurotrack; K.A. Johnson has served as paid consultant for Bayer, GE Healthcare, Janssen Alzheimer's Immunotherapy, Siemens Medical Solutions, Genzyme, Novartis, Biogen, Roche, ISIS Pharma, AZTherapy, GEHC, Lundberg, and Abbvie. He is a site coinvestigator for Eli Lilly/Avid, Pfizer, Janssen Immunotherapy, and Navidea. He has spoken at symposia sponsored by Janssen Alzheimer's Immunotherapy and Pfizer; R.A. Sperling has served as a paid consultant for AC Immune, Alynlam, Cytox, Genentech, Janssen, Neurocentria, Prothena, and Roche. She has received research support as an investigator for Eli Lilly, Janssen and Eisai Alzheimer disease clinical trials. These relationships are not related to the content in the manuscript.

LB03- ALZOSURE® PREDICT, A SIMPLE, NON-INVASIVE BLOOD TEST TO PREDICT THE EARLY ONSET OF ALZHEIMER'S DISEASE WITH THE ABILITY TO IDENTIFY MCI PATIENTS, BEFORE THE CLINICAL SYMPTOMS ARE IDENTIFIABLE (IN THE SAME TEST) 6 YEARS IN ADVANCE OF CLINICAL DIAGNOSIS. Simona Piccirella¹, Leander Van Neste², Christopher Fowler³, James Doecke⁴, Daniela Uberti⁵, Paul Kinnon¹ (1. Diadem Srl - Brescia (Italy), 2. Halixio Bv - Altenaken (Belgium), 3. The Florey Institute Of Neuroscience And Mental Health - Parkville (Australia), 4. The Australian E-Health Research Centre - Herston (Australia), 5. Department Of Molecular And Translational Medicine, University Of Brescia - Brescia (Italy))

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder, starting with a preclinical phase of normal cognition lasting up to two decades. Recently, a conformational variant of p53 in AD (U-p53AZ) has been identified as a lead biomarker for AD (Abate G. et al 2021). Diadem have developed AlzoSure®Predict (Piccirella et al, 2021), a simple, non-invasive, rapid blood-based test that allows the assessment of cognitive decline to AD-dementia up at least 6 years in advance than clinical symptoms by detecting the

concentration of a specific sequence peptide, AZ284®, from U-p53AZ protein. **Objectives:** This study aims to confirm the clinical utility of U-p53AZ in the diagnosis and prognosis of AD. **Methods:** Alzosure®Predict was used to quantify the U-p53AZ biomarker in a subset of individuals from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) cohort. In summary, the cohort comprised of 227 Cognitive Normal (CN) individuals, 98 MCI, 141 AD individuals. 25 CN progressed to MCI or AD and 60 MCI individuals progressed to AD over the follow up period. For 422 (88%) and 472 (98%) of these individuals, information on amyloid (quantified by centiloid) and APOE ϵ 4 allele (through genotyping) status was available, respectively. The diagnostic and prognostic performance of U-p53AZ were assessed and compared with the other AD biomarkers (i.e., amyloid status assessed by amyloid brain imaging, calibrated centiloid or inferred amyloid categories). For both diagnostic and prognostic purposes, logistic regression models were developed adding patient age and APOE allele status to the models. **Results:** U-p53AZ prognostic value was evaluated in the longitudinal AD patient cohort by the quantification of AZ284®, with the lead time to AD diagnosis being assessed through time-dependent ROC statistical analysis. A similar statistical analysis was also performed on amyloid brain imaging data based on PET-centiloid value. In summary, AlzoSure®Predict, prognostic performance showed an area under the curve (AUC) of 98% (CI: 95-100%), a Sensitivity of 100%, Specificity of 95% (both when Youden index was maximised), PPV and NPV of 93% and 100%, respectively to prognose SMC individuals progressing to AD. The prognostic performance of U-p53AZ to predict the progression from MCI to AD was slightly lower but still significant with an AUC of 89% (CI: 82-96%), a Sensitivity of 77%, a Specificity of 93% and a PPV and NPV of 89% and 86%, respectively. Using Alzosure®Predict the U-p53AZ levels were quantified at baseline and the test was able to reliably discriminate the preclinical (NMC and SMC) from subjects with AD with an AUC of 100% (CI: 99%-100%) and respective sensitivity of 100% and specificity of 99%. Additionally, Alzosure®Predict identified individuals at the prodromal stage (MCI) from subjects with AD with an AUC of 97% (CI: 94-99%), a sensitivity of 94% and a specificity of 94%. U-p53AZ (by AZ284®) levels were quantified at baseline, with 141 AD cases and 338 non-AD controls resulting in an AUC of 99% (98% - 99%; 95% DeLong confidence interval (CI)). In comparison amyloid PET imaging had a diagnostic value of AUC 81% (95% CI: 76%-85%) with the centiloid value significantly lower than U-p53AZ ($p < .001$). The diagnostic and prognostic performance of U-p53AZ was greater than logistic regression models based on age, APOE4 status and centiloid. As the AUC values of U-p53AZ alone were nearly 100% at 36m and 72m follow-up times, the addition of other risk factors did not further increase its diagnostic and prognostic performance, of Alzosure®Predict. **Conclusion:** This comprehensive longitudinal study investigated the performance of U-p53AZ a integrative biomarker for AD as detected by AlzoSure® Predict, for early detection of AD in asymptomatic and prodromal individuals. U-p53AZ biomarker detected AD progressors more accurately compared to centiloid, showing its potential to identify with certainty individuals at high risk to develop AD. Additionally, both the diagnostic and prognostic performance of U-p53AZ markedly surpassed those of other risk factors (dichotomous APOE ϵ 4 allele, amyloid status, age) used either alone or in different combinations AUC \geq 98% for non-AD vs AD up 72m of follow up. This data set confirms that U-p53AZ detected by Alzosure®Predict has the potential to improve

patient treatment and longer term outcomes, also allow for the implementation of precision medicine strategies in AD, such as patient stratification and targeted treatments all at least 6 years in advance of clinical symptoms and current diagnosis. More details are available on the preprint: <https://www.medrxiv.org/content/10.1101/2021.08.23.21261848v1>.

LB04- INTRODUCTION OF PLASMA BIOMARKER SCREENING FOR THE AHEAD 3-45 STUDY. Elena Reisa Sperling¹, Keith Johnson², Jin Zhou³, Michael C. Irizarry³, Shobha Dhadda³, Lynn D. Kramer³, Chad J. Swanson³, Yarasheski Kevin⁴, Robert A. Rissman⁵, Michael Rafii⁶, Rema Raman⁶, Michael C. Donohue⁶, Gopalan Sethuraman⁶, Paul S. Aisen⁶ (1. *Brigham And Women's Hospital, Massachusetts General Hospital, Harvard Medical School - Boston (United States)*, 2. *Brigham And Women's Hospital, Massachusetts General Hospital, Harvard Medical School - Boston (United States)*, 3. *Eisai - San Francisco (United States)*, 4. *C 2 N Diagnostics - St. Louis (United States)*, 5. *University Of California San Diego, University Of Southern California - San Diego (United States)*, 6. *University Of Southern California - San Diego (United States)*)

Background: The Alzheimer's disease (AD) continuum is thought to begin with a long asymptomatic or preclinical stage of AD, during which amyloid beta (A β) is accumulating for more than a decade prior to widespread cortical tauopathy, neurodegeneration, and clinical impairment. The AHEAD 3-45 Study is testing whether intervention with lecanemab (BAN2401), a humanized IgG1 monoclonal antibody that preferentially targets soluble aggregated A β , initiated prior to cognitive impairment, can slow accumulation of tau and prevent cognitive decline. The AHEAD Study consists of two sister trials (A3 and A45) in cognitively unimpaired (CU) individuals ages 55-80. The AHEAD study is conducted as a Public-Private Partnership of the Alzheimer's Clinical Trial Consortium (ACTC), funded by National Institute on Aging, National Institutes of Health (NIH), and Eisai Inc. Similar to the experience in the A4 Study and other secondary prevention trials in preclinical AD, the screening process can be time consuming and costly with thousands of PET scans; thus, a need exists to accelerate and improve the efficiency of identifying CU individuals most likely to prove eligible based on PET imaging. Recent advances in blood-based biomarkers suggest that plasma measures can detect evidence of AD pathology with reasonable accuracy, even at the preclinical stage of AD, and thus, may effectively triage individuals most appropriate to undergo screening PET imaging. **Methods:** The AHEAD 3-45 consists of two sister trials (A3 and A45) with specific dosing regimens tailored to baseline brain amyloid levels on screening PET scans: for A3 intermediate amyloid (approximately 20-40 centiloids) and for A45 elevated amyloid (>40 centiloids). Both trials exist under a single protocol, screening process, and common schedule of assessments. In November 2021, we will be introducing plasma screening with C2N Diagnostics' mass spectrometry platform (PrecivityAD™) to quantitate the amyloid beta 42/40 ratio (A β 42/40), which has been previously shown to be a reliable predictor of brain amyloid level. Blood samples will be collected at a brief initial visit and used to determine eligibility to proceed in the screening process to PET imaging. Eligibility to randomize into the A3 or A45 study will still be based on the screening PET imaging results. The precise algorithm for determining eligibility to proceed to PET scanning will be adaptive and may expand over time as additional screening experience and assays become available. **Results:** As of September 1, 2021, over 1150 participants are in

or have completed the screening process for the AHEAD Study at more than 80 active sites in the US, Japan, UK, Singapore and Australia and 717 have completed screening amyloid PET imaging. Currently, 9.9% of those participants are into the intermediate amyloid range (potentially eligible for A3), and 22.4% are in the elevated range (potentially eligible for A45), but these rates vary by age and APOE ϵ 4 carrier status. The first 700 plasma samples are being processed at C2N and the plasma-PET associations will be reported at CTAD in November. The initial threshold for eligibility to proceed to PET imaging will be determined based on the AUC results using receiver operating characteristic (ROC) curve analysis from these first 700 participants, and adaptive assessment will be ongoing to determine the optimal cutpoints and algorithm that best predicts eligibility for the A3 and A45 trials. **Conclusion:** The AHEAD 3-45 Study will be the first secondary prevention trial to employ plasma-based biomarkers to accelerate the screening process and potentially substantially decrease the number of screening PET scans. Importantly, one of the goals of this process will be to refine the cutpoints that are most appropriate for detecting this very early stage of AD pathology. Additional work will be ongoing throughout the screening period of the AHEAD Study, and additional plasma biomarkers and demographic information will be utilized to optimize the screening algorithm. It will be important to balance the ability to select CU individuals most likely to qualify on PET imaging while not missing individuals with intermediate levels of amyloid who may be at the edge of detectability with plasma measures.

LB05- EFFORTS TO IMPROVE RECRUITMENT AND ENGAGEMENT OF UNDERREPRESENTED POPULATIONS IN THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI) STUDY. Miriam T. Ashford¹, Ozioma Okonkwo², Monica Rivera Mindt³, Rema Raman⁴, Garrett Miller⁴, Michael C. Donohue⁴, Godfrey A. Coker⁴, Rachel L. Nosheny⁵, Ronald C. Petersen⁶, Paul S. Aisen⁴, Michael Weiner⁷ (1. *Northern California Institute For Research And Education (ncire), Department Of Veterans Affairs Medical Center - San Francisco (United States)*, 2. *Wisconsin Alzheimer's Disease Research Center And The Department Of Medicine, University Of Wisconsin School Of Medicine And Public Health - Madison (United States)*, 3. *Psychology & Latin American Latino Studies Institute, Fordham University, Joint Appointment In Neurology, Icahn School Of Medicine At Mount Sinai - New York (United States)*, 4. *Alzheimer's Therapeutic Research Institute, University Of Southern California - San Diego (United States)*, 5. *Department Of Psychiatry, University Of California San Francisco - San Francisco (United States)*, 6. *Department Of Neurology, Mayo Clinic - Rochester (United States)*, 7. *Department Of Radiology And Biomedical Imaging, University Of California San Francisco - San Francisco (United States)*)

Background: Disparities in Alzheimer's disease (AD) are a major public health issue. Ethnoculturally diverse individuals from underrepresented populations (URPs, including but not limited to Black/African American, Hispanic/Latino(a) adults) are disproportionately affected by AD. For instance, there is greater AD prevalence and incidence in adults self-identifying as Black/African American and Hispanic/Latino(a) compared to adults self-identifying as non-Hispanic/Latino(a) white (NLW). Yet, URPs are under-enrolled in the majority of clinical research studies, which greatly limits the generalizability of research findings. Similar to most multisite AD clinical studies, the Alzheimer's Disease Neuroimaging Initiative (ADNI) had

relatively low enrollment of URPs up until recently. **Objectives:** The objectives of this study were to describe ADNI's efforts to increase enrollment and engagement of ethnoculturally diverse individuals from URPs in ADNI3 and the results of this effort. **Methods:** ADNI is an ongoing, longitudinal, multicenter study whose overall aim is to develop and validate clinical, imaging, genetic, and biochemical biomarkers for use in AD clinical trials. ADNI participants are classified as cognitively unimpaired (CU), having mild cognitive impairment (MCI) or dementia due to AD. **Results:** Efforts undertaken by ADNI to increase enrollment and engagement of URPs include (1) launching of a Diversity Task Force (DVTf) in July 2020. The DVTf was charged with overseeing ADNI's mission in this space. Specific DVTf activities comprised, (2) establishment, funding, and instrumental support (e.g., training, consultation, resources) of Diversity Recruitment Hubs at 13 ADNI3 sites which deployed a culturally-informed, community-engaged research approach for interacting with URPs; (3) changes to ADNI protocol to facilitate research participation of URPs (e.g., optional lumbar puncture and sharing of amyloid PET results); (4) hiring of a marketing agency which launched intensive, culturally-tailored digital/social media marketing campaigns for the 13 Hub Sites, with local websites available both in English and Spanish with community advisement; (5) development of a RedCap database to capture performance metrics of recruitment efforts at the 13 Hub Sites; and (6) formation of a six-member External Advisory Board comprising leaders in health disparities research, to guide the DVTf efforts. In terms of DVTf accomplishments, the rate of URP enrollment at these 13 Diversity Hub sites improved from 1.1 racial and ethnic URP per month prior to the effort to 4 URPs per month. This is a 264% increase in the "monthly rate" of enrollment. Across all 59 ADNI sites, the overall enrollment of ethnoculturally diverse individuals from URPs went from 89 (16.8%) to 126 (21.1%), which represents a 25% increase in percent-enrollment between May 2020 – and September, 2021. Moreover, since February 1st, 2021, ADNI enrolled 43 new participants of which 33 (77%) were from URPs. **Conclusion:** Based on the success of the DVTf efforts in ADNI3, and the focus of URP enrollment in ADNI4, the DVTf will evolve to become a new Engagement Core in ADNI4. The Engagement core will implement a culturally-informed community engaged research approach to URP recruitment and retention across all 59 ADNI sites. Its strategies include formation of a Community-Scientific Partnership Board and hiring of site-specific Community Research Liaisons for community recruitment and Community Research Navigators for intensive engagement/retention support. These efforts will be supported by culturally-tailored digital advertising and locally-branded websites for Black/African-American, Hispanic/Latino(a), Asian, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander communities. As a path to in-clinic enrollment, and based on learnings from DVTf success, ADNI4 will set up an online, digital screener to enrich for cognitively-impaired participants, prioritizing ethnoculturally diverse adults from URPs. The goal is to recruit approximately 20,000 individuals (50-60% URPs) to complete the screener, from which we will identify 4,000 participants for a plasma AD biomarker study. This would then lead to in-clinic enrollment of 500 participants (50-60% URPs). We anticipate that ADNI's efforts will serve as a potential new approach for increasing diversity in AD clinical research.

LB06- LM11A-31 SMALL MOLECULE P75 RECEPTOR MODULATOR – PHASE 2A RANDOMIZED PLACEBO-CONTROLLED SAFETY AND EXPLORATORY ENDPOINT TRIAL IN MILD-MODERATE ALZHEIMER'S DISEASE. Frank Longo¹, Taylor Schmitz², Hayley Shanks², Eric Reiman³, Kewei Chen³, Stephen Massa⁴, Manfred Windisch⁵ (1. *Pharmatrophix - Menlo Park (United States)*, 2. *Western University - London (Canada)*, 3. *Banner Alzheimer's Institute - Phoenix (United States)*, 4. *Ucsf And Sf Vamc - San Francisco (United States)*, 5. *Neuroscios - Graz (Austria)*)

Background: The p75 neurotrophin receptor (p75NTR) modulates degenerative signaling networks active in Alzheimer's disease and its activity promotes neuronal and synaptic degeneration in APP- and tau-mutant mice. LM11A-31 is a first-in-class, small molecule modulating p75 neurotrophin receptor signaling. Oral administration in APP- and tau-mutant mice inhibits accumulation of pathological forms of tau; and also decreases degeneration of neurites, loss of pre- and post-synaptic markers and upregulation of microglial and astrocyte markers (Yang et al, 2020a, 2020b). p75NTR has not been previously selectively targeted in human disease trials. **Objectives:** Conduct a phase 2a study in mild-moderate Alzheimer's disease (AD) subjects to assess safety as the primary endpoint, along with mechanism-related exploratory endpoints. **Methods:** The trial was conducted by Pharmatrophix in five countries in Europe with each site led by a site principal investigator. It consisted of three study arms: placebo, low dose and high dose LM11A-31 (each twice per day) administered by oral capsules for 26-weeks. Enrollment criteria included a diagnosis of mild to moderate AD and low CSF amyloid-beta levels. Baseline and repeated safety assessments included monitoring of vital signs, laboratory studies and brain MRI imaging. Exploratory endpoint baseline and post-treatment assessments included: FDG-PET and volumetric MRI brain scans; CSF biomarkers including AD core biomarkers and those related to synaptic degeneration and other neurodegenerative processes; ADAS-Cog-13, a Neurological Testing Battery, MMSE and other cognitive-related measures. **Results:** A total of 242 from a target 240 subjects were enrolled and 221 completed the full 26-week treatment period. Results of safety analyses and exploratory endpoint assessments will be presented. **Conclusion:** This study provides an indication for level of safety over a 26-week treatment period in the context of a first-in-class small molecule targeting the p75 neurotrophin receptor and provides an assessment of treatment-related exploratory endpoint interval changes relevant to AD mechanisms and progression. **Acknowledgments:** We thank the participating subjects and families as well as the site teams. Funding: NIA Pilot AD Trial Program. **Conflict of Interest:** FL has equity interest, is a board member and has a consulting relationship with Pharmatrophix. FL and SM are listed as inventors of LM11A-31 and hence entitled to royalties and related payments. **References:** Yang et al. Small molecule modulation of the p75 receptor inhibits multiple amyloid beta-induced tau pathologies. *Sci Reports* 2020a; Yang et al. Small-molecule modulation of the p75 receptor inhibits a wide range of tau molecular pathologies and their sequelae in P301S tauopathy mice. *Acta Neuropath Comm* 2020b

LB07- THE COST-EFFECTIVENESS OF ADUCANUMAB AND DONANEMAB FOR EARLY ALZHEIMER'S DISEASE IN THE UNITED STATES. Eric Ross^{1,2,3}, Marc Weinberg^{1,2,3}, Steven Arnold^{4,5}, Deborah Blacker^{1,6} (1. Department Of Psychiatry, Massachusetts General Hospital - Boston (United States), 2. Department of Psychiatry, McLean Hospital - Belmont (United States), 3. Department of Psychiatry, Harvard Medical School - Boston (United States), 4. Department Of Neurology, Massachusetts General Hospital - Boston (United States), 5. Department of Neurology, Harvard Medical School - Boston (United States), 6. Department of Epidemiology, Harvard T.H. Chan School of Public Health - Boston (United States))

Background: Several anti-amyloid monoclonal antibodies have been proposed to slow disease progression in patients with early Alzheimer's disease (AD). The two furthest developed of these treatments are aducanumab, which received FDA accelerated approval in 2021, and donanemab, which is currently undergoing Phase III clinical trials. The cost-effectiveness of these treatments has not been established. **Objectives:** 1) Estimate the incremental cost-effectiveness of aducanumab and donanemab, relative to standard care, for patients with early AD in the United States. 2) Estimate value-based prices for aducanumab and donanemab, defined as the price at which the medication would achieve an incremental cost-effectiveness ratio (ICER) \leq \$150,000/quality-adjusted life-year (QALY). **Methods:** We developed a novel decision analytic model of AD treatments. We used this model to project the clinical and economic outcomes (from both healthcare sector and societal perspectives) of standard care, aducanumab treatment, and donanemab treatment over a lifetime horizon for a cohort of patients with early AD in the United States. We estimated the efficacy of aducanumab by meta-analysis of patients in the high-dose arms of two 18-month phase III trials, yielding a hazard ratio of disease progression of 0.89 (95% CI 0.63-1.15); restricting this meta-analysis to the post-hoc subgroup who consented to an updated trial protocol enabling more aggressive dosing yielded a hazard ratio of 0.71 (95% CI 0.50-0.92). The efficacy of donanemab was derived from an 18-month phase II clinical trial, yielding a hazard ratio of disease progression of 0.68 (95% CI 0.44-0.99). Additional model inputs included: initial age, mean 75.2 years (SD 5.5); initial dementia stage, mild cognitive impairment 25.9%, mild dementia 57.4%, moderate dementia 16.7%; annual drug cost, aducanumab \$56,000, donanemab \$56,000; initial monthly monitoring and infusion cost, aducanumab \$360, donanemab \$614; screening cost per treated patient (including MRI and PET imaging), aducanumab \$7,141, donanemab \$17,548; amyloid-related imaging abnormality probability, aducanumab 41%, donanemab 39%. Consistent with donanemab's phase II clinical trial, we simulated discontinuation of donanemab in patients with substantial reduction of amyloid plaque on follow-up PET imaging, which occurred in 27% of patients at 6 months and 55% of patients at 12 months; we assumed stable treatment rates after 12 months. **Results:** With standard care, projected life expectancy was 8.13 years, and quality-adjusted life expectancy was 3.95 QALYs. QALYs were increased by 0.12 with aducanumab and 0.37 with donanemab. With standard care, lifetime costs were \$142,000 from a healthcare sector perspective and \$261,000 from a societal perspective. Aducanumab increased healthcare sector costs by \$204,000 and societal costs by \$204,000; cost components included increases of \$183,000 in drug costs, \$18,000 in monitoring and infusions, \$7,000 in screening costs, and \$1,000 in adverse effects, and savings of \$4,000 in background healthcare.

Donanemab increased healthcare sector costs by \$94,000 and societal costs by \$92,000; cost components included increases of \$75,000 in drug costs, \$18,000 in screening costs, \$13,000 in monitoring and infusions, and \$1,000 in adverse effects, and savings of \$13,000 in background healthcare. Notably, drug costs were similar over 12 months (\$31,000 for aducanumab and \$32,000 for donanemab) but diverged thereafter due to greater discontinuation of donanemab. Healthcare sector and societal ICERs relative to standard care were \$1,745,000/QALY and \$1,740,000/QALY respectively for aducanumab, and \$252,000/QALY and \$248,000/QALY for donanemab. The value-based price of donanemab was \$28,000/year under a healthcare sector perspective and \$29,000/year under a societal perspective. With our base-case model inputs, no value-based price could be estimated for aducanumab; that is, even with zero drug cost, its clinical benefits were not great enough to justify the costs of patient screening, infusions, monitoring, and adverse effects. Using more optimistic efficacy assumptions based on subgroup analysis, aducanumab's value-based price was estimated at \$10,000/year under both healthcare sector and societal perspectives. **Conclusion:** At a price of \$56,000/year, neither aducanumab nor donanemab is cost-effective when judged against commonly applied benchmarks in the United States. To become cost-effective, aducanumab would require a >80% price reduction, even under optimistic efficacy assumptions; in contrast, donanemab would become cost-effective with a 50% price reduction. Donanemab's greater health-economic value is partly a reflection of the greater efficacy observed in its phase II trial, and partly a reflection of a dosing and monitoring regime under which most patients suspend treatment within one year.

LB08- KETONES IMPROVE FUNCTIONAL CONNECTIVITY AND APPARENT FIBER DENSITY IN THE DORSAL ATTENTION NETWORK: DIRECT LINKS TO IMPROVED ATTENTION AND BRAIN ENERGETICS IN MILD COGNITIVE IMPAIRMENT. Maggie Roy, Manon Edde, Mélanie Fortier, Valérie St. Pierre, Christian Bocti, Tamas Fulop, Maxime Descoteaux, Stephen Cunnane (Université De Sherbrooke - Sherbrooke (Canada))

Background: Deteriorating brain glucose uptake contributes to the onset of mild cognitive impairment (MCI) and progression to Alzheimer disease (AD). However, it is now clear that uptake of ketones (acetoacetate and beta-hydroxybutyrate) - the brain's main alternative fuel to glucose - remains normal in both MCI and mild-moderate AD. Studies are underway to assess whether interventions providing an endogenous or exogenous source of ketones can improve cognition in MCI or mild-moderate AD by rescuing brain energy metabolism. **Objective:** The objective of the present report is to describe late breaking data on the relationship between improved structure and function of the dorsal attention network (DAN), improved cognitive outcomes and improved brain energetics in MCI after an oral nutritional supplement containing a ketogenic medium chain triglyceride (kMCT) was consumed over six months. **Methods:** All data reported here are from the first phase of the BENEFIC RCT (NCT02551419) in which resting state functional MRI, diffusion imaging and glucose and ketone PET were assessed in MCI before and at the end of the 6-month intervention. A comprehensive cognitive battery was used to screen for MCI (amnestic and non-amnestic MCI combined). The supplement was a lactose-free skim milk emulsion providing 15 g kMCT twice/day or an energy equivalent placebo. Pre- and post-intervention data presented here are for n=17 kMCT and n=15 placebo. Independent component analysis (FSL Melodic) was used to segment seven major

resting-state networks (DAN, ventral-attention, frontoparietal, limbic, somatomotor, default-mode and visual). High angular resolution diffusion imaging acquisitions and Brainnetome parcellations provided structural connectivity matrices computed using apparent fiber density and PET tracers as metrics. ¹¹C-Acetoacetate and ¹⁸F-fluorodeoxyglucose (FDG) PET were used to quantify brain metabolism (mmol/100 g/min) of ketones and glucose, respectively. Imaging data were analyzed with a general linear model using age, sex, education, apolipoprotein E4 status, intracranial volume, and white matter hyperintensity volume as covariates. **Results:** The only network in which functional connectivity (FC) changed significantly was the DAN in which FC was 59% higher in the kMCT group vs placebo with a large effect size (partial $h^2 = 0.17$; $P = 0.040$). Post-kMCT, attention and processing speed composite Z-score ($r = +0.42$; $P = 0.021$), and the Trail Making visual scanning ($r = -0.48$, $P = 0.007$) and number sequencing conditions ($r = -0.36$, $P = 0.05$) all improved in direct association with increased DAN-FC and increased apparent fiber density in DAN cortical regions. Ketone uptake was 111% higher in DAN cortical regions in the kMCT group ($P = 0.001$), an increase that was positively associated with improved DAN-FC, with a large effect size ($r = 0.69$, $P = 0.002$). In DAN white matter connections, mean overall DAN fiber density was significantly higher in the kMCT group ($P = 0.021$). Improved DAN-FC was also positively associated with increased DAN white matter ketone uptake ($r = +0.49$, $P = 0.004$). Global brain ketone uptake doubled on the kMCT arm only without affecting brain FDG uptake, thereby improving brain energy status by 34%, an effect directly related to the increase in plasma ketones ($r = +0.87$, $P < 0.01$). **Conclusions:** Improved DAN-FC was a direct function of improved brain energy status due to higher brain ketone availability in the kMCT group. In the BENEFIC trial, raw scores and normalized Z-scores for three cognitive domains (episodic memory, executive function, and language) improved post-intervention on the kMCT arm only and in direct relationship to higher overall brain ketone uptake. Processing speed also increased in relation to white matter ketone uptake (submitted for publication). The present data add the fifth cognitive domain – attention – which also improved specifically as a function of improved DAN-FC post-kMCT. DAN-FC with the left frontal cortex in particular is associated with higher cognitive reserve, i.e., better memory at any given level of neuropathology, so ketones may have a protective effect on memory in MCI in part because they improve brain energy status and cognitive reserve. The BENEFIC trial has demonstrated efficacy, safety, acceptability, and feasibility of long-term use of kMCT to improve overall cognitive performance in MCI, with a direct mechanistic link between the kMCT supplement, raised brain ketones and improved cognitive performance in all five major cognitive domains. The moderate effect size of several of the changes in cognitive outcomes (raw and Z-scores) indicates that the improvement observed was probably clinically meaningful, suggesting that brain energy rescue with a ketogenic supplement could potentially reduce the risk of MCI progressing toward AD. This should now be prospectively assessed in a multi-center RCT in MCI. **Acknowledgements:** Financial support was provided by the Alzheimer Association USA, FRQS, Université de Sherbrooke, Nestlé Health Science, and MITACS. SCC has consulted for and/or received test products for research from Nestlé Health Science, VitaFlo, Abbott, Pro-Diet, NeuroEnergy Ventures, Bulletproof, Cerecin, and Abitec. SCC is the founder and director of the consulting company, Senotec Inc. MD is CSO and shareholder of Imeka Solutions Inc. MR is consultant for Imeka Solutions Inc.

LB09- CONSISTENCY OF EFFICACY ASSESSMENTS ACROSS VARIOUS STATISTICAL METHODS FROM THE LECANEMAB PHASE 2 PROOF-OF-CONCEPT STUDY, BAN2401-G000-201, IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE. Shobha Dhadha¹, Michio Kanekiyo¹, David Li¹, Chad Swanson¹, Michael Irizarry¹, Donald Berry², Scott Berry², Lynn Kramer¹ (1. Eisai Inc. - Woodcliff Lake (United States), 2. Berry Consultants, Llc. - Austin (United States))

Background: Lecanemab (BAN2401) is a humanized IgG1 monoclonal antibody that shows preferential activity at large soluble A β aggregates (oligomers and protofibrils) with activity at insoluble fibrils. Lecanemab reduced amyloid as early as 3 months, while slowing clinical decline in an 18-month phase 2 proof-of-concept study (Study 201) in early Alzheimer's disease (Swanson et al. *Alz Res Therapy* 13; 2021). Significant plaque reductions occurred as early as 3 months, with greater than 80% amyloid negative on visual read as early as 12 months of treatment. There was low incidence of radiological ARIA-E and very low incidence of symptomatic ARIA-E in the study, with no titration of lecanemab required. **Objectives:** Herein, we describe the results of sensitivity analyses evaluating the consistency of the lecanemab Study 201 efficacy results across multiple statistical methods. **Methods:** Study 201 was a multicenter, double-blind, placebo-controlled, phase 2 study conducted in 856 patients with early Alzheimer's disease. Patients were randomized to five lecanemab 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. Key efficacy assessments included clinical change on the Alzheimer's Disease Composite Score (ADCOMS), Clinical Dementia Rating-Sum-of-Boxes (CDR-SB), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14). Sensitivity analyses were conducted for ADCOMS, CDR-SB, and ADAS-Cog14 to test for consistency across multiple statistical methods: mixed model for repeated measures (MMRM), disease progression model (DPM), natural cubic spline (NCS) model, and quadratic mixed model (QMM). MMRM used treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate. DPM, a disease progression model, was fit using a frequentist approach to evaluate the disease progression ratio (DPR), which measures the proportion of disease progression comparing the treatment group to placebo group. **Results:** The sensitivity analyses showed positive lecanemab treatment effects for ADCOMS, CDR-SB, and ADAS-cog14 at 18 months across all statistical models. Consistent treatment effect was observed for ADCOMS (29% to 37% less decline; nominal p -value <0.05), CDR-SB (26.5% to 32% less decline), and ADAS-Cog (37% to 60% less decline), with separation from placebo observed by 6 months for the top dose. Model assumptions were generally met across DPM, NCS and QMM, providing a reduction in standard error and tighter intervals. **Conclusions:** Lecanemab has demonstrated reduction in brain amyloid accompanied by a consistent reduction of clinical decline across several clinical and biomarker endpoints in a proof-of-concept phase 2 study, supporting the therapeutic concept for preferentially targeting large soluble aggregate amyloid species in early Alzheimer's disease. The results of the phase 2 study are strengthened by demonstrating consistency of the clinical efficacy across multiple statistical models. Phase 3 studies (ClarityAD, AHEAD) for lecanemab in early Alzheimer's disease and preclinical Alzheimer's disease are underway to

confirm efficacy and safety. **Disclosures:** Dr Dhadda is an employee of Eisai Inc.

LB10- A DIGITAL REMOTE MEMORY COMPOSITE TO DETECT COGNITIVE IMPAIRMENT IN MEMORY CLINIC SAMPLES IN UNSUPERVISED SETTINGS USING MOBILE DEVICES. David Berron¹, Ornella Billette², Xenia Grande³, Jeremie Guesten³, Ina Hempen⁴, Annika Spottke⁵, Katharina Buerger⁶, Robert Pernezcky⁶, Christoph Laske⁷, Anja Schneider⁵, Stefan Teipel⁸, Jens Wiltfang⁹, Michael Wagner⁵, Frank Jessen¹⁰, Emrah Duzel¹ (1. Dzne, Magdeburg - Magdeburg (Germany), 2. Neotiv, Magdeburg - Magdeburg (Germany), 3. Univ. Magdeburg - Magdeburg (Germany), 4. Neotiv, Magdeburg - Magdeburg (Germany), 5. Dzne, Bonn - Bonn (Germany), 6. Dzne, Munich - Munich (Germany), 7. Dzne, Tübingen - Tübingen (Germany), 8. Dzne, Rostock - Rostock (Germany), 9. Dzne, Göttingen - Göttingen (Germany), 10. Dzne, Cologne - 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 impairment in clinical and scientific settings. Implementation of unsupervised mobile assessment is particularly challenging for episodic memory measures. **Objective:** We defined a remote memory composite score from an unsupervised remote and mobile cognitive assessment battery focused on episodic memory and long-term recall and assessed its construct validity against the Preclinical Alzheimer's Cognitive Composite (PACC5). We also assessed the test-retest reliability of the remote memory composite across two independent test sessions. Finally, we assessed the diagnostic accuracy of the remote and unsupervised cognitive assessment battery when predicting PACC5-based cognitive impairment in a memory clinic sample. **Setting:** This was an add-on study of the DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) and a separate memory clinic-based sample study. **Participants:** A total of 102 study participants were included as cognitively unimpaired (n=25), cognitively unimpaired first-degree relatives of AD patients (n=7), individuals with subjective cognitive decline (n= 48) or mild cognitive impairment (n=22). **Measurements:** We analyzed results from the objects-in-rooms recall (ORR) test, the mnemonic discrimination for scenes (MDT-S) test and the complex scene recognition (CSR) test implemented in the neotiv digital platform to derive a remote memory composite (all three tests equally weighted). Participants used the neotiv mobile app to complete unsupervised tests on their own mobile device in an environment of their choice at a frequency of one test session per week. We assessed the relationships of the remote memory composite acquired through the mobile app and in-clinic measures of the PACC5 conducted by trained neuropsychologists in the memory clinics participating in the DELCODE study. We also assessed whether the remote memory composite cut-off best suited to discriminate impairment in the PACC5 was related to a functional impairment as measured with the clinical dementia rating scale (CDR). **Results:** 102 participants provided technically complete data for at least one single session of each of the three test paradigms and 87 participants already had the opportunity to perform at least two test sessions of each task. The derived remote memory composite score was highly correlated with the PACC5 score across all participants (R=.75, p<0.001) but also in those without complaints (CU and relatives, R=.51, p=0.003) and those with complaints separately (SCD and MCI,

R=.74, p<0.001). Test-retest reliability for the remote composite score calculated at two different points in time were also robust (R=.74; p<.0001). Diagnostic accuracy for discriminating PACC5-based memory impairment from no impairment was high (AUC = 0.89) with a sensitivity of 0.83 and a specificity of 0.74. In a subsample of individuals for whom the CDR was available (n=77), the same remote memory composite distinguished individuals without any impairment in the CDR (CDR global = 0) from those with impairment (CDR global >= .5) with a specificity of 0.73 (sensitivity 0.52). This indicates that a majority of those identified with impairment in the PACC5 also had some level of clinical functional impairment. **Conclusion:** Our results indicate that unsupervised mobile cognitive assessments in a memory clinic setting, using the implementation in the neotiv digital platform has high construct validity and results in a good discrimination between cognitively impaired and unimpaired individuals based on the PACC5 score. The cognitive impairment thusly identified is accompanied by some level of clinical functional impairment. Thus, it is feasible to complement neuropsychological assessment of episodic memory with unsupervised, remote assessments on mobile devices. This contributes to recent efforts for implementing remote episodic memory assessment for case-finding and monitoring in large research trials and clinical care.

LB11- RANDOMIZED CONTROLLED TRIAL OF GAMMA SENSORY STIMULATION TREATMENT DEMONSTRATES MAINTAINED COGNITIVE AND FUNCTIONAL ABILITIES AND REDUCED BRAIN ATROPHY IN PATIENTS WITH ALZHEIMER'S DISEASE. Mihaly Hajos^{1,2}, Thomas Megerian^{1,3}, Aylin Cimenser¹, Alyssa Boasso¹, Nathan Strozewski¹, Alex Konisky¹, Holly Mrozak¹, Katharine Kolin¹, Martin Williams¹, Evan Hempel¹, Jessie Nicodemus-Johnson⁴, Suzanne Hendrix⁴, Brent Vaughan¹, Zach Malchano¹ (1. Cognito Therapeutics - Cambridge (United States), 2. Yale University School of Medicine - New Haven (United States), 3. Thompson Autism Center, CHOC Children's - Orange (United States), 4. Pentara Corporation - Millcreek (United States))

Background: Recent experimental findings have shown that induction of synchronized 40 Hz gamma oscillation of neuronal networks by optogenetic or sensory (e.g., visual and/or auditory) stimulation effectively diminishes hallmarks of Alzheimer's disease (AD) pathology. Gamma sensory stimulation reduces A β plaques, hyperphosphorylated tau, neurodegeneration, brain atrophy, and reverses synaptic loss and function, leading to improved learning abilities in transgenic mice carrying AD-related human pathological genes (Adaikkan & Tsai, 2020). These results initiated the development and validation of non-invasive, gamma sensory stimulation as a potential therapeutic intervention for AD treatment. **Objectives:** A phase I/II randomized, controlled, double-blinded, US-based multi-center clinical trial (Overture trial; NCT03556280) was designed to evaluate feasibility, safety, tolerability, adherence, and efficacy of gamma sensory stimulation, using Cognito Therapeutics medical device in subjects on the AD spectrum. **Methods:** Participants with clinically diagnosed AD (MMSE 14-26, inclusive) were randomized 2:1 to receive daily, one-hour, EEG-calibrated, 40 Hz noninvasive audio-visual stimulation or sham stimulation. At the start of the therapy, intensity of sensory stimulation was calibrated to each subject; following baseline EEG recordings, sensory evoked 40 Hz steady-state oscillation and cortical coherence were established at the tolerated intensities. The randomized, controlled (RCT) phase of the trial lasted 6

months, during which therapy was self-administered at home with the help of a care partner. Patients, care partners, and assessment raters were blinded to group assignment. The RCT phase was followed by a 12-month open label extension (OLE) during which all participants received active treatment. Safety was evaluated by MRI, a suicidality scale, and physical and neurological exams at baseline, 12-, and 24-weeks, and by monthly assessments of adverse events (AEs) during the trial. Tolerability was measured by device use data, a daily diary, and user experience interviews. Symptomatic changes were assessed daily via a diary, monthly via Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL), Quality of Life, and care partner burden scales, quarterly via the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog14), Neuropsychiatric Inventory, Clinical Dementia Rating sum of boxes (CDR-sb), and bi-annually via Clock Drawing Test, and the Mini-Mental State Examination (MMSE). The Mild/Moderate Alzheimer's Disease Composite Score (MADCOMS), which combines elements of the ADAS-cog, MMSE and CDR-sb was also calculated. Plasma biomarkers, EEG recordings and brain volumetric changes (assessed by MRI), including whole brain, lateral ventricle, occipital and temporal lobe volumes, and temporal lobe composite cortical thickness were assessed at baseline and after 3 and 6-months of treatment. APOE status was characterized at baseline. Actigraphy devices were worn continuously throughout the trial to assess daytime and nighttime activity. **Results:** A total of 135 subjects were screened, 74 (55%) were randomized, and 53 completed (72%) the trial. The rate of AEs during the trial were roughly equivalent between groups (active: 2.5/subject, sham: 2.9/subject). There were no unexpected serious treatment emergent adverse events. Review of MRI data demonstrated absence of ARIA in all subjects. High adherence rates (over 90%) were observed in both sham and treatment subjects. Participants easily adopted and adhered to daily self-administered therapy, with 80% of participants who completed the RCT phase choosing to continue into the OLE. Among clinical instruments assessing cognitive and functional abilities, ADCS-ADL and MMSE were the most sensitive measures demonstrating positive outcomes of the therapy. Over the 6-month treatment period, changes in ADCS-ADL scores were statistically significantly better in the treatment group compared to sham, indicating a 78% slowing in functional decline ($P < 0.0003$). Similarly, the treatment group demonstrated a statistically significant 83% ($p < 0.013$) reduction in cognitive decline, as shown by changes in MMSE scores, compared to sham group. Other independent cognitive tests demonstrated a diminished cognitive decline in the treatment group compared to the sham group, although differences were not statistically significant. The outcomes of MADCOMS, ADAS-Cog14 and CDR-sb were not statistically different between groups. Nighttime active durations in the treatment group were significantly ($p < 0.03$) reduced in the second 3 months compared to the first 3-months and the opposite change was observed in the sham group, indicating an improved sleep quality in the treatment group subjects. Quantitative MRI analysis revealed that whole brain volume loss in the treatment group was 0.6%, whereas in the sham group this value was 1.5%, (comparable to the historic value of 1.12%), demonstrating a significant, 63% reduction in brain atrophy ($p < 0.01$) by gamma sensory stimulation over a 6-month period in this patient population. **Conclusion:** Long-term, daily, self-administered, home-use of gamma sensory stimulation is both safe and well tolerated in AD subjects. Patients given gamma stimulation therapy maintained cognitive and functional abilities and showed improved sleep quality.

In addition to ameliorating clinical symptoms, gamma sensory stimulation reduced brain atrophy, indicating potential disease-modifying effects in AD.

LB12- THE EARLY MILD ALZHEIMER'S COGNITIVE COMPOSITE (EMACC): A MEANINGFUL PRIMARY COGNITIVE ENDPOINT IN A PHASE 2 TRIAL OF XPRO1595 IN ALZHEIMER'S DISEASE (AD) WITH INFLAMMATION (ADI). Judith Jaeger^{1,2}, Melanie Buitendyk³, Christopher J. Barnum⁴ (1. *Cognitionmetrics - Stamford, CT (United States)*, 2. *Albert Einstein College Of Medicine - Bronx, Ny (United States)*, 3. *Cato-Sms - Wilmington, NC (United States)*, 4. *Immunebio - Boca Raton, FL (United States)*)

Introduction: Detecting meaningful signals of cognitive change in AD clinical trials presupposes a cognitive measure suitable for detecting change in the target population. A minimal requirement is the absence of floor and ceiling effects. Clinical trials in Mild Alzheimer's Disease (AD) have almost uniformly used the ADAS-Cog as the primary cognitive endpoint despite extensive empirical evidence of ceiling effects on most items and hence are 1) insensitive to change in the mild stage of the disease and 2) inaccurate measures of change magnitude since it is unknown how much change must occur to move the measure off of the ceiling. As many as 31 modified versions of the ADAS-Cog have been used seeking to overcome these limitations (Kuepers 2018), introducing the additional problem of rendering studies incomparable to one another. Efforts to improve metrics in early AD waned following an FDA draft guidance suggesting that CDR would overcome limitations in the ADAS-Cog and obviate the need for a functional coprimary endpoint. While now almost universally adopted as the endpoint of choice in early AD, study execution risks for CDR remain associated with rater and informant variance and expectancy bias. Further, CDR cannot provide a quantitative estimate of the magnitude of cognitive change, since ratings are rendered by clinical impression from brief testing and informant reports of everyday function. Hence there remains a need for a valid, reliable cognitive composite for treatment trials in early Mild AD. The Early Mild Alzheimer's Cognitive Composite (EMACC) was empirically developed through a multisite, multicohort collaboration (Jaeger, 2018). The EMACC consists of measures from six validated and widely used neuropsychological test paradigms that in combination 1) were shown to be maximally sensitive to disease progression in four independent longitudinal cohorts of amyloid confirmed cases and 2) mapped onto informant reports of clinically meaningful cognitive change on the eCog. EMACC measures have been reliably used in clinical trials assuring feasibility. The statistical power of EMACC was calculated and compared with that of the ADAS-Cog and CDR in planning a phase 2 trial of XPro1595, an immune modulator being tested in early Mild Alzheimer's patients with inflammation (ADi). **Methods:** Statistical power to detect change at 12 months on the EMACC was compared with that of the ADAS-Cog and CDR in the ADNI Cohort. Subjects included amyloid positive patients, CDR global rating of 0.5 or 1 and MMSE > 21 at baseline. Rates of change were compared between ADi and participants lacking inflammatory biomarkers (CRP > 1.5 mg/L and APOE4+). The EMACC score is the mean of standardized scores on: A word list learning paradigm, immediate recall; Digit Span Forward and Backward; Category Fluency (not available in ADNI and excluded from below analyses); Letter Fluency; Trailmaking A&B; Digit Symbol Coding. Sample size assumptions included 80% power, two-sided test, $\alpha = 0.05$. Clinically meaningful

differences over 12 months were prespecified for each measure. For EMACC this assumes placebo patients decline 0.25 while treated subjects will decline by 0.05 or remain stable (expected effect size (ES) = 0.20-0.25) with SD=0.33. For ADAS-Cog, we assumed placebo change of 3 points, that a 3-4 point change is clinically meaningful, that treated subjects will increase by 0.5 points or remain stable (ES= 2.5-3 score points) with SD=6.1. Finally for CDR we assume placebo patients will increase by 3 points, a 3-4 point change is clinically meaningful and that treated subjects will increase by 0.5 points or remain stable (ES=2.5 to 3.0), SD 6.1. **Results:** ADAS-Cog13 change over 12 months in the biomarker negative group (N=428, mean=1.79 (5.29), ES=0.33) was smaller than in the biomarker positive (ADi) group (N=64; 2.84 (6.12), ES=0.46). Overall 12 month change was greater on CDR-SB, but similar between the two biomarker groups. Using the EMACC the effect size difference in 12 month change between biomarker groups substantially larger than for ADAS-Cog or CDR-SB, and the effect size for the biomarker positive (ADi) group was large: Biomarker negative (N=437, mean=-0.13 (0.37), ES=0.37); Biomarker positive (ADi) (N=66, mean=-0.25 (0.33), ES=0.76). The differences in sample size required to determine a treatment affect was substantial when comparing EMACC, CDR-SB and ADAS-Cog 13 for ADi participants. For the prespecified upper and lower assumptions of meaningful difference between groups, respectively for these endpoints, sample size requirements were: EMACC=86 and 56, CDR=224 and 126, ADAS-13=188 and 130). **Conclusions and discussion:** ADi patients have higher rate of cognitive decline than AD patients lacking inflammatory biomarkers. EMACC yields clear sample size advantages over ADAS-Cog13 and CDR. New metrics are needed to accurately measure clinically meaningful cognitive change in mild and early AD clinical trials. The EMACC is an empirically derived composite of rigorously validated neuropsychological tests that measure cognitive operations which map onto clinically meaningful indices of progression in AD. **Conflicts of interest:** JJ is president of CognitionMetrics, LLC and MB is Associate Direct at CATO-SMS, both of which provide scientific consultation to INmune Bio. CJB is Chief Scientific Officer at INmune Bio. JJ and CJB own stock or stock options in INmune Bio. **References:** Kueper JK, Speechley M, Montero-Odasso M. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review. *J Alzheimers Dis.* 2018;63(2):423-444. doi: 10.3233/JAD-170991. PMID: 29660938; PMCID: PMC5929311. Jaeger, J, et al The Early AD/ MCI Alzheimer's Cognitive Composite (EMACC): Development and preliminary validation across four longitudinal cohorts of a cognitive endpoint for clinical trials in the MCI and Early AD stage of disease. (Abstract) *Journal of Prevention of Alzheimer's Disease*:4(4): 415-417, 2017

LB13- AN EXAMINATION OF COMPOSITE ENDPOINTS IN 5 COMPLETED OR TERMINATED AD PREVENTION TRIALS. Howard Mackey¹, Angelika Caputo², Michael Donohue³, Nan Hu¹, Jennifer Bogert⁴, Jingtao Wu⁵, Guoqiao Wang⁶ (1. Genentech - South San Francisco (United States), 2. Novartis Pharma Ag - Basel (Switzerland), 3. Alzheimer's Therapeutic Research Institute University Of Southern California - San Diego (United States), 4. Janssen Research & Development, Llc - Raritan (United States), 5. Takeda - Cambridge (United States), 6. Division Of Biostatistics, Washington University - St. Louis (United States))

Background: The urgent need for effective interventions to prevent and treat Alzheimer's Disease (AD) remains an

unfortunate challenge for the scientific community. Successful interventions will have an enormous, positive impact on public health. Controlled clinical trials, the gold standard for establishing effective treatments, have formidable hurdles in AD. Considerable time and resources are required to execute such trials, magnifying the importance of efficiency in trial design and in the use of powerful statistical methods. The relatively slow and gradual progression of AD requires lengthy and large trials with hundreds to thousands of participants. Prevention trials in particular have the added difficulty of enrolling participants who will measurably progress during the course of a study. As such, clinical endpoints in AD prevention trials need to be especially sensitive to change over time. Composite endpoints have been employed to address such challenges in AD prevention trials due to their potentially increased sensitivity to change over time. **Objectives:** We investigated the performance of composite endpoints in recently completed or terminated controlled clinical trials in order to inform the design and analysis of future prevention trials. **Methods:** We analyzed placebo groups from 5 completed or terminated AD prevention clinical trials: DIAN-TU (in cognitively impaired and unimpaired participants with dominantly inherited AD mutations), EARLY (in amyloid positive cognitively unimpaired participants), Generation 1 (in cognitively unimpaired participants with homozygous APOE4 mutations), Generation 2 (in cognitively unimpaired participants with homozygous APOE4 mutations or APOE4 heterozygous mutations who have elevated amyloid), and TOMMORROW (in cognitively unimpaired participants at high risk for AD). With respect to the primary or secondary composite endpoints used in each study, we explored baseline heterogeneity, prognosis heterogeneity, within subject variability, correlation between baseline and prognosis, as well as these measures' impact on sensitivity to decline over time. The composite endpoints examined were: the DIAN-TU cognitive composite, the Preclinical Alzheimer Cognitive Composite (PACC), the Alzheimer's Prevention Initiative Cognitive Composite (APCC), and the TOMMORROW Cognitive Battery Composite. A random coefficient regression model along with published analyses were used to estimate various parameters including the mean to standard deviation ratio (MSDR). Analyses controlled for the same factors specified in the primary analyses. Unexpected results will be highlighted and investigated. Implications for future AD prevention trials will also be outlined. **Results:** Approximately two thousand and twenty efficacy evaluable participants (TOMMORROW = 1406, Generation 2 = 456, Generation 1 = 186, EARLY = 180, DIAN-TU = 40) were randomized between December 2012 and Aug 2017 into the placebo arms of five clinical trials with unblindings announced between January 2018 and February 2020. The average follow-up exceeded two years in two studies (DIAN-TU and TOMMORROW) and was less than one year in the remaining three. Among the endpoints examined in the respective populations with extensive follow-up, the TOMMORROW Cognitive Battery Composite yielded a viable sensitivity to decline with a four-year MSDR of 0.67. The DIAN-TU cognitive composite yielded a small MSDR estimate in the expected direction, but not large enough to detect clinically meaningful effects. Improvement in the asymptomatic participants, presumably learning effects, appeared to account for the attenuated MSDR in the DIAN-TU cognitive composite. While the average follow-up in Generation 2 was limited to less than one year, its projected four-year MSDR was 0.9, suggesting the potential to detect clinically meaningful differences. EARLY and Generation 1 did not have estimated MSDRs in the

expected direction and learning effects were present, however, average follow-up was limited to less than a year due to early termination. **Conclusion:** In five completed or terminated AD prevention trials, two composite endpoints appeared to be sensitive to decline in their respective populations under study, while learning effects appeared to hinder endpoint performance in the remaining trials. Endpoints with minimal learning effects in cohort or prior studies have the potential to unexpectedly hinder a composite endpoint's performance in future clinical trials when larger learning effects occur. An area for future research may include adaptive methods that are able to adjust for such occurrences in an ongoing trial without inducing bias or inflating type I error.

LBR01- THE PROBABILISTIC MODEL OF ALZHEIMER DISEASE: THE AMYLOID HYPOTHESIS REVISED.

Giovanni Frisoni¹, Daniele Altomare¹, Dietmar Thal², Federica Ribaldi¹, Rik Van Der Kant³, Rik Ossenkoppele³, Kaj Blennow⁴, Jeffrey Cummings⁵, Cornelia Van Duijn⁶, Peter M. Nilsson⁷, Pierre-Yves Dietrich⁸, Philip Scheltens³, Bruno Dubois⁹ (1. *University Of Geneva - Geneva (Switzerland)*, 2. *University Of Leuven - Leuven (Belgium)*, 3. *Amsterdam Umc - Amsterdam (Netherlands)*, 4. *University Of Gothenburg - Gothenburg (Sweden)*, 5. *University Of Nevada Las Vegas - Las Vegas (United States)*, 6. *Erasmus University Medical Center - Rotterdam (Netherlands)*, 7. *Skåne University Hospital - Malmö (Sweden)*, 8. *Geneva University Hospitals - Geneva (Switzerland)*, 9. *Sorbonne Université - Paris (France)*)

The current conceptualization of Alzheimer's disease (AD) is driven by the amyloid hypothesis, a deterministic chain of events leading from amyloid and then tau deposition, to neurodegeneration and progressive cognitive impairment. This model fits autosomal dominant AD but is less applicable to sporadic AD. Owing to emerging information regarding the complex biology of AD and the challenges of developing amyloid-targeting drugs, the amyloid hypothesis needs to be reconsidered. We propose a probabilistic model of AD, in which three variants of AD (autosomal-dominant AD, APOE ε4-related sporadic AD, and APOE ε4-unrelated sporadic AD) feature decreasing penetrance and decreasing weight of the amyloid pathophysiological cascade, and increasing weight of stochastic factors (environmental exposures and lower risk genes). Together, these variants account for a large share of the neuropathological and clinical variability observed in people with AD. The implementation of this model in research might lead to a better understanding of disease pathophysiology, a revision of the current clinical taxonomy, and accelerated development of strategies to prevent and treat this disease.

LBR02- BASELINE EMBARK DATA FROM EMERGE, ENGAGE, AND PRIME PARTICIPANTS IN THE EMBARK RE-DOSING STUDY.

Sharon Cohen¹, Christopher Van Dyck², Catherine Mummery³, Anton Porsteinsson⁴, Jessica Kong⁵, Ryan Miller⁵, Annie Racine⁵, John O'gorman⁵, Samantha Budd Haeberlein⁵, Salloway Stephen⁶ (1. *Toronto Memory Program - Toronto (Canada)*, 2. *Alzheimer's Disease Research Unit, Yale School Of Medicine - New Haven (United States)*, 3. *Dementia Research Centre, Queen Square Institute Of Neurology, University College London - London (United Kingdom)*, 4. *University Of Rochester School Of Medicine And Dentistry - Rochester (United States)*, 5. *Biogen - Cambridge (United States)*, 6. *Alpert Medical School of Brown University - Providence (United States)*)

Background: Insoluble amyloid-β (Aβ) aggregates are a defining pathophysiological feature of Alzheimer's disease

(AD). Aducanumab is a human immunoglobulin gamma 1 monoclonal antibody targeting soluble and insoluble Aβ aggregates. On March 21, 2019, all ongoing aducanumab clinical trials were terminated based on a pre-specified interim futility analysis of the Phase 3 EMERGE (NCT02484547) and ENGAGE (NCT02477800) studies. In the Phase 3 studies, EMERGE (but not ENGAGE) met the pre-specified primary and secondary endpoints, showing significant reduction in clinical decline in participants treated with high dose aducanumab. EMBARK (NCT04241068) is an open-label extension study in participants who were enrolled in aducanumab trials at the time of their termination. EMBARK is designed to address two objectives: (1) the primary objective, to examine the long-term safety and tolerability of aducanumab after a wash-out period (imposed by the discontinuation of prior aducanumab studies) in participants who previously received aducanumab; and (2) to describe the changes in clinical and biomarker measures (exploratory objectives). **Objectives of this presentation:** To describe the demographic and baseline clinical characteristics, evaluate the amyloid positron emission tomography (PET) biomarker, and analyze the effect of amyloid clearance on clinical measures following the treatment gap preceding the EMBARK study in participants formerly enrolled in PRIME, EMERGE, or ENGAGE. **Methods:** EMERGE and ENGAGE were two randomized, double-blind, placebo-controlled (PC) trials to assess the efficacy and safety of aducanumab in participants with mild cognitive impairment (MCI) due to AD or mild AD dementia. The studies consisted of a 78-week PC period followed by an optional, dose-blind long-term extension (LTE) period. PRIME was a Phase 1b, double-blind, randomized clinical trial with a 12-month PC period followed by an LTE. EMBARK is an open-label, single arm study to assess the long-term safety and efficacy of aducanumab (10 mg/kg, the marketed dose), over 24 months in participants with AD who were formerly enrolled in the aducanumab clinical trials (PRIME, EVOLVE, EMERGE, or ENGAGE) at the time of study discontinuation (March 21, 2019). Participants from EVOLVE were not included in this analysis. Participants were eligible for EMBARK if they were enrolled in an aducanumab clinical trial at the time of study discontinuation, when all participants ceased receiving treatment. Other protocol-defined inclusion and exclusion criteria apply. Primary clinical assessments included the Clinical Dementia Rating-Sum of Boxes (CDR-SB), Mini-Mental State Examination (MMSE), AD Assessment Scale-Cognitive subscale (ADAS-Cog13), and AD Cooperative Study-Activities of Daily Living-MCI (ADCS-ADL-MCI). Cerebral Aβ plaque levels were measured by amyloid PET in a subset of participants who took part in the optional longitudinal amyloid PET substudies in EMERGE, ENGAGE, and PRIME. Adjusted mean changes were based on a mixed model for repeated measures (MMRM) with change from prior study baseline amyloid PET composite standardized uptake value ratio (SUVR). **Results:** A total of 902 participants from EMERGE, 868 participants from ENGAGE, and 29 participants from PRIME were screened in EMBARK. At EMERGE/ENGAGE baseline, participants who later enrolled in EMBARK had demographic and disease characteristics similar to those of the overall EMERGE and ENGAGE population. At EMERGE/ENGAGE baseline, demographic and disease characteristics were balanced with respect to: MCI due to AD (85% in patients from EMERGE and 83% in patients from ENGAGE); sex (50% and 54% female); mean age (69.9 and 69.2 years); ApoE ε4 status (65% and 70% carriers); mean CDR-SB score (2.42 and 2.34); mean MMSE score (26.4 and 26.6); and proportion of participants taking AD symptomatic medications (52% and

58%). Across all EMERGE and ENGAGE participants, the median gap period between the last EMERGE or ENGAGE visit and the baseline EMBARK visit was approximately 1.7 years. The median number of doses at EMBARK baseline was also comparable between corresponding high- and low-dose groups from EMERGE and ENGAGE. In the subset of EMERGE and ENGAGE participants who were evaluated by longitudinal amyloid PET, the reductions in amyloid PET composite SUVR observed in aducanumab-treated groups at the final PET scan were maintained during the treatment gap period (~1.7 years) leading up to EMBARK baseline. Analysis of change in clinical measures from EMERGE/ENGAGE/PRIME baseline stratified by amyloid PET composite SUVR (>1.10 or ≤1.10) at the last EMERGE/ENGAGE/PRIME visit will also be presented for the subset of participants with longitudinal amyloid PET data. **Conclusions:** Amyloid plaque reduction achieved with aducanumab treatment was maintained during the off-treatment gap, suggesting a prolonged effect on amyloid plaque levels; whether this effect would persist with a longer interruption of aducanumab treatment will need to be studied in the real world. EMBARK is ongoing and will further elucidate the long-term safety and efficacy of aducanumab.

LBR03- NATIONAL ALZHEIMER'S DISEASE CLINICAL TRIAL SITES' ACCOMMODATIONS TO THE COVID-19 PANDEMIC. Elizabeth Rhodus¹, Paul Aisen², Joshua Grill³, Dorene Rentz^{4,5}, Reisa Sperling^{4,5}, Ronald Petersen⁶, Stephen Salloway⁷, Doris Pierce⁸, Rema Raman⁹ (1. Sanders-Brown Center On Aging, University Of Kentucky - Lexington (United States), 2. Alzheimer's Therapeutic Research Institute, University Of Southern California San Diego - San Diego (United States), 3. University Of California, Irvine - Irvine (United States), 4. Massachusetts General Hospital, Harvard Medical School - Boston (United States), 5. Brigham and Women's Hospital, Harvard Medical School - Boston (United States), 6. Department Of Neurology, Mayo Clinic - Rochester (United States), 7. Butler Hospital And Brown University - Providence (United States), 8. Eastern Kentucky University - Richmond (United States), 9. Alzheimer's Therapeutic Research Institute, University Of Southern California, San Diego - San Diego (United States))

Background: The SARS-CoV-2 (COVID-19) pandemic has required numerous changes in clinical research and study site operations to protect study participants' safety and well-being. In particular, clinical research with older adults was of serious concern due to the increased susceptibility and serious consequences related to COVID-19 for this age group. Underlying health conditions, including Alzheimer's disease and related dementias (ADRD), added additional concerns for morbidity and mortality. Thus, clinical trials research for ADRD was drastically altered during 2020, and in some regions of the United States, has yet to fully re-engage. The Alzheimer's Clinical Trial Consortium (ACTC), led by 3 co-PI's with 11 Units and 35 member sites as a cooperative agreement supported by the National Institute on Aging, is a national clinical trials consortium whose mission is to accelerate and expand studies for therapies in Alzheimer's disease (AD) and related dementias. The lasting implications of halted research, altered methods of data collection, modifications required in statistical analytic approaches to preserve ongoing trial data, and decreased community engagement for ADRD research has yet to be fully identified. Exploring accommodation methods secondary to COVID-19 at ACTC member sites offer substantial opportunity to illuminate processes and mitigation strategies for ongoing clinical trial research during the onset

and height of this global pandemic. Such information may enhance understanding of preserved data and provide direction for emergent planning in future clinical trials development. **Objectives:** 1) To identify the process of accommodation employed by ACTC member sites in response to the COVID-19 pandemic. 2) To develop a theoretical framework of emergent mitigation strategies related to pandemic planning within ADRD clinical trials. **Methods:** This study used a qualitative, grounded theory approach. All thirty-five ACTC member sites were contacted for participation. Participants included ACTC site principal investigators (PI) and associate PIs, site liaisons, and site staff. Data collection included semi-structured one-on-one interviews with participants conducted virtually via Zoom videoconferencing. Analysis used grounded theory methods including: selective sampling; semi-structured interviews; constant comparative review of data; iterative development of coding schemes (open, axial, and thematic levels) from verbatim transcripts using HyperResearch software; triangulation in collection of trial modification reports (i.e., changes to protocols, recruitment, and/or analysis) secondary to COVID-19 pandemic; memo writing; theory development; negative case exploration and refinement of theoretical description; and member checks. **Results:** Forty-three participants were interviewed from 23 ACTC member sites (18 PIs, 4 associate PIs, 18 site liaisons, 4 site staff), which reflects a 63% response rate. Location of included study sites offered a representative sample throughout the United States, including California, Arizona, Washington, Kansas, Kentucky, Florida, South Carolina, Maryland, and New York among others. Open and axial coding have been completed thus far in data analysis. Twelve axial codes have been identified: elements aiding to successful operations, challenges, safety as a priority, office operations, staffing, remote work, policy formation, alterations to research procedures, scientific preservation, mindset, trials' participant outreach and contact, participants' trial leadership experience. These themes are representative of subcategories emergent from the data. Early results indicate heavy emphasis in the need for rapid changes, flexibility with remote work, financial reserve for protection of operations, and maintained safety for trials' participants as driving decisions. Data analysis is ongoing. Next steps include establishing theoretic concepts which illustrate the process of how ACTC sites accommodated to the COVID-19 pandemic. **Conclusion:** The COVID-19 pandemic required an onslaught of immediate changes related to Alzheimer's disease clinical trials operations. ACTC member sites accommodated to COVID-19 calls for safety and social distancing according to their state and university requirements. Adaptation to COVID-19 varied by site and by region throughout the country, as COVID-19 prevalence advanced or receded since the beginning of 2020. The heterogeneity of these adaptations by study site and by region may inadvertently have long-term implications for ADRD clinical trial research. This report offers a historical perspective for future comparison and investigation of the lasting implications. Additionally, the processes used to accommodate for COVID-19 can create a theoretical framework which can offer guidance for pandemic management planning in future clinical trial development. **Funding:** This project was completed in partnership with the Alzheimer's Clinical Trial Consortium (ACTC) and the Institute on Methods and Protocols for Advancement of Clinical Trials in ADRD (IMPACT-AD). ACTC is funded by a Cooperative Agreement from the National Institute on Aging, National Institutes of Health (ACTC grant (NIH/NIA U24 AG057437, Aisen / Sperling / Petersen, Multi-PI) and IMPACT-AD is funded by: NIA U13AG067696, NIA U24AG057437, and Alzheimer's Association SG-20-693744. The

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LBR04- DEFINING A STANDARDIZED MRI ACQUISITION PROTOCOL TO BE PROPOSED TO ICARE AD-US SITES FOR BASELINE AND ARIA MONITORING.

Tammie L. S. Benzinger¹, Frederik Barkhof², Alex Rovira³, Tobias Kober⁴, Christopher T. Whitlow⁵, Michael Smith⁶, Christina, M. Grassi⁶, Elizabeth Fisher⁶ (1. Washington University School Of Medicine, Department Of Neurology - St. Louis (United States), 2. Department Of Radiology And Nuclear Medicine, Amsterdam Neuroscience, Amsterdam Umc, Vrije Universiteit - Amsterdam (Netherlands), 3. Section Of Neuroradiology, Vall D'Hebron University Hospital - Barcelona (Spain), 4. Advanced Clinical Imaging Technology, Siemens Healthcare - Lausanne (Switzerland), 5. Wake Forest School Of Medicine - Winston-Salem (United States), 6. Biogen - Cambridge (United States))

Background: Aducanumab is a human IgG1 monoclonal antibody (mAb) targeting soluble and insoluble amyloid beta (A β) aggregates. Aducanumab was recently granted accelerated approval by the US Food and Drug Administration for treatment of early Alzheimer's disease. Biogen is establishing the International Collaboration for Real-World Evidence in Alzheimer's Disease (ICARE AD-US) as a real-world observational study to evaluate the safety and effectiveness of aducanumab in ~200 centers across the US. Amyloid-related imaging abnormalities (ARIA) represent a spectrum of imaging findings detected on brain magnetic resonance imaging (MRI) and are associated with the use of A β -targeting mAbs, including aducanumab, in patients with Alzheimer's disease. ARIA imaging findings include brain edema or sulcal effusion (ARIA-E) as well as hemosiderin deposits resulting from hemorrhage in the brain parenchyma or on the pial surface (ARIA-H). Although MRIs are typically included in a diagnostic assessment for dementia, they are not currently acquired in a standardized manner. To monitor and manage ARIA events associated with aducanumab treatment, the ADUHELM US prescribing information requires MRI monitoring for ARIA to occur prior to the 7th aducanumab infusion (immediately prior to the first dose of 10 mg/kg) and the 12th infusion (6th 10 mg/kg infusion). These scheduled brain MRIs coincide with the time period of enhanced clinical vigilance for ARIA, informed by Phase 3 trial data. Ad hoc imaging, when clinically indicated, is also a component of the MRI monitoring plan (ie, any time during treatment if there is clinical concern for ARIA). Brain MRI is also used to monitor brain changes, such as atrophy and white matter lesions associated with Alzheimer's disease progression. Consistency in MRI acquisition is important for efficient treatment and to overcome heterogeneity in the generation of real-world evidence. **Objectives:** We describe a core standardized MRI protocol to be implemented at ICARE AD-US study sites for monitoring ARIA and evaluating disease progression. Practical considerations, such as the incorporation of fixed sequence parameters commonly used in clinical practice and/or sequences that have been standardized in previous observational/clinical studies to monitor ARIA events and disease progression, have been implemented. The proposed protocol also adheres to regulatory requirements. **Methods:** ICARE AD-US is a prospective, single-arm, multicenter study of aducanumab as prescribed in routine clinical practice. In the US, this study aims to enroll ~6000 patients with Alzheimer's disease. Patients will be monitored for up to 5 years. The primary objective of ICARE AD-US is to characterize and

evaluate real-world, long-term changes in cognition, function, and neuropsychiatric status in aducanumab-treated patients. Secondary objectives include: (1) evaluating the incidence of adverse events, including serious adverse events (SAEs), and comparing the incidence of SAEs in aducanumab-treated patients with and without ARIA; (2) assessing the incidence and the clinical and radiographic outcomes of ARIA associated with aducanumab treatment; (3) estimating the incidence of symptomatic ARIA in real-world clinical practice; and (4) obtaining descriptive statistics on the characteristics of the aducanumab user population and on drug utilization. MRI will be performed for all patients per standard of care and in compliance with the US prescribing information at baseline, prior to 7th and 12th infusions, and every 6 to 12 months thereafter for up to 5 years. The proposed core standardized MRI protocol includes 4 sequences: 3D T2-weighted fluid-attenuated inversion recovery (FLAIR), 2D T2*-weighted gradient-recalled echo (GRE), diffusion-weighted imaging (DWI), and 3D T1-weighted anatomic imaging (optional). The 3D-FLAIR sequence used in the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol and the T2* GRE sequence used in the Phase 3 EMERGE and ENGAGE trials of aducanumab are recommended to assess and monitor ARIA-E and ARIA-H, respectively. 3D-FLAIR imaging is recommended to detect ARIA-E given that it suppresses cerebrospinal fluid flow artifacts and increases confidence in ARIA-E detection. GRE sequence is recommended for ARIA-H detection rather than SWI given that GRE sequence is optimized for detection of blood and that the increased sensitivity of the SWI sequence may change or invalidate current thresholds for inclusion and monitoring. The core MRI protocol also recommends including DWI for differential diagnosis, and optional 3D T1-weighted imaging to facilitate post-processing and assessment of disease progression. This combination of 4 MRI acquisitions in the core protocol will enable standardized assessment of ARIA and Alzheimer's disease-related changes over time in a manner that is consistent with the clinical trials and regulatory requirements. Furthermore, this combination is feasible in terms of both acquisition time and implementation while remaining clinically relevant and additionally enabling the collection of valuable real-world data. **Results:** The proposed standardized MRI protocol will facilitate monitoring and assessment of ARIA with aducanumab treatment in the real-world and allow for consistent evaluation of Alzheimer's disease progression. **Conclusions:** Establishing a standardized brain MRI protocol will harmonize collection of longitudinal data in the real world and inform the aducanumab benefit/risk profile. The protocol lays a foundation for overcoming existing heterogeneity of data collection in clinical practice.

LBR05- TOP-LINE RESULTS FROM TANGO, A PHASE 2 STUDY OF GOSURANEMAB IN PARTICIPANTS WITH MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE AND MILD ALZHEIMER'S DISEASE.

Melanie Shulman, Raj Rajagovindan, Jessica Kong, John O'gorman, Louis Viollet, Ellen Huang, Heike Hering, Elena Ratti, Danielle Graham, Samantha Budd Haeberlein (Biogen - Cambridge (United States))

Background: Gosuranemab, a humanized IgG4 monoclonal antibody that binds tau at the N-terminus, was evaluated in the TANGO (NCT03352557) phase 2 trial, testing the hypothesis that antibody engagement of extracellular tau in the brain would slow progression of Alzheimer's disease (AD). The trial assessed the safety, efficacy, pharmacokinetics (PK), and

pharmacodynamic (PD) effects of gosuranemab in participants diagnosed with mild cognitive impairment (MCI) due to AD and mild AD. Disease-related biomarkers were also examined. **Methods:** In this global randomized, double-blind, placebo-controlled, parallel-group Phase 2 study, we investigated effects of gosuranemab over 78 weeks in participants with MCI due to AD or with mild AD positive for amyloid-pathology by cerebrospinal fluid (CSF) or positron-emission tomography (PET). Participants were randomized to receive gosuranemab in a low dose (125 mg once every 4 weeks or 375 mg once every 12 weeks), medium dose (600 mg once every 4 weeks), or high dose (2000 mg once every 4 weeks), or placebo (once every 4 weeks) via intravenous infusion in a 1:1:2:2 ratio. For the placebo-controlled period, the primary objective of the study was to evaluate the safety and tolerability of gosuranemab. Secondary objectives of the study included evaluating the clinical efficacy and immunogenicity of multiple doses of gosuranemab over 78 weeks. The study's primary clinical efficacy endpoint was a change from baseline at Week 78 on Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB). Biomarker sub-studies tested the effects of gosuranemab on tau levels in CSF (CSF substudy) and brain (MK6240 tau-PET imaging substudy). **Results:** 654 participants were randomly assigned to treatment; 650 received at least one dose of study drug; gosuranemab (n=436) or placebo (n=214). The TANGO study population was almost equally divided between MCI (n=303, 47%) and mild AD (n=347, 53%). Approximately half of TANGO participants were enrolled in the tau-PET sub-study (n=357), and the other half were in the CSF substudy (n=327); 34 participants enrolled in both substudies. Demographics and baseline characteristics were balanced across treatment groups and were similar to contemporary AD clinical trials. Mean (SD) duration of symptoms was 4.11 (2.66) years and mean (SD) time since diagnosis was 1.54 (1.65) years. The proportion of participants receiving symptomatic AD medications at baseline was 64.6%, and the proportion of APOE4 carriers was 70.9%. A total of 22% of participants discontinued treatment. Gosuranemab was well-tolerated overall, and safety outcomes were consistent with previous studies of the molecule. Primary efficacy endpoint of change from baseline on the CDR-SB at Week 78 was not met. No doses showed a positive separation from placebo on CDR-SB; high dose (2000 mg) mean change from baseline at Week 78 was identical to placebo. No treatment benefit was seen on exploratory efficacy endpoints at Week 78, including but not limited to the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Mini-Mental State Examination (MMSE), and Functional Activities Questionnaire (FAQ). Target engagement was demonstrated with robust lowering of unbound N-terminal tau in the CSF which was sustained over time, consistent with previous studies of gosuranemab. The changes in unbound N-terminal tau in the CSF for gosuranemab versus placebo were statistically significant for all treatment groups and timepoints. No statistically significant treatment effect was observed on tau-PET at Week 78 for any dose group. **Conclusion:** Targeting extracellular N-terminal tau with gosuranemab did not result in clinical benefit in participants with MCI due to AD or mild AD. Based on lack of efficacy in the placebo-controlled period, the TANGO long-term extension study has been terminated, and the clinical development of gosuranemab in AD has been discontinued.

LBR06- ORAL TREATMENT WITH OLX-07010, A SMALL MOLECULE INHIBITOR OF TAU SELF-ASSOCIATION, REDUCED TAU AGGREGATION TO BASELINE IN A THERAPEUTIC STUDY OF AGED TAU P301L JNPL3 MICE. James Moe¹, Patricia Lopez², Heidy Jimenez-Bravar³, Adrien Leslie³, J Eun³, Adam Wolin³, Jeremy Koppel³, Peter Davies³, Dhruv Patel², Eliot Davidowitz² (1. Oligomerix, Inc. - White Plains (United States), 2. Oligomerix, Inc. - Bronx (United States), 3. Feinstein Institutes For Medical Research - Manhasset (United States))

Background: Tau has been implicated in the pathogenesis of multiple neurodegenerative diseases associated with the accumulation of abnormal species of tau. Mutations in the MAPT gene can cause a range of rare inherited tauopathies to develop due to overproduction of specific tau isoforms or changes in the structure of tau, both of which can cause tau to aggregate. Various post-translational modifications regulate normal physiological function of tau but an imbalance in them disrupts tau's normal function causing its aggregation. Neurofibrillary tangles, composed primarily of tau, accumulate in a highly reproducible spatiotemporal order starting in the transentorhinal/entorhinal regions and spreading through the hippocampal structure to the neocortex demonstrating a close association between tau aggregation and AD progression. Although neurofibrillary tangles are pathological hallmarks associated with AD and related tauopathies, their role in causing neurodegeneration has been questioned. Multiple studies have shown that tau oligomers, not fibrils or tangles, are closely correlated with neuronal loss and memory impairment. We have shown that tau oligomers cause disruption of neuronal signaling and inhibit the formation of memory in mice (Moe et al., 2010; F M et al., 2016). Memory formation was impaired following administration of oligomeric tau to hippocampi, areas of the brain involved in short-term memory formation. But similar treatment with tau monomer (that did not self-associate) did not have an effect. This impairment of memory was also found using tau oligomers formed from hyperphosphorylated tau purified from human AD brain specimens. Memory-specific mechanisms involved in gene regulation were shown to be disrupted by these extracellular tau oligomers. We have found that certain forms of tau oligomers are toxic when applied to cultured neurons, whereas tau monomer was not toxic at the same concentrations (Tian H et al., 2013). Our in vivo efficacy studies were carried out in two different transgenic mouse models, the htau model that expresses all 6 human isoforms with no mutations (Davidowitz EJ et al., 2020), and the JNPL3 model that expresses human 4R tau with a P301L mutation. This program seeks to develop an oral, self-administered, small molecule DMT for AD targeting tau self-association, the rate limiting, first step in its aggregation. Oligomerix has developed a lead series of compounds optimized for CNS penetration and drug-like properties using a strategy to block the initial step in tau aggregation to reduce the accumulation of all types of tau aggregates. IND-enabling studies are in progress to advance the lead OLX-07010 into a planned Phase 1a first-in-human study. **Objectives:** The purpose of this study was to evaluate if treatment of aged mice with OLX-07010 could have a therapeutic effect in the context of pre-existing tau aggregates and progressing tau aggregation. As JNPL3 is a model of 4R tau aggregation expressing tau with a mutation causing inherited forms of progressive supranuclear palsy (PSP) and frontotemporal dementia, this study also addressed the potential of evaluating OLX-07010 in a Phase 1b study in patients with PSP. **Methods:** Blinded studies of homozygous

female tau 4R/0N P301L JNPL3 mice were performed at an independent laboratory where mice were treated for five months by administration of our lead compound in feed from 7 to 12 months-of-age. The four groups of mice in the study were baseline (7 months; n=20), vehicle, and two treatment groups (40 and 80 mg compound/kg mouse doses; n=25 each). To quantify levels of Sarkosyl-insoluble tau, self-associated tau, and phosphorylated tau in the treatment and control groups of mice ELISAs were performed (Acker et al., 2012; Forest et al., 2013). Rotarod and open field studies were performed to evaluate motor behavior. **Results:** Treatment groups had baseline levels of self-associated tau, Sarkosyl insoluble tau and heat stable tau. The 40 mg/kg treatment reduced insoluble tau in the hindbrain. Tau aggregates with aberrantly phosphorylated tau were also reduced. Evaluation of motor behavior showed that treatment groups showed improved Rotarod performance compared to baseline and vehicle groups. The results from these studies have statistical significance. **Conclusion:** Treatment with the lead caused significant reduction in tau aggregates in blinded preventive studies in the htau model and showed efficacy in both preventive and therapeutic studies in JNPL3 mice modeling 4R tau aggregation in tauopathies. Taken together these studies support the development OLX-07010 for the reduction of tau oligomers and larger aggregates to modify the course of AD and rare tauopathies. Our small molecule approach allows for ease of administration, complementary therapy and, importantly, a cost-effective treatment option. **References:** Moe JG et al, Prog. No. 527.8. 2010 Neuroscience Mtg. Planner. San Diego, CA: SfN, 2010. Online; F M et al., Sci Rep. 2016 Jan 20;6:19393. PMC4726138; Tian H, et. al., Int J Cell Biol. 2013, 260787, PMC3789488; Davidowitz EJ et al., J Alzheimers Dis. 2020; 73(1):147-161. PMC6957711; Acker CM et al., Neurobiol Aging. 2013 Jan;34(1):338-50, PMC3474864; Forest SK, et al., J Alzheimers Dis. 2013;33(2):463-71, PMC3627375.

LBR07- ANALYZING THE CSF PROTEOME TO SUPPORT DECISIONS IN AN AD CLINICAL TRIAL PROGRAM.

Ian Pike¹, Sasa Koncarevic², Juliane Weisser², Michael Bremang², R J Tesi³, C J Barnum³ (1. Proteome Sciences Plc - London (United Kingdom), 2. Proteome Sciences R&D GmbH & Co Kg - Frankfurt (Germany), 3. Immunebio - Boca Raton (United States))

Background: AD is characterized by synaptic dysfunction and nerve cell death with beta-amyloid (A β) plaques and tau tangles prominent in the hippocampus and cortex, though the causal relationship between those misfolded proteins and the pathogenesis of the disease is still debated. Modern genomic and proteomic technologies are providing a wealth of biomarkers and their early use in clinical trials has been successfully embraced in oncology drug development where the annual approvals of drugs dwarfs that of CNS drugs. This suggests that aggressive use of biomarkers can contribute to this success? However, the currently accepted biomarkers related to A β and pTau 181 do not provide sufficient insight to novel therapeutic strategies. Brain biopsy is not possible in the majority of CNS drug development programs. We have therefore, used unbiased analysis of the CSF proteome to make decisions on future clinical trial design including dose, therapeutic strategies, biomarkers, resource allocation and future development opportunities. **Methodology:** CSF from patients before and after drug treatment was analyzed using Proteome Sciences TMTcalibratorTM that combines tissue and fluid phospho-proteomics to identify disease-related proteins with evidenced availability for peripheral detection. Using

isobaric labelling with TMTproTM reagents, high levels of AD brain cortex lysate were mixed with similarly labelled digests of CSF so that the abundant tissue-derived peptides trigger the mass spectrometer and TMTproTM signals can then readily determine whether the same peptide is also present in the CSF. Use of off-line phosphopeptide enrichment and fractionation allowed a deep analysis of the CSF proteome with a direct link to expression at the site of disease. Sophisticated bioinformatics based on machine learning were used to model variance in peptide, phosphopeptide and protein expression changes in response to treatment. **XPro Case Study:** An open label Phase Ib study of XPro in patients with AD was completed. Patients received XPro once a week for 12 weeks at 0.3, 0.6 or 1.0 mg/kg for 12 weeks. CSF was collected before treatment and after 12 weeks of therapy. Overall, 35,443 distinct peptide sequences associated with 4,966 protein groups were quantified and statistically evaluated in CSF, representing a complex dataset. Functional analysis showed that treatment-responsive CSF proteins were related to biological processes and pathways such as neurodegeneration, CNS neuronal organization, synaptic function, immune and inflammatory response, cytoskeleton, metabolism, Rho GTPases signaling, and myelination. A few examples of changes after 12 weeks of high-dose treatment in individual protein levels related to - neurodegeneration: NFL \downarrow 84%; pTau217 \downarrow 46%; pTau181 \downarrow 2%; Vilip-1 \downarrow 91%; and synaptic function - Contactin 2 (\uparrow 222%; Neurogranin \downarrow 56%); and remyelination: (\uparrow 25% myelin regulatory factor) are listed. Furthermore, analysis of proteome data demonstrates a clear dose response based on total proteins analyzed (volcano plots) and within individual proteins e.g. phosphoTau217 (pT217). **Conclusions:** AD trials need biomarkers beyond amyloid and tau that accurately reflect changes in the biology associated with progression of the disease and/or therapeutic intervention. The CSF proteome can be a valuable "window" into the changing biology of the brain but sensitive detection of subtle treatment effects are hampered by complexity and dynamic range. The Phase I clinical trial testing XPro for the treatment of neuroinflammation in patients with AD has analyzed the CSF proteome using the Proteome Sciences TMTcalibratorTM to: i) learn new effects of XPro on the brain in patients with AD. Neuroinflammation was expected to decline based on pre-clinical data. Effects on neurodegeneration, synaptic function and remyelination were surprises; ii) define the dose to be used in the Phase II trial. The unique biology of a dominant negative protein does not allow for direct measurement of target engagement. Indirect measures of target engagement are based on down-stream effects of target engagement. The effects on proteins measured in the CSF provided an accurate dose response based on changes in the proteome. This allows the company to chose 1mg/kg/week as the only dose in the Phase II clinical program; iii) identified practical biomarkers to use for Phase II program. The dramatic effects on pT217 were unexpected. This biomarker or neurodegeneration in AD patients will be developed as a surrogate biomarker; iv) provides a road-map for the ideal combination therapy which is increasingly seen as necessary for optimized treatment of AD. The detailed vision of the biologic effect on the CNS proteome will help pair XPro with a drug that offers optimal synergy with few safety liabilities; and v) confirmed additional drug development opportunities for XPro. We have directly shown a CSF biomarker (myelin regulatory factor) supporting imaging data (decreased radial density, a biomarker of remyelination measured by MRI/DTI of white matter) and pre-clinical data. This further supports XPro as a drug promoting remyelination providing additional development opportunities, such as in

multiple sclerosis and other de-myelinating disorders in the future.

LBR08- PREDICTION OF BRAIN AMYLOID PATHOLOGY USING PLASMA A β 42/40 RATIO MEASURED USING THE C2N PRECIVITYADTM TEST IN THE MISSION AD STUDY SAMPLES. David Verbel¹, Michelle Gee², June Kaplow¹, Michio Kanekiyo¹, Michael Irizarry¹, Shobha Dhadda¹, Akihiko Koyama¹, Tim West³, Matt Meyer³, Kris Kirmess³ (1. Eisai Inc. - Woodcliff Lake (United States), 2. Eisai Ltd. - Hatfield (United Kingdom), 3. C 2 N Diagnostics - St. Louis (United States))

Background: Alzheimer's disease (AD) is the most prevalent form of dementia with significant global public health impact. Confirming amyloid pathology in the brain will impact the patient's treatment course and from a clinical trial perspective, less invasive tools that can pre-enrich the pool of study candidates with those likely to be amyloid positive will reduce screen failures if amyloid positivity is required for trial entry. Plasma amyloid beta (A β 42/40 ratio) is a candidate biomarker for early detection of amyloid pathology since amyloid PET, the current standard to detect brain amyloid pathology, is limited by cost and accessibility. Previously, the C2N PrecivityADTM test used plasma from several cohorts to predict brain amyloid positivity based on PET SUVR (Schindler et al 2019, West et al 2021). In this study, results generated by the C2N PrecivityAD test were used to estimate the performance of plasma A β 42/40 ratio in predicting brain amyloid positivity based on PET visual read. Samples used in these analyses were provided from Eisai's MissionAD studies in Mild Cognitive Impairment (MCI) and mild AD subjects. **Objectives:** The primary objective of this study was to assess the performance of the blood-based C2N PrecivityADTM test in distinguishing amyloid positive from amyloid negative subjects when applied to outcomes based on PET visual read. **Methods:** Plasma samples from a screening sample of 516 subjects were included in the analysis. Approximately half of the samples were derived from subjects determined to be amyloid negative and half from amyloid positive subjects. MissionAD studies allowed the use of three approved amyloid PET tracers (Neuraceq, Vizamy, and Amyvid). Selection of samples was also balanced in terms of gender and ApoE4 status. Area under the receiver operating characteristic (ROC) curves were generated using logistic regression exploring predictive accuracy of the plasma A β 42/40 ratio and additional covariates. Performance was assessed by calculating the AUC, identifying a cutpoint using the Youden's index, and reporting the sensitivity, specificity, positive- and negative-predictive values. For exploratory purposes, a centiloid (CL) cut-off was also derived using visual read to define amyloid positivity and used as the reference. Analyses were repeated comparing the plasma A β 42/40 ratio to predict brain amyloid positivity when applied to outcomes based on this CL-defined endpoint. **Results:** Samples from 516 subjects were selected. The mean (SD) age of the cohort was 72.5 (6.49) years; 89.7% of subjects were White and 52.3% were Male. ApoE4 status was positive in 45.9% of subjects. 94.4% of subjects were considered as having MCI due to AD. Samples from n=513 subjects were included in the statistical analyses. The C2N PrecivityADTM test showed good performance using only the plasma A β 42/40 ratio in predicting brain amyloid positivity for visual read (AUC=0.81; 95% CI= 0.78-0.85). Performance was unchanged after the addition of age and/or ApoE4 status. When predicting amyloid positivity as defined by a PET CL cut-off of greater than or equal to 32.20 looking again at the plasma A β 42/40 ratio independent of covariates,

AUC increased to 0.84 and sensitivity increased to 91% from 85%; specificity remained the same (69% vs 68%), and the PPV and NPV were similar using the two different approaches to defining a subject as amyloid positive or negative. As with visual read, performance was unchanged after the addition of age and/or ApoE4 status when using a CL-defined endpoint. The cutoff of the plasma A β 42/40 ratio estimated to optimally distinguish between amyloid positive and negative subjects using either visual read or CL-based criteria as the reference was ≤ 0.092 for positivity in both approaches. **Conclusion:** Based on these results after evaluating against both visual read and CL, the C2N PrecivityADTM test measuring A β 42/40 ratio shows potential for use as a screening tool to enrich for subjects considered likely to be brain amyloid positive.

LBR09- EVALUATION OF TAU DEPOSITION USING 18F-PI-2620 PET IN MCI AND EARLY AD – A MISSIONAD TAU SUB-STUDY. Santiago Bullich¹, Andre Mueller¹, Susan De Santi², Norman Koglin¹, Stephen Krause², June Kaplow², Michio Kanekiyo², N ria Ro -Vellv ¹, Audrey Perrotin¹, Aleksandar Jovalekic¹, David Scott³, Michelle Gee², Andrew Stephens¹, Michael Irizarry² (1. Life Molecular Imaging (Germany), 2. Eisai (United States), 3. Bioclinica (United States))

Background: Alzheimer's disease (AD) is characterized by abnormal accumulation of misfolded extracellular amyloid-beta and intracellular neurofibrillary tangles of tau proteins, which are associated with synaptic disruption and subsequent neuronal death. The ability of 18F-PI-2620 PET to measure the spatial distribution of tau pathology in AD was demonstrated previously (Mueller et al., J Nucl Med. 2020;61(6):911-919.). However, the lack of success of therapeutic clinical trials in reducing the cognitive decline in established AD has encouraged investigators to start intervention at the earliest possible phase when abnormalities in amyloid biomarkers are detectable even at the asymptomatic stage. **Objective:** The objective of this work was to evaluate tau deposition using 18F-PI-2620 PET tracer in beta-amyloid positive patients with a diagnosis of MCI or mild AD dementia and characterize it with respect to amyloid deposition, CSF amyloid- β /tTau/pTau, hippocampal volume, and neurocognitive domains of a series of cognitive instruments. **Methods:** The study population consisted of patients with a diagnosis of MCI due to AD (n=72) or mild AD dementia (n=2) from the elenbecestat Mission AD Phase 3 program (n=74, 76 \pm 7 yrs, 38 females) who were invited to join a 18F-PI 2620 tau PET imaging sub-study. For this work, only subjects on the placebo arm of the MissionAD studies and with an amyloid-positive 18F-Florbetaben (FBB) PET scan by central visual assessment were included. Sub-study inclusion criteria were MCI due to AD or mild AD dementia including: MMSE > 24, CDR global score of 0.5, CDR Memory Box score > 0.5, and impaired episodic memory confirmed by a list learning task. All subjects recruited in the tau sub-study underwent a baseline 18F-PI-2620 PET, T1-weighted magnetic resonance imaging (MRI), and several cognitive tests (International Shopping List Test (ISLT), Cogstate Brief Battery (CBB), CDR, MMSE, Alzheimer Disease Assessment Scale-Cognitive (ADAS Cog), and Functional Activities Questionnaire (FAQ)). Cerebrospinal fluid assessment (A β 42-A β 40 ratio, p-tau, t-tau) was performed in a subset of subjects at baseline (n=22). A one-year follow-up including a 18F-PI- 2620 and 18F-Florbetaben PET scan and cognitive assessments (CDR, MMSE, ADAS-Cog, and FAQ) was done in a subset of subjects (n=13). **Results:** Visually positive tau scans increased with the amount of

amyloid-beta deposition. 7.7% (1/13) subjects with <36 CL FBB had a visually positive PI-2620 scan, while 80% (24/30) subjects with >83 CL of FBB had visually positive 18F-PI-2620 scans. Elevated FBB composite SUVR in the brain was associated to low CSF A β 42-A β 40 ratio (p=0.004). Elevated PI-2620 SUVR was associated to high p-tau and t-tau (p=0.0006 and p=0.01 (fusiform gyrus), respectively) in CSF. Low hippocampal volume was associated with increased tau load at baseline. Longitudinally, significant increases in tau SUVR were observed in these untreated subjects after 12 months, particularly in the mesial temporal cortex, fusiform gyrus, and inferior temporal cortex. However, no statistically significant increase in amyloid-beta was observed over time in any of the cortical regions analyzed. Exploratory analyses were performed to identify the association between cognitive measurements and tau deposits in the brain. The MMSE (Recall score), and ADAS-Cog (Word recognition score) and CBB (One-card learning score) showed the strongest association with tau deposition at baseline with consistent p-values below 0.05 (without correction for multiple comparisons) in the mesial temporal, fusiform gyrus and inferior temporal cortex. Other cognitive assessments reaching p-values below 0.05 in some regions were ISLT (delayed recall), CBB (identification), CDR (orientation and global scores), MMSE (registration, repetition, and total scores), and ADAS-Cog (word recall, delayed word recall, naming objects/fingers, and total scores). **Conclusions:** This study supports the utility of 18F-PI-2620 PET to assess tau deposits in an early AD population. 18F-PI-2620 SUVR values demonstrated significant correlations with established structural and CSF biomarkers and inverse correlations with cognitive scores in domain-specific patterns. The findings support the hypothesis that PET imaging of neuropathologic tau deposits may reflect underlying neurodegeneration in AD. The results provide a preliminary characterization of the longitudinal spread of tau in Alzheimer's disease and suggest that the amount and location of tau may have implications both for the spread of tau and the cognitive deterioration that may occur over a 12-month period. Increases in 18F-PI-2620 accumulation can be clearly quantitated over a year and may be an important target engagement marker in clinical trials with either anti-amyloid or anti-tau agents. These results suggest development of tau beyond the mesial temporal lobe is associated with, and may be dependent on, amyloid accumulation. Further, the results are consistent with the hypothesis that cortical tau is associated with cognitive impairment.

LBR10- THE IMPACT OF THE COVID-19 PANDEMIC ON COGNITIVE HEALTH. Helen Brooker¹, Vincent Hayman², Dag Aarsland³, Byron Creese², Clive Ballard², Anne Corbett² (1. Exeter University Medical School - Exeter (United Kingdom) - Exeter (United Kingdom), 2. Exeter University Medical School - Exeter (United Kingdom), 3. 2department Of Old Age Psychiatry, Institute Of Psychiatry, Psychology & Neuroscience, Maurice Wohl Clinical Neuroscience Institute, King's College London - London (United Kingdom))

Background: The challenged presented by the COVID-19 pandemic has had an extraordinary far-reaching impact on society. The clinical impacts of COVID-19 are one thing, but it is evident that the social restrictions have had a considerable impact on individuals mental health. If there is to be any learning from this pandemic, then it is critical that we improve future responses that support mental health. PROTECT presents the perfect cohort to look at the changes that have occurred during the pandemic. **Objectives:** To assess the impact of

the COVID-19 pandemic on a healthy longitudinal cohort. To take measures of depression and anxiety and understand their change in the COVID-19 pandemic and impact to cognition. **Methods:** PROTECT is an innovative online study (www.protect.org.uk) in adults aged 50 and over in the UK, Participants complete annual cognitive assessment and health measures including the PHQ-9 and GAD-7. Using baseline data from the cognitive assessment battery. This analysis utilised data from a total of 6301 participants followed annually over the last 5 years, including the year of the COVID-19 pandemic. It also utilises the newly published FLAME composite cognitive measure that has shown sensitivity to cognitive decline. **Results:** In the participants with worsening PHQ-9 and GAD-7 scores between 2019 and 2020 (63%), composite measures of Speed [p=0.005, d=0.19], and accuracy of Attention [p=0.0021, d=0.18, Memory [p=0.0005, d=0.24] and Executive Function [p=0.0007, d=0.8], as well as the composite FLAME measure [p=0.0010, d=0.6], showed a larger decline over the last 12 months compared to the prior assessment period. Whilst no significant increase in the rate of decline was seen in people without worsening of depression or anxiety. **Conclusion:** The pandemic has had a detectable and significant detrimental impact on key aspects of cognitive health in adults over 50, mediated predominantly through worsening of mental health as a result in large part of lockdowns. **Conflict of interest:** Helen Brooker has worked as an employee for a company supplying some of the cognitive tests used in this research and has also developed some of the cognitive tests used in this research.

LBR11- UTILITY OF PLASMA AB1-42/AB1-40 AS A SCREENING TOOL IS LIMITED DUE TO LACK OF ROBUSTNESS. Christina Rabe¹, Tobias Bittner^{1, 2}, Alexander Jethwa³, Ivonne Suridjan⁴, Ekaterina Manuilova³, Henrik Zetterberg^{5,6,7}, Kaj Blennow^{5,6}, Oskar Hansson^{8,9} (1. Genentech, Inc. - South San Francisco (United States), 2. F. Hoffmann-La Roche Ltd - Basel (Switzerland), 3. Roche Diagnostics GmbH - Penzberg (Germany), 4. Roche Diagnostics International Ltd - Rotkreuz (Switzerland), 5. Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At The University Of Gothenburg - Mölndal (Sweden), 6. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 7. Department of Neurodegenerative Disease, UCL Institute of Neurology and UK Dementia Research Institute at UCL - London (United Kingdom), 8. Clinical Memory Research Unit, Department Of Clinical Sciences Malmö, Lund University - Malmö (Sweden), 9. Memory Clinic, Skåne University Hospital - Malmö (Sweden))

Background: Clinical trials in Alzheimer's Disease routinely screen for accumulation of amyloid in the brain using amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) biomarkers. While these methods have been extensively studied, and analytically and clinically validated, their use is limited by invasiveness, cost, and accessibility, especially within clinical trials in earlier stages of the disease (e.g. secondary prevention) where screen failure rate is high. Therefore, blood-based biomarkers (BBBM) could add substantial value in this setting. Recent advancements in measurement technologies have shown multiple promising candidates, with the ratio of amyloid- β (A β)1-42/A β 1-40 being one of the most studied plasma biomarkers. The majority of these evaluations were performed retrospectively; within a single study, samples were acquired in a standardized way, measurements performed in a batch (e.g. using one lab, instrument, and reagent lot), and study-specific cut-offs identified and applied. This approach

is common for research purposes for initial assessments of the potential value of a novel biomarker. However, this controlled setting does not reflect the sources of variability that can occur in prospective clinical trials or real-world routine clinical practice, where a pre-specified cut-off for normality is used. **Objectives:** We evaluated the utility of plasma A β 1–42/A β 1–40 as a pre-screening tool for clinical trials. Clinical performance of the BBBM test was evaluated (i.e. what proportion of patients were correctly screened out [true negatives], therefore avoiding further unnecessary and expensive screening procedures). We then evaluated how robust clinical decision-making would be in a prospective setting with a pre-specified cut-off and inevitably higher variability in measurements. **Methods:** Evaluations were performed on data from the BioFINDER study in cognitively normal individuals and patients with mild cognitive impairment using prototype Elecsys[®] β -Amyloid(1–42) plasma and Elecsys β -Amyloid(1–40) plasma immunoassays on the cobas e 601 analyzer (Roche Diagnostics) and amyloid PET visual read as the reference standard. Clinical performance was assessed by evaluating negative and positive predictive value (NPV and PPV) and screen-out proportions at a range of potential cut-offs. Such metrics can then be directly translated into reduction of PET scans/CSF procedures and total number of patients that need to be screened for a clinical trial, and hence also give insights into overall cost and duration of screening. Simulations were conducted to evaluate impact of bias and random variability on NPV and PPV; results were compared with well-established CSF biomarkers. In addition, data from the Alzheimer's Disease Neuroimaging Initiative Foundation for the National Institutes of Health (ADNI FNIH) plasma biomarker study was used to evaluate robustness of plasma A β 1–42/A β 1–40 between six measurement technologies (three other immunoassays and three mass spectrometry-based methods). **Results:** In a low prevalence setting, 40–50% of amyloid negative patients could be screened out using plasma A β 1–42/A β 1–40. However, the robustness of plasma A β 1–42/A β 1–40 appears to be low; the difference in mean between amyloid positives and negatives for plasma A β 1–42/A β 1–40 was extremely low (~10%) compared with CSF A β 1–42/A β 1–40 (~100%). The low dynamic range of plasma A β 1–42/A β 1–40 implies potential robustness issues; very small measurement errors and systematic changes could have a dramatic impact on the classification of patients when this biomarker is used in a routine setting. This observation was confirmed in our simulation studies, which demonstrated that under realistic variability and bias assumptions, clinical performance of plasma A β 1–42/A β 1–40 would be eradicated. For example, prospectively applying a pre-specified cut-off derived from a previous study to a new study could falsely classify all patients into amyloid positive or negative since the whole distribution could shift above or below the cut-off. In contrast, if the same systematic errors were assumed for CSF biomarkers, there would be almost no impact on the performance and classification of patients. Results from the ADNI FNIH platform comparison confirmed that lack of robustness was independent of measurement technology and applies to all six investigated plasma A β 1–42/A β 1–40 assays, including mass spectrometry-based methods. **Conclusion:** Despite promising initial results, the utility of plasma A β 1–42/A β 1–40 may be questionable due to lack of robustness. Implementing plasma A β 1–42/A β 1–40 as a pre-screening tool for clinical trials would involve major platform-independent challenges, as analytical performance requirements and assumptions on study-to-study differences would need to be unrealistically strict. In a multi-site study with slightly varying conditions, there would be a high risk

that a pre-specified cut-off used in another study would not be applicable. While other studies have found cut-offs between studies to be numerically similar, they need to be put in context within the dynamic range of the biomarker as these minor differences in cut-offs can have a dramatic effect on classification of patients. Other plasma biomarkers currently under investigation might show more promise for use as a pre-screening tool in clinical trials and routine clinical practice. **Conflicts of interest:** This study was funded by Roche Diagnostics International Ltd, Rotkreuz, Switzerland. Editorial support for the development of this abstract, under the direction of the authors, was provided by Rebecca Benatan, BSc, of Ashfield MedComms, Macclesfield, UK, an Ashfield Health Company, and was funded by Roche Diagnostics International Ltd, Rotkreuz, Switzerland. The results of the study represent the work of the FNIH Biomarkers Consortium "Plasma A β as a Predictor of Amyloid Positivity in Alzheimer's Disease" project. The study was made possible through the scientific and financial support of government, industry, and academia partners. Additional information can be found at <https://fnih.org/our-programs/biomarkers-consortium/programs/plasma-abeta>. Data used in the FNIH study were obtained from the ADNI database. A list of funding sources for ADNI can be found at <http://adni.loni.usc.edu/about/#fund-container>. CR is a full-time employee of Genentech, Inc. (a member of the Roche Group) and owns stock or stock options in Roche. TB is a full-time employee of and owns stock in F. Hoffmann-La Roche Ltd. AJ is a full-time employee of Roche Diagnostics GmbH. IS is a full-time employee of Roche Diagnostics International Ltd. EM is a full-time employee of Roche Diagnostics GmbH. HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies, CogRx and Red Abbey Labs; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure and Biogen; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. KB has served as a consultant and at scientific advisory boards and/or data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. OH is a Wallenberg Clinical Scholar and is supported by grants from the European and Swedish Research Councils; has received research support from Roche, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, GE Healthcare, Pfizer; and has served as a consultant/speaker for Roche, Genentech, Siemens, Biogen, Alzpath, and Cerveau.

LBR12- POLYGENIC RISK SCORES CAN PREDICT EARLY COGNITIVE IMPAIRMENT AS MEASURED BY THE PRECLINICAL ALZHEIMER COGNITIVE COMPOSITE (PACC) SCORE IN THE ADNI COHORT. Qian Gao, Richard Pither, Paula Daunt, Alex Gibson (*Cytox Ltd - Oxford (United Kingdom)*)

Background: The development of diagnostic tools to identify disease risk is critical to enable selection of suitable individuals for inclusion in clinical trials and cohort studies. The utility of Polygenic Risk Scores (PRS) is gaining increasing attention for generating an individual genetic risk profile and subsequent estimation of future disease risk in Alzheimer's Disease (AD). Although APOE has been used routinely in

clinical trials to stratify patients for risk of future onset of AD, it does not account for all genetic risk as clearly evident by the significant prevalence of AD in individuals that do not carry at least one copy of the risk associated APOE ε4 allele. PRS algorithms have been developed to overcome this limitation. We have previously reported on the performance of our PRS to differentiate Alzheimer Disease cases from healthy controls in the ADNI cohort and also cognitive decline using ADAS-Cog13 and CDR-SB scales particularly in individuals who entered that study with a diagnosis of mild cognitive impairment (MCI). **Objectives:** To determine whether our PRS algorithm is able to predict early changes in cognition as measured by longitudinal PACC scores of ADNI cohort participants, including those considered cognitively normal upon entering the study. Furthermore, to demonstrate that PRS algorithms can be cost effective and easily deployable strategies for identifying at risk individuals that may be suitable candidates for clinical trials, especially relevant in studies focussing on preclinical or prodromal stages of disease. **Methods:** This study explored the performance of the Cytos genosCORE™ PRS algorithm as measured using a receiver operating characteristic curve (ROC) curve to predict a PACC score of <-1, as measured upon entry into the study. 724 subjects who entered the study as either cognitively normal, or with a diagnosis of mild cognitive impairment are included in the analysis based on availability of PACC scores and of genetic data in the ADNI database. Further analysis to predict longitudinal changes in PACC have also been performed. **Results:** In a population of 724 individuals genosCORE™ has an accuracy as measured by area under the curve (AUC) of 65.6% in predicting those individuals with cognitive impairment as measured by the PACC scale (threshold <-1). By using a PRS threshold of 0.6 to determine high and low risk groups in both the cognitively normal and MCI populations, it was observed that the high risk group, in each case, declined, on average, over 5 years to a greater extent than the low risk group. Further analyses when looking at APOE3 homozygotes alone showed a similar difference between high and low risk groups. **Conclusions:** Identifying individuals of higher risk for cognitive decline due to Alzheimer's Disease irrespective of their baseline cognitive performance will allow clinical trialists to enrich their studies with more appropriate patients. In addition, use of such risk evaluation techniques in clinical practice will enable clinicians to make more informed decisions on how to manage their patients. Importantly PRS algorithms can identify APOE3 homozygote individuals who have yet to display any cognitive deficit who are most at risk of subsequent onset of symptoms due to Alzheimer's disease. Cytos is able to provide a robust end-to-end process to provide this comprehensive genetic risk assessment.

LBR13- ASSOCIATION OF SERUM DEGRADED TAU BIOMARKERS WITH PRECLINICAL DEMENTIA: A MENDELIAN RANDOMIZATION STUDY. Tobias Melton Axelsen^{1,2,3}, Cecilie Liv Bager⁴, Morten Asser Karsdal⁴, Kim Henriksen⁴, Man-Hung Eric Tang⁴ (1. Sanos Clinic - Herlev (Denmark), 2. Department of Biomedical Science - Copenhagen (Denmark), 3. Nordic Bioscience A/S - Herlev (Denmark), 4. Nordic Bioscience A/s - Herlev (Denmark))

Background: Disease modifying treatments for dementia are only just surfacing, and their development is still significantly hindered by the lack of easy recruitment of subjects with preclinical disease. Much interest has been taken in developing readily available serum biomarkers of neurodegeneration.

Recent studies have identified caspase-3-cleaved tau (Tau-C), and ADAM-10 cleaved tau (Tau-A) as possible markers of preclinical neurodegenerative disease. **Objectives:** This study aims to further characterize the correlation between Tau-A and Tau-C levels and neurodegeneration, with special emphasis on Alzheimer's disease. **Methods:** This study employs genotyping data on participants postmenopausal Danish women from the Prospective Epidemiological Risk Factor (PERF) study (n=4968) with an average follow-up of 14 years. A dementia diagnosis was defined as a composite of an all-cause dementia diagnosis derived from the Danish National Health registries, a self-reported diagnosis of dementia and/or cognitive test scores suggestive of dementia. Serum levels of Tau-A and Tau-C were measured blinded in a CAP certified lab, and the association with dementia was assessed using bi-directional one- and two-sample mendelian randomization. **Results:** A lead SNP for Tau-A (rs10414043) and Tau-C rs429358 was identified, both located in the APOE/C1 cluster on chromosome 19. APOE and EPOC1 variants were associated with lower levels of Tau-A and Tau-C levels - effect size -0.13, 95%CI [-0.17 - -0.09] log2 (ng/mL), p=7.05e-11 for rs10414043 association with Tau-A and effect size -0.12, 95%CI [-0.15 - -0.08] log2 (ng/mL), p=2e-11 for rs429358 association with Tau-C. When incorporating genetic data from a larger genetic study we found that Alzheimer's disease was marginally associated with a decreased Tau-A and Tau-C levels (effect size 0.97, 95%CI [0.93 - 1.00]). No association was found in the forward MR analysis. **Conclusions:** By combining genotype data with serum measurements of the novel biomarkers Tau-A and Tau-C, we conclude that SNPs strongly associated with the analytes are also highly correlated preclinical cognitive defects. By incorporating data from the larger genome wide association study, we can conclude that the targeted SNPs are especially relevant for cognitive defects due to Alzheimer's Disease. These findings further lend credence to the relevance of the biomarkers in regard to preclinical neurodegeneration. The mendelian randomization analysis allows for the conclusion that Tau-A and Tau-C are elevated due to preclinical neurodegeneration rather than the other way around, and thus support their potential as tools for identification of subjects with Alzheimer's disease prior to onset of symptoms. **Conflict of Interests:** Dr. Axelsen has no conflict of interests. Dr. Bager and Dr. Henriksen are both full-time employees of Nordic Bioscience A/S. Dr. Karsdal is the CEO og Nordic Bioscience A/S. Dr. Tang was previously employed at Nordic Bioscience A/S.

LBR14- 18F-APN-1607 TAU PET IN PROGRESSIVE SUPRANUCLEAR PALSY-LIKE SYMPTOMS CAUSED BY TBK1 MUTATIONS. Feng-Tao Liu¹, Tzu-Chen Yen², Chuan-Tao Zuo¹, Chen Yan¹, Jian Wang¹ (1. Huashan Hospital, Fudan University (China), 2. Aprinoia Therapeutics Co., Ltd, Suzhou (China))

Background: Pathogenic mutations in the TANK-binding kinase 1 (TBK1) gene have been associated with progressive supranuclear palsy (PSP)-like extrapyramidal symptoms, amyotrophic lateral sclerosis (ALS), as well as cognitive and behavioral alterations. However, the question as to whether TBK1 mutations may be associated with tau burden remains unanswered. **Methods:** To investigate whether patients presenting with PSP-like extrapyramidal symptoms caused by TBK1 mutations have evidence of tau deposition as reflected by positive 18F-APN-1607 tau PET imaging findings. Four patients who showed PSP-like extrapyramidal symptoms, ALS, and cognitive/behavioral alterations were consecutively enrolled

between August 2019 and August 2020. Patients underwent TBK1 gene sequencing and 18F-APN-1607 tau PET imaging. All PET images were interpreted in a blinded fashion with respect to genetic results. Brain structural changes were investigated with MRI, whereas 11C-CFT or 18F-DTBZ PET imaging was performed to identify dopaminergic degeneration. Results: Pathogenic TBK1 mutations were identified in three of the four study patients. The three mutation carriers – but not the case without – showed positive 18F-APN-1607 binding in PSP-related regions, suggesting the presence of tau pathology. Mesencephalic atrophy (hummingbird sign) was observed in all TBK1 mutation carriers, and two of them

also had evidence of frontotemporal atrophy. Dopaminergic degeneration was evident in all cases, regardless of TBK1 mutations. Conclusions: Pathogenic TBK1 mutations in patients with PSP-like extrapyramidal symptoms are associated with positive 18F-APN-1607 tau PET imaging findings. Our data should prompt additional investigations on the potential role of tau accumulation in the pathogenesis of disease conditions associated with TBK1 mutations. **Disclosure:** The work are now under review in the «European Journal of Neurology» as a reasearch article.