The Journal of Prevention of Alzheimer's Disease - JPAD©
Volume 5, Supplement 1, 2018

SYMPOSIA

S1- APECS TRIAL OF THE BACE1 INHIBITOR VERUBECESTAT FOR PRODROMAL ALZHEIMER'S DISEASE.

Jeffrey L. Cummings *(Cleveland Clinic, Las Vegas, NV, USA)*

Introduction: The amyloid hypothesis proposes that Aβ peptides are intimately involved in the etiology of Alzheimer's disease (AD) via their aggregation to form toxic complexes that lead to neurodegeneration. Aβ is produced via sequential proteolytic cleavage of the parent molecule, amyloid precursor protein, by β-secretase (BACE1) followed by γ-secretase. Inhibition of BACE1 is a potential novel therapeutic strategy for slowing or halting progression of AD by reducing Aβ production. This approach differs from previous anti-amyloid approaches using monoclonal antibodies to clear Aβ. In the first large-scale clinical trial (EPOCH) of a BACE1 inhibitor, verubecestat doses of 12 mg and 40 mg were ineffective at slowing the rate of cognitive or functional decline over 78 weeks in participants with clinically diagnosed mild-to-moderate AD, despite reducing cerebrospinal fluid (CSF) Aβ levels by 63-81% (Egan et al. NEJM 2018;378:1691-1703). One interpretation of these findings is that treatment at the AD dementia stage is too late in the disease process. A second large trial (APECS; clinicaltrials.gov NCT01953601) was initiated in 2013 to evaluate verubecestat in participants with prodromal AD. Eligible participants had subjective memory decline with objective memory impairment and were amyloid positive (determined by amyloid imaging PET scan or CSF tau: Aβ42 ratio) but did not meet criteria for dementia. A decision to terminate the APECS trial was made in February 2018 following a recommendation by the external Data Monitoring Committee, which concluded that it was unlikely that positive benefit/risk could be established if the trial continued to its scheduled completion in 2019. **Objectives:** The objectives of this symposium are to present key efficacy and safety findings from the APECS trial and to have a panel of experts discuss the findings and implications for future development of BACE1 inhibitors. Results will be unveiled at CTAD. **Discussion:** The findings from the APECS trial suggest that blocking Aβ production at the prodromal AD stage does not slow clinical progression. Because the deposition of Aβ takes place years before the prodromal stage, it is possible that administration of an anti-amyloid agent like verubecestat may be effective if given even earlier in the disease process. An alternative possibility is that the production of Aβ peptides may not play a major causal role in the pathophysiology of AD. **Conclusions:** Verubecestat was not effective in slowing clinical progression in participants with prodromal AD.

Communication 1: *Results from the APECS trial*, Michael F. Egan[1], Tiffini Voss[1], Yuki Mukai[1], James Kost[1], Paul S Aisen[2], Jeffrey L. Cummings[3], Pierre N. Tariot[4], Bruno Vellas[5], Christopher H. van Dyck[6], Ying Zhang[1], Wen Li[1], Christine Furtek[1], Erin Mahoney[1], Lyn Harper Mozley[1], Yi Mo[1], Cyrille Sur[1], David Michelson[1] ((1) Merck & Co., Inc., Kenilworth, NJ, USA; (2) University of Southern California, San Diego, CA, USA; (3) Cleveland Clinic, Las Vegas, NV, USA; (4) Banner Alzheimer's Institute, Phoenix, AZ, USA; (5) Gerontopole, INSERM U 1027, Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital, Toulouse, France; (6) Yale University School of Medicine, New Haven, CT, USA)

Communication 2: *Panel discussion*, Paul S. Aisen[1], Maria C. Carrillo[2], Pierre N. Tariot[3], Bruno Vellas[4] ((1) University of Southern California, San Diego, CA, USA; (2) The Alzheimer Association, Chicago, IL, USA; (3) Banner Alzheimer's Institute, Phoenix, AZ, USA; (4) Gerontopole, INSERM U 1027, Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital, Toulouse, France)

S2- IS BACE1 A SUITABLE DRUG TARGET FOR PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE?

Randall J. Bateman *(Department of Neurology, St. Louis, MO, USA)*

Introduction: The beta-secretase BACE1 is a major drug target for Alzheimer's disease (AD), as it catalyzes the first step in amyloid beta (Aβ) generation. Pharmacologic BACE1 inhibition reduces Aβ generation in vitro and in vivo, both in animals and in humans. Several clinical trials currently test BACE1 inhibitors for a treatment or even a prevention of AD. Yet, the suitability of BACE1 as a drug target has been challenged, given the recent termination of several clinical trials with BACE inhibitors, such as verubecestat or atabecestat. **Objectives:** The symposium will address key questions related to the use of BACE1 as a drug target. 1. Have the previous clinical trials really cast doubts on the suitability of BACE1 as a drug target? 2. What is the best time point to do BACE1 inhibitor treatments – primary or secondary prevention or treatment? 3. Can biomarkers beyond Aβ be used to maximize inhibitor efficiency while reducing side effects? If yes, which substrate-based biomarkers are best suited? 4. Are mechanism-based side effects to be expected? If yes, how can they be prevented or managed? **Discussion:** Two of the recent BACE inhibitor trials were stopped because of liver toxicity. This is assumed to be an off-target effect of the specific inhibitors used, because a) it was not observed in the other trials, b) because BACE1 is only expressed at low levels in liver and c) because BACE1-deficient mice do not show signs of liver dysfunction. Other trials were discontinued as no positive outcome was observed on cognition of patients with AD or mild cognitive impairment (MCI). One way to interpret these results is that BACE1 is in general not a suitable drug target for AD. Another interpretation is that BACE1 inhibition and the resulting Aβ reduction is not sufficient once the clinical symptoms have started, and that lowering Aβ generation instead needs to be done even before the MCI stage. Thus, BACE1 inhibitors are expected to be most efficient when tested in secondary or even primary prevention trials. The first such trials have just started. Prevention trials present their own challenges, which partly result from the finding that BACE1 has multiple physiological substrates beyond the amyloid precursor protein from which Aβ is generated. Thus, BACE1 inhibition may not only lower Aβ generation, but also interfere with the other substrates' functions. For example, pharmacologic BACE1 inhibition in adult mice revealed muscle spindle-induced motor deficits through loss of cleavage of the substrate neuregulin-1 (NRG1) and altered long-term potentiation through loss of cleavage of another substrate, seizure protein 6 (SEZ6). As a consequence, prolonged BACE1 inhibition may potentially induce mechanism-based side effects in humans. In fact, an increased rate of falls and psychiatric symptoms were observed in the recently terminated EPOCH trial with one BACE1 inhibitor, but it remains unclear whether these side-

J Prev Alz Dis 2018;5(S1):S1-S44
Published online October 4, 2018, http://dx.doi.org/10.14283/jpad.2018.39

effects were truly mechanism-based and depended on the reduced cleavage of NRG1 and SEZ6. Another challenge of currently tested BACE inhibitors is that they do not only block BACE1, but also the homologous protease BACE2, which has a function in pigmentation. In fact, a recent phase 3 trial revealed changes in hair color in AD patients treated with the BACE inhibitor verubecestat. These challenges become particularly germane in the setting of trials that require years of dosing to test primary outcomes. These challenges have partially led to the belief that safe BACE1 inhibition may not be feasible in humans. Yet, there are multiple ways to control, reduce and manage potential side effects. Exploring and discussing them is a major aim of the symposium. For example, based on animal experiments where approximately 30% Aβ reduction over the lifetime prevented plaque formation, it appears possible that lower inhibitor doses may be sufficient for long-term prevention trials. This may allow enough remaining BACE1 activity to avoid or reduce mechanism-based side effects. Additionally, BACE1 substrate cleavage products are found in body fluids, such as cerebrospinal fluid and may be used as companion diagnostics in addition to Aβ to control individual dosing and the appearance of mechanism-based side effects. Another approach is to develop BACE inhibitors that preferentially inhibit BACE1 over BACE2, thus avoiding side effects resulting from BACE2 biology. **Conclusion:** In summary, a major aim of this symposium is to discuss the current state of BACE inhibitors as well as the challenges, but also the chances that lie ahead to conduct safe clinical trials for efficiently testing the suitability of BACE1 as a drug target to prevent AD.

Communication 1: *Physiological substrates of BACE1: safety issues or biomarkers?* Stefan F. Lichtenthaler (German Center for Neurodegenerative Diseases (DZNE) and Technical University of Munich (TUM), Germany)

Communication 2: *Secretase Inhibitors in AD Prevention Trials: optimizing success and mitigating risk,* Eric McDade (Department of Neurology, St. Louis, MO, USA)

Communication 3: *Considerations and Lessons Learned for the Design and Implementation of AD Clinical Trials Evaluating BACE Inhibitors,* Bruce Albala, Johan Luthman (Eisai, Inc., NJ, USA)

S4- Aβ BLOOD BASED TEST AS SURROGATE MARKERS OF CORTICAL AMYLOID PATHOLOGY FOR CLINICAL TRIALS ON ALZHEIMER'S DISEASE. Pedro Pesini *(Araclon Biotech-Grifols, Spain)*

Introduction: Large research initiatives in biomarkers like ADNI, AIBL and others have been crucial for the current shift in the AD paradigm which is transforming the therapeutic target population for clinical trials from people with dementia or mild cognitive impairment (MCI) to cognitively healthy people at risk. However, these people are not easy to find in community settings and when Aβ positivity is a criterion for eligibility the randomization rate for AD prevention trials falls to 10-20%. Under these conditions, the use of Aβ-PET scans for screening and/or as outcome measure represents a huge operational burden on any clinical trial, reducing its feasibility and increasing costs considerably. While significantly less expensive than Aβ-PET, cerebrospinal fluid (CSF) analysis with the need for repeated lumbar punctures is unsuitable for periodic population assessments, while also acting as a deterrent for enrolment into trials. These trials have been noted as a top research priority to help prevent, and effectively treat AD in the shortest timeframe possible. To that effect, the discovery and development of widely accessible and inexpensive blood-based disease-specific biomarkers will allow selection of a population-based sample, reducing the rate of screening failure for prevention trials. In line with this we have gathered a panel of experts in the field to review the state of the art in blood-based biomarkers correlated to neuroimaging, and its applicability to clinical trials in early AD stages. These could be developed into useful biomarkers for pre-screening, population sample enrichment, and most importantly as part of a viable management strategy of the elderly population in the primary care setting. Eventually, these blood-based biomarkers could be validated to assess target engagement and as outcome measure in clinical trials. **Objectives:** The objectives of this symposium are i) to briefly review the robustness and validation of Aβ quantification in plasma ii) to review the performance of Aβ blood-based test correlated to neuroimaging and CSF biomarkers, and iii) to discuss the next steps for the development of Aβ blood-based tests into useful tools in the framework of current clinical trial and future patient management approaches. **Discussion:** ABtest is an ELISA based test whose most outstanding characteristic is the robust and reproducible quantification of free and total Aβ40 and Aβ42 in plasma. The test is fully validated, including reproducibility against mass spectrometry determinations. Clinical assessment has shown that the best biomarker candidate is the total Aβ42 / total Aβ40 plasma ratio (TP42/40). The AB255 study was a multicenter, longitudinal study to evaluate the potential of plasma Aβ biomarkers in identifying early stages of AD and predicting cognitive decline over the following two years. Participants were recruited and assessed at 19 clinical memory research sites in Spain, Italy, and Sweden. The study included 83 cognitively normal (CN) individuals and 145 with probable amnestic mild cognitive impairment (a-MCI), all over 65 years of age. Firstly, a significantly lower TP42/40 was found in a-MCI patients compared to CN. Secondly, a-MCIs with a high-risk FDG-PET pattern for AD showed even lower plasma ratio levels and, finally, low TP42/40 at baseline increased the risk of progression to dementia by 70%. Additionally, the TP42/40 resulted inversely correlated with neocortical amyloid deposition (measured with PiB-PET) and was concordant with the AD biomarker profile in cerebrospinal fluid (CSF) in different sub-cohorts of the study population. Thus, TP42/40 demonstrated value in the identification of individuals suffering a-MCI, in the prediction of progression to dementia, and in the detection of underlying AD pathology revealed by FDG-PET, Aβ-PET and CSF biomarkers. In line with the shift toward earlier disease stages, we decided to explore the cross-sectional and longitudinal association of Aβ42/Aβ40 plasma ratios with cortical Aβ burden in a sub-cohort of cognitively normal controls CN from the AIBL study. The primary objective was to assess the performance of TP42/40, discriminating between Aβ-PET positive and negative cognitively normal individuals. In concordance with previous results, plasma Aβ ratios were lower in the CN group with positive Aβ-PET scans than in those with negative Aβ-PET scans. For TP42/40 this association reached significance in all the three analyzed visits from the AIBL follow-up, at month 18 ($P<0.001$), month 36 ($P<0.05$) and month 54, ($P<0.001$). In the longitudinal analysis, mixed-effects models showed that the lower the TP42/40 ratio at baseline (month 18), the steeper the SUVR/BeCKeT trajectory at follow-

up [estimate (95%CI): -0.034 (-0.054, -0.015); P=0.0006]. Additionally, the average ROC AUC classification performance of Aβ-PET positive/negative CN for TP42/40, adjusted for age and APOE genotype, was 79% (71% sensitivity, 78% specificity). These values are not enough for a standalone diagnostic test but would be of great utility as a screening tool to preselect individuals for presumptive cortical amyloid pathology who would then move on to a confirmatory Aβ-PET scan. This will be explored further in future work. Recently, we have further replicated these results in a larger AIBL subcohort including CN, MCI and AD patients. The TP42/40 ratio was significantly associated with PET status at all the three time points ($p<0.006$) after adjustment for confounding variables and correlated with SUVR at each time point (rho=0.6, $p<0.0001$). Area under the curve (AUC) values were highly reproducible over time-points, ranging from 83% at 18 months to 87% at 54 months for the TP42/40 ratio. Thus, the ABtest assay demonstrates reproducibility in the separation of amyloid-PET positive and negative individuals over three time points with a further application for use as an indicator for those with preclinical or prodromal AD. The FACEHBI study uses a sample of 200 individuals (age 65.9 ± 7.2) diagnosed with subjective cognitive decline (SCD) who underwent amyloid florbetaben (FBB) PET and ABtest. Cumulative experimental results have shown that subjective cognitive decline (SCD) may represent the earliest point on the AD continuum. In this study we corroborated again that (Aβ FBB-PET) global SUVR significantly correlated with Aβ42/40 plasma ratio levels. For TP42/40, this observation persisted after controlling for age, education, gender and APOE e4 allele carrier status [R^2=0.214, p=2.59E-04, (CI (95%) -0.063 to -0.019)]. The model with the highest ROC AUC included age, APOE e4 carrier status, and TP42/40 levels as predictor variables. However, the highest sensitivity (83%) was achieved by a model that only included TP42/40 level as a predictor variable. It is worth noting that a simple pre-selection step using the TP42/40 classifier with an empirical cut-off value of 0.08 would reduce the number of individuals requiring a Aβ FBB-PET scan by 49%. Aβ plasma measurements, particularly the TP42/40 ratio, could generate a new recruitment strategy independent of the APOE genotype that would improve identification of SCD subjects with brain amyloidosis and reduce the rate of screening failures in pre-clinical AD studies. We are currently implementing this approach in various studies with banked samples and are in the planning stages of placing this in a recruitment scenario as an enrichment tool. In summary, although larger studies will aid in refining cut-offs and practical applications, plasma TP42/40 ratio appears to be a valid, robust, and cost-effective tool, useful in the screening process for secondary prevention clinical trials in AD and, eventually, for population management in primary care settings. Nevertheless, the development of blood-based biomarkers for AD still faces considerable obstacles. In the last two decades there have been numerous papers reporting positive and negative results in this area. From our point of view, concordance of Aβ blood tests among different studies is mainly hindered by the relatively small difference in the Aβ42/40 plasma ratios among Aβ-PET groups and the extensive overlapping plasma ratios levels between diagnostic groups. In these studies the TP42/40 plasma ratio was on average a ~17% lower in the Aβ-PET-ve subjects than in the Aβ-PET+ve (14% lower among the HC subjects) whereas in the CSF Aβ42/40 ratio differences between those two groups are around 50%. In line with this, stringent adherence to the protocols, including pre-analytic handling of the samples, and the use of reference laboratories for the assays is of utmost importance to minimize the variability of determinations that may blur relatively small, but meaningful, differences. However, we should be aware that an early and accurate diagnosis of such a complex disease as AD will most likely require a combination of biomarkers which reflect the different pathological mechanisms driving the disease progression. Yet, regardless of the difficulty involved, this is a necessary task because, as it has been pointed out "neither CSF sampling through lumbar puncture nor amyloid PET investigation is feasible for screening to identify individuals at risk of developing AD in the general population" (Lövheim et al. [2016] Alzheimer's & Dementia. **Conclusion:** TP42/40 has been shown to be consistently associated with different well-established endophenotypes of AD. Although larger longitudinal studies will help establish definite cut-offs and standard operating procedures, plasma TP42/40 ratio appears progressively consolidated as a reliable and cost-effective tool in the screening process for secondary prevention clinical trials in AD. A pre-screening step with TP42/40 can help significantly reduce screen failure rates and associated costs that currently hamper clinical trials in early stages of the disease.

Communication 1: *Developing Aβ blood based test into pre-screening tools for clinical trials in early stages of AD,* Victor L. Villemagne (Dept of Molecular Imaging & Therapy, Austin Health, Dept of Medicine, The University of Melbourne, Australia)

Communication 2: *Plasma ratio of total Aβ42 to total Aβ40 in amnestic MCI patients is associated with FDG-PET, amyloid-PET, CSF and the risk of progression to AD dementia,* Anne Fagan (Washington University. Saint Louis. Missouri, USA)

Communication 3: *Total Aβ42 to total Aβ40 as a biomarker of cortical amyloid burden in subjects with subjective memory complains, Agustín Ruiz* (Research Director, Research Center and Memory Clinic. Fundació ACE. Institut Català de Neurociències Aplicades. Universitat Internacional de Catalunya (UIC)-Barcelona. Spain)

S5- TOWARDS THE DEVELOPMENT OF A COMPLETE SOLUTION FOR PATIENTS WITH ALZHEIMER'S DISEASE (AD). Rachelle Doody[1,2] *((1) Genentech, Inc., South San Francisco, CA, USA; (2) F. Hoffmann-La Roche Ltd, Basel, Switzerland)*

Introduction: AD is a progressive neurodegenerative disease associated with relentless cognitive, functional, and behavioral impairments. Worldwide, AD is the most common form of dementia, impacting an estimated 40 million individuals – a number that is expected to surge to over 100 million individuals by 2050 in the absence of an effective disease modifying therapy (DMT). Although the search for effective DMTs for AD continues, such efforts are challenging due to the complexity of the pathogenic mechanisms involved, the multitude of potential therapeutic targets, and the decades-long period of time between initiation of the underlying pathology and the emergence of symptoms in a potential patient. Considering these challenges against a future landscape in which millions of individuals will potentially need to be evaluated by specialists, undergo diagnostic testing, and be treated with potential DMTs, it becomes clear that transformative clinical paradigms in the management of AD, from screening, to diagnosis, to prevention

and treatment, will be required. Some have postulated that the use of online/digital tools for screening and monitoring cognitive performance, as well as improved understanding and application of biomarkers, may help to address some of the anticipated burdens on the infrastructure of future healthcare systems while facilitating more effective clinical trials in AD. Additionally, with the potential for multiple DMTs targeting different pathways implicated in the pathophysiology of disease to be approved in the near future, increasingly complex treatment algorithms which include considerations of possible combinations of such therapies may need to be developed. **Objectives:** The proposed symposium has the following objectives: 1. Review and discuss the potential benefits and challenges to the use of online/digital tools in the monitoring and screening of cognitive symptoms in patients at increased risk of developing AD. 2. Discuss the role of emerging biomarkers in the identification of patients with AD, the importance of timely, accurate, and reliable diagnosis in such patients, and the potential benefits for both patients and clinicians. 3. Consider approaches for the development of future treatment guidelines and recommendations in AD using lessons learned from the treatment of complex diseases like rheumatoid arthritis (RA) and the 2015 American College of Rheumatology (ACR) guidelines as a model. **Discussion:** Already the most common cause of dementia, estimates suggest that the worldwide population of individuals afflicted by AD will potentially surge to over 100 million patients by the year 2050. As the symptoms of AD begin to emerge in this population over time, there will be a corresponding increase in the need for individuals exhibiting evidence of mild cognitive impairment (MCI) to be evaluated and formally diagnosed by specialists, undergo diagnostic testing, and ultimately to receive treatment with potential DMTs that are on the horizon. Disconcertingly, however, current projections suggest that the capacity and infrastructure of healthcare systems will be insufficient to address the anticipated burden of cases, and further note that more than 2 million patients could end up developing AD during their wait for screening, appropriate diagnosis, and treatment. Based on such analyses, the limited availability of appropriately trained specialists to formally evaluate and diagnose patients, as well as access to the imaging and infusion centers required to confirm diagnoses and administer treatments respectively, emerge as substantial bottlenecks within the future healthcare system. As a result, transformative clinical paradigms in the management of AD, from screening, to diagnosis, to prevention and treatment, will be required to address the unmet needs of these patients moving into the future. One area of advancing research has been in the development and implementation of online- and digital tools for cognitive self-assessment. Designed to monitor cognitive performance and screen for potential cognitive decline in individuals at increased risk of developing AD, these tools offer the potential to: a. Accelerate and enrich populations of patients enrolled in AD clinical trials through identification and tracking of symptoms and cognitive deficits; b. Develop a longitudinal cohort of individuals and document their memory and cognitive performance over time; c. Upon validation, provide a convenient, at-home approach that may streamline the process of referring patients in which early AD is suspect for follow-up and formal diagnosis with appropriate specialists. Despite these potential benefits however, there remain important issues (i.e., psychometric validation, etc…) that may limit the potential utility of these instruments. Thus, a careful consideration of the benefits and challenges supporting the future role of these instruments in the identification and management of patients with AD is warranted. Emerging biomarkers of early (prodromal-to-mild) AD are also poised to change the diagnosis and treatment of patients with AD. At present, the diagnosis of AD is largely based on clinical symptoms, but preclinical and prodromal phases of the disease may occur 20-30 years prior to onset of clinical symptoms. Moreover, clinical diagnosis of AD suffers from poor sensitivity (70.9% - 87.3%) and specificity (44.3% - 70.8%). As a result, between 50% to 75% of patients with dementia have no formal diagnosis, with rates of undocumented or undetected diagnosis varying by severity and age; delays in formal diagnosis can be as high as 32 months. However, promising new biomarkers have the potential to dramatically reshape the landscape, permitting more accurate, reliable, and timely diagnosis of disease. For patients and caregivers, this may facilitate earlier and more aggressive treatment, increased participation in decision making, as well as enhanced opportunities for participation in ongoing clinical trials. For clinicians, incorporation of such biomarkers into the diagnostic workup for patients may increase the certainty of a diagnosis of AD, in addition to providing reliable alternatives to the use of positron emission tomography (PET) and magnetic resonance imaging (MRI). As such, emerging and future biomarkers may help to further alleviate some of the infrastructure and healthcare burdens that may impact timely diagnosis and treatment of AD in the future. Finally, with the anticipated emergence of the first successful DMTs, and the potential to target one or more distinct pathophysiological pathways implicated in AD, clinicians and patients may face a future wherein combinations of therapeutics will need to be considered when treating AD. Although the precise nature and role of combination therapies in AD has yet to be elucidated, it may be helpful to consider lessons learned from other complex disease states where the use of combinations of therapies has become commonplace when developing guidelines for the treatment of AD. Treatment options in RA, for instance, emerged over the course of several decades, evolving from symptomatic therapies to include a range of biologic and non-biologic disease modifying therapies. Many of these treatment options, when administered as monotherapy or combination therapy, have the potential to slow or arrest the progression of this disease. In conjunction with this evolution, organizations such as the ACR have developed evidence-based, pharmacologic guidelines to assist clinicians and patients in making appropriate treatment decisions. As a result, current paradigms of treatment for RA, along with the 2015 ACR treatment guidelines, may serve as an appropriate model upon which similar guidelines and recommendations for the use and application of combinations of symptomatic and DMTs in AD may be developed. Several additional scientific challenges must also be considered in the development of future treatment guidelines, including elucidation of the scientific rationale supporting the use of specific combinations of therapies, as well as an improved understanding of the connection between putative biomarkers and clinical outcomes. **Conclusion:** To date, symptomatic therapies remain as the only treatment options available for patients diagnosed with AD. With expectations that more than 100 million people may be impacted by the year 2050, the need for a transformative, end-to-end, clinical paradigm in the management of AD has never been higher. Collaboration and innovation will be necessary in order to alleviate potential burdens on the infrastructure of future

healthcare systems. Additionally, by expanding on the lessons learned from treatment paradigms developed for other complex diseases, such as RA, future treatment recommendations guiding the eventual use of combinations of DMTs in AD may be developed.

Communication 1: *Self-detection of cognitive problems: benefits and challenges of online- and digital tools in the monitoring and screening of cognitive performance,* Mary Sano[1,2] ((1) Director, Alzheimer's Disease Research Center, Icahn School of Medicine at Mount Sinai, New York, NY, USA; (2) Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA)

Communication 2: *Enhancing earlier and more reliable diagnosis of AD through the use of emerging biomarkers,* Christopher van Dyck[1–4] ((1) Alzheimer's Disease Research Unit, Yale University School of Medicine, New Haven, CT, USA; (2) Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA; (3) Department of Neuroscience, Yale University School of Medicine, New Haven, CT, USA; (4) Department of Neurology, Yale University School of Medicine, New Haven, CT, USA)

Communication 3: *Moving towards combination therapies for disease modification in AD,* Dennis J. Selkoe[1,2] ((1) Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, MA, USA; (2) Harvard Medical School, Boston, MA, USA)

S6- ENDPOINTS FOR EARLY ALZHEIMER'S DISEASE CLINICAL TRIALS: INTERPRETATION AND APPLICATION OF THE DRAFT FDA GUIDANCE. Eric Siemers *(Cogstate Ltd, New Haven, CT, USA)*

A series of important publications have recently been produced that provide critical insights into the current state of the science of Alzheimer's disease and how this should inform research and clinical trials. The new National Institute on Aging and the Alzheimer's Association Research Framework describes the "A, T, N System" (Amyloid, Tau, and Neurodegeneration) using biomarkers and how this may be applied to clinical research and drug development, as well as a six-stage numeric clinical staging framework. A similar clinical numeric staging framework is adopted by the FDA in their recent draft guidance "Early Alzheimer's Disease: Developing Drugs for Treatment". This is used to inform recommendations on clinical outcomes assessment and the demonstration of meaningful treatment benefit at three predementia stages. However, the practical application of these insights requires much careful thought and several lines of additional scientific research may still need to be pursued before optimal trial designs can be proposed. The present symposium will consider how the FDA guidance may be interpreted and consider elements of practical implementation.

Communication 1: *Clinical Endpoints in Stage 1, 2 and 3 Disease,* Paul S. Aisen[1], Reisa Sperling[2], Ronald C. Petersen[3], Gary Romano[4], Paul Maruff[5] ((1) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA; (2) Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA; (3) Department of Neurology, Mayo Clinic, Rochester, MN, USA; (4) Janssen R&D, Titusville, NJ, USA; (5) Cogstate Ltd, Melbourne, Victoria, Australia)

Introduction: It has been recognized for some time that the traditional approach to outcomes assessment for the dementia stage of Alzheimer's disease may be unsuitable for predementia AD patients, even those in the Mild Cognitive Impairment or Prodromal stages of the disease (Stage 3) approaching the onset of overt dementia. **Objectives:** The communication will consider the current state of clinical outcomes assessment tool development and strategies to address challenges of selection of assessment tools suited to given disease stages and trial designs. **Discussion:** In Stage 3, FDA recognizes the presence of functional impairment and the need for sensitive and independent measures of both cognition and function. Integrated approaches to assessment are also mentioned and integration has previously been approached both via composites of functional and cognitive instruments and the conceptual approach of measuring cognition dependent function. In Stage 2, the absence of functional impairment is considered to present a challenge to the demonstration of meaningfulness. Thus, the selection of clinical outcomes assessment tools must consider a range of important factors: the sensitivity of outcomes, the breadth of test batteries, the possibility of establishing surrogate outcomes, the duration of trials, and emergence of additional clinical features etc. Notably, there are some differences in the FDA and NIA-AA numeric clinical staging that may also inform measurement strategy regarding the presence of self-reported cognitive problems and neurobehavioral symptoms. In addition, there may be some differences and subtleties to interpretation of cognition as "performance in the expected range" (NIA-AA), versus "subtle detectable abnormalities on sensitive neuropsychological measures" (FDA). In Stage 1, patients are deemed truly asymptomatic and cognitively unimpaired outcomes assessment must either rely on biomarkers or a sufficient trial duration to allow for the emergence of clinical signs and symptoms. **Conclusion:** Disease stage, trial duration and rate of clinical progression will have a major impact on clinical outcomes assessment and create some degree of complexity. Additional considerations regarding the combination of cognitive, functional, behavioral and self-reported measures, the considerations of independence and integration of cognitive and functional assessment, the face, or ecological validity of tests and the breadth of batteries, creates additional challenges in study design.

Communication 2: *Biomarkers in Stage 1, 2 and 3 Disease,* Samantha Budd Haeberlein[1], Jose Luis Molinuevo[2], Christopher C. Rowe[3], Maria C. Carrillo[4], Clifford R. Jack, Jr.[5] ((1) Biogen, Cambridge, MA, USA; (2) BarcelonaBeta Brain Research Center, Pasqual Maragall Foundation and Hospital Clinic-IDIBAPS, Barcelona, Spain; (3) Department of Molecular Imaging, Austin Health, University of Melbourne, Melbourne, Australia; (4) Alzheimer's Association, Chicago, IL, USA; (5) Department of Radiology, Mayo Clinic, Rochester, MN, USA)

Introduction: Biomarkers may be employed to reflect both the presence (state) and progression (stage) of Alzheimer's disease. The ATN system as outlined in the recent NIA-AA research framework, reflects observations of the relationships between markers of amyloid, tau, and neurodegeneration. **Objectives:** The communication will consider the current state of biomarker development, the requirements to establish a surrogate biomarker, and the relationship between biomarkers and the clinical Stage 1, 2 and 3 patients. **Discussion:** The draft FDA guidance acknowledges that a biomarker could be

selected as a primary endpoint if it is considered "reasonably likely" to predict clinical benefit; however, this would be the basis for an accelerated approval, with a post-approval requirement for a study to confirm the predicted clinical benefit. No surrogate biomarker has yet been established. In addition, the ATN system may be most useful in more accurate staging of disease and is "not intended to infer correlations between AD biomarkers and the efficacy of investigational therapeutic agents". In parallel with neuropsychological tests, FDA comment that a pattern of treatment effects seen across multiple individual biomarker measures would increase the persuasiveness of the putative effect. **Conclusion:** Biomarkers may present the only means by which we can identify the appropriate individuals at the earliest stages of disease, at which time treatment may be most effective, but when no functional, and potentially no cognitive effects are observable.

Communication 3: *Approaches to Establishing the Meaningfulness of Treatment Effects,* Chris J. Edgar[1], George Vradenburg[2], Jason Hassenstab[3] ((1) Cogstate Ltd, London, UK; (2) UsAgainstAlzheimer's and Alzheimer's Disease Patient and Caregiver Engagement (AD PACE), Chevy Chase, MD, USA; (3) Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA)

Introduction: It is well understood that to be approvable by FDA a treatment must demonstrate not only a statistically significant effect, but also a clinically meaningful one. In the recent draft guidance for industry the terms 'meaningful'/'meaningfulness' are used 25 times in different contexts. This is perhaps unsurprising, given continued ambiguity around the meaningfulness of conventional neurocognitive test outcomes, which may not directly measure how patients 'feel, function, or survive', but which are critical in a disease that primarily impacts cognition. **Objectives:** The communication will consider the demonstration of clinical meaningfulness in terms of conceptual relevance of outcome measures, means to establish target effect sizes at the group and patient level, and practical application within clinical trial designs. **Discussion:** The term 'clinical meaningfulness' is often used to refer to two different constructs: 'relevance' and 'effect size'. Relevance refers to those concepts of interest which are measured, whilst effect size refers to the magnitude of any treatment benefit. Since relevance may depend on the perspective of an audience, it is important to differentiate 'clinical relevance' (the measurement of concepts relevant to the clinician) from 'patient relevance' (the measurement of concepts relevant to the patient). This is vital as the means of establishing clinical and patient relevance differ, but also since the history of endpoint development in AD has tended to stress clinician centered approaches; in part stemming from the genesis of measurement in the dementia stage of the disease in which self-report may be unreliable, and in part due to the importance of cognition, which is a concept that may be difficult to self-report and observe, even in healthy people. Effect size can also be subdivided into between groups differences (e.g. 'minimally clinically important difference' and within patient (e.g. 'response', 'progression'). **Conclusion:** The contexts within which meaningfulness is considered provide an important insight into those important elements to be considered i.e. the concepts of interest measured, the size of any treatment effect, and the validation of surrogate outcomes.

S7- DISCLOSURE OF ALZHEIMER'S RISK BIOMARKERS TO COGNITIVELY NORMAL OLDER ADULTS. Athene Lee[1,2], Jessica Alber[1,2] *((1) Warren Alpert Medical School of Brown University, Providence, RI, USA; (2) Butler Hospital, Providence, RI, USA)*

Introduction: Alzheimer's disease (AD) is the most common neurodegenerative disease. With the aging population, AD poses a major public health challenge with significant economic and caregiver burden. Many older adults perceive AD as the most debilitating medical condition, resulting in negative emotional impact even among those who are cognitively normal but may be at-risk for AD. Epidemiological studies have revealed a range of familial, genetic, medical, and lifestyle risk factors. Additionally, biomarkers including amyloid PET imaging, CSF assays, and blood proteomics have been developed to assess AD risk. An important area of research is to synthesize these risk factors for AD risk calculation and to identify pre-clinical individuals for AD prevention trials. While an optimal risk model is yet to be identified and likely depends on the context of use, ethical implications of disclosing AD risk biomarkers should be examined in anticipation of translating this research advancement for clinical use. **Objectives:** The symposium will foster a conversation on the impact of AD risk biomarker disclosure. Specifically, it will focus on disclosure of amyloid PET results and APOE genotype, two of the most commonly used risk assessments for AD prevention trials. Topics for discussion include assessing psychological readiness, ensuring proper communication and comprehension of risk results, and examining the psychological, cognitive, and behavioral impact of risk disclosure. **Conclusion:** Knowledge regarding the process and tolerability of AD biomarker disclosure in prevention trials will lay the groundwork for future clinical practice when disease modifying therapies become available.

Communication 1: *"Not just a colonoscopy" – cognitively normal older adults reactions to learning an amyloid PET result,* Jason Karlawish[1], Kristin Harkins[2], Emily Largent[3], Pamela Sankar[3], Jeff Burns[4], David Sulzer[5], Joshua Grill[6] ((1) Departments of Medicine, Medical Ethics and Health Policy, and Neurology, University of Pennsylvania, Philadelphia, PA, USA; (2) Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA; (3) Department of Medical Ethics and Health Policy, University of Pennsylvania, Philadelphia, PA, USA; (4) Department of Neurology, University of Kansas, Kansas City, KS, USA; (5) Department of Psychiatry, University of California, Los Angeles, CA, USA; (6) Department of Psychiatry and Human Behavior, University of California, Irvine, CA, USA)

The research that will validate a "pre-clinical" stage of AD includes experiments testing drugs in cognitively unimpaired persons who have a biomarker we think stands for AD. The model for these studies is clinical trials testing drugs that target amyloid. Eligible subjects are cognitively unimpaired older adults who have "elevated amyloid" measured by PET scan. Subjects learn this result; thereby simulating the future clinical practice paradigm: an AD biomarker test leads to prescription for anti-AD biomarker drug. The more we understand how these subjects react to this information, the better we can translate this paradigm into clinical practice. METHODS: This presentation will report on the results of (1)

longitudinal semi-structured interviews with 50 persons who learned they have "elevated amyloid" and are in a clinical trial and 30 persons who learned they have "not elevated amyloid" and are in a longitudinal cohort study, and (2) metric measures of future time perspective made from all trial participants and screen fails. RESULTS: An elevated amyloid result is generally expected given family history, cognitive symptoms or both. Feelings about the future range from positive (hopeful, bright), present focused, to negative (pessimistic, limited time remaining), or unknown. These feelings lead about half of people to either plan or enact changes related to health and life plans such as finances and living arrangements. Openness to sharing the results is balanced against concerns about public stigma. Persons who learn a "not elevated" result reinterpret cognitive symptoms as part of aging. Unlike persons with elevated amyloid, feelings about the future are overall positive and range from feeling present focused, relieved, optimistic or having expansive remaining time. Few make changes to plans or behaviors, but most would if their result was elevated. They generally see it as a research result to be shared widely with others. Measures made from all trial participants and screen fails on Future Time Perspective support findings about changes in time perception. In a "pre-clinical" stage of AD, knowledge of AD biomarker result causes notable changes in feelings about the future, plans and interactions with others.

Communication 2: *Remote genetic counseling and disclosure of APOE genotype within the Generation study 1,* Elisabeth McCarty Wood[1], Cara Cacioppo[1], Neeraja Reddy[2], Dare Henry-Moss[1], Demetrios Ofidis[1], Brian L. Egleston[3], Jason Karlawish[1], J Scott Roberts[4], Scott Kim[5], Carolyn Langlois[6], Eric M. Reiman[6], Pierre N. Tariot[6], Jessica B. Langbaum[6], Angela R. Bradbury[1] ((1) University of Pennsylvania, Philadelphia, PA, USA; (2) Mapmygenome, Navi Mumbai, India; (3) Fox Chase Cancer Center, Philadelphia, PA, USA; (4) University of Michigan, Ann Arbor, MI, USA; (5) National Institutes of Health, Bethesda, MD, USA; (6) Banner Alzheimer's Institute, Phoenix, AZ, USA)

The Alzheimer's Prevention Initiative Generation Study 1 is recruiting cognitively normal APOE e4 homozygotes, ages 60-75. While some participants have prior knowledge of their APOE genotype, many have first-time disclosure of APOE and AD risk information as part of study screening. To support complex educational and psychosocial needs of individuals receiving APOE genotype and AD risk information, the protocol requires participants to receive genetic counseling. Traditional presymptomatic genetic counseling models include multiple in-person visits; however, this model presents access and scalability challenges within the context of a large, international clinical trial. Utilization of alternative genetic counseling delivery methods for Generation Study 1 sites within the United States provides a unique opportunity to develop scalable options of genetic counseling for APOE and AD risk assessment. METHODS: A multidisciplinary team with expertise in AD, genetic counseling, and clinical research supported utilization of a condensed one-visit genetic counseling model combining elements of pre- and post-test counseling. To address limited access to genetic counseling providers, the University of Pennsylvania Telegenetics Program (Penn TG) is utilized to provide genetic counseling services by telephone and two-way real-time videoconferencing (RTVC). Penn TG developed an ancillary study, CONNECT 4 APOE (CONNECT), to evaluate the relative short-term and longitudinal advantages of RTVC over telephone. All Penn TG genetic counseling sessions are conducted by a genetic counselor and utilize standardized educational materials, risk estimates, and checklists to ensure session consistency. Participants complete pre-disclosure and post-disclosure (2-7 days) measures of genetic knowledge, result recall, and satisfaction with genetics services, as well as measures of perceived risk, state anxiety, disease-specific anxiety, depression and health behaviors, which are additionally completed at 6 weeks, 6 and 12 months. RESULTS: Penn TG initiated remote genetic counseling services for the Generation Study 1 in November 2015; as of May 2018, over 600 sessions have been completed. Enrollment, genetic disclosure and follow-up are ongoing. The CONNECT study launched in August 2016; as of May 2018, 254 (131 phone, 123 RTVC) CONNECT sessions have been completed. Clinical methods and experiences of remote APOE disclosure using a one-visit model, as well as preliminary results of outcome measures, will be presented. As preventive therapies for AD are developed, clinicians will be increasingly asked to identify and counsel at-risk individuals. Knowledge gained regarding the methods and outcomes of genetic counseling delivery models provides significant insight toward the clinical implementation of APOE genetic testing for AD risk assessment.

Communication 3: *Application of an APOE disclosure model at a clinical trial site and the impact of dual disclosure of amyloid PET results,* Louisa Thompson[1,2], Athene Lee[1,2], Meghan Collier[1,2], Danielle Goldfarb[1], Brittany Dawson[2], Stephen Salloway[1,2], Jessica Alber[1,2] ((1) Warren Alpert Medical School of Brown University, Providence, RI, USA; (2) Butler Hospital, Providence, RI, USA)

Disclosure of AD risk biomarkers to cognitively normal individuals is new territory for clinical trials, making this a critical time to assess its tolerability and utility. APOE genotyping is one risk assessment currently used at the Butler Hospital Memory and Aging Program to pre-screen individuals for AD prevention trials. Our team developed a protocol for APOE disclosure, implementing methods recommended by genetic counselors, to provide education about AD risk, assess the psychological impact of disclosure, and examine its implications for trial enrollment. As more complex AD risk models are developed for prevention trials, the implications for disclosing multiple pieces of risk information (e.g., APOE genotype and amyloid PET status) should be carefully considered. METHODS: We recruit cognitively normal adults from the Butler Alzheimer's Prevention Registry (aged 59-77). Participants complete APOE genotyping, a genetic disclosure session attended with a study partner, and three follow-up assessments (3 days, 6 weeks, 6 months) via online survey. Psychological readiness for APOE disclosure is assessed via a structured psychological interview and self-report measures of depression, anxiety, and suicidal ideation. A clinician reviews the individuals' medical and family history, and discusses their motivation for genotyping, anticipated emotional response and action plan, and intention for sharing the results with others. Psychological outcome is assessed immediately after disclosure and again at each follow-up, which includes measures of depression, anxiety, suicidal ideation, impact of learning the APOE genotype, and perceived risk of AD. Lifestyle outcome measures include self-reported exercise, diet, sleep habits, and alcohol consumption. For individuals who later learn their amyloid PET results through clinical trials, a semi-structured

interview is conducted to assess the impact of dual disclosure. RESULTS: As of June 2018, 109 participants have enrolled in this ongoing study. The current APOE ε4 carrier rate is 41% among participants. We will present 6-month follow-up data with special attention to the process of disclosure, tolerability, and how it has enhanced site enrollment. Outcome measures in APOE ε4 carriers vs. non-carriers will be compared. Preliminary data investigating the impact of dual APOE genotype and amyloid PET disclosure among those screened for clinical trials will also be discussed. Thus far, 71% of ε4 carriers have gone on to screen for clinical trials. Of those who have completed screening, 42% have been randomized. There have been no significant changes in depression or anxiety scores or serious adverse events, such as suicidal thoughts, among participants over the course of the 6-month follow-up period. Significant, but temporary fluctuations in perceived risk of AD and disclosure impact have been reported and were found to be modified by participant genotype. APOE disclosure has been safe and well tolerated in cognitively normal older adults spanning a 6-month period. Our findings suggest that APOE genotyping is an effective tool to maximize recruitment efficiency in AD prevention trials.

PRESENTATION AND PANEL DISCUSSION

AMBAR (ALZHEIMER'S MANAGEMENT BY ALBUMIN REPLACEMENT) PHASE IIB/III RESULTS. Antonio Páez, *(Grifols S.A., Barcelona, Spain)*

Followed by Panel Discussion with:
• Jeffrey Cummings MD, PhD (Chairman), Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA
• Mercè Boada MD, PhD, Fundació ACE, Universitat Internacional de Catalunya, Barcelona, Spain
• Oscar L. Lopez MD, PhD, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
• Zbigniew M. Szczepiorkowski, MD, PhD, Dartmouth Hitchcock Medical Center, Lebanon, NH, USA
• Bruno Vellas, MD, PhD, University Hospital, Toulouse, France

Plasma exchange (PE) with therapeutic albumin replacement (PE-A) as a new therapeutic approach for Alzheimer's disease (AD) has been in development for nearly fifteen years in a series of clinical trials progressing to the current large scale Phase IIB/III AMBAR (Alzheimer's Management by Albumin Replacement) study. Reduction of Aβ burden to prevent the accumulation of amyloid deposits in the brain is one of the current therapeutic strategies for AD. However, clinical trials so far testing small molecule pharmacotherapy and immunotherapies to reduce brain Aβ haven't been positive. Since plasma contains circulating Aβ, mostly bound to albumin, representing a peripheral pool in dynamic equilibrium with Aβ in the central nervous system, PE-A would be a new approach aimed at lowering Aβ accumulation in the AD brain by peripheral sequestration of albumin-bound Aβ and thus mobilizing oligomeric brain Aβ away to plasma through the blood-brain barrier. Moreover, replacement with therapeutic albumin would provide renewed antioxidant, binding and immunomodulatory capacities. Studies aimed to the thorough characterization of Grifols' therapeutic albumin (Albutein®) have shown that this product has undetectable content of Aβ1-40 and Aβ1-42, it is able to bind an Aβ1-42 peptide with the human primary sequence, and it preferentially binds oligomers thus inhibiting further Aβ fibrillization. In another line of research, HPLC and mass spectrometry studies have shown marked differences between AD patients and age-matched healthy controls in their redox state of plasma and CSF albumin. The clinical strategy launched by Grifols started with a pilot study that recruited 10 patients with mild-to-moderate AD to undergo 6 PE-A sessions (with 5% Human Albumin Grifols; Albutein®) for 3 weeks, 2 sessions/week. At one year of follow-up post-treatment, the positive results on patients' biochemical, cognitive, and neuroimaging variables encouraged performing an extension study for confirmation, and the design of a Phase II clinical trial (multicenter, randomized, patient- and rater-blind, controlled, parallel-group; EudraCT 2007-000414-36) with 42 patients. Treated patients received up to 18 PE-A with 3 different schedules: 2 PE-A/weekly (3 weeks), 1 PE-A/weekly (6 weeks), and 1 PE-A/bi-weekly (12 weeks), plus a 6-month follow-up period. Control patients underwent a sham PE-A. Results showed that PE-A induced a measurable modification in Aβ1-42 (the most neurotoxic Aβ form) concentration in CSF (moderately higher after the last PE-A; $p=0.072$) and plasma (lower after each treatment period; $p<0.05$). PE-A treatment was associated with improvement in memory and language functions as assessed with a battery of cognitive tests ($p<0.05$) which persisted after PE-A was discontinued. Neuroimaging studies (SPECT, MRI) revealed that PE-A-treated patients had stabilized cerebral perfusion in frontal, temporal, parietal, and Brodmann area BA38-R ($p<0.05$). Controls showed the cognitive decline and brain perfusion impairment expected in AD. On the basis of these promising results, the AMBAR study was started as a Phase IIB/III, multicenter, randomized, blinded and placebo-controlled, parallel-group trial enrolling mild-to-moderate AD patients from centers in Spain and in USA (NCT01561053). AMBAR is designed to evaluate PE with different replacement volumes of therapeutic albumin (5% and 20% Albutein®), with or without IVIG (Flebogamma® 5% DIF, Grifols) to correct a possible endogenous immunoglobulin decrease. The patients have been randomized to one of three treatment groups or the control (sham PE) group [1:1:1:1]. The intervention regime includes a first 6-week stage of intensive treatment (1 conventional PE-A/week) that is common to all groups, followed by a second 12-month stage of maintenance treatment (1 low-volume plasma exchange [LVPE]/month) distributed in 3 arms: i) Replacement of 20 g 20% Albutein®; ii) Like arm #1 alternated with 10 g 5% IVIG replacement; iii) Like arm #2 but 40 g 20% Albutein® and 20 g Flebogamma® 5% DIF. 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. 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 change from baseline to the end of both intensive and maintenance treatment periods (14 months) in the ADAS-Cog scale and in the ADCS-ADL inventory score are the coprimary efficacy variables. Secondary efficacy variables include: change from baseline in scores on cognitive, functional, behavioral, and overall progression tests; changes in plasma and CSF levels of Aβ1-40, Aβ1-42, T-tau and P-tau; assessment of structural changes in brain areas of interest as detected by MRI;

and assessment of functional changes in the brain as detected by FDG-PET. Safety assessments include monitoring the PE-A/LVPE associated with adverse events that may be related to the study procedure. The study is blind for patients, caregivers and raters. The AMBAR study has enrolled 496 patients (346 randomized) from 41 centers (20 in Spain and 21 in the US), who underwent close to 5000 PE-A/LVPE, approximately 25% of which were sham PE. Detailed results of this trial will be presented.

ORAL COMMUNICATIONS

OC1: PHASE 2A TRIAL OF AZD0530 EVALUATING 18F-FDG PET, SAFETY, AND TOLERABILITY IN MILD ALZHEIMER'S DEMENTIA. Christopher H. van Dyck[1], Haakon B. Nygaard[2], Kewei Chen[3], Michael C. Donohue[4], Rema Raman[4], Robert A. Rissman[4,5], James B. Brewer[5], Robert A. Koeppe[6], Tiffany W. Chow[4], Michael S. Rafii[4], R. Scott Turner[7], Jeffrey A. Kaye[8], Seth A. Gale[9], Eric M. Reiman[3], Paul S. Aisen[4], Stephen M. Strittmatter[1] *((1) Yale University School of Medicine, New Haven, USA; (2) The University of British Columbia, Vancouver, Canada; (3) Banner Alzheimer's Institute, Phoenix, USA; (4) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, USA; (5) University of California San Diego, La Jolla, USA; (6) University of Michigan, Ann Arbor, USA; (7) Georgetown University, Washington, DC, USA; (8) Oregon Health & Science University, Portland, USA; (9) Harvard Medical School, Boston, USA)*

Background: We have described a signaling cascade whereby oligomeric Aβ binds to cellular prion protein on the neuronal cell surface, activating intracellular Fyn kinase to mediate synaptotoxicity and tauopathy. AZD0530 is an investigational kinase inhibitor specific for the Src family, including Fyn, that has been repurposed for the treatment of Alzheimer's disease (AD). **Objectives:** This Phase 2a proof of concept study of AZD0530 evaluated 18F-FDG PET, safety, and tolerability in individuals with mild Alzheimer's dementia. **Methods:** In this double-blind trial, participants with mild Alzheimer's dementia (MMSE = 18-26) and PET evidence of elevated Aβ were randomly assigned to receive AZD0530 (100 or 125 mg daily) versus placebo for 52 weeks. The primary outcome was 18F-Fluorodeoxyglucose (18F-FDG) PET measurement of decline in the cerebral metabolic rate for glucose (CMRgl) at 52 weeks in an AD-related statistical region of interest (sROI). Secondary endpoints included changes in cognition, function, and other biomarkers. **Results:** A total of 293 participants were screened, 159 randomized (79 to AZD0530 and 80 to placebo), and 131 (59 to AZD0530 and 72 to Placebo) received both baseline and follow-up 18F-FDG PET. 19% escalated from 100 to 125 mg at Week 4, based on a Week-2 plasma drug level (Target = 180 ng/ml; 30 nM free). Average plasma levels from weeks 13-52 were 220 ng/ml; 36 nM free. Numerically more participants discontinued treatment on AZD0530 (22) than on placebo (11), primarily due to adverse events. The most frequent adverse events were gastrointestinal (including diarrhea and nausea), which occurred in 48% of participants on AZD0530 and 29% on placebo (P = 0.015). In the primary outcome, the treatment groups did not differ in 52-week decline in CMRgl (diff: −0.006 units/year, 95% CI −0.017, 0.006, P = 0.337, modified intention-to-treat linear mixed model). The treatment groups also did not differ in the rate of decline at 52 weeks for ADAS-Cog, MMSE, ADCS-ADL, CDR or NPI. Secondary volumetric MRI analyses revealed no treatment effect on total brain or ventricular volume but trends for slowing of decline in hippocampal volume (P = 0.089, ANCOVA), and entorhinal thickness (P = 0.073, ANCOVA). **Conclusions:** In this 52-week study, we failed to detect significant effects of AZD530 treatment on CMRgl decline in an AD-related sROI or in secondary clinical or biomarker measures.

OC2: PRIMARY RESULTS FROM A PHASE II/III TRIAL OF INTRANASAL INSULIN: A NOVEL MULTI-TARGET MOLECULE AND DELIVERY MODE FOR AD THERAPEUTICS. Suzanne Craft[1], Rema Raman[2], Tiffany Chow[2], Michael S Rafii[2], Robert A. Rissman[3], James B. Brewer[3], Michael Donohue[2], Chung-Kai Sun[2], Kelly Harless[2], Devon Gessert[2], Paul S. Aisen[2] *((1) Wake Forest School of Medicine, Winston-Salem, USA; (2) University of Southern California, Los Angeles, USA; (3) University of California, San Diego , USA)*

Background: Alzheimer's disease (AD) has been associated with markers of brain insulin resistance in human neuropathological studies, in studies of neural-derived exosomes, and in AD rodent models. Insulin modulates many aspects of brain function relevant to AD. It promotes synaptic health and memory, protects against ß-amyloid-induced synaptotoxicity, and reduces tau hyperphosphorylation. Insulin can be delivered directly to the brain using specialized intranasal delivery devices that enable molecules to bypass the blood-brain barrier and travel via bulk flow along perivascular conduits following olfactory and trigeminal nerves. Insulin then reaches the brain and binds to receptors in regions such as the hippocampus within 30 minutes. Intranasal insulin has been shown to enhance memory in small, single-site studies of adults with mild cognitive impairment (MCI) and AD, and to reduce AD pathology and improve memory in rodent models. **Objectives:** This study tested the effects of 40 IU of intranasal insulin administered daily for 12 months, compared with placebo, on cognition, daily function and safety in adults with MCI or mild AD. Longer-term effects were examined in a six-month open-label extension offered to all participants. Safety and feasibility issues relating to the use of intranasal delivery devices were also evaluated. The trial is nearing completion; all participants will have concluded the blinded phase by June 15, 2018, and primary outcome results will be presented. **Methods:** Twenty-six sites enrolled 289 participants with MCI or mild AD in this randomized, double-blind, Phase II/III trial (NCT01767909). Adults 55 to 85 years of age with diagnoses of amnestic MCI or AD (National Institute on Aging-Alzheimer's Association criteria) with Mini-Mental State Exam (MMSE) scores >19, Clinical Dementia Ratings (CDR) of 0.5 or 1, and delayed Logical Memory scores within a specified education-adjusted range were eligible. Participants with diabetes requiring medication were excluded, as were participants who had used insulin within one year of the screening visit. Participants were randomized on a 1:1 basis using a covariate-adaptive algorithm that weighted MMSE, apolipoprotein E-ε4 (APOE-ε4) allele carriage, study site, sex, and age based on previous work indicating these factors may impact treatment response. Participants received 40 IU of insulin or insulin diluent placebo (Humulin R U-100 or insulin diluent, Eli Lilly, Indianapolis, USA) daily for 12 months. At the end of the 12-month blinded phase, all participants were offered open-

label insulin treatment for 6 months. The primary outcome (Alzheimer's Disease Assessment Scale for Cognition-12/ ADAS-Cog12) was administered at baseline and then at 3 month intervals. Secondary functional outcomes (Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for MCI; CDR Sum of Boxes) were assessed at 6 month intervals, as was a memory composite (Free and Cued Selective Reminding Test and Story Recall). Cerebrospinal fluid biomarkers (Aß42 and Aß42/tau ratio) and magnetic resonance imaging hippocampal and entorhinal cortex volumes were measured at baseline and after 12 months. Safety was reviewed quarterly by an independent Data and Safety Monitoring Board (DSMB). Intranasal delivery device monitoring revealed no safety issues. However, for the first 49 participants, the delivery device had frequent electronic malfunctions that impacted dosing reliability. At that time, a newly available device was introduced (Precision Olfactory Device/POD, Impel NeuroPharma, Seattle, USA) which was used by the remaining 240 participants with good reliability. Accordingly, the primary analysis will be restricted to the intent-to-treat group of participants (n=240) who used the POD; secondary analysis will include all participants (n=289). Mixed model repeated measures analysis will test the hypothesis that the insulin-treated group had a slower rate of decline on the ADAS-Cog 12 during the 12-month blinded phase compared with placebo. Similar analyses will be conducted for secondary outcomes. In other secondary analyses, response to treatment will be examined according to sex, baseline MMSE, CSF biomarker profile, and APOE-ε4 allele carrier status.

Table 1
Baseline Participant Characteristics

N (F/M)	289 (134 / 155)
Age (years)	70.95 ± 7.1
Diagnosis (MCI/AD)	105 / 184
MMSE	24.8 ± 2.7
Logical Memory	2.1 ± 2.7
APOE (ε4+/ε4-)	193 / 96

Results: Demographic characteristics of enrolled participants are presented in Table 1. To date, 248 participants have completed the blinded phase of the study, and 25 participants have discontinued treatment during the blinded phase, with 15 also discontinuing study visits during the blinded phase. Quarterly DSMB reviews have not detected any safety issues and have approved unmodified continuation of the trial. Primary results will be presented, along with available secondary analyses. **Conclusions:** This study represents the first double-blind, multi-site, Phase II/III study of intranasal insulin in MCI and AD. As such the trial is innovative, both in terms of the use of a novel therapeutic agent directed at multiple targets of relevance to AD, as well as in the mode of drug delivery, which may have applications for other therapeutic agents. The results of the trial will provide critical information to guide the future development of insulin-based therapeutics as a novel approach to treating AD. Acknowledgements: This study was supported by NIA RF1AG041845 (S. Craft, PI). Eli Lilly provided insulin diluent for the trial, and Humulin R U-100 for the open-label extension, but provided no input into study design or analyses or content restrictions regarding the communication of study results.

OC3: PHASE3 CLINICAL TRIAL FOR A NOVEL OLIGOSACCHARIDE TARGETING MULTIPLE AB FRAGMENTS IN PATIENTS WITH MILD-MODERATE AD IN CHINA. Shifu Xiao[1], Zhenxin Zhang[2], Meiyu Geng[3], GV-971 Study Group *((1) Department of Gerontology, Shanghai Mental Health Center, Shanghai Jiao Tong University, Shanghai, China; (2) Peking Union Medical College Hospital, Beijing, China; (3) State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China)*

Backgrounds: It is widely accepted that Alzheimer's disease (AD) is characterized by amyloid-beta (Aβ) plaques as well as neurofibrillary tangles. Sodium Oligo-mannurarate (GV-971) is a novel chemical drug targeting multiple Aβ fragments. A phase 3 clinical trial was designed and carried out to evaluate this oligosaccharide based anti-amyloid-β (Aβ) therapy. **Methods:** This trial is a, 36-week, multi-center, randomized, double-blinded and placebo controlled study in Chinese patients with probable AD (mini-mental state examination [MMSE] scores of 11–26). After a 2-week screening and 4-week leading-in period, eligible patients were randomized and accept GV-971 450mg or placebo twice daily for 36 weeks. The inter-group difference in change of the 12-item Alzheimer's disease Assessment Scale-Cognitive subscale (ADAS-cog12) from baseline served as the primary outcome. The inter-group difference in change of the overall clinical response (Clinician's Interview-Based Impression of Change [CIBIC-plus]), the activities of daily living (Alzheimer's Disease Cooperative Study–Activities of Daily Living [ADCS-ADL]) and the behavior (Neuropsychiatric Inventory [NPI]) from baseline were the secondary outcomes. Adverse events were recorded. **Results:** 1291 patients were screened and 818 randomized in the trial. The visit of whole trial ended in June of 2018. The results will be summarized and reported in CTAD 2018. **Conclusions:** This randomized trial is the first 36-week trial in China for a pan anti-Aβ oligosaccharide, a novel AD drug developed by a Chinese pharmaceutical company. Trial registration: ClinicalTrials.gov Identifier: NCT022939

OC4: ACTIVE ANTI-AMYLOID IMMUNOTHERAPY WITH UB-311 VACCINE: DESIGN, BASELINE DATA AND STUDY UPDATE OF A PHASE IIA, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 3-ARM PARALLEL-GROUP, MULTICENTER STUDY. Ajay Verma, Hui Jing Yu, Hui-Chen Chen, Chang Yi Wang on behalf of the UB-311 Phase IIa Study Team *(United Neuroscience, Inc. Hauppauge, NY, USA)*

Background: UB-311 is an synthetic peptide active vaccine targeting the Aβ1-14 epitope of the beta amyloid protein, and is currently in a Phase IIa trial (V203-AD), which is fully enrolled with subjects with mild Alzheimer's disease (AD). In a completed Phase I clinical study, UB-311 was well tolerated and safely elicited anti-Aβ antibody levels with a 100% responder rate in patients with mild-moderate AD (n=19). V203-AD (NCT02551809) is a 78-week, multicenter, randomized, double-blind, placebo-controlled Phase IIa study of UB-311 initiated in December 2015 at 4 sites in Taiwan. A positive amyloid PET scan with florbetapir (18F-AV-45) was used for inclusion of patients with mild AD. Florbetapir PET was also used to determine pharmacodynamic effect at 52 and

78 weeks. MRI was used to track ARIA-E, ARIA-H and brain volumes. The primary endpoints are safety, tolerability and immunogenicity of two different dosing regimens of UB-311 (initial 3 priming doses followed by either 4 booster doses given every 12 weeks or 2 booster doses given every 24 weeks) compared to a placebo group. Secondary outcomes include changes from baseline in cognitive, imaging, functional, and global assessments through the end of the study. **Objectives:** Description of the novel therapeutic vaccine, Ph1 and Ph2a trial design, as well as baseline data and study update from the Ph2a trial will be presented. **Methods:** Eligible subjects were 60 to 90 years old classified clinically with mild AD dementia (CDR 0.5 or 1, MMSE 20-26). Amyloid deposition was confirmed by florbetapir PET at study entry in subjects who met inclusion/exclusion criteria. PET scans were assessed by independent neuroradiologists and classified as positive or negative by both visual and quantitative assessments. The method of Landau et al. was used to quantify the standard uptake value ratios (SUVR) using the mean signal of selected cortical brain regions with cerebellum as reference. A new method for determining brain amyloid load was also utilized. For the confirmatory quantitative read an SUVR threshold of 1.1 was used. MRIs from all subjects who received drug or placebo were obtained at baseline and every 3 months following vaccination in the Phase IIa trial. All images were inspected by a board-certified neuroradiologist for evidence of ARIA-E, ARIA-H and meningoencephalitis. **Results:** A total of 43 subjects enrolled in the ongoing Phase IIa study with 81.4% being ApoE4 carriers. Baseline mean MMSE was 22.5 and baseline Amyloid PET SUVR was 1.31. As of July 1st, 2018, total 295 doses of UB-311/placebo were given with more than 83% of randomized subjects have completed Week 78 assessments. A high correlation was observed between visual read, SUVR and amyloid load analyses of PET data. All subjects except 2 early terminated subjects have completed the treatment period (Week 60), with no incidences of treatment induced meningoencephalitis or ARIA-E were detected from 245 post-vaccination MRI reads. The most common reported adverse events are injection site related reactions and asymptomatic ARIA-H. So far, two subjects terminated early from the study, one subject discontinued after Week 4 and another subject withdrew from the study after Week 52. An extension study has been initiated at Q2 2018 and subjects from the Phase IIa study will be eligible to join a 108-week extension study with UB-311. **Conclusions:** To date, UB-311 has been well tolerated, as continuously assessed by clinical exam and MRI, with nearly 300 vaccine doses administered. Database lock following study completion is expected in Q4 2019. Subjects from the Phase IIa study will be eligible to join the 108-week extension study with UB-311 in which additional safety, immunogenicity and biomarker data will be collected.

OC5: ELENBECESTAT IN MCI-TO-MODERATE ALZHEIMER'S DISEASE: SAFETY AND EFFECTIVENESS AS MEASURED BY AMYLOID PET AND THE ADCOMS CLINICAL ENDPOINTS.

Shau Yu Lynch, June Kaplow, Jim Zhao, Shobha Dhadda, Johan Luthman, Bruce Albala *(Eisai Inc., Woodcliff Lake, NJ, USA)*

Background: Elenbecestat (E2609) is a novel inhibitor of BACE, an enzyme responsible for Aβ peptide production. Elenbecestat inhibits BACE1 enzyme activity and reduces Aβ isoforms in CSF. **Objectives:** This study investigated the safety of elenbecestat in subjects with MCI and mild-to-moderate AD dementia, compared the sensitivity of the clinical outcome measures Alzheimer's Disease Composite Score (ADCOMS) and CDR-SB, and evaluated the relationship between clinical measures and amyloid-PET SUVR. **Methods:** Results were from a Phase 2, 18-month, placebo-controlled study (NCT02322021). Subjects were diagnosed as AD based on NIA-AA criteria and confirmed as amyloid+ by PET before being randomized to placebo, elenbecestat 5, 15, or 50 mg/day. While ongoing, the study was amended; subjects with ≥3 months of treatment remaining were reassigned from elenbecestat 5 and 15 mg/day to elenbecestat 50 mg/day while maintaining the study blind. In this study, subjects with ≥3 months of elenbecestat 50 mg/day treatment were analyzed as the 50 mg/day Total group. Safety measures (the primary objective) included the incidence of TEAEs and results from clinical laboratory (including flow cytometric analysis of CD4, CD8 and CD19), ECGs, and dermatology assessments. The clinical effectiveness of elenbecestat was explored by comparing mean changes from baseline to 18 months in ADCOMS (a post-hoc analysis) and CDR-SB (an exploratory objective) between the placebo and 50 mg/day Total groups using ANCOVA with baseline value as covariate. ADCOMS, comprised of items from MMSE, CDR, and ADAS-Cog, has been suggested to show improved sensitivity detecting clinical decline in MCI-AD subjects versus CDR-SB1. The effect of elenbecestat on amyloid load was evaluated by comparing changes from baseline to 18-month amyloid-PET SUVR between placebo and 50 mg/day Total groups. Longitudinal amyloid PET was obtained from 28 subjects with florbetaben and 7 subjects with florbetapir. Analyses of mean cortical PET SUVR values (ratio of average of tracer-specific cortical regions to whole cerebellum) were based on ANCOVA, with baseline value as covariate. **Results:** Seventy subjects were randomized: 17 placebo, 17 elenbecestat 5 mg/day, 19 elenbecestat 15 mg/day, and 17 elenbecestat 50 mg/day. Following the protocol amendment, 21 subjects were reassigned from elenbecestat 5 and 15 mg/day to elenbecestat 50 mg/day; 38 subjects were included in the 50 mg/day Total group. Forty-three (61%) subjects completed study; 27 (39%) discontinued (5 placebo; 11 elenbecestat 50 mg/day Total; 11 elenbecestat 5 and 15 mg/day). Six of the discontinuations were due to a protocol criterion for lymphocyte subsets (2 placebo, 2 elenbecestat 15 mg/day, 2 elenbecestat 50 mg/day Total). No deaths occurred during the study. Incidences of TEAEs, severe TEAEs, and TEAEs leading to treatment discontinuation were similar for the 50 mg/day Total and placebo groups. No dose-dependent response relationship was observed. The most frequently reported TEAEs that occurred at a higher incidence in the 50 mg/day Total group compared to placebo were contact dermatitis, headache, abnormal dreams, diarrhea, and falls. No drug rash occurred in the study; no subject discontinued due to liver toxicity; no persistent changes in CD4, CD8 and CD19 counts were observed. Clinical outcome as measured by ADCOMS (Figure) in the 50 mg/day Total group (n=29) at 18 months demonstrated a 33% lower decline relative to placebo (n=12) (treatment difference= -0.07, p=0.38) in mean change from baseline. This finding was in line with a previous analysis using CDR-SB. The responsiveness of ADCOMS to disease decline was compared to CDR-SB using MSDR (Mean to Standard Deviation Ratio) analysis. The MSDR ratio showed that ADCOMS had a 27% improvement in responsiveness over CDR-SB (Table). This responsiveness translated to slower

disease decline on the 50 mg/day Total group vs placebo on change from baseline ADCOMS at 18 months (33.3% less decline, p=0.38) as compared to change from baseline CDR-SB at 18 months (31.2% less decline, p=0.55) and demonstrated its greater sensitivity to change as previously predicted. Analysis of amyloid load by PET SUVR with florbetaben (n=21 for 50 mg/day Total; n=7 for placebo) and florbetapir (n=3 for 50 mg/day Total; n=4 for placebo) as tracers showed statistically significant treatment differences of -5.8% (p=0.013) and -13.6% (p=0.014), respectively, between the 50 mg/day Total vs placebo in mean percent change from baseline at 18 months. Whereas amyloid loads increased (3.3% for florbetaben; 5.8% for florbetapir) for placebo, amyloid loads in the 50 mg/day Total group decreased 2.5% for florbetaben and 8.6% for florbetapir at 18 months. **Conclusions:** Elenbecestat was generally well tolerated; no unexpected safety concerns were observed during the study. Although sample sizes were small, PET-SUVR analysis demonstrated a statistically significant treatment difference at 18 months in subjects treated with elenbecestat 50 mg/day vs placebo. Finally, a post-hoc analysis of the ADCOMS showed increased responsiveness to disease decline compared to existing scales, with ADCOMS showing 27% improvement in responsiveness over CDR-SB (Table), thus further supporting use of this endpoint. Reference: 1. Wang J, et al. J Neurol Neurosurg Psychiatry. 2016;87:993–9.

Figure
Changes from baseline in ADCOMS values (mean +/- SE)

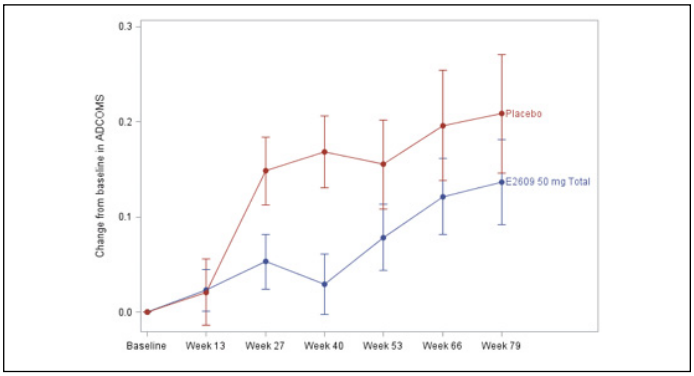


Table 1
Mean to Standard Deviation Ratio (MSDR) for ADCOMS and CDR-SB in placebo group

	ADCOM	CDR-SB	RATIO
MSDR	0.95	0.75	1.27

OC6: ALLOPREGNANOLONE REGENERATIVE THERAPEUTIC FOR MILD COGNITIVE IMPAIRMENT AND MILD ALZHEIMER'S DISEASE: PHASE 1B/2A OUTCOMES UPDATE. Roberta D. Brinton[1], Gerson D. Hernandez[1], Naoko Kono[2], Claudia M. Lopez[1], Christine Solinsky[3], Kathleen Rodgers[1], Jin Gahm[4], Dogu Aydogan[4], Yonggang Shi[4], Sonia Pawluczyk[5], Meng Law[6], Wendy Mack[2], Lon Schneider[5] *((1) Center for Innovation in Brain Science, University of Arizona, Tucson, Arizona, USA; (2) Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA; (3) School of Pharmacy, University of Southern California, Los Angeles, CA, USA; (4) USC Institute for Neuroimaging and Informatics, University of Southern California, Los Angeles, CA, USA; (5) Department of Psychiatry & The Behavioral Sciences, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA; (6) Department of Radiology, University of Southern California, Los Angeles, CA, USA)*

Background: Allopregnanolone (Allo) is a first in class regenerative therapeutic for delaying progression and treating AD with a strong foundation of human safety exposure. Targeting the regenerative system of the brain while simultaneously activating systems to reduce AD pathology burden is a novel therapeutic approach. Allo targets the regenerative neurogenic system of the brain, cholesterol trafficking and cleareance systems to prevent beta amyloid generation, white matter regeneration and anti-inflammatory system. Therapeutics and regimens of treatment that promote endogenous regeneration and are temporally aligned with renewal processes in vivo are more likely to translate from preclinical to clinical efficacy. Preclinical translational analyses indicated that an Allo treatment regimen of once per week over the course of months was optimal. Using a regenerative treatment regimen, Allo significantly increased survival of newly generated neurons, simultaneously reduced beta-amyloid generation in the hippocampus, cortex, and amygdala and reduced microglial activation. **Objectives:** Main objectives were to assess safety and tolerability of different doses of Allo administered intravenously once per week over 12 weeks. Primary outcomes of this multiple ascending dose (MAD) trial were determination of the safety, tolerability, pharmacokinetics and amyloid-related imaging abnormalities (ARIA) of all doses of Allo to establish a safe non-sedative dose for future phase 2 studies of efficacy. Exploratory goals were to evaluate the feasibility and potential effect of Allo on cognitive measures and MRI biomarkers of regeneration. Specific aim 1 objectives were to: 1) complete a MAD analysis of Allo doses ranging from 2mg to 18mg administered intravenously once per week for 12 weeks; 2) determine pharmacokinetic properties of Allo at the start and end of 12 week exposure; 3) determine a maximally tolerated and safe non-sedative Allo dose; 4) as a safety precaution, assess whether Allo might be associated with amyloid-related imaging abnormalities (ARIA) and specifically with micro-hemorrhages. Specific aim 2 objectives were to: 1) assess potential short-term effects of Allo dosing on cognition and segmented hippocampal volume; 2) develop preliminary operational data and methods to inform subsequent phase 2 proof of concept trial and development of biomarkers of regenerative efficacy. **Methods:** Double-blind randomized controlled multiple ascending dose clinical trial design. Eligible participants patients were men and women age ≥ 55 years, with mild cognitive impairment (MCI) due to AD or mild AD, MMSE score ≥20 and clinical dementia rating of 0.5-1. Participants were randomly assigned to receive weekly intravenous treatment of Allo or placebo (3:1 ratio) and were evenly distributed across 3 dosing cohorts (2mg, 4mg and 6-18mg). ClinicalTrials.gov Identifier: NCT02221622. **Results:** A total of 24 participants were enrolled into the trial (18 allopregnanolone + 6 placebo). The trial was completed in February 2018 and data locked in April 2018. Allo was well tolerated and resulted in no detectable adverse effects or ARIA. It exhibited favorable pharmacokinetic parameters and maximally tolerated dose was established by onset of sedation (see Hernandez et al abstract for details). Relative to placebo, Allo treated groups, on average, sustained hippocampal volume over 3 months of treatment. Cognitive function measured by ADAS-cog14 did not improve. However,

Cogstate scores consistently showed modest improvement of Allo treated groups compared to placebo. Subgroup analysis based on APOE genotype suggested greater responsivity in APOE4 carriers. Biomarker development to a priori identify potential regenerative responders was initiated using patient derived PBMCs reprogrammed to inducible pluripotent stem cells (iPSCs) and differentiated to neural stem cells was established. **Conclusion:** Allopregnanolone is a first in class regenerative therapeutic for MCI and mild Alzheimer's disease that targets endogenous neural stem cells and disease modifying mechanisms. Phase 1b/2a clinical trial data indicate safety and potential efficacy. Research supported by National Institute on Aging U01AG031115 to RDB; U01AG047222 to RDB; UF1AG046148 to RDB & LS; Alzheimer Drug Discovery Foundation to RDB P50 AG05142 USC ADRC (Schneider), ClinicalTrials.gov Identifier: NCT02221622.

Figure 1

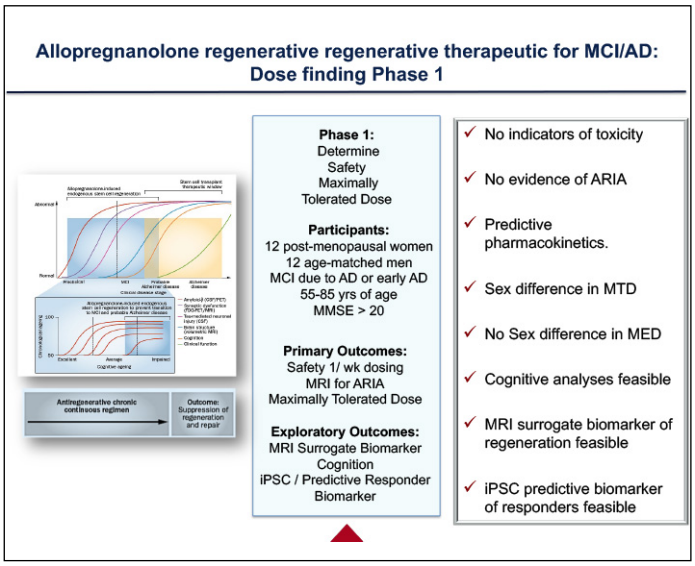
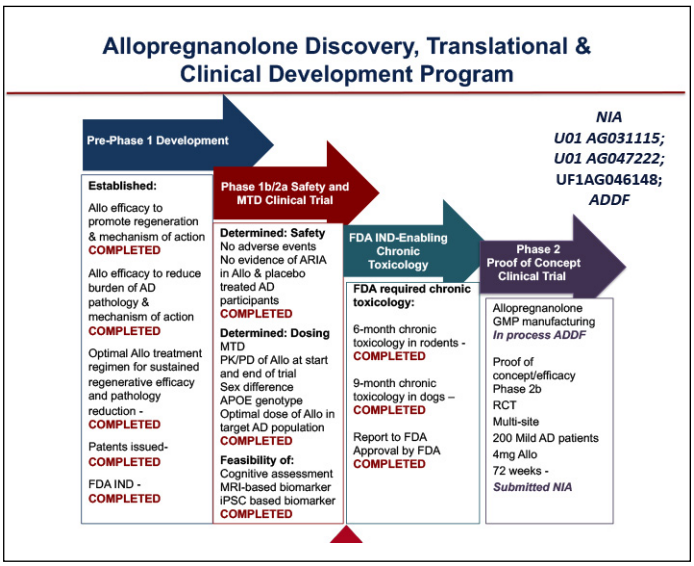


Figure 2



OC7: IMPACT OF AMYLOID PET ON THE MANAGEMENT OF COGNITIVELY IMPAIRED PATIENTS: RESULTS FROM THE IDEAS STUDY. Gil D. Rabinovici[1], Constantine Gatsonis[2], Charles Apgar[3], Kiran Chaudhary[1], Ilana Gareen[2], Lucy Hanna[2], James Hendrix[4], Bruce E. Hillner[5], Cynthia Olson[3], Orit Lesman-Segev[1], Justin Romanoff[2], Barry A. Siegel[6], Rachel A. Whitmer[7], Maria C. Carrillo[4] on behalf of the IDEAS investigators *((1) Department of Neurology, University of California San Francisco, USA; (2) Center for Statistical Sciences, Brown University, USA; (3) American College of Radiology, USA; (4) Alzheimer's Association, USA; (5) Department of Medicine, Virginia Commonwealth University, USA; (6) Department of Radiology, Washington University, USA; (7) Division of Research, Kaiser Permanente, USA)*

Background: The Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study (https://clinicaltrials.gov/ct2/show/NCT02420756?term=NCT02420756&rank=1) assesses the clinical utility of amyloid PET under the Centers for Medicare and Medicaid Services Coverage with Evidence Development program. Participants in IDEAS were enrolled by 1,163 dementia specialists (DS) in 592 clinics and imaged at 343 PET facilities across the United States. Accrual for the first aim of the study, which evaluates the impact of the scan on patient management, began in February 2016 and concluded in July 2017. Participants were Medicare beneficiaries aged 65 years and older meeting Appropriate Use Criteria for amyloid PET (Johnson et al. Alzheimer's & Dementia 2013) as assessed by DS. Patients were sub-classified as meeting criteria for mild cognitive impairment (MCI) or atypical dementia. We have previously reported results from a pre-specified interim analysis in the first ~4,000 participants (Rabinovici et al., AAIC 2017). Here we report complete results for the first aim of the study. **Methods:** DS completed a pre-PET case report form (CRF) documenting the patient management plan assuming they would have no access to amyloid PET. Patients then underwent PET imaging with an FDA-approved beta-amyloid ligand ([18F]florbetaben, [18F]florbetapir or [18F]flutemetamol). Scans were interpreted locally by certified radiologists or nuclear medicine physicians, and results were provided to the DS, who re-evaluated the diagnosis and patient management plan. Patients returned for a post-PET visit 90 ± 30 days following PET. DS completed a post-PET CRF recording the implemented management plan at the post-PET visit. We measured the rate of change between pre- and post-PET management in a composite endpoint that included changes in one or more of the following: (1) use of Alzheimer's disease specific (AD) drug therapy, (2) other drug therapy, or (3) counseling about safety and future planning. The study was powered to detect a ≥ 30% change in the composite endpoint, separately in the MCI and dementia sub-groups (α=0.025, β=0.90). This analysis was performed in the first 11,374 enrolled patients with completed PET scans and protocol compliant post-PET CRFs (Figure 1). **Results:** Demographics and selected clinical information of patients in the analysis set (n=11,374) are shown in Table 1. 60.5% met criteria for MCI and 39.5% were diagnosed with atypical dementia. Prior to PET, AD was the suspected etiology of cognitive impairment in 76.9% of participants, and 44.4% were taking AD medications (cholinesterase inhibitor or memantine). Rates of amyloid PET positivity were 55.3% in MCI and 70.1% in dementia. The patient management composite endpoint changed between the pre-PET and post-PET CRFs in 60.2% of patients with MCI (95% confidence interval: 59.1%-61.4%) and 63.5% of patients with dementia (62.0%-64.9%).

In MCI, changes in management included: changes in AD drugs (43.6%), counseling (24.4%) and non-AD drugs (22.9%), whereas in dementia changes were seen in AD drugs (44.8%), non-AD drugs (25.4%) and counseling (20.7%). Following PET, rates of AD as the primary diagnosis increased from 80.3% to 95.4% in patients with a positive scan, and decreased from 71.5% to 10.2% in patients with a negative scan. Use of AD medications increased from 50.8% to 85.9% in amyloid PET positive participants, and decreased from 34.3% to 29.7% in amyloid PET negative participants. There was a reduction between pre-PET intended and post-PET implemented use of neuropsychological testing (20.9% to 10.0%), additional brain imaging (17.3% to 9.0%) and CSF studies (10.7% to 0.9%). 1,394 patients were referred to clinical trials for AD at the post-PET visit, constituting 18.6% of all amyloid-positive and 2.2% of all amyloid-negative participants. **Conclusion:** Amyloid PET has a major impact on the care plan in patients meeting Appropriate Use Criteria, leading to changes in use of medications, counseling and ancillary diagnostic tests. Further follow-up will determine whether the scan is associated with improved health outcomes and reduced resource utilization. Funding: IDEAS is funded by the Centers for Medicare and Medicaid Services, Avid Radiopharmaceuticals/Eli Lilly, General Electric Healthcare, Piramal Imaging, Alzheimer's Association and American College of Radiology.

Table 1
Patient characteristics

Characteristic	Level of Impairment		All Participants
	MCI	Dementia	
Number of Participants	*(n=6,886)*	*(n=4,488)*	*(n=11,374)*
Age, median, IQR			
Median	75	77	75
IQR (Q1-Q3)	70-79	72-81	71-80
Female, n (%)	3,415 (49.6)	2,371 (52.8)	5,786 (50.9)
Race, n (%)			
Black or African American	206 (3.0)	224 (5.0)	430 (3.8)
White	6,193 (89.9)	3,813 (85.0)	10,006 (88.0)
Other race	487 (7.1)	451 (10.0)	938 (8.2)
Hispanic, n (%)	209 (3.0)	244 (5.4)	453 (4.0)
College or advanced degree	3,307 (48.0)	1,648 (36.7)	4,955 (43.6)
MMSE, median, IQR			
Median	27	22	26
IQR (Q1-Q3)	25-29	18-25	22-28
MoCA, median, IQR			
Median	23	18	22
IQR (Q1-Q3)	21-25	14-21	17-24
Leading Suspected Etiology is AD, n (%)	5,030 (73.0)	3,712 (82.7)	8,742 (76.9)
Taking AD drugs at enrollment, n (%)	2,379 (34.5)	2,666 (59.4)	5,045 (44.4)
Amyloid PET Result, n (%)			
Positive	3,806 (55.3)	3,143 (70.1)	6,949 (61.1)
Negative	3,074 (44.7)	1,342 (29.9)	4,416 (38.9)

OC8: SAFETY AND EFFICACY OF ESTROGEN RECEPTOR-B TARGETED PHYTOSERM FORMULATION FOR COGNITIVE COMPLAINTS AND VASOMOTOR SYMPTOMS: PHASE 1B/2A TRIAL OUTCOMES.

Lon S. Schneider[1], Gerson Hernandez[2], Liqin Zhao[3], Sonia Pawluczyk[1], Wendy J. Mack[1], Roberta D. Brinton[2] *((1) Keck School of Medicine of the University of Southern California, Los Angeles, USA; (2) University of Arizona, Center for Innovation in Brain Science, Tucson, USA; (3) University of Kansas – USA)*

Background: The role of postmenopausal estrogen therapy in cognitive function and Alzheimer disease is of considerable interest. Estrogen-containing hormone therapy, however, has been unsuccessful in Alzheimer disease, mild cognitive impairment, and for preventing cognitive impairment; and, rather, has been cognitive impairing. Women often describe problems with memory and difficulty concentrating during menopausal transition and menopause. Yet, substantial biologic evidence supports the importance of estrogen to cognitive function. Alternative approaches to estrogen replacement include plant-derived structural analogs of mammalian estrogens ("phytoestrogens") that can bind, at weak to moderate affinities to estrogen receptors and exert estrogenic or antiestrogenic activities. Selective estrogen receptor-β (ERβ) may be a novel therapeutic target for the development of therapies for a range of conditions including cognitive impairment and age-related ovarian failure (menopause). The development of a formulation composed of rationally-selected ERβ-selective phytoestrogens (phytoSERMs) provides a greater effect on ERβ than plant based formulations that contain weak ERα and ERβ agonists and antagonists. The rationally-defined content of this new formulation induces synergistic rather than antagonistic effects on estrogen receptors and could potentially generate salutary therapeutic effect. PhytoSERM is a formulation of genistein, daidzein, and S-equol that has an 83-fold selective affinity for estrogen receptor- (ERβ); and, therefore, may enhance neuron function and estrogenic mechanisms in the brain without having peripheral estrogenic activity. **Objectives:** We report here outcomes of a randomized, nested, placebo-controlled clinical trial of this ERβ specific phytoSERM combination for peri- and post-menopausal women. The trial served several purposes in the development of the phytoSERM formulation, including a dose-ranging, placebo-controlled trial to assess pharmacokinetics, tolerability, initial safety, and the potential for efficacy over 4 weeks and 12 weeks, using an embedded 4-week period, 2 period crossover study to assess efficacy again in a within-subject comparative design. **Methods:** We conducted a randomized, placebo-controlled trial of 12 weeks duration comparing 50 mg per day and 100 mg per day of phytoSERM with placebo for non-cognitively impaired, perimenopausal women ages 45 to 60, with intact uteri and ovaries, with at least one cognitive complaint and one vasomotor-related symptom (Clinicaltrials.gov NCT01723917). Goals were to examine the evidence for safety, improved vasomotor symptoms, neuropsychological performance and psychological symptoms with the phytoSERM formulation. Primary objectives were to assess: (1) safety, tolerability of a 50 mg and 100 mg daily dose compared to placebo over 4 and 12 weeks; (2) potential efficacy indicators of phytoSERM on cognition and vasomotor symptoms over 12 weeks and by using an imbedded, 4-week treatment, 2-period, placebo-controlled crossover trial for a subset of participants; and (3) to develop biomarkers for response. **Results:** A total of 71 women were randomized to treatment; 70 were evaluated at 4 weeks; 12 were entered into the crossover study; 5 did not complete the 12 weeks. Reasons for discontinuation were: withdrawal of consent (1), lost to follow-up (4) and concern about dependence (1); none was due to adverse events. Safety outcomes indicated the phytoSERMs were safe and well tolerated. Adverse events associated with phytoSERM exposure occurred in 16.7%, 39.1%, and 29.2%, placebo, 50 mg, and 100 mg, respectively. Vaginal bleeding was observed in 3, 100 mg, 1, 50 mg, and 0 placebo participants. Based on safety outcomes, an optimal dose of 50mg phytoSERM was established. No significant effects on vasomotor symptoms, cognition, or psychological symptoms at 4 weeks, 12 weeks, or within the crossover comparison were observed. **Conclusions:** The phytoSERM formulation was safe and well-tolerated at 50 and 100 mg daily doses with 50 mg established as optimal dose for future testing. Although we did not observe a nominally significant effect on vasomotor symptoms or cognition, effect sizes for some of the outcomes

suggested the potential for efficacy. Funding: Funding for this work was provided by the National Institute on Aging through, NIH R01 AG033288 and NIH P50 AG05142 (USC Alzheimer's Disease Research Center); and the State of California Department of Health Services through grant 15-10291 (USC Alzheimer Disease Center). Clinicaltrial.gov: NCT01723917

OC9: INTERIM SAFETY AND EFFICACY RESULTS OF PILOT TRIAL OF GM-CSF/SARGRAMOSTIM IN MILD TO MODERATE AD. Huntington Potter[1], Jonathan H. Woodcock, Timothy Boyd, Stefan H. Sillau, Thomas Borges, Brianne M. Bettcher, Joseph Daniels *(Rocky Mountain Alzheimer's Disease Center, Department of Neurology University of Colorado School of Medicine, USA)*

Background: Following Rheumatoid arthritis (RA) patients have a reduced risk of developing Alzheimer's disease (AD), which was originally hypothesized as attributable to their usage of non-steroidal anti-inflammatory drugs (NSAIDs). However, clinical trials with NSAIDs were unsuccessful in both AD and MCI subjects. We therefore pursued our hypothesis that intrinsic factors within RA pathogenesis itself may underlie the AD protective effect(s). We focused on the innate immune system, tested several protein cytokines upregulated in RA blood, and found that 20 daily injections of 5 ug GM-CSF reduced AD pathology by greater than 50% and completely reversed the cognitive impairment of transgenic AD mice (Boyd et al., 2010). Additionally, we found that bone marrow transplant (BMT) patients treated with Leukine® (recombinant human GM CSF) plus recombinant G-CSF to treat leukopenia showed significantly improved cognitive functioning at six months compared to BMT patients who received G-CSF alone or no treatment (Jim et al.,). **Objectives:** To determine whether GM-CSF/sargramostim can safely halt or reduce cognitive decline and brain pathology in subjects with mild to moderate Alzheimer's disease. **Methods:** We are conducting two double blind Phase II safety and efficacy trials of Leukine® in mild-to-moderate AD subjects at 250 ug/m2/day SC for 5 days/ week for either three weeks or 24 weeks with follow-up visits at 45 and 90 days. Neurological and neuropsychological assessments, and MRI and amyloid-PET scans are performed to assess the effects of treatment. **Results:** Interim analyses of 15 subjects treated with GM-CSF/sargramostim and 15 subjects treated with placebo in our three-week trial showed no drug-related adverse events, including no evidence of amyloid-related imaging abnormalities (ARIAs), which indicate micro-hemorrhage or vasogenic edema. When comparing measures at the end of treatment to baseline, the mean changes of the MMSE score showed improvement in the GM-CSF group relative to baseline ($p=0.0029$) and to the placebo group ($p=0.0175$) by repeated measures mixed model analysis. Differences were not significant by the follow-up visits. Amyloid PET data for the last 10 subjects also showed a significant reduction in amyloid in the GM-CSF group. **Conclusions:** These results, although preliminary and based on a small number of subjects, indicate that completing the three-week trial and continuing our Alzheimer's Association "Part the Cloud"-funded 24-week trial of GM-CSF/ sargramostim in subjects with mild-to-moderate AD are warranted. We will report on the progress of both trials. References: Boyd, T. D., S. P. Bennett, T. Mori, N. Governatori, M. Runfeldt, M. Norden, J. Padmanabhan, P. Neame, I. Wefes, J. Sanchez-Ramos, G. W. Arendash and H. Potter (2010). «GM-CSF upregulated in rheumatoid arthritis reverses cognitive impairment and amyloidosis in Alzheimer mice.» J Alzheimers Dis 21(2): 507-518. Jim, H. S., T. D. Boyd, M. Booth-Jones, J. Pidala and H. Potter (2012). «Granulocyte Macrophage Colony Stimulating Factor Treatment is Associated with Improved Cognition in Cancer Patients.» Brain Disord Ther 1(1)

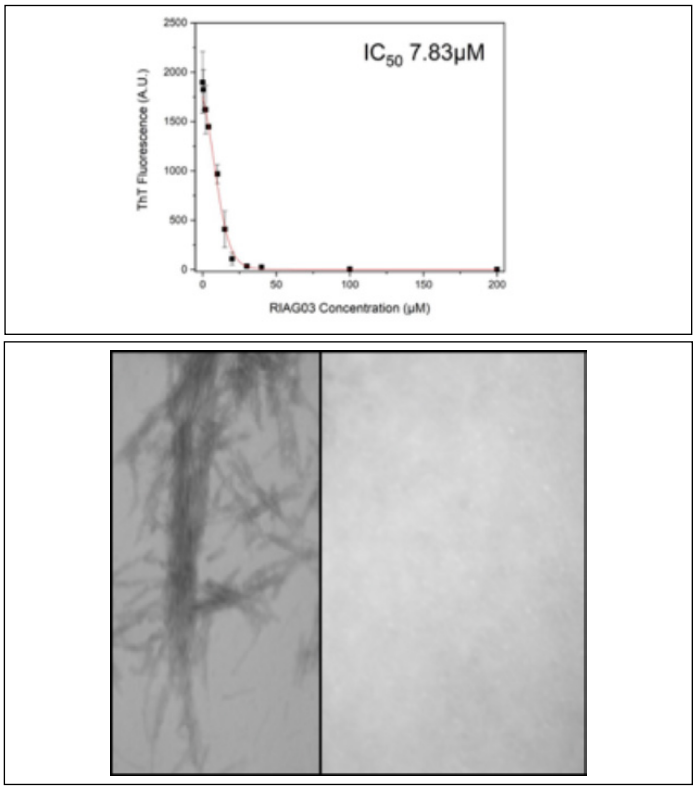
OC10: UNTANGLED – PEPTIDE-BASED INHIBITORS OF TAU AGGREGATION AS A POTENTIAL TREATMENT FOR ALZHEIMER'S DISEASE. David Allso[1,2], Anthony Aggidis[1], Nigel Fullwood[1], Mark Taylor[1,2], Penny Foulds[1,2], Shoona Vincent[2], Mark Dale[2] *((1) Division of Biomedical and Life Sciences, Faculty of Health and Medicine, Lancaster University, Lancaster, UK; (2). Peptide Innovations Limited, Affiliated Company of MAC Research, Blackpool, UK)*

Background: It Neurofibrillary tangle (NFT) formation within neuronal cells is one of the two main pathological hallmarks of Alzheimer's disease (AD). The extent of tangle formation in the brain shows a better correlation with clinical disease severity than that of amyloid plaque formation, although Aβ aggregation is likely to precede and induce tangle formation [1]. Clinical trials involving immunological removal of β amyloid (Aβ) from the brain, or the use of secretase inhibitors to limit production of Aβ, have so far shown little or no improvement in clinical outcome measures in mild cognitive impairment (MCI) and AD patients, and this type of therapy may require very early intervention in the course of the disease. Inhibition of tau aggregation, or dual inhibition of amyloid and tau, could provide a better treatment for more advanced disease. We have previously developed very effective small peptide and peptide-liposome inhibitors of Aβ aggregation, and have achieved blood-brain barrier penetration, reduction in amyloid plaque load, inhibition of oligomer formation, reduction in oxidation and inflammation, and prevention of memory loss, in transgenic mouse models [2-4]. Here, we describe a similar approach to development of peptide-based inhibitors of tau aggregation. **Objectives:** Our objective is to prevent tau aggregation based on the rational design of inhibitory peptides and peptide derivatives focussed around the self-binding motifs of tau protein - with additional solubilising residues, and the addition of cell-penetrating and brain-penetrating peptide transit sequences. Further work will involve covalent attachment of these peptides to the surface of nanoliposomes, along with the development of a dual-acting liposome that inhibits both Aβ and tau aggregation. **Methods:** To optimise the tau binding sequence, we tested a series of peptides, over a number of iterations, for their effects on tau aggregation, and then looked at the effects of retro-inversion and N-methylation on the resulting optimal peptide, in order to increase its stability. The misfolding and aggregation of recombinant tau Δ250 (at 20 μM in the presence of 5 μM heparin) were examined in the presence of various concentrations of these inhibitory peptides, using thioflavin fluorescence, Congo red polarization microscopy, CD spectroscopy and negative stain EM. **Results:** The retro-inverted form of the optimal peptide, RIAG03, was an effective inhibitor of tau aggregation, with an IC50 of around 7.8 μM against 20 μM of tau Δ250 (see Figure, left). Examination by negative stain EM showed that an equimolar concentration of this inhibitor almost completely blocked tau fibril formation (Figure, right). Various control peptides (e.g. with a scrambled binding sequence, or the transit peptide alone) were ineffective. RIAG03 also inhibited β-sheet formation, as determined by CD spectroscopy and Congo red binding. The

solubilising residues incorporated into the amino acid sequence of RIAG03 prevented self-aggregation of this inhibitor peptide. **Conclusions:** We have identified an effective cell-penetrating and stabilized inhibitor of tau aggregation for further preclinical development and testing in cell and animal models. One of our next steps will be to attach RIAG03 to our nanoliposomes to give a multivalent inhibitor that should have enhanced potency [4]. One of our main objectives is to attach inhibitory peptides directed at both Aβ and tau to the same liposomes, to produce a dual aggregation inhibitor. Due to the complex heterogeneous aetiology of AD, It is becoming increasingly apparent that combination therapies may be required, and liposomes are a biocompatible and highly flexible vehicle for achieving this.

[1] Hardy J. & Allsop D. (1991) Trends Pharmacol. Sci. 12, 383-388; [2] Taylor M., et al. (2010) Biochemistry 49, 3261–3272; [3] Parthsarathy V., et al. (2013) PLoS ONE 2013;8(1): e54769; [4] Gregori M., et al. (2017) Nanomed: Nanotech. Biol. Med. 13, 723-732.

Figure 1
Inhibition of tau Δ250 aggregation in a thioflavin assay (left) and by negative stain EM (right)



OC11: SAFETY AND EFFICACY OF LEMBOREXANT FOR SLEEP-WAKE REGULATION IN PATIENTS WITH IRREGULAR SLEEP WAKE RHYTHM DISORDER AND ALZHEIMER'S DISEASE DEMENTIA. Margaret Moline[1], Mohammad Bsharat[1], Manuel Kemethofer[2], Gleb Filippov[1], Naoki Kubota[3], Patricia Murphy[1] *((1) Eisai, Inc., Woodcliff Lake, USA; (2) The Siesta Group, Vienna, Austria (3) Eisai Co. Ltd., Tokyo, Japan)*

Background: Disturbances in sleep-wake regulation appear early in the course of Alzheimer's disease dementia (AD-D) and are correlated with impaired cognition and adverse clinical outcomes. One such manifestation of this disturbance in sleep-wake regulation is the circadian rhythm sleep disorder Irregular Sleep-Wake Rhythm Disorder (ISWRD). There are currently no treatments approved for ISWRD.Recent data suggest that the orexin neurotransmitter system may be involved in the neuropathology of ISWRD, and may be a suitable target for therapeutic intervention. Lemborexant is a dual orexin receptor antagonist in development for the treatment of multiple disorders of sleep-wake regulation including ISWRD and insomnia disorder. A Phase 2 proof-of-concept and dose-finding clinical trial is underway to evaluate whether lemborexant affects nighttime sleep, daytime wakefulness, circadian rhythm parameters, and other clinical measures of ISWRD in patients with mild to moderate AD-D. **Methods:** Subjects 60 to 90 years who met criteria for both AD and ISWRD were recruited from sites in the United States and Japan. Eligible subjects had Mini-Mental State Exam (MMSE) scores between 10 and 26 and were not clinically depressed. During the screening period, subjects underwent a polysomnogram either at home or in the clinic to rule out moderate to severe sleep apnea. Subjects wore actigraphy devices (MotionWatch 8, CamNtech; MW8) continuously on the non-dominant wrist for approximately 14 days, and were eligible for randomization after meeting criteria indicating both disrupted nighttime sleep and daytime wakefulness. At baseline, subjects and caregivers were interviewed to obtain pre-treatment information using a modified global scale, the Clinician Global Impression of Change – ISWRD version (CGIC-ISWRD), based on the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change and Clinicians' Interview-Based Impression of Change – Plus Caregiver Input, which included domains that could reasonably be expected to change with successful treatment of sleep and wake symptoms. Additional assessments of the subject obtained at baseline included the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog), EuroQual 5-dimension 5-level version (EQ-5D-5L), Neuropsychiatric Inventory – 10 items (NPI-10) and Sleep Disorders Inventory (SDI). At baseline, caregivers were also assessed regarding their sleep (Pittsburgh Sleep Quality Index [PSQI]), health status (EQ-5D-5L), and levels of caregiver burden (Zarit Burden Interview [ZBI]). Subjects were randomized to placebo or 1 of 4 treatment arms of lemborexant (2.5, 5, 10, or 15 mg), and provided instructions to take the study medication at bedtime. Actigraphy parameters were derived from the actigraphy data at screening, baseline, and over 1 month of treatment, and included but were not limited to actigraphy-based sleep efficiency (aSE), sleep fragmentation index, wake efficiency (aWE), wake fragmentation index, relative amplitude, intradaily variability, and interdaily stability. Caregivers maintained a log each day of the study to indicate when the subjects went to bed for the night and when they got out of bed in the morning as well as times when the actigraph was not recording data, e.g. if the device had been removed for some reason. At the end of treatment, the CGIC-ISWRD, ADAS-cog, MMSE, NPI, SDI, EQ-5D-5L, PSQI, and ZBI were administered to subjects and/or caregivers. Safety was assessed at all visits throughout the study. Following the 4-week treatment period, there was a 2-week follow-up period without study medication to assess for possible rebound ISWRD symptoms and for safety. **Results:** To date, 230 subjects were screened; 61 were randomized. The major reasons for screen failure included ineligible scores on actigraphy measures of aSE or aWE or an apnea-hypopnea index greater than 15

events per hour of sleep. Baseline MMSE scores were 12-26. All subjects who were randomized completed the 4 weeks of treatment. Results from the study will be provided at the time of presentation. **Conclusions:** This randomized clinical trial is the first in the ISWRD patient population with a drug affecting orexin neurotransmission. The results will provide important new information regarding the potential utility of this investigational medication to address both nighttime and daytime symptoms that impact the quality of life of ISWRD/AD-D patients and their caregivers and families.

OC12: TAU PET IMAGING AS A SCREENING TOOL FOR CLINICAL TRIALS OF DISEASE MODIFYING THERAPIES.

Adam S Fleisher[2], Michael J Pontecorvo[2], Michael D Devous[2], Ming Lu[2], Sergey Shcherbinin[1], Anupa K Arora[2], Mark A Mintun[1,2] *((1) Eli Lilly & Co, Indianapolis, IN, USA; (2) Avid Radiopharmaceuticals, Inc., Philadelphia, PA, USA)*

Background: Imaging biomarkers can facilitate identifying appropriate patient populations for disease modifying therapy trials based on the presence of known pathologies that predict likelihood of clinical progression, and by selecting individuals that are most likely to respond to a given therapy. Understanding how to best utilize tau PET as a screening tool for such trials may improve their efficiency and potentially increase the probability of their success. The present study tested the hypothesis that flortaucipir F18 PET imaging can identify early symptomatic AD Aβ+ populations that are likely to experience cognitive decline during eighteen-month clinical trials, and, can exclude patients with advanced pathology that may not be as amenable to some disease modifying therapies. We evaluated visual pattern categories and quantitative uptake ranges of flortaucipir PET for their association with 18 month change on cognitive outcome measures. We propose a combination of both visual patterns and quantitative standardized uptake value ratios (SUVr's) that can serve as inclusion/exclusion criteria for clinical trials. **Methods**: Data sets were pooled across two completed 18 month clinical trials: Expedition3 (solanezumab phase III: NCT01900665) and AV-1451-A05 (flortaucipir phase II: NCT02016560). Participants with dementia or mild cognitive impairment due to AD received flortaucipir PET (30 min scan, ~75 min post 240 MBq iv in EXP3; 20 min scan, ~80 min post 370 MBq iv in A05), florbetapir PET (10 or 20 min scan ~50 min after a 370 MBq dose in A05 and EXP3 respectively), and cognitive tests including the MMSE and ADAScog11. Baseline florbetapir PET scans were read as either amyloid positive (Aβ+) or negative (Aβ- ; Note, EXP3 tau scans were obtained only after a positive florbetapir scan; all Aβ- cases came from the A05 study). Baseline flortaucipir PET scans were visually interpreted as 1) non-AD pattern (τAD-): either no neocortical signal or elevated neocortical signal limited to mesial temporal, anterolateral temporal and/or frontal lobe, 2) early-AD pattern (τAD+): posterior lateral temporal (PLT) and/or occipital signal consistent with an AD pattern, or 3) advanced-AD pattern (τAD++): signal beyond PLT/occipital. τAD++ was further subdivided into scans without frontal (τAD++ w/oF) and with frontal (τAD++ w/F) involvement. Flortaucipir SUVr's were determined in a neocortical region of interest (MUBADA; Devous et al, JNM, 2017) with respect to a white matter reference region (Southekal S et al, JNM, 2017). Flortaucipir scans were also divided into four SUVr quartiles based on the EXP3 SUVr distribution (Mintun et al AAIC 2017, Alz&Dem, O5-01-01) resulting in approximately 25% of the Aβ+ dementia patients in each group. We assessed baseline visual and quantitative flortaucipir classifications for association with 1) amyloid positivity and 2) progression over 18 months on the ADAScog11. Least Square Mean change from baseline and relative p-values were derived from Mixed Model Repeated Measures (MMRM) controlling for age, education, and baseline ADAS score.**Results**: Two hundred forty-six study completers were included (MCI: N=65, age=71±9.4, MMSE=27.9±1.9; AD dementia: N=181, age=74±7.6, MMSE=22.6±2.9). From the A05 study, elevated flortaucipir PET signal (visual pattern ≥ τAD+, or SUVr quartiles 2-4) was associated with a positive florbetapir PET scan (>98% PPV for Aβ+), but not all Aβ+ subjects had elevated flortaucipir PET signal (23% of Aβ+ subjects were visually τAD-; 43% were in SUVr quartile 1). The magnitude of cognitive decline increased significantly as a function of SUVr quartile (Table, Figure 1a). The smallest decline in the ADAScog11 was seen in quartile 1, which was not statistically different between Aβ+ (N=65) and Aβ- (N=46) subjects (p=0.5957). Only visual patterns with uptake beyond the temporal and occipital lobes (τAD++) were associated with significant 18 month progression on the ADASCog11 (p≤ 0.0001) (Table, Figure 1b). However, there is a suggested interaction between flortaucipir quantitation and visual read status (Figure 1c); among individuals with τAD++w/F visual patterns, increasing SUVr quartile membership was associated with worsened cognitive decline (Figure 1c). And, all individuals within SUVr quartile 4 had widespread flortaucipir uptake that included the frontal lobes (τAD++w/F)(Figure 1c). **Conclusions**: Flortaucipir PET potentially can be utilized as a screening tool in clinical trials to minimize enrollment of slow cognitive decliners and amyloid (florbetapir) PET negative patients. This may be accomplished by excluding subjects with non-AD patterns of flortaucipir (τAD-) or individuals with low neocortical SUVr's (quartile 1) that do not have an advanced-AD pattern (τAD++). Further, for disease modifying therapies that are more likely suited for earlier AD pathology, excluding individuals with high SUVr (quartile 4) may eliminate rapid cognitive decliners that are less likely to be responsive to these therapies. Thus, enrollment algorithms utilizing both tau PET visual reads and quantitative thresholds may help select pathologically homogeneous populations customized for the needs of disease modifying therapy trials. Flortaucipir PET is now being used as a screening biomarker in proof of concept phase II studies (NCT03367403, NCT03518073.

Figure 1

Eighteen month ADAScog11 change by 1a) visual pattern categories, 1b) SUVR quartiles, and 1c) visual reads subdivided by SUVr quartiles. Error bars represent standard error from the mean

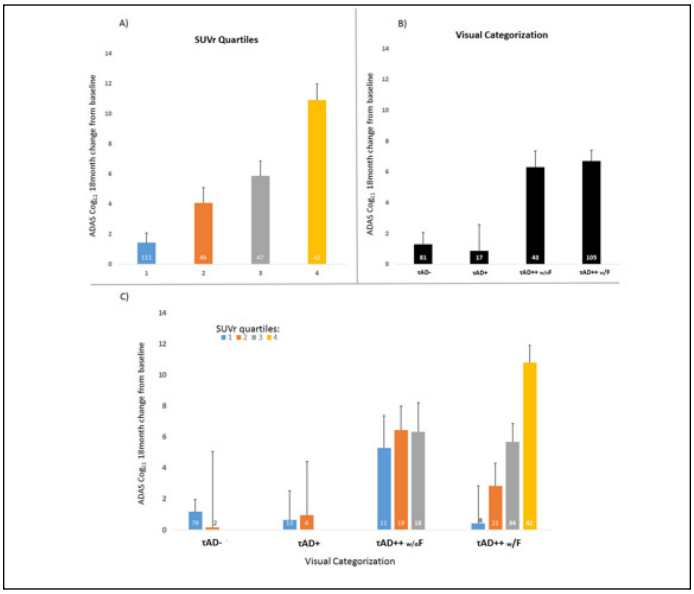


Table 1

Eighteen month ADAScog11 scores change from Baseline by Visual Read or SUVr Quartile. Least Square Mean change from baseline and relative p-values were derived from Mixed Model Repeated Measures controlling for age, education, and baseline ADAS score

18 month progression on the ADAScog$_{11}$		
Visual Category	Sample size	ADAScog11
AD-	81	1.28 P=0.1078
AD+	17	0.86 P=0.6185
AD++ w/oF	43	6.28 **P<0.0001**
AD++ w/F	105	6.70 **P<0.0001**
SUVR Quartiles		
1 (SUVR<1.10)	111	1.43 **P=0.0303**
2 (SUVR 1.10-1.23)	46	4.08 **P<0.0001**
3 (SUVR 1.24-1.46)	47	5.85 **P<0.0001**
4 (SUVR >1.46)	42	10.89 **P<0.0001**
Pair-wise comparison; visual categories; p-values		τAD – vs. τAD+ : 0.821 **τAD – vs. τAD++ w/oF: 0.0002** **τAD – vs. τAD+ w/F: <0.0001** **τAD+ vs. τAD++ w/oF: 0.008** **τAD+ vs. τAD+ w/F: 0.0019** τAD++ vs. τAD++ w/F: 0.746
Pair-wise comparison; SUVR quartiles; p-values		**Q1 vs. Q2: 0.0286** **Q1 vs. Q3: 0.0003** **Q1 vs. Q4: <0.0001** Q2 vs. Q3: 0.2138 **Q2 vs. Q4: <0.0001** **Q3 vs. Q4: 0.0008**

OC13: BACE INHIBITION BY VERUBECESTAT PRODUCES A RAPID, NON-PROGRESSIVE REDUCTION IN BRAIN AND HIPPOCAMPAL VOLUME IN ALZHEIMER'S DISEASE. Cyrille Sur[1], James Kost[1], David Scott[2], Katarzyna Adamczuk[2], Nick C Fox[3], Jeffrey Cummings[4], Pierre Tariot[5], Paul Aisen[6], Bruno Vellas[7], Tiffini Voss[1], Yuki Mukai[1], David Michelson[1], Michael Egan[1] *((1) Merck & Co., Inc., Kenilworth, NJ, USA; (2) Bioclinica, Newark, CA, USA; (3) University College London, London, UK; (4) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; (5) BannerAlzheimer's Institute, Phoenix, AZ, USA; (6) University of California San Diego, San Diego, CA, USA; (7) Gerontopole, Toulouse University Hospital, Toulouse, France)*

Introduction & Objectives: Beta secretase (BACE) inhibitors have the potential to slow or prevent Alzheimer's Disease (AD). Verubecestat (MK-8931), a potent BACE inhibitor, failed to improve cognition or function in participants with mild-to-moderate AD and also reduced MRI hippocampal volume in a 78 week Phase 2/3 trial (EPOCH; Egan et al. NEJM 2018;378:1691-1703). One interpretation of these findings is that BACE inhibition could exacerbate neurodegeneration. Here, we present kinetic analyses of volumetric MRI changes at earlier time points in trial participants to assess the time course of the volumetric changes. **Methods:** Participants between ≥ 55 and ≤ 85 years of age with probable AD and an MMSE score ≥ 15 and ≤ 26 were enrolled. MRI scans were obtained in a subset of participants at "baseline" (mean of 5 weeks before the start of treatment), and at weeks 13, 26, 52 and 78 of the treatment period. Using a standardized imaging protocol 3D T1-weighted MRI sequences were collected on various 1.5T and 3T MRI scanners from more than 200 centers worldwide. Images were centrally collected and curated for quality, segmented using Freesurfer and analyzed using a proprietary tensor based morphometry method at Bioclinica. **Results:** At baseline, the mean (S.D.) whole brain and hippocampal volumes were similar across treatment groups. For whole brain, the volumes in mL (and sample sizes) for placebo, 12mg and 40 mg groups were, respectively, 966 (99)(n=475), 973 (105)(n=461), 960 (104)(n=455) and, for hippocampal volume, 5.79 (1.04)(n=477), 5.85 (1.20) (n=464), 5.80 (1.17)(n=455). At week 78, brain and hippocampal volumes were lower in all three groups, but the reductions in the verubecestat treated groups were greater than those in the placebo group. The mean (S.D.) percent reductions in brain volumes in placebo, 12 mg and 40 mg groups, respectively were -2.5 (1.2)%, -2.9 (1.3)%, -2.9 (1.3)%, and in the hippocampus, -4.9 (2.4)%, -5.4 (2.6)%, -5.6 (2.4)%. The larger reductions in the verubecestat groups versus placebo were apparent at the earliest time point after treatment initiation (week 13). For the whole brain, mean (S.D.) percent reduction in volumes for the 12 or 40 mg groups were -0.9 (0.7)% and -1.0 (0.8)%, respectively compared to -0.6(0.7)% for participants on placebo. For the hippocampus, reductions were -1.9 (1.5)% and -1.8 (1.5)% for the 12 and 40 mg groups, respectively whereas a reduction of -1.2(1.4)% was observed in the placebo group. The differences between verubecestat and placebo were maintained, but did not increase further, over the subsequent treatment period. Using a longitudinal ANCOVA model, least-squares means (95% CI) for the week 78 – week 13 differences for whole brain volume were 0.0 (-0.2, 0.1) and 0.0 (-0.2, 0.1) for the 12 mg and 40 mg groups versus the placebo group, respectively. The least-squares means (95% CI) for hippocampus volume were 0.1 (-0.2, 0.4) and 0.0 (-0.3, 0.3) for the 12 and 40 mg groups versus

the placebo group, respectively. **Conclusions:** Volumetric MRI data from EPOCH trial participants showed a larger reduction in brain and hippocampal volumes at week 78 in the verubecestat groups than in the placebo group. Kinetic analyses of brain and hippocampal changes suggest that volumetric differences between verubecestat groups and the placebo group were driven by an early change (within the first 13 weeks of treatment) that was maintained but did not further increase over the subsequent weeks of the trial. It is interesting to note that there was an apparent modest initial worsening in mean cognition scores for verubecestat versus placebo at week 13 that was not maintained at week 78. The mechanism underlying the differences in MRI volume changes between verubecestat and placebo is uncertain but their time course argues against a sustained increase in rate of neurodegeneration.

OC14: DISTINCT TAU PET PATTERNS IN ATROPHY-DEFINED SUBTYPES OF ALZHEIMER'S DISEASE. Rik Ossenkoppele[1,2], Gil D. Rabinovici[3], Chul H. Lyoo[4], Oskar Hansson[1,5] *((1) Lund University, Clinical Memory Research Unit, Lund, Sweden; (2) VU University Medical Center, Department of Neurology and Alzheimer Center, Amsterdam Neuroscience, Amsterdam, the Netherlands; (3) Department of Neurology, University of California San Francisco, San Francisco, USA, Memory and Aging Center; (4) Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; (5) Memory Clinic, Skåne University Hospital, Malmö, Sweden)*

Background: Although both Alzheimer's disease (AD) pathological hallmarks (i.e. accumulation of amyloid-β plaques and tau neurofibrillary tangles) presumably follow a stereotypical spreading pattern1, significant inter-individual variability in the regional distribution of pathology has been observed. Based on the relative amount of neocortical vs hippocampal tangle pathology, researchers have identified "typical", "limbic-predominant", and "hippocampal-sparing" subtypes of AD2, which showed robust associations with age, APOE ε4 status, clinical phenotype and brain atrophy patterns.3 Objectives: To i) replicate these neuropathological subtypes in vivo using a clustering approach of quantitative structural MRI data, and ii) to examine the biological relevance of these subtypes by comparing differences in regional [18F] flortaucipir (tau) PET uptake. Methods: We included 260 amyloid-β+ AD patients from the Memory Disorder Clinic of Gangnam Severance Hospital (Seoul, South Korea), the Swedish BioFINDER study (www.biofinder.se) at Lund University (Lund, Sweden) and the University of California San Francisco (UCSF) Alzheimer's Disease Research Center (San Francisco, USA) who underwent T1-weighted MRI and [18F]flortaucipir PET between June 2014 and November 2017. In previous work4, visual MRI rating scales of medial temporal lobe atrophy [MTA], posterior atrophy [PA] and global cortical atrophy – frontal subscale [GCA-F]) were used to determine atrophy-defined subtypes. Each visual rating scale score was binarized into "normal" or "abnormal" based on established clinical cut-offs4, and the combination of the scales resulted in classification into distinct subtypes of AD. For example, abnormal MTA + normal PA/GCA-F = "limbic-predominant". We aimed to apply a quantitative (clustering) implementation that preserves the simplicity and potential clinical utility of this method. We therefore calculated the mean surface-area weighted thickness of the entire occipital/parietal cortex and frontal cortex (resembling PA and GCA-F scales, respectively), and total intracranial volume weighted hippocampal volumes (resembling MTA scale). The continuous measures for these three variables were entered into a two-step clustering algorithm in SPSS version 22.0. In the first step ("pre-clustering"), we performed a sequential clustering approach by constructing a modified cluster feature tree using model-based distance criterion.6 In the second step ("clustering"), we applied an agglomerative hierarchical clustering method using the pre-clusters from step 1 as input, with the number of clusters constrained to four. To test whether the clusters indeed resembled the neuropathological subtypes, we standardized the posterior and frontal thickness and the hippocampal volume measures (z=0 represents the mean of the entire group) and examined the relative impairment of these three variables for each cluster. Differences across atrophy-defined subtypes in [18F]flortaucipir PET uptake in the enthorinal cortex, lateral temporal cortex, lateral and medial parietal cortex, occipital cortex, frontal cortex and whole-brain, were assessed using ANOVA with post-hoc LSD tests. **Results:** Cluster 1 (n=70) showed negative z-scores (representing greater atrophy) on all atrophy measures and was labeled "typical AD". Cluster 2 (n=77) had low hippocampal volumes but relatively preserved posterior and frontal atrophy and was labeled "limbic-predominant AD". Cluster 3 (n=76) showed the opposite pattern and was labeled "hippocampal-sparing AD". Finally, cluster 4 (n=37) showed relative preservation of all atrophy measures and was labeled "minimal atrophy AD". Table 1 shows the demographic and clinical features of each atrophy-defined subtype. The limbic-predominant subtype had greater [18F] flortaucipir uptake in the enthorhinal cortex compared to the hippocampal-sparing subtype ($p<0.05$) and – at trend level –typical ($p=0.051$) and minimal atrophy subtypes ($p=0.055$, Figure 1B). The hippocampal-sparing subtype demonstrated greater [18F]flortaucipir uptake than limbic-predominant and minimal atrophy subtypes in all cortical regions (all $p<0.05$). Typical AD subjects displayed greater [18F]flortaucipir uptake than limbic-predominant and minimal atrophy subtypes in lateral temporal, lateral parietal, occipital and whole-brain, and in greater [18F]flortaucipir uptake than the minimal atrophy subtype in medial parietal and frontal cortices (all $p<0.05$). The limbic-predominant subtype showed greater [18F]flortaucipir uptake than the minimal atrophy subtype in lateral temporal, medial parietal, frontal and whole-brain regions (all $p<0.05$). **Conclusions:** Spatial patterns of tau PET corresponded well with atrophy-defined subtypes. This indicates that clustering approaches using quantitative MRI data as input can be used to mimic neuropathological subtypes of AD in vivo. References: [1] Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82:239-59. [2] Murray ME, Graff-Radford NR, Ross OA, et al. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. Lancet Neurol. 2011;10:785-96. [3] Whitwell JL, Dickson DW, Murray ME, et al. Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. Lancet Neurol. 2012;11:868-77. [4] Ferreira D, Verhagen C, Hernandez-Cabrera JA, et al. Distinct subtypes of Alzheimer's disease based on patterns of brain atrophy: longitudinal trajectories and clinical applications. Sci Rep. 2017;7:46263. [5] Ferreira D, Cavallin L, Larsson EM, et al. Practical cut-offs for visual rating scales of medial temporal, frontal and posterior atrophy in Alzheimer's disease and mild cognitive impairment. J Intern Med. 2015;278:277-90. [6] Banfield JD, Raftery AE. Model-based

Gaussian and non-Gaussian clustering. Biometrics. 1993;49:803-21.

OC15: COCOA SUPPLEMENT AND MULTIVITAMIN OUTCOMES STUDY OF COGNITIVE FUNCTION (COSMOS-MIND): DESIGN OF A LARGE RANDOMIZED CLINICAL TRIAL. Laura D. Baker[1], Mark A. Espeland[1], Stephen R. Rapp[1], Sally A, Shumaker[1], Sarah A, Gaussoin[1], Howard D. Sesso[2], JoAnn E. Manson[2] *((1) Wake Forest School of Medicine, Winston-Salem, USA; (2) Brigham and Women's Hospital, Harvard Medical School, Boston, USA)*

Background: Large simple trials are designed to be efficient and cost-effective. New promising evidence from animal and preliminary clinical studies indicates that intake of high-dose cocoa flavanols may protect cognitive function in older adults and warrants testing in a rigorous, sufficiently-powered randomized clinical trial. COSMOS-Mind is an ancillary study to the large 2x2 factorial randomized controlled trial, the COcoa Supplement and Multivitamin Outcomes Study (COSMOS), and provides one such opportunity. **Objectives:** We present the rationale, design, and baseline characteristics of the COSMOS-Mind trial. **Methods:** COSMOS-Mind examines whether high-potency cocoa flavanol extract, with and without co-administration of a standard multivitamin, provides cognitive benefits in adults 65 years and older. The primary endpoints for the large-scale parent COSMOS trial are cardiovascular disease and cancer, and randomized and double-blinded study pills are provided by mail. For COSMOS-Mind, recruitment materials are also sent by mail and telephone interviews are conducted to establish eligibility and to collect cognitive data at baseline and over three years of follow-up. The primary outcome for COSMOS-Mind is a composite of validated and standardized cognitive tests focused on executive function and episodic memory. **Results:** COSMOS-Mind screened 3224 women and men who responded to mailed recruitment materials. Of these, 2449 (76%) underwent telephone screening; 2262 (92%) of those screened by telephone were then enrolled and randomized by the parent COSMOS trial (Figure 1). The 2262 participants included 60% women, 11% from traditionally under-represented racial/ethnic groups, and 12% with high school educations or less, and were geographically diverse. The mean (standard deviation) age was 74.0 (6.2) years. The composite cognitive outcome is the mean of standardized scores from the Telephone Interview for Cognitive Status-modified (global cognitive function); immediate and delayed Story Recall (episodic memory); Oral Trail Making Test – Parts A and B; Category and Letter Word Fluency; and Digit Span (executive function). COSMOS-Mind is designed to provide >90% power to detect a sustained mean difference in composite cognitive function over time of 0.10 standard deviation. Figure 2 portrays the cross-sectional relationship between age and the composite cognitive outcome at baseline. COSMOS-Mind has enrolled a cohort that is heterogeneous in its cognitive function. While the association is not linear, across the 30-year age range the median level of performance decreases by about 1 standard deviation, suggesting that 3 years of follow-up may be associated with a difference of 0.10 standard deviations, i.e. equal to the intervention effect targeted by COSMOS-Mind. **Conclusions:** COSMOS-Mind is designed to demonstrate that large simple trials with validated telephone-based cognitive assessments are feasible and can result in cohorts that are geographically and cognitively diverse. If cocoa flavanols are demonstrated to preserve cognitive function, high potency cocoa flavanol supplementation may provide a novel, safe, affordable, and widely translatable strategy to slow cognitive decline associated with normal and pathological aging.

Figure 1
COSMOS-Mind Enrollment

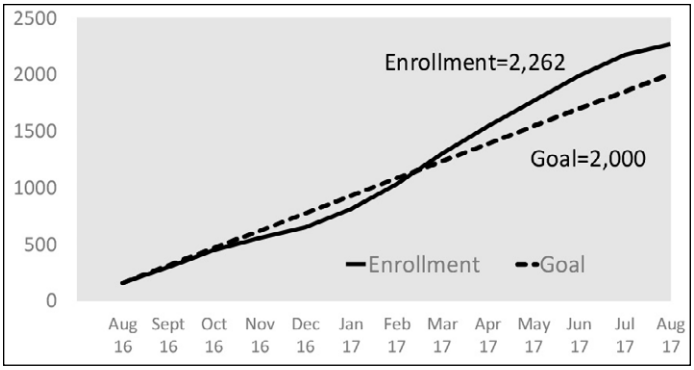
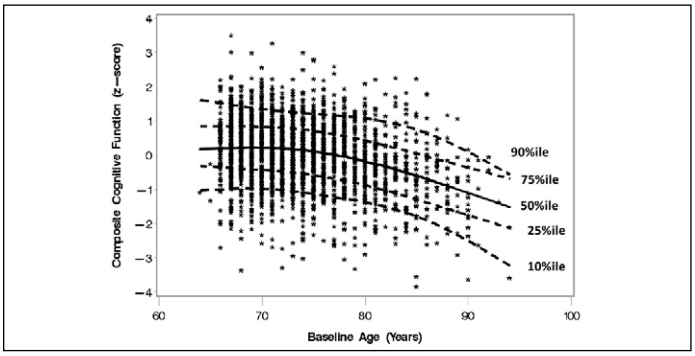


Figure 2
Percentile regression of composite function on age: COSMOS-Mind Baseline

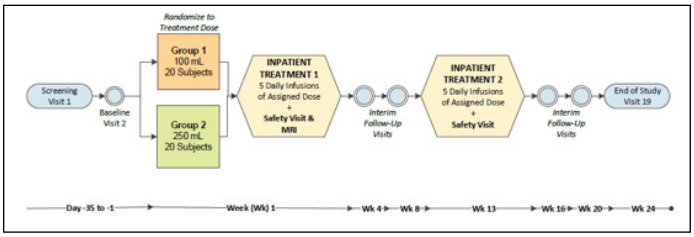


OC16: RATIONALE AND DESIGN OF A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, DOSE-COMPARISON SAFETY AND TOLERABILITY STUDY OF GRF6019 IN MILD-TO-MODERATE ALZHEIMER'S DISEASE. Jonas Hannestad, Ian Gallager, Katie Koborsi, S. Sakura Minami, Darby Stephens, Viktoria Kheifets, Steven Braithwaite *(Alkahest, Inc., San Carlos - USA)*

Background: Published studies by Villeda et al1,2 have demonstrated beneficial effects of intravenous (IV) administration of plasma from young mice on activity, locomotion, and cognition in aged mice. The data also indicated that exposure of aged mice to young plasma was capable of rejuvenating synaptic plasticity late in life. Subsequent studies performed at Alkahest extended these results and showed significant improvements in cognitive performance and histological correlates in aged mice following IV infusions of young human plasma and of GRF6019, a proprietary human plasma protein fraction. The rationale for using a plasma protein fraction was based on several factors. Although plasma is widely used, there are risks such as the potential transfer of pathogens, histoincompatibility, and allergic reactions to proteins such as clotting factors and immunoglobulins. Safer products have been developed by pooling plasma

from multiple donations, fractionating the plasma into more defined products, and including additional processing steps to minimize the potential for pathogen transmission. Leveraging this fractionation technology, GRF6019 is a human plasma protein fraction depleted of coagulation factors and gamma globulins that maintains whole plasma's beneficial effects on cognition and histological correlates in aged mice. **Objectives:** To conduct a Phase 2, randomized, double-blind study to test the safety, tolerability, and potential therapeutic effects of a novel infusion regimen of GRF6019 in human subjects with mild-to-moderate Alzheimer's Disease (AD). **Methods:** Studies performed at Alkahest with plasma fractions in aged mice compared intermittent dosing (2 to 3 times per week for up to 12 weeks) with pulsed dosing (daily infusion for 5 to 7 consecutive days). Pulsed dosing was superior to intermittent dosing on multiple endpoints, including cognition and neurogenesis. Benefits after pulse dosing lasted up to 3 months, demonstrating that continuous dosing was not required in mice. Therefore, a pulsed dosing regimen of 5 consecutive days, with a subsequent booster pulse several weeks later, was chosen for the initial human study of GRF6019 [Figure 1]. In this ongoing Phase 2 study, men and women 60 years or older with mild-to-moderate AD are randomly allocated in a 1:1 ratio to receive pulsed dosing with either 100 mL or 250 mL of GRF6019. Approximately 40 subjects are currently being recruited. During the two 5-day treatment periods, subjects reside in inpatient observation units to facilitate safety evaluation. Subjects undergo a screening visit, baseline visit, treatment visits, follow-up visits, and an end of study/early termination visit over a period of approximately 7 months. Safety and tolerability assessments occur at every visit. Neurocognitive assessments are performed at baseline and at periodic interim visits following treatment. The approved Phase 2 study is now recruiting male and female subjects, 60 years or older with mild-to-moderate AD. Subjects are randomly allocated to receive 10 infusions of either 100 mL or 250 mL of. **Results:** The primary endpoints are safety, tolerability, and feasibility of the dosing regimen. Safety is measured by the incidence of treatment-emergent adverse events, and tolerability by the number of subjects completing the two pulse dosing periods. Secondary endpoints will assess potential effects on cognition using various established cognitive measures including the Alzheimer's Disease Assessment Scale-Cognitive Subscale and the Clinical Dementia Rating Scale. Exploratory endpoints include a tablet-based cognitive battery, assessment of changes in composition and distribution of biomarkers in serum and cerebrospinal fluid (in consenting patients) as well as structural and functional magnetic resonance imaging. **Conclusions:** Robust preclinical evidence in rodents provided the foundation to test the translatability of these findings in humans. In this Phase 2 study, the safety, tolerability, feasibility, and potential therapeutic effects of multiple infusions of GRF6019 in subjects with mild-to-moderate AD will be assessed. Continued clinical development in AD will be informed by safety and efficacy data emerging from this trial. References: 1. Villeda SA, et al. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature. 2011;477:90-94. 2. Villeda SA, et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nature Med. 2014;20:659-663.

Figure 1
Schematic of Study



OC17: MACHINE LEARNING ALGORITHM HELPS IDENTIFY NON-DIAGNOSED PRODROMAL ALZHEIMER'S DISEASE PATIENTS IN GENERAL POPULATION. Olga Uspenskaya-Cadoz[1*], Chaitanya Alamuri[2*], Sam Khinda[3], Yuliya Nigmatullina[2], Carolina Rubel[3], Lanhui Wang[2], Mengting Yang[2], Tao Cao[2], Nikhil Kayal *((1) IQVIA CNS Center of Excellence; (2) IQVIA Analytics Center of Excellence; (3) IQVIA Project Leadership. *Both authors contributed to the abstract equally)*

Background: Effective diagnosis of Alzheimer's disease (AD) at its initial pre-dementia stages (early prodromal AD) remains one of the most important healthcare challenges. An accurate prediction of prodromal AD in community dwelling subjects can aid early AD detection at primary care physician (PCP) level, timely referral to expert sites for biomarker confirmation of diagnosis, enrolment in a clinical trial and - in the future – initiation of disease-modifying drugs (DMDs). Current technology advances and big data predictive disease algorithms may be of important value to help solve this healthcare problem. **Objective:** Leverage big data assets to build Machine Learning (ML) predictive algorithm helping with high precision to identify non-diagnosed prodromal AD subjects in the general population. **Methods:** A total of 88,298,289 subjects aged between 50 and 85 years were identified from IQVIA US data assets (LRx and Dx database). We identified 667,288 subjects having over 24 months of medical history and at least one record with AD or prescribed with symptomatic anti-dementia drugs. We only considered data 3 years prior to AD diagnosis/AD drugs initiation. The model included multiple variables such as non-AD drug/device prescription data, medical interventions, concomitant pathologies data, and lifestyle factors. This positive cohort was further sub-divided per age range, and patient data was analysed for age groups of 50-55, 55-60, 60-75, and 75-85. Based on the prevalence rates per age group we selected 3,670,254 negative patients with similar length of medical histories and matched them to positive subjects from initial scoring cohort, combining positive and negative subjects from a sample dataset representing real world setting for modelling phase. Supervised ML techniques were used to develop algorithms to predict the occurrence of prodromal AD cases. Sample dataset was divided randomly into a training dataset, a test dataset, in the following proportions: 80% and 20%, respectively. The classification algorithms were used to train the prediction models. The hyper-parameters were determined by applying 5-fold cross-validation to the training set to guard against over-fitting the data. Gradient-boosted Tree (GBT), Random Forest, Decision Tree and Logistic Regression were all trained on the data. Precision-recall curves of the test set were used for evaluation of each algorithm (Figure 1). Best-performing methods were selected based on evaluation

of the resulting confusion matrices and overall precision-recall curves. After best performing model was determined, GBT algorithm was retrained with complete 100% sample dataset having all positive and negative subjects. Scoring cohort was then selected based on availability of recent medical data of at least 5 years and included 72,670,283 subjects between ages of 50 to 85 years. Precision value of 80% was selected to determine threshold values on GBT model and prediction was performed on entire scoring cohort with determined threshold values. We identified all potential subjects currently in prodromal AD stage as per this model. Predicted subjects with prodromal AD are then linked to only specialty physicians managing AD patients with complex business logic implemented and also looking at the most recent health history of these subjects. Technology stack: Algorithm was developed by utilising cutting edge technology stack like distributed computing, HDFS, PySpark and ML libraries. **Results:** Precision-recall (PR) curve for data-trained GBT model by age group are shown in Figure 1. GBT model has identified 222,721 subjects in prodromal AD stage with 80% precision. These subjects from 4 different age groups have a minimum probability threshold for prodromal AD prediction of 72.2%. Top 5 risk factors were ranked based on their contribution from 1 to 5 and are presented in Table 1. Data suggests that 81% of subjects predicted by model are in general medicine setting and only 19% are already seen by physicians specialized in cognitive disorders. (Neurologists, Psychiatrists, Geriatricians). **Conclusion:** Proposed prediction ML algorithm tested on 72,670,283 US subjects allows identification of prodromal AD at early stages. Applying ML predictive algorithm may bring several major advancements for future AD research: • Allow for more accurate and much earlier prodromal AD diagnosis already at PCP level with timely referral to expert site for in-depth neuropsychological and biomarker assessment; • Much earlier referral for inclusion in clinical trials with significantly decreased screen failure rate, allowing to test DMDs at early prodromal stage as opposed to late prodromal/dementia stage; • Allow better patient and PCP engagement (early interventions on AD risk factors, accurate early diagnosis, improved treatment plans and timely initiation of DMDs should such become available). Real world validation of predictive algorithm is currently underway to further confirm its diagnostic accuracy (positive and negative prediction values) and will be presented in further communications.

Figure 1

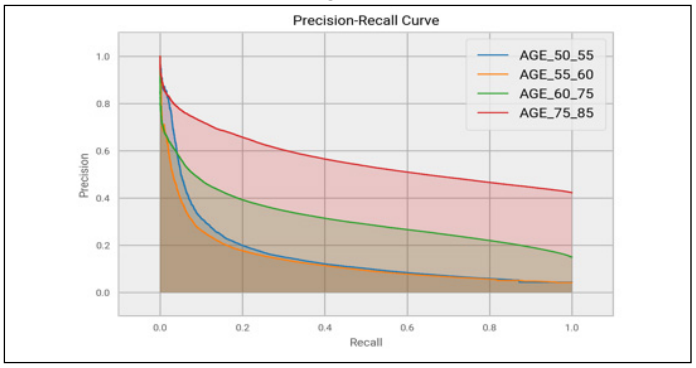


Table 1

Risk Factors	Age_50_55	age_55_60	age_60_75	age_75_85
Amnesia	1	1	1	3
Neuroimaging Procedure	2	4	3	4
Metabolic Disorder	3	2	4	2
Hypertension	4	3	5	1
Depression	5	5	-	5
MCI	-	-	2	-

OC18: ABBV-8E12, A HUMANIZED ANTI-TAU MONOCLONAL ANTIBODY, FOR TREATING EARLY ALZHEIMER'S DISEASE: UPDATED DESIGN AND BASELINE CHARACTERISTICS OF PHASE 2 STUDY.

Hana Florian[1], Steven E. Arnold[2], Randall J. Bateman[3], Joel B. Braunstein[4], Kumar Budur[1], Diana R. Kerwin[5], Holly Soares[1], Deli Wang[1], David M. Holtzman[3] *((1) AbbVie, Inc., North Chicago, IL, USA; (2) Massachusetts General Hospital, Boston, MA, USA; (3) Washington University, St. Louis, MO, USA; (4) C2N Diagnostics LLC, St. Louis, MO, USA; (5) Texas Health Presbyterian Hospital, Dallas, TX, USA)*

Background: Large simple trials are designed to be efficient and cost-effective. NABBV-8E12 is a humanized anti-tau monoclonal antibody that targets extracellular human tau, and is currently being developed as a treatment for early Alzheimer's disease (AD) and progressive supranuclear palsy (PSP). In preclinical studies in transgenic mice that develop tau pathology, ABBV-8E12 treatment resulted in less overall tau pathology and brain atrophy as well as less decline in motor/sensorimotor functions, compared with placebo. In a phase 1 single ascending-dose study in patients with PSP, ABBV-8E12, administered as a single dose up to 50 mg/kg, had an acceptable safety and tolerability profile to support repeat-dose studies in larger cohorts of patients with tauopathies. We present the updated design and baseline characteristics of an ongoing phase 2 study of ABBV-8E12 in patients with early AD. **Methods:** This is a 96-week, randomized, double-blind, placebo-controlled, phase 2 study evaluating the efficacy and safety of ABBV-8E12 in patients with early AD. This study will enroll approximately 400 male and female patients (55 to 85 years of age) who meet the clinical criteria for early AD (has a Clinical Dementia Rating [CDR]-Global Score of 0.5, Mini-Mental State Examination [MMSE] score of 22 to 30, Repeated Battery for the Assessment of Neuropsychological Status-Delayed Memory Index [RBANS-DMI] score of 85 or lower, and had a positive amyloid PET scan). Patients will be randomized (1:1:1:1) to one of the three doses of ABBV–8E12 or placebo. As of the second half of 2018, a subset of patients will undergo tau PET imaging at screening, after completion of week 44 and week 96. **Results:** Primary efficacy endpoint is the change from baseline up to week 96 in CDR-Sum of Boxes score. Secondary efficacy outcomes will assess the pharmacokinetics of ABBV-8E12 and its efficacy in slowing cognitive and functional impairment, as measured by changes from baseline up to week 96 in MMSE, RBANS, and 14-Item Alzheimer's disease Assessment Scale Cognition Portion. Tau PET imaging will be used to assess whether ABBV-8E12 slows the accumulation and spread of tau deposits in the brain. Adverse events will be recorded. Table 1 includes baseline demographics and disease characteristics of the first 135 patients enrolled in the study. **Conclusions:** There

is a huge unmet medical need for a treatment for early AD that stops or delays the disease progression, thereby reducing patients' cognitive and functional decline and improving quality of life for patients and caregivers. This ongoing phase 2 study was designed to evaluate ABBV-8E12 as a potential disease modifying therapy for patients with early AD.

Table 1
Baseline demographics and disease characteristics

Demographics and Disease Characteristics	N=135*
Age, y, mean (SD)	72.1 (6.9)
Sex, n, male (%)	75 (56%)
Race, n, white (%)	132 (98%)
MMSE score, mean (SD)	24.7 (3.0)
RBANS score, mean (SD)	73.6 (11.5)

*As of April 11, 2018.

OC19: ASSESSMENT OF CLINICAL MEANINGFULNESS OF ENDPOINTS IN THE GENERATION PROGRAM BY THE INSIGHTS TO MODEL ALZHEIMER'S PROGRESSION IN REAL LIFE (IMAP) STUDY. A. Graf[1], V. Risson[1], S. Tzivelekis[2], A. Gustavsson[3], V. Bezlyak[1], A. Caputo[1], P.N. Tariot[4], J.B. Langbaum[4], C. Lopez Lopez[1], V. Viglietta[2] *((1) Novartis Pharma AG; (2) Amgen, Inc.; (3) Quantify Research; (4) Banner Alzheimer's Institute)*

Background: The Alzheimer's Prevention Initiative (API) is a collaborative funded by the NIH, philanthropy, and industry to conduct preclinical Alzheimer's disease (AD) trials in people who, based on age, genetics, and in some cases biomarkers, are at elevated risk for developing AD symptoms. The API Generation Program consists of two trials, Generation Study 1 and Generation Study 2. Both trials are currently recruiting cognitively unimpaired participants ages 60-75. Generation Study 1 is including APOE4 homozygotes; Generation Study 2 APOE4 carriers (homozygotes and heterozygotes, heterozygotes must also have elevated brain amyloid). Primary endpoints are time-to-event (TTE), with event defined as diagnosis of mild cognitive impairment (MCI) or dementia due to AD, and change in the Alzheimer's Prevention Initiative Cognitive Composite (APCC) Test Score. Secondary endpoints include CDR-Sum of Boxes (CDR-SB) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Both APCC and RBANS were chosen as sensitive composites for tracking preclinical cognitive decline in individuals who subsequently progress to the clinical stages of late-onset AD. The ability of APCC and RBANS to predict clinically meaningful changes in later disease stages needs to be established outside of the interventional clinical trial program. **Methods:** We are launching the Insights to Model Alzheimer's Progression in real life study (iMAP) in parallel to the Generation Program. iMAP is a 5-years, multinational, prospective, longitudinal, non-interventional cohort study that will collect data across the spectrum of AD. The primary objective is to assess the ability of APCC and RBANS to predict clinically meaningful outcomes like diagnosis of MCI or dementia due to AD, and change in Clinical Dementia Rating – Global Score (CDR-GS). Secondary objectives are to describe disease progression throughout the full spectrum of AD as depicted by cognitive (e.g. APCC, RBANS, CDR-GS, CDR-SB, ECog, MMSE), functional (e.g. ADCS-ADL) and behavioral (e.g. NPI-Q) scales and to assess the measurement properties of APCC and RBANS. **Results:** The study will include 1270 subjects, out of which 620 subjects will be cognitively unimpaired, 300 will be in MCI stage, and 350 will have mild AD. To increase the likelihood of progression in the cohort of cognitively unimpaired subjects, a higher proportion of APOE4 carriers will be invited, along with APOE4 non-carriers. In other diagnostic groups, no enrichment is foreseen. The sample size of the study was determined via trial simulations based on patient-level data from longitudinal observational cohorts. The primary objectives will be investigated in the cohort of cognitively unimpaired participants. The predictive value of early changes in APCC and RBANS will be explored by investigating the predictive value of change from baseline to year 1, 2, and 3, respectively, of APCC and RBANS on the endpoints of interest. The primary analysis of the time-to-event endpoint will be based on a Cox proportional hazards model including change from baseline in APCC/RBANS as a factor and adjusted for important factors as baseline value of the APCC/RBANS, age, APOE genotype. Similarly, a generalized linear mixed model for repeated measures will be estimated for change in CDR-GS. **Conclusions:** iMAP is the first large scale, prospective effort, to establish the clinical meaningfulness of cognitive test scores used for tracking longitudinal decline in preclinical AD. The study is being conducted outside the context of the Generation Program in order to capture later disease stages as well as to comply with regulatory requirements. Furthermore, this study will contribute to the understanding of the relationship between outcomes in the different disease stages and modelling of individual trajectories during the course of the disease.

OC20: CHARACTERIZING CLINICAL SEVERITY AMONG BIOMARKER POSITIVE INDIVIDUALS: APPLYING THE 2018 NIA-AA RESEARCH CRITERIA FOR ALZHEIMER'S DISEASE TO FOUR LARGE STUDY COHORTS. Roos J. Jutten[1], Rebecca E. Amariglio[2,3], Gad A. Marshall[2,3], Dorene M. Rentz[2,3], Wiesje M. Van der Flier[1], Philip Scheltens[1], Keith A. Johnson[2,4], Reisa A. Sperling[2,3], Sietske A.M. Sikkes[1,3], Kathryn V. Papp[2,3] *((1) Alzheimer Center, VU University Medical Center, Amsterdam - The Netherlands; (2) Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston MA, USA; (3) Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston MA, USA; (4) Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston MA, USA)*

Background: There has been an increased focus on assessing disease-modifying therapies targeting biomarker positive individuals at earlier stages of Alzheimer's disease (AD). In the recently updated guidelines and criteria from NIA-AA and the related draft industry guidance from the FDA (2018), AD is reframed as a biomarker-based diagnosis with 4+ stages of increasing clinical severity. These stages are described as: no evidence of clinical impact (Stage 1); a transitional stage of cognitive decline, i.e. subtle abnormalities on sensitive neuropsychological tests, decline from previous level of functioning but no functional impairment (Stage 2); more apparent abnormalities on neuropsychological tests and mild functional impairment (Stage 3); and overt dementia (Stage 4+). Grouping individuals into these more refined clinical stages will likely be beneficial in optimizing the selection and

assessment of participants in future clinical trials. However, specific procedures to operationalize these stages have yet to be delineated. **Objectives:** We aimed to operationalize the NIA-AA clinical staging schema into measurable criteria, and apply these criteria across four different existing study cohorts. **Methods:** We selected individuals (N=1213) with abnormal amyloid levels as determined by PET imaging or CSF from the Harvard Aging Brain Study (HABS, n=76), the Alzheimer's Disease Neuroimaging Initiative (ADNI, n=526), the National Alzheimer's Coordination Center (NACC, n=281), and the Amsterdam Dementia Cohort (ADC, n=330). We translated the stage descriptions into measurable variables that can be obtained from commonly used screening measures. More specifically, level of cognitive impairment was operationalized using 1) the MMSE (or a MOCA transformed score if MMSE was unavailable); and 2) a memory retention score reflecting the proportion of items recalled from either story or word list on delay. Subjective cognitive decline (SCD) was quantified as either a memory clinic visit or endorsing 2 or more questions extracted from exisiting SCD questionnaires, addressing whether there has been: 1) recent change in memory functioning; 2) consistent change over the last few months; and 3) concern associated with the memory change (resulting in a SCD screening score ranging from 0-3). The severity of functional impairment was determined using the CDR sum of boxes (CDR-SB) score (or global CDR if CDR-SB was unavailable). For all measures, we created stage-specific cut-off scores based on previously published data. We tested several classification cut-offs to minimize incongruences whilst reflecting the stages accurately. We ultimately applied a strict approach in that all clinical features needed to be present for categorization for each stage. Finally, we assessed demographic and clinical characteristics separately for each stage.**Results:** Table 1 presents our proposed operationalization criteria, including the selected stage-specific cut-offs. Forty subjects had missing data on the required measures and were therefore excluded from the classification. From the remaining group (n=1173) we classified 994 individuals (84.7%), of which 189 (19%) were identified as Stage 1; 91 (9.2%) as Stage 2, 378 (38%) as Stage 3; and 336 (33.7%) as Stage 4 (Table 2). A total of 179 individuals (18%) remained unclassified because of incongruences amongst measurements (e.g., high MMSE, but impairment on the CDR), of which the majority had a global CDR of 0.5. Also, 65 of the Stage 3 subjects actually fell in the Stage 2 range for cognitive and subjective criteria but had a global CDR of 0.5. Table 2 presents resulting demographic and clinical characteristics of the stages. Most of the cognitively normal and SCD subjects were classified among Stage 1 and 2, whereas most people with a former syndrome diagnosis of MCI fell in Stage 3. **Conclusions:** We operationalized the NIA-AA clinical scheme into measurable criteria using previously collected data. When applying these criteria, we demonstrated that most amyloid positive individuals could be classified in each of the stages. A proportion of individuals remained unclassified due to incongruent data, which reflects our strict approach in order to create distinct, non-overlapping categories most relevant for clinical trials that aim to recruit individuals at a specific clinical stage of disease. In addition, it underlines the need for better classification measures, especially to identify Stage 2 participants in a transitional stage of cognitive decline. Next steps include applying staging criteria a priori in future studies, as well as optimizing composite cognitive and functional outcomes by each specific stage.

OC21: EXTENSION AND VALIDATION OF AN AMYLOID STAGING MODEL: ASSOCIATIONS WITH CLINICAL MEASURES.

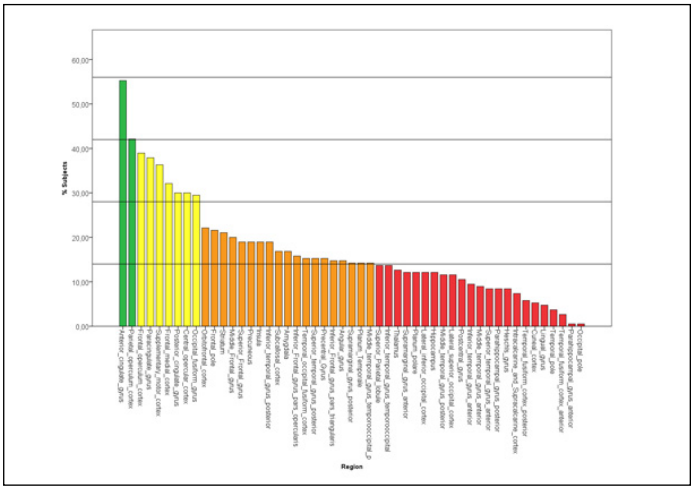
Lyduine Collij[1], Fiona Heeman[1], Gemma Salvadó Blasco[2], Elles Konijnenberg[3], Anouk den Braber[4], Maqsood Yaqub[1], Pieter Jelle Visser[3], Alle Meije Wink, Ir[1], Philip Scheltens[3], Ronald Boellaard[1], Bart N.M. van Berckel[1], Juan Domingo Gispert López[2], Mark Schmidt[5], Frederik Barkhof[1,6], Isadora Lopes Alves[1] *((1) Dept. of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands; (2) BarcelonaBeta Brain Research Center, Barcelona - Spain; (3) Alzheimer Center and Dept. of Neurology, VU University Medical Center, Amsterdam - The Netherlands; (4) Dept. of Biological Psychology, VU University Amsterdam - The Netherlands; (5) Janssen Pharmaceutica, Beerse - Belgium; (6) Institute of Neurology and Healthcare Engineering, University College London, London - United Kingdom)*

Background: Recently, Grothe and colleagues explored the feasibility of developing an in vivo amyloid staging model (ASM) using amyloid PET, showing a highly consistent regional hierarchy of [18F]florbetapir PET-evidence for amyloid deposition across cognitively normal participants. **Objectives:** We aimed to extend and validate the proposed ASM using a different control population and amyloid tracer. **Methods:** [18F]flutemetamol (FLUT) PET acquisition using the coffee-break protocol (0-30 and 90-110 minutes scan) was performed in 190 cognitively normal participants (mean age 70.4 years, 60% female, mean MMSE score 29). Standard uptake value ratio (SUVR) parametric images with cerebellar grey matter (Hammers atlas) as a reference region were generated. A global amyloid positivity cut-off (SUVR ≥ 1.52) was computed based on the majority visual read negative/positive classification of the SUVR images. This cut-off was subsequently used to determine regional positivity. The frequency of regional positivity was used to construct the ASM using Harvard-Oxford ROIs. All participants were classified according to the previously proposed and the newly constructed model. Subsequently, the newly constructed model was optimized by removing regions with a low effect-size between global negative and positive cases and deemed too small considering PET methodological issues (i.e. resolution;. mainly small subcortical regions, including the amygdala and hippocampus, were removed from the optimized model. Classifications based on the optimized model were associated with clinical measures. **Results:** The spatial-temporal ordering of cortical brain regions was different in the first two stages, but more consistent in the later stages between the previously proposed and the newly constructed staging model. The main difference was the absence of basal temporal regions in phase I in the FLUT-based model (Figure 1). The Anterior Cingulate Cortex (ACC) was consistently early in both models. Classification of our data based on the two models showed an agreement of K = .17. This low agreement was mainly due to the disagreement in classification of stage I subjects (Figure 1b). Comparison between the FLUT-ASM model classification and visual read showed that most (92,3% -98,5%) stage 0/I/II had a negative majority visual read, stage III was 50/50, and in stage IV most (91.7%) subjects had a positive majority visual read. The relationship improved when merging smaller regions, considering the low resolution in PET. Subsequently, small subcortical regions were removed from the staging model in order to optimize classification (Figure 2). The optimized FLUT-ASM-based classifications showed a positive age effect,

but no relationship with APOE ε4 carriership, visual scores of global cortical and white matter hyperintensities, or CSF Aβ42 levels. However, a significantly higher average medial temporal lobe atrophy score was observed in stage III vs. 0/I/II classified subjects. Also, using the Aβ40/Aβ42 ratio resulted in a significantly lower ratio in stage III vs. stage 0/I classified subjects ($p < 0.5$). **Conclusions:** Our amyloid staging model based on a different control population and amyloid tracer, showed difference in the early regions compared to the previously proposed ASM, apart from the ACC. The later stages demonstrated higher consistency. In further work we aim to investigate whether this is mainly a population or tracer driven difference by applying Grothe's methods to an independent [18F]-Florbetapir PET dataset. Our models supports the conclusion that regional amyloid burden can be present in cognitively healthy elderly subjects before a global positive visual read is given. This observation can have implications for secondary prevention studies in a preclinical population focused on the development of an anti-amyloid therapy.

Figure 1
Amyloid Staging Model using [18F]flutemetamol in a control population

A) Spatio-temporal distribution of cortical brain regions defined based on the Harvard-Oxford atlas.
B) Distribution of stage classification of our cohort based on (left) model previously proposed by Grothe and (right) new model based on methods of Grothe applied to VUmc data.



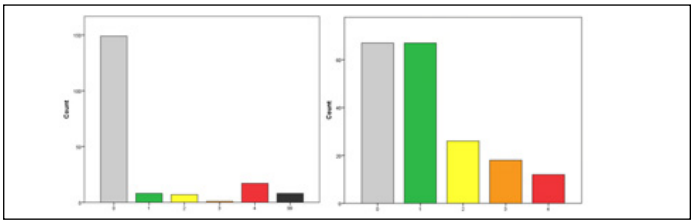
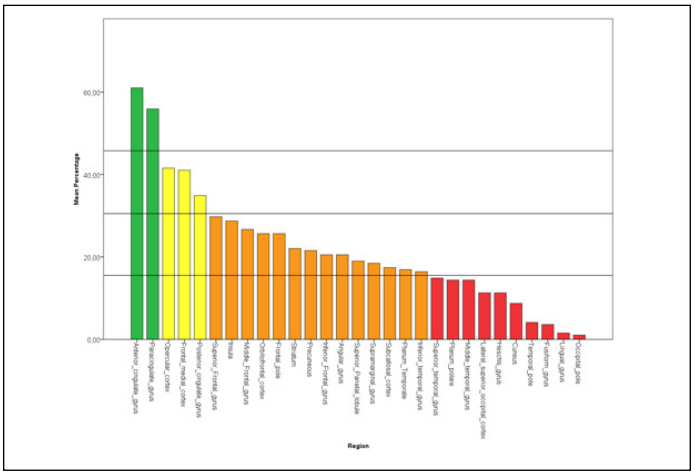
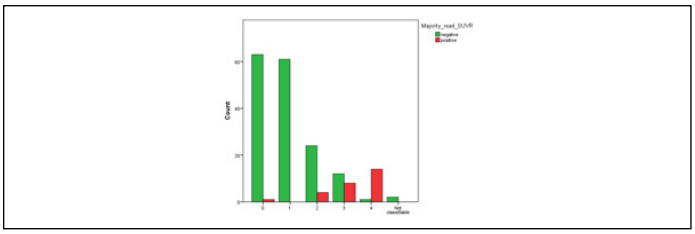


Figure 2
Amyloid Staging Model using [18F]flutemetamol in a control population

A) Spatio-temporal distribution of cortical brain regions defined based on the merged regions of the Harvard-Oxford atlas. Regions with a low effect-size (mainly small subcortical structures) were removed from this model to optimize classification.
B) Classification of control population based on the optimized model and its relationship to majority visual read (green negative / red positive).





OC22: TWENTY-FOUR–MONTH AMYLOID PET RESULTS OF THE GANTENERUMAB HIGH-DOSE SCARLET AND MARGUERITE ROAD OPEN-LABEL EXTENSION STUDIES.
Gregory Klein[1], Paul Delmar[2], Carsten Hofmann[1], Danielle Abi-Saab[2], Mirjana Andjelkovic[2], Smiljana Ristic[2], Nicola Voyle[3], Jacob Hesterman[4], John Seibyl[4], Ken Marek[4], Ferenc Martenyi[2], Monika Baudler[2], Paulo Fontoura[2], Rachelle Doody[2] *((1) Roche Pharma Research and Early Development, Basel, Switzerland; (2) Roche/Genentech Product Development, Neuroscience, Basel, Switzerland; (3) Roche Products Ltd, Welwyn Garden City, UK; (4) InviCRO, LLC, Boston, MA, US)*

Background: The Gantenerumab is a fully human, anti-amyloid-β (Aβ) monoclonal antibody currently under evaluation for the treatment of early Alzheimer's disease (AD). Gantenerumab binds to aggregated Aβ to promote amyloid removal. In the ongoing open-label extension (OLE) studies of SCarlet RoAD (SR; NCT01224106) and Marguerite RoAD (MR; NCT02051608), preliminary analysis showed that titrated dosing schemes targeting 1,200 mg per month (high dose) resulted in up to 3 times more amyloid reduction over 12 months versus 24 months of fixed low-dose treatment (225 mg) observed in the double-blind (DB) SR study.1 **Objective:** This update discusses the effects of high-dose gantenerumab (1,200 mg/

month) over 24 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 the cerebrospinal fluid and a positive visual scan at the OLE baseline visit were eligible for the positron emission tomography (PET) substudy; those who received ≥ 6 doses of ≥ 900 mg were included in this analysis. Owing to considerable differences in titration schedules and duration of time off treatment between DB and OLE dosing, patients were analyzed in three groups: the MR DB placebo cohort (MR-Pbo), the MR DB cohort pre-treated with gantenerumab (MR-Gant) and an SR DB cohort combining patients originally 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 acquired at OLE baseline, Month 12 (Year 1) and Month 24 (Year 2). **Results:** Initial analyses of 40 patients (MR-Pbo, 14; MR-Gant, 17; SR, 9) who completed OLE Year 1 (data cutoff, August 31, 2017) showed mean (SD) 12-month changes in absolute SUVR units of −0.24 (0.21), −0.27 (0.14) and −0.13 (0.16) in the MR-Pbo, MR-Gant and SR groups, respectively.1 Initial findings among 27 patients who completed OLE Year 2 as of May 30, 2018 (MR-Pbo, 11; MR-Gant, 5; SR, 11), showed continued large reductions in amyloid burden with continuous gantenerumab treatment, with 48% of patients having SUVR values below the amyloid positivity threshold at the OLE Year-2 scan. The change in amyloid burden from baseline to Month 24 in absolute SUVR units was: mean (SD) −0.42 (0.23), −0.29 (0.14) and −0.25 (0.18) in the MR-Pbo, MR-Gant and SR groups, respectively. Using the centiloid scale,2 this finding translated to amyloid mean (SD) reductions of 78.0 (41.8), 53.0 (24.9) and 45.7 (32.2) absolute centiloid units. This corresponds to 73.3%, 87.6% and 59.2% median percent reductions compared with OLE baseline centiloid values, respectively. Reductions in amyloid burden and percentage of patients below the amyloid positivity threshold using an updated data cut (August 31, 2018) will be reported, including approximately 50 patients with completed 12-month OLE PET scans and 49 patients with completed 24-month OLE PET scans, not accounting for patient dropout. **Conclusions:** Updated findings are expected to confirm preliminary Year-1 and Year-2 results. These results support the planned Phase III program of using high doses of gantenerumab. 1. Klein G, et al. Presented at CTAD 2017, Boston, MA, US. Klunk WE, et al. Alzheimers Dement 2015;11:1-15.

OC23: MULTI-DOMAIN INTERVENTIONS TO PREVENT DEMENTIA: FROM FINGER TO WORLD-WIDE FINGERS. Miia Kivipelto, On behalf of the World-Wide FINGERS network *((1) Karolinska Institutet, Department of Clinical Geriatrics, Center for Alzheimer Research, Stockholm, Sweden; (2) University of Eastern Finland, Institute of Clinical Medicine/Neurology, Kuopio, Finland; (3) Imperial College London, NEA, School of Public Health, UK)*

Rationale: Given the multifactorial etiology of dementia and late-onset Alzheimer, multi-domain preventive interventions targeting several risk factors and mechanisms simultaneously are most likely to be effective. **Methods:** This presentation provides updates and new results of recent multinational multimodal lifestyle dementia prevention trials and discusses future directions in the field. **Results:** The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is the first large trial showing that a multi-domain lifestyle intervention may prevent cognitive impairment. New results from the trial will be presented concerning extended follow-up, adherence and biomarkers. The ongoing MIND-AD project (Multimodal preventive trials for Alzheimer Disease: towards multinational strategies) is testing the FINGER intervention model together with Medical food in patients with prodromal Alzheimer disease and lifestyle/vascular risk factors. FINGER represents a pragmatic model, which is now also being tested in diverse populations and settings (Europe, USA, China, Singapore, and Australia). To promote synergy across these trials and optimize efforts towards dementia prevention, we recently launched the World-Wide FINGERS Initiative. WW-FINGERS is an interdisciplinary network, to share experiences and data, and plan joint initiatives focusing on dementia prevention. Updates from the MIND-AD and new trials within WW-FINGERS will be presented. **Conclusions:** There is increasing evidence that it is possible to prevent or postpone late-life cognitive impairment and dementia with multi-domain lifestyle interventions. WW-FINGERS will facilitate synergistic use of data from several countries, creating a unique opportunity for rapid implementation of knowledge and definition of effective and feasible prevention programs for diverse populations. With a narrowing gap between non-pharmacological and pharmacological trials, and new adaptive trial designs, it may not be too long before multimodal interventions can be personalized using lifestyle + drugs combinations for best preventive effect.

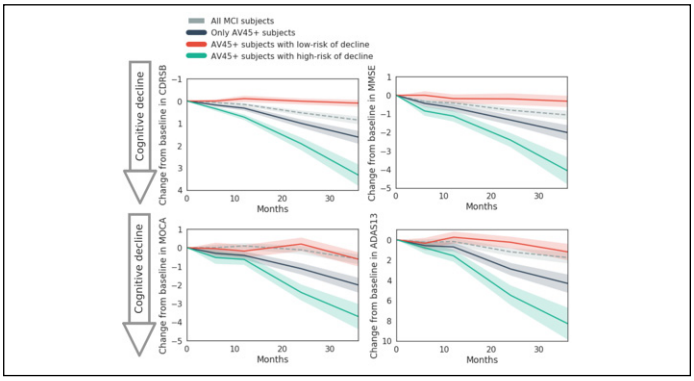
OC24: IDENTIFYING RISK OF COGNITIVE DECLINE IN MILD COGNITIVE IMPAIRMENT FOR POPULATION ENRICHMENT OF CLINICAL TRIALS. Christian Dansereau[1,2], Maor Zaltzhendler[1], Angela Tam[2,3], Pedro Rosa-Neto[3], Serge Gauthier[3], Pierre Bellec[2,4] *((1) Perceiv Research Inc., Montreal, Canada; (2) Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Canada; (3) Douglas Mental Health University Institute, McGill University, Canada; (4) Department of Computer Science and Operations Research, University of Montreal, Canada)*

Background: Subjects with cognitive decline are of paramount importance for an effective evaluation of new drugs in Alzheimer's clinical trials. The heterogeneity of cognitive trajectories in subjects with mild cognitive impairment (MCI) and Alzheimer's dementia (AD) significantly reduces our ability to detect the effectiveness of treatment. As a result, there is an urgent need to identify non-demented subjects who will decline cognitively versus those who will remain stable. **Objectives:** We propose to use highly specific signatures (based on neuroimaging and cognitive tests) that are indicative of the risk of cognitive decline in the MCI population. Our first goal was to subdivide a group of subjects with MCI showing significant β-Amyloid deposit into two cohorts of high- and low-risk of decline and obtain a less heterogeneous cohort with more drastic cognitive changes. The second objective was to compare the high-risk and low-risk groups with the initial cohort which was based only on β-Amyloid positive criteria. Lastly, we wanted to evaluate if the predicted risk was confirmed using common cognitive endpoints when the subjects are followed longitudinally. **Methods:** The volume-based morphometry (VBM), obtained from structural Magnetic Resonance Imaging (MRI), and the ADAS13 score at baseline were provided to

a machine learning enrichment tool from Perceiv Research Inc. Canada in order to select subjects with low- and high-risk of cognitive decline. β-Amyloid protein deposits were measured using AV45 PET tracer and a cut-off of 1.1 was used to identify positive β-Amyloid subjects (referred to as AV45+). The resulting four cohorts of MCI subjects were: (a) all MCI, (b) all MCI AV45+ subjects, (c) MCI AV45+ and low-risk of decline according to the enrichment tool, and (d) MCI AV45+ and high-risk of decline according to the enrichment tool. Finally, the clinical endpoints used to evaluate the trajectory of each cohort are CDR-SB, MMSE, MOCA, and ADAS13. **Results:** From the 235 MCI subjects selected from the ADNI2 sample [1], 129 were AV45+ at baseline. Using the enrichment tool, we identified 63 marked as low-risk and 66 marked as high-risk. The average CDR-SB change from baseline for all MCI subjects was stable with an average of 0.16 points/year and the AV45+ cohort showed a gain of 0.33 points/year. The subcohort of low-risk of decline was indeed stable with 0 points/year on average and the remaining subjects with AV45+ and a high-risk of decline showed a gain of 1 points/year on average (see Figure 1 top left panel) a difference of 0.67 points/year compared to the AV45+ only cohort. Similar trajectories and conclusions were found for all the other endpoints observed. **Conclusions:** The use of multimodal biomarkers and the machine-learning-based targeted selection was successful in identifying a sub-cohort that will decline faster than the reference selection based only on AV45+. The proposed identification of decliners has the potential of reducing trial costs and risks associated with the inclusion of cognitively stable subjects. [1] The data was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).

Figure 1

Four cohorts and their respective average cognitive trajectories for the CDR-SB, MMSE, MOCA, and ADAS13. Error bars are the standard error of the mean. For ADAS13 and CDR-SB, positive values indicate cognitive decline from baseline, for MMSE and MOCA negative values indicate cognitive decline from baseline



OC25: STUDY UPDATE ON XANADU: PHASE II STUDY OF XANAMEM™ IN SUBJECTS WITH MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE. Craig Ritchie *(Centre for Dementia Prevention, University of Edinburgh UK)*

Introduction: Xanamem™ (UE2343) is a novel, potent, and selective 11β-HSD1 inhibitor. 11β-HSD1 amplifies the active glucocorticoid hormone cortisol in brain regions, including hippocampus, and in peripheral tissues, such as liver and adipose tissue. There is abundant evidence from animal and clinical studies linking chronic cortisol excess with hippocampal dysfunction, leading to poor learning, recall, and objective memory impairment. Thus, interventions that reduce intracellular cortisol levels may induce short-term improvements in cognition and have long-term benefits in reducing the risk of glucocorticoid toxicity to the hippocampus and in reducing the risk of dementia. XanADu is a Phase II double-blind, 12-week, randomised, placebo-controlled study to assess the safety, tolerability and efficacy of Xanamem in subjects with mild dementia due to Alzheimer's disease. XanADu, will enrol 174 patients at 20 research sites across Australia, the UK and the USA. The progress to date in the Phase 2 trial will be discussed, including the Interim Analysis performed by an independent Data Safety and Monitoring Board (DSMB) in May 2018. **Objectives:** The objectives are to [1] describe the progress of the ongoing Xanamem™ Phase 2 trial XanADu to date [2] provide an overview of the general development plan for Xanamem in Alzheimer's disease [3] provide a summary of additional, complementary research that endorses the cortisol hypothesis in dementia. **Discussion:** 11β-HSD1 catalyses the intracellular regeneration of active cortisol from its inert metabolite cortisone. Inhibitors of 11β-HSD1 lower cortisol selectively within the tissues without preventing the normal elevation of plasma cortisol during stress. Beneficial effects of 11β-HSD1 inhibitors on cognition and amyloid deposition have been described in preclinical animal models of ageing and dementia. Xanamem™ has been extensively profiled in preclinical and clinical studies and has successfully completed Phase 1 clinical trials with twice daily doses of 10-35mg achieving adequate plasma levels to achieve full pharmacodynamic inhibition of 11β-HSD1 in peripheral tissues as evidenced by urinary steroid measurements. Xanamem™ was also present in the CSF of individuals given 35mg bd for 4 days at levels expected to deliver relevant inhibition of 11β-HSD1 enzyme in brain. Progress of XanADu will be discussed, including recruitment, the Interim Analysis, and an overview of complementary research currently being performed that further endorses the cortisol hypothesis in the development of potential treatments for neurocognitive disorders. In recent years Alzheimer's drugs have failed in phase III because of lack of efficacy; in some cases, the engagement of the intended target in humans has not been demonstrated in phase II trials and the biological basis for the expected clinical response has not been established. The lessons derived from a review of previous Alzheimer's disease research programs is that demonstration of target engagement is a key means to de-risking a development program, and that proceeding to phase III without target engagement places the program at high risk for a negative outcome. Actinogen initiated a Target Occupancy program that began in April 2018 (Q2) and is due to complete in Q2 2019. In parallel, Actinogen will initiate an additional clinical dosage escalation study to demonstrate safety in healthy elderly for 20mg and 30mg once daily doses of Xanamem; this study is anticipated to initiate in Q4 2018. These two additional clinical studies combined with XanADu will enrich Actinogen's dataset for Xanamem and position the company for initiation of a Phase III program. To complement these clinical studies, Actinogen will in parallel conduct a range of standard non-clinical toxicology studies required by global Regulatory Agencies in preparation for Phase III clinical studies. These pre-clinical studies are anticipated to be initiated in Q4 2018. Xanamem™ has potential to treat additional indications, and Actinogen are actively investigating these alternate indications and

developing a robust development plan. These new indications for Xanamem will be explored in pre-clinical and early clinical studies that are anticipated to initiate by Q4 2018. **Conclusion:** Xanamem provides a mode of action wherein it inhibits cortisol production; this remains an elegant and scientifically robust target for both symptomatic treatment and disease course modification in Alzheimer's disease and potentially non-Alzheimer's dementias and neurodegenerative disorders. XanADu is Actinogen's Phase II trial targeting cortisol inhibition for the treatment of Alzheimer's disease and early indications are positive towards this approach. This approach is thoroughly researched and continues to attract further evidence within the scientific community as being a robust target for drug development. Further development of Xanamem is required in the form of additional pre- and clinical studies, in both Alzheimer's disease as well as additional alternate indicaitons. The company awaits the final results from XanADu expected in Q2 2019, as well as results from the planned additional trials that will be initiated with Xanamem throughout 2018.

OC26: FIRST LONGITUDINAL EVALUATION OF THE TAU TRACER [18F]MK-6240 FOR THE USE IN CLINICAL TRIALS. Tharick A. Pascoal[1], Sulantha Mathotaarachchi[1], Mira Chamoun[1], Joseph Therriault[1], Robert Hopewell[2], Gassan Massarweh[2], Andrea L. Benedet[1], Min Su Kang[1], Jean-Paul Soucy[2], Serge Gauthier[1], Pedro Rosa-Neto[1] *((1) Translational Neuroimaging Laboratory, McGill University Research Centre for Studies in Aging, McGill University, Montreal, Canada; (2) Montreal Neurological Institute, McGill University, Montreal, Canada)*

Background: The Over the last decade, numerous molecular imaging tracers have effectively quantified amyloid-β in the human brain. However, amyloid-β has been repeatedly proven not to be sufficient to determine dementia, which suggests tau as a key causal factor for Alzheimer's disease (AD), and therefore, as an important target for therapeutic interventions. It is likely that an imaging agent able to accurately quantify tau pathology in the human brain will enable a more precise enrichment of clinical trials and monitor of the efficacy of the emerging anti-tau therapies. Although the available tau tracers show affinity to neurofibrillary tangles, compelling evidence has observed that non-specific binding heavily influences their signal. For example, recent studies suggest that the binding specificity of [18F]THK5351, [18F]AV1451, and [11C]PBB3 may suffer significant influence from MAO-B, MAO-A, and α-synuclein availability. Therefore, a reliable tau-imaging agent with a low brain off-target binding remains as an urgent need for the use in AD-related therapeutic clinical trials. [18F]MK-6240 has shown in an early evaluation conducted in our center the desired characteristics of a promising new generation tau tracer, such as reduced off-target binding, fast kinetics, and the absence of brain permeable metabolites. Here, we evaluated for the first time longitudinal changes in [18F]MK-6240 uptake in AD and preclinical AD. Moreover we determined the target sample size needed to confirm the effects of a disease-modifying therapy on 1-year tau accumulation using [18F]MK-6240 in individuals in the preclinical stages of AD. **Methods:** Fifteen individuals (8 AD and 7 preclinical AD individuals) underwent [18F] MK-6240 scans at baseline and at 1-year follow-up. [18F]MK6240 standardized uptake value ratios (SUVRs) used the cerebellum grey matter as reference region and were calculated between 90 to 110 min post-injection. Paired t-test assessed significant differences in [18F]MK6240 uptake over time. In addition, we estimated the number of subjects per trial arm required to test a hypothetical 25% drug-effect (reduction in accumulation) on 1-year [18F]MK-6240 accumulation for a disease-modifying therapy versus placebo with 80% of power at a 5% level (two-tailed) (1). **Results:** At baseline, [18F]MK-6240 uptake clear differentiated AD from controls across the whole brain cortex. In AD, the region with the highest increase in [18F]MK-6240 uptake was the primary visual cortex (36% (SD (51)). Baseline and 1-year follow-up [18F]MK-6240 scans of a representative preclinical AD individual are presented in Figure 1a. In CN, there was a significant increase in [18F]MK-6240 uptake over 1 year in the posterior cingulate (PCC) (21% (13)), medial prefrontal (18% (11)), and hippocampus (12% (12)) cortices (Fig. 1b). Importantly, we found that to test a 25% drug effect using [18F]MK-6240 quantification over 1-year, a clinical trial using preclinical AD would require as few as 93 individuals per trial arm to assess changes in clusters in the PCC, 96 in the medial prefrontal, and 174 in the hippocampus cortices. **Conclusion:** In this preliminary analysis, our results highlight [18F]MK-6240 as a valuable tool for testing the effect of the emerging disease-modifying therapies on tau accumulations over a 1-year clinical trial period in preclinical AD. (1) Pascoal, T. A. et al. Amyloid and tau signatures of brain metabolic decline in preclinical Alzheimer's disease. European journal of nuclear medicine and molecular imaging 45, 1021-1030, doi:10.1007/s00259-018-3933-3 (2018).

OC27: IMPLEMENTATION OF THE NIA-AA RESEARCH FRAMEWORK: TOWARD A BIOLOGICAL DEFINITION OF ALZHEIMER'S DISEASE IN AIBL. Samantha C Burnham[1,2], Preciosa M Coloma[3], Qiao-Xing Li[4], Steven Collins[5], Greg Savage[6], Simon Laws[2], James Doecke[7], Paul Maruff[8], Ralph N Martins[2,9], David Ames[10], Christopher C Rowe[11], Colin L Masters[4], Victor L Villemagne[4,11] *((1) eHealth, CSIRO, Parkville, VIC, Australia; (2) School of Medical Sciences, Edith Cowan University, Joondalup, Australia; (3) Product Development Personalised Health Care - Data Science, F. Hoffmann-La Roche Ltd., Basel, Switzerland; (4) The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Victoria, Australia; (5) Department of Pathology, University of Melbourne, Parkville, Australia; (6) Macquarie University, Sydney, Australia; (7) eHealth, CSIRO, Herston, QLD, Australia; (8) Cogstate Ltd., Melbourne, Australia; (9) Macquarie University, North Ryde, Australia; (10) National Ageing Research Institute, Melbourne, Australia ; (11) Austin Health, Melbourne, Australia)*

Background: The NIA-AA have released a new research framework: Toward a biological definition of Alzheimer's disease1. This is based on a three-marker construct classification for the diagnosis of AD with biomarkers in living persons. It uses normal (-) or abnormal (+) levels of Aβ-amyloid deposition (A), pathologic tau (T), and neurodegeneration ((N)) as constructs to create the AT(N) classification system. By examining this framework in different populations, its potential to enable a more accurate characterization and understanding of the stages of the Alzheimer's disease (AD) continuum can be interrogated. **Objectives:** (1) To apply the AT(N) classification system to well-characterised participants in the Australian Imaging, Biomarker and Lifestyle (AIBL) Study of Aging. (2) To characterise the long-term clinical and cognitive trajectories of AIBL elderly cognitively normal controls (NC) as well as the AIBL Mild Cognitively Impaired (MCI) individuals using the three-marker construct. **Methods:** Data from 200 (27 AD; 33

MCI; 140 NC) AIBL participants were analysed. Cerebrospinal fluid (CSF) samples from these participants were evaluated for Aß-amyloid 1-42 (Aß42), phosphorylated tau 181 (pTau) and total tau (tTau) biomarkers using the fully automated Elecsys-immunoassays. Thresholds for abnormality were derived using the optimisation of Youden's Index: A+ was defined as CSF Aß42 levels ≤1054pg/mL; T+ as CSF tTau levels ≥21.34pg/mL and (N)+ as CSF pTau levels ≥212.6pg/mL. Participants were then assigned to one of 8 groups (A-T-(N)-; A+T-(N)-; A+T+(N)-; A+T-(N)+; A+T+(N)+; A-T+(N)-; A-T-(N)+; A-T+(N)+) based on having normal (-) or abnormal (+) levels of CSF Aß42, tTau and pTau levels. The prevalence of these 8 AT(N) groups was assessed across the clinical classification groups. In line with the NIA-AA research framework1, the 8 AT(N) groups were collapsed into 4 main groups of interest, those with normal AD biomarkers (A-T-(N)-), those with non-AD pathologic change (A-T+(N)-; A-T+(N)+; A-T+(N)-), those with AD pathologic change (A+T-(N)-; A+T-(N)+) and those with AD (A+T+(N)-; A+T+(N)+). Boxplots were used to evaluate the baseline clinical and cognitive performance across these 4 groups within the NC and MCI sub-cohorts. Change in clinical and cognitive performance over time were also evaluated using boxplots of the random slopes obtained from linear mixed effect models. In the linear mixed effect models the cognitive measure represented the dependent variable; age, sex and APOE ß4 status were included as interacting independent factors and time since CSF evaluation was included as a random factor. **Results:** The prevalence of the 4 AT(N) classification groups within the AIBL NC, MCI and AD sub-cohorts are given in Figure 1. Notably, the three-marker construct A+T-(N)+ was not present among any of the AIBL sub-cohort. The highest proportion of NC individuals (38%) have normal AD biomarkers; 33% of NC have AD pathologic change and 29% have non-AD pathologic change. In the MCI and AD sub-cohorts 75% and 70% of participants have AD pathologic change, respectively. Results from analysis using the AIBL Preclinical Alzheimer's Cognitive Composite (PACC) are provided by Figure 2, as an example of findings. In general, NC participants with AD pathologic change or AD performed the worst on the clinical and cognitive tests (cross-sectional analysis, Figure 2A). There were no apparent differences in the rates of decline for the 4 groups considered (longitudinal analysis, Figure 2B). For MCI, there was a stepwise decrease in performance from those with normal AD biomarkers, to those with AD pathologic change and then AD (cross-sectional analysis, Figure 2C). MCI participants with AD pathologic change and AD also appeared to have faster rates of decline than participants with normal AD biomarkers (longitudinal analysis, Figure 2D). **Conclusions:** By examining the new NIA-AA Research Framework in the AIBL study population, we were able to show that higher prevalence of biomarker abnormality is associated with worse cognitive performance. These data support the notion that the implementation of the AT(N) biomarker construct could be used to identify those at-risk individuals, more likely to progress, for their inclusion in therapeutic trials. References: 1. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & dementia: the journal of the Alzheimer's Association 2018; 14(4): 535-562.

OC28: THE NEUROPROTECTIVE EFFECT OF A NEW PHOTOBIOMODULATION TECHNIQUE ON AB25-35 PEPTIDE-INDUCED TOXICITY DRAMATICALLY IMPACT GUT MICROBIOTA DYSBIOSIS.

Jacques Touchon[1,2], Laura Auboyer[3], Johann Meunier[4], Laura Ceolin[4], François J. Roman[4], Rémy Burcelin[5], Guillaume J. Blivet[3] *((1) INSERM U1061, Montpellier, France; (2) Neurology Department, University of Montpellier, France; (3) REGEnLIFE SAS, Montpellier, France; (4) Amylgen SAS, Montferrier-sur-Lez, France; (5) Vaiomer SAS, Labège, France)*

Background: A decade of evidence demonstrated the major role of gut microbiota dysbiosis on the control of several chronic disease including metabolic and intestinal inflammatory disease. However, recent data suggested a role of gut microbiota on Alzheimer's Disease (AD) without proposing a coherent therapeutic strategy. A photobiomodulation approach, using photonic and magnetic emissions, recently demonstrated encouraging results and normalized memory performances in a rodent model of AD. We previously showed a neuroprotective effect, including oxidative stress, neuroinflammation, apoptosis markers, and specific markers related to the amyloid or tau processes, of the RGn500 device against central-Aβ25-35 peptide-induced neurotoxicity when applied to both the head and the abdomen (Blivet et al., Alzheimers Dement (NY), 2018). Furthermore, the technology was improved to obtain similar results while drastically reducing the treatment duration thanks to a new device RGn530 optimized from RGn500. To reconcile the role of gut microbiota dysbiosis in AD with this new biophotonic-based therapeutic strategy we treated Aβ25-35 peptide injected mice with RGn530 device and characterized gut microbiota. **Methods:** Aβ25-35 peptide or control scramble peptide were injected intracerebro-venticularly to Swiss male mice (12 per group) and treated once a day for 7 days following injection, during 6 min on both the head and abdomen with the RGn530 device. The caecum microbiota was characterized at the end of treatment 7 days later via the sequencing of the 16SrRNA gene (MiSeq) followed by bioinformatics and biostatistics analyses. Protection against Aβ25-35 neurotoxicity was assessed via a memory evaluation in the Y-maze and the step through passive avoidance (STPA) tests. Markers of inflammation (TNFα) and oxidative stress (lipid peroxidation levels) were measured in the hippocampus. **Results:** The injection of the Aβ25-35 induces a strong caecal microbiota dysbiosis where the Bacteroidetes to Firmicute ratio was deeply disrupted showing the relevance of such model in the screening of AD-therapeutic strategies. The RGn530 treatment, when applied for 6 min on both head and abdomen, not only reversed this ratio but allowed the emergence of specific microbial communities (Tenericutes and Deferribacteres) as biomarkers of the treatment efficacy. In addition, the Actinobacteria and Proteobacteria were two major phyla specifically affected by the treatment, suggestive of their role on the therapeutic efficacy. This impact was associated with the total reversal of memory deficits produced by Aβ25-35 injection in the two tests that were investigated. Oxidative stress elevation, as assessed by hippocampal lipid peroxidation levels, and neuroinflammation i.e. TNFα elevation, were fully down-regulated. **Conclusion:** The application on both head and abdomen of RGn device-based treatments have demonstrated a striking efficacy on memory performances in the Aβ25-35 mouse model of AD. We here show for the first time that first this animal model is characterized by a gut microbiota dysbiosis which second,

could be reversed by RGn530 device-based treatments. More experiments are ongoing to evaluate the contribution of the treatment impact on gut microbiota on the neuroprotective effects and improved memory performances observed in AD-rodent models. In the light of anti-amyloid therapeutic approaches lack of success, RGn530 dual treatment, contributing to a change in microbiota composition, appears as an innovative and extensive treatment strategy for AD. Eventually, our data even provide biomarkers companion for treatment efficacy, that can result hence in adapting treatment to patients.

OC29: ELECSYS® CSF BIOMARKER IMMUNOASSAYS DEMONSTRATE CONCORDANCE WITH RESULTS OF AMYLOID-PET IMAGING IN AIBL PATIENT SAMPLES.

Larry Ward[1], Samantha C. Burnham[4,7] Victor L. Villemagne[5,6], Qiao-Xin Li[5], Steven Collins[5], Christopher J Fowler[5], Ekaterina Manuilova[2], Monika Widmann[3], Stephanie Rainey-Smith[7], Colin L Masters[5], James D Doecke[1,8] *((1) Cooperative Research Council for Mental Health, Melbourne, Vic, Australia; (2) Roche Diagnostics GmbH, Penzberg, Germany; (3) Roche Diagnostics GmbH, Mannheim, Germany; (4) Commonwealth Scientific Industry and Research Organisation/Australian E-Health Research Centre, Parkville, Melbourne, QLD, Australia; (5) The Florey Institute, The University of Melbourne, Parkville, Australia; (6) Austin Health, Department of Molecular Imaging and Therapy, Center for PET, Heidelberg, Victoria, Australia; (7) School of Medical and Health Sciences, Edith Cowan University, Joondalup, Australia; 8. Commonwealth Scientific Industry and Research Organisation/ Australian E-Health Research Centre, Brisbane, QLD, Australia)*

Background: Alzheimer's disease (AD) pathology, separate from clinical presentation, is characterised by de-regulated cleavage of Amyloid precursor protein (APP), resulting in accumulation of ß-amyloid (Aß) into senile plaques coupled with degeneration of neurons via the abnormal hyperphosphorylation of the tau protein, resulting in the formation of tau tangles. To date, visual reads of Aß Position Emission Tomography (PET) scans is the only FDA approved method to support the diagnosis of AD, however PET imaging is costly and a radiation burden to patients. Roche Diagnostics is developing electrochemiluminescence immunoassays (Elecsys®) for measurement of AD biomarkers Aß42, phosphorylated tau 181 (pTau) and total tau (tTau) in the cerebral spinal fluid (CSF). Recent studies have shown good concordance between Aß42, tTau/Aß42 and pTau/Aß42 levels measured in CSF using the automated Roche Elecsys® assays and amyloid PET outcome obtained using different tracers in diverse study cohorts (Hansson etal, 2018; Schindler etal, 2018). This study aims to further validate these results, contributing to the NIA-AA research framework that utilises the measurement of biomarkers to define an AD continuum. **Objectives:** In the current study we assessed the concordance of Elecsys® CSF biomarker immunoassays Aß40, Aß42, tTau and pTau and their ratios to neocortical Aß burden as measured by PET imaging. **Methods:** Two hundred and two stored CSF samples from AIBL, with Aß status defined as either PET-Aß- or PET-Aß+, were evaluated. Patient samples were measured with the fully automated Elecsys® immunoassays for Aß40 (for research use only), Aß42, tTau and pTau biomarkers. Neocortical Aß burden was measured using three different tracers; Pittsburgh Compound B (PiB) (N=90), Flutemetamol (N=70) and Florbetapir (N = 42). PET-Aß status was defined using standardised uptake value ratios (SUVR) dichotomized at pre-specified thresholds for each individual tracer. Population demographic characteristics (gender, age, APOEε4 allele status, cognitive scores, PET tracer frequency and diagnoses distribution) were compared using Chi-Squared test, Independent Samples t-test and Mann Whitney U-test between PET-Aß status where appropriate (Table 1). Elecsys® CSF biomarkers and their respective ratio's (Aß42/40, tTau/Aß42 and pTau/Aß42) were analysed with respect to their concordance with PET-Aß status. The capability of individual CSF biomarkers and combined ratios to distinguish participants classified as PET-Aß positive/negative was assessed using Receiver Operating Characteristic (ROC) analyses. Biomarker thresholds were derived using the optimization of Youden's Index. Overall, positive and negative percentage agreements (OPA, PPA and NPA) to the PET-Aß status were calculated at the optimized cut-offs. Area under the curve (AUC) values of individual biomarkers and biomarker ratios were compared using DeLong's method. **Results:** Thirty eight of 140 cognitively normal (CN, 27%), 23 of 33 participants with mild cognitive impairment (MCI, 70%), 23 of 27 participants with AD (85%) and 0 of 2 subjects with frontotemporal dementia (FTP, 0%) were PET-Aß+ (Table 1). Comparing mean CSF biomarker levels between PET-Aß groups, tTau, pTau and the Tau/Aß42 and pTau/Aß42 ratios were significantly greater in the PET-Aß+ group, whilst the Aß42 and Aß42/40 ratios were significantly lower in the PET-Aß+ group compared with the PET-Aß- group ($p<0.0001$). Among the individual biomarkers, Aß42 had the highest AUC (0.87), followed by pTau (0.84) and tTau (0.80) (Figure 1a, 1b). Biomarker ratios demonstrated considerably higher performance, that was similar for all ratios (AUC=0.94). Among the individual biomarkers Aß42 had the highest concordance to PET-Aß status at the optimized threshold (PPA and NPA both 81%), tTau had PPA 86%, NPA 66%, and pTau PPA 81% and NPA 76%. Ratios Aß42/40 and pTau/Aß42 showed similar performance at the derived thresholds (PPA and NPA close to 90%), whilst the tTau/Aß42 ratio showed stronger NPA (97%) but weaker PPA (83%). Assessing agreement to PET-Aßstatus in the CN population only, we saw a decrease in PPA and NPA of only 1% for both Aß42/40 and pTau/Aß42 ratios. Comparing ROC models between Aß42 alone and Aß42 within a ratio, all three ratios were significantly better at predicting PET-Aß status (Aß42/40 $p=0.0001$, tTau/Aß42 and pTau/Aß42 $p<0.0001$). Scatter plots for Aß42 with tTau and Aß42 with pTau showed two clusters. The majority of PET-Aß- participants had values aligning close to the x-axis, and those participants who were PET-Aß+, had values aligning close to the y-axis (Figure 1C and 1D). Diagonal lines corresponding to the optimized thresholds for ratios tTau/Aß42 (Figure 1C) and pTau/Aß42 (Figure 1D) separated subjects with positive and negative PET-Aß status. These results from the AIBL cohort are consistent with the published results of PET-CSF concordance studies within BioFINDER and ADNI cohorts. **Conclusions:** The current study showed high concordance of the Elecsys® biomarkers with the PET-Aß outcome in both the complete cohort, and in a subset with only CN participants. Furthermore, we showed the superior capability for the Elecsys® biomarker ratios to predict PET-Aß status as compared with Aß42 alone. These results together demonstrate the potential diagnostic utility of Elecsys® biomarkers in prodromal/preclinical patient populations with normal cognition, as well as participant selection for therapeutic trials.

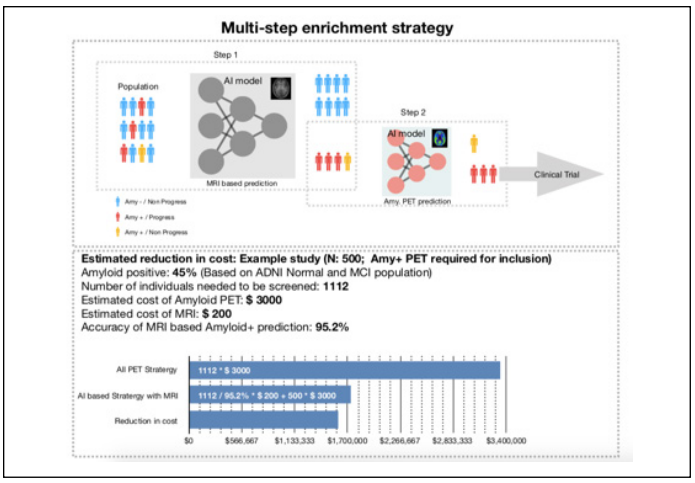
Table 1
Study population demographic characteristics

Characteristic	Total Sample	PET- Aß-	PET-Aß+	p-value
N (%)	202 (100)	118 (58)	84 (42)	-
Gender Male, N(%)	100 (50)	51 (43)	49 (58)	0.0340
Mean Age, years (SD)	73.5 (6.2)	72.5 (6.2)	74.8 (6.0)	0.0110
APOE ß4 Carriage, N(%)	64 (32)	24 (21)	40 (48)	<0.0001
Mean PACC score, (SD)	-3.0 (6.8)	-0.5 (4.2)	-6.8 (8.1)	<0.0001
Median MMSE, (IQR)	28 (4.0)	29 (2.0)	27 (4.2)	0.0002
Median CDR score, (IQR)	0 (2.4)	0 (0)	0.5 (3.2)	0.0002
Tracer				
PIB, N (%)	90 (44)	46 (23)	44 (22)	
Flutemetamol, N (%)	70 (35)	41 (20)	29 (14)	
Florbetapir, N(%)	42 (21)	31 (15)	11 (6)	0.048
Diagnosis				
CN, N (%)	140 (70)	102 (51)	38 (19)	
MCI, N (%)	33 (16)	10 (5)	23 (11)	
AD, N (%)	27 (13)	4 (2)	23 (11)	
FTP, N (%)	2 (1)	2 (1)	0 (0)	<0.0001

OC30: COST-EFFECTIVE, MULTI-STEP ENRICHMENT STRATEGY FOR CLINICAL TRIALS USING ARTIFICIAL INTELLIGENCE. Sulantha Mathotaarachchi, Tharick A. Pascoal, Mira Chamoun, Andrea L. Benedet, Min Su Kang, Joseph Therriault, Serge Gauthier, Pedro Rosa-Neto *(McGill University Research Centre for Studies in Aging, McGill University, Montreal, Canada)*

Background: One of the biggest challenges in Alzheimer's disease (AD) clinical trials is identifying the most suitable candidates for an intervention. It has been shown that -amyloid based- imaging biomarkers provide the best method in enrichment in clinical trials selection (CTAD 2016 – Oral Presentation – OC7) [1] but the associated cost of a PET scan for screening individuals is an economical burden as only 15% of Mild Cognitive Impairment (MCI) individuals progress to AD. Over the recent years, artificial intelligence has shown promise in image identification particularly in detecting latent pattern identification and feature extraction. We propose a multi-stage strategy based on artificial intelligence to identify the most suited candidates for AD clinical trials. First stage consists of using an economically viable imaging biomarker (T1 MRI) to select suspected amyloid positive individuals. The second stage entails the use an amyloid PET scan on these identified individuals to calculate their time to progress to AD. **Methods:** We trained a convolution neural network (CNN) on Voxel Based Morphometry (VBM) images to predict amyloid positive status of an individual. We used 3057 VBM images from the Alzheimer's disease neuroimaging initiative (ADNI) database to train the CNN to predict the amyloid status and used separate 541 VBM scans to evaluate the performance of the trained CNN. We then evaluated the probability of progressing to AD of the individuals identified as amyloid positive within a 24 months' time frame. For this purpose, we used 44 MCI individuals previously identified to progress to AD within 2 years of the amyloid PET scan. **Results:** The CNN could predict the suspected amyloid positivity with an accuracy of 95.2% for the 541 testing samples. To the best of our knowledge this is the highest accuracy reported in predicting amyloid positive status based on MRI based biomarker. Out of the 44 progressing individuals, only 37 individuals were amyloid positive, and the CNN were able to identify 35 of them to be amyloid positive. We then calculated the probability of progression of these 35 individuals using the amyloid PET based prediction algorithm [1] with an accuracy of 85%. **Conclusion:** The proposed multi-stage enrichment strategy is an economically feasible method that can be used in the screening phase of the clinical trials [Figure 1] and could significantly reduce the false positive recruitment and can reduce the associated costs and in turn increase statistical power of the clinical trial.

Figure 1
Flow diagram of the multi-step enrichment strategy and its economic impact. The MRI based AI model was able to identify the features most relevant for amyloid positivity as brain regions related to AD without any prior information about disease or pathology localization



OC31: TRC-PAD: ACCELERATING PARTICIPANT RECRUITMENT IN AD CLINICAL TRIALS THROUGH INNOVATION. Gustavo A. Jimenez-Maggiora[1], Rema Raman[1], Michael S. Rafii[1], Reisa Anne Sperling[2,3], Jeffrey Lee Cummings[4], Paul S. Aisen[1] *((1) Alzheimer's Therapeutics Research Institute, University of Southern California, San Diego, CA, USA; (2) Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; (3) Department of Radiology, Division of Nuclear Medicine and Molecular Imaging, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; (4) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA)*

Background: Participant recruitment for clinical trials in Alzheimer's Disease (AD) remains a major challenge to the development of effective treatments. Screening evaluation,

which often includes amyloid PET imaging and disclosure of results, has proven to very burdensome and time-consuming to site personnel and participants alike. Screen fail rates, many times reaching 80-90%, inflate study budgets, increase effort, and delay study conduct, especially in early-stage clinical trials. **Objectives:** The Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease (TRC-PAD), funded by a $25 million USD award by the National Institute on Aging (NIA) to the TRC-PAD investigators (grant number 1R010AG053798), seeks to accelerate drug development for AD through the establishment of an infrastructure to ensure timely recruitment of targeted individuals into optimally-designed trials. Specifically, TRC-PAD has the following aims: • Aim 1: To build an efficient and sustainable recruitment system in order to enroll an initial TRC-PAD Cohort; • Aim 2: To optimize an innovative, adaptive risk algorithm to efficiently identify the most appropriate trial participants. • Aim 3: To develop and validate web-based cognitive and functional outcome measures for future clinical trials. Progress to date toward these aims is reported in the following sections. **Methods:** TRC-PAD will establish a trial-ready, biomarker-positive cohort (initial N=2000, 1000 preclinical, 1000 prodromal) at sites across North America, to facilitate recruitment into preclinical and prodromal AD trials. Conceived as a multi-tiered infrastructure (Fig. 1), TRC-PAD consists of 1) the Alzheimer Prevention Trials (APT) Webstudy registry (aptwebstudy.org); 2) the in-person Trial-Ready Cohort (TRC); 3) a collection of "feeder" registries, which include the Brain Health Registry (BHR) (www.brainhealthregistry.org), Alzheimer's Prevention Registry, hosted by the Banner Alzheimer's Institute (APR) (endalznow.org), and Healthy Brains by Cleveland Clinic registry (healthybrains.org), among others; and 4) an adaptive algorithm that will utilize demographic, medical, lifestyle, and genetic factors, as well as longitudinal performance on web-based cognitive testing collected via APT, to assess participant risk for amyloid positivity. Participants determined to have elevated risk will be invited to have in-person assessments; those who are amyloid biomarker positive will be eligible for the TRC, where they will be followed (in-person and remotely), ready for enrollment in preclinical and prodromal therapeutic trials. Once fully operational, TRC-PAD will provide NIA- and industry-funded clinical trials with a steady stream of well-characterized, biomarker-confirmed participants with a goal of reducing screen failure rates to <50%, thus yielding significant savings in time, effort, and expense. **Results:** The first tier of TRC-PAD infrastructure, the APT Webstudy, was launched on December 22nd, 2017. Designed to invite participants over the age of 50 with an interest in AD research and clinical trials to commit to a brief battery (15-20 minutes) of remote cognitive assessment on a 3-month longitudinal basis, the webstudy has already demonstrated feasibility. As of May 29th, 2018, 6,309 individuals have registered for an APT account by creating a username and password or via social login. Of these registered individuals, 5726 enrolled in the study via online consent. Recruitment into the webstudy has been driven by both owned/earned media and feeder-based referrals and has resulted in a geographically dispersed cohort that covers all 50 U.S. states clustered primarily at present in the Southwestern and Mid-Atlantic United States. Participant demographics, described in Table 1, suggest opportunities for improvement in the current approach which the investigators will address in future versions of the webstudy site and recruitment strategies. Importantly, 5491 enrolled participants confirmed an interest in participating in clinical trials. **Conclusions:** TRC-PAD infrastructure development efforts continue to move forward at a rapid pace, with TRC in-person assessment of participants scheduled to begin at TRC-PAD performance sites before the end of 2018. Furthermore, the addition of emerging innovations in biomarkers (e.g. plasma Abeta, cognitive tools), offer the potential to increase the effectiveness of the TRC-PAD approach to participant selection and recruitment into future early stage clinical trials. Acknowledgments: This work was supported by the National Institute on Aging (grant number 1R010AG053798).

OC32: DETECTING BRAIN AMYLOID STATUS USING FULLY AUTOMATED PLASMA AB BIOMARKER ASSAYS.

Sebastian Palmqvist[1], Shorena Janelidze[1], Erik Stomrud [1], Henrik Zetterberg[2], Johann Karl[3], Niklas Mattsson[1], Kaj Blennow[2], Udo Eichenlaub[3]; Oskar Hansson[1] *((1) Clinical Memory Research Unit, Lund University, Sweden; (2) Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Sweden (3) Roche Diagnostics GmbH, Penzberg, Germany)*

Background: There is a great need to identify blood-based biomarkers of cerebral Aβ pathology that can easily be implement in primary care settings and large screenings. *Objectives:* Here we investigated the accuracy of plasma Aβ measured using the fully automated ELECSYS® platform to detect Aβ positivity (using CSF biomarkers as the reference standard). *Materials and methods:* The study population consisted of 850 individuals (the Swedish BioFINDER study), including elderly participants without objective cognitive impairment (n=515 of which 196 had subjective cognitive decline, SCD), and patients with mild cognitive impairment (MCI, n=266) or AD dementia (n=69). In SCD/MCI patients, the accuracies were compared with the diagnostic accuracy of memory clinic physicians (blinded to Aβ data). Concentrations of Aβ42 and Aβ40 were assessed in plasma and CSF using ELECSYS® assays. Plasma Aβ42 and Aβ40 were tested as predictors of Aβ positivity (using the CSF Aβ42/40 ratio as reference standard) in logistic regression analyses. APOE genotype (grouped as ε2ε2/ε2ε3, ε3ε3, ε2ε4/ε3ε4 and ε4ε4) and cognitive tests were also tested as predictors in these models. The results were cross-validated using a repeated 10-fold cross-validation procedure. **Results:** In the total population, plasma Aβ42 and Aβ40 predicted Aβ status with an area under the receiver operating characteristic curve (AUC) of 0.80 (95% CI 0.77-0.83). The addition of age and APOE genotype increased the AUC to 0.86 (0.84-0.89). These models had similar accuracies in cognitively unimpaired and MCI, respectively (AUC ±0.02; AD participants were all Aβ+ and could not be tested separately). Adding cognitive tests to the models for the total population increased the AUCs to 0.88-0.89, but no improvement was seen within the diagnostic subgroups. In SCD and MCI participants, the physicians diagnosed Aβ positivity correctly in 65% of the cases, compared to 75% using plasma Aβ42 and Aβ40, and 79% using plasma Aβ42, Aβ40, age and APOE. **Conclusion:** In this large clinical study, we demonstrate that plasma Aβ42 and Aβ40 biomarkers measured with the ELECSYS® platform accurately estimates presence of brain Aβ in all different stages of AD. They are superior to a tertiary care physician's diagnosis and the accuracy can be further increased by analyzing APOE genotype.

OC33: CONCORDANCE OF FLORBETAPIR (18F) PET AND ELECSYS® B-AMYLOID(1-42) CSF IMMUNOASSAY IN THE CREAD (BN29552) STUDY OF CRENEZUMAB IN PRODROMAL-TO-MILD AD. Timo Grimmer[1], Christina Rabe[2], Mercidita Navarro[2], David Clayton[2], Ekaterina Manuilova[3], Udo Eichenlaub[3], Jillian Smith[4], Susanne Ostrowitzki[2], Lee Honigberg[2], Tobias Bittner[5] *((1) Department of Psychiatry, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany; (2) Genentech, Inc., South San Francisco, CA, USA; (3) Roche Diagnostics GmbH, Penzberg, Germany; (4) Roche Products Ltd., Welwyn Garden City, UK; (5) F. Hoffmann-La Roche Ltd., Basel, Switzerland)*

Background: Amyloid positivity in patients at risk for Alzheimer's disease (AD) can be assessed in vivo using two methodologies: amyloid positron emission tomography (PET) imaging or analysis of amyloid-beta (Aβ) (1–42) levels in cerebrospinal fluid (CSF); both methods are currently in use in clinical practice. Good concordance between amyloid PET and Aβ(1–42) levels in CSF has been demonstrated in multiple studies in AD1–5 using several different amyloid PET tracers and commercially available immunoassays. Crenezumab is a humanized anti-Aβ monoclonal immunoglobulin G4 antibody in development for the treatment of AD. It binds to monomeric and aggregated forms of Aβ, with high affinity for oligomers.6,7 Crenezumab is currently under investigation in two Phase III studies in patients with prodromal-to-mild AD: BN29552 (CREAD; NCT02670083) and BN29553 (CREAD 2; NCT03114657). One of the eligibility criteria to enrol in studies BN29552 and BN29553 is amyloid positivity, determined by either an amyloid PET scan or a CSF Aβ(1–42) measurement on the recently released Elecsys® β-Amyloid(1–42) CSF immunoassay system (Roche Diagnostics, Indianapolis, IN).8 In order to assess the concordance between CSF and PET eligibility criteria in the context of study BN29552, a substudy was conducted in which patients who consented to participate and met all other eligibility requirements were evaluated by both amyloid PET imaging and CSF Aβ(1–42) assessment at screening. **Objectives:** To assess the concordance of CSF Aβ(1–42) and amyloid PET eligibility criteria in a substudy of the Phase III study BN29552 of crenezumab in patients with prodromal-to-mild AD. **Methods:** A total of 107 subjects participated in the concordance substudy and provided both a CSF sample and underwent a florbetapir (18F) PET scan at screening. Individual qualified readers at a central reading facility performed a visual read of all PET scans according to the package insert of florbetapir (18F). A positive florbetapir (18F) PET scan for evidence of amyloid burden was determined by agreement on the read between two qualified readers, independent of each other. In case of discordance between the readers, a third qualified reader determined amyloid status. For CSF, a patient was classified as amyloid positive in the BN29552/BN29553 studies if the Aβ(1–42) level was less than or equal to 950 pg/mL as measured on the Elecsys β-Amyloid(1–42) CSF immunoassay system.8 This cut-off was determined based on data available at the time that BN29552 was initiated. Concordance was described by the overall agreement between the florbetapir (18F) PET and CSF Aβ(1–42) amyloid status. A lower 95% confidence limit is presented for the concordance estimate. Positive and negative agreement assuming PET as the reference test, and positive and negative predictive values will also be presented. **Results:** In total, 83 (78%) of the 107 patients enrolled in the substudy were classified as amyloid positive by PET and 84 (79%) patients were classified as amyloid positive by CSF. Ninety-two patients were classified concordantly (76 patients were positive for both CSF and PET and 16 patients were negative for both CSF and PET), resulting in an overall concordance between florbetapir (18F) PET and CSF Aβ(1–42) of 86% (with a lower one-sided 95% confidence limit of 79%). Similar results were observed in the recently published Elecsys immunoassay studies.9,10 Out of the 15 patients with discordant amyloid results, eight (77%) patients were classified as amyloid positive by CSF but not by PET and seven (6%) patients were classified as amyloid positive by PET but not by CSF. **Conclusions:** The concordance of 86% between CSF Aβ(1–42) and amyloid PET methodologies demonstrated in the context of this substudy was in line with that of previous studies and supports the use of either amyloid PET or the Elecsys β-Amyloid(1–42) CSF immunoassay as eligibility criteria in the BN29552 and BN29553 Phase III studies of crenezumab in patients with prodromal-to-mild AD. 1. Jagust WJ, et al. Neurology 2009;73:1193–1199. 2. Fagan AM, et al. Arch Neurol 2011; 68: 1137–1144. 3. Landau SM, et al. Ann Neurol 2013;74:826–836. 4. Zwan M, et al. J Alzheimers Dis. 2014;41:801–7. 5. Toledo JB, et al. JAMA Neurol 2015;72:571–816. 6. Adolfsson O, et al. J Neurosci 2012;32:9677–9689. 7. Ultsch M, et al. Sci Rep 2016;6:39374. 8. Bittner T, et al. Alzheimers Dement 2016;12:517–526. 9. Hansson O, et al. Alzheimers Dement. 2018 [ePub ahead of print] 10. Schindler SE, et al. Alzheimers Dement. 2018 [ePub ahead of print]

OC34: DEVELOPMENT OF Aβ, TAU AND COGNITIVE CHANGES DURING THE TIME COURSE OF SPORADIC ALZHEIMER'S DISEASE. Niklas Mattsson[1], Oskar Hansson[1], Michael W. Weiner[2], Philip S. Insel[1,2] *((1) Clinical Memory Research Unit, Faculty of Medicine, Lund University, Lund, Sweden; (2) Center for Imaging of Neurodegenerative Diseases, Department of Veterans Affairs Medical Center, San Francisco, CA, USA)*

Background: Background: The time-course of the spread of Aß, tau and the onset of clinical symptoms in sporadic AD is unknown. **Objective:** In this study, we sought to estimate the time to significant Aß pathology for each individual and use this temporal proximity to Aß-positivity to estimate the time of initial increases in CSF tau, tau PET and cognitive decline. **Methods:** In 126 ADNI subjects, we used longitudinal Aß PET information to estimate the time to significant Aß pathology. We then used this measure of temporal proximity to Aß-positivity to estimate the time of the initial drop in CSF Av42, increases in CSF tau and tau PET, and decreases in memory and global cognition. **Results:** The time to Aß-positivity ranged from 49 to -30 years. Individuals already Aß+ at baseline will have negative time estimates. A one standard error (SE) drop in CSF Aß42 occurred 22 years before Aß-PET positivity, increases in CSF tau and ptau occurred 20 and 18 years before Aß-positivity (Figure 1, first row), followed by increases in medial temporal lobe tau (16 years before) and medial parietal lobe tau 13 years before Aß-positivity (Figure 1, second row). Delayed logical memory started to decline 10 years before Aß+, followed by decreases in MMSE one year after Aß-positivity. In Figure 1, one and two SE increases from the lowest pathology levels are plotted. Similar estimates are shown for decreased cognitive performance. Biomarker levels and cognitive performance in mild cognitive impairment and dementia are observed ~10-25 years after Aß-positivity. Figure 2 shows the points at which the 1 and 2 SE increases in pathology occurred for all responses. **Conclusions:**

Explicit estimates of the time at which CSF tau levels start to increase, tau pathology spreads beyond the temporal lobe and the proximity of these events to the onset of cognitive symptoms provide a clearer picture of the time course of the amyloid cascade. The close temporal relationship between changes in tau and Aß-biomarkers points to a need for early interventions against Aß for effective prevention of AD. Precise estimates of the temporal changes of AD biomarkers will facilitate the efficient design of clinical trials in early AD.

Figure 1

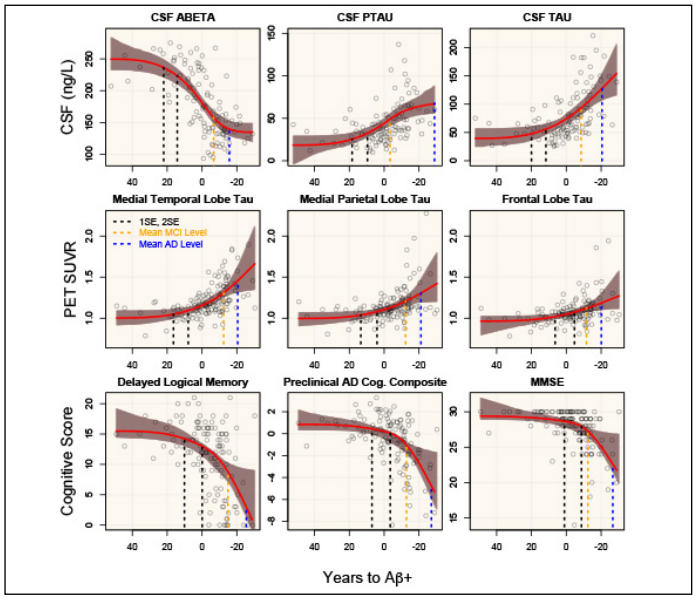
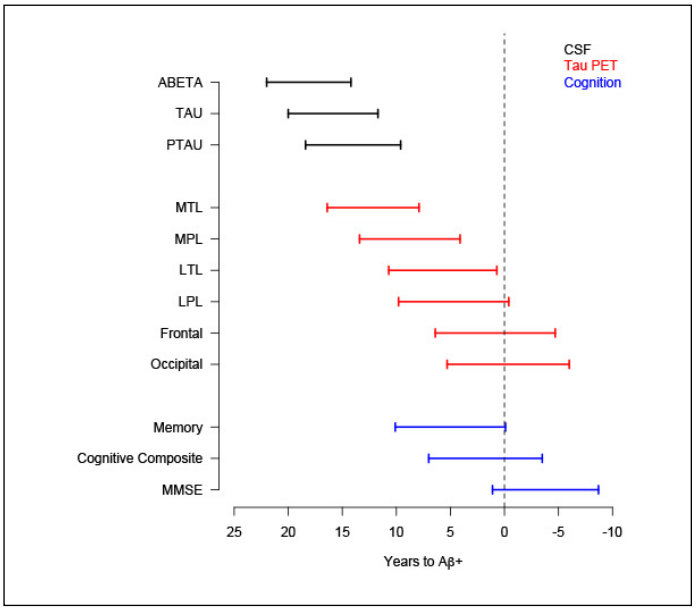


Figure 2



OC35: U.S. POINTER: STUDY DESIGN AND TRIAL KICK-OFF. Laura Baker[1], Mark Espeland[1], Miia Kivipelto[2,3], Gustavo Jimenez-Maggiora[4], Martha Clare Morris[5], Rema Raman[4], Scott Rushing[1], Heather M. Snyder[6], Jeff Williamson[1], Rachel Whitmer[7], Nancy Woolard[1], Maria C. Carrillo[6] On Behalf of the U.S. POINTER Study Team (*(1) Wake Forest School of Medicine, Winston-Salem, NC, USA; (2) Karolinska Institutet, Solna, Sweden; (3) National Institute for Health and Welfare, Helsinki, Finland; (4) Alzheimer's Therapeutic Research Institute, University of Southern California, Los Angeles, CA, USA; (5) Rush University Medical Center, Chicago, IL, USA; (6) Alzheimer's Association, Chicago, IL, USA; (7) University of California - Davis, Davis, CA, USA)*

Background: Lifestyle interventions that combine multiple behaviors focused on improving physical and cognitive health show promise as a therapeutic strategy to protect brain function with advancing age. The 2-year randomized controlled trial (RCT) conducted in Finland a few years ago (the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability, or FINGER) reported that simultaneously targeting increased physical activity, nutritional guidance to support a healthy diet, cognitive training, increased social engagement, and better management of cardiovascular risk factors effectively improved cognition in cognitively normal older adults who were at increased risk of decline. So far, there are no pharmacological interventions that rival this effect. There is an urgent need to expand this work to test the generalizability, adaptability and sustainability of the FINGER findings in geographically and culturally diverse populations in the U.S. and across the globe. The U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER) is a 2-year RCT to evaluate whether lifestyle interventions that simultaneously target many risk factors for cognitive decline and dementia can protect cognitive function in older adults (60-79 years old) at increased risk for cognitive impairment and dementia. POINTER is the first such study to be conducted in a large group of individuals across the U.S. **Methods:** U.S. POINTER will enroll 2,000 older adults (60-79 years) who are at increased risk for cognitive decline owing to first degree family history of significant memory impairment, sedentary lifestyle, poor diet, and suboptimum cardio-metabolic health status. Electronic medical records of large clinical networks will be utilized in the first phase of screening to identify candidates within pre-specified zip-code areas so that participants can be enrolled in waves by geographical region. Enrolled participants will be randomized to one of two lifestyle intervention groups that differ in intensity and format. Those randomized to the Self-Guided Lifestyle Intervention will receive annual medical monitoring, and health education information, tools, and support to encourage increased physical and cognitive activity and a healthier diet through biannual group meetings. Those randomized to the Structured Lifestyle Intervention will receive a coordinated program of physical exercise (primarily aerobic) 4 days per week, nutritional counseling to encourage adherence to the MIND diet, regular cognitive training and social engagement, and frequent medical monitoring of cardiovascular health. The local chapters of the Alzheimer's Association together with community exercise specialists, dietitians and health educators will be instrumental in delivering and monitoring intervention uptake and adherence. This type of community partnership is critical to develop and test the sustainability of a community-based brain health program, one that has the

potential to outlive the trial if the results are positive. **Results:** The primary outcome will be 2-year cognitive trajectory using a global composite score that will allow harmonization with FINGER, and with large pharmacologic prevention trials in cognitively normal older adults (e.g., A4) and with single domain lifestyle intervention studies in adults with early stage cognitive impairment (e.g., EXERT). Intervention effects on vascular and metabolic health, physical function, mood, sleep, healthcare utilization and quality of life will also be assessed. The trial will be launched at two Vanguard Sites in the Fall of 2018 and Winter of 2019, and at 2-3 other sites in the Spring of 2019. **Conclusion:** U.S. POINTER provides an unprecedented opportunity to test whether intensive lifestyle modification can protect cognitive function in older Americans who are at increased risk of cognitive decline and dementia. The study will be challenging to implement given the amount of support required to effectively change lifestyle in those who have developed long-standing unhealthy lifestyle practices that put them at increased risk. The design of the study is innovative in that it includes meaningful partnerships with the community for intervention delivery, and use of user-friendly innovative technology to facilitate intervention uptake and dynamic adherence monitoring. The lessons learned in U.S. POINTER will inform the design and implementation of future studies, studies that may one day drive pharmacologic approaches to include lifestyle modification with the goal of improving brain health and thus responsivity to an investigational agent.

OC36: : IMPLICATIONS FOR AD CLINICAL TRIALS AND OPPORTUNITIES TO LEVERAGE THE FIRST ALZHEIMER'S ASSOCIATION U.S. NATIONAL BEST CLINICAL PRACTICE GUIDELINES FOR THE EVALUATION OF COGNITIVE BEHAVIORAL SYNDROMES, ALZHEIMER'S DISEASE AND RELATED DEMENTIAS. Alireza Atri[1,2], Mary Norman[3], David S. Knopman[4], Jason Karlawish[5], Mary Sano[6], Carolyn Clevenger[7], Chiadi U Onyike[8], Susan Scanland[9], Paige Lin[10], James Hendrix[11], Maria C. Carrillo[11], Brad C. Dickerson[12] and Alzheimer's Association Best Clinical Practices Workgroup *((1) Banner Sun Health Research Institute/Banner Health, Sun City, AZ, USA; (2) Center for Brain/Mind Medicine, Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; (3) Erickson Living, Dallas, TX, USA; (4) Mayo Clinic, Rochester, MN, USA; (5) University of Pennsylvania, Philadelphia, PA, USA; (6) James J. Peters VA Medical Center, New York, NY, USA; (7) Emory University, Atlanta, GA, USA; (8) Johns Hopkins University, Baltimore, MD, USA; (9) Dementia Connection, Clarks Summit, PA, USA; (10) Tufts Medical Center, Boston, MA, USA; (11) Alzheimer's Association, Chicago, IL, USA (12)Massachusetts General Hospital/Harvard Medical School, Charlestown, MA, USA)*

Introduction: Lack of timely and accurate detection and good characterization of individuals along the Alzheimer's disease (AD) clinical spectrums of MCI and dementia hampers recruitment and enrolment eligibility in AD clinical trials. One reason for the variability, inefficiency, and suboptimal rates of timely diagnosis and well-characterization of patients with AD is the lack of multidisciplinary evaluation guidelines to inform clinicians in the United States who encounter and manage affected individuals in primary and specialty care settings. **Objectives:** Over two years (2017-2018) the Alzheimer's Association convened a multidisciplinary Best Clinical Practices Guidelines (CPG) Workgroup charged to evaluate relevant literature, delineate gaps, and integrate evidence and clinical experience to provide consensus recommendations for the clinical evaluation of Cognitive Behavioral Syndromes (CBS) and AD and related dementias (ADRD). The CPG workgroup aimed to delineate best practice points and provide practical and specific U.S. guidelines that were hierarchical and multitiered in approach and relevant to both primary and specialty settings. Systematic evidence reviews and literature searches for articles in the last 30 years (of ~8000 published articles, ~2000 were included for full review); and a modified Delphi method were utilized to develop recommendations and grade the level of obligation. **Discussion:** Consensus best CPG recommendations for primary and specialty care settings were developed and graded for the evaluation of CBS, and AD/ADRD clinical spectrums. An overview of the process and the specific recommendations are presented at the Alzheimer's Association International Conference (AAIC) in July 2018 (Chicago, IL). The CPG recommendations are to define the type of individual who should be evaluated; and delineate a hierarchical multi-tiered patient-centered approach to using standardized assessments, tests, and studies that are tailored to the individual to establish the overall level of cognitive impairment; define the clinical syndrome (e.g. type of MCI/dementia); and establish the cause(s) of the symptoms (e.g. AD). Additionally, recommendations are made regarding when and which type of patients should be referred (e.g. to neuropsychology, dementia subspecialist, genetic counseling); and what types of tests should be done and when, such as laboratory tests, brain imaging (e.g. MRI/CT, metabolic imaging: FDG-PET/SPECT, Amyloid PET), CSF analysis, and genetic testing. The CPG also makes recommendations regarding appropriate education; communication of findings and disclosure of diagnosis; and for planning of ongoing care and support. Finally the CPG identifies important gaps in knowledge that should be addressed with future research. This presentation identifies the implications and opportunities to leverage CPG recommendations that can impact US-based clinical trials. These include better subject recruitment, through an increase in the pool of available subjects; and higher likelihood that screened subjects will meet eligibility criteria due to better clinical and biomarker characterization of diagnosed subjects. **Conclusions:** Broad dissemination and clinical implementation of recommendations from the Alzheimer's Association Best Clinical Practice Guidelines for the evaluation of neurodegenerative Cognitive Behavioral Syndromes, Alzheimer's disease and Related Dementias in the United States may, over time, have a substantial impact to mitigate some of the challenges related to subject recruitment (by improving early diagnosis and increasing the pool of available subjects) and enrollment eligibility (by improving clinical and biomarker characterization of diagnosed subjects that are necessary for inclusion/exclusion criteria) in clinical trials conducted in the United States.

OC37: PROS AND CONS OF AD COMPOSITE ENDPOINTS CONSIDERING RECENTLY REVISED REGULATORY GUIDANCE AND 2018 NIA-AA RESEARCH FRAMEWORK. Michael T. Ropacki[1], Suzanne Hendrix[2] *((1) Strategic Global Research & Development, Half Moon Bay, USA; (2) Pentara Corporation, Salt Lake City, USA)*

Alzheimer's disease (AD) composite endpoints have been trendy in the recent past with most major players in AD clinical

development evaluating the pros/cons of implementing them as clinical trial primary/secondary endpoints. The purpose of this presentation is to provide clinical researchers the needed background and information (i.e., tools) to critically evaluate the benefit/risk of potentially implementing composites into their development program. Composite endpoints come in essentially four varieties: 1) composite scores from traditional psychometrically validated neuropsychological tests and batteries; 2) theoretically-derived composites; 3) statistically-derived composites; and 4) a combination of 1-3. Dependent upon the composite approach taken there are trade-offs in terms of supporting validation, availability of needed data for power calculations/sample size estimates and clinical meaningfulness. Theoretically driven composites don't always consider the correlations and potential redundancy between included items. Statistically-derived composites often vary depending on the dataset in which they were derived and may over report performance based on an overfit model that may not be reproducible in a new dataset. In addition, ceiling and floor effects can impact item selection in unexpected ways, and weights may not appropriately represent clinically relevant domains. Taking original scale items out of context and changing the order of item measurement from that used for the original data collection can result in unexpected changes in performance. Considering the inherent risk in using a new scale in a clinical trial for potential registration, it is not surprising that many companies are sticking with traditional measures such as the ADAS-cog and CDR-sb. Overall, considering the recently revised regulatory guidance (FDA: Early AD: Developing Drugs for Treatment; EMA: Guideline on the clinical investigation of medicines for the treatment of AD) and 2018 National Institute on Aging -Alzheimer's Association (NIA-AA) Research Framework, this presentation will highlight some commonly employed clinical outcome assessments (COAs) and composites from preclinical AD trials as examples and point out some potential cons of composite endpoints use.

OC38: THE EUROPEAN PREVENTION OF ALZHEIMER'S DEMENTIA (EPAD); SUMMARY OF FIRST FORMAL DATA LOCK (EPAD V500.0) AND PREDICTORS OF AMYLOID STATUS. Craig Ritchie[1], Graciela Muniz-Terrera[1], Serge Van der Geyten[2], Miia Kivipelto[3], Alina Soloman[3], Brian Tom[4], Jose Luis Molinuevo[5] *((1) Dementia Prevention Research Group, University of Edinburgh, UK; (2) Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium; (3) Division of Clinical Geriatrics, Center for Alzheimer Research, Karolinska Institutet and Karolinska University Hospital, Sweden; (4) MRC Biostatistics Unit, University of Cambridge, UK; (5) Barcelona Beta Brain Research Centre, Spain)*

Background: Challenges in the development of disease modifying interventions for the secondary prevention of Alzheimer's dementia were catalysts for the establishment of the EPAD (European Prevention of Alzheimer's Dementia) project, which initiated in January 2015 and the sister project AMYPAD (Amyloid Imaging for the Prevention of Alzheimer's Dementia) that opened in October 2016. Both projects are funded through the Innovative Medicines Initiative and will develop improved disease models in the preclinical and prodromal phases of Alzheimer's Dementia, which will inform the embedded Phase 2 EPAD Proof of Concept (PoC) Adaptive Clinical Trial and other research efforts in the prevention of Alzheimer's dementia. Fundamental to this research effort has been the development of the EPAD Longitudinal Cohort Study (LCS). This project will create a readiness cohort for the Bayesian Adaptive Proof of Concept Phase 2 EPAD Clinical Trial scheduled to commence in Q1 2019. In June 2018 the first data release was undertaken of the first 500 research participants who had all baseline data completed and available including imaging and CSF biomarkers referred to here as EPAD V500.0. **Objectives:** The primary objective of the EPAD project is to deliver a readiness cohort for the embedded EPAD PoC trial and concurrently deliver very large amounts of longitudinal data from ultimately several thousand, deeply phenotyped research participants across Europe. This data will provide researchers globally with the opportunity to improve disease models for preclinical and prodromal Alzheimer's dementia. The objectives of this presentation are to [1] present the full baseline characteristics (demographics, cognitive profiles, ApoE and biomarker status) of EPAD V500.0 and [2] analyse this dataset to indicate which baseline factors are associated with a positive amyloid status (CSF Aß<1,000pg/ml). **Methods:** In the EPAD LCS: after consent, research participants undergo detailed clinical assessment and provide blood, CSF and saliva for thorough biomarker analysis. Each research participant also has detailed MRI evaluation and in the majority, PET-Amyloid imaging will eventually be undertaken through the AMYPAD Prognostic and Natural History Study due to open in Q3 2018. EPAD V500.0 data will be presented using standard descriptive statistics across multiple demographic, clinical, cognitive and biomarker variables. The analysis of predictors of amyloid positivity will calculate odds ratios for multiple potential explanatory variables and then using regression analysis identify the adjusted contributions of each to the final model correcting for those variables which either demonstrate a strong association in univariate analyis ($p<0.1$) or have strong historical associations from previous research with amyloid status. To help support recruitment efforts to optimize the readiness of the cohort, we will also present results on the yield of the best data-driven algorithm from readily available data in parent cohorts to predict amyloid status. **Results:** The EPAD LCS has at time of abstract submission recruited 725* research participants across 19 Trial Delivery Centres in Europe with approximately 100 new research participants being recruited each month. Our previous interim analysis (n=232) [REF] showed that 28% of the cohort then were amyloid positive and suggested that increasing age [OR=1.08 (95%CI=1.01-1.15); p=0.01], carrying an ApoEε4 allele [OR=2.6 (95% CI=1.27-5.48); p=0.001] and having a first degree relative with a diagnosis of Alzheimer's dementia [OR=3.1 (95% CI=1.29-8.01); p=0.01] were all significantly associated with amyloid positivity. Hippocampal volume and baseline CDR score were not; though there was a trend suggesting that with increasing RBANS total score (indicating better cognitive function) there were reduced odds of being amyloid positive [OR=0.97 (95% CI=0.94-0.99) p=0.09]. Analysis of EPAD V500.0 will increase the power considerably to elaborate upon these interim analyses conducted in 2017. **Discussion:** The LCS readiness cohort is the key deliverable in EPAD to be able to undertake the ambitious PoC trial itself that has multiple utilities that provide significant scientific, methodological and economic advancement from the status quo. These utilities include [1] existing fully trained and high quality TDCs [2] a single master protocol to allow shared placebo between interventions [3] a readiness cohort to reduce screen failure rates targeted to <10% and [4] a pre-existing trial platform with CRO and vendors contracted and operational. This creates an optimal

testing environment for Phase 2 interventions for the secondary prevention of Alzheimer's dementia. **Conclusions:** The EPAD LCS is making significant progress towards its aims of being a readiness cohort for the EPAD PoC as well as providing vast amounts of high quality data for disease modeling of the preclinical and prodromal phase of Alzheimer's disease. The EPAD V500.0 data release constitutes the first formal data release from the project and represents a significant milestone for EPAD. These data will show how 'ready' the cohort is for the primary and secondary objectives and our analysis also will demonstrate how in the future we can increase the yield of amyloid positivity in our cohort using the best, data-driven algorithms which can be applied to data in our associated parent cohorts and registers.

LATE BREAKING NEWS

LB1: RESULTS FROM THE PHASE 2 NAVIGATE-AD CLINICAL TRIAL EVALUATING LY3202626 BACE INHIBITOR IN PATIENTS WITH MILD ALZHEIMER'S DISEASE DEMENTIA. Albert C Lo[1], Cynthia Duggan Evans[1], Michele Mancini[1], Qun Lin, Hong Wang[1], Peng Liu[1], Sergey Shcherbinin[1], Ming Lu[2], Arnaud Charil[1], Brian A Willis[1], Michael Irizarry[3] *((1) Eli Lilly and Company, Indianapolis, IN, USA; (2) Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly and Company, Indianapolis, IN, USA; (3) Eli Lilly and Company, Indianapolis IN, USA; now at Eisai Inc, Woodcliff Lake, NJ)*

Backgrounds: LY3202626 is a brain-permeable oral inhibitor of human beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1) that reduces β-amyloid peptide (Aβ) production. Aβ peptides aggregate to form amyloid plaques, a hallmark pathology in Alzheimer's disease (AD). Amyloid precedes and predisposes to the development and neuroanatomical spread of tau neurofibrillary tangles, which can be measured by flortaucipir F 18 PET imaging. The main purpose of the NAVIGATE-AD phase 2 trial (NCT02791191) is to evaluate the safety and the effect on brain tau of the study drug LY3202626 in participants with mild AD dementia. Furthermore, the NAVIGATE-AD study assesses downstream effects of LY3202626 on amyloid plaques (florbetapir PET), neurofibrillary tangles (flortaucipir PET), neurodegeneration (vMRI, florbetapir perfusion PET), and clinical outcomes (cognition, function). **Objectives:** The presentation will provide data on safety and tolerability of LY3202626, and the longitudinal change from baseline for clinical outcomes and imaging biomarker data from the NAVIGATE-AD trial. **Methods:** NAVIGATE-AD is a randomized, double-blinded, placebo-controlled phase 2 clinical study. Amyloid positive mild AD patients meeting study entry criteria were randomized to receive either placebo, 3 mg or 12 mg of LY3202626 in 1:1:1 ratio as a single daily oral dose for 52 weeks. Doses were selected to reduce cerebrospinal fluid (CSF) Aβ species by 70% and 90% for 3 mg and 12 mg, respectively, based on Phase 1 data. Safety is assessed by AEs and SAEs, clinical laboratory tests, vital signs, body weight measurements, physical and neurological examinations, ECG, suicidality assessment (C-SSRS), MRI imaging, ophthalmologic exams, and dermatologic exams. The primary biomarker endpoint is change in tau burden by flortaucipir PET imaging (MUBADA SUVr) over 52 weeks from baseline, as an evaluation of disease progression. Secondary endpoints include clinical outcomes (13-item Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog13), Alzheimer's Disease Cooperative Study Instrumental Activities of Daily Living inventory (ADCS-iADL), integrated Alzheimer's Disease Rating Scale (iADRS), pharmacokinetics (PK) and pharmacodynamics (PD; plasma Aβ). Exploratory outcomes include vMRI, florbetapir SUVr and perfusion PET. The study had 80% power to detect 50% slowing on ADAS-Cog or tau PET with either dosing arm. **Results/Conclusion:** After approximately 165 patients were enrolled, the protocol was amended to change the original 1:1:1 randomization ratio to 1:1 for placebo and 12 mg of LY3202626, in order to prioritize the higher dose. The study was terminated early after an interim analysis determined that there was a statistically low probability of study success. A total of 315 amyloid positive mild AD subjects were randomized and took at least 1 dose of study drug. Among those randomized, 133 received placebo, 55 received 3 mg of LY3202626, and 127 received 12 mg of LY3202626. Longitudinal safety profiles and the change from baseline on clinical cognitive outcomes and biomarker measures will be presented.

LB2: TOMMORROW: A TRIAL TO DELAY THE ONSET OF MCI DUE TO AD AND QUALIFY A GENETIC BIOMARKER ALGORITHM: TOPLINE RESULTS. Robert Alexander[1], Daniel K. Burns[2], Kathleen A. Welsh-Bohmer[3], Carl Chiang[2], Meredith Culp[4], Janet O'Neil[4], Brenda L. Plassman[3], Craig Metz[2], Deborah Yarbrough[4], Jingtao Wu[1], Rebecca Evans[1], Kumar Budur[4], Stephen K. Brannan[4], Ann M. Saunders[2], Emiliangelo Ratti[1] for the TOMMORROW Study Investigators *((1) Takeda Development Center Americas, Inc., Cambridge, MA, USA; (2) Zinfandel Pharmaceuticals, Inc., Durham, NC, USA; (3) Duke University Bryan ADRC, Durham, NC, USA; (4) Takeda Development Center Americas, Inc., Deerfield, IL, USA)*

Backgrounds: The TOMMORROW trial (NCT01931566) is a phase 3 global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. **Objectives:** The trial was designed to evaluate two objectives simultaneously: 1) to qualify the biomarker risk assignment algorithm (BRAA) based on apolipoprotein E (APOE) genotype, genetic variation at translocase of outer mitochondrial membrane 40 homolog (TOMM40), and age for the prognosis of the risk of developing mild cognitive impairment (MCI) due to Alzheimer's disease (AD); within 5 years; and 2) to evaluate the efficacy of pioglitazone 0.8 mg sustained release (SR) compared with placebo to delay the onset of MCI due to AD in cognitively normal subjects at high risk as assigned using the BRAA. The key secondary endpoints were to evaluate the effect of pioglitazone compared with placebo on the change from baseline in cognitive performance and in instrumental activities of daily living (ADCS ADL-PI). **Methods:** Takeda Pharmaceuticals and Zinfandel Pharmaceuticals designed the TOMMORROW study in 2010, with assistance from a neuropsychology advisory board for the development of the neurocognitive test battery and with feedback from global regulators incorporated prior to initiation. The battery evaluated cognitive performance by utilizing standard neuropsychological tests assessing multiple domains, including attention, memory, executive function, and visuospatial abilities. The battery of tests was selected to be sensitive to the detection of MCI due to AD, as operationalized for this trial, and cognitive change in healthy older adults. Genetic testing for the BRAA was done at

screening. High-risk subjects identified based on the BRAA were randomized 1:1 to pioglitazone SR 0.8 mg once daily or placebo. A group of approximately 300 low-risk subjects meeting the inclusion criteria received placebo. All subjects were required to have a project partner to provide information for informant interviews and questionnaires. Subjects were followed at 6-month intervals for a planned overall study duration of 5 years, which was the estimated time needed for 202 events of incident MCI due to AD or AD dementia to occur. A clinical diagnosis of MCI due to AD was made by the examining neurologist or psychiatrist in consultation with the site neuropsychologist. The primary endpoint event of MCI due to AD was determined by an independent adjudication committee of dementia experts and required meeting core clinical criteria for MCI due to AD across 2 consecutive visits 6 months apart. **Results:** The study started screening potential subjects in August 2013, and enrollment completed in December 2015. A total of 24,235 individuals were screened; 4856 individuals underwent baseline evaluations, and 3494 cognitively healthy subjects (Clinical Dementia Rating Scale = 0) between 65 and 83 years of age were randomized into the study. Study procedures were conducted in the clinic, with project partners queried on site, or when necessary; informant information was obtained by telephone. The study passed a planned, blinded operational futility analysis in April 2017, which assessed the actual event accrual rate versus that estimated for the study. The study continued until a planned pioglitazone efficacy futility analysis was conducted in January 2018, when approximately one-third of the target number of total primary events had been achieved. The futility statistical analysis plan was to evaluate the conditional power, the probability of achieving the primary efficacy objective at the end of the study as planned, given the data at the time of the futility analysis. An assumption of a 40% drug effect and a conditional power threshold of 30% was prespecified for the efficacy futility analysis; this analysis was performed by an unblinded statistician, and results were provided to the study's independent Data Safety Monitoring Board (DSMB). The DSMB reviewed the findings and provided a recommendation to the sponsor executive committee. The sponsor committee reviewed the DSMB recommendation and the study findings, and a decision was made to terminate the study for efficacy futility. After the study termination decision, administration of study medication was stopped for all study subjects. Subjects whose data at the time of the study decision indicated cognitive decline and potential to be diagnosed as MCI due to AD continued on their regular visit schedule to a final end-of-study visit. As specified in the protocol, those subjects with evidence of cognitive decline were adjudicated. The last subject's final in-clinic study visit occurred on 24 July 2018. **Conclusions:** Topline TOMMORROW study results will be presented for the first time, and the primary and key secondary efficacy endpoints and overall safety findings will be discussed.

LB3: LU AF20513, AN ACTIVE IMMUNOTHERAPY AGAINST AMYLOID BETA, IN DEVELOPMENT FOR PATIENTS IN EARLY STAGES OF ALZHEIMER'S DISEASE. Bjørn Sperling, Lars Østergaard Pedersen, Neli Boneva, Dorthe Daugaard, Yudong Zhao *(H. Lundbeck A/S, Valby, Denmark)*

Background: Lu AF20513 is an active immunotherapy targeting amyloid beta (Aβ), under development for the treatment of early stages of Alzheimer's disease (AD) with the aim to demonstrate a persistent effect on the disease course. This abstract describes a phase Ib multi-center, multiple immunization, sequential cohort, open label, first-in-human study (NCT02388152) in patients with mild Alzheimer's disease. The main objective of this presentation is to present results from the still ongoing phase Ib study. In addition, we will provide an overview of the development program. **Methods:** Patients in the phase Ib study fulfilling clinical criteria for mild AD and CSF biomarker criteria for amyloid positivity, were included. The study consists of two parts, Parts A and B, each including 4 immunizations of Lu AF20513. Patients were divided into four sequential dose cohorts, with 10, 10, 15, and 15 patients, receiving each dose of Lu AF20513, respectively. The duration of patient participation in Part A is 48 weeks, consisting of a treatment period of 24 weeks and a follow-up period of 24 weeks. During the treatment period, all patients receive an immunization of Lu AF20513 at Weeks 0, 4, 12 and 24. Part B consists of a run-in period of up to 9 months, followed by a treatment period of up to 36 weeks and a follow-up period of 12 weeks. The patients in Part B receive an immunization of Lu AF20513 every 12 weeks. Only patients in Cohorts 1 to 3 can participate in Part B and there is no enrolment of new patients. Safety assessments included MRI scans for evaluating ARIA-E and ARIA-H. Antibody levels against Aβ were measured before and four weeks after immunizations, at 36 and 48 weeks, and in Part B. Based on the safety profile of the first three cohorts, Part B was initiated. **Results:** A total of 48 patients were enrolled (cohort 4 is still ongoing); 34 completed Part A and 28 were enrolled into Part B. Treatment-emergent adverse events were mainly local immunization related events (IREs) at the injection site. The vast majority of these IREs were mild and short-lasting, all were non-serious and none led to discontinuation. There were no ARIA-E findings. Four patients developed ARIA-H reported on the MRI scans during Part A and Part B, all events were asymptomatic. Two of the four patients had preexisting ARIA-H at screening. There was a total of 9 serious adverse events in 6 patients, all considered not related to treatment, and among these 3 deaths: two resulting from complications after falls and one due to a myocardial infarction. Positive antibody responder rate increased with increasing dose. Antibody response was reversible; however, levels were maintained with quarterly immunizations in Part B. **Conclusions:** Multiple immunizations with Lu AF20513, an active immunotherapy against Aβ, did not raise any safety concerns in this phase Ib study. The results support further clinical development of Lu AF20513.

LB4: PREDICTORS OF [18F]FLORTAUCIPIR (TAU) LOAD IN ALZHEIMER'S DISEASE AND OTHER NEURODEGENERATIVE DISORDERS. Oskar Hansson[1,2], Gil D. Rabinovici[3], Chul H. Lyoo[4], Rik Ossenkoppele[1,5] *((1) Lund University, Clinical Memory Research Unit, Lund, Sweden; (2) Memory Clinic, Skåne University Hospital, Malmö, Sweden; (3) Department of Neurology, University of California San Francisco, San Francisco, USA, Memory and Aging Center; (4) Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; (5) VU University Medical Center, Department of Neurology and Alzheimer Center, Amsterdam Neuroscience, Amsterdam, the Netherlands)*

Backgrounds: The PET tracer [18F]flortaucipir allows in vivo quantification of paired helical filament tau, a core neuropathological feature of Alzheimer disease (AD). Previous

studies have shown a considerable range of [18F]flortaucipir uptake in AD dementia but also in non-AD neurodegenerative disorders. It is currently not fully understood which factors are associated with low tau load in AD dementia patients and with high tau load in non-AD neurodegenerative disorders. **Objective:** To identify factors that contribute to [18F]flortaucipir negativity in AD dementia patients and to [18F]flortaucipir positivity in non-AD neurodegenerative disorders. **Methods:** We included 593 participants from three dementia centers in South Korea, Sweden and the United States between June 2014 and November 2017 (Table 1). The study population included 160 cognitively normal controls, 179 patients with AD dementia and 254 patients with various non-AD neurodegenerative disorders (Parkinson disease with [n=70] or without [n=23] cognitive impairment, progressive supranuclear palsy [n=40], behavioral variant frontotemporal dementia [n=33], dementia with Lewy bodies [n=24], corticobasal syndrome [n=23], non-fluent variant primary progressive aphasia [n=17], semantic variant primary progressive aphasia [n=11], vascular dementia [n=7], multiple system atrophy [n=3], chronic traumatic encephalopathy [n=2] and unspecified primary progressive aphasia [n=1]). We first defined "tau-positivity" based on the mean + (2*SD) of [18F]flortaucipir uptake in a temporal Meta-ROI in the cognitively normal control group (SUVR: 1.34) (definition of cut off recently described in detail in Ossenkoppele et al, JAMA, in press). Using this cut-off, 18/179 (10.1%) of AD dementia patients were [18F]flortaucipir-negative, while 24/254 (9.4%) of patients with non-AD neurodegenerative disorders were [18F]flortaucipir-positive. To identify factors associated with "tau-negativity" in AD dementia and "tau-positivity" in non-AD neurodegenerative disorders, we performed bivariate binary logistic regression models with [18F]flortaucipir status as dependent variable, and age, sex, APOE ε4 status, Aβ-status (only in non-AD analyses) and MMSE as predictors. Additionally, we performed multivariable binary logistic regression models using observed data only and multiple imputations (with 25 multiple imputations and 40 iterations) to account for missing data. **Results:** Bivariate binary logistic regression models in AD dementia patients showed that "tau-positivity" in the temporal Meta-ROI was associated with lower odds for age (OR: 0.90[0.84-0.96], p=0.001) and MMSE score (OR: 0.81[0.71-0.93], p<0.01), but not with sex and APOE status (p>0.05, Table 2). Late-onset (≥65 years, 17/114[14.9%] tau-negative AD dementia patients were more often tau-negative compared to early-onset (<65 years, 1/65[1.5%] tau-negative) AD dementia patients (X2=8.2, p<0.01). In patients with a non-AD neurodegenerative condition, "tau-positivity" was associated with higher odds for age (OR: 1.14[1.07-1.21], p<0.001) and Aβ-positivity (OR: 2.08[1.27-3.41], p<0.01), lower odds for MMSE (OR: 0.87[0.82-0.93], p<0.001) and not with sex and APOE status (p>0.05, Table 2). Multivariable binary logistic regression models in both the original and imputed dataset revealed the same significant predictors as the bivariate models (Tables 2). **Conclusions:** In the AD dementia group, ~10% were classified "tau-negative", which was associated with older age and higher MMSE scores. Certain elderly individuals may develop clinical AD dementia in the presence of a lower tau burden due to age-related reductions in cognitive reserve and/or the development of multiple comorbid pathologies. Higher MMSE scores (i.e. better general cognitive performance) indicate that patients in less advanced stages of AD dementia may not have accumulated sufficient tau to exceed the threshold. Another possible explanation for the absence of [18F]flortaucipir signal is that Aβ was present as comorbid pathology in addition to a primary pathology (e.g. hippocampal sclerosis, vascular lesions or argyrophilic grain disease) that is typically not associated with AD-like tauopathy. Although specificity of [18F]flortaucipir was high, ~9% of patients with a non-AD neurodegenerative disorder were classified "tau-positive". In this study, the strongest predictor for "tau-positivity" in non-AD cases was Aβ-positivity. A proportion of the "tau-positive" cases may have been clinically misdiagnosed as having a non-AD disorder, with AD as underlying pathological substrate for their symptoms. Alternatively, paired helical filament-tau may have been present as a secondary pathology whereas the clinical syndrome was driven by non-AD pathologies.

Table 1
Participant characteristics

	Cognitively normal *(n=160)*	Alzheimer disease dementia *(n=179)*	Non-Alzheimer disease *(n=254)*
Age, mean (SD), years	69.1 (9.5)	68.8 (9.6)	68.7 (8.0)
Sex (% male)	40.6	40.8	57.5
Education, years of school (SD)	12.3 (4.1)	13.3 (5.1)	13.0 (5.3)
MMSE score, mean (SD)[a]	28.5 (1.6)	20.2 (5.5)	23.6 (6.0)
CDR - global, mean (SD)[b]	0.0 (0.1)	1.0 (0.6)	0.6 (0.6)
Amyloid-β positivity	26.3% (42/160)	100% (179/179)	23.8% (50/210)
APOE ε4 positivity	31.8% (49/154)	56.4% (88/156)	30.1% (43/143)
Time between PET and diagnosis, days (SD)	108 (156)	48 (76)	47 (142)
Center/Cohort (n, Seoul/BioFINDER/UCSF)	90/66/4	55/52/72	89/73/92
Temporal meta-ROI	1.16 (0.09)	1.95 (0.47)	1.20 (0.19)

MMSE = Mini-mental state examination; CDR = Clinical dementia rating scale; SUVR = Standardized uptake value ratio.

Table 2
Factors contributing to tau-negativity in AD dementia and tau-positivity in non-AD diseases in the temporal meta-ROI

AD dementia					
	Tau-negative (n=18)	**Tau-positive (n=161)**	**OR (95% CI)**	**P**	
A. Bivariate model					
Age (n=179)	76.3 (8.1)	68.0 (9.4)	0.90 (0.84-0.96)	**0.001**	
Sex, %male (n=179)	44.4	40.4	0.85 (0.32-2.26)	0.739	
APOE ε4, % positive (n=156)	38.5	58.0	2.21 (0.69-7.10)	0.182	
MMSE (n=169)	24.1 (4.2)	19.8 (5.4)	0.81 (0.71-0.93)	**0.002**	
	Tau-negative (n=13)	**Tau-positive (n=138)**	**OR (95% CI)**	**P**	**Imputed OR (95%CI)**
B. Multivariable model* (n=151)					
Age	76.8 (9.0)	68.6 (5.3)	0.89 (0.82-0.97)	**0.006**	0.88 (0.81-0.95)
Sex, %male	38.5	38.4	0.96 (0.27-3.42)	0.946	0.84 (0.27-2.60)
APOE ε4, % positive	38.5	59.4	2.31 (0.65-8.15)	0.194	2.14 (0.63-7.24)
MMSE	22.9 (3.9)	19.9 (5.3)	0.82 (0.69-0.97)	**0.022**	0.77 (0.65-0.90)
Non-AD neurodegenerative conditions					
	Tau-negative (n=230)	**Tau-positive (n=24)**	**OR (95% CI)**	**P**	
A. Bivariate model					
Age (n=254)	68.1 (7.7)	75.1 (7.2)	1.14 (1.07-1.21)	**<0.001**	
Sex, %male (n=254)	57.8	54.2	0.86 (0.37-2.01)	0.730	
APOE ε4 status, % positive (n=143)	28.2	42.1	1.85 (0.69-4.98)	0.220	
Aβ status, % positive (n=210)	17.9	80.0	2.08 (1.27-3.41)	**0.004**	
MMSE (n=212)	24.3 (5.7)	17.7 (5.9)	0.87 (0.82-0.93)	**<0.001**	
	Tau-negative (n=118)	**Tau-positive (n=15)**	**OR (95% CI)**	**P**	**Imputed OR (95%CI)**
B. Multivariable model* (n=133)					
Age	68.1 (7.8)	76.3 (7.6)	1.16 (1.03-1.31)	**0.016**	1.09 (1.01-1.18)
Sex, %male	60.2	46.7	1.04 (0.22-4.88)	0.959	1.04 (0.37-2.94)
APOE ε4 status, % positive	27.1	46.7	1.10 (0.22-5.55)	0.909	0.99 (0.21-4.75)
Aβ status, % positive	16.1	86.7	34.58 (4.92-243.19)	**<0.001**	8.90 (2.21-35.87)
MMSE	24.1 (5.0)	17.1 (6.3)	0.85 (0.75-0.96)	**0.009**	0.90 (0.84-0.98)

Reported odds ratios, 95% confidence intervals and p-values were derived from bivariate (A) and multivariable (B) binary logistic regression models. * The multivariable model only included participants with all four variables available. The multivariable analyses were also done on imputed data sets, with results shown in the two right-most columns (with N=179 for AD dementia, upper part; and N=254 for non-AD neurodegenerative conditions, lower part).

LB5: 18F-AV-1451-A16: A CLINICO-PATHOLOGICAL STUDY OF THE CORRESPONDENCE BETWEEN FLORTAUCIPIR PET IMAGING AND POST-MORTEM ASSESSMENT OF TAU PATHOLOGY. Mark A. Mintun[1,2], Adam S. Fleisher[2], Michael D. Devous[2], Ming Lu[2], Anupa K. Arora[2], Thomas G. Beach[3], Thomas J. Montine[4], Michael J. Pontecorvo[2] *((1) Eli Lilly and Company, Indianapolis, IN, USA; (2) Avid Radiopharmaceuticals, Inc., Philadelphia, PA, USA; (3) Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Phoenix, AZ, USA; (4) Department of Pathology, Stanford University, Stanford, CA, USA)*

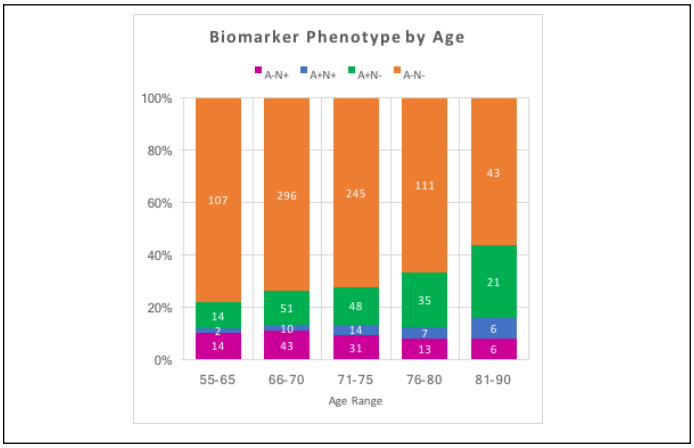
Backgrounds: Neocortical tau neurofibrillary tangles are believed to be a characteristic neuropathology of Alzheimer's disease. Flortaucipir (aka AV-1451 and T-807) PET imaging was developed to estimate the pattern and extent of neurofibrillary tangles (NFT) in patients with Alzheimer's disease. **Objectives:** This clinico-pathological study (NCT02516046) was designed to assess the relationship between ante-mortem flortaucipir PET imaging and post-mortem neurofibrillary degeneration associated with Alzheimer's disease (AD), and associated NIA-AA pathological diagnosis. **Methods:** The study enrolled 156 end-of-life patients to receive flortaucipir F 18 injection (370 MBq iv) followed by a 20 min PET scan beginning approximately 80 min post injection, with 67 participants undergoing brain autopsy per protocol during the course of the study. The first three cases (frontrunners) were unblinded and assessed to confirm imaging and pathologic evaluation methods. Thus, the primary analysis included 64 autopsy cases: clinical diagnosis of AD (N=33), atypical dementia (mixed dementia, Lewy body disease, Parkinson disease dementia, other)(N=16), mild coginitve impairment (N=1), and normal cognition (N=14). A NIA-AA neuropathologic evaluation was performed by a 2-person expert panel blinded to the neuroimaging results to serve as the truth standard for assessing diagnostic performance of flortaucipir PET imaging. The NIA-AA assessment included classification of the subjects' neurofibrillary degeneration into Braak stages, as well as an assessment of amyloid and neuritic plaque density. For study endpoints, a NIA-AA score of B3 (Braak stage V or VI) was truth positive, and a NIA-AA score of 0, 1, or 2 (Braak stage IV or lower) was truth negative. NIA-AA 'high' level of AD neuropathologic change was considered truth positive, and 'intermediate', 'low', or 'no' AD neuropathologic change was truth negative. Flortaucipir PET images were interpreted by five independent readers blinded to the neuropathologic evaluation for the presence or absence of tau AD (τAD) patterns: • Non-τAD: neocortical uptake not consistent with an AD pattern; no increased neocortical activity in any region, or increased activity isolated to mesial temporal, anterolateral temporal and/or frontal regions, or • τAD: neocortical uptake consistent with an AD pattern; increased activity in any posterolateral temporal (PLT), parietal or occipital regions. Primary endpoints consisted of: 1) the diagnostic performance (sensitivity/specificity) of 5 independent readers' interpretations of ante-mortem flortaucipir PET images for detection of a pattern of neocortical uptake that corresponds to an NFT score of B3; 2) the diagnostic performance (sensitivity/specificity) of 5 independent readers' interpretations of ante-mortem flortaucipir PET imaging for detection of a pattern of flortaucipir neocortical uptake that corresponds to a high level of AD neuropathologic change as defined by NIA-AA criteria (Hyman et al., 2012). Success on these endpoints was defined as at least 3 out of 5 readers having a lower bound of the 95% confidence intervals for both sensitivity and specificity ≥ 50% for predicting NIA-AA score of B3 and and high level of AD neuropatalogic change (i.e., τAD vs non-τAD relative to truth standard for both endpoints). **Results:** The study was successful at meeting both of its co-primary endpoints. The pair-wise agreement across the 5 PET scan readers was 90%. **Conclusions:** Flortaucipir PET imaged the distribution and density of pathologic tau in a manner that allowed accurate prediction of brain autopsies with high neurofibrillary degeneration (NIA-AA score B3) burden and high AD neuropathologic change. Details of this study and its results will be presented. Reference: Hyman, B.T., Phelps, C.H., Beach, T.G., et al. "National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease". Alzheimers Dement. 2012;8(1):1-13.

LB6: AGE AND APOE GENOTYPE-SPECIFIC POPULATION FREQUENCIES OF CEREBRAL B-AMYLOIDOSIS AND HIPPOCAMPAL ATROPHY AMONG COGNITIVELY NORMAL INDIVIDUALS IN CHARIOT-PRO. Hany Rofael[1], Gerald Novak[1], Luc Bracoud[2], Nandini Raghavan[1], Ziad Saad[3], S Einstein[1], Robert Brashear[1], David Scott[4], Joel Schaerer[2], Celeste de Jager[5], Chi Udeh-Momoh[5], the Alzheimer's Disease Neuroimaging Initiative (ADNI), Lefkos Middleton[5] *((1) Janssen Research and Development, Titusville, NJ, USA; (2) Bioclinica, Lyon, France; (3) Janssen Research and Development, La Jolla, CA, USA; (4) Bioclinica, Newark, CA, USA; (5) Imperial College of London, London, UK)*

Background: Clinical trials in preclinical AD typically recruit subjects based on assessment of cerebral amyloid burden by PET or CSF analysis ("A" biomarkers). Evidence of neuronal injury, whether by FDG PET, CSF tau, or structural MRI ("N" biomarkers), predicts more rapid clinical change1,2, and this may be of additional use in subject selection. An estimate of the proportion of prospective subjects with abnormal A or N biomarkers would be advantageous in planning a preclinical trial, but this has a complex relation to age and ApoE4 status3. Extension of these observations to datasets from geographically and ethnically diverse cohorts is needed to establish whether these relationships hold generally. **Objectives:** To describe the proportion of cognitively normal elders with abnormal amyloid and/or neuronal injury biomarkers as a function of age and apolipoprotein E genotype in a large UK cohort of cognitively normal elders. **Methods:** The CHARIOT-PRO study aims to assess the rate of longitudinal cognitive change in equal numbers of normal elders with and without biomarker evidence of increased cerebral amyloid burden (total n=500). The present sample represents 1117 subjects that received at screening an amyloid assessment by PET and measurement of hippocampal volume by MRI. Subjects ranged from 60 to 85 years of age, were in satisfactory general health with no significant neurological comorbidities or MRI abnormalities, save for incidental age-related atrophy, mild white matter hyperintensity, isolated lacunes, or small (< 10mm) microhemorrhages. All were deemed cognitively normal (CN), based on CDR=0 and performance on RBANS. MRI scans were obtained at one of 4 imaging sites using GE 1.5T (n=3) or Siemens 3T scanners (n=1114). 3DT1 data consisted of sagittal MP-RAGE scans with a 1.25x1.25x1.2 mm3 voxel size and an acceleration factor of 2, consistent with the ADNI-2 MRI protocol. All data were centrally quality controlled and processed using FreeSurfer v5.3 to derive hippocampal volume

(HV) and intracranial volume (ICV). HV was then adjusted for age, MRI scanner field strength and ICV, using a linear regression on a normative population comprised of 165 CN subjects from ADNI-1 and 118 from ADNI-2. A cutpoint to dichotomize subjects as N- (larger HV) or N+ (smaller HV) was derived, using Receiver Operating Characteristic (ROC) analysis to discriminate amyloid-negative (A-) CN in ADNI from amyloid-positive (A+) AD subjects in ADNI (n=80). A cutpoint of 6510 mm3 corresponded to the maximal Youden's index (sensitivity = 91.8%, specificity = 88.9%, area under the ROC curve = 0.95. 1117 subjects subsequently underwent an Amyloid PET scan using either of the approved 18F tracers (Florbetapir n=179, Florbetaben n=617, or Flutemetamol n=321). PET positivity was determined using a hybrid approach. A blinded neuroradiologist, out of a pool of 3 readers, centrally reviewed the PET and MRI data jointly according to each tracer's label, e.g. based on a visual assessment. Following this, PET SUVr was calculated, using the cerebellar grey matter (Florbetaben) or whole cerebellum as a reference region. In case of discordances between the visual and quantitative assessments, a second reader would make the call, taking previous results into account. Subjects in CHARIOT-PRO were characterized as A+ or A-, and N+ or N-, and were then further stratified by age (by 5-year intervals) and APOE status (in the n=522 subjects (47.8%) where this was available). **Results:** The number and proportion of subjects with each biomarker phenotype is presented by age interval in the Figure. The proportion of A+ subjects increased with age ($\chi 2$ = 26.6, p<0.001) but the differences were not significant for N. The characteristics of subjects within each biomarker phenotype are presented in the Table. There were no differences in gender, though A+ subjects were older than A-. ApoE genotype was available for less than half of all subjects. More A+ subjects were genotyped (73.1%) than A- (40.7%), reflecting the fact that genotyping was prioritized among subjects enrolled in the study (half of whom were A+) and not prioritized among A- screen failures. However, the proportion of ApoE*ε4 carriers within each biomarker phenotype also reflected the fact that A+ subjects were more likely to be E4 carriers ($\chi 2$=59.7, p<0.001). **Conclusions:** In this large sample of cognitively normal subjects, 18.6% of subjects were A+ based on PET, and 13.1% were N+ based on low HV. The proportion of A+ subjects increased with age; this was not seen for N+, perhaps because HV was adjusted for age. The proportion of ApoE*ε4 carriers was greater in A+ than A- subjects, but no differences were apparent between N+ and N- subjects. References: 1Vos SJ et al, Lancet Neurology, 2013;12:957-65; 2Knopman D et al, Neurology 2012;78:1576-82; 3Jack C et al, Lancet Neurology, 2014;13:997-1005

Figure



Table

Summary by Biomarker Phenotype

	A-N-	A-N+	A+N-	A+N+	Total	p-value
n (%)	802 (71.8%)	107 (9.6%)	169 (15.1%)	39 (3.5%)	1117	
Age	70.5 (5.2)	70.2 (5.2)	72.6 (5.8)	73.4 (5.3)	70.9 (5.3)	<0.001
n ApoE*ε4 carrier (%)	68/335 (20.3%)	9/35 (25.7%)	64/122 (54.4%)	19/30 (63.8%)	160/522 (29.0%)	<0.001
% Female	54.2%	53.3	52.1%	51.3%	53.5%	0.946
Mean adjusted HV, mm^3 (sd)	7498 (592)	6132 (361)	7452 (568)	6186 (354)	7314 (558)	<0.001

LB7: SAFETY AND EFFICACY RESULTS FROM THE PHASE 3, MULTICENTER, 18-MONTH STEADFAST TRIAL OF AZELIRAGON IN PARTICIPANTS WITH MILD ALZHEIMER'S DISEASE. Marwan Sabbagh[1], Imogene Dunn[2], Ann Gooch[2], Tom Soeder[3], Karl Kieburtz[4], Carmen Valcarce[2], Larry D Altstiel[2], Aaron H Burstein[2] *((1) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; (2) vTv Therapeutics LLC, High Point, NC, USA; (3) Cato Research LTD, Durham, NC, USA; (4) Clintrex LLC, Longboat Key, FL, USA)*

Backgrounds: Azeliragon is an oral antagonist of the Receptor for Advanced Glycation Endproducts (RAGE) that may act on several steps in the underlying etiology of Alzheimer's Disease (AD) with respect to Aβ transport into the brain, chronic inflammation, phosphorylation of tau, vascular dysfunction, metabolic dysregulation, and neurotoxicity. Animal data have demonstrated azeliragon interactions with important aspects of AD etiology including synaptic dysfunction caused by RAGE, inflammation, the transport of Aβ from the blood to the brain, Aβ toxicity and the amplification of the effects of Aβ and AGEs by RAGE. Initial evidence in a Phase 2b study showed decreased decline in ADAS-cog (delta=3.1, p=0.008 at 18 months, ANCOVA with multiple imputation), relative to placebo in patients with mild-to-moderate AD. A more pronounced benefit was observed among a mild AD subset (Mini-Mental Status Examination (MMSE) 21 26), with a 4-unit placebo-subtracted change in ADAS-cog (nominal p=0.018) and a 1-unit placebo-subtracted difference in Clinical Dementia Rating–sum of boxes (CDR-sb; nominal p=0.02; Wilcoxon test). STEADFAST phase 3 trial evaluated the safety and efficacy of azeliragon in patients with mild AD. **Methods:** This was a randomized, double-blind, placebo-controlled trial in approximately 800 participants

with probable mild AD (MMSE 21-26, CDR global 0.5-1), receiving stable standard of care therapy (acetylcholinesterase inhibitor and/or memantine; SoC) evaluating the efficacy and safety of 18 months of treatment with azeliragon 5 mg/day relative to placebo. The clinical trial design (conducted under a Special Protocol Assessment (SPA) agreement with the FDA) included two separate studies (A-Study and B-Study) operationally conducted under a single protocol. Each study was independently powered to evaluate efficacy with respect to co-primary endpoints of ADAS-cog and CDR-sb and each study was randomized independently. In each study participants were randomized 1:1 (site-based randomization) to azeliragon (5 mg/day) plus SoC or placebo plus SoC. Primary efficacy outcomes included co-primary endpoints of change from baseline in the ADAS-cog at Month 18 and change from baseline in the CDR-sb at Month 18. The key secondary endpoint was change from baseline in brain volumetrics (e.g., whole brain volume, ventricular volume, hippocampal volume) at Month 18. **Results:** A total of 880 patients were randomized (405 in A-Study, 475 in B-Study) at 88 sites in the US and Canada (A-Study) and 99 sites in the US, Canada, Ireland, UK, South Africa, Australia, and New Zealand (B-Study). At baseline, A-Study participants were 53% male, mean age was 75 (SD 8.5) years, mean baseline MMSE score was 23.2 (SD 2.72) and mean baseline ADAS-cog score was 15.5 (SD 5.40). B-study participants were 55% male, mean age of 75 (SD 8.6) years, and had a mean baseline MMSE score of 23.2 (SD 2.81) and mean baseline ADAS-cog score of 16.6 (SD 5.54). Both the A-Study and B-Study failed to achieve statistical significance for pre-specified analyses on the co-primary endpoints of ADAS-cog and CDR-sb. **Conclusions:** Neither study met its primary outcome measures. Results for primary and secondary efficacy outcome measures, as well as safety measures will be presented for both the A-Study and B-Study.

LB8: ADUCANUMAB TITRATION DOSING REGIMEN: 36-MONTH ANALYSES FROM PRIME, A PHASE 1B STUDY IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE.

Samantha Budd Haeberlein[1], Carmen Castrillo-Viguera[1], Tianle Chen[1], John O'Gorman[1], Raj Rajagovindan[1], Dakshaben Patel[2], Philipp von Rosenstiel[1], Guanfang Wang[3], Spyros Chalkias[1], LeAnne Skordos[1], Claudia Prada[1], Christoph Hock[4], Roger M Nitsch[4], Alfred Sandrock[1] *((1) Biogen, Cambridge, MA, USA; (2) Biogen, Maidenhead, UK; (3) Cytel, Cambridge, MA, USA; (4) Neurimmune, Schlieren-Zurich, and University of Zurich, Switzerland)*

Backgrounds: Aducanumab (BIIB037), a human anti-amyloid beta (Aβ) monoclonal antibody, is being investigated as a disease-modifying treatment for early Alzheimer's disease (AD). PRIME is an ongoing Phase 1b study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of aducanumab in patients with prodromal AD and mild AD dementia. Amyloid-related imaging abnormalities–vasogenic edema (ARIA–E) were the main safety and tolerability findings in an interim analysis of PRIME.1 A titration regimen was tested in ApoE ε4 carriers to explore the impact of titration on ARIA incidence. **Objectives:** Here, we report 36-month amyloid positron emission tomography (PET) and clinical endpoint data for both fixed-dose and titration cohorts, including 12 months from the PRIME placebo-controlled period and 24 months from the PRIME long term extension (LTE). Cumulative safety data for all cohorts, as of the most recent interim analysis, is also reported. **Methods:** Patients in this randomized, double-blind, placebo-controlled study (PRIME; NCT01677572) were aged 50–90 years, had a positive florbetapir PET scan, and met clinical criteria for prodromal or mild AD dementia. During the double-blind, placebo controlled period, patients received aducanumab or placebo q4w for 52 weeks. In a staggered, parallel-group design, patients were randomly assigned (3:1) to fixed doses of aducanumab (1, 3, 6 or 10 mg/kg) stratified by ApoE ε4 status (carrier/non-carrier) or placebo. After patient enrollment in fixed-dose cohorts was complete, the protocol was amended to include a cohort of ApoE ε4 carriers who received either titrated doses of aducanumab (1 mg/kg [2 doses]; 3 mg/kg [4 doses]; 6 mg/kg [5 doses]; 10 mg/kg thereafter) or placebo. At Week 56, eligible patients could enroll into the LTE, where all patients were assigned to receive aducanumab. LTE dose assignments were as follows: patients initially randomized to receive placebo were assigned treatment in the LTE to either aducanumab 3 mg/kg, a titration regimen of aducanumab 3 to 6 mg/kg (2 doses of 3 mg/kg followed by subsequent doses of 6 mg/kg), or a titration regimen of aducanumab up to 10 mg/kg (as described above). Patients initially randomized to receive aducanumab 1 mg/kg were assigned to receive aducanumab 3 mg/kg in the LTE. Patients randomized to the aducanumab titration regimen or to fixed doses of aducanumab (3, 6, or 10 mg/kg) in the placebo-controlled period continued at their original dose assignment in the LTE. By Week 166, average expected dose of the titration arm was 8.4 mg/kg. The primary endpoint for the PRIME LTE was safety. Other endpoints (amyloid PET, Clinical Dementia Rating–Sum of Boxes [CDR–SB] and Mini-Mental State Examination [MMSE]) were exploratory. A mixed model for repeated measures was used for analysis of change from baseline in amyloid PET, CDR–SB and MMSE. **Results:** Of 196 patients randomized and dosed in PRIME within the fixed-dose and titration cohorts, 143 were dosed in the LTE and 97 completed treatment at Month 36. Patients from the titration cohort who continued aducanumab treatment up to 36 months experienced a reduction in brain amyloid plaque levels, as measured by PET, which was consistent with the dose- and time-dependent results previously reported in fixed-dose cohorts.2 Mean amyloid plaque levels in both the 10 mg/kg fixed-dose and titration cohorts reached and remained at an SUVR level below 1.1, which is considered the quantitative cut-point suggested to discriminate between a positive and negative scan.3 Clinical effects as measured by CDR-SB and MMSE with titrated aducanumab in the second year of the LTE were generally consistent with findings in the 10 mg/kg fixed-dose cohorts and suggest continued slowing of cognitive and functional decline. Since the start of the PRIME study, 185 patients from fixed-dose and titration cohorts have been dosed with aducanumab. 46 of these patients experienced ARIA-E. Of those patients, 61% were asymptomatic and 39% were symptomatic. The majority of symptomatic cases of ARIA-E exhibited symptoms which were mild to moderate in severity. 8 patients experienced more than one episode of ARIA-E. These recurrent ARIA events were generally consistent with first incidences of ARIA from the PRIME study reported to date; they were typically asymptomatic, and most patients continued in the study. **Conclusions:** Amyloid plaque levels continued to decrease in a dose- and time-dependent manner in patients from the titration and fixed-dose cohorts who completed the second year of the LTE. Analyses of exploratory clinical endpoints CDR–SB and MMSE suggest a continued benefit on the rate of clinical decline over 36 months. Clinical

effects with titrated aducanumab in the second year of the LTE were generally consistent with findings in the 10 mg/kg fixed-dose cohort. The safety profile of aducanumab remains unchanged. These data support further investigation of aducanumab in patients with early AD in the ENGAGE and EMERGE Phase 3 trials. 1. Sevigny J, et al. Nature. 2016;537:50-56; 2. Budd Haeberlein S, et al. J Prev Alz Dis. 2017;4:313; 3. Joshi AD, et al. J Nucl Med. 2015;56:1736-1741.

LB9: LONGITUDINAL 148-WEEK EXTENSION STUDY FOR ANAVEX®2-73 PHASE 2A ALZHEIMER'S DISEASE DEMONSTRATES MAINTAINED ACTIVITIES OF DAILY LIVING SCORE (ADCS-ADL) AND REDUCED COGNITIVE DECLINE (MMSE) FOR PATIENT COHORT ON HIGHER DRUG CONCENTRATION AND CONFIRMS ROLE OF PATIENT SELECTION BIOMARKERS. Harald Hampel[1], Mohammad Afshar[2], Frédéric Parmentier[2], Coralie Williams[2], Adrien Etcheto[2], Federico Goodsaid[3], Christopher U Missling[4] *((1) Department of Neurology, Sorbonne University, Paris, France; (2) Ariana Pharma, Paris, France; (3) Regulatory Pathfinders LLC, San Francisco, CA; (4) Anavex Life Sciences Corp., New York, NY)*

Backgrounds: ANAVEX®2-73, a selective sigma-1 receptor (SIGMAR1) agonist was investigated in a 57-week Phase 2a study with 32 mild-to-moderate Alzheimer's disease dementia patients showing a favorable safety profile. An ANAVEX®2-73 concentration-dependent response was observed using exploratory functional (ADCS-ADL) and cognitive (MMSE) endpoints. According to the precision medicine concept, data-driven unbiased genomic analysis was used to identify biomarkers. Status of a single genetic variant on the ANAVEX®2-73 target SIGMAR1 was shown to significantly impact the drug effect. Here we report the current results of the extension study (148 weeks). **Methods:** Relationship between all biomarkers and efficacy outcome measures were investigated using a non-linear rule based Formal Concept Analysis (FCA, implemented in Ariana's KEM® software). This approach identifies all biomarkers in an unbiased data-driven mode. In order to model functional and cognitive progression over time, Mixed Model Repeated Measures (MMRM), with a linear time effect hypothesis, and Linear Mixed Effect (LME) modeling, was performed. The outcome for patient cohort with the highest tertile drug concentrations was compared to the patient cohort with medium and low tertile concentrations. Standard covariate adjustments were based on age, sex, APOE ε4 allele carrier status, concomitant treatment with donepezil, and the interaction between APOE ε4 allele, time and ANAVEX®2-73 concentration. Three further parameters previously identified with KEM were included into the model: baseline MMSE score, polymorphisms of both SIGMAR1-Q2P (rs1800866) and COMT-L146FS (rs113895332/ rs61143203), as well as their interaction with time and ANAVEX®2-73 concentration. **Results:** The significant association between ANAVEX®2-73 concentration and both MMSE and ADCS-ADL changes was confirmed over the extended 148-week period using the MMRM-LME method. The analysis shows that the cohort of patients treated with higher ANAVEX®2-73 concentration maintains ADCS-ADL performance compared to the lower concentration cohort ($p<0.0001$), with a significant impact of SIGMAR1 ($p<0.0080$) and COMT ($p<0.0014$) biomarkers on the drug response. Higher delta MMSE is also maintained for the higher drug concentration cohort compared to lower concentration cohort ($p<0.0008$). The observed impact of the APOE ε4 allele was statistically significant for both ADCS-ADL ($p<0.0001$) and MMSE ($p<0.0001$) irrespective of ANAVEX®2-73 concentration. Notably, APOE ε4 allele carriers were 2.4x more frequent in the higher concentration cohort. **Conclusions:** The longitudinal 148-week data show that patient cohort with the higher concentration of ANAVEX®2-73 maintains the ADCS-ADL score and better perform at MMSE, along the trial duration, when compared to the lower concentration cohort. A significant impact of SIGMAR1 and COMT biomarkers on the drug response level was confirmed over the 148-week period, irrespective of the fact that APOE ε4 carriers were more frequent in the higher concentration cohort. Taken together, these findings are consistent with the hypothesis that ANAVEX®2-73 induces an improved clinical outcome with adequate effect size. Results demonstrate robustness by using both DNA- and RNA-based biomarkers, multiple endpoints and time points. Excluding the patients with the two identified biomarker variants (approximately 20% of the population), the resulting 80% of the enrolled population would lead to further clinically significant improved functional and cognitive scores. The combination of KEM FCA and MMRM-LME data analysis methodologies shows the innovative ability to identify early biomarkers in clinical trials with small size-population recruited. Our data support the clinical development of ANAVEX®2-73 by using genetic biomarkers identified within the study population itself. Indeed, this innovative approach allowed to select pre-specified population (SIGMAR1 and COMT) in forthcoming larger studies, with the expectation to confirm the observed response to ANAVEX®2-73. Further clinical studies in several indications are underway, including a Phase 2b/3 study in 450 patients with early Alzheimer's disease. This approach may expand the access to precision medicine and precision pharmacology for a wide range of neurodegenerative diseases, thus, identifying the right patients that can benefit from the right drug(s), at the right moment. Detailed methodology and results will be presented at the conference.

LB10: PREDICTIVE PERFORMANCE OF CSF AND IMAGING AD BIOMARKERS IN ADNI1/GO/2 MCI PARTICIPANTS USING THE NIA-AA RESEARCH FRAMEWORK. Leslie M Shaw[1], Michal Figurski[1], Susan Landau[2], William Jagust[2], Clifford R Jack[3], Paul S Aisen[4], Ronald C Petersen[3], Michael W Weiner[5], John Q Trojanowski[1] *((1) University of Pennsylvania, Philadelphia, USA; (2) University of California, Berkeley, Berkeley, USA; (3) Mayo Clinic, Rochester, USA; (4) University of Southern California, San Diego, USA; (5) University of California, San Francisco – San Francisco, USA)*

Backgrounds: A key characteristic of Alzheimer's disease is its multifactorial nature. Important developments in this field include the standardization of biomarker measures that detect different aspects of the underlying pathologic processes of the disease. The recently described National Institute on Aging-Alzheimer's Association research framework on Alzheimer's disease provides a systematic approach to defining the state of Alzheimer's pathologic change in patients using a combination of amyloid (A), tau(T) and neurodegeneration (N) biomarkers. **Objectives:** To assess the combination of 3 biomarkers, A-CSF Aβ1-42, T-CSF p-tau181 and N-FDG PET, measured at baseline, for their prediction of progression from MCI to AD dementia and for decline in memory (MMSE), cognition (CDRsob) and function (FAQ). All ADNI1/GO/2 MCI participants who provided CSF and who underwent FDG PET at baseline

were included in these analyses (n=505). **Methods:** The CSF biomarkers Aβ1-42, and p-tau181 were measured using the Roche Elecsys® automated immunoassay platform according to the protocol used for ADNI1/GO/2 CSF samples (Methods document-ADNI.LONI.usc.edu). FDG PET data were generated using a standardized protocol (ADNI PET Technical Procedures Manual-ADNI.LONI.usc.edu). MCI progression to AD was assessed over 4 years from baseline in each participant, using Cox Proportional Hazards modeling with adjustments for age, gender and APOE ε4, status for each of 8 ATN categories (A-T-N-, A+T-N-, A-T+N-, A-T+N+, A-T-N+, A+T+N-, A+T-N+ and A+T+N+). Cut-points for CSF Aβ1-42 and p-tau181 were 980 pg/mL and 24 pg/mL, respectively, based on ROC analyses using Florbetapir PET as the objective index for AD pathology for Aβ1-42 or ROC analyses of ADNI1/GO/2 AD and healthy controls for p-tau181. An SUVR value of 1.21 was used for FDG PET cutoff, based on the UC Berkeley/ADNI dataset uploaded on the ADNI website. **Results:** Cox Proportional Hazards modeling results are summarized in Figure 1. The lowest rate of progression was observed for A-T-N- participants (4.7%, 8.1% at 2 and 4 yrs, respectively), and the highest rate of progression for A+T+N+ (55.5%, 80.9% at 2 and 4 yrs, respectively). Interestingly for A+T-N- the 2 and 4 yr rates were 4.9% and 11.6%, respectively, whereas for A+T+N- the rates were 23.9% and 40.0%. These observations are consistent with the hypothesis that T and N positivity reflect later downstream tau pathology and degeneration, respectively, and a finding of A+T-N- in an individual suggests a very early stage, for those individuals, in the AD continuum with a considerably longer time likely for disease progression than for A+T+N+ or A+T+N. Mean values for the slopes of decline in MMSE, CDRsob and FAQ are summarized in Table 1. The overall trends in the average rates of decline match up well with that observed for progression to dementia described above over the 8 ATN categories supporting the internal consistency of these analyses.**Conclusions:** These study results are consistent with the predictive performance predicted by the ATN system that defines the state of AD pathology in an individual. Based on analyses of progression to AD dementia (Figure 1) there were a total of 58.4% of participants who were in one of 4 A+ categories (13.3% A+T-N-; 17.2% A+T+N-; 8.7% A+T-N+ and 19.2% A+T+N+) and there were 41.6% in one of 4 A- (non-AD) categories (26.5% A-T-N-; 9.1% A-T+N-; 2.8% A-T+N+; and 3.2% A-T-N+). Results of interest include prediction of more refined progression rates in the ADNI MCI population compared to doing this based on the CSF A and T biomarkers alone or using an imaging biomarker for N alone. This observation is likely of importance in making use of biomarkers in treatment trials and supports use of combinations of biomarkers to provide a more refined prediction for disease progression in an MCI target population with AD pathology and who would have significant disease progression in the absence of treatment (A+T+N- and A+T+N+). Since A+T-N- is associated with a much lower rate of progression at 4 yrs in comparison to the latter two biomarker states, this state in MCI subjects is predictive of a much longer period of clinical stability compared to A+T+N- and A+T+N+. The finding that measures of memory, cognition and function parallel the observed pattern of differing rates of progression to dementia is reassuring regarding the parallelism between clinical measures and prediction of progression to dementia.

References: Weiner M, etal. Recent publications from the ADNI study: Reviewing progress toward improved AD clinical trials. Alzheimer's Dement 2017; 13:e1-e85. Jack C, etal. NIA-AA research framework: towards a biological definition of Alzheimer's disease. Alzheimer's Dement 2018; 14:535-62. James BD, etal. TDP-43 stage, mixed pathologies, and clinical Alzheimer's-type dementia. Brain 2016; 139:2983-93. Landau S, etal. Comparing predictors of conversion and decline in mild cognitive impairment. Neurology 2010; 75:230-238. Hansson O, etal. CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimers Dement. 2018; https://doi.org/10.1016/j.jalz.2018.01.010 [Epub ahead of print].

Table 1
Annual rates of decline in MMSE, CDRsob and FAQ in MCI(ADNI1/GO/2, n=487) participants.

	N	MMSE	CDRsob	FAQ
A-T-N-	126	-0.121±1.17	0.032±0.56	0.178±1.13
A+T-N-	64	-0.308±0.96	0.167±0.46	0.486±1.48
A-T+N-	44	-0.314±0.82	0.152±0.40	0.143±1.73
A-T+N+	14	-0.582±1.67	0.550±1.11	1.675±2.51
A-T-N+	15	-0.141±0.75	0.441±0.77	0.956±2.93
A+T+N-	84	-0.856±2.00	0.561±0.82	1.417±3.585
A+T-N+	44	-1.389±1.67	0.86±1.01	2.753±3.87
A+T+N+	96	-1.76±2.03	1.35±1.21	4.014±3.39
Each annual rate of decline is the mean slope ± SD value for the participants in each ATN category				

Figure 1
Cox proportional-hazards analyses-comparisons across ATN categories of AD. Progression from MCI(ADNI1/GO/2, N-505) to a clinical diagnosis of dementia of the AD type.