SYMPOSIA

S1- NEW RESULTS ON THE RELATIONSHIP BETWEEN INTENSIVE BLOOD PRESSURE CONTROL AND COGNITIVE FUNCTION FROM SPRINT-MIND. Nasrallah ILYA (1), Sarah GAUSSION (2), Nicholas PAJEWSKI (2), Kristine YAFFE (3) *((1) University Of Pennsylvania School of Medicine, United States, (2) Wake Forest School of Medicine, United States, (3) University Of California, San Francisco, United States)*

The Systolic Blood Pressure Intervention Trial (SPRINT) has contributed substantially to recent advances in the management of hypertension and the prevention of both cognitive impairment and cardiovascular disease. Results from SPRINT have indicated that targeting a lower systolic blood pressure (BP) target of <120 mm Hg (intensive treatment), as opposed to a target of <140 mm Hg (standard treatment), reduces cardiovascular morbidity and mortality, as well as the occurrence of mild cognitive impairment (MCI). However, there remain significant gaps in our understanding of the effect of intensive BP control on cognitive impairment and dementia in older adults. This symposium will leverage more extensive analyses of data from SPRINT to examine the effect of intensive BP control on 1) the occurrence of subtypes of MCI, 2) longitudinal trajectories of domain-specific cognitive function including global function, memory, and executive function, and 3) specific brain biomarkers based on a brain imaging substudy using magnetic resonance imaging (MRI).

Presentation 1: *Effect of intensive blood pressure control on subtypes of mild cognitive impairment*, Sarah GAUSSOIN (Winston-Salem, NC, USA)

SPRINT recently demonstrated that intensive blood pressure control significantly reduces the occurrence of MCI (Hazard Ratio, 0.81; 95% CI, 0.69-0.95), a strong risk factor for dementia, over a median follow-up of 5.1 years. However, results related to the subtype of MCI have not been reported. We will present data on the effect of intensive BP control on the occurrence of amnestic versus non-amnestic MCI, as well as evaluating its effect on single versus multi-domain MCI. SPRINT also employed a somewhat unique, conservative definition for MCI events, requiring two consecutive adjudications of MCI to confirm an event. We will also explore how this definition compares to an event definition that considers time to the first adjudication of MCI. We will also report the agreement of MCI subtype between the first and second adjudications of MCI for participants with a MCI event. Combined, these findings will help give a better understanding of the positive relationship between intensive blood pressure control and MCI, a known risk factor for dementia.

Presentation 2: *Lessons Learned from Cognitive Outcomes in SPRINT: Neuropsychological Test Scores, Domain-Specific Cognitive Function, and Adjudicated Outcomes*, Nicholas M. PAJEWSKI (Winston-Salem, NC, USA)

This presentation will discuss data on the impact of intensive systolic BP control on longitudinal trajectories for domain-specific cognitive function (such as global function, memory, and executive function) based on a subgroup of participants (N=2,913) administered a comprehensive neuropsychological battery biannually over the course of follow-up. In general, these data indicate no significant differences between the intensive and standard treatment groups, standing in contrast to adjudicated results indicating a reduction in mild cognitive impairment with intensive BP control. We will discuss several contributing factors to these discrepant results, including: the broad age spectrum evaluated in SPRINT, the specific definition of MCI with respect to fluctuations in cognitive performance, subgroup-specific effects, and the impact of length of follow-up. These results should indicate opportunities for improved design of future randomized trials of cognitive impairment.

Presentation 3: *Effect of intensive blood pressure control on brain MRI biomarkers*, Ilya NASRALLAH (Philadelphia, PA, USA)

We will present more extensive analyses of brain MRI data examining the impact of intensive SBP control on the structure and physiology of the brain. Initial results from a brain imaging substudy in SPRINT have indicated a significantly lower increase in cerebral white matter lesions, a biomarker of small vessel ischemia, in participants randomized to intensive BP control. However, participants in the intensive treatment group also experienced a larger decline in total brain volume, on the order of an additional ~3-4 cm3 over 4 years. This analysis will evaluate group differences in MRI biomarkers associated with neurodegeneration and cerebrovascular disease, such as hippocampal volume, cerebral blood flow, and network connectivity from functional MRI. Taken together these results will advance our understanding of the possible mechanisms of action for intensive SBP control on brain health and provide a basis for inquiries into the possible role of blood pressure control in the prevention of cognitive impairment and dementia.

S2- NEW PREDICTIVE PLATFORMS FOR ADVANCING DRUG COMBINATION APPROACHES FOR ALZHEIMER PATHOLOGY. Lon S. SCHNEIDER (1), Richard E. KENNEDY (2), Thomas J. ANASTASIO (3), Hugo GEERTS (4) *((1) Keck School of Medicine of USC, United States, (2) University of Alabama, Birmingham, United States, (3) University of Illinois at Urbana-Champaign, United States, (4) In Silico Biosciences, United States)*

During the past two decades, clinical trials in Alzheimer's disease with highly selective, well-defined interventions have generated substantial information on individual patient outcomes, despite their disappointing results. Outcomes are driven by complex clinical, phenotypic, environmental, and pharmacodynamic (PD-PD) interactions between the drug (placebo) and disease process, various co-medications, and genotypes. It is apparent that single, targeted interventions are unlikely to be sufficiently effective in the face of complex, multi-determined neurodegeneration. From the inception of AD clinical trials in the 1980s combination therapy approaches were informed by available drugs, related mechanisms, assumed pharmacodynamic complementarity, or by simply adding a new drug to an available drug with advantageous properties. For example, combining cholinesterase inhibitors with muscarinics or Abeta antibodies with BACE inhibitors. Tools, however, for prioritizing or gaining prior knowledge for empirically-based combinations among the many possibilities are lacking so that choices are based on ad hoc judgments rather than evidence. Panelists will discuss new predictive analytical techniques to "quantify" PD-PD interactions from previous studies, generating actionable knowledge about new treatment combinations. In silico platforms may be required to

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prioritize therapies and optimize trial designs and predictive or personalized medicine approaches.

Presentation 1: *In Silico Screening of Medications for Slowing Alzheimer's Disease Progression in a Clinical Trials Meta-database*, Richard E. KENNEDY (Birmingham, Alabama, USA)

Increasing demand for combination therapies to address the complexities of Alzheimer's disease presents multiple challenges for clinical trial design. A key problem is selection of medications to combine and investigate. Current approaches have relied on combinations of therapies affecting postulated pathways in AD rather than repurposing drugs used for other disorders. Although there are large databases of medications taken by patients with AD, the number of potential combinations vastly exceeds the number of patients. Methods for analyzing this kind of data (often called "n << p" or "high-dimensional" data) has a long history in biostatistics with practical applications in genetics and neuroimaging. These approaches, however, have rarely been applied for clinical trials and drug development. We will present an overview of methods for analyzing drugs for combination therapies, showing the advantages of machine learning approaches over traditional statistical analyses, to approach such high-dimensional data. We will illustrate these concepts by applying random forests to concomitant medications taken by participants in clinical trials, to determine which of these show promise for repurposing as therapies for AD. We conclude by describing the limitations of machine learning approaches for drug discovery, particularly the need for validation in independent datasets. Such in silico approaches show considerable potential for designing clinical trials of combination therapies that have previously been intractable (NIH AG057684 RE Kennedy, LS Schneider).

Presentation 2: *Drug Combination Identification through Correlation between a Clinical Dataset and a Computational Model*, Thomas J. ANASTASIO (Urbana, Illinois, USA)

The identification of potentially effective drug combinations for Alzheimer's disease is made difficult by their sheer number. In general there are too few participants in clinical datasets for each unique drug combination to allow statistically valid comparisons. One way to reduce uncertainty is to assess the efficacy of the same drug combinations using a computational model based on experimental data that is entirely independent from the clinical dataset. A significant correlation between drug combination benefit, as determined from the clinical dataset, and efficacy as predicted from the computational model, would reduce the uncertainty associated with each assessment separately. We conducted a proof of concept study using the Rush Alzheimer Disease Center (RADC) database on cognitively impaired elderly individuals and a computational model of neuroinflammation based on the cellular physiology of microglia as the main mediators of the neuroinflammation observed in aging and Alzheimer brain. The RADC database benefit was assessed in terms of the cognitive ability of individuals taking a specific drug combination versus that of individuals taking no drugs. The microglia model efficacy was assessed in terms of the reduction in the simulated inflammatory response due to a specific drug combination. RADC database benefit and microglia model efficacy for over 200 specific drug combinations were positively correlated, with p value less than 0.004. The 10 highest ranking drug combinations, as determined jointly from both the RADC database and the microglia model, were highly consistent in composition, including drugs from several key classes. Combinations of these drugs should be evaluated clinically and then in clinical trials for their treatment effectiveness.

Presentation 3: *Evaluating Pharmacodynamic Interactions in Drug Combinations Using Quantitative Systems Pharmacology Analysis of Clinical Trials*, Hugo GEERTS (Berwyn, Pennsylvania, USA)

The large number of therapeutic combinations in Alzheimer's disease precludes the use of traditional preclinical animal models. We present Quantitative Systems Pharmacology as a high-throughput computer-based approach for prioritizing interesting drug combinations with positive pharmacodynamic interaction. This biology-informed model of humanized brain neuronal circuits calculates the effect of pathology and therapeutic interventions on the firing dynamics of anatomically informed neuronal circuits which in the human brain drives clinical readouts. This approach allows to study the impact of comedications (based on their pharmacology), a few common genotypes variants (based on imaging) and disease status (based on the physiology of beta-amyloid and tau peptides) on cognitive readout in a unique virtual patient model. We illustrate (1) the complex nature of both negative and positive pharmacodynamic interactions between memantine, acetylcholinesterase inhibition and antipsychotics on cognition, (2) the outcome of amyloid modulating agents due to the differential effect of COMTVal158Met, APOE and 5-HTTLPR s/L genotype together with pro-cognitive medication on the dose-response using a virtual trial design identical to the aducanumab trial and (3) the pharmacodynamic interaction between amyloid and tau pathology on neuronal firing and cognitive readout. Validation of these models through comparison of individual patient responses with actual clinical outcomes even from 'failed' trials will enhance significantly the predictive value. After validation, these models will be able to (1) screen systematically in silico all possible drug combinations for a maximal synergistic effect and (2) optimize clinical trial design by identifying possible negative pharmacodynamic interactions.

S3- EPIGENETICS AND THE BET-SYSTEM IN VASCULAR DEMENTIA, ALZHEIMER'S DISEASE AND MIXED DEMENTIA – THE PROBLEM AND POTENTIAL REMEDIES. Bengt WINBLAD (1), Charles DECARLI (2), Henrik ZETTERBERG (3), Ewelina KULIKOWSKI (4), Jeffrey CUMMINGS (5) *((1) Karolinska Institute, Sweden, (2) UC Davis, United States, (3) Sahlgrenska Academy, Sweden, (4) Resverlogix Corp., Canada, (5) Cleveland Clinics, United States)*

The current world-wide prevalence of dementia is estimated at 35 million, and this number is projected to rise to over 100 million by 2050 if means of preventing, delaying, slowing or improving cognitive symptoms are not found. Most dementia is attributable to mixed age-related pathologies with Alzheimer's disease (AD) and vascular pathology being the two most common contributing elements. Vascular risk factors such as age, lack of exercise, cigarette smoking, hypertension, and obesity are associated with the risk of cognitive decline, dementia, vascular cognitive impairment (VCI), and AD. There is a need to detect and differentiate disease early and

to treat its' root cause. Serum biomarkers that relate to different aspects of AD and VCI pathology include markers of neurodegeneration: neurofilament light chain and visinin-like protein (VILIP-1); markers of amyloidogenesis and brain amyloidosis: apolipoproteins; markers of inflammation: YKL-40 and monocyte chemoattractant protein 1; marker of synaptic dysfunction: neurogranin. Serum alkaline phosphatase (ALP) has emerged as a marker of global dementia potentially by effects on tau processing and/or vascular calcification. These markers can highlight on the state and stage-associated changes that occur in AD, VCI and mixed disease with disease progression. Recent data suggest that epigenetic regulation is important in vascular pathophysiology, cerebral small vessel disease and vascular health. Gene expression mediated by activated BET system results in medial vascular calcification, increased levels of cytokines and endothelial adhesion molecules which are associated with compromised blood flow, neuroinflammation and cognitive impairment in non-clinical animal models. Bromodomain and extraterminal domain (BET) proteins are transcription-readers. They decondence/open chromatin and activate cytokine-associated transcription. BET proteins have two bromodomains (BD1 and 2) that bind acetylated lysines on transcription factors and chromatin with high affinity and are recruited through these interactions to the promoters and enhancers of genes that control cell identity, differentiation, and proliferation. On the promoters and enhancers, the BET proteins act as a scaffold, binding positive transcription elongation factor b to stimulate RNA polymerase II dependent transcription of the proximal genes. Many diseases alter acetylation marks, directing BET proteins to inappropriate genes, and pathological protein production. Apabetalone is a BD2-selective BET-inhibitor that returns mRNA and protein production towards physiological levels leading to improvement in vascular integrity, reduction in medial vascular calcification and decreased expression of inflammatory cytokines. Intensive research is ongoing in discerning their effects on neuron and glial cell (patho-) physiology. Bromodomain and extraterminal domain (BET) proteins are a family of four epigenetic readers (BRD2, BRD3, BRD4 and BRDT) that regulate gene transcription. Apabetalone modulates the expression of immune, inflammatory and pro-atherosclerotic genes in ex vivo treated human whole blood cells, as well as in the apoE knockout mouse model of atherosclerosis. Prophylactic and therapeutic treatment with apabetalone significantly reduced aortic lesion formation and lowered levels of circulating adhesion molecules and cytokines in hyperlipidemic apoE-/- mice. Apabetalone also impacts gene transcription within the acute phase response, complement and coagulation pathways in primary human hepatocytes, and vascular calcification in vascular smooth muscle cells. As part of correcting acute phase reactants apabetalone induces hepatic synthesis of apolipoprotein (apo) A-I enhancing cholesterol efflux capacity of high density lipoprotein (HDL) particles. The BET inhibitor apabetalone reduced endothelial and microglial activation in preclinical models of neuroinflammation. Apabetalone is a small molecule administered orally. It is metabolized by the liver and exhibits dose-proportional pharmacokinetics for single and multiple doses. Food increases its bioavailability; the pharmacokinetics are not affected by renal compromise. The half-life of apabetalone is 11 hours within the relevant dose range. In phase 2 studies apabetalone showed a reduction in broad-based CVD events of 44% which was most pronounced in patients with diabetes or with metabolic inflammation as defined by a high sensitive C-reactive protein (hsCRP) >2mg/L. Apabetalone lowers ALP gene-expression and serum ALP in a dose-response manner which is seen as a proxy for the multiple pathways that are regulated towards normal profiles, including inflammation, acute phase reactants, complement and coagulation. Sporadic elevated transaminases (>3x normal) occur in 7-8% of those exposed to apabetalone. After apabetalone treatment in more than 2000 patients for up to 3.5 years no combined bilirubin and ALT elevations have been observed indicating benign nature of the transaminase elevations. Apabetalone is being assessed in a Phase 3 multicenter double blind, parallel group, placebo-controlled trial in post-acute coronary syndrome patients with type 2 diabetes, low levels of HDL-C, to determine whether BET inhibition increases the time to major adverse cardiovascular events (MACE). The primary outcome of the BETonMACE study is time to a composite event of any of cardiovascular death, nonfatal myocardial infarction, or stroke. A pre-specified secondary analysis of BETonMACE will examine the effects of apabetalone on cognitive function using the Montreal Cognitive Assessment (MoCA) in patients 70 and older at randomization. In BETonMACE, MoCA was performed at baseline in 19% (n=470) of the population across 195 centers and 13 countries. Of those, approximately 52% (n=246) had a baseline MoCA score , suggesting potentially compromised cognition, and approximately 18% (n=84) had MoCA score <21 suggesting dementia. Significant contributors to a lower MoCA score came from domains of language and memory (both p A low MoCA score was associated with Caucasian race, history of hypertension, and previous percutaneous coronary intervention. At baseline, a lower MoCA score was associated with higher serum ALP. Exploration of the effects of apabetalone on MoCA scores and effects on quality of life (QoL, EQ-5D) will provide preliminary insight into the potential benefits of BET modulation on cognition and effects on QoL. A variety of biomarkers are being collected as secondary outcomes in the trial including ALP, hsCRP, fibrinogen ApoA-I, ApoB, LDL-C, HDL-C, triglycerides, HbA1c, fasting glucose, fasting insulin, transcription factor change in whole blood, and proteomic profiles. As pre-specified, provided a favorable signal of apabetalone treatment on MOCA in this diabetes population archive plasma samples are available. Archive samples would be used for assessing apabetalone treatment effects in population with neurodegenerative pathology and AD burden. Depending on results apabetalone would be expanded to neurodegenerative indications. Interrogation of the relationship between changes in biomarkers and drug-placebo differences on the MoCA will inform understanding of the biology of observed differences.

S4- AMBAR (ALZHEIMER'S MANAGEMENT BY ALBUMIN REPLACEMENT) PHASE 2B/3 TRIAL: COMPLETE CLINICAL, BIOMARKER AND NEUROIMAGING RESULTS. Antonio PÁEZ (1), Mercè BOADA (2), Oscar LÓPEZ (3), Zbigniew SZCZEPIORKOWSKI (4), Montserrat COSTA (1), Bruno VELLAS (5), Jeffrey CUMMINGS (6) *((1) Grifols, Spain, (2) Fundació ACE, Universitat Internacional de Catalunya, Spain, (3) University of Pittsburgh School of Medicine, United States, (4) Dartmouth Hitchcock Medical Center, United States, (5) University Hospital, France, (6) Cleveland Clinic Lou Ruvo Center for Brain Health, United States)*

Presentation 1: *AMBAR (Alzheimer's Management By Albumin Replacement) Phase 2B/3 Trial: complete clinical, biomarker and neuroimaging results*, Antonio PÁEZ (Grifols, Barcelona, Spain)

Plasma exchange (PE) with therapeutic albumin replacement (PE-A) as a potential therapeutic approach for Alzheimer's disease (AD) initiated by Grifols, started with promising results in patients' biochemical, cognitive, and neuroimaging assessments reported in a pilot study and a Phase 2 clinical trial. To further evaluate these findings, the AMBAR study was designed as a Phase 2B/3, multicenter, randomized, blinded and placebo-controlled, parallel-group trial enrolling mild-to-moderate AD patients (NCT01561053). AMBAR evaluates PE-A with different replacement volumes of therapeutic albumin (Albutein®), with or without intravenous immunoglobulin (IVIG; Flebogamma® 5% DIF) to correct a possible endogenous immunoglobulin decrease. PE-A consists of removal of 2.5-3 L of plasma, replaced with the same volume of 5% Albutein® using a conventional apheresis device (a procedure known as therapeutic plasma exchange [TPE]). Low-volume plasma exchange (LVPE) consists of extraction of 650-880 mL of plasma (similar to a plasma donation), replaced by 100-200 mL of 20% Albutein® using a new prototype apheresis device for low-volume exchange. The AMBAR study enrolled 496 patients (347 randomized) from 41 centers (19 in Spain and 22 in the US). The patients were randomized to one of three treatments or placebo (sham PE) [1:1:1:1]. The intervention regime includes first, a 6-week stage of intensive treatment (one conventional PE-A/week) that is common to all groups, followed by a 12-month stage of maintenance treatment (one LVPE/month) distributed in three arms: 1) Replacement of 20 g of 20% Albutein®; 2) Like arm #1 alternated with 10 g of Flebogamma® 5% DIF; 3) Like arm #2 but 40 g of 20% Albutein® and 20 g Flebogamma® 5% DIF. Primary clinical efficacy endpoints showed that, in the three PE-A treatment arms (i.e., low dose albumin; low dose albumin + IVIG; high dose albumin + IVIG), 40-75% less decline was observed as measured by the change from the baseline scores of ADAS-Cog and ADCS-ADL tests compared to placebo (sham PE-A) at 14 months, although not statistically significant. However, in all PE-treated patients, 66% less decline was observed as measured by ADAS-Cog ($p=0.06$) and 52% in ADCS-ADL ($p=0.03$) compared to placebo. While the mild dementia cohort (mean baseline MMSE: 23.6) showed no decline neither in PE-A-treated nor placebo, the moderate dementia cohort (mean baseline MMSE: 19.3) showed 61% less decline in both ADAS-Cog ($p=0.05$) and ADCS-ADL ($p=0.002$) compared to placebo. In addition, the change from baseline on ADCS-ADL for each of the individual treatment arms was statistically significant compared to placebo (p value ranging 0.01 to 0.02). Regarding secondary clinical efficacy endpoints, all PE-A-treated patients showed statistically significant improvements with respect to placebo in Verbal Memory, Language, Processing Speed and quality of life (QoL). Interestingly, the high dose albumin + IVIG arm was the one more frequently associated with statistically significant improvement. The mild dementia cohort showed statistically significant improvement with respect to placebo in Language, Processing Speed and QoL, while the moderate dementia cohort did so in Verbal Memory and QoL. Maximun improvement was observed for QoL and Verbal Memory. The rest of secondary clinical endpoints in the AMBAR Phase 2B/3 study include: Neuropsichiatric Inventory (NPI), Clinical Dementia Rating Sum of Boxes (CDR-Sb), Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), Cornell Scale for Depression in Dementia (CSDD), Columbia-Suicide Severity Rating Scale (C-SSRS), and Resource Utilization in Dementia (RUD-Lite®). Results will be presented. CSF biomarker levels showed Aβ42 stabilization in the PE-A-treated group compared with a decline observed in placebo-treated group. Results of plasma biomarkers (Aβ40, Aβ42, tau, and P-tau proteins) in the AMBAR Phase 2B/3 study will be presented. Results of neuroimaging (structural changes in volume of the hippocampus, posterior cingulate area, and other associated areas assessed by MRI, and analysis of functional brain changes through FDG-PET) of the AMBAR Phase 2B/3study will be presented. In the AMBAR study, 4,709 PE-A procedures were performed including 1,223 sham and 3,486 actual procedures (1,718 TPE; 2,991 LVPE) with 72% of patients completing the study, confirming feasibility and tolerability in mild-to-moderate AD patients. A low rate of PE-A procedures was associated with adverse events (AEs) (0.3-1.4%) but this rate seemed to depend on volume infused and IVIG dose, as expected. The distribution of AEs over time showed an accumulation of events during the conventional TPE period with a progressive decrease during the LVPE period. Percentage of patients with infections was higher in patients treated with PE-A without IVIG (62.8%), not only than those treated with high dose and low dose albumin + IVIG (39.2 and 39.5%, respectively) but also than those in the placebo arm (41.8%).

S5- ALZHEIMER'S DISEASE IN DOWN SYNDROME: NEW INSIGHTS AND OPPORTUNITIES. Juan FORTEA (1), Michael RAFII (2), Andre STRYDOM (3), Brad CHRISTIAN (4) *((1) Hopital Saint Pau, Spain, (2) USC, United States, (3) King's College London, United Kingdom, (4) University of Wisconsin, United States)*

The discovery that individuals with Trisomy 21, or Down syndrome (DS) have neuropathological features identical to those with sporadic Alzheimer's disease (AD) played a critical role in the identification of the amyloid precursor protein gene on chromosome 21 supporting the amyloid cascade hypothesis. People with DS have a lifetime risk for dementia in excess of 75% and comprise the world's largest population of genetically-determined AD. Just as studying DS helped identify the role of amyloid precursor protein mutations in AD pathogenesis, it is also likely to inform us of the potential benefit of manipulating the amyloid pathway on treatment outcomes in AD. It is critically important to the DS population and to the AD therapeutics field to conduct clinical trials, particularly those targeting amyloid accumulation, in individuals with DS. In this symposium, we will provide an update on recent developments in understanding the natural history of AD in DS as we prepare for clinical trials in this population. The

predictable development of AD pathology and high incidence of dementia in individuals DS suggests that this is an important group in which trials in the preclinical or prodromal stage of AD to prevent or delay dementia should be considered. Recent work has demonstrated that AD biomarkers in DS behave similarly to those observed in both the sporadic and autosomal dominant AD populations. Dr. Michael Rafii, the symposium chair, will present a brief overview of the current state of the field. Dr. Andre Strydom will present 'Cognitive markers of preclinical and prodromal Alzheimer's disease in Down syndrome' based on results from the LonDowns consortium. We conducted the largest cognitive study to date with 312 adults with DS to assess age-related and Alzheimer's disease–related cognitive changes during progression from preclinical to prodromal dementia, and prodromal to clinical dementia. We have investigated cross-sectional changes in cognitive abilities associated with AD development in over 300 adults with DS. Memory and attention measures were most sensitive to aging, with significantly poorer performance starting in the early 40s. Similarly, performance for memory and attention outcomes was most sensitive to progression from preclinical to prodromal dementia, whereas performance for memory outcomes was most sensitive to progression from prodromal to clinical dementia. Using outcomes identified as sensitive to AD progression, we estimated possessing an APOE ε4 allele accounted for approximately 8% of variance in scores, and modest sample sizes would be sufficient to detect a significant treatment effect to delay cognitive decline in an RCT. Dr. Brad Christian will present 'Neuroimaging biomarkers of AD in DS' based on results from the Alzheimer's Biomarker Consortium for Down syndrome (ABC-DS). Fifty-two nondemented adults with DS underwent two cycles of carbon 11-labeled Pittsburgh compound B ([11C]PiB) and T1 weighted magnetic resonance imaging (MRI) scans 3.0 ± 0.6 years apart. Standard uptake value ratio (SUVR) images (50-70 minutes; cerebellar gray matter [GM]) and GM volumes were analyzed in standardized space (Montreal Neurological Institute space). 85% of PiB(-) subjects remained PiB(-), whereas 15% converted to PiB(+), predominantly in the striatum. None reverted from PiB(+) to PiB(-). Increases in SUVR were distributed globally, but there were no decreases in GM volume. The PiB positivity groups differed in the percent rate of change in SUVR [PiB(-): 0.5%/year, PiB converters: 4.9%/year, and PiB(+): 3.7%/year], but not in GM volume. Results on Tau PET and FDG PET imaging in adults with DS will be presented as well. Dr. Juan Fortea will present 'Plasma and CSF biomarkers for the diagnosis of AD in DS.' We did a cross-sectional study of adults aged 18 years and older with Down syndrome enrolled in a population-based health plan in Catalonia, Spain. Every person with Down syndrome assessed in the health plan was eligible to enter the Down Alzheimer Barcelona Neuroimaging Initiative, and those with a plasma or CSF sample available were included in this study. Participants underwent neurological and neuropsychological examination and blood sampling, and a subset underwent a lumbar puncture. Adults with Down syndrome were classified into asymptomatic, prodromal Alzheimer's disease, or Alzheimer's disease dementia groups by investigators masked to biomarker data. Non-trisomic controls were a convenience sample of young (23-58 years) healthy people from the Sant Pau Initiative on Neurodegeneration. Amyloid-β (Aβ)1-40, Aβ1-42, total tau (t-tau), 181-phosphorylated tau (p-tau; only in CSF), and neurofilament light protein (NfL) concentrations were measured in plasma with a single molecule array assay and in CSF with ELISA. Plasma and CSF biomarker concentrations were compared between controls and the Down syndrome clinical groups. Diagnostic performance was assessed with receiver operating characteristic curve analyses between asymptomatic participants and those with prodromal Alzheimer's disease and between asymptomatic participants and those with Alzheimer's disease dementia. We collected plasma from 282 participants with Down syndrome (194 asymptomatic, 39 prodromal Alzheimer's disease, 49 Alzheimer's disease dementia) and 67 controls; CSF data were available from 94 participants (54, 18, and 22, respectively) and all 67 controls. The diagnostic performance of plasma biomarkers was poor (area under the curve [AUC] between 0·53 [95% CI 0·44-0·62] and 0·74 [0·66-0·82]) except for plasma NfL concentrations, which had an AUC of 0·88 (0·82-0·93) for the differentiation of the asymptomatic group versus the prodromal Alzheimer's disease group and 0·95 (0·92-0·98) for the asymptomatic group versus the Alzheimer's disease dementia group. In CSF, except for Aβ1-40 concentrations (AUC 0·60, 95% CI 0·45-0·75), all biomarkers had a good performance in the asymptomatic versus prodromal Alzheimer's disease comparison: AUC 0·92 (95% CI 0·85-0·99) for Aβ1-42, 0·81 (0·69-0·94) for t-tau, 0·80 (0·67-0·93) for p-tau, and 0·88 (0·79-0·96) for NfL. Performance of the CSF biomarkers was optimal in the asymptomatic versus Alzheimer's disease dementia comparison (AUC ≥0·90 for all except Aβ1-40 [0·59, 0·45-0·72]). Only NfL concentrations showed a strong correlation between plasma and CSF biomarker concentrations in participants with Down syndrome (rho=0·80; p<0·0001). Our findings support the utility of plasma NfL for the early detection of Alzheimer's disease in Down syndrome in clinical practice and clinical trials.

ROUNDTABLE

ROUNDTABLE 2: BACE INHIBITION: WHAT DO WE KNOW AND WHAT DO NEED TO KNOW?
Maria CARRILLO (1), Reisa SPERLING (2) *((1) Alzheimer's Association, United States, (2) Brigham & Women's Hospital, United States)*

Presentation 1: *Improve synaptic dysfunction in association with BACE1 inhibition*, Yan RIQIANG (University of Conneticut, United States)

Presentation 2: *The Generation Program: Preliminary data on baseline characteristics of participants randomized in Generation Study 1 and Generation Study 2*, Pierre N TARIOT (1), Beth BOROWSKY (2), Fonda LIU (2), Marie-Emmanuelle RIVIERE (3), Marie-Laure ROUZADE-DOMINGUEZ (3), Laurie DUFF (2), Matt QUINN (2), Ingo SCHOLTEN (3), Jessica LANGBAUM (1), Angelika CAPUTO (3), Vissia VIGLIETTA (4), Eric REIMAN (1), Ana GRAF (3) ((1) Banner Alzheimer's Institute, United States, (2) Novartis Pharmaceuticals, United States, (3) Novartis Pharma, Switzerland, (4) Amgen, Inc., United States)

Background: The Alzheimer Prevention Initiative (API) Generation Program assessed the effectiveness of the BACE1 inhibitor umibecestat or an active immunotherapy (CAD106) in delaying the onset of AD symptoms in APOE4 carriers. The Generation Program included two studies-Generation Study 1 (GS1, NCT0256551) and Generation Study 2 (GS2,

NCT03131453) (Lopez Lopez et al., 2019) and was conducted in cognitively unimpaired people at risk for onset of clinical symptoms due to AD based on their age, APOE4 genotype and, for GS2, brain amyloid load. Recruitment and treatment with umibecestat was terminated in July 2019 after an early signal of mild worsening in some measures of cognitive function with umibecestat, similar to what had been seen previously with several other BACE inhibitors. **Method:** Both Generation studies planned treatment over 5-8 years in a double-blind, placebo-controlled, parallel design (Lopez Lopez et al., 2019). Participants were 60 to 75 years of age, had a study partner and were cognitively unimpaired at screening based on the RBANS delayed memory index score ≥ 85 and CDR global score of 0 (with investigator judgment allowed if either score was slightly out of range). Significant medical conditions were exclusionary. GS1 recruited only APOE4 homozygotes (HMs) while GS2 enrolled both HMs and APOE4 heterozygotes (HTs) who also showed elevated brain amyloid (PET or CSF). All participants underwent either CSF sampling for p-Tau/Abeta42 concentration or Amyloid PET scan. If the visual read of PET scan was negative, the SUVr was calculated and converted to centiloids for the three F18 tracers in order to rescue borderline cases using corresponding thresholds for amyloid positivity. Participants received disclosure of their risk estimates for developing clinical symptoms of AD based on their APOE genotype and, if HT, evidence of elevated brain amyloid. **Results:** Preliminary baseline data from all randomized participants from both Generation studies are summarized below. Generation Study 1: 478 HM participants were randomized across both cohorts. In Cohort I with CAD106 or placebo, the 65 participants had mean age (SD) of 65.0 (4.2) years, 16.7 (3.5) years of education, 67.7% were women and 84.6% had a family history of AD. In Cohort II with CNP520 50mg or placebo, the 413 participants had a mean age (SD) of 66.2 (4.15) years, 16.3 (3.3) years of education, 56% were women and 83.8% had a family history of AD. In Cohort I / Cohort II respectively, the mean (SD) baseline cognitive scales were: MMSE 29.2 (0.98) / 29.0 (1.23), RBANS total 106.0 (12.5) / 102.9 (12.2), CDR-SB 0.1 (0.25) / 0.2 (0.4), ECog (subject) 46.3 (6.8) / 47.5 (7.8). A total of 314 participants underwent amyloid PET scan with Florbetapir: the mean SUVR was 1.23 (0.2) in cohort I (N=54) and 1.22 (0.19) in cohort II (N=260). Close to 64% of the subjects had elevated brain amyloid in both cohorts. Generation Study 2: 1143 participants were randomized (CNP520 15mg or 50mg or placebo), 226 were APOE4 HMs and 917 were HTs. The mean (SD) age was 68.4 (4.0) years , 15.8 (3.5) years of education, 62.8% were women and 69% had a family history of AD. Mean (SD) baseline cognitive scales were: MMSE 29 (1.2), RBANS total 100.9 (12.2), CDR-SB 0.2 (0.4), ECog (subject) 49.4 (9.35). The only marked differences observed in Baseline characteristics between HMs and HTs, included HMs being 2.4 years younger than HTs, and less female HMs (53%) than HTs (65%). 575 participants had an amyloid PET scan with Florbetapir (222 HMs and 890 HTs. Mean (SD) SUVR was 1.22 (0.21) in HMs randomized with any level of brain amyloid (66.2% were elevated), and 1.31 (0.17) in HTs randomized with elevated brain amyloid. Underlying AD pathology was assessed with a broad panel of biomarkers. In Study 1, 223 FDG PET scans were performed. Across both studies at Screening, 1111 LPs, 2934 amyloid PET scans with either florbetapir, flutemetamol or florbetaben, and 145 tau PET scans with flortaucipir, were performed. All 1617 participants randomized contributed blood samples (plasma and serum) and performed MRI scans to measure brain volumes as well as microhemmorhages (a subset also did resting-state functional MRI). These biomarkers will be analyzed later. **Conclusion:** This is the largest cohort of APOE4 HMs (including about 35% below amyloid elevation threshold) and amyloid-positive APOE4 HTs recruited in a global clinical trial program. Baseline characteristics of participants enrolled in the Generation Program were consistent with the target early AD population without objective cognitive impairment. Striking similarities in most Baseline characteristics reflect the main eligibility criteria shared across both trials. The anonymized study data, biomarker samples as well as images collected will be shared with the scientific community after study completion and reporting. **References:** Lopez Lopez et al. The Alzheimer's Prevention Initiative Generation Program: Study design of two randomized controlled trials for individuals at risk for clinical onset of Alzheimer's disease. A&D TRCI (2019) 5, 216-227.

Presentation 3: *API Perspective what we would learn from the discontinuation phase*, Eric REIMAN (Alzheimer's Prevention Initiative, United States)

Presentation 4: *A review of volumetric MRI changes in AD treatment trials and a framework for their interpretation*, Adam SCHWARZ (Takeda, Cambridge, MA, USA)

Background: Volumetric MRI (vMRI) has excellent biomarker characteristics in natural history studies, including monotonic dependence on disease severity and strong correlations with clinical and cognitive outcomes. It is routinely used as an outcome biomarker in AD clinical trials, but there has been some concern in the field about treatment effects on brain atrophy being sometimes inconsistent with those on clinical outcomes. **Objectives:** To review the relationship between magnitudes of change in vMRI and primary clinical outcomes in published late-phase AD treatment trials, and to evaluate a simple framework to help distinguish disease-related from non-specific treatment effects on atrophy. **Methods:** We reviewed the relative magnitudes of treatment vs. control arm differences (irrespective of statistical significance) in published clinical and MRI results for clinical trials with AN1792, semagacestat (IDENTITY), avagacestat, bapineuzumab (301 and 302), solanezumab (EXPEDITION 3) and leucomethylthioninium bis(hydromethanesulphonate) (LMTM). ADAS-Cog was the primary clinical endpoint for all trials. AN1792, semagacestat, bapineuzumab, solanezumab and LMTM trials were conducted in subjects with AD dementia; avagacestat in subjects with prodromal AD. Placebo + treatment arm sample sizes for analysis ranged from 85 to 1462. All trials reported vMRI changes for whole brain (WBV) and hippocampus (HV) volumes; all except semagacestat reported vMRI changes for the lateral ventricular volume (VV); only solanezumab reported changes for additional brain regions (12 in total). Adjusted group-mean changes in ADAS-Cog and vMRI outcomes were converted to % change relative to control arms with respect to reported baseline measurements, for control and treatment arms, and directionality of change was harmonized to reflect worsening or improvement consistently across studies. To further interpret the vMRI changes, we considered how a set of brain regions affected to different degrees by the disease process, and that exhibit volume loss at different rates, would be affected by a treatment that modifies these rates of volume loss. A plausible disease-modification effect might be expected

to alter the rate of atrophy in each region by a similar relative amount (e.g., 25% slowing). In contrast, a non-specific effect (e.g., inflammation or fluid shift) might be expected alter the rate of atrophy in each region by a similar absolute amount. Examining the pattern of relative and absolute differences in volume change between treatment and control arms, plotted against the change in the control arm, across different brain regions may thus indicate whether the observed effects are more consistent with a disease-related or with a non-specific effect. We examined published brain atrophy data from the above treatment trials in this framework. **Results:** The magnitudes of both ADAS-Cog and vMRI treatment vs. control arm differences ranged from small (a few percent) to large (40-50% for ADAS-Cog, WBV and HV; up to 130% for VV); some changes favored control and others favored treatment. When percent difference in each vMRI measure was plotted against percent difference in ADAS-Cog, with the exception of AN1792 these differences were overall directionally concordant and consistent in magnitude. Linear regression lines passed close to the origin and described the data well (WBV R2=0.84, VV R2=0.97, HV R2=0.82). Nominally discordant results (relative increase in ADAS-Cog and decrease in vMRI, or vice versa) were associated with small magnitudes of effect and/or lower doses (semagacestat, bapineuzimab) and/or shorter follow-up time (avagacestat); for these treatments the differences tended toward the overall regression lines as dose or follow-up time increased. In contrast to the pattern exhibited by the other trial results, AN1792 showed a relative difference in ADAS-Cog of approximately 26% that favored treatment, but relative differences in vMRI measures of 32-129% that favored placebo, and was a clear outlier. Considering the cross-region patterns of relative and absolute vMRI differences from control, most of the above trials exhibited relative percent changes that were approximately proportional to the rate of change in the control arm and absolute percent changes that were approximately constant, although the directionality of effect (favoring treatment or placebo) was trial-dependent. AN1792 was the only data set to exhibit a pattern more closely resembling what would be expected for a non-specific effect, but we note that the VV changes were reported in a slightly different way to other trials which may affect this finding. This analysis is however limited by the fact that most trials reported only WBV, VV and HV. The 12 regions reported for solanezumab revealed a proportional slowing pattern that could be interpreted more confidently. **Conclusion:** With the exception of AN1792, the data from the treatment trials reviewed here (12 comparisons across 7 trials) revealed an overall pattern of directionally concordant changes between ADAS-Cog and WBV, VV and HV. Discordant findings were small in magnitude and more likely associated with lower doses or shorter follow-up times. Interrogating atrophy in a larger set of brain regions, and examining the patterns of relative and absolute treatment-placebo differences across brain regions, may help further interpret volumetric changes in intervention trials.

Presentation 5: *DIAN: Primary Prevention Discussion*, Eric MCDADE (University of Connecticut, United States)

Presentation 6: *Modeling of verubecestat Ph3 PK/PD data against to amyloid PET*, Julie STONE (Merck, USA)

Discussion:

1) Is there a lowest dose that could be efficacious, using modeling or preclinical models, i.e. not just to avoid side effects but to identify a therapeutic window?

2) To what could still be done non-clinically to understand if anything would have predicted the adverse effects. Michael F. EGAN (1), Michael IRIZARRY (2), John SIMS (3), Craig SHERRING (4) ((1) Merck, USA, (2) Eisai, USA, (3) Eli Lilly & Co., USA, (4) AstraZeneca, USA)

Oral Communications

OC1: COMPARATIVE EFFECTIVENESS OF BEHAVIORAL INTERVENTIONS IN MILD COGNITIVE IMPAIRMENT: 12-MONTH OUTCOMES OF A RANDOMIZED CLINICAL TRIAL. Glenn SMITH *(University of Florida, United States)*

Recommendations to engage in behavioral strategies to combat cognitive decline are increasingly given to persons with Mild Cognitive Impairment. This is especially true following the publication of the Finnish Geriatric Intervention to Prevent Impairment and Disability trial and the initiation of US POINTER trial. However, the comparative effectiveness of these behavioral interventions is not well understood. This session will present results of a 5 year Patient Centered Outcomes Research Institute funded comparative effectiveness trial of behavioral interventions for Mild Cognitive Impairment. This presentation will describe 1) the design of this multisite, cluster-randomized, multi-component, comparative effectiveness trial, 2) the 50-hour group intervention, including memory compensation training, computerized cognitive training, yoga, patient and partner support groups, and wellness (e.g., sleep, diet) behavior change. 3) the outcome measures and 4) demographics of the 272 patients meeting for Mild Cognitive Impairment that enrolled 5) the patient findings that withholding wellness education was estimated to have the most negative impact on patient quality of life, while withholding computerized cognitive training was estimated to have the least negative impact. Partners and 6) the finding of no significant impact for care partners at 12 months follow-up. Implications and future directions will be presented.

OC2: AADVAC1 TAU VACCINE COMPLETING THE PHASE 2 STUDY: A PARADIGM SHIFT FOR THE AD TREATMENT HYPOTHESIS. Matej ONDRUS, Petr NOVAK, Zilka NORBERT *(AXON Neuroscience CRM Services SE, Slovakia)*

Pathological tau protein is recognized as a target for development of disease-modifying treatments in Alzheimer's disease (AD). AADvac1 is an active vaccine targeting an epitope in the microtubule-binding repeat region of tau, the domain responsible for aggregation and common for all forms of tau pathology. The induced serum antibodies are strongly selective for pathological forms of tau and inhibit the progress of tau pathology in animals (Kontsekova et al., Alzheimers Res Ther, 2014). In the phase 1 study, AADvac1 has shown to be safe and highly immunogenic (Novak P, et al., Lancet Neurol., 2017). In addition, signals of efficacy have been observed (Novak P, et al., Alzheimers Res Ther, 2018). AXON Neuroscience is in the process of completing the randomized, placebo-controlled, phase 2 study in patients with mild AD to assess safety and efficacy of AADvac1. **Objectives:** The primary objective of the study is safety, the secondary objectives are efficacy and immunogenicity after two years of treatment with AADvac1 or placebo. Clinical efficacy has been assessed by CDR-SB,

ADCS-ADL-MCI, MMSE and a custom battery of validated cognitive tests evaluating all important cognitive domains. A panel of biomarkers has been evaluated, including brain volumetry, brain metabolism, and biomarkers in plasma and CSF. **Methods:** The study population consists of very mild to mild AD patients (MMSE from 20 to 26 inclusive), defined by the NIA-AA criteria (McKhan 2011), and supported by evidence of hippocampal atrophy (Scheltens score ≥2) or positive CSF biomarkers. Study participants have been randomized to either AADvac1 or placebo in a 3:2 ratio. Treatment was administered 11 times during the study. The study has been conducted in 8 European countries; the last patient last visit is expected in June 2019. **Results:** 208 patients have been randomized, while close to the end of the study the dropout rate is 17.3%. No safety signal has been detected in blinded data, nor by the unblinded DSMB. As per the blinded preliminary analysis, the vaccine displays superior immunogenicity among all other active vaccines in AD, 98% of all tested vaccinated patients developed antibody response. At the conference, we will present the study results of efficacy, immunogenicity and safety assessments. Conclusion: The AADvac1 phase 2 study is on track to confirm the favorable safety profile and high immunogenicity, and is powered to confirm the compelling efficacy signals observed in the phase 1 study.

OC3: TREATMENT WITH DONANEMAB, A B-AMYLOID PLAQUE-SPECIFIC ANTIBODY, RESULTS IN RAPID AND SUSTAINED REDUCTION OF AMYLOID MEASURED BY F-18 FLORBETAPIR IMAGING IN ALZHEIMER'S DISEASE. Stephen LOWE (1), Cynthia D. EVANS (2), Sergey SHCHERBININ (2), Yun-Jo CHENG (2), Arnaud CHARIL (2), Brian A. WILLIS (2), Gary MO (2), Albert C. LO (2), Adam S. FLEISHER (3), Ann HAKE (2), Masako NAKANO (4), Jeffrey DAGE (2), Michael HODSTON (2), Paul ARDAYFIO (2), Guilherme AGUIAR (5), Go TAKAICHI (4), Mark A. MINTUN (2), Ronald B. DEMATTOS (2), John R. SIMS (2) *((1) Lilly Centre for Clinical Pharmacology, Singapore, (2) Eli Lilly and Company, United States, (3) Avid Pharmaceuticals, United States, (4) Eli Lilly Japan, K.K., Japan, (5) Eli Lilly and Company, United Kingdom)*

Background: Donanemab (LY3002813) is a humanized IgG1 antibody directed at an Aβ epitope (N3pG – N term, 3rd amino acid pyro-glutamate) that is present only in amyloid plaques. Donanemab triggers microglial-mediated removal of cortical amyloid plaques. An initial Phase I study AACC (NCT01837641) demonstrated robust amyloid reduction by florbetapir PET imaging after administration of the highest dose, 10 mg/kg. Here, the results of AACD (NCT02624778), a study designed to explore amyloid reduction by donanemab at doses higher than 10 mg/kg, are presented. **Objectives**: AACD, a dose-escalation trial, is an investigator- and subject-blind, randomized study in patients with mild cognitive impairment due to Alzheimer's disease (AD) and mild to moderate AD dementia. The primary objective is to assess the effect of donanemab on brain plaque load measured by florbetapir PET after single and multiple doses. Additional objectives of the study are to assess the safety and pharmacokinetics (PK) of donanemab. **Methods:** Florbetapir PET-positive AD patients with MMSE 16-30 were enrolled into AACD in 6 dosing cohorts, either single dose 10, 20 or 40 mg/kg of donanemab or multiple doses of 10 or 20 mg/kg for either 24 weeks or 72 weeks, or placebo. Brain plaque load, using florbetapir PET as a pharmacodynamic (PD) measure of donanemab, was assessed up to 72 weeks. Safety was evaluated by adverse events, MRI, ECGs, vital signs, safety laboratories, neurological monitoring, and immunogenicity. PK was assessed, along with exploratory measures including volumetric MRI, flortaucipir PET, and serum/plasma/CSF biomarkers. **Results:** 61 patients (mean age 73, mean MMSE 22.1, 75 % APOE ε4 (E4) carriers were dosed with either placebo (N=15) or donanemab (N=46) into the 6 different longitudinal cohorts. For the single dose cohorts, 12 week change from baseline on florbetapir PET for donanemab was: 10mg/kg (n=7) = -11.8 centiloids (CL) (SD 21.0), 20mg/kg (n=7) = -39.0 CL (SD 18.1), and 40mg/kg (n=4) = -46.2 CL (SD 13.8). Reduction of amyloid for donanemab multiple dose cohorts at 24 weeks were: 10mg/kg Q2Wk (n=10) = -56.6 CL (SD 33.8), 10mg/kg Q4Wk (n=8) = -49.2 CL (SD 44.9), and 20mg/kg Q4Wk (n=10) = -59.7 CL (SD 51.4). Repeated dosing resulted in continued florbetapir PET reductions over time compared to single dosing, with 21 % patients (6 out of 28) attaining a negative florbetapir PET scan within 6 months after start of dosing. Following a single dose of donanemab, florbetapir PET did not return to pre-dose baseline levels for any subject within 72 weeks post-dosing. Donanemab was generally well tolerated. There were 12 of 46 treated subjects with amyloid related imaging abnormalities - edema (ARIA-E), 2 of which were symptomatic, with one reported as a SAE. Greater than 85% of patients had positive TE-ADAs during the course of treatment with donanemab. However the TE-ADAs were generally not associated with infusion related or hypersensitivity reactions. Up to date safety, tolerability, PK and PD data will be presented. **Conclusion:** Donanemab demonstrates a rapid, robust and sustained reduction in brain amyloid plaque. Safety, tolerability, PK, and PD findings support continued development in a Phase 2 study with donanemab. A Phase 2 study, AACG (NCT03367403, TRAILBLAZER-ALZ), has completed enrollment and is ongoing in patients with early symptomatic Alzheimer's disease.

OC4: AUTOMATIC SPEECH RECOGNITION CAN DELIVER LARGE-SCALE, REMOTE ASSESSMENTS OF COGNITION. Francesca CORMACK (1, 2), Merina SU (1), Jennifer H. BARNETT (1, 2), Nick TAPTIKLIS (1) *((1) Cambridge Cognition, United Kingdom, (2) University of Cambridge, United Kingdom)*

Background: Verbal neuropsychological tests are often used in the context of neurodegeneration in older adults. However, the potential for verbal assessments as large-scale, sensitive screening tools has yet to be reached because of their dependence on skilled raters. We conducted a large, at home feasibility study into whether a device-agnostic web-based technology (Cambridge Cognition's NeurovocalixTM platform) offers a reliable method of administering and scoring verbal neuropsychological tests across devices, platforms and demographics. **Objectives:** To determine the acceptability and feasibility of using Cambridge Cognition's NeurovocalixTM platform to remotely administer and score verbal neuropsychological tests, at scale and on participants own devices. **Methods:** 3,264 participants aged 17-86 years (M=34.5, SD=12.32) completed a battery of three automated tasks: digit span, serial subtraction and verbal paired associates. Repeated assessment was carried out at a delay of 3 months in 1,151 participants. Participant demographics, native language and information regarding the operating system, browser and platform on which the tasks were completed, were all

collated. Voice data was recorded and stored for analysis and quality control. **Results:** Nearly half (47%) of participants completed the testing on a Microsoft Windows platform, and a further third (36%) completed the assessment on a mobile phone. There was no significant difference in performance depending on platform, suggesting that testing is feasible across a range of different devices. We observed expected differences in performance depending on task difficulty (e.g. easy vs hard word pairs, digits forward and back), and predicted relationships between demographic variables (e.g. age) and task performance. Qualitatively, participants reported that the automated instructions were clear and easy to understand, and that the tasks were enjoyable. We also present data on the repeatability of the assessments on these different platforms, and by participant age brackets. **Conclusion:** Together, these results demonstrate that remote, automated, voice-based, cognitive assessments are feasible and acceptable for younger and older adults. Furthermore, automatic speech recognition was shown to be scalable as participants' completed the verbal tasks in their own homes, and on their own devices (laptop, smartphone). These findings suggest potential for automatic speech recognition as a home-based monitoring or assessment methodology in the context of remote clinical trials.

OC5: DEVELOPMENT OF GO/NO-GO DECISION-MAKING CRITERIA IN EARLY CLINICAL DEVELOPMENT OF AGENTS TO TREAT ALZHEIMER'S DISEASE. Alette WESSELS (1), Chris EDGAR (2), Gregory LIGHT (3), Pradeep NATHAN (4), Eric SIEMERS (5), Paul MARUFF (6), John HARRISON (7) *((1) Eli Lilly and Company, United States, (2) Cogstate, United Kingdom, (3) Department of Psychiatry, University of California, United States, (4) SoseiHeptares, United Kingdom, (5) Cogstate, United States, (6) Cogstate, Australia, (7) Metis Cognition Ltd, United Kingdom)*

Introduction: Go/No Go decision making in early phase clinical trials remains critical and challenging for drug developers working in Alzheimer's disease (AD). Despite multiple agents entering Phase II and III clinical trials, it has now been more than 15 years since the introduction of memantine, the last drug to be approved for AD. Recent negative trials have been due to lack of efficacy, perhaps related to dose selection or participant selection based on biomarker and clinical status, and also important safety concerns. At the same time, trends evident in the current pipeline such as greater numbers of trials in preclinical and prodromal populations, increasing and changing use of biomarker confirmed diagnoses, and increasing numbers of non-amyloid mechanisms, result in a continually evolving set of information and requirements to support decision making. Enduringly though, evidence in humans that an agent engages with molecular targets in the brain, and that this leads to relevant behavioral/functional consequences, is needed to support development decisions to undertake large, expensive Phase 3 trials. Cognitive tests are used as measures of treatment efficacy and as pharmacodynamic/behavioral biomarker outcomes in early clinical development to support the Go/No Go decision-making process. Furthermore, in addition to typical safety considerations (e.g. liver toxicity), unexpected cognitive worsening has been reported for both gamma secretase inhibitors and BACE inhibitors, highlighting the importance of cognitive outcomes to safety Go/No Go decision-making. **Objectives:** This presentation will focus on the use of cognitive tests as part of the Go/No Go decision making process, with a focus on the estimation of the desired magnitude of clinical effect size and subsequent clinical relevance in later stage development. Other issues that will be addressed include instrument selection appropriate to the context of use (disease stage, stage of development and mechanism of action), the research question (pharmacodynamic, safety, proof of concept), and the translation of clinical effects observed in early stage development to later stages of development. **Discussion:** Challenges in respect of the stability, sensitivity, reliability and validity of the most commonly used measures will be discussed, including breadth and relevance of coverage of cognitive domains. For some cognitive domains, such as working memory and aspects of executive function, issues of measurement reliability and validity have been particularly prominent. This is in spite of the acknowledgement that these domains are of key functional relevance, are compromised early in the disease process, and are responsive to pharmacological interventions. It is noteworthy that on the rare occasions when these domains are assessed using sensitive, reliable and valid tools, positive treatment effects have been obtained. Considerations specific to the context of use, including disease stage and development phase will be applied. An additional critical consideration, beyond the employment of better measures is the topic of magnitude of effect. Currently marketed treatments for AD are observed to yield positive treatment impact with effect sizes of as high as c.0.3. This is still a relatively modest effect, in standard statistical characterizations, qualifying as 'small'. However, such determinations in respect of a 'Go/No Go' decision may be highly context dependent and issues around selection of a meaningful magnitude of effect in the context of a given mechanism of action and study design will also be reviewed. **Conclusion:** Whilst Go/No Go decisions have proven particularly difficult in AD drug development where demonstrated target engagement doesn't necessarily translate into demonstrable clinical efficacy, cognitive data may provide valuable insights at various points during development of a drug. A thoughtful and robust set of decision-making criteria, specified a priori, can and should be applied under many circumstances. However, the specific criteria for these Go/No Go decisions may differ depending on the context e.g. stage of development, stage of disease, mechanism of action, trial design, competitive landscape and opportunity costs, and must be well tailored to the needs of each program.

OC6: EFFICACY AND SAFETY RESULTS OF REVERSE-SD, PHASE-2B CLINICAL STUDY OF THE SELECTIVE P38A KINASE INHIBITOR NEFLAMAPIMOD IN EARLY-STAGE ALZHEIMER'S DISEASE (AD). Philip SCHELTENS (1), John ALAM (2), John HARRISON (1, 3), Kelly BLACKBURN (2), Niels PRINS (1, 4) *((1) Department of Neurology and Alzheimer Center, Amsterdam UMC, Netherlands, (2) EIP Pharma, Inc, United States, (3) Metis Cognition Ltd, United Kingdom, (4) Brain Research Center, Netherlands)*

Background: REVERSE-SD is a double-blind, placebo-controlled, phase 2b clinical study of the oral investigational drug neflamapimod in early-stage Alzheimer's disease (AD) with the primary objective of demonstrating the ability of the drug to reverse synaptic dysfunction ("SD") in the hippocampus, as evaluated by a test of episodic learning and memory – the Hopkins Verbal Learning Test. Neflamapimod is a highly selective brainpenetrant small molecule inhibitor

of the alpha isoform of p38 MAP kinase (p38α). In 6- and 12-week duration phase 2a clinical studies in patients with early AD, neflamapimod demonstrated within-subject improvement in episodic memory function (Scheltens et al, ACTN, 2018; CTAD, 2016 & 2017) consistent with the potential for reversing hippocampal synaptic dysfunction derived from preclinical studies. P38α, which is expressed in neurons under conditions of stress and disease, plays a major role in inflammation induced synaptic toxicity, including the impairment of synaptic function (i.e. synaptic plasticity) in the hippocampus (Watterson, 2013; Prieto, 2015). Accordingly, small molecule p38α kinase inhibitors fully reversed spatial learning deficits in three distinct animal models (APP/PS1, aged rats, and aged hTau mice; Roy, 2015; Maphis, 2016; Alam, 2016), and genetic reduction of neuronal p38α in APP/PS1 mice improved synaptic transmission, reduced memory loss, and reduced amyloid pathology (Colié, 2017). Genetic reduction of neuronal p38α also protected mice from developing age-related hippocampal dysfunction (Cortez, 2017). Furthermore, a recent human GWAS study implicated the p38α pathway in the development of age-related decline in episodic memory (Huentelmann, 2018). **Methods:** Inclusion: Aged 55 to 85, with CDR-Global score of 0.5 or 1.0; CDR memory sub-score of at least 0.5; MMSE score of 20 to 28, inclusive; positive biomarker for AD, as defined by CSF Aβ1-42 <1000 pg/mL and phospho-tau/Aβ1-42 >0.24 in the Roche Eclesys® immunoassay; receiving either no AD-specific therapy or on stable dose monotherapy (either cholinesterase inhibitor or memantine; dual therapy excluded). **Treatment:** randomized 1:1 to receive neflamapimod 40 mg capsules or matching placebo capsules twice daily with food for 24 weeks, stratified by baseline CDR-global score (0.5/1.0) and whether the subject is receiving background AD-specific therapy (yes/no). Primary endpoint: Episodic memory, as assessed by change from baseline to week 24 in combined z-score of total recall and delayed recall in Hopkins Verbal Learning Test – Revised (HVLT-R) in neflamapimod-treated subjects compared to placebo-recipients. Secondary endpoints: Change in Wechsler Memory Scale immediate or delayed recall composites, CDR-SB, MMSE, CSF biomarkers (total tau, p-tau181, Aβ1-40, Aβ1-42, neurofilament light chain, neurogranin, BDNF) in neflamapimod-treated subjects compared to placebo-recipients. Sample size: Approximately 76 patients per treatment arm (152 patients total). Provides 90% statistical power to detect effect size (ES) of 0.53 and 80% to detect ES of 0.46. Assuming a z-score decline of between 0.15 to 0.25 in the placebo-recipient group, neflamapimod treatment would need to show an increase in z-score of at least 0.21 to 0.38 to demonstrate a statistically significant positive treatment effect on the primary endpoint. **Results:** 477 subjects screened, and 161 patients were enrolled at 38 sites in the Czech Republic (5 sites), Denmark (3 sites), Netherlands (3 sites), United Kingdom (11 sites) and USA (16 sites). The last patient enrolled commenced dosing in early January 2019. The most frequent reasons for screen failure were out of range MMSE score and not meeting CSF criteria. At baseline, among patients randomized, mean age was 72 and 50% were female. 77% had a CDR-global score of 0.5 (CDR-memory sub-score was 0.5 in 48%, 1.0 in 51%, 2.0 in 1%); mean MMSE score was 23.8 (s.d.=2.5; median=24); mean HVLT total recall score was 15.9 (s.d.=5.7; 87% < 22) and mean HVLT delayed recall score was 3.0 (s.d=3.1: 42% had score of 0.0). As of June 1, 2019, 154 patients have completed week 12 assessments and 118 have completed treatment. There have been 10 early terminations, of which 4 were related to adverse events (nausea, fatigue, 2 unrelated intercurrent medical events); no new safety risks have been identified. Last patient, last visit will occur in July 2019 and database lock is anticipated by end of August 2019. All prospectively planned efficacy and safety analyses will be available for the meeting. **Conclusion:** The study has enrolled a well-defined early AD patient population with significant episodic memory defects at baseline. It is designed to provide clinical proof-of-concept for neflamapimod, and p38α kinase inhibition generally, as an approach to improve episodic memory function in patients with early AD. Further, the secondary clinical endpoints combined with CSF biomarkers will provide an initial assessment of the potential of neflamapimod to impact AD disease progression globally. Finally, as the first study to evaluate an approach that targets intra-neuronal molecular mechanisms underlying synaptic dysfunction, the findings will provide insights (e.g. responsiveness of the clinical and biomarker endpoints to such approaches) for the field to designing clinical trials evaluating therapies directed at synaptic dysfunction. Note: Authors presenting on behalf of REVERSE-SD investigators and study team.

OC7: PHASE III STUDIES OF CRENEZUMAB IN EARLY (PRODROMAL-TO-MILD) ALZHEIMER'S DISEASE (CREAD/CREAD2): BIOMARKER RESULTS.

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Background: Crenezumab is a humanized anti-beta-amyloid (Aβ) monoclonal immunoglobulin G4 antibody that has been evaluated in clinical trials in patients with sporadic Alzheimer's disease (AD) [1,2], with a study in autosomal-dominant AD currently ongoing [3]. Crenezumab binds to monomeric and aggregated forms of Aβ, with a high affinity for Aβ oligomers [4,5], which may protect neurons from oligomer-induced toxicity [5]. The Phase III CREAD (NCT02670083 [6]) and CREAD2 (NCT03114657) studies that investigated the safety and efficacy of crenezumab at 60 mg/kg administrated intravenously (IV) every 4 weeks (q4w) in early (prodromal-to-mild; Mini-Mental State Examination (MMSE)) ≥22) AD were recently stopped based on an interim analysis of CREAD that indicated that the study was unlikely to meet its primary endpoint of change from baseline to Week 105 in Clinical Dementia Rating–Sum of Boxes (CDR-SB); no safety signals were observed in this analysis and the overall safety profile was similar to that seen in previous studies [7]. Post hoc analyses of preceding Phase II studies suggested an efficacy signal at the higher of two doses of crenezumab tested (15 mg/kg IV q4w). Biomarker results from Phase II studies suggested an increase in Aβ(1-42) and Aβ(1-40) in cerebrospinal fluid (CSF) and plasma, a decrease in soluble Aβ oligomer levels in CSF, and reduced accumulation of fibrillar amyloid as measured by florbetapir-PET SUVR after 69 weeks of treatment with crenezumab, compared with placebo [2,8]. The CREAD and CREAD2 studies

also included assessments of imaging and fluid biomarkers to better understand the effects of crenezumab on the underlying pathology of AD, including amyloid plaques, neurofibrillary tangles, and neuronal degeneration and inflammation. **Objectives**: To assess the effect of crenezumab compared with placebo on changes in imaging and fluid biomarkers in patients with early (prodromal-to-mild) AD enrolled in CREAD and CREAD2. **Methods**: CREAD and CREAD2 were multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase III studies enrolling patients aged 50–85 years with early AD and confirmed evidence of cerebral amyloid pathology (by CSF and/or amyloid PET). At screening, patients were required to have an MMSE score of ≥22, a Clinical Dementia Rating Global Score (CDR-GS) of 0.5 or 1, and Free and Cued Selective Reminding Test (FCSRT) immediate free recall and cueing index scores of ≤27 and ≤0.67, respectively. Enrolled patients were randomized 1:1 to receive placebo or crenezumab (60 mg/kg q4w IV). Randomization was stratified by dementia status (prodromal vs. mild AD), APOE ε4 allele status (presence or absence), baseline anti-dementia medications (presence or absence), and geographic region. The primary endpoint for both studies was the change from baseline to Week 105 on the CDR-SB score. Biomarker data were collected in the main study or in one of four substudies to measure target engagement and evaluate treatment response and disease progression. Assessments as per protocol included: amyloid PET, tau PET, volumetric MRI, CSF biomarkers (Aβ(1-42), Aβ(1-40), total tau, phosphorylated tau), and plasma biomarkers (Aβ(1-42), Aβ(1-40)). Additional exploratory measurements included CSF biomarkers of Aβ oligomers, neurofilament light chain (NfL), neurogranin, YKL-40, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), glial fibrillary acidic protein (GFAP), s100b, alpha-synuclein, and interleukin-6 (IL-6)), as well as plasma NfL. **Results**: Data from the CREAD and CREAD2 biomarker analyses will be presented. **Conclusions:** CREAD and CREAD2 were discontinued based on a pre-planned interim analysis of CREAD, which indicated that the study was unlikely to meet its primary endpoint. However, biomarker data from patients enrolled in these trials will help to advance our understanding of the potential change in these biomarkers under treatment with crenezumab, and of their role in the pathology and progression of AD. **References:** 1. Cummings JL, et al. Neurology 2018;90:e1889–e1897; 2. Salloway S, et al. Alzheimers Res Ther 2018;10:96 3. Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease; ClinicalTrials.gov Identifier: NCT01998841; 4. Adolfsson O, et al. J Neurosci 2012;32:9677–9689; 5. Ultsch M, et al. Sci Rep 2016;6:39374; 6. Lin H, et al. AAIC 2018; 7. F. Hoffmann-La Roche Ltd. Media release. January 30, 2019; 8. Yang T, et al. Ann Neurol 2019 in press.

OC8: DHA BRAIN DELIVERY PILOT STUDY: A RANDOMIZED CLINICAL TRIAL. Hussein YASSINE (1), Isabella CORDOVA (1), Nicholas CHOE (1), Xulei HE (1), Brian KAVIN (1), Naoko KONO (1), Nalini HAZRA (1), Giselle KIM (1), Alfred FONTEH (2), Howard HODIS (1), Lina D'ORAZIO (1), Carol MCCLEARY (1), Helena CHUI (1), Michael HARRINGTON (2), Meredith BRASKIE (1), Wendy MACK (1), Lon SCHNEIDER (1) *((1) USC, United States, (2) HMRI, United States)*

Background: A lower ratio of docosahexaenoic acid (DHA) to Arachidonic Acid (DHA/AA) in plasma is associated with increased risk of cognitive decline, Alzheimer's disease (AD) pathology and neuroinflammation. In patients with AD, carrying the APOE4 allele is associated with reduced brain DHA delivery. Very few studies have evaluated the delivery of DHA to the brain after DHA supplementation before the onset of AD. Thus, exploring DHA delivery to the human brain as determined by cerebrospinal fluid (CSF) DHA/AA after supplementation is critical for designing appropriate prevention interventions. **Methods**: A randomized pilot clinical trial was conducted to measure changes in CSF DHA/AA following 6-month supplementation with high dose (2 grams daily) of DHA vs Placebo in 33 non-demented older adults, stratified (1:1) by APOE e4 genotype. The inclusion criteria were age 55-90 and family history of dementia. The main exclusion criteria were a diagnosis of dementia, omega-3 supplement use, DHA consumption >200 mg/day, > 7.5 Mets of exercise/week. The primary outcome was the change in CSF DHA/AA ratio. We also explored the effect of DHA intervention on cognitive outcomes and hippocampal volumes. **Results**: 33 individuals were randomized (placebo, n=15, DHA, n=18); 29 completed cognitive assessments and 26 individuals completed lumbar punctures and MRI imaging. The primary outcome, CSF DHA/AA differed between the Placebo and DHA arms (mean (95% CI): -0.01 (-0.08, 0.06) vs 0.10 (0.02, 0.17) respectively, p=0.04). Exploratory outcomes (Placebo vs DHA, mean (95% CI)) included CVLT2 trial 5 raw scores (-0.77, (-1.94, 0.4) vs (1.12 (-0.02, 2.27), p=0.03), CVLT2 delayed recall raw scores (1.26 (-0.16,2.68) vs 1.88 (0.49, 3.27), p=0.53), mean bilateral hippocampal volume % of ICV (-0.004 (-0.009, 0.001) vs -0.002 (-0.007, 0.003), p=0.66) and mean bilateral entorhinal cortex thickness mm (-0.1 (-0.2, -0.0005) vs 0.007 (-0.09, 0.1), p=0.13). **Discussion**: This pilot trial provides supportive feasibility data to test the effect of large doses of DHA supplementation on CSF DHA/AA, cognitive and imaging outcomes. A larger trial is planned to assess the effect of APOE e4 genotype and brain amyloidosis on brain DHA delivery before the onset of AD (clinicaltrials.gov NCT02541929 and funded by Alzheimer's Association grant NIRG-15-361854, NIA R01AG054434, P50AG05142 and ADDF GC-201711-2014).

OC9: ANCHOR- AND DISTRIBUTION-BASED METHODS TO ESTABLISH CLINICALLY MEANINGFUL SCORE CHANGES ON THE CLINICAL DEMENTIA RATING SCALE – SUM OF BOXES IN PATIENTS WITH PRODROMAL ALZHEIMER'S DISEASE. Claire J. LANSDALL (1), Lesley M. BUTLER (2), Geoff KERCHNER (2), Fiona MCDOUGALL (2), Paul DELMAR (2), Nathalie PROSS (2), Shanshan QIN (3), Lori MCLEOD (3), Monika BAUDLER (2), Paulo FONTOURA (2), Rachelle DOODY (2, 4) *((1) Roche Products Limited, United Kingdom, (2) F. Hoffmann-La Roche Ltd, Switzerland, (3) RTI Health Solutions, United States, (4) Genentech, Inc., United States)*

Introduction: The Clinical Dementia Rating Scale – sum of boxes (CDR-SB) is often the primary endpoint of choice for clinical trials in early Alzheimer's Disease (AD). However, consensus among stakeholders (including health care professionals, payers, regulators, patients and caregivers) regarding what constitutes a clinically meaningful change on the CDR-SB is lacking. Establishing a threshold or range of score changes that reflect a meaningful change on the CDR-SB is of critical importance to aid the interpretation of clinical trial data and to demonstrate the value of novel therapies

in AD. Objective: To establish a range of score changes that constitute a meaningful within-person (individual level) change on the CDR-SB in patients with prodromal AD. **Methods**: This was a secondary analysis of data from the Alzheimer's Disease Cooperative Study ADC-008 phase III clinical trial of Donepezil and Vitamin E, in patients with amnestic Mild Cognitive Impairment (MCI) (Inclusion criteria: Age = 55-90, MMSE = 24-30, Logical Memory delayed-recall score = 1.5-2 standard deviations below an education-adjusted norm and CDR-global score = 0.5, consistent with prodromal AD [non-biomarker confirmed]). Following standard methodology (Patient Focused Drug Development FDA draft guidance 2018; Coon & Cook, 2017), anchor- and distribution-based approaches were used to establish a range of score changes associated with a clinically meaningful change/decline at the individual level on the CDR-SB (collected every 6 months throughout the 36- month study). Anchors included the Global Deterioration Scale (GDS), a 7-point measure of cognitive impairment severity rated by the clinician, completed at baseline and every 6 months thereafter, and the Mild Cognitive Impairment-Clinician Global Impression of Change (MCI-CGIC), completed at months 6 and 12. Mean- and median- score changes on the CDR-SB in those experiencing a 1- or 2-category decline on the GDS and minimal- or moderate-worsening on the MCI-CGIC were calculated. Distribution-based analyses included 0.5 standard deviation (SD) and standard error of measurement (SEM), denoting the minimum score change that is considered to be greater than measurement error. Cumulative distribution function and probability density function plots were generated to explore appropriate thresholds further. The proposed meaningful change thresholds focus on the 12 month time point, taking into consideration the sample sizes in each anchor category and the anchor-CDR-SB correlation. Additional time points will be presented. **Results**: A total of 769 prodromal patients with a CDR global score of 0.5 were included in the analyses (mean [SD] = age 72.9 [7.3] years, 46% female, 55% APOE ε4 carrier, mean [SD] CDR-SB = 1.8 [0.8], MMSE = 27.3 [1.9]). The CDR-SB demonstrated good psychometric performance overall (good test-retest reliability ICC ≈ 0.7, no floor/ceiling effects) and showed adequate correlation (r) with the GDS (r=0.50) and MCI-CGIC (r=0.53) changes at 12 months. For the GDS anchor, those experiencing a 1-category change (interpreted as a minimum decline) at 12 months had a mean [SD]/median score change of 1.08 [1.18]/1.00 (n=132) on the CDR-SB, while those experiencing a 2-category change (interpreted as a moderate decline) had a mean [SD]/median score change of 3.39 [1.92]/2.75 (n=14). For the MCI-CGIC anchor, those experiencing a minimal-deterioration had a mean[SD]/median CDR-SB score change of 0.64 [1.02]/0.50 (n=192), while those experiencing a moderate-deterioration had a mean[SD]/median change of 2.35 [1.66]/2.00 (n=43). Distribution-based thresholds for within-person changes were 0.39 (½ SD) and 0.45 (SEM), indicating that changes of 0.5 or greater are larger than measurement error. Taken together, these data suggest that a 1- point change is a reasonable threshold for a minimal deterioration, whilst a 2.5- point change might be a more appropriate reflection of a moderate deterioration. **Conclusion**: These values may be considered when defining a "progressor threshold" for the CDR-SB. Choice of the specific threshold will depend on the study design characteristics, in particular the target patient population and the length of trial. Such thresholds can be used to determine the proportion of patients who experience a meaningful decline and can contribute to the assessment of treatment benefit in the context of a clinical trial.

OC10: AWARENESS OF GENETIC RISK IN THE DOMINANTLY INHERITED ALZHEIMER NETWORK (DIAN). Jason HASSENSTAB (1), Bryan D JAMES (2), Andrew A ASCHENBRENNER (1), Eric M MCDADE (1), Guogiao WANG (1), Yen Ying LIM (3), Tammie L S BENZINGER (1), Carlos CRUCHAGA (1), Alison GOATE (4), Chengjie XIONG (1), Virginia BUCKLES (1), John C MORRIS (1), Randall J BATEMAN (1) *((1) Washington University in St. Louis, United States, (2) Rush University, United States, (3) The Florey Institute of Neuroscience and Mental Health, Australia, (4) Icahn School of Medicine at Mount Sinai, United States)*

Introduction: While some members of families with Autosomal dominant Alzheimer disease (ADAD) mutations may choose to learn their mutation status, most do not. Family members cite anxiety, the lack of available treatments, and many other reasons for abstaining from genetic testing. The extent to which awareness of mutation status might affect clinical disease progression is currently unknown. Objective: We quantified the influence of awareness of mutation status on clinical symptoms, cognition, and biomarkers. We also examined whether learning one's mutation status mid-study might affect these same outcomes. **Methods**: Mutation carriers (n = 200) and noncarriers (n = 127) from the Dominantly Inherited Alzheimer Network (DIAN) were stratified based on knowledge of mutation status. Baseline levels and longitudinal rates of change on clinical assessments, cognitive measures, structural MRI, and amyloid PET were examined. A subset of participants learned their mutation status after baseline (n = 31 carriers; n = 25 noncarriers) and were compared against participants who never learned their status to determine the effect of learning mutation status mid-study. **Results**: At baseline and longitudinally, mutation knowledge had no associations with cognition, clinical progression, amyloid deposition, hippocampal volume, or depression in either carriers or noncarriers. Carriers who learned their status mid-study had slightly higher levels of depressive symptoms (β = 0.80, p = 0.03, Cohen's d = 0.21), and lower scores on the cognitive composite (β = -0.24, p = 0.005, Cohen's d = 0.25) compared to unaware mutation carriers. **Discussion**: Knowledge of mutation status does not impact rates of change on cognition, clinical progression, amyloid deposition, hippocampal volume, or mood. Learning of status mid-study may confer short-term changes in cognitive functioning and mood, or changes in cognition and mood may influence the determination of mutation status. Thus, learning of mutation status mid-study may have implications for observational studies and clinical trials in ADAD.

OC11: ALZHEIMER'S PREVENTION INITIATIVE GENERATION PROGRAM: UPDATE AND NEXT STEPS. Ana GRAF (1), Beth BOROWSKY (2), Pierre TARIOT (3), Fonda LIU (2), Marie-Emmanuelle RIVIERE (1), Marie-Laure ROUZADE-DOMINGUEZ (1), Jessica LANGBAUM (3), Angelika CAPUTO (1), Vissia VIGLIETTA (4), Eric REIMAN (3) *((1) Novartis Pharma, Switzerland, (2) Novartis Pharmaceuticals, United States, (3)Banner Alzheimer's Institute, United States, (4) Amgen Inc., United States)*

Background: The Alzheimer's Prevention Initiative (API) Generation Study 1 (GS1) has been evaluating the BACE1 inhibitor umibecestat (CNP520) and the active amyloid-b (Ab) immunotherapy CAD106 in cognitively unimpaired

60-75 year-old APOE4 homozygotes, including those with and without elevated amyloid levels. API Generation Study 2 (GS2) has been evaluating umibecestat in APOE4 heterozygotes with elevated amyloid levels and additional homozygotes, independent of the amyloid status (Lopez Lopez et al., 2019). Two doses of umibecestat were used in GS2: 50mg and 15 mg, with expected median CSF Aβ lowering of 86% and 68%, respectively. In GS1: Cohort I, CAD106 at 400ug/l with Alum and Cohort II umibecestat at 50mg were used. Umibecestat was discontinued in July 2019 due to mild worsening in several measures of cognitive function, and the participants continue to be followed to clarify the reversibility of these and any other observed effects. In this presentation, we will briefly describe the studies' original and revised design and aims and current status. **Design/Methods:** Randomization was initiated in March 2016 for Cohort I of GS1, in February 2017 for Cohort II and in December 2017 for GS2. Studies were implemented across 23 countries worldwide at 207 sites, with over half of the sites participating in both trials. Recruitment was supported by the Alzheimer's Prevention Registry and GeneMatch Program in the US, other local engagement and recruitment activities, and specially developed genetic counseling and disclosure programs. Enrollment to Cohort I with CAD106 was halted in November 2017 after 65 participants had been randomized to mitigate the risk that a large number of participants are exposed prior to the futility analysis of CNS activity. Following the disclosure of mild cognitive detrimental effects with verubecestat and atabecestat at CTAD in October 2018, Novartis and its partners, Banner Alzheimer's Institute and Amgen, implemented a series of measures to enhance oversight of the safety of study participants receiving umibecestat or placebo. Study protocols were amended to include earlier cognitive, neuropsychiatric assessments, MRI scans as well as fluid biomarkers collection. Frequency of Data Monitoring Committee (DMC) meetings was increased, focusing on cognitive measures. An option to lower doses of umibecestat was added to the protocols, as this was considered to be an effective mitigation strategy. All trial participants and their study partners were informed of the findings with other BACE inhibitors. At that time recruitment across both studies continued unaltered and reached steady rate over 100 participants randomized per month. **Results**: In July 2019, recruitment and treatment with umibecestat was halted following a planned DMC review of the unblinded data. At that time, >1'200 cognitively unimpaired APOE4 homozygotes and > 10'000 APOE4 heterozygotes were identified by genetic screening; 704 homozygotes (35% of whom were amyloid negative) were enrolled in GS1 or GS2; and 913 amyloid-positive heterozygotes were enrolled in GS2. Umibecestat was associated with mild worsening in some measures of cognitive function with both doses tested (15 and 50 mg daily). The data available at the time of DMC review included 1260 participants randomized to umibecestat or placebo (369 in GS1 and 891 in GS2), with cognitive data available for 578 participants at month 3 and 483 at month 6. This early effect was similar to external data reported with several other BACE inhibitors. The mechanism leading to this worsening remains unknown. All participants were informed to stop treatment within 10 working days. They were all scheduled to attend a final evaluation and a follow-up visit after treatment discontinuation. GS1 Cohort 1 with CAD106 was not affected at the time of the CNP520 termination. **Conclusions**: The Generation Program has introduced programs and procedures to support enrollment in multi-study prevention trials, and it has demonstrated the ability to conduct them in an exceptionally large number of cognitively unimpaired participants willing to learn their AD risk estimate. Results from the Generation Program will be analyzed including follow-up visits off-treatment to evaluate the potential reversal of the observed early worsening of cognitive measures. Trial findings, data, biological samples, and motivated amyloid-positive and -negative participants will provide important resources for the advancement of AD prevention research. Upon study completion, findings will be reported and data and samples will be shared following CAP principles. API is exploring ways in which to continue to follow interested participants, provide a trial-ready cohort, and prepare for new prevention trials. **Reference:** Lopez Lopez et al. The Alzheimer's Prevention Initiative Generation Program: Study design of two randomized controlled trials for individuals at risk for clinical onset of Alzheimer's disease. A&D TRCI (2019) 5, 216-227.

OC12: RECRUITMENT STRATEGIES FOR THE GENERATION PROGRAM AD PREVENTION CLINICAL TRIALS: LESSONS FROM THE BUTLER HOSPITAL MEMORY & AGING PROGRAM.

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Background: Alzheimer's disease risk assessment is critical in screening cognitively normal individuals for AD prevention trials, such as the Amgen/Novartis Generation Program, which recruits preclinical AD participants with at least one copy of the APOE ε4 allele. The Generation 1 trial recruits cognitively normal APOE ε4 homozygotes, regardless of amyloid PET status. The companion Generation 2 trial recruits APOE ε4 homozygotes, as well as APOE ε4 heterozygotes who are also amyloid positive (PET scan or CSF). Therefore, APOE genotyping is a critical first step in the recruitment process. The Butler Hospital Memory & Aging Program (MAP) has created several efficient and effective recruitment pathways, establishing active pipelines for APOE genotyping and disclosure, as well as a high randomization rate in the Generation 1 & 2 trials. **Methods**: There are three primary recruitment pipelines used by the Butler Memory & Aging Program for the Generation 1 & 2 trials. All pipelines begin with public engagement. We have 3-full time outreach coordinators, a social media specialist and several part-time staff dedicated to community events. The first recruitment pipeline is through the Banner Health Genematch Program, which refers participants who have completed a cheek swab test at home to local study sites. Butler is a Genematch site, meaning that we can also distribute these APOE genotyping kits to the public and mail them to Genematch for analysis, and we tend to use this method to genotype at large community events, where participants are not known to our program. If referred to our site, these participants are disclosed through the Generation Program consent mechanism. The second pipeline is through the Butler Alzheimer's Prevention Registry (BAPR), our trial-eligible cohort database of approximately 1500 adults aged 50-85. Interested volunteers can sign up online or at our community events. BAPR has several sub-studies, one of which is a local APOE genotyping and disclosure program. At visit 1, participants undergo brief cognitive screen, mood and

functional assessments, and a clinical interview to determine psychological readiness for APOE genotype disclosure. At a second visit, participants receive counseling and APOE genotype is disclosed, and participants complete follow-up assessments at 3 days, 6 weeks, and 6 months. The third pipeline is a brief cheek swab consent through the Generation 1 study that can be used to genotype qualified participants. We use this consenting process to obtain swabs at local "swab parties" for interested registrants, which are conducted on Butler campus. Importantly, these individuals have already signed up for BAPR and meet general inclusion/exclusion criteria for clinical trials. Participants are disclosed through our local registry disclosure protocol, and if they meet entry criteria for Generation 1 or 2, are given the option to move forward in the screening process. In addition, we have started using the Spartan Cube, a research-only device for rapid APOE genotyping, at local events or "swab parties". **Results**: Since the inception of the Generation Program at Butler MAP in 2016, we have conducted 337 public events, speaking to approximately 34,000 individuals. We have conducted 360 Genematch swabs at 22 community events, and received 58 Genematch referrals to our site. 246 individuals have been recruited through our local registry. Of these, 129 have been APOE genotyped through our registry APOE substudy, and 117 have been genotyped through the Generation 1 mechanism at local "swab parties". Our current enrollment numbers for Generation 1 (APOE ε4 homozygotes) and Generation 2 (APOE ε4 heterozygotes) are as follows: Generation 1 – 40 screened (33 Genematch referrals, 6 local registry referrals, 1 self-referral (23 & Me)), 8 enrolled (20% randomization rate). Generation 2 – 59 screened (19 Genematch referrals, 40 local registry referrals), 21 enrolled (36% randomization rate). **Conclusion**: A multi-faceted recruitment approach, community outreach targeting at-risk individuals, and the development of a local APOE genotyping program have been essential for successful recruitment in the Novartis/Amgen Generation Program.

OC13: THIRTY-SIX-MONTH AMYLOID PET RESULTS SHOW CONTINUED REDUCTION IN AMYLOID BURDEN WITH GANTENERUMAB. Gregory KLEIN (1), Paul DELMAR (2), Geoffrey KERCHNER (2), Carsten HOFMANN (1), Danielle ABI-SAAB (2), Smiljana RISTIC (2), Andrew DAVIS (3), Nicola VOYLE (3), Monika BAUDLER (2), Paulo FONTOURA (2), Rachelle DOODY (2, 4) *((1) Roche Pharma Research and Early Development, Switzerland, (2) Roche/Genentech Product Development, Switzerland, (3) Roche Products Ltd, United Kingdom, (4) Genentech, Inc., United States)*

Background: Gantenerumab is a fully human, anti-amyloid-β (Aβ) monoclonal antibody currently under evaluation for the treatment of early Alzheimer's disease (AD) using subcutaneous, titrated dosing schemes targeting 1,200 mg monthly in the SCarlet RoAD (SR; NCT01224106) and Marguerite RoAD (MR; NCT02051608) open-label extension (OLE) studies. Gantenerumab binds to aggregated Aβ to promote amyloid removal. In the SR and MR OLE studies, previous analyses of all 39 patients who received positron emission tomography (PET) scans at 24 months showed large mean (SD) amyloid reductions of 59.0 (35.2) centiloids, and 51% of patients were brought below the amyloid positivity threshold [1]. **Objectives**: This updated analysis reports the effects of high-dose gantenerumab (1,200 mg/month) on amyloid PET after 36 months of ongoing treatment in the SR and MR OLE studies. **Methods**: In the SR and MR OLE studies, patients were assigned to one of five titration schedules (ranging from 2 to 10 months) targeting a dose of 1,200 mg per month. Patients with low Aβ in cerebrospinal fluid and a positive visual amyloid PET scan at the time of the double-blind (DB) screening visit were eligible for the OLE PET substudy; those who were scanned at the 36-month time point were included in this analysis. Due to differences in titration schedules and time between DB and OLE dosing, the analyses divided patients into three cohorts: MR DB placebo (MR-Pbo), MR DB pretreated with gantenerumab (MR-Gant), and SR DB assigned to placebo or gantenerumab (SR). Change from OLE baseline in amyloid burden was assessed via global and regional standard uptake value ratio (SUVR) analysis of florbetapir PET scans acquired at OLE baseline, Month 12 (Year 1), Month 24 (Year 2), and Month 36 (Year 3). The prespecified SUVR method used a volume-weighted, gray matter–masked SUVR of 6 bilateral cortical regions from the automated anatomical labeling (AAL) template, normalized to a cerebellar cortex reference region [2]. SUVR values were translated to the centiloid scale using the linear regression method described by Klunk et al. [3]. **Results**: Preliminary pooled analyses of 23 patients (MR-Pbo, 8; MR-Gant, 6; SR, 9) who had a 36-month scan by May 30, 2019 showed continued amyloid reduction between the 24- and 36-month scans. Mean (SD) centiloid values at 0, 12, 24, and 36 months over all three cohorts were 84.9 (54.5), 41.2 (39.0), 22.1 (33.9), and 2.4 (29.2), respectively. Seventeen of 23 patients (73.9%) were below the amyloid-positivity threshold of 24 centiloids after 36 months of gantenerumab treatment. The mean (SD) reductions from OLE baseline for the three groups at 36 months were 87.9 (53.4), 92.1 (29.7), and 71.4 (42.1) centiloids, respectively. An additional ≈ 8 patients are expected to have their OLE 36-month PET scan by December 2019. The safety profile of gantenerumab remained unchanged compared with prior reports [4, 5]. **Conclusion**: Updated findings are expected to confirm preliminary results and show continued reduction in amyloid burden with ongoing gantenerumab treatment for ≤ 36 months. These data support the ongoing investigation of the clinical efficacy of gantenerumab in two Phase III trials in patients with early (prodromal-to-mild) AD (GRADUATE I [NCT03444870]; GRADUATE II [NCT03443973]). **References:** 1. Klein G, et al. Presented at CTAD 2018, Barcelona, Spain; 2. Barthel H, et al. Lancet Neurol 2011;10:424—435; 3. Klunk WE, et al. Alzheimers Dement 2015;11:1—15; 4. Ostrowitzki S, et al. Alzheimers Res Ther 2017;9:95; 5. Abi-Saab D, et al. Presented at AAIC 2018, Chicago, IL, USA.

OC14: A PHASE 1 STUDY OF AL002 IN HEALTHY VOLUNTEERS AND PATIENTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE. Robert PAUL, Michael WARD, Omer SIDDIQUI, Spencer MADELINE, Long HUA, King ROBERT, Schwabe TINA, Lu SHIAO-PING, Rosenthal ARNON *(Alector, LLC, United States)*

Background: AL002 is a human anti-TREM2 monoclonal antibody in development for the treatment of Alzheimer's Disease (AD) patients. AL002 specifically binds to and activates TREM2, a receptor that is expressed on microglia cells; heterozygous mutations in TREM2 that reduce its function were found to increase the risk of sporadic AD. Non-clinical studies have demonstrated that activating TREM2 can induce microglia proliferation and effectively suppress AD pathology

in vivo to prevent cognitive decline in a mouse model of AD. No adverse effects of AL002 were observed in non-clinical safety studies to date, enabling the first-in-human study. **Objectives**: This is a Phase 1 study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of AL002 in healthy volunteers and patients with mild to moderate AD. **Methods**: The single ascending dose (SAD) part of this study is a randomized, placebo-controlled, double-blind investigation in healthy volunteers (HV). This is followed by a randomized, placebo-controlled, double-blind, multiple-dose (MD) part in patients with a diagnosis of probable AD, aged 50-85 years, with a MMSE score of 16-28, a CDR global score of 0.5, 1, or 2, and a positive amyloid-PET scan based on visual read. The primary objective of this study is to evaluate the safety of single and multiple doses of AL002. **Results**: All single-dose healthy volunteer cohorts in this Phase 1 study have been dosed and preliminary safety and PK data are available. The multiple-dose AD cohort has also been initiated. **Conclusions**: To date AL002 has been seen to be generally safe and tolerable and is being considered for investigation in a proof-of-concept Phase 2 study.

OC15: PREDICTING SPORADIC ALZHEIMER'S PROGRESSION VIA INHERITED ALZHEIMER'S-INFORMED MACHINE LEARNING. Nicolai FRANZMEIER (1), Nikolaos KOUTSOULERIS (2), Tammie BENZINGER (3), Alison GOATE (4), Celeste KARCH (3), Anne FAGAN (3), Marco DUERING (1), Martin DICHGANS (1), Johannes LEVIN (5), Brian GORDON (3), Yen Ying LIM (6), Colin MASTERS (6), Nick C FOX (7), Jasmeer CHHATWAL (8), Stephen SALLOWAY (9), Eric MCDADE (3), John MORRIS (10), Randall BATEMAN (10), Michael EWERS (1) *((1) Ludwig Maximilians University, Institute for Stroke and Dementia Research, Germany, (2) Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-Universität LMU, Munich, Germany, Germany, (3)Knight Alzheimer's Disease Research Center, Washington University in St. Louis, St. Louis, MO, USA, United States, (4) Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA, United States, (5) Department of Neurology, Ludwig-Maximilians-Universität München, Munich, Germany, Germany, (6) The Florey Institute, The University of Melbourne, Parkville, Victoria, Australia, Australia, (7) Dementia Research Centre, University College London, Queen Square, London, UK, United Kingdom, (8) Massachusetts General Hospital, Department of Neurology, Harvard Medical School, MA, USA, United States, (9) Department of Neurology, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA, United States, (10) Department of Neurology, Washington University in St. Louis, St. Louis, MO, USA, United States)*

Background & Objectives: Non-demented subjects with biomarker evidence of Alzheimer's disease (AD) are at increased risk to develop dementia. However, there are considerable differences in the rates of cognitive decline between individuals, which poses significant challenges for clinical prognosis and risk enrichment in clinical trials. While biomarkers of AD have been established for diagnostics, there is an unmet need of biomarker models for predicting the rate of future cognitive decline. Here, we propose a cross-validated machine learning approach combining biochemical and neuroimaging biomarkers in order to 1) predict the rate of cognitive decline in AD and 2) for risk-enrichment and thus enhancement of statistical power to detect treatment effects in clinical trials. **Methods**: We included 121 subjects with autosomal dominant AD from DIAN (training sample) and 216 subjects with sporadic prodromal AD (i.e. amyloid-positive mild cognitive impairment) from ADNI (test sample). In the autosomal dominant AD sample, we applied support vector regression to biomarkers of primary AD pathology (i.e. amyloid-PET and cerebrospinal fluid) and neurodegeneration (FDG-PET and structural MRI) to identify the best performing models, using repeated nested cross-validation. The dependent variable was the estimated years to symptom onset as a proxy for future dementia manifestation in autosomal dominant AD. The trained prediction model was subsequently applied to an independently recruited sample of sporadic prodromal AD patients to predict the longitudinal rate of global cognitive and memory changes over 1-4 years. Further, we extensively simulated treatments with variable follow-up times (1-4 years) and efficacy rates (10-40%) in the sporadic AD group and tested whether machine learning based risk-enrichment can reduce the number of subjects required for detecting simulated treatment effects. **Results**: In autosomal-dominant AD, the trained prediction model using multi-modal biomarkers showed excellent accuracy for predicting the estimated years to symptom onset (R2=53%). When applying the model to the unseen sample of sporadic AD patients, we found high prediction accuracy for the 4-year rate of global cognitive (R2=24%) and memory (R2=25%) decline, controlled for baseline cognition and other covariates such as age, gender and education. Importantly, the model's prediction accuracy was also significant for shorter follow up periods (range 1-4 years), but increased for longer follow-up durations. In simulated interventions with varying durations and efficacies, we demonstrate that machine-learning based risk enrichment can consistently reduce subject numbers required for detecting intervention effects by up to 50-75%, (e.g. from 839 subjects to 211 subjects per treatment arm for detecting an intervention effect of 30% at an intervention duration of 2 years, with memory performance as the primary endpoint) even when using restricted modalities. **Conclusion**: Overall, our independently-validated multimodal biomarker model predicted the rate of cognitive decline at the symptomatic stage of sporadic AD, which has important implications for risk-enrichment in clinical trials and identifying individuals at highest need for treatment.

OC16: CONTINUOUSLY ACQUIRED, HOME-BASED DIGITAL BIOMARKERS OF ACTIVITY AND FUNCTION ARE RELATED TO ALZHEIMER'S DISEASE NEUROPATHOLOGY. Jeffrey KAYE, Nora MATTEK, Hiroko DODGE, Nicole SHARMA, Thomas RILEY, Zachary BEATTIE, Randy WOLTJER *(Oregon Health & Science University, United States)*

Background: Current outcome measures available for use in clinical trials in early stage 1-3 (FDA 2018 Guidelines) Alzheimer's disease rely on combinations of self-report and episodic cognitive testing with test batteries that are relatively inefficient, not engaging or ecologically valid. Measures of everyday function and cognition assessed unobtrusively at home using embedded sensing and computing methods generates "digital biomarkers" (DBs) that decline during the pre-dementia period. This approach generates continuous everyday measures that are ecologically valid and can improve the efficiency of trials (reducing sample size or decreasing the time of observations, Dodge et al. 2015). Although, face-

valid, DBs have not been assessed for their relationship to AD neuropathology. Objective: To determine the association of digital biomarkers to AD neuropathology in an initially cognitively intact community-based population. **Methods**: Individuals were enrolled in longitudinal cohort studies of DBs approved by the Oregon Health & Science University's Institutional Review Board (Life Laboratory IRB #2765; ISAAC IRB #2353). Details of the sensor systems and study protocols have been published elsewhere (Kaye et al., 2018; Lyons et al., 2015). Participants included in this study were 65 years and older, living independently, of average health for age, not demented at study entry, followed until death, and had brain autopsy data available. Participants were assessed both conventionally with standardized clinical function and cognitive tests including the Uniform Data Set protocol of the National Alzheimer's Coordinating Center. From the array of DB's, four measures representing four domains of function known to change with the progression of AD were selected based on their prior demonstration of differentiating those cognitively normal verses those with mild cognitive impairment: cognitive function (number of days with computer use measured by CPU activity), mobility (daily mean walking speed (cm/sec derived from in-series passive infra-red ceiling sensors), socialization (time out of home, hrs) derived from passive infra-red room occupancy and door contact sensors), and sleep (total sleep time (hrs) derived from PIR bedroom and other room-occupancy sensors). A composite DB measure including the four activity domains (mobility, cognition, socialization and sleep) was constructed by z-normalizing the four individual domain metrics. Fixed post-mortem brains were evaluated for neurofibrillary tangle (NFT) and neuritic plaque (NP) pathology and staged by Braak and CERAD systems. Information related to NP and NFT burdens, amyloid angiopathy, large vessel strokes or lacunes, presence of Lewy bodies (LB), hippocampal sclerosis (HS), and degree of arteriolosclerosis were summarized using the NACC Neuropathology Data reporting format. Data analysis was conducted using the home monitored data from the 12-month period prior to death. Summary statistics were generated for participant characteristics and pathologic variables. Differences in digital biomarkers according to individual neuropathological categories (e.g., Braak stages, plaque severity), as well as the DB composite metric were compared with analysis of variance (ANOVA). **Results**: Forty-one participants had a brain autopsy and in-home sensor activity data. The median interval from last day of home monitoring to post-mortem examination was one day (SD 1.8 years). Mean age at death was 92.2 years (SD 5.1); 83% were female. Median Mini-Mental State Examination score before death was 27 (5.9). Antemortem clinical diagnoses were: 46% cognitively normal, 22% MCI and 32% dementia. Eighty-three percent of the cohort were found to have Braak stage III or higher NFTs on autopsy. Twenty percent were found to have moderate/frequent neuritic plaques. Other pathologies were relatively infrequent: Large vessel stroke or lacunar stroke (17%), amyloid angiopathy (46%), hippocampal sclerosis (5%), and Lewy bodies (7%). The four DBMs showed consistent patterns relative to both Braak stage and plaque score severity, i.e., increasing pathology with reduced computer use time, walking speed, time-out-home, and increased sleep time). Other pathologies did not show a clear pattern relative to the DBs, but the infrequency of these pathologies in this sample limit this analysis. The composite DB measure was significantly associated with greater neuritic plaque severity ($p<0.01$) and amyloid angiopathy $p=0.01$). **Conclusion**: Continuous, home-based DB's are real-world measures of everyday function and cognition which index the severity of AD neuropathology present at the time the digital data is collected. DB measures with their potential to reduce trial sample sizes may serve as novel, ecologically valid outcome measures for early stage AD clinical trials. References: Dodge HH, et al. Use of High-Frequency In-Home Monitoring Data May Reduce Sample Sizes Needed in Clinical Trials. PLoS One 10:e0138095, 2015; Lyons BE, et al. Pervasive computing technologies to continuously assess Alzheimer's disease progression and intervention efficacy. Frontiers in Aging Neuroscience 7:102, 2015; Kaye J, et al. Methodology for Establishing a Community-Wide Life Laboratory for Capturing Unobtrusive and Continuous Remote Activity and Health Data. J Vis Exp 137, 2018. Acknowledgements: Supported by National Institute on Aging and Department of Veterans Affairs: grants numbers - R01AG024059, U2CAG054397, P30AG024978 and P30AG008017.

OC17: THE ALZHEIMER'S CLINICAL TRIALS CONSORTIUM SEEKS PARTNERS FOR THERAPEUTIC TRIALS. Sarah WALTER (1), Reisa SPERLING (2), Ron PETERSEN (3), Laurie RYAN (4), Rema RAMAN (1), Jason KARLAWISH (5), Christopher VAN DYCK (6), Paul AISEN (1) *((1) Alzheimer's Therapeutic Research Institute (ATRI), University of Southern California, United States, (2) Brigham and Women's Hospital, Harvard University, United States, (3) Mayo Clinic, United States, (4) National Institute on Aging, National Institutes of Health, United States, (5) University of Pennsylvania, United States, (6)Yale University, United States)*

Background: The Alzheimer's Clinical Trials Consortium (ACTC) was funded by the National Institute on Aging (NIA), National Institutes of Health (NIH) in 2018 with the mission to provide an optimal infrastructure, utilizing centralized resources and shared expertise, to accelerate the development of effective interventions for Alzheimer's disease (AD) and related disorders. Specifically, the ACTC is tasked with developing and conducting 5-7 studies over the next 5 years, targeting therapies for use across the spectrum of AD: from prevention to late stages of disease. The ACTC Leadership team is comprised of three Principal Investigators (PIs); Drs. Aisen, Sperling and Petersen, as well as the Project Scientist from NIA, Dr. Ryan. Leadership is guided by the consortium through the Steering Committee, Executive Committee and External Advisory Board. In addition, each PI has oversight responsibility over specific Units, which conduct the day to day work of the Consortium, and the Committees, which are brought in to advise within their specialized area of clinical trial and disease expertise. **Methods**: Member Sites were selected from the top academic research institutes across the United States. Each member site agreed to utilize the single IRB (Advarra) and Master Clinical Trial Agreement, towards the goal of expediting study start-up for ACTC Projects. Member Sites receive an infrastructure award to ensure trial readiness, sufficient to cover cost for one full time research coordinator and 5% of the Member Site PI's time. In addition, each site is encouraged to identify an Associate Site PI, ensuring longevity and stability of the consortium. A majority of the ACTC Units which serve as the ACTC Coordinating Center are located at the Alzheimer's Therapeutic Research Institute (ATRI) at USC. These include Administration, Biomarker, Biostatistics, Clinical Operations, Informatics, and Medical Safety. PET and Neuropathology Units are based at Harvard

University. The Clinical Outcome Instrument Unit, MRI and Recruitment Units are all led by investigators across multiple institutions (Brigham and Women's Hospital, UC Irvine, Mayo Clinic, and UC San Francisco). Committees contribute to specialized areas of expertise in study design, conduct, or disease. These include the Project Evaluation Committee (PEC), Internal Ethics, Biospecimen Allocation Resources Committee, Non-AD Dementia, Non-Pharmacological Interventions, Neuropsychiatric Symptoms, Publications, Site Metrics and Study Budget, and the Committee for Inclusion, Diversity, Education in Alzheimer's disease clinical trials (IDEA-CT). The ACTC encourages both academic and industry groups to submit proposals for consideration. Public-private partnerships are also encouraged. Applicants must agree to NIH-stipulated data-sharing requirements. Proposal review occurs 3 times per year, coordinated with the deadlines for grant submission to the NIA. Each Proposal is reviewed and scored for feasibility, appropriateness for ACTC and scientific merit, and must be approved by the ACTC Project Evaluation Committee and the Steering Committee. Once approved, a small collaborative team is formed to develop a competitive grant application. Development and endorsement of a proposal by ACTC does not guarantee NIA funding. **Results**: Within a few weeks of funding announcement, ACTC operationalized the proposal review process and the Steering Committee approved one study for grant development, which was funded. Three projects have been approved as affiliated with ACTC, leveraging components of the infrastructure. Two other projects focused on different mechanisms across the clinical continuum of Alzheimer's disease have been approved, and one has been submitted as a grant pending review by the NIA. The infrastructure of the consortium was successfully launched within the first year, including governance, committees, processes for policy and standard operations, communication platforms, and the Biomarker Repository as well as executed Site Master Clinical Trial Agreements and Central IRB agreements at Member Sites. **Conclusion**: The ACTC offers state-of-the-art clinical trials infrastructure, extensive expertise on trial design and execution, and a strong network of expert clinical trial sites. ACTC is continuing to request Phase Ib-Phase III proposals from the field for collaboration and is particularly interested in evaluating novel mechanisms for Alzheimer's disease and related disorders. Interested investigators may find more information at www.actcinfo.org. The performance of the ACTC will be assessed by metrics on project launch timelines, recruitment and diversity goals, development and validation of new trial methodologies, monitoring our sharing of data and methods, and training of new investigators.

OC18: THE EXERT TRIAL: TESTING A MODEL FOR EFFECTIVE COMMUNITY-BASED EXERCISE INTERVENTION DELIVERY FOR ADULTS WITH MCI.

Jeffrey KATULA (1), Elizabeth CHMELO (1), Valerie LAWSON (2), Heather HODGE (2), Cara JOHNSON (2), Barbara NICKLAS (1), Rosemary MORRISON (3), Sean KIPPERMAN (3), Howard FELDMAN (3), Carl COTMAN (3), Laura BAKER (1) *((1) Wake Forest School of Medicine, United States, (2) YMCA of the USA, United States, (3) Alzeimer's Disease Collaborative Study, University of California, San Diego, United States)*

Background: There are no effective therapeutic options to delay the progression of Alzheimer's disease. The benefits of exercise on brain health in older adults at risk for dementia have become an important potential therapeutic intervention. There is an urgent need to evaluate the effectiveness of exercise in a large diverse population using accessible, cost-effective, and sustainable programs that can be readily implemented in community settings. The EXERT trial (NCT02814526) is a Phase 3, multicenter, randomized single-blind study to examine the effects of aerobic exercise on cognition and other measures of brain function in 300 adults with amnestic mild cognitive impairment (MCI). Here we describe the infrastructure and support system that was developed for delivery of the EXERT intervention programs in partnership with the YMCA. Objective: To test a model for exercise intervention delivery that could provide regular support for adults with MCI and a sustainable community-based program if the trial results are positive. **Methods**: The Alzheimer's Disease Cooperative Study (ADCS) and Wake Forest School of Medicine (WFSM) partnered with the YMCA of the USA (Y-USA) to assist with intervention delivery for EXERT at 14 sites nationwide. A total of 300 sedentary older adults (65-89 years old) will be randomized to one of two interventions: 4 days/week of either moderate-high intensity aerobic exercise (AX) or low intensity stretching, balance and range of motion (SBR) activities, which serves as the control. Each participating ADCS site has partnered with a YMCA regional association that includes several local branches. The ADCS sites are responsible for recruitment, outcomes assessments, medical safety and regulatory compliance, and the YMCAs for intervention implementation. Participants in both groups complete their exercise routines at participating YMCAs under the supervision of a study-certified trainer for the first 12 months, and independently in the final 6 months. Protocols were developed to provide education to trainers about MCI and personalized exercise prescriptions that can be readily implemented. Ongoing support is provided to trainers through regular phone conferences that offer opportunities for sharing experiences with participants to address challenges as they arise. During trainer-supervised sessions, objective measures of exercise duration and intensity are collected. Intervention implementation is overseen by an Intervention Oversight Committee (IOC) consisting of representatives from the ADCS, WFSM, and the Y-USA. Intervention fidelity is monitored through (a) web-based reports of participant adherence generated by the study data management system, (b) YMCA trainer reports during monthly conference calls, and (c) intervention fidelity site visits conducted by the IOC. EXERT is projected to complete enrollment in late Fall 2019. **Results**: To date, over 8300 supervised sessions have been completed at the YMCA, which reflects attendance rates of 79% across both intervention groups. The collaboration between the ADCs and the YMCA regional associations has generated effective procedures and systems to facilitate participant flow from recruitment to outcomes assessments and intervention delivery. YMCA trainer testimonials during monthly conference calls reflect their unwavering commitment to the trial and its participants, increased knowledge about and appreciation of cognitive impairment and its impact on daily function, as well as recognition of their role in patient care and quality of life. The results of intervention fidelity site visits confirm that YMCA trainers rigorously adhere to the protocol and are successful in creating an environment that study participants value. The partnership with the YMCA national office (Y-USA) has been instrumental in engaging appropriate YMCAs at participating sites, facilitating training and certification of YMCA staff, and problem-solving issues as they arise. Promoting high adherence

to the EXERT interventions relies on a strong infrastructure with multiple resources to support participants and YMCA staff who provide a safe and motivating environment. **Conclusion**: Our success to date in achieving high rates of attendance at supervised exercise sessions at the YMCA and compliance to the EXERT interventions by once-sedentary participants with MCI provides growing support for a sustainable and cost-effective community-based model of intervention delivery. Such a model has the potential to be readily developed as a nationwide prevention strategy if the trial results are positive. Funding: NIA U19 AG010483

OC19: THE EFFECTS OF RASAGILINE UPON CEREBRAL GLUCOSE METABOLISM, COGNITION, AND TAU IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE. Dawn MATTHEWS (1), Aaron RITTER (2), Ronald THOMAS (3), Randolph ANDREWS (1), Ana LUKIC (1), Carolyn REVTA (3), Babak TOUSI (2), James LEVERENZ (2), Howard FILLIT (4), Kate ZHONG (2), Howard FELDMAN (3), Jeffrey CUMMINGS (2) *((1) ADM Diagnostics Inc, United States, (2) Cleveland Clinic - Lou Ruvo Center for Brain Health, United States, (3) Alzheimer's Disease Cooperative Study - University of California San Diego, United States, (4) Alzheimer's Drug Discovery Foundation, United States)*

Background: A Phase II clinical trial was conducted to evaluate the potential benefit of rasagiline, a selective monoamine oxidase B (MAO-B) inhibitor, in patients with mild to moderate Alzheimer's disease (AD). Previous studies of rasagiline in patients with Parkinson's disease and schizophrenia have suggested cognitive and clinical benefit beyond motor improvement (Biglan, 2006; Hanagasi, 2011, 2018). Through MAO-B inhibition rasagiline increases the availability of dopamine, which mediates cognitive processes including executive function, working memory, attention, and reward. Pre-clinical models have demonstrated neuroprotective activities of rasagiline including lessening of amyloid accumulation, tau hyperphosphorylation, and neurofibrillary tangle formation. This evidence and the cognitive benefit of selegiline, a related MAO-B inhibitor, in AD and PD provided the rationale to conduct this trial. FDG and tau PET imaging were used in combination with clinical cognitive outcomes in this proof of concept (POC) study design. **Objectives**: The primary objective was to determine if exposure to 1 mg of rasagiline once daily is associated with improved regional brain metabolism compared to placebo after a 24-week double blind study treatment in patients with mild to moderate AD. Secondary objectives were to evaluate: a) efficacy of rasagiline compared to placebo on cognition (including ADAS cog 11 and measures of executive function (Digit Span test, COWAT for verbal fluency)), activities of daily living (ADCS-ADL), global impression of change (CGIC), and neuropsychiatric symptoms (NPI); b) safety and tolerability; c) correlation of FDG-PET to flortaucipir PET findings; and d) the relationship of flortaucipir imaging to clinical measures. **Methods**: The study design was a 24-week, double blind, parallel group, placebo controlled trial of 50 participants randomized in a 1:1 ratio at baseline to receive rasagiline 1 mg or placebo for 24 weeks followed by a 4 week follow up. Inclusion criteria: clinical diagnosis of probable AD supported by evidence of an AD-like FDG PET pattern at screening using previously developed image classifiers; ages 50 to 90; and MMSE 11 to 26. FDG and flortaucipir PET imaging were performed at screening or baseline and week 24, and an MRI at screening. MMSE and QoL-AD were administered at baseline and 24 weeks. The ADAS-Cog, NPI, ADCS-ADL, DS, and COWAT were administered at baseline, 4, 8, 24, and 28 weeks. FDG and tau PET were analyzed using Standardized Uptake Reference Values (SUVRs) in prespecified regions of interest and data driven classification methods. Imaging and clinical endpoints were evaluated using linear mixed effects models with adjustment for covariates including age, sex, and baseline values. **Results**: The study successfully met its primary outcome of demonstrating an improvement in longitudinal glucose metabolism changes with rasagiline compared to placebo in prespecified regions. Further, all mean clinical endpoint changes directionally favoured rasagiline compared to placebo except ADL, in which trajectories were comparable. Of 50 subjects enrolled, 43 completed treatment. Subject age (74+/-7.2, range 57 to 90), sex (44%F), education, genotype, and baseline NPI, DS, and COWAT scores did not differ between study arms. MMSE (20.1+/-4.2), ADAS-Cog (25.6+/-8.8), and QoL-AD (37.7+/-5.9) differed at trend level for the Intent-to-Treat population. Placebo treated subjects worsened over the 24 week period in their expression of the FDG AD Progression pattern ($p<0.01$), and in AD-relevant regions ($p<0.001$ to $p<0.03$). Rasagiline treated subjects showed less decrease (less worsening) than placebo treated subjects in middle frontal cortex (left $p<0.012$, bilateral $p<0.04$), anterior cingulate ($p<0.04$), superior frontal cortex ($p<0.053$), and striatum, with slightly but not significantly less worsening in posterior cingulate-precuneus, inferior parietal, medial temporal, and lateral temporal regions. Differences between rasagiline and placebo reached significance in QoL-AD ($p<0.04$) and trend for COWAT ($p<0.08$). Clinical results suggested that 48 subjects per arm would be required to show a significant ($p<0.05$) benefit for rasagiline in ADAS-cog at 80% power. (P-values uncorrected). Change in QOL-AD correlated with change in anterior cingulate FDG SUVR ($R = 0.47$, $p < 0.002$). Longitudinal flortaucipir values exhibited measurement stability over the 24 week period and showed increase in cortical regions in some subjects in both study arms, with some subcortical decreases noted in the rasagiline arm. Rasagiline was well tolerated, differing from placebo in the number of subjects having falls (2 rasagiline vs. 1 placebo) and psychosis or agitation (0 rasagiline vs. 5 placebo). **Conclusion**: These findings, whereby rasagiline benefitted longitudinal FDG metabolism over 24 weeks of treatments coupled to directional benefit on clinical outcome measures, support its potential for further development as an AD therapeutic intervention. FDG PET suggests that rasagiline may act on cognitive outcomes through its effects on frontostriatal pathways. A larger, fully powered phase 3 clinical trial of rasagiline is warranted beyond this POC trial, recognizing as well the value of this approach with a repurposed generic medication. Further, results demonstrated the utility of a POC design using imaging biomarkers for patient inclusion and evaluation as a path to increase the probability of success of larger AD trials.

OC20: TOWARDS A FLORBETAPIR-BASED DUAL -BIOMARKER SCREENING STRATEGY. Sergey SHCHERBININ (1), Georgia CHAO (2), Fanni NATANEGARA (1), Arnaud CHARIL (1), Jennifer ZIMMER (1), Alette WESSELS (1), Cynthia EVANS (1), Albert LO (1), Mark MINTUN (1), John SIMS (1) *((1) Eli Lilly and Company, United States, (2) Covance, United States)*

Background: It has been recognized that a combination of abnormal neurodegeneration biomarkers with a positive amyloid status provide a more powerful prediction of future cognitive decline than an amyloid marker measurement alone (Jack CR et al, Alzheimer's and Dementia, 2018). In particular, more rapid conversion to Alzheimer's disease (AD) dementia for an amyloid-positive prodromal population with glucose hypometabolism measured by 18F-fluorodeoxyglucose (FDG) PET has been reported (Iaccarino L et al, Journal of Alzheimer's Disease, 2017). However, the implementation of FDG-PET in clinical trials in AD has been operationally challenging as AD-specific PET scans to monitor Aβ plaques and pathologic fibrillar tau may be required, which increases patient burden and radiation exposure. In this respect, regional perfusion estimates derived from "early frames" imaging sessions supplementing conventional amyloid scans can serve as a tractable alternative to the FDG-PET measurements, with benefits of reducing trial expenses, radiation exposure, and time commitment of subjects. We used data from two interventional trials with BACE inhibitors to examine the potential utility of the "early frames" florbetapir PET to stratify risk of cognitive and functional decline among amyloid positive (determined using "late frames" florbetapir PET) AD patients. **Methods**: NAVIGATE-AD (NCT02791191) and DAYBREAK-ALZ (NCT02783573) were double-blind, placebo-controlled multi-center phase 2 and phase 3 trials, respectively. Both trials enrolled amyloid-positive (florbetapir PET) patients with mild AD dementia and stopped early after interim analyses determined a low likelihood of study success. The majority of participants in both trials underwent dual-phase florbetapir PET sessions. While a "late frames" acquisition starting 50 minutes after tracer administration served to establish amyloid positivity at screening and to evaluate longitudinal change in amyloid, an "early frames" session starting at the time of tracer administration measured regional cerebral perfusion. Amyloid endpoint was calculated (Clark CM et al, JAMA, 2011) using six target cortical regions and whole cerebellum as a reference region (aSUVR). Perfusion outcome was quantified as the average signal in a composite AD-vulnerable target region with respect to pons as a reference region (pSUVR). The association between baseline perfusion and the future decline over 6 months follow-up (short duration was selected due to early termination of both trials) was examined in placebo arms only using the Mini-Mental Status Examination (MMSE), 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog13), instrumental subscale of the AD Cooperative Study (ADCS-iADL), and Integrated AD Rating Scale (iADRS, Wessels AM et al, JPAD, 2015). To do so, perfusion scans were pooled across two trials and divided into four quartiles based on the pSUVR distribution resulting in 52-63 Aβ+ mild AD dementia patients in each quartile. Least Square (LS) mean changes from baseline in aforementioned cognitive and functional characteristics were compared across those perfusion quartiles. LS mean change and corresponding p-values were derived from ANCOVA model controlling for age and baseline cognitive / functional value. Baseline comparison between the trials was assessed to ensure pooling of the data is appropriate. To assess ability of baseline aSUVR to predict future decline in Aβ+ mild AD dementia participants, a similar comparison between amyloid quartiles (72-90 patients in each quartile) was performed. **Results**: On average, individuals with lower cerebral perfusion at baseline demonstrated more rapid cognitive and functional decline over 6 months follow-up. Specifically, the magnitude of clinical worsening measured using all four assessments (MMSE, ADAS-Cog13, ADCS-iADL, and iADRS) gradually and significantly (p0.005) increased as a function of decreased baseline perfusion pSUVR quartile. The most pronounced LS mean change was always observed in the lower perfusion quartile – -2.89, 3.41, -3.21, and -6.25 for MMSE, ADAS-Cog13, ADCS-iADL, and iADRS, respectively. Importantly, participants with the higher perfusion did not have a statistically significant mean change from baseline over 6 month follow-up as seen in MMSE (-0.58), ADAS-Cog13 (-0.75), ADCS-iADL, (-0.05), and iADRS (0.56). At the same time, different levels of baseline amyloid burden measured using aSUVR were not associated with differences in cognitive and functional decline during the 6 months follow-up. **Conclusions**: Our results demonstrate that a dual-phase florbetapir scanning protocol holds promise as a dual -biomarker screening approach, which can be operationalized within multi-center interventional trials in AD. Specifically, the amyloid-positive mild AD dementia population could be further stratified into perfusion-based subgroups with significantly different cognitive and functional decline. Importantly, the two outcomes provided by a dual-phase florbetapir scanning protocol will play complementary roles in clinical trials. Unlike "late frames" amyloid scan, "early frames" perfusion measurements are not specific for neurodegeneration due to AD. However, they may provide additional staging information identifying sub-populations more likely to progress on trial endpoints. Therefore, further understanding of cognitive decline in relation to both amyloid status and hypoperfusion may minimize enrollment of slow cognitive progressors and select populations customized for the needs of clinical trials.

OC21: FCSRT INCLUSION CRITERIA SUPPORT RECRUITMENT OF A POPULATION WITH EARLY ALZHEIMER'S DISEASE LIKELY TO PROGRESS OVER 24 MONTHS: RESULTS FROM THE CREAD TRIAL. Kaycee SINK (1), Stevan DJAKOVIC (1), Janice W. SMITH (2), Jillian SMITH (2), Nan HU (1), Howard MACKEY (1), Susanne OSTROWITZKI (1), Rachelle DOODY (1, 3) *((1) Genentech, Inc., United States, (2) Roche Products Ltd, United Kingdom, (3) Product Development, F. Hoffmann-La Roche Ltd, Switzerland)*

Background: When testing a potential disease-modifying drug for Alzheimer's disease (AD) that is expected to slow progression, the ability to show a treatment difference depends in part on predictable decline in the placebo group. Despite requiring an episodic memory deficit and amyloid positivity, approximately 30% of patients in the SCarlet RoAD trial (NCT01224106)—one of the first trials in prodromal AD (pAD)—did not show a decline in the Clinical Dementia Rating–Sum of Boxes (CDR-SB) score over 24 months, with a reported

overall rate of decline in the placebo arm of 1.6 points [1]. The Free and Cued Selective Reminding Test (FCSRT) identifies the type of memory loss characteristic of AD (i.e., poor free recall not benefited by cuing). Based on learnings from SCarlet RoAD (stopped early following a futility analysis), we implemented FCSRT inclusion criteria for the Phase III Crenezumab in Alzheimer's Disease (CREAD/NCT02670083) trials to enrich for participants with early AD likely to progress in the 24-month trial. Objective: To describe the screening performance using FCSRT inclusion criteria and CDR-SB progression rates for trial participants in CREAD. **Methods**: Of 3,575 participants screened, 813 with early AD (n = 346 pAD and n = 467 mild AD [mAD]; National Institute on Aging and Alzheimer's Association criteria) were randomized in the CREAD trial from March 2016 to November 2017. Key inclusion criteria included a Clinical Dementia Rating global score of 0.5 or 1, a Mini-Mental State Exam score of 22–30, a FCSRT immediate free recall score of ≤ 27 (sum of 3 immediate recall trials), a Cuing Index (CI) of ≤ 0.67, and amyloid positivity by cerebrospinal fluid analysis or amyloid positron emission tomography scan. Cutoff values for FCSRT CI were derived from modeling the SCarlet RoAD data; a CI cutoff value of 0.67 provided adequate balance between sensitivity (84.2%) and specificity (34.8%) for distinguishing participants who progressed in CDR-SB from those who did not [2]. CREAD was powered to detect a 30% difference in rate of decline in CDR-SB between the overall placebo and treatment arms based on an estimated decline of 2.6 points over 24 months in the placebo arm. Mixed model for repeated measures analyses were used to assess the change in CDR-SB over time in the trial population as a whole and in the pAD and mAD subgroups separately. Nonprogression in CDR-SB was defined as a change in CDR-SB (last assessment – baseline) of ≤ 0. **Results**: The CREAD trial was stopped early based on a preplanned interim analysis that indicated that the study was unlikely to meet its primary endpoint of change in CDR-SB from baseline to Week 105; no safety signals were observed, and the overall safety profile was similar to that observed in previous studies [3]. Baseline characteristics have been previously presented [4]. Approximately 47% of FCSRT administrations resulted in a screen failure. Among participants who met FCSRT eligibility and were ultimately randomized, the mean (SD) baseline CDR-SB in the placebo arm was 3.8 (1.6) for the whole early AD population, 3.1 (1.3) for pAD, and 4.3 (1.6) for mAD. The mean (SE) decline in CDR-SB in the placebo arm at 24 months was 3.6 (0.3) points for the entire early AD study population and 2.8 (0.4) points in the pAD and 4.2 (0.4) points in the mAD subsets (preliminary data; database not yet locked). Among placebo participants with at least one postbaseline CDR assessment (n = 393), 28% of patients with pAD and 20% of patients with mAD had no progression in CDR-SB over a median time of 17.5 months. Results were similar when both treatment arms were combined. This non-progression rate is compared with 30% of patients with pAD in SCarlet RoAD treated for 24 months. **Conclusion**: The CREAD trial was stopped early for low likelihood of meeting the primary endpoint. Adequate progression in CDR-SB, not only in the overall population, but also in both the pAD and mAD subpopulations, allowed for clear interpretation of the interim analysis results. While approximately half of the participants screened for CREAD failed early in the screening process due to not meeting FCSRT inclusion criteria, these FSCRT inclusion criteria may have helped to identify a population of patients with early AD with higher rates of progression. Further analyses on the impact of the chosen FCSRT inclusion criteria are ongoing and will be presented. Références: 1. Ostrowitzki S, et al. Alzheimers Res Ther 2017;9:95; 2. Smith J, et al. Presented at AAIC 2016, Toronto, Canada; 3. F. Hoffmann-La Roche Ltd. Roche to discontinue Phase III CREAD 1 and 2 clinical studies of crenezumab in early Alzheimer's disease (AD)—other company programmes in AD continue. Accessed online at: http://bit.ly/2TiSUX0 on March 18, 2019; 4. Lin H, et al. Presented at AAIC 2017, London, UK.

OC22: ASSESSING IN POWER IN PHASE II PROOF-OF-CONCEPT TRIALS IN PRODROMAL ALZHEIMER'S DISEASE. Michelle NUÑO (1, 2), Daniel GILLEN (1, 2), Joshua GRILL (3, 4, 5) (*(1) Department of Statistics, University of California, Irvine, United States, (2) Institute for Memory Impairments and Neurological Disorders, University of California, Irvine,, United States, (3) Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, United States, (4) Department of Psychiatry and Human Behavior, University of California, Irvine, United States, (5 Department of Neurobiology and Behavior, University of California, Irvine, United States)*

Background: Prodromal Alzheimer's disease (AD) clinical trials enroll patients with Mild Cognitive Impairment (MCI) who demonstrate biomarker changes associated with AD. Cerebrospinal fluid (CSF) levels of amyloid beta (AB), phosphorylated tau (p-tau), and total tau (t-tau) can be used as such biomarkers, as well as outcome measures for these trials. Relatively few data are available, however, to describe longitudinal within-subject changes in these proteins over time. This makes it difficult for investigators to design proof-of-concept clinical trials of putative disease-slowing therapies, including especially trials for which the primary outcome is t-tau or p-tau. **Objectives**: This study aimed to model proof-of-concept clinical trials with either t-tau or p-tau as the primary outcome. Specifically, we sought to estimate the sample sizes required to obtain 80% power for plausible treatment effects using empirical estimates of outcome variability and within-subject correlation. Noting that homogeneity of responses within eligible subpopulations reduces variability and increases power, we also quantified longitudinal changes in t-tau and p-tau and the variability in within-subject changes for participants satisfying different potential trial eligibility criteria. **Methods**: We examined data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) using subjects who had a baseline diagnosis of MCI and at least two measures of CSF tau, one of which must have been collected during the baseline visit. We modeled two-year, two-arm phase II trials and investigated the sample sizes required to estimate various treatment effects (50%, 75%, and 100% slowing of progression) with 80% power for different CSF biomarker eligibility criteria. Biomarker eligibility criteria were based on the cutoffs for CSF AB, t-tau, p-tau, the ratio of t-tau/AB and the ratio of p-tau/AB as defined in (1). We used empirical estimates of the within-subject correlation and the variance of t-tau and p-tau at two years. Sample sizes were calculated using an analysis of covariance (ANCOVA) model. To quantify longitudinal changes, we estimated the subject- specific slopes of t-tau and p-tau using a linear mixed effects model with a random intercept and random slope. We also compared the variability in the random slopes and intercepts associated in each of these subpopulations to investigate how these differed when different

eligibility criteria were applied. **Results**: We observed increases in t-tau over time for every subpopulation (range: 4.87-6.07 pg/mL change for two years). The smallest sample size required to obtain 80% power to detect a 50% treatment effect was in a trial using low AB as an enrollment criterion. Such a trial required 4,734 subjects. The according sample sizes required to detect 75% and 100% decreases were n = 2,104 and n = 1,184, respectively. For subjects in this subpopulation, we estimated that, on average, t-tau increased by approximately 5.58 pg/mL in two years (95% confidence interval (CI): 2.51, 8.65) with a within-subject correlation of 0.84 (95% confidence bound (CB): 0.79, 0.88). The standard errors associated with the random effects were 54.31 and 0.54 for the random intercept and random slope, respectively. We also observed increases in p-tau for every subpopulation (range: 6.97 – 9.96 pg/mL change per year).The smallest sample size required to obtain 80% power to detect a 50% treatment effect was in a trial using high t-tau as an enrollment criterion. Such a trial required 1,284 subjects. The according sample sizes required to detect 75% and 100% decreases were n = 572 and n = 322, respectively. For subjects in this subpopulation, we estimated that on average, p-tau increased by approximately 9.96 pg/mL (95% CI: 6.54, 13.39) in two years, with a within-subject correlation of 0.43 (95% CB: 0.30, 0.57). The standard errors associated with the random effects were 19.03 and 0.52 for the random intercept and random slope, respectively. **Conclusion**: These results indicate that proof of concept trials with CSF tau as an outcome may be challenging, requiring large sample sizes to demonstrate even dramatic treatment effects. Nevertheless, in these models p-tau outperformed t-tau as an outcome, requiring fewer participants due to greater change over time and reduced variance. The empirical estimates provided in this study may aid the design of future trials. **Reference:** 1. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Annals of neurology. 2009;65(4):403-13.

OC23: THE ALZHEIMER'S DISEASE THERAPY WITH NEUROAID (ATHENE) STUDY: ASSESSING THE SAFETY AND EFFICACY OF NEUROAID II (MLC901) IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE STABLE ON CHOLINESTERASE INHIBITORS OR MEMANTINE: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL: BASELINE RESULTS. Christopher CHEN (1), Purabi Reang SHARMA (2), Boon Yeow TAN (3), Lu QINGSHU (4), Kee Ling TEO (5), Narayanaswamy VENKETASUBRAMANIAN (6) *((1) National University of Singapore, Singapore, (2) Moleac Pte Ltd, Singapore, (3) St Luke's Hospital, Singapore, Singapore, (4) Singapore Clinical Research Institute, Singapore, (5) Memory Ageing and Cognition Centre, Singapore, (6) Raffles Neuroscience Centre, Singapore)*

Background: MLC901 has its origins from Traditional Chinese Medication (TCM) and has been shown to promote cell proliferation, neurite outgrowth and the development of dense axonal and dendritic networks (1). MLC601 (the precursor of MLC901 with similar properties) is a possible modulator of amyloid precursor protein (APP). In human neuroblastoma cell line SH-SY5Y culture, it was shown to increase the level of sAPPα, which is a non-pathogenic soluble fragment of APP produced by physiological cleavage of APP by α and γ secretase (2). An in-vitro study (3) showed that MLC901 significantly reduced tau phosphorylation at various epitopes recognized by AT8, AT270 and PHF-13 antibodies. It also showed increased phosphorylation of glycogen synthase kinase 3β along with concurrent decrease in activation of cyclin dependent kinase (5). These pharmacological properties make MLC901 a possible disease modifying treatment for Alzheimer's Disease (AD). **Objectives**: The primary objective was to evaluate the safety of MLC901 as an add-on treatment for 6 months in patients with mild-to-moderate probable AD on standard treatment with acetylcholinesterase inhibitors (AChEIs) or memantine. The secondary objectives were to investigate 1) effect of MLC901 as add on therapy to standard treatments for 6 months on cognitive function in patients with mild to moderate AD. (2) long term safety of MLC901 as add-on treatment to standard treatments for up to 1 year in an open extension study. (3) long term effect of MLC901 on disease progression as an add-on treatment to standard treatments for up to 1 year in an open extension study. **Methods**: This is a one-year trial in mild to moderate probable AD where the first 6-months will be a randomized, double-blind, placebo-controlled trial during which MLC901 will be given as an add-on therapy to standard AD treatment (AChEIs or memantine). This is followed by 6-month extension study, where all subjects will be treated with open-label MLC901 in addition to standard treatment. Safety is measured by adverse events, vital signs, electrocardiogram (ECG), laboratory tests, physical and neurological examinations. For efficacy outcomes, cognitive function, behavior and activities of daily living are assessed by tests including the Alzheimer's Disease Assessment Scale- cognitive subscale (ADAS-Cog), Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL23), Neuropsychiatric Inventory (NPI), and Mini Mental State Examination (MMSE). The trial is registered at Clinicaltrials.gov- NCT03038035 and the methods published recently (4). **Results**: ATHENE recruited a total of 125 patients who are currently scheduled to complete follow up by end November 2019. The mean age of the study population was 78.6 ±6.7 years with 87 (70%) women and 111(88%) of Chinese ethnicity. The majority of patients (93%) were on AChEI as standard treatment (79% donepezil, 22% rivastigmine capsules and 12% rivastigmine patches) whilst 7% were on memantine. Baseline characteristics in the treatment arms were well balanced except in overall education and diastolic blood pressure, with more obtaining tertiary level education in arm B than arm A (22% compared to 5%; p=0.03); additionally, arm A had more illiterate patients than arm B (34% compared to 24%). The diastolic blood pressure was 71mmHg in arm B vs 67mmHg in arm A (P=0.01) but this was considered clinically non-significant. The most common comorbidity was hypertension (75%) followed by hyperlipidemia (71%) diabetes mellitus (37%) and stroke/TIA (14.9%). There were no significant differences between treatment groups in mean baseline ADAS-Cog (31±12 and 29±10), ADCS-ADL23 (47±17 and 50±16), NPI (11.1±14 and 11.0±12) and MMSE (15±4 and 16±4) in arms A and B respectively. **Conclusions**: ATHENE is investigating the safety and efficacy of MLC901 in mild to moderate Alzheimer's disease patients who are stable on standard available treatment. The trial is being performed in compliance with international guidelines and using Western clinical trial standards and the results will be available by early 2020. References: 1. Heurteaux C et al. NeuroAiD: properties for neuroprotection and neurorepair. Cerebrovasc Dis 2013;35 Suppl 1:1-7; 2. Lim YA,

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OC24: PHASE 1 STUDY OF NDX-1017: SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS IN HEALTHY VOLUNTEERS AND DEMENTIA PATIENTS.

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Background: Alzheimer's disease (AD), the most common form of dementia, is a complex systemic failure involving multiple self-reinforcing pathologies, leading to neurodegeneration and cellular dysfunction, intensified by misregulated immune responses (1,2). Amyloid plaque build-up occurs long before the onset of cognitive deficits, while synaptic loss, neuro-fibrillary tau tangles, and neuron loss accompany the cognitive decline (3). Synaptic loss is the most reliable correlate of cognitive decline in AD (4). Neurotrophic factors represent a new therapeutic target to treat AD by inducing regenerative mechanisms and restoring brain homeostasis. Drugs that stimulate neurotrophic systems, like hepatocyte growth factor (HGF) and its MET receptor, have the potential to treat all stages of AD, by directly targeting neurodegeneration, improving cognition, and addressing multiple aspects of the AD pathology including inflammation, cerebral blood flow, and glucose metabolism (5). AD patients exhibit reduced neuronal MET expression, particularly in the cortex and hippocampus, which may contribute to synaptic loss, neurodegeneration, and functional decline (6). Athira Pharma's lead compound, NDX-1017, is a small-molecule drug that penetrates the blood-brain barrier and aims to augment HGF/MET, a critical neurotrophic system underpowered in AD. NDX-1017 has the potential to relieve dementia symptoms and permanently alter the course of disease progression. In nonclinical studies, NDX-1017 has been shown to activate the HGF/MET system, induce pro-survival and regenerative mechanisms, stimulate spinogenesis and synaptogenesis, and reverse cognitive deficits in rat models of dementia. Treatment has also been shown to shift patterns of quantitative electroencephalogram (qEEG) activity in the APP/PS1 AD mouse model, with an immediate and sustained increase in gamma power. Doses that stimulate qEEG changes overlapped with the efficacious range in animal models of dementia, suggesting the utility of EEG as translatable biomarkers to guide dose optimization in clinical trials. **Objectives**: Phase 1 (NCT03298672) was a randomized, placebo-controlled, double-blind trial of NDX-1017. It involved single- and multiple-ascending doses in healthy volunteers, and multiple doses in AD patients. The study was designed to facilitate the translation of the safety, tolerability, and pharmacokinetics (PK) of NDX-1017 from healthy volunteers to the intended treatment population. qEEG and event-related potential (ERP) techniques were used to indicate brain penetration and explore pharmacodynamics, serving as translatable biomarkers to guide dose optimization. **Methods**: A total of 80 subjects received once-daily (o.d.) subcutaneous (s.c.) administration of NDX-1017 or matching placebo (n=8/cohort; 3:1 randomization). Subjects included 48 healthy young males (33.4 ± 6.3 years; 2, 6, 20, 40, 60, or 90 mg, s.c., o.d.), 24 healthy elderly (63.8 ± 3.9 years; 12 males [M]/12 females [F]; 20, 40, or 60 mg, s.c., o.d., 9 days), and eight AD patients (68.8 ± 7.8 years; 5M/3F; baseline mini-mental state examination [MMSE] 18 ± 7.5; 40 mg, s.c., o.d., 9 days). Safety and PK were assessed throughout the study. In single-dose studies, qEEG was conducted at pre-dose baseline and 1-hour post-dose. In multiple-dose studies, qEEG and ERP were conducted at pre-dose, 1 hour and 3 hours post-dose, on Days 1, 4, and 8. **Results**: NDX-1017 and placebo were safe and well-tolerated in healthy young, healthy elderly, and AD patients, at all doses evaluated. The PK were dose proportional, with no accumulation. In the single-dose studies, the main effect of qEEG was a dose-related increase in gamma induction, observed at doses between 20 and 90 mg; placebo and low doses (2 and 6 mg) had no effect on EEG. In the multiple-dose studies in healthy elderly, an immediate effect in gamma power induction was observed, confirming the findings in the single-dose studies. Additionally, a sustained effect on gamma power was observed, lasting beyond five times the half-life (half-life = 1.5 hours). In AD patients, gamma power and P300 demonstrated a positive shift after multiple doses of NDX-1017, supportive of target-related pharmacodynamics relevant for the treatment of AD. **Conclusion**: This study established preliminary safety, tolerability, and PK of NDX-1017. The positive qEEG response in humans replicated the EEG signature identified in nonclinical studies, suggesting brain penetration and target engagement, and informs dosing for future clinical trials. The normalization of qEEG components and P300 in AD patients suggests a treatment-dependent promotion of synaptic activities, and further demonstrates the therapeutic potential of NDX-1017. References: 1. Golde, T.E., et al. (2018). 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OC25: REGULATION OF GLIAL CELL ACTIVATION AND NEURODEGENERATION BY ANTI-SEMAPHORIN 4D ANTIBODY PEPINEMAB (VX15/2503), A POTENTIAL TREATMENT FOR ALZHEIMER'S AND HUNTINGTON'S DISEASE. Elizabeth EVANS (1), Terrence FISHER (1), John LEONARD (1), Alisha READER (1), Vikas MISHRA (1), Crystal MALLOW (1), Leslie BALCH (1), Alan HOWELL (1), Ernest SMITH (1), Andrew FEIGIN (2), Maurice ZAUDERER (2) *((1) Vaccinex, United States, (2)Huntington Study Group, United States)*

Background: Chronic inflammation is believed to play an important role in neuronal degeneration. Semaphorin 4D (SEMA4D) and its Plexin receptors (PLXNB1, PLXNB2) are expressed on brain neural, endothelial, and inflammatory cells. SEMA4D signaling through its cognate receptors triggers activation of inflammatory glial cells, inhibits migration and differentiation of glial progenitor cells that can replenish glia and repair damage to myelin, and disrupts endothelial tight junctions that are required for the integrity of the BBB. Antibody neutralization of SEMA4D ameliorates neurodegenerative processes in several preclinical models, including transgenic mouse models of Huntington's Disease (HD) and Alzheimer's Disease (AD). These data provided the rationale for initiating SIGNAL, a randomized (1:1), double-blind, placebo-controlled phase 2 study of treatment with anti-SEMA4D antibody, pepinemab (VX15/2503), in subjects with HD. **Objectives**: To evaluate safety and feasibility of treatment with pepinemab, a semaphorin 4D blocking antibody, and to incorporate FDG-PET as an early biomarker of brain metabolic activity and restoration of normal astrocytic activity. **Methods**: Mechanistic studies include histopathological investigation of SEMA4D expression and localization in brain cell types, as well as effects of SEMA4D on astrocyte function. Preclinical studies suggest that SEMA4D plays an important role in inflammatory activation of astrocytes, in which state they downregulate glucose transporter and glutamate receptor, reducing their normal function in brain energy metabolism and synaptic activity. We hypothesize that blocking SEMA4D-induced F-actin depolymerization may reduce inflammatory transformation, increase glucose uptake, and indirectly restore effects on synaptic activity and neural networks. The SIGNAL clinical trial has an adaptive design in which the results of 36 subjects randomized in Cohort A informed group size and treatment duration in Cohort B. Because of the important role astrocytes play in glucose transport and metabolism together with supporting data from several prior studies demonstrating that loss of FDG-PET signal correlates with cognitive decline in AD, FDG-PET imaging was included as a key endpoint related to the potential mechanism of action. Additional study endpoints include volumetric MRI, cognition (HD-CAB), quantitative motor assessments, UHDRS and patient-reported outcomes. **Results**: Preliminary histopathological observations demonstrate marked changes in expression, distribution, and colocalization of SEMA4D with neuronal and glial cells in brains of diseased mice. Rat astrocyte cultures express high levels of PlexinB1 receptor, and binding of SEMA4D triggers significant depolymerization of F-actin, reducing astrocyte function. These effects on astroctyes are reversed with addition of blocking antibody. Antibody blockade of SEMA4D in preclinical studies in the murine CVN AD model also show beneficial effects on synaptic activity and improvements in behavioral deficits. Cohort A (n=36) of the SIGNAL clinical trial is complete and Cohort B (n=265) is fully enrolled. No concerning safety signals were identified following up to 12 monthly IV administrations in Cohort A or following 12 to 35 months of treatment in Cohort B subjects. Pepinemab treatment of Cohort A subjects trended toward stabilization of disease-related reduction in MRI volume and was favored over placebo in 24/31 ROI. FDG-PET also favored pepinemab in all ROI. The mean FDG-PET Index +/-standard error for pepinemab treatment (n=11) across all brain ROI examined was 0.46 +/- 0.25 (95% CI, -0.10 to 1.02); for placebo (n=8) it was -0.32 +/- 0.16 (95% CI, -0.69 to 0.05). The estimated difference between the means was 0.78 +/- 0.31 (95% CI, 0.11 to 1.40; p=0.025). Analysis of cohort A guided the design of Cohort B, which has enrolled 265 HD subjects for 17 to 35 months of treatment. Enrollment in cohort B was completed Dec 31, 2018 and clinical evaluation will continue through June 2020. **Conclusions**: Initial results have shown pepinemab to be well tolerated in subjects with neurodegenerative disease. In addition, the demonstrated increase in FDG-PET signal in Cohort A together with preclinical data demonstrating beneficial effects on synaptic activity and improvement in behavioral deficits in a murine AD model suggest that pepinemab warrants clinical investigation in AD as well. A randomized, placebo-controlled study of monthly infusions of pepinemab enrolling AD subjects is planned.

OC26: THERAPEUTIC ULTRASOUND AS A TREATMENT STRATEGY FOR ALZHEIMER'S DISEASE - PRECLINICAL DATA (INCLUDING ADUCANUMAB) AND CLINICAL TRIAL DESIGN. Jürgen GÖTZ, Gerhard LEINENGA, Rebecca NISBET, Rachel DE LAS HERAS *(The University of Queensland, Queensland Brain Institute, Australia)*

Background: A major challenge in treating brain diseases is presented by the blood-brain barrier (BBB) that constitutes an efficient barrier not only for toxins but also a wide range of therapeutic agents (1,2). In overcoming this impediment, ultrasound in combination with intravenously injected microbubbles (used as contrast agents in a clinical setting) has emerged as a powerful technology that allows for the selective brain uptake of therapeutic agents and blood-borne factors by transiently opening the blood-brain barrier (1). We have shown previously, that ultrasound in combination with microbubbles, but in the absence of a therapeutic agent, can clear protein aggregates that constitute the hallmark lesions of Alzheimer's disease, amyloid-beta (Abeta) in APP23 mice and Tau in pR5 mice (3,4,5). We have also shown that therapeutic ultrasound can be used as a general drug delivery tool, as demonstrated by a 10-fold increased uptake of a single chain antibody variable fragment (scFv) targeting the 2N isoform of Tau (4). We have further obtained safety and efficacy data in both mice and sheep (6) allowing us to move towards a phase 1 clinical trial using a custom-made therapeutic ultrasound probe. Of note, a recent trial proved safety of ultrasound-mediated BBB opening in five patients with early to moderate AD (7), and another trial in patients with glioblastomas revealed that even implanted transducers were well tolerated by the patients, without inducing neurotoxicity (8). **Objectives**: (i) To prepare a phase 1 clinical trial using ultrasound in combination with microbubbles in a small cohort of early-stage AD patients (MMSE >25). (ii) To evaluate the potential of ultrasound to achieve improved outcomes of the anti-Abeta antibody Aducanumab in APP23 mice. **Methods**: (i) To resolve which ultrasound parameters result in safe and efficacious opening of the BBB, we tested a matrix of ultrasound parameters

(frequency, acoustic pressure, pulse length, pulse repetition frequency and sonication duration) in mice, using a single element probe. We further conducted sonications in sheep using a subset of these parameters, factoring in the attenuation of the sheep skull. We optimized the sonication work-flow in sheep. (ii) We have previously shown that ultrasound on its own, after 5-8 weekly treatment sessions, clears Abeta effectively and restores memory functions (3). To determine whether ultrasound would also facilitate the uptake and efficacy of the anti-Abeta antibody Aducanumab, we treated APP23 mice between 13 and 22 months of age monthly and compared the effects of Aducanumab with ultrasound and with combined treatments. **Results**: (i) We established a safe range of ultrasound parameters in mice and sheep. We successfully validated our custom-made probe demonstrating safe and efficacious BBB opening in sheep and establishing a treatment workflow in sheep, assisted by pre-treatment planning. (ii) Ultrasound-mediated BBB opening significantly increases Aducanumab uptake by the brain (using fluorescently labeled Aducanumab). We further found significant reductions in amyloid pathology in the combination treatment compared to either delivering Aducanumab on its own or using ultrasound on its own. **Conclusion**: Our preclinical data demonstrate the potential of microbubble-assisted ultrasound treatments as a new treatment modality for AD and other brain diseases. Ultrasound presents a cost-effective strategy in the context of using therapeutic antibodies to treat diseases of the brain. **References:** (1) Leinenga G et al. (2016) Ultrasound treatments of neurological diseases - current status and emerging applications, Nature Reviews Neurol 12:161-174; (2) Götz J et al. (2018) Animal models for Alzheimer's disease, Nature Reviews Neurosci, 19: 583-598; (3) Leinenga G, Götz J (2015) Scanning ultrasound efficiently removes amyloid-beta and restores memory in an Alzheimer's disease mouse model, Science Transl Med 11: 276ra33; (4) Nisbet R et al. (2017) Combined effects of scanning ultrasound and a tau-specific single chain antibody in a tau transgenic mouse model, Brain 140(5): 161-74; (5) Pandit R, Leinenga G & Götz J (2019) Repeated ultrasound treatment improves motor function and clears neuronal tau by autophagy, Theranostics, 9(13): 3754-3767; (6) Pelekanos M, Leinenga G et al. (2018) Establishing sheep as an experimental species to validate ultrasound-mediated blood-brain barrier opening for potential therapeutic interventions, Theranostics 8: 2583-2602; (7) Lipsman N et al. (2018). Blood-brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. Nat Commun 9, 2336; (8) Idbaih A et al. (2019). Safety and Feasibility of Repeated and Transient Blood-Brain Barrier Disruption by Pulsed Ultrasound in Patients with Recurrent Glioblastoma. Clin Cancer Res., in press

OC27: BASELINE CLINICAL AND BIOMARKER CHARACTERISTICS FROM A PHASE 2 TRIAL OF RO7105705 IN PRODROMAL-TO-MILD ALZHEIMER'S DISEASE (TAURIEL).

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Background: RO7105705 is a humanized anti-tau IgG4 monoclonal antibody in development for the treatment of Alzheimer's disease (AD). RO7105705 is designed to bind tau in the extracellular space of the brain and intercept the cell-to-cell propagation of pathological tau. Data from pre-clinical safety studies and a completed Phase 1 study suggested an acceptable safety profile and good tolerability for RO7105705 at all doses administered (up to 16,800 mg). **Objectives**: The Tauriel Study (NCT03289143) is an ongoing Phase 2 multi-center randomized double-blind placebo-controlled parallel-group clinical trial that is assessing the safety and efficacy of multiple doses of RO7105705 in patients with prodromal-to-mild AD over an 18-month interval. **Methods**: The Tauriel study enrolled patients aged 50-80 who fulfilled National Institute on Aging-Alzheimer's Association criteria for probable AD dementia or mild cognitive impairment (MCI) and had MMSE scores of 20-30, global Clinical Dementia Rating (CDR) scores of 0.5 or 1, significant amyloid pathology per positron emission tomography (PET) or cerebrospinal fluid (CSF) analysis, and significant episodic memory impairment by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) delayed memory index (DMI; scores ≤85). Participants have been randomized to receive placebo or low, medium, or high doses of RO7105705 for 68 weeks. Randomization was stratified by clinical diagnosis (MCI vs. mild dementia) and APOE status (ε4+ vs. ε4-). Primary endpoints include safety, tolerability, and change from baseline on the CDR sum of boxes. Secondary and exploratory endpoints include change from baseline in cognition and function, as measured by the RBANS, 13-item version of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13), and Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL), and in tau pathological burden, as assessed by [18F]GTP1 tau PET imaging. **Results**: The Tauriel study has completed recruitment and enrolled 457 participants. Average participant age at screening was 69.6 (SD=7.0). Within the study cohort, 55.1% were women, 67.6% met diagnostic criteria for mild AD dementia, and 74.4% were APOE ε4+. Baseline [18F]GTP1 tau PET imaging was obtained in 84.2% of participants. Mean [18F]GTP1 PET SUVR in the temporal lobe was significantly higher in the mild AD subgroup than in the prodromal AD subgroup. Screening and/or baseline cerebrospinal fluid (CSF) tau indices were obtained in 28.9% of participants. CSF levels of total tau and phospho-tau were similar between the two AD subgroups. Additional baseline data will be presented. **Conclusion**: The Tauriel study has enrolled a cohort of participants with prodromal-to-mild AD that is comparable to other interventional studies in this patient population. It is designed to provide preliminary data investigating the safety and efficacy of the anti-tau monoclonal antibody RO7105705 in AD and explore the utility of such interventions in reducing tau spread and clinical decline. Additionally, the tau biomarker (imaging and fluid) analyses incorporated into this study will further clarify their potential use cases in the development of AD therapeutics.

OC28: COR388, A NOVEL GINGIPAIN INHIBITOR, DECREASES FRAGMENTATION OF APOE IN ALZHEIMER'S DISEASE CENTRAL NERVOUS SYSTEM.

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Background: Cortexyme recently completed a Phase 1b clinical study of COR388, a lysine-gingipain inhibitor,

in Alzheimer's disease (AD) patients. COR388 is an orally bioavailable, brain penetrant small-molecule that was developed after the discovery of the bacterial pathogen, Porphyromonas gingivalis (Pg), and its protease virulence factors, known as gingipains, in the brains of AD patients. Gingipain levels in AD brains (both lysine-gingipain and arginine-gingipain) were shown to significantly correlate with AD diagnosis and tau and ubiquitin pathology. Fragments of Pg DNA were identified in the cerebrospinal fluid (CSF) of clinical AD patients. Preclinical studies demonstrated that Pg invades the brain after infection of the oral cavity, resulting in the development of neuropathology that is consistent with that of AD. These effects were blocked in mice after oral administration of COR388. In the recent Phase 1b clinical study, COR388 was shown to be safe and well tolerated in AD patients, with rapid absorption and therapeutic plasma levels. COR388 was detected in CSF at ratios consistent with that in other species, indicating therapeutic central nervous system levels. In an analysis of exploratory CSF biomoarkers, it was discovered that administration of COR388 for 28 days significantly reduced the level of apolipoprotein E (ApoE) protein fragments. Since fragmentation of ApoE has previously been proposed as a pathogenic mechanism in sporadic AD, studies were conducted to explore the possible involvement of gingipains in cleaving ApoE. **Methods**: In the Phase 1b study, 6 AD patients received 50mg of COR388 and 3 AD patients received placebo twice daily for 28 days. The level of a set of ApoE fragments in CSF, before and after treatment, was measured by an antibody that was raised against full-length human ApoE4 protein. In vitro experiments to assess proteolytic cleavage were conducted with recombinant ApoE4 and ApoE3 proteins incubated with purified gingipains or lysates prepared from Pg infected cells. ApoE4 and ApoE3 fragmentation was monitored over time. **Results**: A significant decrease was observed in ApoE fragments in CSF after 28 days of COR388 treatment in AD patients compared to placebo treated patients. In vitro experiments demonstrated that ApoE was a target of lysine- and arginine-gingipain cleavage, with gingipains cleaving ApoE4 more readily than ApoE3. Both lysine- and arginine-gingipain exhibited specific patterns of ApoE proteolysis. Similarly, cells infected with Pg exhibited ApoE cleavage activity similar to that seen in AD brain and CSF, with uninfected cells having no significant proteolytic activity. Gingipain inhibitors blocked the ApoE cleavage activity of Pg infected cells, and COR388 alone was sufficient to block ApoE fragmentation. **Conclusion**: COR388, a small-molecule inhibitor of lysine-gingipain, significantly decreased presumptively pathogenic ApoE fragments in CSF of AD patients. Experiments indicated that ApoE4 was more susceptible to gingipain cleavage than ApoE3, providing a link to why the APOE4 gene is a major risk factor for AD. COR388 may thus protect against gingipain-induced APOE loss of function and generation of pathological fragments.

OC29: BINDING PROFILES OF BAN2401 AND ADUCANUMAB TO DIFFERENT AMYLOID-BETA SPECIES. Lars LANNFELT (1), Linda SÖDERBERG (2), Hanna LAUDON (2), Malin JOHANNESSON (2), Charlotte SAHLIN (2), Patrik NYGREN (2), Christer MÖLLER (2) *((1) Uppsala University, Sweden, (2) BioArctic, Sweden)*

Development of several monoclonal antibodies targeting amyloid-β (Aβ) in Alzheimer's disease (AD) has been discontinued due to lack of efficacy and/or adverse events. There has been an increasing interest in soluble aggregated Aβ species, i.e. oligomers (<75 kDa) and protofibrils (>75 kDa), as key pathogenic species. We examined differences in binding characteristics of BAN2401, an antibody continuing in development in phase 3 and aducanumab, an antibody which met futility in phase 3, to better understand the apparent differences in mechanism of action. BAN2401 was designed based on the Arctic mutation (Aβ E22G) which causes AD due to an enhanced propensity to form protofibrils. The antibodies binding profile to oligomers and protofibrils was investigated with inhibition ELISA and surface plasmon resonance (SPR, Biacore). Binding properties was also investigated using immunoprecipitation of TBS soluble Aβ from AD brain tissue. The binding strength (IC50value) of BAN2401 and aducanumab to Aβ protofibrils, as measured by inhibition ELISA, was 35 nM for aducanumab and 1.1 nM for BAN2401. Thus, BAN2401 binds more than 30 times stronger to Aβ protofibrils as compared with aducanumab. SPR analysis demonstrated similar data, with fast on-rates for both antibodies but with a much slower off-rate for BAN2401. BAN2401 binds Aβ protofibrils with a KDof 0.3 nM and aducanumab with a KDof 15 nM. Thus, BAN2401 binds 50 times stronger to protofibrils than aducanumab in this experimental setting. Preliminary results indicate that the binding differences between the antibodies are even greater when analyzing smaller Aβaggregates (<75 kDa), i.e. oligomers. Immunoprecipitation experiments demonstrated more efficient depletion of Aβprotofibrils from AD brain extracts with BAN2401 compared to aducanumab. 24-39% of protofibrils were left in the brain extract as compared to 42-75% with aducanumab. Several clinical trials in AD with monoclonal antibodies against Aβhave recently failed.One explanation for these failures might be that these antibodies have been targeting the wrong forms of Aβ. Protofibrils and oligomers are attractive species for therapy, as these Aβ forms are toxic. BAN2401 has a 30-50 fold higher binding to Aβ protofibrils in vitro compared to aducanumab and is more effective in depleting Aβ protofibrils from AD brain extracts. These differences in binding to toxic Aβ species may mediate differences in clinical responses observed between the two antibodies.

OC30: NON-GLP TOXICITY AND TOXICOKINETICS STUDIES OF P8, A PEPTIDE DRUG CANDIDATE FOR THE TREATMENT OF ALZHEIMER'S DISEASE. Nazneen DEWJI (1), Michael BLEAVINS (2), Archie THURSTON (3) *((1) Cenna Biosciences Inc., United States, (2) White Crow Inovation, LLC, United States, (3) Admesolutions Inc., United States)*

Background: We previously demonstrated that P8, a water-soluble peptide from PS-1 NH2-terminal domain can substantially and specifically inhibit total Aß production in the brains of APP transgenic mice. These peptide-induced reductions of total Aß (and of Aß40 and 42) do not target the secretases and so do not modify or inhibit either ß- or g-secretase activities. The mechanism by which P8 reduces Aß includes its specific binding to the APP ectodomain resulting in an inhibition of APP processing to Aß. Subsequent studies have shown that P8 can be delivered to the rat brain by subcutaneous (SC) administration. **Objectives**: The primary objectives of this study were to evaluate the toxicity and toxicokinetic (TK) profiles of P8 in cynomolgus monkeys and in Sprague-Dawley rats when administered by SC administration once daily for 14 consecutive days. 2-Week Repeat-Dose Study of

P8 in Cynomolgus Monkey. **Methods**: Animals received 14 daily doses at 0, 30, 100, or 300 mg/kg. Doses were chosen to provide exposures that were significant multiples of active levels seen in APP transgenic (Tg) mice. In-life parameters included clinical observations, body weights, blood pressure, electrocardiography, and clinical pathology (urinalysis, hematology, coagulation, and serum chemistry). Blood samples and CSF were collected at specified timepoints for TK. At terminal necropsy, gross observations, and organ weights were recorded. Tissues were collected, sectioned, stained with hematoxylin and eosin, and examined microscopically. **Results and Conclusions:** P8 was well tolerated by Cynomolgus monkeys at all doses, including 300 mg/kg/day. No P8-related mortalities occurred. Histologically, P8-treated animals had minimal subcutaneous fibroplasia, muscle cell degeneration/regeneration and mononuclear infiltrates at the injection site. Reductions in red cell parameters (RBC, hemoglobin and hematocrit) were noted across all treatment groups on Day 15, which could be secondary to the scheduled blood collections. Evidence of plasma systemic exposure was observed in all treated monkeys. The mean plasma Tmax values were at 0.5 hours post dose administration for all doses. The Tmax values appeared to independent of dose and day. The mean plasma exposure (Cmax and AUClast values) increased in a dose dependent manner. The mean plasma Cmax values increased in a dose proportional manner on Day 1 and Day 14. The mean plasma AUClast values increased in a dose proportional manner on Day 1 and in a greater than dose proportional manner on Day 14. The mean half-life values ranged from 0.55 to 2.1 hours and appeared to increase with dose. Day 1 to Day 14 values were comparable, suggesting no accumulation of P8 upon multiple dosing. None of the findings were considered adverse. 2-Week Repeat-Dose Non-GLP Study of P8 in Sprague-Dawley (SD) Rats. **Methods**: To evaluate the toxicity and TK profile of P8, SD rats were dosed once daily for 14 consecutive days via SC injection at 0, 30, 100, or 300 mg/kg. Doses were chosen to provide exposures that were significant multiples of active levels seen in APP Tg mice. In-life parameters included clinical observations, body weights, food consumption, and clinical pathology (hematology, coagulation, and serum chemistry). Blood samples and CSF were collected at specified time-points for TK. At terminal necropsy, gross observations and organ weights were recorded. Tissues were collected, sectioned, stained with hematoxylin and eosin, and examined microscopically. **Results and Conclusions:** P8 was well tolerated by rats, including at 300 mg/kg/day. No P8-related mortalities occurred and no changes attributed to administration of test article were apparent upon assessment of clinical observations, body weights, food consumption, hematology, coagulation, serum chemistry, gross pathology, or organ weights data. Microscopically, slightly increased incidences of minimal subcutaneous fibroplasia in the injection site were observed at ^{3}100 mg/kg. Evidence of plasma systemic exposure was observed in all treated rats. The mean plasma Tmax values were generally at 0.5 hours post dose administration. The Tmax values appeared to be independent of dose and day. The mean plasma exposure (Cmax and AUClast) increased in a dose dependent manner. On Day 1, the mean plasma Cmax values increased in a less than dose proportional manner for female rats and in a dose proportional manner for male rats. On Day 14, the mean plasma Cmax values increased in a dose proportional manner for female rats and in a greater than dose proportional manner for male rats. On Day 1, the mean plasma AUClast values increased in a dose proportional manner for female rats and in a greater than dose proportional manner for male rats. On Day 14, the mean plasma AUClast values increased in a greater than dose proportional manner for both female rats and male rats. The mean half-life ranged from 0.28 to 0.56 hours and increased with dose. The mean plasma exposure (Cmax and AUClast) was higher in females than males (less than 2-fold). Day 1 to Day 14 values were comparable, suggesting no accumulation of P8 upon multiple dosing. None of the findings were considered adverse.

OC31: AN EXPLORATORY EXAMINATION OF NEUROTOOLKIT BIOMARKERS ACROSS AD STAGES. Carol VAN HULLE (1), Tobey BETTHAUSER (1), Erin JONAITIS (1), Richard BATRLA (2), Norbert WILD (2), Katherina BUCK (3), Gwendlyn KOLLMORGEN (3), Ulf ANDREASSON (4), Cynthia CARLSSON (1), Sterling JOHNSON (1), Henrik ZETTERBERG (4), Kaj BLENNOW (4) *((1) University of Wisconsin-Madison, United States, (2) Roche Diagnostics International Ltd, Switzerland, (3) Roche Diagnostics GmbH, Germany, (4) Uppsala University, Sweden)*

Background: Alzheimer's disease (AD) has an extended preclinical phase when proteinopathies develop involving aggregation of β-amyloid (Aβ) into plaques and tau protein into neurofibrillary tangles and neurodegeneration starts. These processes are measureable in CSF using validated in-vitro diagnostic (IVD) immunoassays for Aβ42, Phospho-Tau (181P) and Total-Tau protein concentrations in CSF. An expanded biomarker panel also covering other pathophysiologies, including glial activation and inflammation (GFAP, sTREM2, s100b, IL6), synaptic degeneration (neurogranin, α-synuclein) and damage to long axons (neurofilament light-chain; NFL), based on high-precision techniques, is warranted. To accomplish this, the NeuroToolKit (NTK) is a panel of automated Elecsys® CSF immunoassays, developed to complement established IVD methods for Aβ42, pTau and tTau, with the aim of providing new insights for assessing disease progression and to serve as tools for diagnostics and monitoring of treatments. **Objectives**: This is a preliminary report of the distribution of NTK biomarkers across AD stages (unimpaired, MCI, dementia) by biomarker profile (pTau/Aβ42). **Methods**: Three hundred CSF samples were obtained from N = 206 adults ages 50-92 (M = 70.7, SD = 8.3; 51.4% female) participating in the Wisconsin Registry for Alzheimer's Prevention (WRAP) or the Wisconsin Alzheimer's Disease Research Center (WADRC); n = 47 were diagnosed with Alzheimer's clinical syndrome (dementia-ADcs), n = 40 had mild cognitive impairment (MCI), while n = 115 were cognitively unimpaired (CN), and n = 4 had non-AD related cognitive impairments. Clinical diagnosis was determined by consensus conference based on NIA-AA criteria (2011) without reference to biomarkers. CSF samples were acquired with a uniform preanalytic protocol between 2010 and 2018. Samples were assayed in batches at the Clinical Neurochemistry Laboratory at the Sahlgrenska Academy of the University of Gothenburg. IVD markers of Aβ42, pTau and tTau were assayed on a cobas e 601 analyzer. The exploratory NTK panel was assayed on a cobas e 411 analyzer and consisted of several markers of neuronal degradation (neurogranin, NFL, and α-synuclein) and inflammation (GFAP, YKL-40, IL6, S100, and sTREM) (not commercially available). A subset of participants (n = 82) underwent dynamic PiB-PET imaging.

Amyloid+/- status, ascertained by visual reads of parametric distribution volume ratio images, was used as the standard of comparison for a ROC analysis to derive an optimal pTau/Aβ42 threshold with 92% positive agreement. This cut-point was then applied to all participants with CSF data. Because this is an initial subsample of a larger ongoing project, the results reported here are descriptive. We compared biomarker levels across clinical groups and pTau/Aβ42 biomarker status. We also describe trends in biomarker concentrations across age by pTau/Aβ42 biomarker status in individuals with multiple CSF samples (n = 58). **Results**: The pTau/Ab42 to PIB ROC area under the curve was 0.98. A cut-off of 0.033 resulted in a 98% negative agreement. 44/47 (94%) dementia-ADcs, 13/40 (33%) MCI, and 30/115 (26%) CN participants were identified as pTau/Aβ42 positive. Although biomarker distributions tended to overlap across groups, we observed several trends in biomarker levels by clinical stage and pTau/Aβ42 status. As expected, Aβ42 level was clearly differentiated by pTau/Aβ42 status, although levels declined slightly across clinical stage in both groups. Tau indicators and their ratios exhibited stepwise differences across clinical stage among pTau/Aβ42 positive participants but remained low in pTau/Aβ42 negative participants. Neurogranin moderately increased with pTau/Aβ42 status, but appeared unrelated to clinical stage. In contrast, NFL and α-synuclein were related to pTau/Aβ42 status and clinical stage; impaired pTau/Aβ42 positive participants had higher levels than pTau/Aβ42 negative or CN participants. Inflammatory biomarkers (GFAP, s100, sTREM2, and YKL40) followed a similar pattern. Biomarker levels appeared to increase in the presence of impairment among pTau/Aβ42 positive participants; inflammatory biomarker levels remained relatively stable among pTau/Aβ42 negative participants. IL6 was unrelated to either clinical stage or amyloid status. Participants with longitudinal CSF samples were divided into stably positive (n = 34) and stably negative (n = 18) pTau/Aβ42 groups (n = 6 converted from negative to positive over the course of the study and are not reported on here). 90% were cognitively unimpaired at their last visit. CSF levels of tTau, GFAP, NFL, sTREM2, s100, and YKL40 (and to a lesser extent α-synuclein and neurogranin) appeared to increase with age, although these changes were more noticeable among pTau/Aβ42 negative participants. Aβ42 values remained steadily low among pTau/Aβ42 positive participants but varied considerably with age in pTau/Aβ42 negative participants. **Conclusion:** The NTK panel is designed to cover a broad spectrum of pathophysiologies known to play a role in neurodegenerative diseases to identify individuals in the early stages of AD as well as individuals with mixed pathologies. This is the first study to compare all currently available NTK biomarkers across the AD spectrum by CSF pTau/Ab42 status. Although results are preliminary, core AD biomarkers were differentiated by CSF pTau/Aβ42 early in AD progression while biomarkers for neurodegeneration and inflammation were differentiated by CSF pTau/Aβ42 during symptomatic phases.

OC32: IMPROVING POLYGENIC RISK SCORES FOR ALZHEIMER'S DISEASE. Samuel P DICKSON (1), Suzanne B HENDRIX (1), Bruce L BROWN (2), Perry G RIDGE (2), Marci L HARDY (3), Allison M MCKEANY (3), Steven B BOOTH (3), Ryan R FORTNA (3), John S K KAUWE (2) *((1) Pentara Corporation, United States, (2) Brigham Young University, United States, (3) ADx Healthcare, United States)*

Background: Heritability for Alzheimer's Disease (AD) has been estimated at between 50% and 80%. AD prevention studies enroll pre-clinical participants based on a participant's genetic risk from presenilin 1 and 2 mutations or APOE4, which combined account for only approximately 25% of AD genetic risk. Several polygenic risk scores (PRS) have been developed to explain additional genetic risk, but due to a few common oversights, they do not capture the remaining missing heritability as well as they could. Polygenic risk assessment can be improved by accounting for correlations between SNPs, rigorously validating models, and incorporating population prevalence rates, improving their usefulness in a general population. **Objectives**: The objectives of this presentation are to discuss the purpose and usefulness of polygenic risk scores and some of the different methods that have been used to develop PRSs then show how they can be improved and present a new AD PRS called GenoRisk. **Methods**: Case-control data from the Alzheimer's Disease Genetics Consortium (ADGC) database were used to compare four general types of statistical models: logistic regression, probit regression, and lasso and elastic net selection with logistic regression. Odds ratios were for known Alzheimer's disease SNPs were used to calculate a risk score for each individual that was used as a covariate in some of the statistical models. The models included terms for age and sex, and sometimes an age by sex interaction term. The accuracy of the model was measured with a Brier score and the average Brier score across validation samples was used for model selection. **Results**: Creating a model that estimates risk simultaneously for all SNPs reduces the risk of overfitting. The elastic net model using an allelic ApoE term and including the age × sex interaction term was most accurate. The GenoRisk score, which is based on this model, explains an additional 19% of the heritable risk compared to APOE status alone. Use of a model with ApoE as allelic improved performance over models with individual ApoE SNPs or genotypic ApoE models. The selected model explained 44% of the genetic risk of AD and provides both a lifetime risk curve for an individual and also a conditional risk curve based on an individual's current age and non-AD status. **Conclusions**: The GenoRisk score provides a way of quantifying the polygenic risk for an individual, independent of age, gender, and other risk factors. It explicity accounts for correlation between SNPs and provides a simple way to show individual probabilities of developing AD by age. It was designed to fit on a scale from 0 to 40 based on the 2,504 subjects from the 1000 Genomes Project. This polygenic risk score could improve the risk assessment of individuals identified for prevention studies.

OC33: EVALUATING MIXED EFFECTS MODELS FOR BURST COGNITIVE DATA IN ALZHEIMER DISEASE CLINICAL TRIALS. Guoqiao WANG (1), Yan LI (2), Andrew ASCHENBRENNER (2), Jason HASSENSTAB (2), Eric MCDADE (2), Jorge LLIBRE-GUERRA (2), Randall BATEMAN (2), Chengjie XIONG (1) *((1) Division of Biostatistics, Washington University School of Medicine, St. Louis, MO, United States, (2) The Dominantly Inherited Alzheimer Network Trials Unit, Department of Neurology, Washington University School of Medicine, St. Louis, MO, United States)*

Background: Burst designs describe an assessment methodology in which extremely brief cognitive tests are administered frequently over a short time period. These methods have been shown to dramatically increase reliability and sensitivity to disease stage over standard cognitive measures. The Ambulatory Research in Cognition (ARC) smartphone application was recently developed and implemented in the Dominantly Inherited Alzheimer Network (DIAN) and the DIAN-Trials Unit (DIAN-TU). Briefly, the ARC app requests that participants take brief (<1 minute each) tests four times per day continuously for one week, leading to a large amount of data collected (a maximum of 28 sessions per one week "burst"). These weeklong bursts can then be repeated (e.g., every 3 months). Methods to analyze these types of data are still in development. Traditionally, AD clinical trial data have been analyzed using the mixed effects model for repeated measures (MMRM) or the linear mixed effects ((LME) model with a single data point at each study visit. It may be challenging to apply these methods directly to burst designs where many more data points are available with different time intervals (quarterly, weekly, and daily), and little research has been done to explore the appropriateness of potential analytical models. **Objectives**: Comprehensively evaluate the appropriateness of different models and describe new models to analyze burst cognitive data for Alzheimer Disease (AD) clinical trials. **Methods**: We investigated model behaviors for three types of models: (i) two-stage MMRM and LME models; (ii) hierarchical MMRM models with random time effects at the quarterly level and at the weekly level to account for the correlation at each level; and (iii) hierarchical LME models that estimate the rate of change at the quarterly level and at the weekly level (for each individual). For the two-stage approach, the weekly data (28 data points) were averaged to a single data point in the first stage, then the traditional MMRM and LME models were applied to the weekly means in the second stage. The hierarchical MMRM and LME can simultaneously estimate the individual trajectories both at the quarterly level and at the weekly level (time as categorical or continuous variable). We will use the burst data obtained from the DIAN observational study and from ongoing studies of older adults at risk for AD to conduct extensive simulations to evaluate these models. **Results**: We developed procedures/macros that were implemented using the SAS programming. The hierarchical models offer multiple advantages: (1) more efficiently utilize the clustered weekly data than the two-stage models by estimating the quarterly trajectory and the weekly trajectory simultaneously; (2) more flexibility in that hierarchical models can assume the weekly trajectory to be the same or different; (3) yield more power than the two-stage methods (more simulations are being conducted); (4) may be easily accepted by regulatory agencies such as FDA since they are an extension of the traditional MMRM and LME. Simulations based on the data obtain from observational studies are ongoing. Conclusion: Comprehensive evaluations of different models for analyzing burst cognitive data are critical before they are considered as appropriate primary analysis models for AD clinical trials. The hierarchical MMRM or LME models optimizes the increased reliability of the clustered weekly data. Our study demonstrates that these hierarchical models are superior to the two-stage traditional MMRM/LME models, and could be considered as a primary endpoint analysis model in AD clinical trials. **Funding:** The DIAN observational study is supported by grant U19 AG032438, PI Randall Bateman. The DIAN-TU study is supported NIH U01 AG042791-01A1; PI: Randall Bateman, MD; NIA R01 AG059798; PI: Eric McDade. The ARC smartphone application is supported by funds from An Anonymous Foundation, the GHR foundation, and R01AG057840; PI: Jason Hassenstab.

OC34: SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF RDN-929: A POTENT AND SELECTIVE HDAC-COREST COMPLEX INHIBITOR FOR THE TREATMENT OF SYNAPTOPATHIES. J. Michael RYAN (1), Christine VOORS-PETTE (2), Christel ROMEIJN (2), Minh VO (3), Magnus IVARSSON (1), Berkely A. LYNCH (1), Antonella PIRONE (1), Michael C. HEWITT (1), Nathan O. FULLER (1), Amy DIRICO (1), Steven P. SWEENEY (1) *((1) Rodin Therapeutics, United States, (2) QPS, Netherlands, (3) Certara, United States)*

Background: RDN-929 is a potent and selective inhibitor of the HDAC-CoREST complex that is being developed as a potential therapy for neurologic diseases driven by synaptic loss or dysfunction. Post-translational modification of histones, through HDAC modulation, have been shown to be important regulators of neuronal gene expression and synaptic function. Pre-clinical proof of concept has been demonstrated in mouse models of dendritic spine density, coincidence of synaptic proteins and hippocampal long-term potentiation [Fuller, 2019]. As such, inhibition of the HDAC-CoREST complex may play a key role in targeting synaptic structure and function and provide a new therapeutic approach for treating multiple synaptopathies. **Objectives**: The objectives of this first-in-human study were to determine the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of RDN-929, a small molecule inhibitor of the HDAC-CoREST complex. **Methods**: A Phase 1, double-blind, randomized, placebo-controlled trial was performed in healthy young and older subjects at a single center. This initial human trial of orally-administered RDN-929 consisted of 84 subjects enrolled into 3 parts: (1) healthy young male subjects aged 18-54 years (n= 48) who received either placebo, or 2, 10, 30, 100, 250 or 500 mg as a single dose, (2) healthy older male and female subjects aged 55-80 years (n=12) who received a single 100 mg dose following an overnight fast and second 100 mg dose following a high fat, high calorie meal, and (3) healthy older male and female subjects aged 55-80 years (n=24) who received either placebo, or 30, 100 or 300 mg once daily doses for twelve (12) days. Serial plasma PK samples were collected for all subjects in all Parts. Part 3 subjects also underwent cerebral spinal fluid (CSF) sampling by lumbar puncture for PK and PD analysis. In Parts 1 and 3, target engagement was assessed by analysis of peripheral blood mononuclear cell (PBMC) histone acetylation. **Results**: RDN-929 was safe and well-tolerated over the dose range tested from 2 to 500 mg as a single oral dose and from 30 to 300 mg when given once

daily for twelve (12) days. No dose-limiting toxicities were identified and no SAEs were reported. All AEs recorded were of mild severity with the exception of one moderate severity headache reported in Part 3. No subject discontinued due to an AE. There were no RDN-929 dose-related changes observed for vital signs, hematologic assessments, clinical chemistries, coagulation parameters or ECG parameters. RDN-929 was rapidly absorbed and exposure increased slightly less than proportionally over the single dose range of 2 to 500 mg. Steady state concentration was reached after four (4) days of once daily dosing with no significant accumulation in RDN-929 exposure observed. Co-administration of RDN-929 with a high-fat meal increased RDN-929 peak and total exposure by 1.4 and 1.7 fold, respectively. RDN-929 CSF concentrations increased with increasing dose at levels that cover the targeted therapeutic range predicted by mouse spine density models. RDN-929 administration produced a significant increase in PBMC histone acetylation compared to placebo in Parts 1 and 3. Conclusion: RDN-929 administered orally as a single dose up to 500 mg and multiple daily doses up to 300 mg in healthy young males and healthy older males and females demonstrates an excellent safety, tolerability and PK profile. The significant increases observed in PBMC histone acetylation confirm peripheral target engagement. These initial data suggest that RDN-929 represents a novel, brain-penetrant, complex-selective HDAC inhibitor with a safety profile that is supportive of further clinical development in patient populations characterized by synaptic loss or dysfunction. **References:** Fuller, N. O., Pirone, A., Lynch, B. A., Hewitt, M. C., Quinton, M. S., McKee, T. D., & Ivarsson, M. (2019). CoREST Complex-Selective Histone Deacetylase Inhibitors Show Prosynaptic Effects and an Improved Safety Profile To Enable Treatment of Synaptopathies. ACS Chemical Neuroscience, 10, 1729-1743.

OC35: A PHASE 2 TRIAL OF GRF6019 IN MILD-TO-MODERATE ALZHEIMER'S DISEASE. Jonas HANNESTAD (1), Tiffanie PEDERSON (1), Whitney CHAO (1), Katie KOBORSI (1), Vicki KLUTZARITZ (1), Steven BRAITHWAITE (1), Suzanne HENDRIX (2), Karoly NIKOLICH (1) *((1) Alkahest, United States, (2) Pentara Corporation, United States)*

Background: The proprietary plasma protein fraction GRF6019 shows multiple benefits in aged mice. Functional benefits include improved memory and increased cortical activity; morphological benefits include increased synaptic density and neurogenesis, and reduced neuroinflammation. In mice, daily administration of GRF6019 for 5 or 7 consecutive days produced benefits lasting up to 3 months. Therefore, a similar dosing regimen was chosen for Alkahest's first clinical trial in Alzheimer's disease, ALK6019-201 (NCT03520998), which evaluated the safety and tolerability of two dose levels of GRF6019 in mild-to-moderate AD. **Methods**: The main inclusion criteria were: age 60-90; probable AD according to NIA-AA criteria; Mini Mental State Examination (MMSE) score 12-24. The main exclusion criteria were: any neurological disorder other than AD; > 2 lacunar strokes on Magnetic Resonance Imaging (MRI); change in the dose of cholinesterase inhibitor or memantine in the last 3 months. Each subject had a baseline visit, two 5-day inpatient dosing periods each followed by a 3-month treatment-free period, for a total study duration of 6 months. Subjects were randomized in a 1:1 ratio to receive either 100 mL or 250 mL of GRF6019 per day for five days, and dose allocation was blinded to subjects, caregivers, raters, and investigators. There was no placebo control arm. The primary endpoint was safety and tolerability, while secondary endpoints included the AD Assessment Scale-Cognitive Subscale (ADAS-Cog), the Clinical Dementia Rating Scale (CDR), the AD Cooperative Study Activities of Daily Living (ADCS-ADL), the MMSE, and the Savonix Mobile Battery. Exploratory endpoints included blood and cerebrospinal fluid biomarkers, and structural and functional MRI. The study was conducted at 9 U.S. sites between March 2018 and May 2019. **Results**: 89 subjects were screened, 52 subjects were randomized, 51 subjects received at least one dose, 43 subjects completed the first 5-day dosing period, and 40 subjects completed both dosing periods. Among the 51 subjects dosed, there were a total of 81 adverse events, of which 28 were assessed as related to study drug. The most common adverse events were mild headaches, infusion site reactions, transient lab abnormalities, and transient blood pressure changes. There were two serious adverse events; one was a hypersensitivity reaction assessed as related to GRF6019, while the other was related to a history of deep venous thrombosis (a pre-existing condition). There were no deaths. The baseline demographics and level of cognitive and functional impairment for all subjects who were randomized (n=52) are summarized in Table 1. Over the course of the 6-month study period, there was no significant cognitive or functional decline as measured by the ADAS-Cog, the ADCS-ADL, and the CDR-SB. The expected decline over a 6-month period in AD subjects of similar baseline severity who received placebo in other trials is a 2- to 3-point worsening on the ADAS-Cog and a 3- to 4-point worsening on the ADCS-ADL. **Conclusions**: This Phase 2 trial in AD demonstrates that daily infusions with up to 250 mL of the plasma protein fraction GRF6019 for 5 consecutive days is safe and well-tolerated in this population. Furthermore, progression of disease in GRF6019-treated subjects was slower than what would be expected in this population. Based on these data, the benefit-risk of continued clinical development of plasma protein fractions in AD is favorable, and a placebo-controlled Phase 2b trial is currently being planned.

OC36: HOPE4MCI TRIAL: TARGETING REDUCTION OF HIPPOCAMPAL OVERACTIVITY TO TREAT MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE WITH AGB101. Sharon ROSENZWEIG-LIPSON (1), Russell BARTON (1), Michela GALLAGHER (2), Richard MOHS (1) *((1) AgeneBio, Inc, United States, (2) Johns Hopkins University, 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 amnestic 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 connectional 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. The HOPE4MCI trial (currently in progress) is investigating the effects of AGB101 (220 mg) vs placebo in patients with MCI due to AD. **Objectives**: 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 objectives: To assess the efficacy of AGB101 compared to placebo on: 1) FAQ and MMSE scores, 2) neuronal injury, as measured by a change in the entorhinal cortex thickness. Additional secondary objectives: To assess the efficacy of AGB101 compared to placebo on: 1) CDR (global, memory box), BPS-O task, and ISLT scores, 2) hippocampal volume, 3) the levels of tau protein in the brain using the tau PET ([18F]MK-6240). **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 830 subjects will be randomized (415/treatment group). Inclusion criteria: Subjects must meet all of the following inclusion criteria at screening: 1) Subjects between 55 and 85 years old (inclusive) in good general health; 2) Have a study partner who has sufficient contact with the subject to be able to provide assessment of memory changes, who can accompany the subject to the screening and all major clinic visits for the duration of those visits, and who is able to provide an independent evaluation of the subject's functioning. 3) Have MCI due to AD as defined by all of 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. - Essentially preserved activities of daily living. - Cognitive decline not primarily caused by vascular, traumatic, or medical problems (alternative causes of cognitive decline are ruled out). 4) Evidence of an amyloid-positive PET scan. **Results**: The HOPE4MCI trial is currently underway. Sites are currently enrolling in the US and Canada with plans to expand to Europe. Up to date subject demographics, screen failure information, safety and dropout information will be presented at the meeting. **Conclusions**: HOPE4MCI represents the first and only Phase 3 clinical trial targeting the reduction of hippocampal overactivity for slowing the progression of MCI due to AD. The HOPE4MCI trial is supported, in part, by R01AG061091 to RM and R01AG048349 to MG.

Late Breaking News

LB1: HARMONY RELAPSE-PREVENTION STUDY: PIMAVANSERIN SIGNIFICANTLY PROLONGS TIME TO RELAPSE OF DEMENTIA-RELATED PSYCHOSIS.

Erin FOFF (1), Jeffrey CUMMINGS (2), Maria SOTO-MARTIN (3), Bradley MCEVOY (1), Srdjan STANKOVIC (1) ((*1) ACADIA Pharmaceuticals Inc., United States, (2) Cleveland Clinic Lou Ruvo Center for Brain Health, United States, (3) Gerontopole Alzheimer Clinical Research Center/University Hospital of Toulouse, France)*

Background: Approximately 2.4 million patients with dementia in the US alone experience delusions and hallucinations associated with dementia-related psychosis (DRP). Occurrence of DRP symptoms is further associated with poor outcomes such as increased likelihood of nursing home placement, progression to severe dementia, increased morbidity, and mortality. No available therapies have been approved for treatment of DRP. Pimavanserin is an atypical antipsychotic that acts as an inverse agonist/antagonist at the 5-HT2A receptor. Its efficacy and safety in treating hallucinations and delusions has been demonstrated in patients with Parkinson disease psychosis, with or without cognitive impairment. Additionally, in a short-term study in Alzheimer disease psychosis, pimavanserin has shown significant efficacy and favorable tolerability. The present study seeks to investigate the use of pimavanserin across a broad population of patients with dementia-related psychosis. **Objectives**: The aim of HARMONY study (NCT03325556) is to evaluate the efficacy and safety of pimavanserin for treatment of delusions and hallucinations associated with DRP in a broad spectrum of dementias including Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), Alzheimer's disease (AD), frontotemporal degeneration spectrum disorders (FTD), and vascular dementia (VaD). **Methods**: HARMONY is a Phase 3, placebo-controlled, randomized withdrawal study. The relapse-prevention design was chosen to allow for systematic evaluation of long-term efficacy in a clinically relevant manner. Participants with dementia and moderate to severe psychosis were enrolled. Eligible patients received pimavanserin 34 mg once daily for 12 weeks during the open-label period, with a possibility of dose adjustment to 20 mg within the first 4 weeks. After 12 weeks, participants who sustained a clinically meaningful improvement relative to open-label baseline (≥30% reduction on the SAPS-H+D Total Score AND a CGI-I score of 1=very much improved or 2=much improved) at both Weeks 8 and 12 were randomized 1:1 in a double-blind fashion to continued pimavanserin or to placebo, for up to 26 weeks. Patients were monitored for re-occurrence of psychotic symptoms in the double-blind period. The primary endpoint was time from randomization to relapse of psychosis. **Results**: Overall, 794 patients were screened during approximately 24 months study enrollment. A total of 392 patients were enrolled into the open-label treatment period with the following distribution of dementia subtypes: 66.8% AD, 14.3% PDD, 9.7% VaD, 7.4% DLB, and 1.8% FTD. Most of the patients achieved sustained improvement, suggesting robust response rates, with fewer than 21% of eligible patients failing to meet sustained response criteria. Pimavanserin was well tolerated, and more than 90% of patients remaining on the initial 34-mg dose and fewer than 10% having dose reduced to 20 mg. Over 61% of eligible patients were randomized into the double-blind phase of the study. At

the time of interim analysis, 40 patients were judged by the independent adjudication committee to have reached study criteria for relapse, 19 patients were arbitrated as discontinued due to other reasons, 70 patients were ongoing, and 65 patients had completed 6-month double-blind treatment. The study was stopped early for efficacy when the result of the prespecified interim analysis revealed highly statistically significant benefit of pimavanserin treatment over placebo (1-sided P<0.0033) in delaying time to relapse. Selected results from the open-label portion of the trial will be presented, including demographics of the study population, response rates overall and by dementia subtype, safety information and reasons for discontinuations. Additionally, interim analysis primary efficacy results, including hazard ratio, will be presented. Further data from the double-blind relapse population may be presented as available. **Conclusions**: There currently are no approved therapies for the treatment of DRP. Variable and only modest efficacy, along with safety concerns, complicate the off-label use of available antipsychotics, leaving a high unmet need for safe and effective treatment for this debilitating condition. The HARMONY study evaluated pimavanserin's potential to address this need by employing a randomized withdrawal design with clinically meaningful endpoints. In the open-label portion of the trial, pimavanserin was well tolerated, with robust treatment response across dementia subtypes. The statistically significant superiority for pimavanserin over placebo in time to relapse of DRP during the subsequent double-blind period supports efficacy and durability of effect of pimavanserin in this patient population.

LB2: MASUPIRDINE (SUVN-502), A 5-HT6 RECEPTOR ANTAGONIST IN COMBINATION WITH DONEPEZIL AND MEMANTINE IN MODERATE ALZHEIMER'S PATIENTS: STUDY OUTCOMES FROM A PHASE-2 STUDY.
Jeffrey CUMMINGS (1,2), Alireza ATRI (3), Ramakrishna NIROGI (4), John IENI (4), Vinod GOYAL (4), Pradeep JAYARAJAN (4), Jyothsna RAVULA (4), Satish JETTA (4), Venkat JASTI (4) *((1) Department of Brain Health, School of Integrated Health Sciences, University of Nevada; Cleveland Clinic, Lou Ruvo Center for Brain Health, United States, (2) Cleveland Clinic, Lou Ruvo Center for Brain Health, United States, (3) Banner Sun Health Research Institute, Banner Health, United States, (4) Suven Life Sciences, India)*

Background: Masupirdine (SUVN-502) is a selective 5-hydroxytryptamine-6 (5-HT6) receptor antagonist being investigated for the symptomatic treatment of moderate Alzheimer's disease (AD). Animal data show that masupirdine has potential to improve cognitive performance. Phase-1 studies of masupirdine in healthy humans suggest favorable properties including once daily oral treatment and a lack of food, gender and age effect. Masupirdine added to background treatment with donepezil and memantine was evaluated in moderate AD subjects in a double-blind placebo controlled, randomized, 26-week treatment phase-2 study. **Objectives**: To evaluate the efficacy and safety of masupirdine in combination with donepezil and memantine for the symptomatic treatment of moderate AD. **Methods**: In this phase-2 study, a total of 564 moderate AD patients with MMSE scores between 12–20 receiving stable doses of donepezil and memantine were randomized (1:1:1) to receive either 50 mg or 100 mg of masupirdine, or placebo once daily for 26 weeks. The primary efficacy endpoint was change from baseline in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog 11). Secondary efficacy endpoints included CDR-SB, ADCS-ADL, NPI, C-SDD and MMSE. The efficacy endpoints were analyzed using MMRM of the modified intent-to-treat (mITT) and the evaluable population (EP). Safety was assessed by recording adverse events and laboratory measurements, vital signs, electrocardiograms, physical and neurological examinations and C-SSRS. **Results**: Out of 564 randomized patients, 183 assigned to placebo, 184 who received 50 mg masupirdine, and 176 who received 100 mg masupirdine were included in the final analysis. Patient baseline characteristics were consistent with moderate AD with MMSE scores ranging from 12-20. The mean (SD) age of patients was 73.6 (7.46) years and the mean (SD) duration of AD diagnosis was 3.73 (2.7) years. Two-thirds of the patients were ApoE-4 carriers. Masupirdine was well-tolerated in patients with moderate AD. The study missed its primary and secondary efficacy endpoints . Triple therapy of Masupirdine + Donepezil + Memantine resulted in unique and unconventional datasets. Masupirdine is the first and the only 5-HT6 receptor antagonist which was evaluated as triple therapy. Post-hoc and hypothesis-generating observations of interest emerged from the detailed data analyses. In the exploratory subgroup analysis, masupirdine treatment arms showed significant improvement in cognitive functions in subjects stratified by memantine regimen, memantine plasma concentrations and memantine treatment duration. Improvement in the behavioral and psychological symptoms was also observed with masupirdine in NPI domains. The primary, secondary and exploratory efficacy analysis and safety outcomes of the study will be presented. **Conclusions**: Masupirdine is safe and well tolerated. The current study involving Triple therapy of Masupirdine + Donepezil + Memantine missed its primary and secondary efficacy endpoints. Post-hoc and hypothesis-generating observations of interest emerged from the detailed data analyses. These findings support further exploration of the potential of masupirdine.

LB3: RESULTS OF THE REDUCING PATHOLOGY IN ALZHEIMER'S DISEASE THROUGH ANGIOTENSIN TARGETING (RADAR) TRIAL.
Patrick G KEHOE (1), Nicholas TURNER (1), Elizabeth HOWDEN (1), Lina JARUTYTE (1), Shona CLEGG (2), Ian MALONE (2), Josephine BARNES (2), Carole SUDRE (3), Aileen WILSON (1), Jade THAI (1), Peter S BLAIR (1), Elizabeth COULTHARD (1), Athene LANE (1), Anthony P PASSMORE (4), Jodi TAYLOR (1), Henk-Jan MUTSAERTS (5), David L THOMAS (2), Fox NICK (2), Ian WILKINSON (6), Yoav BEN-SHLOMO (1), Radar INVESTIGATORS (1) *((1) University of Bristol, United Kingdom, (2) University College London, United Kingdom, (3) Kings College, United Kingdom, (4) Queens University Belfast, United Kingdom, (5) Academic Medical Centre, United Kingdom, (6)Addenbrookes Hospital, United Kingdom)*

Background: In the last decade there has been a significant growth in evidence suggesting that angiotensin II, as the main effector of the classical Renin Angiotensin System (cRAS), is a therapeutic target for Alzheimer's disease (AD). Fortunately there are a number of 'sartans' or angiotensin II type I receptor (AT1R) blockers that could be repositioned to treat Alzheimer's disease (AD). Losartan, the prototype AT1R blocker, through its inhibition of angiotensin II signalling, is one of a number of possible interventions proposed for AD. This is based on

now numerous in pre-clinical studies whereby pathological changes in patient cohorts, or where various experimental in vivo and some human observational studies have shown that angiotensin II has a role in evident pathological mechanisms including cholinergic transmission, declining memory, cerebral blood flow (CBF) and white matter damage, as well as overarching neurodegeneration attributed to amyloid and tau neuropathology. The potential therapeutic value of losartan and other AT1R blockers in AD is also supported by several observational studies reporting that people taking these medications have lower incidence and slower progression of AD compared to other anti-hypertension drug types, suggesting that these drugs also produce effects above and beyond their roles to reduce hypertension. **Objectives**: To test the therapeutic potential of losartan in mild-to-moderate Alzheimer's disease in a 12-month Phase II double-blinded randomised controlled trial. **Methods**: A multi-centre phase II, two arm, double-blind, placebo-controlled, randomised trial was undertaken to evaluate the effect of losartan in patients diagnosed with Alzheimer's disease. The primary outcome for the RADAR Trial (ISRCTN: 93682878; EudraCT: 2012-003641-15) was the level of change, after 12 months of losartan treatment, in whole brain and ventricular volume by volumetric MRI (T1-MPRAGE). Several secondary outcomes of interest included: (i) change in cognitive function, activities of daily living and quality of life (using standard assessment battery including ADAS-Cog, Neuropsychiatric Inventory, Bristol Activities of Daily Living and DEMQOL); (ii) change (in a subset of cases) in CBF (measured by arterial spin labelling (ASL)); (iii) change (in a subset of cases) in white matter hyperintensities (T2/FLAIR brain MRI); (iv) association between MRI measures and rate of cognitive decline; (v) change in blood pressure and (vi) drug compliance and tolerability. Participants were randomised to either encapsulated 100mg of losartan or placebo taken once daily for 12 months and MRI measures were taken with appropriate wash-out conditions (a least 4 days intervention free) at baseline and follow-up. Entry to the randomised phase for all participants was subject to their successful completion of a two-week open-label phase on the intervention drug and a successful baseline MRI scan. The main inclusion criteria included patients, with capacity to consent for themselves and whom were at least 55 years old. Participants could be hypertensive or normotensive meeting a definition of probable AD according to NINCDS-ADRDA (supported by imaging MRI/CT that was consistent with a diagnosis of AD). Eligible participants had to have a baseline MMSE at screening of (18-28) or Montreal Cognitive Assessment (MoCA) (12-26); as well as a modified Hachinski score of 5 or less. **Results**: From our intended sample size of 228 patients we recruited from 23 centres across the UK and Northern Ireland and randomised 211 participants of whom 93% (n=197) completed the study and which yielded primary outcome data for 173 individuals (88% of those randomised). This has provided us with 82% statistical power for our analyses. We randomised 127 (60%) males and 84 (40%) females of whom 46% were hypertensive and 96% were taking dementia medications at the time of entry. The recruited population of patients, whom each had a study partner. had an average age of 72years where 37% were 55-69 years, 38% were 70-79years and 25% were 80 years or older. A more detailed presentation of the baseline characteristics according to treatment arms as well as a full presentation of the trial primary and secondary outcome results that are currently being analysed will be presented for the first time. **Conclusions**: This will be the first formalised Phase II double-blinded randomised controlled trial to report on the testing of an AT1R blocker losartan in mild-to-moderate AD patients. It will present findings from the first attempt to formally test the angiotensin hypothesis in AD. We will demonstrate the success of our robust study design, that performed excellently, in a multi-centre context, at managing the recruitment and retention of both hypertensive and normotensive patients whom were uniquely tested for this type of intervention. Our findings and methodologies will inform trial designs for the future testing of other repurposable RAS-targeting drug candidates the urgency of which continue to grow with the continuous emergence of supportive data for the angiotensin hypothesis in AD. Key words: losartan, Alzheimer, intervention, angiotensin II, MRI, RCT.

LB4: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL DESIGN, PROSPECTIVE, PHASE II CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF GV1001, A NOVEL PEPTIDE MIMICKING HUMAN TELOMERASE REVERSE TRANSCRIPTASE, FOR THE TREATMENT OF MODERATE TO SEVERE ALZHEIMER'S DISEASE.

Seong-Ho KOH (1), Seong Hye CHOI (2), Jee Hyang JEONG (3), Chan Nyoung LEE (4), Young Soon YANG (5), Ae Young LEE (6), Jae-Hong LEE (7), Kyung Won PARK (8), Hyun Jeong HAN (9), Byeong Cha KIM (10), Jin Se PARK (11), Jee-Young LEE (12), Sangjae KIM (13) *((1) Hanyang University Guri Hospital, Korea, Republic of, (2) Inha University Hospital, Korea, Republic of, (3) Ewha Womans University Mokdong Hospital, Korea, Republic of, (4) Korea University Anam Hospital, Korea, Republic of, (5) Veterans Health Service Medical Center, Korea, Republic of, (6) Chungnam National University Hospital, Korea, Republic of, (7) Asan Medical Center, Korea, Republic of, (8) Dong-A University Hospital, Korea, Republic of, (9) Myongji Hospital, Korea, Republic of, (10) Chonnam National University Hospital, Korea, Republic of, (11) Inje University Haeundae Paik Hospital, Korea, Republic of, (12) Seoul National University Boramae Medical Center, Korea, Republic of, (13) Teloid Inc., United States)*

Background: GV1001 is a peptide of 16 aminoacids from human telomerase reverse transcriptase (hTERT), corresponds to a fragment from the catalytic site of telomerase. GV1001 has been shown to inhibit neurotoxicity, apoptosis, and production of reactive oxygen species in neural cells by mimicking the extra-telomeric functions of hTERT. In both mild (early stage) and severe (late stage) Alzheimer's Disease (AD) mouse models, GV1001 has been shown to improve cognitive function and memory, as well as significantly reduce the amount of amyloid beta and tau proteins. The multifunctional effect of GV1001 makes it a promising therapeutic option for the treatment for AD. **Objectives**: To evaluate the safety and efficacy of GV1001 in patients with moderate to severe AD. **Methods**: Patients 55 to 85 years of age, Korean-Mini-Mental State Examination (K-MMSE) score ≤ 19, were recruited and randomized to treatment with Group 1 (GV1001 0.56 mg), Group 2 (GV1001 1.12 mg), or placebo (normal saline) in a 1:1:1 ratio. The intervention course was 24 weeks, study treatment (GV1001 0.56 mg, GV1001 1.12 mg, or placebo) was administered by subcutaneous (SC) injection every week for 4 weeks (4 times) followed by SC administration every 2 weeks through Week 24 (10 times) for a total of 14 SC administrations of study treatment. Primary outcome was change from baseline(CFB)

in Severe Impairment battery (SIB) and secondary endpoints were CFB in K-MMSE, Geriatric Depression Scale (GDS), Clinical Dementia Rating-Sum of Boxes(CDR-SB), AD Cooperative Study-Activities of Daily Living(ADCS-ADL), and Neuropsychiatric Inventory(NPI). Adverse events, relevant laboratory, and vital signs were assessed. **Results**: A total of 90 participants from 11 sites were included (Group 1, Group 2 and Placebo: n = 30). At week 24, a statistically significant difference in the mean CFB in SIB score was seen in GV1001 treatment Groups 1 and 2 vs the control group for the full analysis population ($p < 0.05$). There was also a significant improvement in the mean CFB in ADCS-ADL at week 24 in all GV1001 treatment Groups vs control group ($p < 0.05$). There were no statistically significant differences found in other secondary outcome measures. Adverse event (AE) reporting was similar across all three groups. No treatment-emergent AEs were considered to be related to the study drug. **Conclusion:** The results indicate that GV1001 was effective and well tolerated without safety concerns, and may provide potential beneficial effects in patients with AD. Further investigation will be required to confirm these observations in a large-scale and longer-term clinical evaluation. TRIAL REGISTRATION: ClinicalTrials.gov, NCT03184467 Registered on 12 June 2017.

LB5: ORAL MICROBIAL DYSBIOSIS AND AMYLOID PATHOLOGY IN COGNITIVELY NORMAL SUBJECTS. Angela R. KAMER (1), Deepthi GULIVINDALA (1), Smruti PUSHALKAR (1), Qianhao LI (1), Lidia GLODZIK (2), Tracy BUTLER (2), Elizabeth PIRRAGLIA (1), Yi LI (2), Kumar ANNAM (1), Patricia CORBY (3), Henrik ZETTERBERG (4), Kaj BLENNOW (4), Deepak SAXENA (1), Mony J. DE LEON (2) *((1) New York University, United States, (2) Cornell Medicine, United States, (3) UPENN, United States, (4) University of Gothenburg, Sweden)*

Background: Inflammation and dysbiosis could contribute to Alzheimer's disease pathogenesis. We previously have shown that periodontal disease, a dysbiotic condition is associated with lower cognition, and brain amyloid pathology. **Objectives**: Based on our prior studies, we hypothesize that elderly cognitively normal people with CSF biomarker evidence for amyloid pathology would have subgingival microbiota enriched in periodontal bacteria compared to those with less biomarker evidence. We will also examine the effect of subgingival periodontal dysbiosis on the continuous measures of amyloid pathology. **Methods**: Subgingival bacterial composition was assessed using 16S rRNA sequencing in 26 subjects with higher (normal) CSF Ab42 (Ab>=600pg/ml) and 22 subjects with lower (amyloid positive) CSF Ab42 (Ab<600pg/ml). We used Linear discriminant effect size analysis (LEfSe) and univariate analysis of variance adjusted for relevant covariates (ApoE, age, smoking) to determine the bacterial taxa different between our groups. To determine the predictive effect of high/low dysbiotic index on CSF Ab42, 2-way analysis of variance was used with the relevant covariances (age, BMI, APOE). Dysbiotic index (DI) was defined as a ratio of periodontal bacteria (Porphyromonas, Treponema and Tannerella) to healthy bacteria (Rothia and Corynebacterium). Hi vs. low DI was classified by dichotomizing the DI scores using the upper vs. lower half with the cut-point of 3 (<3 vs. 3+). **Results**: LEfSe showed that subgingival samples of subjects with low CSF Ab42 were enriched in bacterial taxa characteristic of periodontal disease such as genera Prevotella, Porphyromonas, Alloprevotella, and Fretibacterium while subjects with high CSF Ab42 were enriched in bacterial taxa belonging to genera characteristic of periodontal health such as Corynebacterium, Actinomyces, Leptotrichia, and Capnocytophaga. The subgingival dysbiotic index (DI) was statistically significant lower in subjects with high CSF Ab42 compared to those with low CSF Ab42 even after adjustment for age, ApoE and smoking (Adjusted log means±SE: 0.26±0.15 vs. 0.82±0.18; F=4.80, p=0.03). In 2-way analysis of variance, with high/low DI and APOE4 as independent variables, we found that there was a significant interaction between DI and APOE on CSF Ab42. Among APOE4- subjects, those with high DI (n=13) vs those with low DI [(n=13) had significantly lower CSF Ab42 (adjusted means±SE: 600.48±47.07 vs. 885.25±47.07; F=17.48 p<0.001)]. Moreover, there was a significant inverse correlation between DI and CSF Ab (partial R=-0.52, p=0.01). However, in APOE4+ subjects the CSF Ab42 was not different between the 2 DI groups (low DI: n=13; adjusted means±SE: 572.07±56.43 vs. high DI: n=9; 582.26±68.25; F=0.13, p=0.91). **Conclusion**: These results add to our understanding of a relationship between oral bacteria and brain Ab. Our results also show that the oral bacterial effect on CSF Ab may be APOE dependent or best recognized in E4 negative. Periodontal disease is a prevalent condition that can be treated non-invasively. Therefore, to further determine the roles of specific oral bacteria in Alzheimer's disease pathogenesis, longitudinal and interventional studies are warranted.

LB6: MODULATION OF MICRORNA PATHWAYS BY GEMFIBROZIL IN PREDEMENTIA ALZHEIMER DISEASE: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND CLINICAL TRIAL. Gregory JICHA, Richard KRYSCIO, Brooke BEECH, Wangxia WANG, Bert LYNN, Frederick SCHMITT, Beth COY, Omar AL-JANABI, Erin ABNER, Peter NELSON *(University of Kentucky, United States)*

Background: Previous research has indicated that miR-107 may play important roles in both metabolism and AD pathogenesis that may be modulated by "fibrates" (PPAR-alpha agonists). Fibrates increase miR-107 expression, leading to down-regulation of BACE1 protein. We evaluated the safety and efficacy of gemfibrozil administration in predementia Alzheimer's disease in a parallel-design, double-blind, placebo-controlled clinical trial funded by NIH/NIA R01 AG042419 and registered on clinicaltrials.gov NCT02045056. **Methods**: Patients with pAD, MCI, or early AD (CDR 0.5) were randomized to receive gemfibrozil (600 mg twice daily) for 48 weeks or placebo. Primary endpoints included: 1) safety of administration of gemfibrozil in the specific study population, 2) CSF levels of gemfibrozil to demonstrate target engagement, and 3) change in miR-107 expression and CSF A-beta levels. Exploratory outcome measures included change in ptau-181, MRI hippocampal volume, fasting glucose and lipid levels among others. **Results**: There were no significant differences in frequency and/or occurrence of AEs classified by MeDRA classification in treatment (63%) versus placebo (53%) arms of the study (p=0.37). No serious adverse events related to the study medication were observed. CSF levels of gemfibrozil were reliably detected in the treatment group only at the end of treatment study visit. Change in A-beta42 and ptau-181 CSF levels between baseline and week 48 were not significantly different between active treatment and placebo arms of the study (p=0.34 & p=0.18, respectively). A nonspecific trend

towards reduction in hippocampal atrophy in the treatment versus placebo group was seen (p=0.15). Change in glucose and lipid levels across study visits demonstrate favorable metabolic changes in the gemfibrozil treatment versus placebo arms of the study. **Conclusions**: While the primary outcome measures were negative, positive trends associated with gemfibrozil treatment included reductions in CSF A-beta42, CSF ptau-181 and rate of hippocampal atrophy. Gemfibrozil showed excellent CSF penetration and was safe for administration in the elderly population at risk for Alzheimer's disease including those in the prodromal state of mild cognitive impairment. Further secondary and subgroup analyses are underway to explore the outcome measures and metabolic influences of gemfibrozil on risk for dementia in this predementia population.

LB7: ONE-MONTH ORAL TREATMENT WITH PTI-125, A NEW DRUG CANDIDATE, REDUCES CSF AND PLASMA BIOMARKERS OF ALZHEIMER'S DISEASE.

Lindsay BURNS (1), Hoau-Yan WANG (2), Zhe PEI (2), Kuo-Chieh LEE (2), Carrie CROWLEY (2), Michael MARSMAN (2), Nadav FRIEDMANN (2) *((1) Cassava Sciences, Inc., United States, (2) City of New York School of Medicine, United States)*

Background: PTI-125 is an oral small molecule drug candidate that binds and reverses an altered conformation of the scaffolding protein filamin A (FLNA) found in Alzheimer's disease (AD) brain. Altered FLNA links to the α7-nicotinic acetylcholine receptor (α7nAChR) to allow Aβ42's toxic signaling through this receptor to hyperphosphorylate tau. Altered FLNA also links to toll-like receptor 4 (TLR4) to enable Aβ-induced persistent activation of this receptor and inflammatory cytokine release. Restoring the native shape of FLNA prevents or reverses FLNA's linkages to α7nAChR and TLR4, thereby blocking Aβ42's activation of these receptors. The result is reduced tau hyperphosphorylation and neuroinflammation, with multiple functional improvements demonstrated in transgenic mice and postmortem AD brain tissue. PTI-125 was safe and well-tolerated in a Phase I trial in healthy volunteers. Objective: Safety, pharmacokinetics (PK), and CSF and plasma biomarkers were assessed in a Phase 2a clinical trial of mild-to-moderate AD patients following treatment for 28 days. Target engagement and mechanism of action were assessed in patient lymphocytes by measuring 1) the reversal of FLNA's altered conformation, 2) linkages of FLNA with α7nAChR or TLR4, and 3) levels of Aβ42 bound to α7nAChR or CD14, the co-receptor for TLR4. **Methods**: In this open-label, Phase 2a trial conducted in the US, 12 patients with mild-to-moderate AD received PTI-125 in 100 mg oral tablets b.i.d. for 28 days. Key inclusion criteria were MMSE ≥ 16 and ≤ 24, age 50-85 and CSF total tau/Aβ42 ratio ≥ 0.30. Safety was assessed by ECGs, clinical labs, adverse event (AE) monitoring and physical examinations. Blood samples for PK analysis were collected over 12 h on Days 1 and 28. CSF samples were collected at screening and on Day 28. Blood samples for plasma and lymphocyte biomarkers were collected on Days 1 (pre-dose), 14 and 28. CSF and plasma biomarkers were analyzed using commercial ELISA kits. Biomarkers assessed AD pathology (pT181-tau, total tau and Aβ42), neurodegeneration (neurofilament light chain [NfL] and neurogranin), and neuroinflammation (YKL-40, IL-6, IL-1β and TNFα). Cytokines were not measured in plasma. CSF and plasma samples were stored at -80°C, thawed and treated with protease and phosphatase inhibitors prior to aliquoting and refreezing until analysis. For each ELISA biomarker, pre-dose and Day 28 samples were tested in triplicate in the same ELISA plate. Values were adjusted to a regression analysis run on standards, and background for chromogen blanks and the no-CSF controls was subtracted. R2 values for regression analyses ranged from 0.85 to 0.99. Plasma levels of phosphorylated tau were assessed by immunoprecipitation of tau with anti-tau followed by immunoblotting of three different phospho-epitopes elevated in AD (pT181-tau, pS202-tau and pT231-tau). Changes in conformation of FLNA in lymphocytes were measured by isoelectric focusing point (pI). FLNA linkages to α7nAChR and TLR4 were assessed by immunoblot detection of α7nAChR and TLR4 in anti-FLNA immunoprecipitates from lymphocytes. Aβ42 complexed with α7nAChR or CD14 was also measured by co-immunoprecipitation. **Results**: PTI-125 was safe and well-tolerated in all patients, consistent with a previous Phase I trial. Plasma half-life was approximately 4.5 h. Approximately 30% drug accumulation was observed by comparing AUC0-12 on Day 28 vs. Day 1. Consistent with the drug's mechanism of action and preclinical data, PTI-125 reduced CSF biomarkers of AD pathology, neurodegeneration and neuroinflammation from baseline to Day 28. T-tau, neurogranin, and NfL decreased by 20%, 32% and 22%, respectively. P-tau (pT181) decreased 34%, evidence that PTI-125 suppresses tau hyperphosphorylation induced by Aβ42's signaling through α7nAChR. CSF biomarkers of neuroinflammation (YKL-40, IL-6, IL-1β and TNFα) decreased by 5-14%. Biomarker effects were seen in all patients and were similar in plasma. Aβ42 increased slightly – a desirable result because low Aβ42 in CSF and plasma indicates AD. This increase, significant only in plasma, is consistent with PTI-125's 1,000-fold reduction of Aβ42's femtomolar binding affinity to α7nAChR. All reductions of CSF and plasma biomarkers were at least $p \leq 0.001$ by paired t test. Target engagement was shown in lymphocytes by a shift in FLNA's conformation from aberrant to native: 93% of FLNA was aberrant on Day 1 vs. 40% on Day 28. As a result, FLNA linkages with α7nAChR and TLR4, and Aβ42 complexes with α7nAChR and CD14, were all significantly reduced by PTI-125 treatment. **Conclusions**: This first-in-patient trial with PTI-125 demonstrated reductions in both CSF and plasma biomarkers of AD pathology, neurodegeneration, and neuroinflammation. All patients responded to treatment. The magnitude and consistency of reductions in established, objective biomarkers imply that PTI-125 treatment counteracted disease processes and reduced the rate of neurodegeneration. These encouraging early results support PTI-125 as a new, highly differentiated and potentially disease-modifying treatment for AD. This work was funded by NIA grant AG060878.

LB8: EARLY CHANGES IN ALZHEIMER'S DISEASE BIOMARKERS SHOW INTERPLAY BETWEEN TAU METABOLISM, INFLAMMATION, SYNAPTIC DAMAGE AND NEURODEGENERATION: RESULTS FROM THE ALFA STUDY. José Luis MOLINUEVO (1), Gemma SALVADO (1), Marta MILA (1), Kaj BLENNOW (2), H ZETTERBERG (3, 4, 5), Grégory OPERTO (1), Carles FALCÓN (1), R BATRLA (6), G KOLLMORGEN (7), Gonzalo SÁNCHEZ-BENAVIDES (1), Juan Domingo GISPERT (1), Marc SUAREZ-CALVET (1) *((1) Barcelonabeta Brain Research Center, Fundació Pasqual Maragall, Pompeu Fabra University, Spain, (2) Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, University of Gothenburg, Sweden, (3) Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Sweden, (4) Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, United Kingdom, (5) UK Dementia Research Institute at UCL, United Kingdom, (6) Roche Diagnostics International Ltd, Switzerland, (7) Roche Diagnostics GmbH, Germany)*

Background: Amyloid and tau cerebrospinal fluid (CSF) biomarkers have been shown to change early in the Alzheimer's disease (AD) continuum. However, their relation with synaptic and inflammatory markers is not completely understood. More specifically, these biomarkers have not been assessed in middle-aged individuals. **Objectives**: The aim of this study is to describe the interplay among amyloid, tau, synaptic, inflammatory and neurodegeneration markers in middle-aged cognitively unimpaired individuals at increased risk for AD. To this end, we capitalized on the ALFA+ cohort comprising a substantial percentage of participants at the very beginning of the AD continuum. **Methods**: CSF Ab42, Ab40, t-tau, p-tau, neurogranin, GFAP, IL-6, YKL-40, sTREM2, NFL, S100B and α-synuclein were measured with Elecsys® robust prototype assays in 383 participants of the ALFA+ cohort, which comprises middle aged, from 45 to 65 years, cognitively unimpaired individuals. Participants also underwent cognitive assessments, APOE genotyping, structural and functional MRI and FDG, as well as amyloid PET. All CSF biomarker levels were described and compared across ATN groups. In addition, the variation of CSF and amyloid Centiloid values against the Ab42/Ab40 ratio and p-tau were plotted continuously. To this end, biomarker levels were converted to Z-scores by subtracting the mean and normalising to the standard deviation of a normal group for each biomarker. Cut-offs for abnormality were defined as 2 SD departing from the mean of the Gaussian distribution corresponding to the most frequent group. Then, a polynomial fitting was applied to model biomarker trajectories. For each individual biomarker, the optimal order of the model was selected using the Akaike information criterion. SPM12 was used to perform voxelwise correlations between CSF biomarkers and both gray matter volumes (GMv) from MRI and cerebral glucose consumption from FDG PET. All imaging correlation analysis were adjusted for the following covariates: age, sex, education and the other CSF biomarkers, as well as total intracranial volume in GMv and global uptake in FDG-PET. **Results**: Neurogranin, YKL-40, sTREM2, NFL and α-synuclein show significantly increased concentrations in the A+T+ group compared with the A-/T- and A+/T- ones. Plots vs Ab42/Ab40 show a steep increase in p-tau, neurogranin and YKL-40 happening after the amyloid positivity cut-off was reached. On the other hand, increments against p-tau were also evident before reaching the p-tau positivity cut-off. Average centiloid value of the A+ group was 11.75 CL (range: [-15.65, 81.63]). The association between CSF biomarkers and age was not modified by APOE status. Semantic fluency was significantly associated with neurogranin, as well as, p-tau and t-tau. GMv in medial and lateral temporal areas and posterior cingulate was positively associated with inflammatory CSF markers and, negatively, with NFL. Negative associations were found between neurogranin and FDG PET in the medial parietal and prefrontal cortex as well as in medial temporal cortex and the temporal pole. **Conclusions**: These results provide evidence of an early involvement of tau, synaptic and inflammatory pathways occurring after soluble amyloid reaches abnormal levels even in subjects with minimal cerebral amyloid deposition. Inflammatory markers were associated with brain swelling in key AD-related areas, whereas the contrary was observed for NFL. Increased CSF neurogranin was associated with lower cerebral glucose metabolism. Overall, these results provide evidence that multiple biological pathways are altered and actively affecting brain structure and metabolism at the very beginning of the AD continuum.

LB9: BLOOD PLASMA PHOSPHO-TAU ISOFORMS DETECT CNS CHANGE IN ALZHEIMER'S DISEASE. Nicolas BARTHÉLEMY, Kanta HORIE, Chihiro SATO, Randall BATEMAN *(Washington University School of Medicine, United States)*

Background: Highly sensitive and specific plasma biomarkers for Alzheimer's disease (AD) have the potential to improve diagnostic accuracy in the clinic and facilitate research studies including enrollment in prevention and treatment trials. Blood-based biomarkers of AD pathology will be needed to screen the general population when prevention treatments for AD become available, as cerebrospinal fluid (CSF) and PET scan approaches are not feasible. Total tau (t-tau) and some phosphorylated tau (phospho-tau or p-tau) isoform levels are significantly increased in AD CSF. However, relatively poor correlations between plasma tau and CSF tau levels have been a challenge in developing plasma tau as a biomarker for AD. Recent reports using immunoassays suggest more promising developments; for example, some reports indicate slight plasma total-tau increases in mild cognitive impairment (MCI) and AD, and several studies demonstrated plasma phospho-tau at threonine 181 (pT181) increases in AD at MCI and moderate stages. However, AD diagnosis using blood t-tau and pT181 has been restricted to the symptomatic stages of AD and with moderate levels of accuracy. Recent advances in blood amyloid-beta biomarkers measures by mass spectrometry (MS) have transformed the approach to AD clinical research. We sought to determine the relationship of blood tau-based measures to CNS measures of AD pathology and clinical stage of dementia using similar MS-based approaches. **Objectives**: 1) To determine the potential utility of plasma phosphorylated tau (phospho-tau or p-tau) isoforms to detect AD pathology and clinical stages of AD dementia. 2) To assess CSF and plasma tau isoform profile relationships to inform about the biology of tau in AD. 3) To design a MS assay for potential use as a reference method for plasma tau and phospho-tau quantitation. **Methods**: Plasma collected from the tau Stable Isotope Labeling Kinetics (SILK) study were pooled for each participant in order to obtain large volumes and detect minor tau species and phospho-tau isoforms in plasma by MS. The plasma tau isoform profile was compared to matching CSF tau isoform profiles, amyloid status,

and clinical stage of AD dementia for each participant. This discovery cohort includes 34 participants selected according to their amyloid status. Amongst them, 15 amyloid positive participants had various Clinical Dementia Rating (CDR) scores of 0 (5 participants), 0.5 (8 participants), and 1 (2 participants). All preclinical AD participants (amyloid positive, CDR=0) had tau PET AV-1451 SUVR measures not significantly different from amyloid negative participants. Total-tau (t-tau) and phosphorylated tau peptides at T181, T217 and S202 detected in plasma extracts were quantified by MS. Absolute levels of tau and phospho-tau along with p-tau/t-tau ratios were measured and compared to results obtained from matching CSF. **Results**: Similar to CSF tau, plasma tau was truncated. As previously reported, no correlation was found between CSF and plasma total-tau levels. Similarly, we found no correlation between CSF and plasma pS202. In contrast, CSF and plasma pT217 measures (absolute level and pT217/T217 ratio) were highly correlated (r=0.78), and a lower correlation was determined for those of pT181 (r=0.68). Further, pT217 and pT181 were highly specific for amyloid plaque AD pathology (AUROC=0.99 and 0.95 for pT217 and pT181 levels and 0.98 and 0.98 for pT217/T217 and pT181/T181 ratios respectively). **Conclusions**: The results of this study demonstrate higher phosphorylation status of CNS tau on T217 and T181 compared to peripheral tau. This makes AD-specific tau modification detectable in plasma despite the major contribution of peripheral tau to overall plasma tau level. This finding appears to support the use of plasma pT217 and pT181 as blood biomarkers of AD pathology even at the asymptomatic stage.

LB10: PERSISTENCE OF BAN2401-MEDIATED AMYLOID REDUCTIONS POST-TREATMENT: A PRELIMINARY COMPARISON OF AMYLOID STATUS BETWEEN THE CORE PHASE OF BAN2401-G000-201 AND BASELINE OF THE OPEN-LABEL EXTENSION PHASE IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE. Chad SWANSON (1), Yong ZHANG (1), Shobha DHADDA (1), Jinping WANG (1), June KAPLOW (1), Heather BRADLEY (1), Martin RABE (1), Keiichiro TOTSUKA (2), Robert LAI (3), Robert GORDON (3), Lynn KRAMER (1) *((1) Eisai Inc., United States, (2) Eisai Co., Ltd., Japan, (3) Eisai Ltd., United Kingdom)*

Background: BAN2401, a humanized IgG1 monoclonal antibody, selectively binds Aβ protofibrils over monomers (≥1000-fold) and fibrils (≥10-fold) and has a different binding profile versus other monoclonal antibodies. BAN2401 treatment demonstrated a robust and dose-dependent brain amyloid reduction in the core phase 2 study (BAN2401-G000-201), with up to 81% subjects returning on visual read from amyloid positive to negative at 18 months in the 10mg/kg-biweekly group. The objective of the present analysis was to assess amyloid PET status from the first 111 subjects at baseline in the ongoing open-label extension (OLE) of BAN2401-G000-201. **Methods**: Subjects who fulfilled OLE inclusion/exclusion criteria were eligible. All subjects were required to be amyloid positive at baseline in the core study, based on PET visual read or CSF. In the present analysis, amyloid PET status was determined at baseline in the OLE by visual read using an identical approach to the visual read conducted at baseline in the core, with the radiological reviewer blinded to treatment allocation in the core. The OLE was implemented after the initial analysis of the core study showed clinical potential for BAN2401. Due to the timing of OLE implementation, there was no limitation on the amount of time a subject may have been off drug prior to entering the OLE. **Results**: A total of 111 subjects from the core study have undergone an amyloid PET at OLE baseline as of the cutoff for this analysis, including 84 BAN2401-treated subjects with a mean duration off study drug of 23.7 months (min=9.2 months; max=52.5 months). At follow-up, 80% (68/84) of all BAN2401-treated subjects from the core study were amyloid negative at baseline in the OLE. All subjects entering the OLE who were treated with BAN2401 (any dose) and who were amyloid negative in the core study after their last longitudinal amyloid assessment were also amyloid negative at baseline in the OLE (N=36; mean 32.1 months off drug). Mean core baseline PET standard uptake value ratio (SUVr) for the 10 mg/kg biweekly group in core was 1.36 (N=14). Mean PET SUVr change from core baseline for these subjects to OLE Baseline (N=12; -0.29) was comparable to the mean change observed from core baseline to core 18 months treatment (N=13; -0.30), despite a mean time off study drug of 29.4 months. **Conclusions**: In this preliminary analysis, BAN2401-mediated returning to amyloid PET negativity by visual read persists from the end of treatment in the core to baseline of the OLE, which is consistent with PET SUVr data, despite subjects being off BAN2401 for 9 to 52 months.

LB11: IMPROVING MEASUREMENT OF AGITATION IN DEMENTIA INCORPORATING IPA AGITATION WORKING GROUP DEFINITION. Zahinoor ISMAIL (1), Adelaide DE MAULEON (2), Jeannie LEOUTSAKOS (3), Cedric O'GORMAN (4), David MILLER (5), Paul ROSENBERG (3), Maria SOTO MARTIN (2), Constantine LYKETSOS (3) *((1) University of Calgary, Canada, (2) Centre Hospitalier Universitaire, France, (3) Johns Hopkins, United States, (4) Axsome, United States, (5) Signant Health, United States)*

Background: Research and clinical work in agitation has been hampered by a lack of agreed upon definition for agitation. In the absence of a gold standard, clinical response has been measured as a function of overall clinical impression, or improvement on either agitation specific rating scales or agitation domains of general psychopathological measures. In 2015, the International Psychogeriatric Association (IPA) Agitation Definition Working Group developed a definition for agitation to help facilitate research in the field. Important features of the definition are the requirement of distress due to the behaviours, and the breakdown of agitation into three domains: excessive motor activity (EMA), verbal aggression (VA), and physical aggression (PA). However, despite the development of the criteria, there are no definition specific measurements, nor any information on how to measure meaningful change using the new definition. **Objectives**: To describe the modified Delphi process for the mapping of items from the Cohen Mansfield Agitation Inventory (CMAI) and the Neuropsychiatric Inventory Clinician rating (NPI-C), onto IPA agitation definition domains to generate derivative measurement instruments, the CMAI-R and and NPI-R. To assess psychometric properties of these derivative instruments and to estimate a minimal clinically important difference (MCID) in agitation, when compared to the Clinician Global Impression of Change (ADCS-CGIC) in participants from a multi-center observational study. **Methods**: The modified Delphi process included clinicians (N=7) and researchers (N=2) with expertise in agitation in dementia. As a first, step,

items from the CMAI and the NPI-C were reviewed by ZI for relevance to any of the three domains: EMA, VA, or PA. For the CMAI, all items were included, and for the NPI-C, all questions from the agitation, aggression, aberrant motor activity, abnormal vocalizations, disinhibition, and irritability/lability domains were included. As a next step, all relevant questions were incorporated into an online survey and rated by the Delphi Panel as 1 (none), 2 (weak), or 3 (strong) for association to each of the three IPA definition domains. For each item, if mean score was ≥2.5, the item was included and applied to the corresponding domain, and if <1.5, the item was discarded. Items with scores from 1.5-2.5 were retained for further discussion. These residual items were discussed via teleconference and assigned to a domain if 80% consensus was reached. Items that did not distinctly map onto one domain were discarded. To determine the association with parent and derivative change scores and MCID, data were analysed for 262 participants in the multi-centre French A3C study, an observational cohort of clinic and nursing home patients with Alzheimer's Disease (AD) dementia and clinically significant agitation. The CMAI, NPI-C and ADCS-CGIC were assessed on all participants at baseline and 3 months. MCID was estimated as the CMAI, CMAI-R, or NPI-R scale change score between baseline and 3 months that predicted an ADCS-CGIC score of 1 or 2 (Marked or Moderate Improvement) at the 3-month study timepoint. Sensitivity, Specificity, and Area Under the ROC Curve (AUC) were calculated for each using the Youden Point. **Results**: The correlation between the CMAI and CMAI-R was 0.84. For the original CMAI, a -4 point change captured the MCID with a sensitivity of 76% and specificity of 89% (AUC 0.82). For the derivative CMAI-R, a -2 point change captures MCID with a sensitivity of 76% and specificity of 89% (AUC 0.82). For the derivative NPI-R, a -4 point change captured the MCID with a sensitivity of 79% and a specificity of 90% (AUC 0.85). The AUCs were not significantly different between CMAI-R and NPI-R. **Conclusion**: The CMAI-R had comparable psychometric properties to the parent CMAI, and to the NPI-R. These findings demonstrate the utility of derivative scales in capturing improvement in agitation in those with clinically significant symptoms. IPA agitation domain-specific measures are an important advance in measurement and management of agitation in dementia. In the absence of current gold standard outcome, these results may optimize future clinical trials of treatments for agitation symptoms in AD. Next steps include assessing the contribution of each individual domain in MCID for agitation.

LB12: MAPT TRIAL: 5-YEAR FOLLOW-UP RESULTS. Bruno VELLAS (1), Sophie GUYONET (1), Jacques TOUCHON (2), Christele CANTET (1), Sandrine ANDRIEU (1) *((1) Toulouse University Hospital, France, (2) Montpellier University Hospital, France)*

Background: We present the results of the Multi-Domain Alzheimer's disease Preventive Trial (MAPT): 5-years long-term follow up and 2-year observational follow-up after the 3-year interventions. Method: the Multidomain Alzheimer Preventive Trial was a 60-month, multicenter, randomized, placebo-controlled superiority trial with 4 parallel groups including 3 interventions and one placebo group for 36 months plus 24 months observational follow up to track long-term effect of the interventions. Non-demented subjects aged 70 years and older with memory complaints were randomly assigned in a 1:1:1:1 ratio to: (i) combined intervention (i.e. multidomain intervention (cognitive + physical exercise) plus n-3 polyunsaturated fatty acids (two capsules a day, 800mg docosahexaenoic acid (DHA) + 225mg eicosapentaenoic acid (EPA)), (ii) multidomain intervention plus placebo, (iii) n-3 polyunsaturated fatty acids alone, or (iv) placebo alone. The primary outcome was change from baseline to 60 months on a composite Z-score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding test, MMSE Orientation, Digit Symbol Substitution Test, and Category Fluency Test). The trial was registered at ClinicalTrials.gov (NCT00672685). Result: In the intention-to-treat population (n= 1525), the combined intervention group declined by -. -0.13 points ([95%CI]: [-0.20;-0.05]) over 60 months on the composite score, while the placebo group declined by -.20 points ([95%CI]: [-0.27;-0.12]) (difference [95%CI]: 0.07 [-0.04;0.17]). This difference was non-significant after correcting for multiple comparisons in the intention-to-treat analyses but remained significant in biomarker-based subgroups (APOE ε4 carriers, amyloid-positive) ; (difference [95%CI]: 0.29 [0.06;0.53], adjusted p=0.042) for the APOE ε4 carriers subgroup, (difference [95%CI]: 0.95 [0.50;1.40], adjusted p <0.0001) for the amyloid + subgroup. For the low Red Blood Cell DHA+EPA subgroup the difference in decline between PUFAs alone vs. placebo is 0.22 ([95%CI]: [-0.01;0.44], adjusted p=0.171). **Conclusion**: Our 5-year data confirm the results of the multidomain intervention plus omega 3 in subject who are more likely to decline (APOE ε4 carriers, amyloid-positive and low Red Blood Cell DHA+EPA). **Funding:** French Ministry of Health, Pierre Fabre Research Institute, Gerontopole, Exhonit Therapeutics SA, Avid Radiopharmaceuticals Inc.

LB13: ITEM RESPONSE THEORY ANALYSIS OF THE CLINICAL DEMENTIA RATING. Yan LI (1), Chengjie XIONG (1), Andrew ASCHENBRENNER (1), Chih-Hung CHANG (1), Virginia BUCKLES (1), Krista MOULDER (1), Michael WEINER (2), Dan MUNGAS (3), Rachel NOSHENY (2), Taylor HOWELL (2), John MORRIS (1) *((1) Washington University in St. Louis, United States, (2) University of California, San Francisco, United States, (3) University of California, Davis, United States)*

Background: The Clinical Dementia Rating (CDR) is an instrument used to detect the presence or absence and, when present, the severity of dementia symptoms. It assesses change from previously attained levels in 6 cognitive and functional domains. The CDR is widely used in observational studies of Alzheimer disease and in clinical trials, both as a screening measure and a primary outcome. It has established reliability and is able to identify even very mild symptoms of dementia with high diagnostic accuracy based on neuropathogical examination. To determine the CDR, an experienced clinician conducts semi-structured interviews with the individual and with a study partner to assess change from prior levels of performance to determine the presence or absence of dementia and its severity. Although all available information is synthesized to generate the global CDR score using an established algorithm, it is likely that specific questions are more sensitive to disease stage than others. The current study seeks to use Item Response Theory (IRT) to identify specific items from the semi-structured interviews that contribute most to CDR staging to produce a shorter version of the CDR without compromising its reliability, and to facilitate the development of an online CDR (eCDR). A shortened version will ultimately aid in its deployment as a screening instrument

in the general population and accelerate enrollment into clinical and observational studies. **Objectives**:To evaluate the difficulty, discrimination, and information levels of each item in the CDR and identify the most informative items or the need to exclude some least-informative items. To develop the best fitting IRT models for predicting cognitive impairment and validate its performance using existing measures: CDR global and box scores. **Methods**: Baseline data from 2894 participants enrolled in the Washington University Memory and Aging project who had a global CDR no greater than 1 were analyzed in this study. Items were modeled as ordinal variables containing 2-5 response options. Confirmatory factor analysis was performed to compare various IRT models to identify the best fitting model for further measure development/refinement. The tested models included (1) a unidimensional IRT model with all items contributing to a general factor; (2) a multidimensional IRT model with six correlated factors for 6 domains in the CDR; (3) a bi-factor model with a general factor indicated by all items and six factors corresponding to the 6 domains of the CDR. The general factor was specified to be independent of the domain specific factors, while the correlations between the domain specific factors were estimated; and (4) same bi-factor model as in (3) but with separate factors for study participants and their informants nested within each domain. The difficulty and discrimination parameters of each item were examined, and item information curves were compared across items to select the most informative items. General factor scores and domain specific factor scores were generated using the best fitting model, and their relationship with the CDR global and box scores were evaluated using 10 fold cross-validation. **Results**: Among the 2894 participants, 46% were CDR 0, 32% were CDR 0.5 and 22% were CDR 1. Sixty-four items from the CDR with available data were included in IRT models. The Home and Hobbies domain only has one item with data available and therefore was excluded from the IRT analysis. The fourth model (bi-factor model with correlated domain and participants/informant specific factors) provided the best representation of the factor structure of the CDR. Moderate correlations were observed among Community Affairs, Memory, Orientation, and Judgement and Problem Solving domains, while the Personal Care domain was less correlated with other domains. Of the original 64 items, 53 that demonstrated high discriminative power and factor loadings were kept in the final bi-factor model for estimation of general factor scores and domain specific factor scores. These estimated scores were highly predictive of the CDR global and box scores: volume under the surface (VUS) of 0.94 for the overall factors in predicting global CDR, VUS of 0.82, 0.87, 0.91, 0.85 and 0.96 for the domain specific factor scores in predicting Community Affairs, Judgement and Problem-Solving, Memory, Orientation, and Personal Care domain box scores respectively. **Conclusion**: The IRT analysis indicates that majority of the items in the CDR discriminate well at mild and very mild levels of cognitive impairment, which is consistent with the reliability of the CDR. A small number of least-informative items could be excluded to reduce the burden on study participants and clinicians. The shortened version of the CDR still demonstrated very high classification accuracy and is well suited for development of an online CDR (eCDR). The general and domain specific factor scores estimated from the bi-factor model potentially could be used as a continuous outcome (as opposed to an ordinal ranking of CDR) in clinical trials to increase the sensitivity in detecting cognitive decline.

LB14: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED PHASE 2A CLINICAL TRIAL OF NA-831 IN PATIENTS WITH MCI AND MILD AND MODERATE ALZHEIMER'S DISEASE. Lloyd TRAN, Fern VU, Brian TRAN, Stephanie NEAVE *(NeuroActiva, Inc., United States)*

Background: Cognitive decline, the hallmark of dementia and Alzheimer's disease, is caused by the loss of nerve cells and synaptic dysfunction. NA-831 is an endogenous small molecule that exhibits neuroprotection, neurogenesis, and cognitive protective properties across a range of disease models. In the Phase 1 studies, no adverse effects were observed. It is well-tolerated up to 100 mg/day in healthy volunteers. Predictable pharmacokinetics including dose-dependent exposure linearity and low variability. **Method:** A randomized clinical trial of NA- 831 was performed in a total of 56 patients: 32 Alzheimer patients with MCI, and 24 patients with early onset of Alzheimer's disease over 24 weeks, with an additional follow-up over 24 weeks. The patients with MCI received 10 mg of NA-831 or placebo orally per day. The patients with mild and moderate Alzheimer's disease received 30 mg of NA-831 or placebo orally per day. The study was conducted in accordance with the Declaration of Helsinki and ICH and GCP guidelines. Inclusion criteria included: (a) male or female, at 55-80 years of age at screening, (b) For MCI patients, MMSE score ≥20. For patients with mild and moderate Alzheimer's disease, MMSE score> 17 (c) Center for Epidemiological Studies-Depression (CES-D) score <27. Patients were randomly assigned to NA-831 at a daily dosage of 10 mg- 30 mg or matched placebo (1:1). The primary outcome measures were the changes in ADAS-Cog-13, Brief Cognitive Rating Scale (BCRS) and Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus) after 24 weeks. **Result:** Based on the BCRS, the effects of NA-831 were apparent after 12 weeks of treatment (p=0.001), with the significant improvement in: fatigue, anxiety, irritability, affective lability, disturbance to waking, daytime drowsiness, headache, and nocturnal sleep. NA-831 showed a significant improvement for patients with MCI with ADAS-Cog-13 score change of an average of 3.4 as compared to the placebo (p=0.01). In addition, NA-831 showed a significant improvement for patients with mild and moderate Alzheimer's disease, with ADAS-Cog-13 score change of an average of 4.1 as compared to the placebo (p=0.001). CIBIC-Plus showed 79.3% vs. 21.7 % patients improved; P = 0.01). NA-831 was well-tolerated at high dosage up to 50 mg per day. No adverse effects were observed. **Conclusion**: Over the 24 week treatment period, NA-831 was effective for improving cognitive and global functioning in patients with mild cognitive impairment. As an endogenous compound, NA-831 is well-tolerated and has excellent safety profile. Future Studies: The company plans to start two phase 3 programs: (1) the TREATMENT Phase 3 clinical trial on 465 patients with mild and moderate Alzheimer' disease taking one capsule of 30 mg per day orally over 52 weeks; (2) the PREVENTION Phase 3 clinical trial on 585 asymptomatic subjects taking one capsule of 10 mg per day over 104 weeks.

LB15: THE CHARIOT-PRO SUBSTUDY: BASELINE CHARACTERISTICS OF THE FULLY ENROLLED COHORT. Gerald NOVAK (1), Susan BAKER (1), Chi UDEH-MOMO (2), Geraint PRICE (2), Tam WATERMEYER (3), Celeste LOOTS (2), Natalia REGLINSKA-MATVEYEV (3), Luc BRACOUD (4), Craig RITCHIE (3), Lefkos MIDDLETON (2) *((1) Janssen R&D, United States, (2) Imperial College London, United Kingdom, (3) University of Edinburgh, United Kingdom, (4) Bioclinica, France)*

Background: There is limited information to guide choice of cognitive outcomes for clinical trials in the earliest stages of Alzheimer's disease (AD), where biomarker evidence of Alzheimer's pathology is present without overt cognitive change. Ideal cognitive outcomes at this stage should show a rate of change attributable to nascent Alzheimer's pathological change that is measurable within clinical trial timeframes. Recently, Donohue et al (2017) proposed using a modified Preclinical Alzheimer's Cognitive Composite (PACC), consisting of the sum of standardized z-scores on 4 cognitive measures of memory, executive function and global cognition. As several different observational datasets have been used retrospectively to derive the PACC (Donohue et al, 2014), the specific cognitive components have varied. A prospectively-defined version of the PACC has been used as the primary outcome in 2 randomized clinical trials of preclinical AD, the ongoing A4 study of solanezumab (NCT02008357) and the recently-discontinued EARLY study of atabecestat (NCT02569398). This version of the PACC has been adopted for the present study. Conversely, in our initial CHARIOT PRO Main Study and in the European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (NCT02804789), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) - composite score has been chosen as primary outcome. **Objectives**: CHARIOT-PRO Substudy (CPSS) aims to compare the rate of change over 3.5 years for the PACC and RBANS in cognitively unimpaired elders with biomarker evidence of above-threshold brain amyloid, compared to elders with below-threshold for amyloid. We present here an interim summary of data obtained at baseline in the fully-enrolled CPSS cohort. **Methods**: Participants were men and women aged 60-85 years with global Clinical Dementia Rating (CDR) scale = 0 and all RBANS index scores no worse than -1.5 sd (though some individuals with isolated scores falling below this were included upon adjudication). All participants had a reliable study partner and were in good general and psychiatric health with no other potential causes of dementia or exclusionary MRI findings; none were receiving medications that might affect cognition. Participants completing clinical and MRI screening underwent an amyloid assessment via PET or lumbar puncture. The investigators and study participants were blinded to amyloid status; an interactive web response algorithm ensured that equal numbers of amyloid positive (A+) and negative (A-) individuals were enrolled. Other screening assessments included the PACC, the CDR, the cognitive function index (CFI) and the Alzheimer Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) questionnaires. The RBANS was administered after the PACC at screening, and again within 1-10 days prior to the baseline visit. At baseline, the National Adult Reading Test and the Neuropsychological Assessment Battery – Memory and Executive subscales were administered. The PACC consists of the Free and Cued Selective Reminding Test (FCSRT), the Logical Memory story from the Wechsler Memory Scale – Revised, the Coding subtest on the Wechsler Adult Intelligence Scale IV, and the MMSE. Each component score was transformed into a z-score based on the mean and standard deviation of the entire population, and these were summed to form the composite. The RBANS includes 12 subtests combined within 5 cognitive domains, Immediate and Delayed Memory, Language, Attention and Visuospatial Construction, yielding a standardized index score for each domain as well as a composite index score. In addition to the sequences used to determine MRI eligibility, 3DT1 MRI sequences were obtained. Regional volumes and cortical thickness were derived using Freesurfer 5.3; volumes were corrected for total intracranial volume. **Results**: Amyloid status was determined in 228 participants by CSF and in 1156 by PET (639 florbetaben, 195 florbetapir, 322 flutemetamol) PET. A total of 519 were enrolled, including 258 A+ and 261 A-. The 2 groups were well matched demographically, except that A+ participants were slightly older (72.4 [5.7] vs 70.4 [5.3] years) and more likely to be ApoE4 carriers (55.6% vs 23.0%). There were no differences in gender (overall, 50.5% female), education (overall, 73.2% with some college), concomitant medications, or other medical diagnoses. A+ participants showed worse performance for the PACC sum of z-scores (-0.40 [2.56] vs 0.39 [2.71]; p<-0.0007) and for the RBANS immediate memory index score (107.4 [13.6] vs 111.2 [12.9]; p=0.001) and delayed memory index score (102.4 [11.7] vs 105.3 [9.8]; p=0.002), though differences were not significant for the total index score (105.8 [13.2] vs 107.5 [12.6]; p=0.15). There were no significant differences in whole brain, ventricular, hippocampal volume or in cortical thickness in AD-signature regions. **Conclusions**: The CPSS will provide a head-to-head comparison of the rate of change in 2 cognitive outcomes proposed for use in therapeutic trials of preclinical AD. While cross-sectional comparisons may not be predictive of longitudinal changes, lower values on both scales for the amyloid positive individuals indicate a potential sensitivity to the impact of Alzheimer's pathology in this cohort.

LB16: ASSOCIATION BETWEEN NEURACEQ LEVELS AND [18F]PI-2620 TAU PET TRACER ACCUMULATION IN BASELINE SCANS OF THE ELENBECESTAT MISSIONAD PROGRAM. Andrew STEPHENS (1), Santi BULLICH (1), Andre MUELLER (1), Mathias BERNDT (1), Susan DE SANTI (1), David SCOTT (2), Katarzyna ADAMCZUK (2), Joyce SUHY (2), June KAPLOW (3), Monique GIROUX (3), Stephen KRAUSE (3), Julia CHANG (3), Bruce ALBALA (3) *((1) Life Molecular Imaging, Germany, (2) Bioclinica, United States, (3) Eisai Inc, United States)*

Objectives: [18F]PI-2620 is a novel tau PET-tracer that accumulates in regions of tau pathology. The study objective was to evaluate regional tau deposition using [18F]PI-2620 PET tracer in a sub-study of the elenbecestat MissionAD program in patients with MCI due to AD or mild AD dementia and to correlate it to the amount of amyloid-beta deposition as determined by Neuraceq PET in this unique patient population. **Methods**: Patient 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 were amyloid PET positive by visual read of Neuraceq PET scan. Neuraceq composite SUVr (cSUVr) was calculated using the mean SUVR from frontal, parietal, lateral temporal, anterior and posterior cingulate and occipital cortex. The study

population was divided into 4 groups based on Neuraceq cSUVr levels. The lowest threshold, cSUVr =1.25, was determined from 2 SD above a group of 70 young healthy controls (age: 20-40). The 2nd threshold 1.48 was determined from the Phase 3 histopathology data as the point that differentiated low/sparse plaques from moderate/frequent plaques. The Neuraceq positive group, cSUVr > 1.48, was divided in half to create two equal size groups. These groups are designated very low, low, intermediate and high amyloid-beta. [18F]PI-2620 PET scans were obtained from 60-90 min p.i.. Individual MRI-based subregions including hippocampus (HC), parahippocampus (PHC), amygdala, fusiform gyrus and others were investigated by SUVr analysis. Cerebellar cortex was used as reference region (vermis and anterior cerebellar gray matter contiguous to the vermis was excluded). Z-score maps were generated using a template of n=10 healthy control subjects for comparison. In a region-by-region comparison between the HC and MissionAD subjects, SUVr mean +3 SD was used. Visual assessment of [18F] PI-2620 tau PET scans was performed as well. Scans with uptake above cerebellar background in mesial-temporal, temporo-parietal and cortical regions were considered positive. **Results**: 78 visually amyloid-beta positive subjects were included in the tau PET substudy. Tau PET scans of 77 subjects were evaluable (mean age 75.9 ± 6.5 yrs). The MMSE in the tau PET group was 27.0±1.7; CDR-SB was 2.34±0.97. [18F]PI-2620 accumulation was observed in 52% and 61% by visual and quantitative assessment, respectively, in the overall population. 38 subjects were positive both visually and quantitatively (49%), 9 subjects were only positive quantitatively (12%) and 2 subjects were visually positive only. 28 subjects were negative both visually and quantitatively (36%). A third of the apparent tau positive cases had isolated mesial temporal uptake consistent with early disease. A strong correlation was seen between amyloid-beta load and [18F]PI-2620 accumulation. All subjects with very low amyloid-beta (cSUVr < 1.25) were visually tau PET negative. 19% of Subjects in the low amyloid "grey-zone" (1.25 ≤ cSUVr ≤ 1.48) were visually tau PET positive. 48% of subjects with intermediate amyloid-beta 1.48<cSUVr ≤ 1.73 and 79% of subjects with high amyloid-beta cSUVr > 1.73 were found tau PET positive. **Conclusion**: Tau PET positivity was highly associated with amyloid-beta load. The lowest amyloid load with positive [18F]PI-2620 deposition in this population was cSUVr = 1.43. The subjects recruited in the MissionAD tau PET substudy represents a very early AD population.

LB17: EXPLORING THE PATTERNS OF COGNITIVE SYMPTOMS TRACKED BY CAREGIVERS AND PATIENTS IN ONLINE SYMPTOM PROFILES. Kenneth ROCKWOOD (1, 2), Taylor DUNN (2), Jovita BALCAITIENE (3), Susan HOWLETT (1, 2) *((1) Dalhousie University, Canada, (2) DGI Clinical, Canada, (3)Nutricia, Netherlands)*

Background: Existing mild cognitive impairment (MCI) guidelines suggest no treatment. This conclusion stems from performance on standardized tests. Might data from patients or their carers on the symptoms that they experience, and their importance, suggest a different understanding? The SymptomGuide® Dementia app (SG-D) tackles the heterogenous manifestations of cognitive impairment by allowing users (patients and/or caregivers) to identify, describe, and track their most important symptoms. Since its web launch in 2006, over 4000 users have created individualized profiles, from a menu now grown through clinician, patient and caregiver input to 67 symptoms. These many symptoms highlight how the heterogeneity of cognitive impairment challenges measurement and treatment. Objective: Using a novel supervised staging algorithm, we explored, in the SG-D database, how symptom characteristics and patterns varied across degrees of cognitive impairment. **Methods**: Staging: We analyzed baseline profiles recorded from 2006-05-15 to 2018-11-15. Patient age and symptoms formed inputs to a supervised Support Vector Machine learning algorithm to classify profiles as either MCI, or Mild, Moderate or Severe dementia. We trained the algorithm using symptom profiles from a memory clinic and two dementia clinical trials that each used Goal Attainment Scaling. (See poster 00164 for details on the algorithm training and performance of the model.) Analysis: Across stages, we compared symptom tracking frequency and descriptions (each symptom lists 8-12 descriptors of specific manifestations; users can also add their own). We also analyzed symptom potency. Users can rank symptoms by importance from 1 (least important) to N (most important; the number of symptoms tracked). We calculated individual potency rankings as a weighted rank (rank/N) for each user's symptoms. Descriptive statistics were calculated as percentages, means ± standard deviations, or medians [25-75th percentiles], as appropriate. **Results**: Of 4213 users, data were insufficient for staging on 304 (7.2%; no age provided, and/or only one symptom) yielding 3909 baseline profiles. The staging algorithm classified 916 MCI, 1592 Mild, 514 Moderate and 876 Severe profiles. Average patient age generally increased with stage: 71±13, 74±13, 81±13, and 78±13, for MCI, Mild, Moderate and Severe, respectively. MCI profiles tracked fewer symptoms (median 2) versus profiles in Mild (5), Moderate (7), and Severe (4) dementia. The most frequently tracked MCI symptoms were Recent Memory (33.4% of profiles), Verbal Repetition (22.8%), and Language Difficulty (15.6%). Eight of the 10 most frequently tracked symptoms were common to both MCI and Mild profiles. Insensitivity and Social Withdrawal ranked higher in MCI, versus Comprehension, and Sleep Disturbances in Mild. Symptom overlap decreased with increasing severity: 5/10 and 1/10 of the top MCI symptoms were shared with Moderate and Severe profiles, respectively. Language Difficulty was the symptom shared by MCI (15.6% of profiles) and Severe dementia (14.4%) but was distinguishable in its specific descriptions. At the descriptor level, Language Difficulty in MCI most often referred to "Complains of not being able to say what they mean" versus "Has trouble explaining a thought or idea" or "Relies on others to guess what they mean" in Severe. The most important symptoms typically were among the least frequent. For example, the top three symptoms tracked among all profiles were Travel, Hobbies/Games and Looking After Grandchildren. Their median weighted ranks were 0.90, 0.83 and 0.82, but were tracked only in 4.2%, 8.4% and 2.0% of profiles, respectively. Only Impaired Initiative was both frequent (14.3%) and potent (median weighted rank 0.75). This discrepancy between frequency and potency was consistent across stages. The most important symptoms ranked by MCI profiles were Inappropriate Language (median rank 1; 4.0%), Incontinence (1; 1.1%), and Operating Gadgets/Appliances (1; 1.0%). Across all stages, four symptoms were common to all top 10 most important: Hobbies/Games, Looking After Grandchildren, Operating Gadgets/Appliances and Travel. In contrast, no symptoms among the top 10 were the most frequent at any stage. **Conclusion**: In complex illnesses with cognitive impairment, involving patients and their families/

caregivers through individualized symptom tracking is self-evidently clinically meaningful. Here, we used an online cognitive symptom tracking tool to gain insights into what is most important to people with cognitive impairment and their caregivers at each stage. We found a high degree of overlap in the most frequent MCI and Mild dementia symptoms. In contrast there was little overlap between MCI and later stage dementia. Across all stages, symptom potency was inversely related to symptom frequency. The most important symptoms consistently concerned leisure and family. Online tracking can help clinicians to take a personalized approach towards management of patients with cognitive impairment. These findings will inform further research in MCI.

LB18: APTUS-AB™: MEASUREMENT OF PLASMA AB42/40 CONCENTRATION RATIOS BY MASS SPECTROMETRY PREDICTS BRAIN AMYLOIDOSIS IN BANKED SAMPLES FROM MULTIPLE, DIVERSE COHORTS. Tim WEST, Kristopher KIRMESS, Matthew MEYER, Mary HOLUBASCH, Stephanie KNAPIK, Yan HU, Philip VERGHESE, Erin SMITH, Scott HARPSTRITE, Ilana FOGELMAN, Joel BRAUNSTEIN, Kevin YARASHESKI *(C2N Diagnostics, United States)*

C2N Diagnostics has developed the APTUS-Aβ™ blood test, a mass spectrometry-based assay that measures concentrations of Aβ42 and Aβ40 in a single 0.5 mL plasma sample. In 2018 the APTUS-Aβ™ test received a Breakthrough Device Designation from the U.S. FDA as a test to screen for Alzheimer's disease risk. In the process of completing preliminary validation of the APTUS-Aβ™ test, C2N has analyzed over 350 samples (blinded) from 5 different existing biobank cohorts and compared the plasma Aβ42/40 concentration ratios to each cohort's definition of amyloid positivity. Three cohorts used amyloid imaging by either PIB or Amyvid, one cohort used CSF Aβ42/40 by ELISA, and one cohort used CSF Aβ42/40 by mass spectrometry. Plasma Aβ42/40 ratio was significantly ($p < 0.001$) lower in the amyloid positive vs. negative subgroups in each cohort. When analyzing diagnostic performance using receiver operator characteristic curves (ROC), the area under the curve (AUC) ranged between 0.81 and 0.91 for the 5 cohorts. As a complement to the APTUS-Aβ™ blood test, C2N has developed an ApoE proteotyping assay that establishes APOE genotype from the same plasma sample used for measuring Aβ. For each cohort the diagnostic accuracy and ROC-AUC improved to 0.85-0.94 when the Aβ42/40 ratio was combined with the APOE genotype status and participant age at the time of plasma sample collection. For cohorts using similar methods of sample collection and similar definitions of amyloid positivity, the cut point for the APTUS test was similar, demonstrating the versatility of the APTUS™ test when applied to samples from diverse participant cohorts. C2N also found significant agreement when APOE genotypes were compared to ApoE proteotypes (ApoE genotype defined by presence or absence of various ApoE2/3/4 specific peptides). In conclusion, the APTUS-Aβ™ blood test accurately predicts brain amyloidosis, especially when combined with ApoE proteotyping, and has potential to screen cognitively normal and impaired individuals for brain amyloidosis.

LB19: IN VIVO MEASUREMENT OF WIDESPREAD SYNAPTIC LOSS IN EARLY ALZHEIMER'S DISEASE WITH SV2A PET. Christopher VAN DYCK, Adam MECCA, Ming-Kai CHEN, Ryan O'DELL, Mika NAGANAWA, Takuya TOYONAGA, Tyler GODEK, Joanna HARRIS, Hugh BARTLETT, Wenzhen ZHAO, Nabeel NABULSI, Brent VANDER WYK, Pradeep VARMA, Amy ARNSTEN, Yiyun HUANG, Richard CARSON *(Yale School of Medicine, United States)*

Background: Synaptic loss is an early and robust pathology in Alzheimer disease (AD) and the major structural correlate of cognitive impairment. In a small preliminary study using [11C] UCB-J–PET we have previously shown significant reductions in hippocampal SV2A specific binding as a marker of synaptic density in participants with AD (Chen M, et al. Assessing synaptic density in Alzheimer disease with synaptic vesicle glycoprotein 2A positron emission tomographic imaging. JAMA Neurol. 2018;75:1215). However, postmortem studies have suggested more widespread neocortical reductions in synaptic density in AD. **Methods**: In the present study we measured SV2A binding in a larger sample of participants with early AD and cognitively normal (CN) individuals. Participants were scanned on the HRRT after bolus injection of [11C]UCB-J. We first re-examined and compared the suitability of reference regions (the white matter of centrum semiovale [CS]—which we previously used—versus cerebellum [Cb]) in a subset of participants who had undergone arterial blood sampling for 1-tissue compartment (1TC) modeling to estimate the distribution volume VT. We compared VT between groups for Cb and CS. We then generated parametric images of BPND for the full participant sample using SRTM2 and CS as the reference region. DVR with a CS reference region (DVRCS) = BPND+1. Finally, DVR with a Cb reference region (DVRCb) of each voxel was computed from DVRCS as (BPND+1)/(BPND[Cb]+1). **Results**: The study sample consisted of 34 participants with early AD (MMSE = 23.1±4.1, CDR = 0.5-1.0), who were all Aβ+ by [11C]Pittsburgh Compound B [11C]PiB) PET and spanned the disease stages from amnestic Mild Cognitive Impairment (aMCI, n = 14) to mild dementia (n = 20); and 19 who were CN (MMSE = 29.3±1.1, CDR = 0) and confirmed Aβ– by [11C]PiB PET. In the subset of participants (18 AD, 12 CN) with arterial blood sampling, values of VT were very similar between groups for CS and Cb, supporting the validity of both reference regions. Moreover, values of DVRCb converted from DVRCS (obtained from SRTM2) were very highly correlated with values of DVRCb obtained with the 1TC model across all brain regions. Finally, values of DVRCb showed considerably lower variability than DVRCS across brain regions of interest, suggesting it's practical superiority in AD studies. Our primary analysis of group differences in SV2A binding demonstrated a significant effect of group ($F(1,51) = 33.4$, $P < 0.00001$) and group*region ($F(10,510) = 2.4$, $P = 0.01$) as predictors of SV2A binding (DVRCb). Post-hoc comparisons revealed significant group differences in all medial temporal regions, as well as more broadly in neocortical regions. SV2A reductions in AD compared to CN participants were most pronounced in the hippocampus (DVRCb –17.3%, $P < 0.00001$; BPND –19.8%) and entorhinal cortex (DVRCb –15.7%, $P < 0.00001$; BPND–17.6%) but were also present in the parahippocampal cortex, amygdala, lateral temporal cortex, prefrontal cortex, posterior cingulate cortex/precuneus, lateral parietal cortex, and pericentral cortex.

These reductions were largely maintained after correction for volume loss and were more extensive than decreases in gray matter volume. **Conclusion**: We observed widespread reductions of synaptic density with [11C]UCB-J PET in medial temporal and neocortical brain regions in early AD compared to CN participants. Most of these reductions were maintained after PVC and thus are not attributable solely to gray matter tissue loss. Further longitudinal studies are needed to characterize the temporal course of synaptic alterations in AD in relation to amyloid and tau deposition, as well as the associations with cognitive and functional change. Future studies will continue to evaluate the utility of SV2A PET for tracking AD progression and for monitoring potential therapies.

LB20: NOVEL ANALYTICS FRAMEWORK FOR AUGMENTING SINGLE-ARM PHASE 2A OPEN LABEL TRIALS WITH REAL-WORLD EXTERNAL CONTROL DATA: APPLICATION TO THE BLARCAMESINE (ANAVEX®2-73) STUDY IN ALZHEIMER'S DISEASE MATCHED WITH PROPENSITY CORRECTED PATIENTS FROM ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI) EXPLORING TREATMENT EFFECT ON COGNITION AT INTERIM TWO-YEAR (104-WEEK) TIMEPOINT. Mohammad AFSHAR (1), Coralie WILLIAMS (1), Nanthara SRITHARAN (1), Frederic PARMENTIER (1), Federico GOODSAID (2), Christopher MISSLING (3) *((1) Ariana Pharma, France, (2) Regulatory Pathfinders, United States, (3) Anavex, United States)*

Background: Employing a real-world (RW) external control arm to obtain registration and accelerate reimbursement is gaining momentum. Recent examples have been described in Oncology where a RW external control arm cohort of 77 ceritinib-treated patients was compared to the Phase II single-arm alectinib patients and successfully submitted to regulatory authorities. Additionally, FDA's Framework for Real World Evidence document released in December 2018 demonstrates how Real World Evidence can be incorporated into regulatory decision making. This framework was applied to the study of Blarcamesine(ANAVEX®2-73), a selective sigma-1 receptor (SIGMAR1) agonist that was investigated in an open-label 57-week Phase 2a study of Alzheimer's Disease (AD) patients (N=32) showing a favourable safety profile (NCT02244541) and was further extended by 208 weeks (NCT02756858). A hypothesis free data-driven analysis using Formal Concept Analysis Machine Learning as implemented in Knowledge Extraction and Management (KEM) software platform was used to identify exploratory efficacy and patient selection biomarkers including SIGMAR1 p.Q2P (rs1800866). Individual patient-level data (IPD) was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is a longitudinal multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD. A total of 1891 patients were followed in this study including 345 AD patients with available Mini Mental State Examination (MMSE) scores. **Objectives**: The overall goal of developing external control arms is to enable single-arm registration trials to be executed with reduced time and costs. An additional goal of this study is to evaluate the efficacy of Blarcamesine,measured by MMSE and comparing treated patients with an external control AD cohort of patients from ADNI database over a 104-week period. **Methods**: A matching on propensity scores (PS) was applied to select patients with similar baseline characteristics and any confounding factors between AD patients in the Phase 2a Blarcamesinecohort and AD patients from the ADNI control cohort. The logit propensity score was estimated by regressing treatment assignment on previously identified and similarly defined key prognostic factors and baseline characteristics within the population (i.e. age, sex, SIGMAR1 p.Q2P, APOE4 and MMSE at baseline). MMSE change from baseline (DeltaMMSE) was modeled using Mixed Model Repeated Measures (MMRM), with a linear time effect hypothesis, and Linear Mixed Effect (LME). DeltaMMSE was compared between the treated cohort having high concentration and treated cohort with low concentration with the external ADNI control cohort. DeltaMMSE scores were adjusted for age, sex, carrier status of the APOE4 allele, the interaction between the APOE4 allele and the time. The carrier status of variant SIGMAR1 p.Q2P (rs1800866) was also included in the model. **Results**: Change in MMSE score from baseline at week 104 of matched cohorts was adjusted using LME models using descriptors of age, sex, SIGMAR1 p.Q2P carrier status, APOE4 allele and MMSE at baseline. It shows that Blacarmesinetreated cohort has a significantly lower adjusted DeltaMMSE decline (-0.7) compared to the ADNI control cohort (-5.2) at week 104 ($p = 0.05$). Furthermore, the cohort with a high Blacarmesineplasma concentration showed a significantly lower adjusted DeltaMMSE decline (-1.1) compared to the ADNI control cohort (-4.4) at week 104 ($p < 0.01$). The cohort with a low Blacarmesineplasma concentration showed a non-significant smaller DeltaMMSE decline at week 104 (-3.9) compared to the ADNI control cohort (-4.4) ($p= 0.71$). **Conclusions**: Compared to the matched external AD control patient cohort, the presented exploratory efficacy analysis at interim 104-week shows that the cohort of patients with high Blarcamesineconcentration had less cognitive decline based on change of MMSE scores from baseline throughout the duration of the trial. APOE4 carrier status was significantly associated with DeltaMMSE. Although this analysis is limited by the small number of patients treated, this new approach of precision medicine, which incorporates RW data such as IPD could become a template for efficacy analysis of small cohort single-arm open label studies in AD. Robust analytics and quality data will be required to avoid issues of selection bias, confounding factors and misclassification leading to biased interpretation. A larger placebo-controlled AD Phase 2b/3 Blarcamesine study is currently ongoing.

LB21: SHOULD WE BE USING ARTIFICIAL INTELLIGENCE, MACHINE LEARNING, AND BIG DATA TECHNIQUES TO IMPROVE OUR CHANCES OF SUCCESS IN ALZHEIMER'S CLINICAL RESEARCH? Newman KNOWLTON, Sam DICKSON, Suzanne HENDRIX *(Pentara Corporation, United States)*

Background: Alzheimer's disease studies have a high rate of failure. Because clinical trials are regulated, the analysis methods are often traditional approaches that are standard for each disease area. In the past several years, significant advances have been made in analytic approaches based on increased computing power and the availability of more sophisticated models. Can the application of machine learning, artificial intelligence, and big data techniques increase the chances of success in Alzheimer's clinical trials or are these

just buzzwords thrown out to impress people? **Objectives**: Educate the research community about jargon associated with analytic approaches, enabling appropriate use of these techniques to advance AD research. **Methods**: We provide an overview of newer analytic approaches and their strengths and weaknesses. We compare these methods to traditional approaches to determine where the newer approaches offer an advantage. We describe data and scenarios that lend themselves to the strengths of each of these methods as well as situations where they aren't helpful. **Results**: Newer Techniques: AI: Artificial intelligence (AI) is merely intelligence demonstrated by machines, as opposed to naturally evolved intelligence. It can be used to spot errors in data entry and may be valuable for identifying components of a treatment that should be targeted to specific individuals based on response. Machine Learning: "Machine learning (ML) is the scientific study of algorithms and statistical models that computer systems use to perform a specific task without using explicit instructions, relying on patterns and inference instead." It is a subset of AI that can process big data and find patterns unrecognizable by humans. It can reduce human bias. Big Data: "Big data usually refers to data sets with sizes beyond the ability of commonly used software tools to capture, curate, manage, and process data within a tolerable elapsed time." Analytic methods specific to big data can be used to query big health databases to look for patterns. Brain scans such as EEG and MRI images result acquisition of big data. Data Mining: Data mining is the process of discovering patterns in large data sets involving methods at the intersection of machine learning, statistics, and database systems. Most of what we currently do with historic datasets could fall into this category. Neural Network: "An artificial neural network is a network or circuit composed of artificial neurons or nodes and describes a machine learning technique often used for solving artificial intelligence (AI) problems." Other ML Techniques: Support Vector Machines, Random Forest Models, and Naive Bayes Classifiers are all examples of machine learning approaches based on different modeling approaches.Traditional Techniques: Principal Components and Factor Based **Methods**: These are dimension reduction techniques that identify similar and separate aspects of disease severity on the basis of correlations and redundancy. Cluster analysis and Discriminant Analysis: These are straightforward analytic methods that are used in machine learning but are equally effective as traditionally applied. Regression analysis Standard regression models have been around since 1805 but are still the basis of many machine learning approaches. More sophisticated logistic regression models are related and equally useful for many analytical problems. **Conclusions**: In general, newer analytic approaches are impressive sounding, but are often just rebranded versions of methods that have been around for centuries. They often don't fit the problems that we need to address most in AD clinical development. There are AD research settings where they are valuable, but in most clinical settings, they add complexity without added value. Sometimes searching for a good application for a novel-sounding and fashionable method can add value to an analysis, however, the AD field should be identifying the best analytic tools for solving each specific problem that comes up, rather than looking for a way to apply a trendy analytic approach for its own sake. Traditional techniques such as dimension reduction using principal components based methods, standard clustering methods, and longitudinal statistical modeling almost always provide more value with less convolution.

LB22: CUT POINTS FOR COGNITIVE DECLINE USING MMSE DEFINE BASELINE AND LONGITUDINAL DIFFERENCES IN BOTH CLINICAL AND PATHOLOGICAL ALZHEIMER'S DISEASE BIOMARKERS. James DOECKE (1), Marcela CESPEDES (1), Cai GILLIS (2), Nancy MASEREJIAN (2), Pierrick BOURGEAT (3), Chris FOWLER (4), Victor VILLEMAGNE (5), Qiao-Xin LI (4), Steven COLLINS (4), Stephanie RAINEY-SMITH (6, 7), Paul MARUFF (4), Ralph MARTINS (6, 8, 9), David AMES (10), Colin MASTERS (4)
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Background: Heterogeneity of disease progression among patients with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) has been observed in multiple observational and clinical studies. Prior work has examined classifying progression into "fast" or "slow" based on change in MMSE score over time. However, definitions of what qualifies as fast and slow progression have varied among studies. Understanding how decline in MMSE score is related to future disease progression has the potential to inform how other pathological and clinical measures, are associated with more severe decline. **Objectives**: In this study, we examined prespecified cut-points of MMSE score change over 18 months to determine how these cut-points were associated with baseline and annual rates of change in other cognitive and clinical measures. **Methods**: Amyloid positive participants (classified as either PET-Aβ+ via a Centiloid value of greater than 20, or a CSF Aβ42 (INNOTEST) value of less than 544ng/L) diagnosed with either MCI or AD from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing were included in the study. Cognitive decline groups were defined as either fast: those participants with a six point or greater loss on the MMSE over a period of 18-months; moderate: those participants with a loss of at least three but less than six points on the MMSE over a period of 18-months; and slow: those participants with a loss on the MMSE of less than three points over 18-months. Unadjusted pairwise comparisons between cognitive decline groups (slow vs. fast decliners, moderate vs. fast decliners) at baseline were performed using Welch's T-test. For longitudinal comparisons of imaging and cognitive measures between cognitive decline groups, Linear Mixed Effects models (LME) with a random intercept was used. **Results**: In our study, a total of 52 participants were classified as fast decliners, 56 participants were classified as moderate decliners and 74 participants were classified as slow decliners. No participants were in two or more groups. Compared with moderate and slow decliners at baseline, fast decliners had lower mean grey matter values (slow decliners: 444.49 [SD: 23.71], moderate decliners: 434.75 [SD:22.8], p=0.02 & fast decliners: 419.69 [SD: 23.57], p=0.0001); lower mean hippocampal volume (compared

with slow decliners only, slow decliners: 5.38 [SD:0.58], fast decliners: 4.65 [SD: 0.77], p=0.0002); lower mean levels of CSF Aβ42 (compared with slow decliners only, slow decliners: 698.44 [SD: 146.49], fast decliners: 512.33 [SD: 50.71], p=0.0007); higher mean CDR Sum of Boxes (CDR-SB) score (slow decliners: 1.05 [SD: 1.07], moderate decliners: 2.74 [SD: 2.2], p<0.0001 & fast decliners: 4.64 [SD: 3.3], p<0.0001); and higher mean AIBL Preclinical Alzheimer's Cognitive Composite (AIBL PACC) scores (slow decliners: -4.39 [SD: 2.75], moderate decliners: -5.9 [SD: 2.6], p=0.002 & fast decliners: -8.36 [SD: 3.04], p<0.0001). Fast, moderate and slow decliners were not significantly different in age, gender, level of education, or APOE ε4 allele status (p>0.05). Annual rates of decline were significantly worse for fast decliners compared to moderate and slow decliners in relation to AIBL PACC score (slow decliners: β: -0.022 [SE:0.02], moderate decliners: β: -0.357 [SE:0.04], fast decliners: β: -0.719 [SE: 0.13], p<0.0001) and CDR-SB (slow decliners: β: 0.025 [SE: 0.02], moderate decliners: β: 0.254 [SE: 0.03], fast decliners: β: 0.579 [SE: 0.03], p<0.0001). Amongst the imaging measures, beta coefficients representing group-wise rates of atrophy for ventricular volume showed the strongest stepwise increases (slow decliners: β: 0.066 [SE: 0.01], moderate decliners: β: 0.154 [SE: 0.02], fast decliners: β: 0.176 [SE: 0.19], p<0.002). Given the majority of participants had only one follow up, values from testing other imaging measures were not stable, and as such are not shown here. Group-wise comparisons from the LME assessments are shown adjusted for age, gender and APOE ε4 allele status, and are conservative estimates given the relative group sample sizes. **Conclusion**: Classifying individuals as fast, moderate and slow decliners by change in MMSE score over 18 months, indicated significant differences among these groups both at baseline and for rate of change in cognitive and imaging measures. These findings suggest that these markers may be useful in identifying those individuals that will have a clinically meaningful change in a short period of time.

LB23: USING AI TO CREATE DIGITAL TWINS TO ACCELERATE ALZHEIMER'S DISEASE CLINICAL TRIALS.
Aaron SMITH, Jonathan WALSH, Charles FISHER *(Unlearn. health, United States)*

Background: Drug development for Alzheimer's disease (AD) is increasingly expensive and time-consuming. Over the last decades, hundreds of well-justified, and well-funded AD clinical trials have failed. This situation has become more dire because increasing competition for subjects from a limited pool of patients will cause more trials to fail.* Thus, to decrease the high failure rate of these trials, it will be necessary to improve clinical trial design by reducing total trial size and/or recruitment time. The randomized controlled trial (RCT) has long been the gold-standard among clinical trial designs. However, RCTs in AD can be very inefficient. Because the standard-of-care has not significantly changed over the years, each new AD RCT recollects the same dataset each time it studies the disease progression of the control group. This redundancy provides an opportunity to improve the efficiency of AD trials, which has been highlighted by the FDA in a number of communications.** With data collected from the control groups of many prior AD trials and state-of-the-art statistical methods, it is possible to build an artificial intelligence (AI) model that can generate synthetic control subject records that are statistically indistinguishable from the records of actual control subjects. Synthetic control subject records can replace or supplement control groups in clinical trials and thus accelerate recruitment—both because the trials would require fewer total subjects, and because subjects have a greater incentive to join a study in which they are highly likely to receive a real treatment.As a further benefit, the AI model can generate a synthetic control subject record paired to each subject in the treatment arm, meaning that the baseline variables of the synthetic record exactly match those of one of the treated subjects. The synthetic control record can thus be regarded as a digital twin of the treated subject and shows how that subject might have progressed had he/she not received the treatment. A trial incorporating digital twin control subjects has even better statistical power than an otherwise identical RCT, further reducing the number of subjects necessary to observe a positive effect. * Based on screening ratio estimates here (https://alzres.biomedcentral.com/articles/10.1186/alzrt58) and up-to-date statistics from CT.gov. **How FDA Plans to Help Consumers Capitalize on Advances in Science (https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/how-fda-plans-help-consumers-capitalize-advances-science) (paragraph 10). **Objectives**: Generating synthetic clinical records of patients with AD that are statistically indistinguishable from those of actual patients under standard-of-care treatment (or placebo). This technology has promise for replacing or supplementing control arms of trials, which will accelerate recruiting and ultimately the time to trial readout. **Methods**: We created an AI model that generates synthetic subject records for AD progression. This is a computational model that captures the relationships between clinical variables relevant to AD (e.g. age, lab test results, ADAS-Cog scores, MMSE scores) as they change over time in an individual. One can specify baseline values of these variables and then use the model to generate synthetic clinical records which predict how these variables are likely to change over time. To get a large and diverse sample of AD control data, we took records from roughly 5,000 subjects with early or moderate AD from the control arms of 16 clinical trials. These data included roughly 50 variables (e.g. vitals, lab test results, ADAS-Cog component scores, MMSE components, ApoE4 allele count) at three month intervals over 18 months. After fitting our model to the dataset, we validated its accuracy by comparing predicted values for all of these variables with those of subjects from a diverse set of data that were not used in fitting the model. **Results**: Our AI model generates synthetic AD subject records that are statistically indistinguishable from actual AD control subject records. In particular, the model accurately captures means, standard deviations, correlations, and autocorrelations of the 50 variables from the dataset. Our results show that our model can provide synthetic subject records that can replace actual control subjects in trials or exploratory studies for AD. It is worth noting that the model recapitulates some of the established knowledge about the disease. For example, analysis of the model demonstrates that the ADAS word recognition score is strongly correlated with fast disease progression even when controlling for overall ADAS-cog score. **Conclusions**: This work highlights a new technology that can significantly decrease the time required to run clinical trials in AD. Unlearn's model, which can generate digital twin control subjects, can provide purely synthetic controls for single-arm exploratory trials or supplementary control data for pivotal trials. Both of these applications significantly reduce the number of trial subjects, reducing recruitment time and bringing new therapeutics to market more rapidly.