SYMPOSIA

S1: CTAD 2017 STATISTICAL WORKSHOP : ESTIMANDS AND PRIMARY ANALYSES IN AD CLINICAL TRIALS. Hong Liu-Seifert[1], Fabian Model[2], Paul Aisen[3] *((1) Eli Lilly and Company, Indianapolis, USA; (2) Roche, Basel Switzerland; (3) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, USA)*

The primary objective of a clinical trial should be clearly defined with regard to the target of estimation (estimand) for the efficacy of an investigational drug. The fully specified treatment effect of interest should then determine the data collection, data analysis, handling of missing data, and other trial design elements. However in practice, this rational sequence is rarely followed; specification of estimands often follows data collection and analysis decisions. To address this issue, an ICH E9 Addendum on estimands is being developed to provide regulatory guidance and promote harmonized standards on the process of estimand determination, and is anticipated to be released in mid-year 2017 for public consultation. An Alzheimer's Disease Scientific Working Group (AD SWG) has been formed to provide statistical leadership in the research and drug development efforts in AD. This SWG consists of statistical representations from the industry, academia and regulators and enables cross sector scientific research and collaboration to address key and pressing research issues in Alzheimer's. One of the topics the SWG is tackling is the proper selection of estimands. With the backdrop of the ICH E9 Addendum approaching, the AD SWG strives to align with the estimand framework in the upcoming regulatory guidance, and make recommendations to the AD field regarding the appropriate determination of estimands and the implications for statistical estimation methods for clinical trials in Alzheimer's disease. This workshop at CTAD 2017 will bring the audience up to speed with the most current regulatory guidance on how to define estimands for treatment effect in confirmatory clinical trials, and provide a recommendation on the appropriate estimand choices specifically for Alzheimer's trials. Important topics of methods of estimations and sensitivity analyses will also be discussed. As the estimand decision is not purely a statistical consideration, but rather a decision that needs to be made jointly based on medical and statistical consideration, a clinician's insight and perspective will be given as well. In addition to these presentations, opinions from practicing physicians and regulatory bodies will be solicited as well.

S3: THE IMPORTANCE OF SEROTONIN IN ALZHEIMER'S DISEASE PSYCHOSIS AND THE POTENTIAL ROLE OF PIMAVANSERIN. Jeffrey Cummings *(Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, USA)*

Communications 1: *Role of 5-HT2A Receptors in the Pharmacology of Alzheimer's disease Psychosis,* Stephen M. Stahl[1], Ethan S. Burstein[2] ((1) University of California, San Diego, CA, USA; (2) ACADIA Pharmaceuticals Inc., San Diego, CA, USA)

Communications 2: *Clinical Trial of Pimavanserin in Alzheimer's disease Psychosis,* Clive Ballard[1], Carol Banister[2], Jim Youakim[3], Bruce Coate[3], Srdjan Stankovic[3], on behalf of the ADP Investigators ((1) University of Exeter Medical School, Exeter, United Kingdom; (2) King's College, London, United Kingdom; (3) ACADIA Pharmaceuticals Inc., San Diego, USA)

Communications 3: *Review of Pimavanserin Clinical Results in the Context of Historical Alzheimer's disease Psychosis Trials*, Pierre N. Tariot[1], Randall Owen[2], Doral Fredericks[2] ((1) Banner Alzheimer's Institute and University of Arizona College of Medicine, Phoenix, USA; (2) ACADIA Pharmaceuticals Inc., San Diego, CA, USA)

Introduction: Treatment research for Alzheimer's disease (AD) focuses mostly on cognitive deficits, but it is often the behavioral and neuropsychiatric symptoms that are most troublesome to patients and caregivers. Psychotic symptoms expressed as delusions and hallucinations are observed in approximately 25-50% of AD patients. In contrast with the psychotic symptoms of schizophrenia, delusions in patients with AD are typically non-bizarre and of the paranoid type, and hallucinations are more often visual than auditory typically with a remitting and relapsing course. The presence of psychotic symptoms in patients with AD is a poor prognostic sign, and is associated with more rapid cognitive and functional decline and institutionalization. There are no approved therapies for the treatment of patients with AD psychosis (ADP). Atypical antipsychotics such as risperidone, aripiprazole, olanzapine, and quetiapine are most commonly prescribed off label in an attempt to manage symptoms in patients with ADP; however, there are significant disadvantages to the use of these medications from both efficacy and safety perspectives. Published results from studies with some of these agents show modest efficacy in psychosis, although many trials show no improvements compared to placebo for psychotic symptoms, frequently due to a high placebo response rate. It is well known that most antipsychotics have acute or sub-acute side effects in elderly persons such as extra-pyramidal symptoms, sedation, postural hypotension, cerebrovascular, metabolic effects, and falls. In addition, atypical antipsychotics carry a warning of increased risk of mortality in elderly patients with dementia. There is a significant unmet need for new treatments for ADP with favorable benefit/risk ratios. Pimavanserin, with its highly selective antagonist/inverse agonist activity at the serotonin 2A receptor and absence of appreciable activity at dopaminergic, adrenergic, histaminergic, or muscarinic receptors, was recently approved in the US for treatment of hallucinations and delusion associated with Parkinson's disease psychosis. The potential utility of pimavanserin for treatment of ADP is discussed. *Objectives:* The proposed symposium has the following objectives: 1. Review the role of serotonin neurotransmitter system and specifically 5-HT2 receptors in the neuropathophysiology of ADP. 2. Discuss the results of a recently completed exploratory study of pimavanserin in ADP and evaluate the potential utility of pimavanserin as treatment for psychotic symptoms in this condition. 3. Review pimavanserin study results in the context of data from available trials of other atypical antipsychotics in this indication from both an efficacy and a safety perspective. *Discussion:* The serotonin system, specifically 5-HT2A/2C receptors, has increasingly been implicated in the neuropathophysiology of ADP. Polymorphism of serotonin receptors and transporters has been associated with ADP. Furthermore, in preclinical models of ADP, animals with disrupted cholinergic function display diminished pre-pulse inhibition responses and augmented responses to the psychostimulants 2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) and amphetamine. Selective 5-HT2A inverse agonists effectively reversed the augmented responses to DOI and amphetamine, and normalized pre-pulse inhibition, suggesting potential therapeutic utility of such compounds for treating ADP. Pimavanserin is a novel small molecule designed specifically to block serotoninergic neurotransmission mediated by the 5-HT2A receptor. At higher doses, pimavanserin blocks 5HT2C receptors and shows no appreciable activity at dopaminergic, adrenergic, histaminergic, or muscarinic receptors. In the United States, pimavanserin is approved for the treatment of hallucinations and

delusions associated with Parkinson's disease psychosis. Clinical evaluation of pimavanserin in psychosis associated with other neurodegenerative disorders is ongoing. Study ACP-103-019 was a Phase 2, double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of pimavanserin as a treatment for subjects with ADP. The primary endpoint of the study was antipsychotic efficacy as measured by the mean change in the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) psychosis score (combined hallucinations and delusions domains) from baseline to Week 6 of dosing. Subjects continued dosing through Week 12 to gather information on safety and other secondary endpoints, including changes in cognition. A total of 181 subjects were randomized (n=90 pimavanserin and n=91 placebo) with 178 subjects included in the full/efficacy analysis set (FAS). The mean age of subjects was 85.9 years. The mean baseline NPI-NH psychosis score for all FAS subjects was 9.8 with comparable mean scores in the pimavanserin (9.5) and placebo (10.0) groups. The mean baseline MMSE score for all FAS subjects was 10.0. Pimavanserin demonstrated efficacy on the primary endpoint with a 3.76-point improvement in psychosis at Week 6 compared to a 1.93-point improvement for placebo, representing a statistically significant treatment improvement in the NPI-NH psychosis score (delta=-1.84, Cohen's d=-0.32, p=0.0451). Pre-specified sensitivity analyses corroborated the primary endpoint results. Moreover, the pre-specified subgroup analyses showed that subjects with severe psychotic symptoms at baseline (NPI NH psychosis score ≥12) had substantively larger treatment effects compared to subjects with less severe symptoms (delta=-4.43, Cohen's d=-0.734, p=0.0114). Non-significant, but large effect sizes were observed for subgroups with prior antipsychotic use (-0.905) and concomitant SSRI use (-0.556). Responder analyses also demonstrated a significant and clinically relevant treatment effect of pimavanserin compared to placebo. A significantly greater proportion of the pimavanserin group had a treatment response, defined as ≥30% improvement from baseline and ≥50% improvement from baseline on their NPI NH psychosis score. In the subgroup of patients with more severe psychotic symptoms even larger separation from placebo and higher responder rates were observed in the pimavanserin group. On the endpoint of mean change in NPI-NH psychosis score at Week 12, pimavanserin generally maintained the improvement on psychosis observed at the Week 6 primary endpoint, but the statistical difference from placebo was not maintained due to improvement in the placebo group observed between Weeks 6 and 12. Similarly, no significant separation from placebo was observed on the secondary efficacy outcomes at Week 6. With respect to safety, in this elderly and very frail patient population, pimavanserin appeared to be well-tolerated with no new safety observations compared to previous studies. A balanced number of deaths post-randomization was observed: four deaths each in pimavanserin and placebo group. More subjects reported SAEs in the pimavanserin group (16.7%) than in the placebo groups (11.0%) but there were fewer discontinuations due to adverse events (AEs) in the pimavanserin group (8.9%) compared to placebo group (12.1%). The overall rate of AEs was similar between treatment groups. The most frequently reported AEs in the pimavanserin group were falls, urinary tract infection (UTI), and agitation. The rates of UTI and falls were similar in both treatment groups while agitation was more frequently reported in the pimavanserin group vs. placebo (21.1% and 14.3%, respectively). The mean change from baseline in the QTcF interval in subjects treated with pimavanserin was 9.4 msec after 12 weeks of treatment. The QTcF outlier analysis demonstrated no meaningful difference in outliers with a QTcF≥500 msec or delta ≥60 msec (1 subject in each group had a delta ≥60 msec at Day 15). Mean weight change was comparable between the two treatment groups, but weight loss ≥7% was reported more frequently in the pimavanserin group. Pimavanserin had no negative effect on cognition as measured by the Mini-Mental State Examination and was similar to placebo in this regard. In this study, pimavanserin, the first of a new class of nondopaminergic antipsychotic drugs, has produced an efficacy signal in AD patients with psychotic symptoms with an apparently favorable safety and tolerability profile. Postmortem and genetic studies suggest that in AD, delusions and hallucinations are linked to alterations in the 5-HT system. Considering significant public health implications of psychosis in this patient population, lack of approved treatments and encouraging results of Study ACP-103-019, data from this study are further reviewed and discussed in the context of previously reported studies of atypical antipsychotics in this patient population. *Conclusion:* There is no proven safe and effective treatment for moderate to severe ADP. Neither cholinesterase inhibitors nor memantine confer significant benefit. Atypical antipsychotics are the only drug class for which there is clinical trial evidence for the treatment of ADP. While the evidence is limited the majority of studies show no or limited benefit. Adverse effects related to antipsychotics included sedation, parkinsonism, gait disturbances, peripheral edema, chest infections, pneumonia, thrombo-embolic events and stroke. In addition, a doubling in the expected rate of cognitive deterioration was reported in a separate meta-analysis among patients treated with atypical antipsychotics for 6-12 weeks. All atypical antipsychotics including pimavanserin carry a boxed warning for mortality in elderly patients with dementia. Encouraging results from the exploratory study of pimavanserin in ADP patients warrant further clinical investigation to elucidate utility and a therapeutic role of this selective 5 HT2A antagonist/inverse agonist as treatment for ADP.

S5: SYNAPTIC AND NETWORK DYSFUNCTION IN ALZHEIMER'S DISEASE (AD): TRANSLATIONAL INSIGHTS AND THERAPEUTIC OPPORTUNITIES.

Arjen Brussaard *(Amsterdam Neuroscience, VU Medical Center, Amsterdam, Netherlands)*

Communication 1: *Targeting unfolded protein response and synaptic dysfunction to enhance memory function and prevent neurodegeneration,* Giovanna Mallucci[1,2,3] ((1) Dept. of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom; (2) UK Dementia Research Institute at University of Cambridge, Cambridge, United Kingdom; (3) MRC Toxicology Unit, Leicester, United Kingdom)

Introduction: Recently, reversing synaptic dysfunction and loss has emerged as a therapeutic objective to addressing AD disease progression, particularly in the early- and mid-stages of disease prior to the onset of significant neurodegeneration. Specifically, it appears the synapse is the convergence point for amyloid-beta, tau and inflammation, with synaptic dysfunction and loss potentially being the fundamental pathogenic event within the neuron that leads to the defining characteristic of AD, memory deficits (Spires-Jones & Hyman, 2014). Moreover, for AD disease progression, targeting synaptic dysfunction has potential advantages over targeting neurodegeneration. In particular, in animal models, synaptic dysfunction and loss is reversible and reversal of synaptic dysfunction in the early stages of clinical disease leads to improvement in function (i.e., reversal of disease progression) that is measurable within weeks of treatment initiation. In addition, even in animal models of rapidly progressive neurodegeneration synaptic dysfunction is upstream of neurodegeneration as indicated by interventions that reverse synaptic dysfunction both improve function and have long term neuroprotective effects, preventing the neurodegenerative process

(Mallucci et al; Science 2003 and Neuron 2007; Moreno et al; Nature 2012 and Sci Trans Med 2013; Peretti et al; Nature 2015). Moreover, impaired neuronal synchrony is reported in the pre-symptomatic stage of an AD mouse model (Iaccarino et al., 2016). Thus, therapeutic interventions that target synaptic and network dysfunction have the potential to both reverse and slow disease progression in the early stages of clinical disease when neurodegeneration may not be the primary driver of disease progression. Further, within the past five years, advances in our understanding of both synaptic dysfunction in neurodegenerative diseases and memory formation have converged on upon neuronal stress and proteostasis (i.e. physiologic regulation of protein turnover) mechanisms, the molecular machinery of which provides new opportunities for development of therapeutics. *Objectives:* (1) To review the impact of synaptic dysfunction and impaired oscillatory neuronal activity on the neurodegenerative process in preclinical models; (2) To provide evidence that synaptic and network dysfunction is reversible in preclinical models, leading to improvement in memory function; (3) To review molecular mechanisms linking both impaired proteostasis and vesicular trafficking to synaptic and network dysfunction; and (4) To review the available translational (pre-clinical and early clinical) data with therapeutic interventions targeting synaptic and network dysfunction in Alzheimer's disease. *Discussion:* Communication 1 (Prof. Mallucci): The central theme of our research is the identification of common pathways across the spectrum of the neurodegenerative disorders (which include Alzheimer's) that are relevant for both mechanistic insights and therapy. Using mouse models, we have described the pathogenic role of the unfolded protein response (UPR) in neurodegeneration, in particular the role of an activator of this pathway, PKR-like endoplasmic reticulum kinase (PERK). Over-activation of PERK contributes to neurodegenerative disease pathogenesis through reduction in neuronal protein synthesis rates via the phosphorylation of eIF2α (Moreno et al; Nature 2012), in particular, the reduction in levels of synaptic proteins is critical to maintaining neuronal viability. Protein synthesis rates, controlled by levels of eIF2α phosphorylation are also crucial to synaptic plasticity, learning and memory (Costa-Mattioli et al; Neuron 2009; Chen et al; Neuron 2003; Ma et al; Nat Neurosci 2013; Trinh et al; Learning and Memory 2014; Sidrauski et al; eLife 2014). In the protein misfolding neurodegenerative disorders, over-activation of the UPR due to accumulation of misfolded protein, leads to high levels of eIF2α-P, resulting in synaptic dysfunction and synapse loss that progress to neuronal loss. Targeting eIF2α-mediated translational repression, both genetically and pharmacologically, in mouse models of neurodegenerative disease is highly neuroprotective. Thus, lowering of eIF2α-P levels with small molecule inhibitors reinitiating translation to avert synaptic dysfunction and neuronal loss, leading to prevention of behavioral deficits and extended life span in both prion and tauopathy mouse models (Moreno et al; Nature 2012; Moreno et al; Sci Trans Med 2013; Radford et al Acta Neuropathol 2015; Halliday et al; CD&D 2015); as well as in modes of ALS Kim et al; Nat Genetics 2014) and Parkinson's diease (Celardo et al; CD&D 2016). Most recently, remarkable recovery of memory and neuroprotection in FTD and prion diseased mice, has been achieved with repurposed drugs targeting this pathway that are licensed for use in patients (Halliday et al; Brain 2016). Since UPR activation and impaired synaptic plasticity occur across a spectrum of neurodegenerative disorders, targeting the UPR presents an attractive, generic approach for boosting memory and the prevention of neurodegeneration through rescue of synapses in Alzheimer's and other neurodegenerative diseases, with few exceptions, independent of disease-specific proteins.

Communications 2: *Modulation of synaptic and network activity and endocytosis with light flicker therapy reduces amyloid pathology in mouse model of AD,* Li-Hueh Tsai (Picower Institute of Memory and Learning, Massachusetts Institute of Technology, Cambridge, USA)

In general, molecular and cellular pathology is thought to alter neural circuit and network activity. However, in Alzheimer's disease (AD), changes in network activity may also feedback to alter molecular pathology. For example, studies have shown that increases in neural activity Tg2576 mouse model increase levels of Aβ (Bero et al, Nat Neusosci, 2011) and it was recently proposed from an analysis of the ADNI dataset that synaptic events within connectivity hubs related to shifting of processing burden from the posterior Default Mode Network to other hubs leads to aberrant amyloid-beta precursor protein processing and amyloidosis (Jones et al, Brain, 2016). We recently demonstrated that entraining gamma frequency (40 Hz) oscillations, using optogenetics in the hippocampus of 5XFAD mice and using a non-invasive light flicker treatment to affect primary visual frequency in multiple mouse models, resulted in marked reduction of Aβ peptides and amyloid pathology (Iaccarino et al, Nature 540:230-235, 2016). More specifically, flicker stimulation at 40 Hz reduced Aβ in multiple mouse models, including 5XFAD, APP/PS1, and WT mice. This replication in multiple mouse models shows that these findings are not specific to one animal model and, importantly, extend to situations where Aβ is produced from APP expressed by its physiological promoter as it is in WT animals. In addition, we found that 40 Hz oscillations reduced phosphorylated tau staining in a mouse model of tauopathy, TauP301S, showing that the protective effects of gamma stimulation may be generalized to other pathogenic proteins. Our mechanistic studies indicated the effect was probably mediated both by decreased amyloidogenesis and by increased amyloid endocytosis by microglia. In addition, as a GABAA antagonist treatment completely abrogated the effects of 40 Hz stimulation on Aβ levels GABAergic neurotransmission is likely to be critical for these effects. Because this approach is fundamentally different from previous AD therapies, further study is needed to determine its potential as a therapeutic in human AD.

Communications 3: *Preclinical rationale and early clinical results of p38 alpha kinase inhibition to reverse hippocampal synaptic dysfunction*, John Alam (EIP Pharma, LLC, Cambridge, USA)

Neuronal expression of the alpha isoform of the stress-activated kinase p38 MAPK (p38α) is considered to be a critical contributor in the toxicity of amyloid-beta, inflammation (particularly the cytokine interleukin-1 beta), and tau to synapses (Birnbaum et al, 2015; Koppensteimer et al, Sci Rep, 2016; Li et al, J Neurosci 2011; Prieto et al, PNAS, 2015, Watterson et al, PLOSOne, 2013). Consistent with that science, in three distinct animal models (APP/PS1, aged rats and hTau mice) in which spatial learning deficits are induced by amyloidbeta, inflammation, or tau, respectively, the functional deficits are fully reversed with 2 to 3 weeks of treatment with p38α selective small molecule kinase inhibitors (Roy et al, ACS Neurosci 2015; Alam, JAD, 2015; Maphis et al, Alzh Res Ther, 2016). It was also recently shown that genetic reduction of neuronal p38α in Amyloid-Precursor-Protein (APP) overexpressing transgenic mice improved synaptic transmission and plasticity (i.e. reversed synaptic dysfunction), reduced memory loss, and reduced amyloid pathology (Colié et al, Sci Rep, 2017). Moreover, genetically knocking down p38α protected mice from developing age-related hippocampal dysfunction and decline in neurogenesis (Cortez et al, Behav Brain Res 2017). From a mechanism standpoint, emerging evidence

indicates the p38α mediates synaptic dysfunction and amyloid beta generation via disruption of autophagy-mediated protein degradation within neurons (Schnöder et al, JBC, 2016; Alam & Schepper, Autophagy, 2016). One p38α kinase inhibitor (neflamapimod, VX-745) recently reported phase 2a clinical trials results in patients with MCI due to AD or mild AD (9th CTAD meeting, Dec 2016). 6- to 12- weeks treatment with neflamapimod led to significant within-subject improvement on tests of episodic memory function (WMS Immediate & Delayed Recall Composite measures, HVLT-R), strongly suggestive of reversal of hippocampal synaptic dysfunction. In addition, brain amyloid plaque reductions by PET scanning were seen in the 12- week study, consistent with the preclinical science pointing to the potential to reduce amyloid-beta generation through p38α inhibition. A six-month placebo-controlled study is planned to commence by end of 2017 to confirm these preliminary clinical findings. *Conclusion:* Synaptic dysfunction appears to integrate a broad range of pathogenic drivers as therapeutically reversing synaptic dysfunction improves memory function and/or pathology in a diverse range of animal models with a variety of approaches. Moreover, reversing synaptic and network dysfunction in animal models rapidly improves memory function, potentially providing the opportunity to clinically translate the science to clinical proof-of-concept in limited duration (3-6 month) phase 2 clinical studies. The preclinical translational data, along with early clinical data with an investigational drug, indicates that targeting synaptic and network dysfunction to treat AD has great therapeutic potential.

S6: PRESCREENING INITIATIVES TO IDENTIFY INDIVIDUALS WITH PRECLINICAL OR EARLY ALZHEIMER'S DISEASE FOR CLINICAL TRIALS.

Jamie A Mullen *(AstraZeneca, Waltham, USA)*

The number of clinical trials in Alzheimer's disease (AD) has expanded dramatically in recent years (Cummings et al. Alzheimers Res Ther 2014). However, there has not been a commensurate increase in the number of patients identified as potential candidates for these trials, with a resulting dearth of subjects (Fargo et al. Alzheimers Dement 2016). This is particularly true as investigators seek to intervene earlier in the disease, including at the pre-symptomatic and mild cognitive impairment (MCI) stages. Individuals with earlier-stage disease are generally seen in primary care settings and may not self-identify, especially in the pre-symptomatic stage. Better mechanisms are needed to identify these individuals in the general population and in primary care settings, communicate the nature of clinical research, expedite evaluation at the research site, and ensure good communication with primary care providers. The Alzheimer's Association is formulating an action plan to address these problems, and its plan will depend on data from existing strategies. Panel participants will present the results of two initiatives that identified enriched populations of MCI and mild AD patients from the CHARIOT registry (Dr. Price) and amyloid PET imaging referrals (Dr. Rowe), with a focus on the relative merits and learnings. Dr. Boada will present an Innovative Medicines Initiative (IMI) to examine four alternative strategies to engage individuals at risk for AD (IMI-MOPEAD).

Communications 1: *The Funnel study: Prescreening for MCI and mild AD patients from the CHARIOT Register*, Geraint J Price, Maxwell J Benjamin, Lisa K Curry, Sabrina WL Smith, Lefkos T Middleton (Neuroepidemiology and Ageing Research Unit, School of Public Health, Imperial College London, United Kingdom)

Background: To evaluate the effectiveness of delivering interventions at the earliest stages of cognitive decline, an effective and efficient prescreening method of identifying and recruiting suitable trial participants is required. The Funnel study aimed to identify previously undiagnosed, treatment-naïve mild cognitive impairment (MCI) patients suitable for referral to a randomized clinical trial for MCI and mild Alzheimer's disease. This presentation describes the selection, implementation, evaluation and modification of a brief cognitive 'prescreening' assessment to identify individuals most likely to be appropriate for such trials. *Method:* Participants were recruited from the Cognitive Health in Ageing Register for Interventional and Observational Trials (CHARIOT) of healthy elderly volunteers (n~28,000), at Imperial College London (Larsen et al. 2015). Volunteers were eligible if they were aged 55–85 years with subjectively-reported cognitive decline, a reliable informant, and no potentially confounding significant comorbidities. 711 CHARIOT participants underwent a prescreening procedure to ascertain suitability for referral into an early intervention trial for MCI. The initial prescreening protocol comprised the Informant AD-8 and RAVLT Learning Trials. This initial protocol was found to yield low rates of suitable referrals and the protocol was extended, based on a review of available instruments, to include the full RAVLT, the MoCA and IQCODE. We will also describe the clinical adjudication protocol for borderline cases. *Results:* The initial protocol (N=418) yielded a 5% rate of patients eligible for referral. Following the introduction of the additional procedures (N=268), 54% of participants were eligible for clinical adjudication, and the rate of patients eligible for referral increased to 19%. Preliminary data suggest that performance on these additional procedures was associated with appropriateness for the trial, and that self-report cognitive decline was less strongly associated. Qualitative observations suggested increased participant satisfaction and engagement with the amended protocol. *Conclusions:* The introduction of brief prescreening instruments that include a delayed recall/recognition component, and provision of a basic clinical adjudication procedure potentially increases the sensitivity of protocols to select appropriate participants from the community who may be at greater risk of amnestic cognitive impairment and who are suitable for clinical trials. Self-reported cognitive difficulties appear to be less helpful to determine suitability.

Communications 2: *A prescreening study using amyloid PET to improve recruitment for early Alzheimer's disease drug trials,* Christopher C Rowe (Austin Health, Melbourne, Australia)

Background: Recruitment of patients with mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) for trials is difficult with the current average rate per site being 0.8 patients per month. This lengthens trials and drives up cost. *Methods:* We made available amyloid PET scans at no cost to dementia specialists across Melbourne (population 4 million) for their patients with suspected MCI or early AD with a Mini-Mental Status Exam (MMSE) score >19, who indicated they would be interested in participating in drug trials should amyloid PET confirm AD pathology. Specialists were provided with a simple referral form containing the criteria and contact details of the study co-ordinator. Study staffing was two nurse co-ordinators and a part-time physician. Amyloid PET scans were purchased from Austin Hospital. The study was supported

financially by AstraZeneca. *Results:* Over 18 months, 342 referrals were received. Of these, 108 were excluded by telephone screening due to severe medical or neurological illness, MRI contraindication, exclusionary medication, dementia severity (known MMSE<20), or known normal cognitive scores. 82 were excluded at first visit as found to be outside the required cognitive range or to have serious medical or psychiatric illness; the remaining 150 patients were sent for scans. 115 of 150 (77%) were positive for amyloid plaques. The results were sent to the patients' specialists who discussed the scan findings and all available drug trial options with the patients and their families. All amyloid-positive patients requested referral to an interventional drug trial. At 3 months after study completion, 44 were randomized to a trial, 34 were waiting for their trial screening assessment, and 37 had failed screening for the trial to which they were referred. Referrals dramatically exceeded all of the Melbourne trial sites' recruitment targets necessitating an increase in staffing. The cost of this screening program per patient entered into a trial was approximately USD$12,000. *Conclusion:* In the Australian context where amyloid PET is not available for clinical use, offering no-cost amyloid PET scans to specialists to assist their clinical practice was very successful in increasing recruitment for MCI/mild AD drug trials.

Communications 3: *Models of Patient Engagement in Alzheimer´s Disease (MOPEAD): a European project to move Alzheimer´s disease environment towards an earlier diagnosis,* Mercè Boada[1], Laura Campo[2], Dhaval Desai[3], Hans Peter Hundemer[4], Octavio Rodriguez-Gomez[1], Bengt Winblad[5], Frank Jessen[6], Peter Jelle Visser[7], Milica Kramberger[8], Rafael Simó[9], Rafael Navajo[10], Annette Dumas[11], Jean Georges[12], David Krivec[13], Peggy Maguire[14], Derek MacKenzie[15] ((1) Fundació ACE. Barcelona Alzheimer Treatment & Research Center, Barcelona, Spain; (2) Eli Lilly and Company Ltd, Basingstoke, United Kingdom; (3) AstraZeneca AB, Sodertalje, Sweden; (4) Lilly Deutschland GmbH, Bad Homburg, Germany; (5) Karolinska Institutet, Center for Alzheimer Research, Div. of Neurogeriatrics, Huddinge, Sweden; (6) German Center for Neurodegenerative Diseases (DZNE), Bonn-Cologne, Germany; (7) Stichting VUmc, Amsterdam, Netherlands; (8) University Medical Centre Ljubljana, Ljubljana, Slovenia; (9) Institut de Recerca Hospital Universitari Vall d'Hebron (VHIR), Barcelona, Spain; (10) GMV Soluciones Globales Internet S.A.U., Barcelona, Spain; (11) ASDM Consulting, Auderghem, Belgium; (12) Alzheimer Europe, Luxemborg, Luxembourg; (13) Spomincica – Alzheimer Slovenia, Ljubljana, Slovenia; (14) European Institute of Women's Health, Dublin, Ireland; (15) KITE Innovation (Europe) Ltd, Huddersfield, United Kingdom)

Background: Numerous health-economic studies have shown that early diagnosis of Alzheimer´s disease (AD) leads to significant economic and social benefits. It has been also suggested that an earlier intervention results in a higher probability of success when testing new drugs. Despite this evidence, AD diagnosis is still made at late stages in Europe, and a proportion of cases remain undiagnosed. In this context, the development of new and more efficient patient engagement (PE) strategies should be a priority. Important differences exist between European countries in terms of socioeconomic situation, organization of the health systems, or ethnic and cultural background. These differences can affect key factors related to PE such as: ease of access to memory clinics, cultural beliefs about the disease, and scientific research or the rate of internet use among the elderly. Therefore, the best strategy to promote PE could be different for each country. Therefore, a need exists to test different approaches in each specific environment to find the most effective PE strategy. *Methods:* The MOPEAD concept will test and evaluate 4 PE models (Runs) to help identify undiagnosed individuals with prodromal AD or mild AD dementia in a five-country, multicentre setting. Run 1 is a prescreening procedure based on online tools. Run 2 is an Open House Initiative in which individuals are welcome to test their cognition in a memory clinic without the need of a physician's referral. Individuals from the general population will be attracted to Runs 1 and 2 through online and offline advertisement campaigns, respectively. Runs 3 and 4 are campaigns to detect cognitive impairment in the primary care setting and with diabetes specialists, respectively. No advertisement campaigns will be needed in Runs 3 and 4 as the participants will be regular patients attending the clinic for other reasons. The different Runs will use prescreening tools adapted to the real world of each setting, although they will share certain commonalities allowing comparison of these strategies with each other. The 4 Runs will be conducted simultaneously in 5 European countries: Spain, Germany, Netherlands, Sweden and Slovenia. At least 2000 individuals (500/Run and 400/country) will undergo prescreening. A sub-sample of approximately 660 individuals classified as positive in the prescreening will be referred to a memory clinic to undergo a full diagnostic examination enhanced with biomarkers. A health-economic analysis will be conducted to identify the most successful and cost-effective PE strategies in each specific environment. MOPEAD will be conducted by a multinational consortium, and involves academic partners, IT experts, the pharmaceutical industry and patient associations among others (Table). *Results:* MOPEAD is funded by the Innovative Medicines Initiative (IMI) (GA 115985-MOPEAD-H2020-JTI-IMI2015-05). The grant agreement was signed in October 2016 and the time frame for the completion of the project is 33 months. *Conclusions:* MOPEAD is an innovative project based on a synergy of several private and public institutions with different expertise profiles which aim to promote a change in the paradigm of early AD diagnosis and PE strategies.

ORAL COMMUNICATIONS

OC1: A PHASE 2A EXPLORATORY ENDPOINT TRIAL IN MILD-MODERATE ALZHEIMER'S DISEASE OF LM11A-31-BHS P75 NEUROTROPHIN RECEPTOR LIGAND. Frank M. Longo[1], Manfred Windisch[2], Niels Andreasen[3], Agneta Nordberg[4] *((1) Department of Neurology and Neurological Sciences, Stanford University, Palo Alto, CA, USA and Chairman of the Board, PharmatrophiX, Inc.; (2) NeuroScios, GmbH, St. Radegund/Graz, Austria; (3) Department of Neurobiology, Karolinska Institute, Stockholm, Sweden; (4) Department NVS, Division for Neurogeriatrics, Center for Alzheimer's Research, Karolinska Institute, Stockholm, Sweden)*

Background: The intracellular signaling network regulated by the p75 neurotrophin receptor has a broad overlap with pathways likely underlying synaptic degenerative processes in Alzheimer's disease (AD). LM11A-31 is a first-in-class, orally bioavailable, small molecule ligand that inhibits p75 degenerative signaling. Preclinical studies demonstrate its ability to inhibit the following amyloid-beta (Aβ)-induced events, without directly changing Aβ load: activation of multiple tau kinases, tau misfolding, tau missorting, and tau oligomer formation; excess RhoA activation and CREB inactivation. Consistent with these mechanisms, LM11A-31 blocks Aβ inhibition of LTP, normalizes cognitive deficits in different AD mouse models, reverses synaptic spine loss in late-stage mouse models and blocks tau oligomer-induced spine loss. Taken together, these mechanistic effects point to the possibilities of both fast onset symptomatic effects and long term disease modification. *Methods:* In a phase 2a safety and

and exploratory endpoint, randomized, double blinded, controlled, parallel group trial, subjects with mild to moderate AD (McKhann, Knopman et al. 2011) receive placebo or drug capsules twice daily for 6 months. Three study arms include placebo, low dose and high dose (60 subjects enrolled in each arm). Assessments include pre- and post-treatment cognitive (NTB composite, ADAS-cog13, Clinical Global Impression Scale, Amunet spatial navigation) and biomarker (CSF Aβ/tau/p-tau/tau oligomer, 18F-FDG-PET, structural MRI) measures. *Results:* A designed salt formulation of LM11A-31, termed LM11A-31-BHS, was well tolerated in phase 1 safety and PK single ascending dose and multiple ascending dose trials in young and elderly normal subjects. Phase 2a enrollment for mild-moderate AD subjects has begun. Multiple sites in each of Austria, the Czech Republic and Germany are approved and open for enrollment. Safety, PK and exploratory endpoint analysis is expected in 2019. *Conclusion:* This study is the first trial of a therapeutic agent targeting the p75 receptor and its neurodegenerative signaling in AD or any related human brain disorder. It is of particular interest that LM11A-31 addresses fundamental synaptic degeneration mechanisms directly relevant to both Aβ and tau oligomers. Funding. Preclinical studies supported by NIA U01 AG032225 (FL), Alzheimer Drug Discovery Foundation (ADDF) (FL) and the Alzheimer's Association (FL); phase 1 studies supported by the ADDF (FL) and the Alzheimer's Association (FL) and phase 2a trial supported by NIA AD Pilot R01AG051596 (MW, NA, AN) along with private support. Conflict of interest. Dr. Longo holds intellectual property for LM11A-31 and is an equity holder in PharmatrophiX, Inc. McKhann, G. M., D. S. Knopman, et al (2011). Alzheimers Dement 7(3): 263-269.

OC2: TAU ACCUMULATION OBSERVED USING REPEATED TAU PET MEASURES PREDICTS COGNITIVE DECLINE IN NORMAL ELDERLY. Bernard Hanseeuw[1,2], Beth Mormino[3], Alex Becker[1], Aaron Schultz[3], Jorge Sepulcre[1], Kathryn Papp[3,4], Heidi Jacobs[1], Jasmeer Chhatwal[3], Dorene Rentz[3,4], Reisa Sperling[3,4], Keith Johnson[1,3,4] *((1) Department of Radiology, Massachusetts General Hospital, Boston, USA; (2) Department of Neurology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; (3) Department of Neurology, Massachusetts General Hospital, Boston, USA; (4) Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA)*

Background: Autopsy and early tau-PET data suggest that cognition is more closely associated with tau than with amyloid pathology, including in clinically normal (CN) older adults. Recently acquired serial tau-PET data allowed us to assess in CN the association between cognitive performances, tau, and amyloid, not only at baseline, but also over a two-year follow-up. We hypothesized that the rate of tau accumulation in the temporal lobe would best predict the rate of cognitive decline. *Methods:* One hundred and forty-one CN (age=55-90 years (y) old; education-adjusted MMSE≥26 and Logical Memory≥9) had baseline evaluations within a three-month period [0.0-0.7y]: Neuropsychological assessment included the PACC (Preclinical Alzheimer Cognitive Composite); Flortaucipir-PET SUVr assessed tau; and PiB-PET SUVr assessed amyloid using subcortical white matter as reference for both tracers. Subsequently, 130 participants had annual cognitive evaluations [follow-up duration: 0.5-3.3y] and 54 had repeated tau-PET [1.1-3.0y] and PiB-PET [1.2-4.0y]. Tau was measured in bilateral inferior temporal gyri and amyloid in a large neocortical aggregate. Partial volume effects were corrected for. Data were z-transformed using baseline mean and standard deviation to allow fair comparison between different measures. Linear regressions investigated the association between PACC, tau, and amyloid at baseline. Linear mixed-effect models with random intercepts investigated the association between PACC decline and baseline tau and amyloid, and then between PACC decline and the annual rate of change in tau and amyloid. The rates of change in PACC, tau, and amyloid were compared. Analyses were adjusted for age, sex, and education. *Results:* At baseline, high tau (Est.=-0.28±0.09, p=0.002) and high amyloid (Est.=-0.23±0.08, p=0.005) were both associated with lower PACC z-scores. When modeled simultaneously, tau was significantly associated with baseline PACC (Est. adjusted for amyloid=-0.21±0.10, p=0.036), but amyloid was not (Est. adjusted for tau=-0.14±0.09, p=0.11). Tau (Est.=-0.09±0.04, p=0.018) and amyloid (Est.=-0.07±0.03, p=0.025) predicted longitudinal decline in PACC over the next two years. However, when competing in the same model, neither tau (Est.=-0.06±0.04, p=0.11) nor amyloid (Est.=-0.04±0.03, p=0.15) at baseline predicted subsequent decline in PACC scores. The rate of tau accumulation predicted the rate of PACC decline (Est.=-0.71±0.24, p=0.003). In contrast, the rate of amyloid accumulation did not (Est.=-0.16±1.40, p=0.91). Predicting change in PACC with baseline tau (Est.=-0.06±0.06, p=0.3), baseline amyloid (Est.=-0.05±0.05, p=0.3), change in tau (Est.=-0.67±0.27, p=0.01), and change in amyloid (Est.=+1.7±1.5, p=0.3) demonstrated that cognitive decline was best predicted by tau accumulation. Rates of change were significantly different between tau (+0.24±0.19 z-score/y), cognition (-0.11±0.28 z-score/y, p=0.005), and amyloid (+0.05±0.03 z-score/y, p<0.0001). *Conclusions:* Cognitive decline in CN is associated with tau accumulation in the temporal lobe, beyond the association with tau or amyloid burden at baseline. Tau-PET signal changes faster than cognition or amyloid, which makes it a promising marker to track disease progression and evaluate the efficacy of potential new drugs. Blue dots are individuals with low-amyloid at baseline; red dots are high-amyloid individuals

Figure 1

Illustrative images of tau accumulation in an older adult with normal cognition

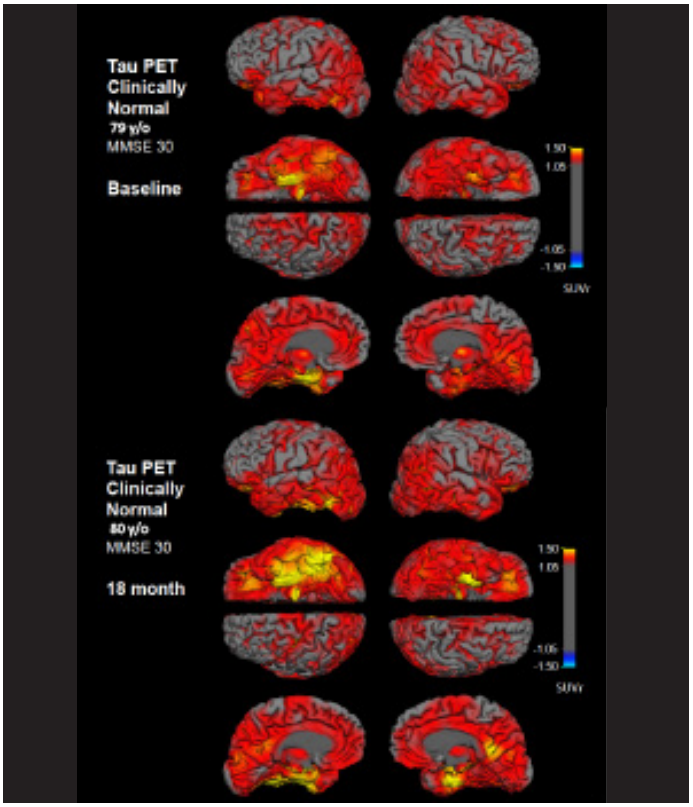
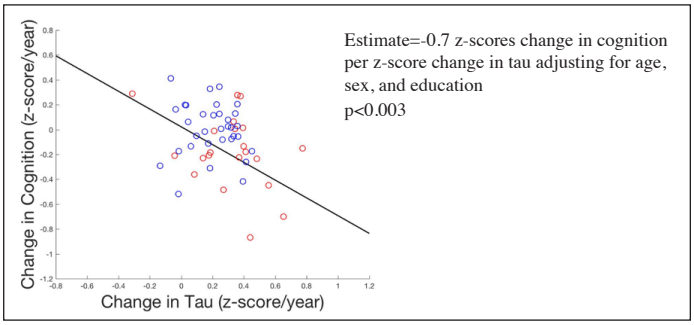


Figure 2
Scatterplot relating change in PACC scores and change in tau PET signal



OC3: CLINICAL EVALUATION OF 18F-PI-2620, A NEXT GENERATION TAU PET AGENT IN SUBJECTS WITH ALZHEIMER'S DISEASE AND PROGRESSIVE SUPRANUCLEAR PALSY. Andrew Stephens[1], John Seibyl[2], Andre Mueller[1], Olivier Barret[2], Mathias Berndt[1], Jennifer Madonia[2], David Alagille[2], Hanno Schieferstein[1], Heiko Kroth[3], Santiago Bullich[1], Andrea Pfeifer[3] Andreas Muhs[3], Gilles Tamagnan[2], Kenneth Marek[2], Ludger Dinkelborg[1] *((1) Piramal Imaging, Berlin, Germany; (2) Molecular Neuroimaging, New Haven, USA; (3) AC Immune SA, Lausanne, Switzerland)*

Background: Intracellular tau deposition is a key pathologic feature of Alzheimer's disease (AD) and other neurodegenerative disorders. Several positron emission tomography tau probes have been developed for in vivo detection of brain tau load, although quantification is challenging due to high off target binding and slow kinetics. Additionally, several tau radiotracers seem to be limited for the detection of tau in non-AD tauopathies like Progressive Supranuclear Palsy (PSP). 18F-PI-2620 is a novel tracer with a high affinity for binding to aggregated tau 18F-PI-2620 binds specifically to tau deposits in AD brain sections from different Braak stages, Pick's, and PSP pathologies. This first-in-human study reported here assesses the potential of 18F-PI-2620 to visualize tau deposition in subjects with AD and PSP, in comparison with non-demented controls (NDCs). *Methods:* In an ongoing clinical imaging study, participants diagnosed with mild AD, non-AD tauopathies like PSP, or NDCs undergo dynamic PET imaging for 180 min following 10 mCi bolus injection of 18F-PI-2620. Venous blood is obtained to characterize the kinetics of parent compound and metabolites. *Results:* Initial imaging data shows robust brain uptake and fast wash-out in non-target regions with peak SUV = 4-4.5. There was no increased uptake seen in choroid plexus, basal ganglia, striatum, amygdala, meninges or other regions noted in first generation tau agents. In AD, focal asymmetric uptake was evident in temporal and parietal lobes, precuneus, and cingulate. SUVr time curves demonstrate a plateau at 90-100 min post injection with resultant SUVrs of 2.5-2.8 in abnormal regions, whilst NDCs demonstrated shorter time to secular equilibrium (60-70 min) and lower SUVrs (1.0-1.2) in comparable brain regions. Importantly, PSP subjects demonstrated focal increased uptake in the globus pallidus (SUVr = 2.0-2.1) and substantia nigra (SUVr = 2.4-2.6). Blood data confirmed fast kinetics with 20% of parent compound present at 60 min and presence of polar metabolites. Comparison of SUVr to non-invasive pharmacokinetic modeling showed a strong correlation and linear relationship with binding potential, BPND. *Conclusion:* Initial 18F-PI-2620 PET first-in-human data in AD, PSP and NDC demonstrate excellent brain penetrance, favorable kinetics, and high target specificity with low nonspecific binding and high signal in regions of expected tau pathology.

OC4: OPTIMIZING THE PRECLINICAL ALZHEIMER'S COGNITIVE COMPOSITE (PACC) WITH SEMANTIC PROCESSING: THE PACC 5. Kathryn V. Papp[1,2], Dorene M. Rentz[1,2], Irina Orlovsky[1], Reisa A. Sperling[1,2], Elizabeth C. Mormino[2,3] *((1) Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA; (2) Department of Neurology, Massachusetts General Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, USA; (3) Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Palo Alto, USA)*

Background: Amyloid related decline in semantic memory was recently shown to be observable in the preclinical period of Alzheimer's disease (AD). Cognitive composites designed to be sensitive to cognitive change in preclinical AD (e.g. Preclinical Alzheimer Cognitive Composite- PACC) and currently used in secondary prevention trials do not currently integrate measures of semantic processing. Our objective was to determine whether a standard semantic measure (i.e. category fluency to animals, fruits, and vegetables) adds independent information above and beyond Aβ related decline captured by the PACC. *Methods:* Clinically normal older adults from the Harvard Aging Brain Study were identified at baseline as Aβ+ (n=70) or Aβ- (n=209) using PiB-PET imaging and followed annually with neuropsychological testing for 3.87±1.09 years. The relationship between PACC, category fluency and variations of the PACC including/excluding category fluency were examined using linear mixed models (LMM) controlling for age, sex, and education. We additionally examined decline on CAT by further grouping Aβ+ participants into preclinical Stage 1 and Stage 2 on the basis of neurodegeneration markers. *Results:* Category fluency explained unique variance in amyloid-related decline, with Aβ+'s continuing to decline relative to Aβ-'s in category fluency even after controlling for overall PACC decline. In addition, removal of category fluency from the PACC resulted in a longitudinal Aβ+/- effect size reduction of 20% at 3-year follow-up and 12% at 5-year follow-up. Finally, both Stage 1 and Stage 2 participants declined on CAT in comparison with Stage 0, suggesting CAT declines early within the preclinical trajectory. *Conclusion:* Addition of category fluency to the PACC provides unique information about early cognitive decline not currently captured by the episodic memory, executive function, and global cognition components and may therefore improve detection of early Aβ related cognitive decline.

OC5: CAN IT HELP WITH THE SCREENING FOR ALZHEIMER'S DISEASE TRIALS? FROM EHR TO WEB-BASED COGNITIVE TESTS AND E-CONSENT. Peter Schueler[2,3], Michael W. Weiner[1], J. Wesson Ashford[4,5,6], Bruno Vellas[7,8] *((1) UCSF, San Francisco, USA; (2) ICON, Langen, Germany; (3) University Duisburg-Essen, Germany; (4) Stanford/VA Alzheimer's Disease and Aging Clinical Research Centers, CA, USA; (5) VA Palo Alto Health Care System, CA, USA; (6) Stanford University, CA, USA; (7) University Hospital's Department of Internal Medicine and Clinical Gerontology, Toulouse, France; (8) Toulouse Gérontopôle, Toulouse, France)*

Background: Even though Alzheimer's is a common disease, individual study centers have difficulty identifying a sufficient number of eligible patients for clinical research. One reason is that only 3-6% of affected patients contribute to clinical research, and after reading a standard written informed consent form, only between 21% and 86% of patients are able to recall the content, what may partially explain high screen-fail and drop-out rates. *Method:* We assessed the ability of various IT technologies to address these problems during

patient recruitment. For Subject pre-identification: we compared the commercially developed EHR database TriNetX with the EU commission-funded Innovative Medicines Initiative (IMI) EHR4CR and a registry (BrainHealth). For cognitive screening: an internet-based Continuous Recognition Tests (Memtrax), measuring episodic memory, inhibition, and recognition time, was applied online to 36,021 individuals. For enrolment: in a randomized fashion, subjects enrolling in an ongoing clinical trial in AD at the Toulouse site were assigned to receiving a conventional, paper-based Informed Consent Sheet, while the other half received an electronic information form with embedded animations. *Results:* EHR: All involved institutions have access to at least 150 AD patients. There is no relevant difference between regions (US versus EU) or location of the center (urban or rural area). All datasets provide information about age, gender, concomitant medication and concomitant diseases, what can help with the evidence-based design of study protocols. However, only less than 10% of these institutions have data on file about cognitive performance or biomarkers, what limits the ability to upfront model in silico the impact on recruitment of all key subject selection parameters. CRT: On average 1,500 individuals performed the test per month. It took them less than 2 minutes per assessment, indicating this is a very user-friendly test for mass-screening. Errors and speed have less than a 16% relationship, so this rapid test evaluates different areas of cognition. e-Consent: Final results will only be available in 2019, but an initial summary of the pros and cons of an electronic informed consent process, its acceptance by IEC, French CA, site staff, study subjects, and their caregivers will be presented. *Conclusion:* All these electronic tools are easy to use, and support existing process in AD clinical research at low costs. They optimize the subject identification and enrolment activities. Only data obtained from randomized studies like the one assessing the informed consent process would provide full evidence about the cost-efficiency of such tools.

OC6: AMYLOID BETA OLIGOMERS IN ALZHEIMER'S DISEASE: A MISSING PIECE OF THE ALZHEIMER'S PUZZLE. Jeffrey Cummings[1], Sandrine Andrieu[2], Philip Scheltens[3], Kaj Blennow[4], Petr Kocis[5], John A. Hey[5], A. Power[5], Martin Tolar[5], Susan Abushakra[5] *((1) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada; (2) University of Toulouse, Toulouse, France; (3) VU University Medical Center, Amsterdam, Netherlands; (4) The Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden; (5) Alzheon, Inc., Boston, MA, USA)*

Background: Amyloid targeted agents have been extensively evaluated as disease modifying agents for treatment of Alzheimer's disease (AD), but success has proven elusive. Negative trial results have raised questions about the relevance of amyloid pathology to clinical progression in AD and about its validity as a therapeutic target. The lack of correlation of fibrillar amyloid burden on PET imaging to symptoms has further fueled this controversy. However, a large and growing body of nonclinical and clinical studies have shown that soluble toxic Aβ oligomers appear early and are closely correlated with clinical symptoms and disease progression (Esparza et al. 2013, Viola and Klein 2015). Soluble toxic Aβ oligomers have been shown to induce synaptic dysfunction and neuronal degeneration (Sakono and Zako 2010, Larson and Lesne 2012). APOE4/4 homozygotes are known to have a high burden of Aβ oligomers (Hashimoto et al. 2012). ALZ-801 is in development as an oral disease modifying treatment for AD. Tramiprosate, the active agent in in ALZ-801, was recently shown to inhibit the aggregation of Aβ42 monomers into soluble oligomers. Tramiprosate was previously evaluated in Phase 3 trials of Mild to Moderate AD, and showed efficacy signals in the APOE4/4 homozygous subgroup. We therefore examined the agreement between clinical efficacy, pharmacokinetic data, and the observed anti-oligomer effects in nonclinical studies. *Methods:* Clinical Data. ALZ-801 is a pro-drug of tramiprosate that provides substantially improved pharmacokinetics and GI tolerability. The active agent tramiprosate, was previously evaluated in two placebo-controlled, 78-week Phase 3 AD studies, one in North America (NA study), and the other in Europe (EU study), and included 2 active doses. The ADAS-cog and CDR-SB were the co-primary outcomes. The NA study did not show efficacy in the overall Mild to Moderate AD population, and the EU study was terminated. Re-analyses of the NA efficacy dataset based on APOE4 genotype were performed (Abushakra et al. 2016). The APOE4/4 homozygotes showed the largest effects, and their efficacy results were further analyzed according to baseline disease severity. The largest effects were observed in the Mild subgroup of patients defined as baseline MMSE 22 and above. Efficacy analyses used a standard MMRM model, p-values are considered nominal. The NA study included measurement of plasma and CSF drug levels. Nonclinical Data. Tramiprosate in transgenic CRND8 mice had shown reduced amyloid plaque and soluble Aβ42 in brain (Gervais et al. 2007). In vitro studies using new techniques, including ion mobility mass spectrometry (IMS) and nuclear magnetic resonance (NMR) were performed. These examined the Aβ42 monomer aggregation in the presence of increasing tramiprosate concentrations (Kocis et al. 2017). *Results:* Demographics and baseline characteristics were recently pusblished (Abushakra 2016 and 2017). In the NA study, efficacy analysis by APOE4 genotype showed a "gene dose effect": largest efficacy in homozygotes, intermediate in heterozygotes, and lowest in noncarriers. In the overall APOE4/4 homozygous subgroup (MMSE 16-26) tramiprosate showed significant efficacy at 78 weeks on ADAS-cog at the 150mg BID dose, but not at the low dose. In the APOE4/4 Mild subgroup (MMSE 22 and above), the efficacy benefit compared to placebo was larger and achieved significance on both ADAS-cog (LS mean 5.66, p= 0.0001) and CDR-SB (LS mean 1.14, p= 0.0197) at 78 weeks. The ADAS-cog effects increased with time (significant difference of slopes, p= 0.015). The CDR-SB benefits were also sustained for 65 weeks. The low dose showed only a positive trend on the ADAS-cog at 78 weeks. Across the whole safety population (n=2,025) from both studies, the safety profile was favorable with the most common adverse events being nausea, vomiting, and weight loss; most were mild to moderate in severity. The safety profile in APOE4/4 homozygous subgroup was similar. There were no events of vasogenic edema on active drug. The in vitro studies showed that several tramiprosate molecules envelope a Aß42 monomer, stabilize Aß42 in its monomeric form and prevents the initiation stage of aggregation (seeding). Complete prevention of Aß42 oligomer formation was achieved with tramiprosate excess at 1:1000 ratio. Modelling analyses indicated this ratio was achieved with projected brain concentrations at 150mg BID clinical dose. *Conclusions:* Multiple studies support a critical role of soluble toxic Aβ oligomers in AD pathogenesis, and this toxicity is thought to be an early trigger of a cascade of downstream events leading to synaptic dysfunction and neurodegeneration. ALZ-801/tramiprosate is one of few oral agents in development that specifically targets monomer aggregation into toxic oligomers. In APOE4/4 homozygotes known to have a high burden of Aβ oligomers, tramiprosate has shown promising efficacy signals at concentrations shown to inhibit Aβ42 oligomer formation. This translation of Aβ oligomer inhibition effects into meaningful clinical efficacy at the Mild stage of disease provides strong support for the importance of soluble Aβ oligomers in AD pathogenesis, and their exciting potential as a therapeutic target.

OC7: ABBV-8E12, A HUMANIZED ANTI-TAU MONOCLONAL ANTIBODY FOR THE TREATMENT OF EARLY ALZHEIMER'S DISEASE: A 96-WEEK, MULTIPLE DOSE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 STUDY. Kumar Budur[1], Hana Florian[1], Deli Wang[1], Weining Robieson[1], Holly Soares[1], Joel B. Braunstein[2], David M. Holtzman[3], Randall J. Bateman[3], Beatrice Rendenbach-Mueller[4], Nuno Mendonca[1] *((1) AbbVie Inc, North Chicago, IL, USA; (2) C2N Diagnostics LLC, Saint Louis, MO, USA; (3) Washington University, St. Louis, MO, USA; (4) AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany)*

Background: ABBV-8E12 is a humanized anti-tau monoclonal antibody currently being developed for the treatment of Early Alzheimer's Disease (AD) and progressive supranuclear palsy (PSP). Compared to placebo, administration of anti-tau antibodies to transgenic mice that develop tau pathology showed (i) reduction in the progression of tau pathology, (ii) reduction in brain volume loss, and (iii) improvements in various cognitive and behavioral tests. A phase 1 double-blind, placebo-controlled, single ascending dose study that assessed the safety, tolerability, and pharmacokinetics of ABBV-8E12 in patients with PSP (NCT02494024) was recently completed. The phase 1 results showed that ABBV-8E12, when administered as a single dose up to 50 mg/kg, exhibited an acceptable safety and tolerability profile to support repeat-dose testing in larger cohorts of patients with tauopathies. Here we present the design of an ongoing double-blind, placebo-controlled phase 2 study of ABBV-8E12 in patients with Early AD. *Methods:* The phase 2, double-blind, placebo-controlled study will assess the 96-week efficacy of ABBV-8E12 in slowing disease progression and its safety in patients with Early AD (NCT02880956). A total of 400 male and female patients, aged 55 to 85 years, will be enrolled at approximately 65 global study sites. Prior to enrollment, patients will have met the criteria for early AD (a Clinical Dementia Rating [CDR]-Global score of 0.5, Mini-Mental State Examination [MMSE] score of 22-30, and a Repeatable Battery for Assessment of Neuropsychological Status [RBANS-DMI] score of ≤ 85) and have had a positive amyloid Positron Emission Tomography scan. Patients will be randomized to one of 3 ABBV-8E12 dose arms or placebo. *Results:* The primary efficacy outcome is the CDR – Sum of Boxes (CDR-SB) at Week 96. Key secondary endpoints include, but are not limited to, pharmacokinetic assessment of ABBV-8E12, and the change from baseline to Week 96 for the MMSE, the Alzheimer's Disease Assessment Scale (14-Item) Cognition Portion, and the RBANS. Adverse events will be monitored. *Conclusion:* A significant unmet medical need exists for the development of disease-modifying drugs for AD which directly impact the biology of the disease and reduce its associated burdens. ABBV-8E12 has shown an acceptable safety and tolerability profile in patients with PSP during phase 1 testing. The current study is designed to evaluate the 96-week efficacy and safety of ABBV-8E12 in patients with Early AD.

OC8: STRATIFICATION OF PRE-SYMPTOMATIC AND COGNITIVELY NORMAL INDIVIDUALS USING POLYGENIC SCORING. Maryam Shoai[1], Richard Pither[2], Valentina Escott-Price[3], Simon M Laws[4], Harald Hampel[5], Simone Lista[5], Rik Vandenberghe[6], Isabelle Cleynen[6], David Irwin[7], Vivian Van Deerlin[8], Greg Davidson[9], Virginia M.-Y. Lee[10], John Q. Trojanowski[10], John Hardy[1] *((1) UCL Institute of Neurology, London, United Kingdom; (2) Cytox Ltd, UK, Oxford, United Kingdom; (3) Cardiff University, Cardiff, United Kingdom; (4) Edith Cowan University, and Cooperative Research Centre (CRC) for Mental Health, Perth, Australia; (5) AXA Research Fund & UPMC Chair, Paris, France; (6) Katholieke Universiteit Leuven, Leuven, Belgium; (7) Hospital of the University of Pennsylvania, Department of Neurology, University of Pennsylvania, Philadelphia; (8) Hospital of the University of Pennsylvania, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia; (9) Ledcourt Associates, UK; (10) Centre for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine, Philadelphia)*

Introduction: It is well documented that early symptomatic (MCI) or elderly pre-symptomatic individuals who are amyloid-positive, as assessed using either PET imaging or CSF testing, are at relatively increased risk of future cognitive decline and AD. *Objective:* The identification of subjects at high risk of AD will be important for early diagnosis and successful treatment. Strong evidence exists to support a highly significant role for a genetic risk component for the development of Late-Onset Alzheimer's Disease (LOAD). The identification of a panel of genetic variants which could be used in the definition of an algorithm to predict risk of future progression to AD in pre-symptomatic individuals, would have utility to researchers, drug developers and clinicians alike. *Methods:* An array of 130,000 variants (variaTECTTM) was developed in partnership with Affymetrix, comprising, amongst others, a comprehensive list of variants indicated in pathways relating to AD, whole exome association analysis, and variants identified through literature. All samples within the study were genotyped on the variaTECTTM (Affymetrix Axiom™) plates and processed on an Affymetrix GeneTitan® scanner. A training set, consisting of very well clinically and biomarker-phenotyped cases and control samples was genotyped using the variaTECTTM array, and the data used to identify two models describing risk of Aβ 42 positivity, as assessed by PET imaging or post-mortem pathology examination. The two models were identified using machine learning; a hypothesis driven naïve Bayes approach and a hypothesis free variant selection with elastic net regularization and tested against 800 samples from the ADNI cohort. *Discussion:* The genotyping data derived from a training set of ca. 1700 neuropathologically confirmed cases and controls, consisting of samples from the University of Pennsylvania and the TGEN study, as well as 600 samples from the AIBL study, have been used to derive and test novel polygenic risk score (PRS) algorithms. Our initial results indicate that PRS algorithms can be successfully deployed with sensitivities of ca. 90% in order to identify and enrich amyloid-positive individuals from early symptomatic and prodromal cohorts. *Conclusion:* The variaTECT array is currently the most wide-ranging research panel available for the detection of AD informative SNPs. The results of our polygenic risk scoring indicate that the failure rate and associated costs of testing for Aβ 42 cohorts can be significantly reduced with the application of these models, providing a suitable upstream test for clinical trials and identification of those most at risk of developing AD.

OC9: OBJECTIVE COGNITIVE DECLINE IN PRECEDING YEARS RELATES TO SELF-REPORT ON THE COGNITIVE FUNCTION INDEX IN THE HARVARD AGING BRAIN STUDY. Rebecca E. Amariglio[1,2,3], Rachel F. Buckley[2,3,4,5], Elizabeth C. Mormino[2,3], Dylan R. Kirn[2], Gad A. Marshall[1,2,3], Keith A. Johnson[1,2,3], Dorene M. Rentz[1,2,3], Reisa A. Sperling[1,2,3] *((1) Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA; (2) Department of Neurology, Massachusetts General Hospital, Boston, MA, USA; (3) Harvard Medical School, Boston, MA USA; (4) Florey Institutes of Neuroscience and Mental Health, Melbourne, Australia; (5) Melbourne School of Psychological Science, University of Melbourne, Australia)*

Background: As Alzheimer's disease (AD) treatment strategies increasingly emphasize prevention during the preclinical stage, these efforts will require a corresponding focus on detection of the earliest clinically meaningful changes in cognitive functioning. Patient-reported outcomes (PRO) offer the opportunity to observe the functional impact of disease and treatment, particularly at the stage of preclinical AD when symptoms are subtle and are not easily captured with traditional clinical measures. The Cognitive Function Index (CFI) is a PRO developed to detect subjective changes in cognitive function in older individuals at risk for cognitive decline that can be given to both the participant and a study partner (Walsh et al., 2006). Previously, we found that the CFI tracked with longitudinal clinical and cognitive outcomes in the Alzheimer's Disease Cooperative Study Prevention Instrument Project (Amariglio et al., 2015). Recently, the CFI was added to the ongoing Harvard Aging Brain Study (HABS), a longitudinal cohort of older individuals (clinically normal at baseline) who have undergone PIB-PET imaging and have been followed with annual cognitive assessments for up to 6 years. In the current study, we sought to determine whether self-report on the CFI was associated with longitudinal cognitive decline in the preceding years and whether this association was stronger in individuals with high levels of amyloid. *Methods:* Individuals from HABS who were clinically normal at baseline (CDR Global =0, above cut-off on MMSE and Logical Memory Delayed Recall) and who had been administered the self CFI were selected for the current study (n=107, age at CFI= 79.3 ±6.2, education= 15.8±3.0, female= 58%). We did not examine study partner CFI in the current study. Most participants completed the CFI in the 6th year of the study (n=84), but some were administered the CFI in the 4th year (n=8) or the 7th year of the study (n= 15). Higher scores on the CFI indicate greater endorsement of subjective symptoms. The average score of the CFI (14-items) was used for the current analyses. Objective cognitive performance was examined using the Preclinical Alzheimer's Cognitive Composite (PACC; Donohue, et al. 2014, Mormino et al., 2017). Participants were administered the PACC annually. PIB retention was assessed using an aggregate cortical ROI including frontal, lateral temporal, and retrosplenial cortices. Amyloid positivity (n = 34) was classified using a previously reported Gaussian mixture modeling approach (Mormino et al., 2014). Median delay between PIB PET and CFI collection was 224 days. Using a series of linear mixed models, we examined whether self CFI was associated with PACC decline in the preceding years, controlling for age, education and sex. In secondary analyses, we examined the interaction between the self CFI and amyloid positivity and its association with PACC decline with covariates. *Results:* We found that retrospective PACC decline was associated with self CFI ($p<0.0001$), such that higher self CFI was associated with greater PACC decline in the preceding years. When we examined the impact of amyloid on the relationship between self CFI and PACC decline, the interaction term was significant ($p<0.0001$), indicating that greater self CFI was more strongly associated with PACC decline in amyloid positive individuals compared to amyloid negative individuals. *Conclusions:* Self-reported decline in cognitive functioning on the CFI was associated with objective cognitive decline in the years leading up to the time of CFI. This relationship was stronger in individuals with high amyloid burden compared to those with low burden. Findings provide further support for the CFI's ability to detect subtle changes in cognitive functioning that correspond with objective cognitive decline in individuals at risk for AD. Currently, the CFI is a secondary outcome measure included in the A4 trial. Future clinical trials might also consider using CFI as an outcome measure to determine response to therapeutic interventions.

OC10: THE GENERATION PROGRAM: EVALUATING CNP520 EFFICACY IN PRECLINICAL ALZHEIMER'S DISEASE. Cristina Lopez Lopez[1], Pierre N. Tariot[2], Angelika Caputo[1], Fonda Liu[1], Marie-Emmanuelle Riviere[1], Marie-Laure Rouzade-Dominguez[1], Ronald G. Thomas[3], Jessica B. Langbaum[2], Rob Lenz[4], Eric M. Reiman[2], Ana Graf[1] *((1) Novartis Pharma, Basel, Switzerland; (2) Banner Alzheimer's Institute, Phoenix, AZ; USA; (3) University of California-San Diego, San Diego, CA, USA; (4) Amgen, Thousand Oaks, CA, USA)*

Background: CNP520, a Beta-site-APP cleaving enzyme-1 (BACE-1) inhibitor, is in clinical development for the treatment of preclinical Alzheimer's disease under the Alzheimer's Prevention Initiative in the Generation program. *Methods:* The Generation Program comprises two pivotal (phase 2/3) studies with a similar design to assess the efficacy and safety of CNP520 in a cognitively unimpaired population at increased risk for developing AD based on their age and APOE4 genotype. Generation Study 1 is a randomized, double-blind, placebo-controlled, two cohort parallel group study to evaluate the efficacy of CNP520 (one dose), and CAD106 (an active immunotherapy) in participants who are homozygous (HM) for APOE4. Generation Study 2 is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy of two doses of CNP520 in subjects who carry 1 or 2 copies of the APOE4 gene. In order to increase the risk of progression to a comparable level as HMs, the heterozygotes (HTs) in Generation Study 2 will require elevated brain amyloid as measured by amyloid PET imaging or Aβ levels in CSF. Approximately 3500 participants will be randomized worldwide across studies. Participants will be treated for at least 60 months up to a maximum of 96 months. *Results:* Efficacy of CNP520 will be evaluated by two primary endpoint variables: (i) time to event (TTE), with event defined as diagnosis of MCI due to AD or dementia due to AD, and (ii) changes from baseline in APCC test score, a cognitive test battery developed as a sensitive tool to detect and track cognitive decline in individuals at risk to progress to clinical stages of AD. For the time to event outcome, the diagnostic criteria proposed by the National Institute on Aging Alzheimer's Association working group will be used alongside a centralized adjudication process. APCC will allow examination of drug effects using a continuous measure of cognition from unimpaired throughout the mild impairment stages expected to occur in the study. CDR-SOB, RBANS, and ECog, will be included as secondary endpoints, in order to fully capture potential drug effects on cognition and function and to further contribute to the assessment of clinical relevance of potential treatment effects. The program will also investigate the effects of CNP520 on the underlying AD pathology assessed by biomarker data based on voluntary participation. *Conclusions:* The Generation Program is designed to provide efficacy, safety and tolerability data for CNP520 compared to placebo in people at risk for the onset of clinical symptoms of AD. Generation Study 1 and Generation Study 2 are currently enrolling

OC11: A PHASE 1B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SEQUENTIAL COHORT, DOSE-RANGING STUDY OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY EFFICACY OF TPI 287 (ABEOTAXANE) IN PATIENTS WITH PRIMARY FOUR REPEAT TAUOPATHIES: CORTICOBASAL SYNDROME OR PROGRESSIVE SUPRANUCLEAR PALSY; OR THE SECONDARY TAUOPATHY, ALZHEIMER'S DISEASE. Adam Boxer[1], Zachary Miller[1], Richard Tsai[1], Mary Koestler[1], Julio Rojas[1], Peter Ljubenkov[1], Howie Rosen[1], Gil Rabinovici[1], Anne Fagan-Niven[2], Yann Cobigo[1], June Jung[1], Phi Luong[1], Emmeline Chuu[1], Ryan Powers[1], Paige Mumford[1], Bruce Miller[1], Erik Roberson[3] *((1) Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA, USA; (2) Department of Neurology, Washington University School of Medicine, Saint Louis, MO, USA; (3) Department of Neurology, University of Alabama School of Medicine, Birmingham, AL, USA)*

Background: TPI-287 (abeotaxane) is a blood brain permeable, synthetic taxane derivative that has previously been evaluated at high doses for CNS cancers. Studies in a variety of preclinical models including tau transgenic mice have demonstrated that low doses of similar microtubule stabilizing agents can reduce microtubule hyperdynamicity, tau pathology and ameliorate a variety of physiological and behavioral effects of pathogenic tau. *Methods:* The primary objective of the study was to determine the safety and tolerability [maximum tolerated dose [MTD] of IV infusions of TPI 287 administered once every 3 weeks for 9 weeks (for a total of 4 infusions) in three sequential dose cohorts (2, 6.3, and 20 mg/m2) in patients with the primary four repeat tauopathies (4RT), amyloid PET (-) corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP), or the secondary tauopathy, Alzheimer's Disease (AD). Each dose cohort was randomized 8 drug : 3 placebo, followed by an optional, two month open label extension. In the 4RT group two low dose cohorts (one CBS, one PSP) were recruited. The secondary objective was to determine the pharmacokinetic (PK) profile of TPI 287 in plasma after a single IV infusion and the steady-state cerebrospinal (CSF) concentration of TPI 287 one week after completion of the fourth infusion. Exploratory objectives were to screen for pharmacodynamic effects on CSF biomarkers including tau, ptau and neurofilament light chain concentration, volumetric and diffusion tensor MRI measurements, as well as clinical rating scales in 4RT (PSP Rating Scale, Schwab and England, CGI) or AD (ADAS-cog and ADCS-ADL). *Results:* 55 4RT patients were screened, 44 randomized, and 42 completed the randomized, double blind, placebo-controlled (RCT) phase of the study. 39 AD patients were screened, 29 were randomized and 22 completed the RCT phase of the trial. The AD portion of the trial was stopped in the high dose cohort due after two dose-limiting toxicities (DLT; hypersensitivity reactions) were observed. No DLT were observed in the 4RT cohort. More frequent falls were observed in TPI-treated than placebo treated PSP patients. No treatment effects were observed on clinical rating scales in either group. PK, fluid biomarker and MRI analyses are underway and will be available for presentation at the meeting. *Conclusions:* The MTD for TPI 287 was 6.3 mg/m2 in AD and 20 mg/m2 in 4RT. Decisions regarding further development of this drug for tauopathies will depend on the results of the PK and exploratory PD analyses.

OC12: HIGH DOSE B VITAMIN THERAPY SELECTIVELY IMPROVES COGNITIVE FUNCTION INDICATIVE OF CEREBROVASCULAR STATUS IN THE RANDOMIZED FAVORIT ANCILLARY COGNITIVE TRIAL. Tammy M. Scott[1,2], Aron M. Troen[1,3], Irwin H. Rosenberg[1,2] *((1) Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston MA; (2) Friedman School of Nutrition Science and Policy, Tufts University, Boston MA; (3) Institute of Biochemistry, Food Science and Nutrition, The Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, Rehovot, Israel)*

Background: We argue that the importance of cerebrovascular pathology and hypoperfusion are underestimated in considering the etiopathogenesis of age-related dementia and Alzheimer Disease. Reported nutritional interventions, especially B vitamins in high dose, are more likely to affect cerebrovascular integrity than other elements in the maintenance of cognitive function. Among measures of cognitive function and decline, executive function may be most strongly representative of cerebrovascular status. We have re analyzed data from the FAVORITE Ancillary Cognitive Trial to focus on the benefit of B-vitamin in therapeutic dosage on executive function over time in a cohort of stable kidney transplant recipients at high risk for vascular pathology and cognitive decline. *Methods:* The study was a longitudinal ancillary of the FAVORIT trial, a randomized, placebo-controlled multi-site trial of high-dose B vitamins to reduce cardiovascular and cerebrovascular events in clinically stable kidney transplant recipients with elevated tHcy, and included 584 participants from 18 sites across North America. The intervention consisted of a daily multivitamin containing high-doses of folate (5.0 mg), vitamin B12 (1.0 mg) and vitamin B6 (50 mg). The placebo consisted of a daily multi-vitamin containing no folate and recommended daily allowances of vitamins B12 and B6 (0 mg folate; 2.0 μg vitamin B12; 1.4 mg vitamin B6). Annual neuropsychological assessment for up to 5 years (mean 3.3 years) using a standardized test battery. Efficacy was analyzed on an intention-to-treat basis using end-of-trial data. Subgroup analyses included stratification for baseline plasma B-vitamin and tHcy concentrations. *Results:* At baseline, cognitive impairment was common with 61% of participants falling more than one standard deviation below published norms for at least one cognitive test. At follow-up, executive function/processing speed was better in the B-vitamin supplement group than in controls ($p \leq 0.05$) after controlling for age, sex, race, education, hypertension, diabetes, duration of transplant, number of testing timepoints, FAVORIT site, and eGFR in multivariate analysis . Fewer than 1% of participants had insufficient plasma folate < 5 ng/ml or vitamin B12 < 148 pmol/L. However, 44.6% had plasma B6 concentrations < 30 nmol/L. *Conclusions:* High dose B Vitamin therapy provided modest cognitive benefit for kidney transplant recipients at high risk of cardiovascular and cerebrovascular disease and cognitive decline. Such benefit particularly affected cognitive measure of processing speed, a measure of executive function which has been associated with cerebrovascular integrity. Since nearly all participants were folate and vitamin B12 sufficient at baseline, the potential cognitive benefits of folate and B12 supplementation in individuals with poor B-vitamin status should be determined in trials in which nutritional insufficiency in relation to cerebrovascular risk is specifically targeted.

OC13: INVESTIGATIONAL NEW ALZHEIMER'S DRUG TRICAPRILIN: RESULTS OF A PHASE 3 STUDY IN MILD-TO-MODERATE ALZHEIMER'S DISEASE PATIENTS. Samuel Henderson[1], Michael Gold[2], Judith Walker[1], Sabrina Greer[1], Janet Vogel[1], Aaron Shenkin[1] *((1) Accera Inc, Boulder, CO, USA; (2) PPD Inc, Wilmington, NC, USA)*

Background: Tricaprilin, a ketogenic compound, is in clinical development for the treatment of mild-to-moderate Alzheimer's disease (AD). In a previous Phase 2b study, Tricaprilin demonstrated significant improvement relative to placebo in a sub-group of subjects (n=29 tricaprilin, 26 placebo) who were non-carriers of the epsilon 4 allele (ε4) of the APOE gene and received 20 grams of tricaprilin QD for 90 days. *Methods:* We conducted a 26 week, double-blind, randomized, placebo-controlled, Phase 3 trial involving patients with mild-to-moderate Alzheimer's disease. The study population included men and women between the ages of 66 and 90 years old who met the NINCDS-ADRDA criteria for probable AD. Use of cholinesterase inhibitors and/or memantine was permitted (in stable doses). Eligible subjects were stratified by APOEε4 carriage status (+, -) and baseline MMSE score (14-20, 21-26). Subjects were randomized 1:1 to receive either oral tricaprilin at 20 grams/day or a matching isocaloric placebo. Upon completion of the double-blind treatment phase, participants were eligible to receive tricaprilin in an optional 26 week open-label extension. The primary analysis population was the APOEε4 non-carriers and the primary outcome measures were the ADAS-cog(11) and ADCS-CGIC. Secondary outcomes included the ADCS–ADL, QoL-AD, RUD-Lite, Clock Draw Interpretive Study (CDIS), and the MMSE. *Results:* The study enrolled 285 APOEε4 non-carriers and 128 carriers at 61 sites in the USA. Eighty percent of APOEε4 non-carriers completed the study. In the primary analysis population, the mean age (SD) was 76.9 (6.88) and the MMSE score at baseline was 21.2 (3.50). No significant differences between tricaprilin and placebo in change in ADAS-Cog at 26 weeks (least squared means: tricaprilin 1.1; placebo 0.3; p=0.25) or in ADCS-CGIC (p=0.27) were detected. *Conclusion:* The study did not meet primary and secondary endpoints. Subsequent analyses revealed two factors that may have influenced study outcome: (1) the formulation used in the study produced lower levels of ketones than formulations used in the earlier studies; (2) there was a marked lack of cognitive decline among the APOEε4 non-carriers. Detailed results of this trial will be presented as well as plans for continued development.

OC14: CHARACTERIZATION OF THE SELECTIVE IN VIVO AND IN VITRO BINDING PROPERTIES OF CRENEZUMAB: INSIGHTS INTO CRENEZUMAB'S UNIQUE MECHANISM OF ACTION. William J. Meilandt[1], Janice A. Maloney[1], Jose Imperio[1], Travis W. Bainbridge[2], Mike Reichelt[3], Danielle Mandikian[4], Yanmei Lu[5], James A. Ernst[2], Reina N. Fuji[6], Jasvinder K. Atwal[1] *((1) Department of Neuroscience, Genentech, South San Francisco, CA, USA; (2) Department of Protein Sciences, Genentech, South San Francisco, CA, USA; (3) Department of Research Pathology, Genentech, South San Francisco, CA, USA; (4) Department of Preclinical and Translational Pharmacology, Genentech, South San Francisco, CA, USA; (5) Department of Biochemical and Cellular Pharmacology, Genentech, South San Francisco, CA, USA; (6) Department of Safety Assessment, Genentech, South San Francisco, CA, USA)*

Background: Crenezumab is a monoclonal anti-amyloid beta (Aβ) immunoglobulin G4 (IgG4) antibody that is currently being developed for the treatment of Alzheimer's disease (AD). Crenezumab binds to monomeric as well as aggregated forms of Aβ in vitro, with high affinity to Aβ oligomers, the form of Aβ hypothesized to mediate neurotoxicity in AD. Here, we investigated the binding characteristics of crenezumab to endogenous Aβ oligomers in vivo in a mouse model of AD, as well as to various forms of synthetic or native Aβ oligomers in vitro. *Methods:* We characterized the in vivo binding pattern of crenezumab to Aβ in brains of PS2APP mice by immunohistochemistry and electron microscopy following a single intravenous injection at various dose levels. Using immunoprecipitation and Western blotting analysis, we also evaluated the interaction between crenezumab and (1) different forms of synthetic Aβ oligomers, (2) native Aβ present in human cerebrospinal fluid (CSF) from AD patients, and (3) native Aβ isolated from soluble brain homogenates from the PS2APP mouse model of AD. *Results:* In vivo studies show that crenezumab, but not a control antibody, binds to brain regions in the PS2APP mice that are enriched in oligomeric Aβ including the periphery of amyloid plaques and to the mossy-fiber axons in an age and dose-dependent manner. Crenezumab binding was also enriched at dystrophic neurites surrounding plaques. No crenezumab binding was observed in non-transgenic mice. Electron microscopy was performed to gain ultrastructure resolution of the brain regions that showed crenezumab binding. It was also noted that crenezumab does not bind to vascular amyloid at the dose levels evaluated. In vitro, crenezumab is able to immunoprecipitate different synthetic oligomeric Aβ preparations. In addition, we were able to immunoprecipitate putative high molecular weight Aβ oligomers from human CSF isolated from AD patients. Crenezumab also immunoprecipitated a mixture of different Aβ forms including dimers from soluble brain homogenates prepared from PS2APP mice. *Conclusions:* Crenezumab's preferential in vivo and in vitro binding to Aβ oligomers, the form of Aβ hypothesized to mediate neurotoxicity in AD, supports the clinical rationale for crenezumab as a potential treatment for AD. The lack of binding to vascular amyloid in our mouse model of AD at the doses tested, in addition to the reduced effector function on the IgG4 backbone, may explain crenezumab's low risk of amyloid related imaging abnormalities in clinical trials to date.

OC15: LONG-TERM COGNITIVE DECLINE IN PATIENTS WITH ALZHEIMER´S DISEASE IN ASSOCIATION WITH TREATMENT WITH CHOLINESTERASE INHIBITORS-DATA FROM SVEDEM, THE SWEDISH DEMENTIA REGISTRY. Maria Eriksdotter[1,2], Sara Garcia-Ptacek[1,2], Ingemar Kåreholt[3,4], Dorota Religa[1,5], Peter Nordström [6], Anders Wimo[1,5,7], Bengt Winblad[1,5] *((1) Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division of Clinical Geriatrics, Karolinska Institutet, Huddinge, Sweden; (2) Department of Geriatric Medicine, Karolinska University Hospital, Huddinge, Sweden; (3) Aging Research Center, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden; (4) Institute of Gerontology, School of Health and Welfare, Jönköping University, Jönköping, Sweden; (5) Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division for Neurogeriatrics, Karolinska Institutet, Huddinge, Sweden; (6) Department of Community Medicine and Rehabilitation, Geriatric Medicine, Umeå University, Umeå, Sweden; (7) The primary Health care of Hudiksvall-Nordanstig, Sweden)*

Background: Despite three decades of intensive research, cholinesterase inhibitors (ChEIs) are the main anti-dementia drugs currently in clinical use as treatment in AD and several randomized trials for 6 -12 months have shown a moderate benefit. It has also been suggested from observational studies that ChEI treatment reduces the

risk for myocardial infarction and mortality in AD patients (Nordström et al 2013). Data from the Swedish Dementia registry show that about 60-70% of AD patients are treated with ChEI at the time of diagnosis. This suggests that AD patients in clinical trials are on ChEI treatment and that clinical trials on AD-patients in Sweden are in fact add-ons. To compare effects on cognition using new drugs, the long-term cognitive trajectory for patients on ChEIs needs to be studied. Clinical trials conducted with ChEIs hitherto, however, include limited follow-up time, and information is lacking on the long-term cognitive effects of treatment with ChEIs. The objective of this study is to determine the association between ChEIs at the time of dementia diagnosis and long-term cognitive decline in a large national cohort of patients with Alzheimer's disease and mixed (Alzheimer's and vascular) dementia. *Methods:* The Swedish Dementia Registry (SveDem) was created in 2007 to increase the quality and equality of care for dementia patients in Sweden. Patients are registered in SveDem at the time of dementia diagnosis, classified in eight separate dementia diagnoses, together with information on demographics, living situation, and results from the Mini-mental State Examination (MMSE). SveDem includes yearly follow-up visits, with updates on living situation and cognition (MMSE). Additionally, all diagnoses performed in Sweden in hospitals or specialized care from the year 1998 onwards (International Classification of Diseases, ICD-10) were obtained from the Patient Registry for the cohort. Information on all prescription drugs dispensed in Swedish pharmacies from 2000 onwards was included (Anatomical Therapeutic Chemical-ATC) from the Prescribed Drug Registry (PDR), with near 100% coverage. The death registry contributed date and causes of death. Between 2007 and 2014 there were 28278 patients with AD or mixed dementia registered in SveDem. Number of yearly follow-ups ranged from 1 (13604 patients) to 9 (1 patient). Descriptives are presented for the cohort characteristics at baseline and visits 1, 2 and 3 (n=2276), with p-values obtained from Chi-Square, t-tests or other appropriate methods. Mixed models were used to examine the association between baseline use of ChEI and MMSE decline over time, presented as coefficients with confidence intervals. Date of study entry was the date of first registration into SveDem or date of first prescription of ChEI. The different medications within the ChEI group and dosages were also considered. *Results:* Baseline registration consisted in 28278 patients, of which 17676 (63%) had AD. Women made up 63% of the cohort and the median age was 80 (interquartile range—IQR 11). MMSE was available for 98% of patients on first registration, with a median of 22 (IQR 7). First follow-up occurred a median of 10 months (IQR 6) after baseline registration and was performed on 13604 patients. Patients who were followed-up tended to be younger than the general cohort: their median age at baseline had been 78 (IQR 10) and their median age at first visit was 80 (IQR 10). MMSE was available in 10451 (77%) with a median of 21 (IQR 8). Visit 2 included 5246 patients with a median MMSE of 20 (IQR 10) points, while visit 3 included 2276 patients with a median MMSE of 18 (12). In preliminary analyses adjusted for age, sex and ChEI use, ChEI use at baseline was associated with higher baseline MMSE (2.5 points, confidence interval—CI 2.30-2.68). MMSE changed over time -2.7 points per year (CI -2.9 to -2.5) irrespective of treatment. ChEI were associated with less MMSE decline over time (mean difference, 0.7 more points per year (CI 0.56-0.91), compared to the rest of the cohort. Additionally, adjusted analyses and analyses taking into account ChEI type and dosage will be presented. *Conclusion:* in this large national registry based cohort, the use of ChEI at baseline was associated with less cognitive decline measured by MMSE over three years. These preliminary, age- and sex- adjusted analyses need to be confirmed in fully adjusted models, taking into account specific medications and dosages.

OC16: SELECTION OF AMYLOID POSITIVE PRE-SYMPTOMATIC SUBJECTS USING AUTOMATIC ANALYSIS OF NEUROPSYCHOLOGICAL AND MRI DATA FOR COST EFFECTIVE INCLUSION PROCEDURES IN CLINICAL TRIALS.

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Background: Drug development in Alzheimer's Disease (AD) targets mostly the mechanisms of amyloid plaques formation. AD clinical trials now aim to test such drugs in pre-symptomatic at risk subjects, thus raising the need to form cohorts of pre-symptomatic amyloid positive (Aβ+) subjects. Recruitment of such subjects is often based on the analysis of a PET scan with amyloid ligands in subjective memory complainers, with an average of only 1 of 3 subjects being amyloid positive. To reduce the cost of the recruitment procedures, we propose a pre-screening phase based on the automatic analysis of neuropsychological and structural imaging data. We propose to use machine learning techniques to identify a sub-set of subjects with a much higher prevalence of amyloid positive cases (Figure 1). This pre-selection comes with a higher number of subjects to pre-screen, but results overall in a reduction of recruitment cost. *Methods:* The prediction of Aβ+ subjects is made training a classifier, namely a Random Forest, based on socio-demographic, genetic information and cognitive assessments. The performances are measured using the area under the ROC curve (AUC) and the cost for recruiting 100 subjects. To compute the minimal cost, a value of S (number of subjects to be scanned) and R (number of subjects to be recruited) is computed for each point on the ROC curve to create a S vs R curve where each point is associated to a cost based on the hypothesis that a subject recruitment (with cognitive scores and APOE genotype) costs 100€, an MRI 400€ and a PET scan 1000€. The number and depth of the Random Forest trees are automatically tuned. Cross-validation using 50 random-splits is used, thereby guarantying that tested subjects have not been used for training. The 50 splits give 50 outcomes used to compute the average outcome, standard deviation (std), and then t-tests. We validate our method on 3 cohorts: INSIGHT, ADNI-CN, ADNI-MCI. INSIGHT is a monocentric cohort following cognitively normal (CN) subjects with a subjective memory complaint (SMC). 318 subjects with an AV45 PET scan are available. We also use 431 CN subjects and 596 MCI subjects from ADNI with amyloid status assessed by AV45 PET scan or CSF biomarkers in the absence of PET scan. Genetic (APOE alleles) and socio-demographic information (age, gender, education), and a battery of cognitive assessments are used as inputs. MRI is available for all subjects. Percentages of average cortical thicknesses in 72 regions of interest are computed using FreeSurfer. The hippocampal volume is computed using FreeSurfer for ADNI and in-house SACHA software for INSIGHT. *Results:* All validation cohorts (Table 1) show a significant cost reduction when recruiting 100 subjects ($p<0.001$). Our method combining multiple measures yields better results than using a single measure. The prediction using APOE genotype only is the best univariate one (Table 2 line 2), but yields significantly lower AUC than the multivariate model ($p<0.001$ for INSIGHT). The

neuropsychological assessments give significantly lower AUC than the selected MRI variables (Table 2 lines 1 and 3, p<0.001).

Table 1

Results on the different cohorts and comparison with the estimated initial costs for recruiting K=100 amyloid positive subjects

	Current method	Proposed method				
Dataset	Estimated current cost in €	% of AUC (std)	Subjects to be recruited	Subjects to be scanned	New cost in € (std)	Estimated savings in €
INSIGHT (27.7% Aβ+)	397,499 (N=361)	68.0 (5.4)	995	196	295,560 (58,123)	101,939
ADNI-CN (37.6% Aβ+)	292,654 (N=266)	69.1 (4.0)	599	175	234,591 (23,106)	58,063
ADNI-MCI (62.9% Aβ+)	174,828 (N=159)	83.8 (2.1)	248	111	136,205 (3,678)	38,623

Table 2

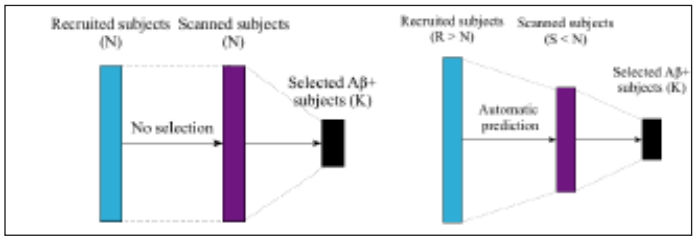
Results in different experimental conditions

	% of AUC on the INSIGHT cohort (std)	% of AUC on the ADNI-CN cohort (std)	% of AUC on the ADNI-MCI cohort (std)
Proposed approach	68.0 (5.4)	69.1 (4.0)	83.8 (2.1)
APOE	63.7 (4.6)	62.1 (3.5)	75.1 (2.9)
Using MRI	59.8 (5.0)	61.3 (4.4)	80.8 (3.2)
After correction for age	68.5 (5.0)	67.7 (3.9)	80.9 (2.4)
With longitudinal variations	NA	71.7 (8.3)	87.7 (4.8)
Learned on ADNI-CN (MRI)	57.8 (7.2)	NA	NA

The impact of longitudinal measurements is evaluated by including the rate of change of cognitive scores (using a 12-month visit) in the inputs. The results (Table 2 line 5) show an increase in the AUC for ADNI-CN (p<0.05) and for ADNI-MCI (p<0.001). The Aβ+ subjects are older than the Aβ− subjects, especially in ADNI. After correcting data values for age using linear regression, the performance of the classifier (Table 2 line 4) does not decrease significantly for ADNI-CN (p>0.05), but does for ADNI-MCI (p<0.001). The new cost for ADNI-MCI (141,221 ±4,391€) is still significantly better than the estimated recruitment cost with confirmatory PET scan for all subjects (p<0.001). Our method thus captures patterns associated with amyloid formation and not only with age as a risk factor for amyloidosis. Finally, the classifier is trained on the socio-demographic, genetic and MRI features on ADNI-CN and tested on INSIGHT (Table 2 line 6). There is a 2-point decrease in AUC compared to training on the same data, i.e. INSIGHT, which is not significant (p>0.1). Our method therefore generalizes well when the classifier is trained on one cohort and validated on an independent one. *Conclusions:* We proposed a method to automatically select pre-symptomatic subjects likely to be Aβ+ based on multimodal data analysis and machine learning techniques. It leads to a significant cost decrease when creating cohorts of such subjects, compared to the current method, consisting in scanning all potential subjects. It is also significantly better than each measure used individually. Our results are significantly better when cognitive assessments (especially their rate of change in longitudinal assessments) are used rather than MRI features. Those results might be improved by using a more extensive set of measures extracted from the images.

Figure 1

Current (left) and proposed (right) process for Aβ+ subject selection



OC17: PHYSICAL ACTIVITY AND LONGITUDINAL COGNITION: RESULTS FROM THE HARVARD AGING BRAIN STUDY. Hannah M. Klein[1], Dylan R. Kirn[1], Aaron P. Schultz[1,3], Jennifer S. Rabin[3,4], Rachel Buckley[1,3,5,6], Dorene M. Rentz[1,2], Kathyrn V. Papp[1,2], Keith A. Johnson[1,2,3], Reisa A. Sperling[1,2,3], Jasmeer P. Chhatwal[1,2,3] *((1) Department of Neurology, Massachusetts General Hospital, Boston, MA, USA; (2) Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA; (3) Harvard Medical School, Boston, MA USA; (4) Department of Psychiatry, Massachusetts General Hospital, Boston, MA USA; (5) Florey Institutes of Neurosciences and Mental Health, Melbourne, Australia; (6) Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia)*

Background: Variations in levels of physical activity (PA) have been associated with risk of cognitive impairment and progression to Alzheimer's disease (AD) dementia, with more active individuals showing less cognitive decline over time. In turn, PA may represent a potentially modifiable risk factor for cognitive impairment, especially in the earliest stages of AD. However, studies examining objectively measured PA in clinically normal (CN) older adults in relation to preclinical AD pathology show mixed results. This study was designed to investigate whether objectively measured PA can prospectively predict change in cognition in a cohort of CN older adults who have been extensively characterized with imaging biomarkers of AD. *Methods:* 217 CN older adults (mean age at baseline=73.92yrs±6.26, Female=56%, global CDR at baseline=0.0) from the Harvard Aging Brain Study (HABS) were included in this study. We defined PA as the daily mean number of steps, measured at baseline using a waistband-mounted pedometer (Omron Healthcare, Inc., Bannockburn, Illinois). Mean number of steps was log transformed to account for a positive skew. Cognition was measured using the Preclinical Alzheimer Cognitive Composite (PACC), an instrument designed to measure amyloid related cognitive decline in clinical trial settings. The PACC is a composite of WAIS-R Digit Symbol Substitution Test, Mini Mental State Exam, Free and Cued Selective Reminding Test, which included both free recall and total score indices, and Logical Memory IIADelayed Recall. PACC scores were calculated annually for 2-6 years in our participants (median followup of 4 years). Linear regression was used to assess cross sectional relationships between PA and PACC scores at study entry. Longitudinal relationships between PA on PACC decline were assessed using two linear mixed effects models. The first model included age, sex, and years of education as covariates, and the second model additionally co-varied for a suite of AD imaging biomarkers, including cortical white matter hyperintensities (WMH), measured with T2-weighted magnetic resonance imaging (MRI), bilateral hippocampal volume (HV) from MRI, 18F fluorodeoxyglucose positron emission tomography (FDG-PET) in AD vulnerable regions, and a measure of global Aβ burden using an aggregate of frontal, lateral and retrosplenial (FLR) regions from 11C Pittsburgh compound

B (PiB)-PET. A post-hoc analysis dichotomized amyloid status according to a published cut-off (high Aβ burden: distribution volume ratio (DVR) >1.2) to determine if effects were differential with respect to high or low amyloid burden. *Results:* No significant cross-sectional relationship between PA and the PACC was observed (r = 0.068, p = 0.320). There was a relationship between baseline PA and longitudinal change in PACC when adjusting for age, sex and years of education (t(832) =3.20, p=0.001), with greater PA predicting less decline. The relationship between PA and PACC decline remained quite similar even after adjusting for amyloid burden, WMH, HV, and FDG-PET (t(813)=3.23, p=0.001). Using a previously derived cutoff for amyloid status, we observed that PA was significantly predictive of cognitive decline in high Aβ participants (t(216) = 3.01, p = 0.003) but not in low Aβ HABS participants (t(588) = 1.46, p=0.144). *Conclusion:* We observed a significant relationship between objectively measured PA and longitudinal change in cognition. Interestingly, this relationship was essentially unchanged when simultaneously controlling for WMH, HV, FDG-PET, and Aβ burden, suggesting that PA measurements may provide unique information regarding cognitive decline that does not overlap with these core AD biomarkers. These findings support the inclusion of objective PA measures in AD clinical research, and perhaps in stratification for risk of cognitive decline.

OC18: VALIDATION OF TAU PET IMAGING IN ALZHEIMER'S DISEASE AND OTHER TAUOPATHIES.

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Background: Several tau PET ligands including 18F-AV1451 are available that can detect tau aggregates in vivo. Visualization of regional deposition of tau aggregates might improve the diagnostic work-up of Alzheimer's disease (AD) and other tauopathies, including progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and patients with MAPT mutations. Tau PET imaging might also be used to study the regional spread of tau pathology in both observational cohort studies as well as when evaluatng the effects of disease-modifying therapies. *Methods:* We used 18F-AV1451 PET to examine ca 260 cases from the Swedish BioFINDER study, including healthy controls, patients with AD, PSP, CBD, as well as MAPT R406W mutation carriers. Scans were performed 80-120 min post injection of 18F-AV1451, except in a subcohort of cases (n=15) where we performed dynamic scans over 180 min together with arterial blood sampling. *Results:* Using an arterial input functions, the Logan graphical analysis provides the best estimate of tau binding. Assuming that cerebellum is a valid reference region, simplified methods such as the Logan reference plot with 100 min scan time seem to provide robust alternatives for quantification (R^2=0.91). Furthermore, SUV ratios between target and cerebellar uptake obtained from a 80-100 min static scan offer promising potential for clinical routine application (R^2=0.93). In patients with AD, we observed robust retention of 18F-AV1451 in the temporoparietal cortex. The regional 18F-AV-1451 uptake was markedly elevated in AD dementia, and moderately elevated in prodromal AD. Retention of 18F-AV-1451 (in a priori specified regions selected for known associations with tau pathology in AD) had very high diagnostic accuracy for AD (area under the receiver operating characteristics curve, AUROC, ~100%), and was significantly better than CSF T-tau (92.9%), CSF P-tau (92.8%), hippocampal volume (93.0%) and temporal cortical thickness (90.3%). For prodromal AD, there were no significant AUROC differences between cerebrospinal fluid tau, 18F-AV-1451, and MRI measures (84.3-94.0%). These results support a model where CSF tau and 18F-AV-1451 have equal accuracy in early stages of AD, but 18F-AV-1451 is superior in the dementia stage, and exhibits close to ideal diagnostic accuracy for mild to moderate AD. Further, we studied the associations between CSF tau and 18F-AV-1451 retention. We found that CSF T-tau and P-tau were highly correlated (R=0.92, p<0.001), but they were only moderately associated with retention of the tau PET ligand 18F-AV-1451, and mainly in demented AD patients. 18F-AV-1451 retention, but not CSF T-tau or P-tau, was strongly associated with medial temporal lobe atrophy and cognitive impairment. CSF T-tau was increased in many preclinical AD cases who yet had normal tau PET scans. However, not all dementia AD patients exhibited increased CSF T-tau or P-tau, even though 18F-AV-1451 retention was always increased at this disease stage. We conclude that CSF T-tau and P-tau mainly behave as "disease state markers", since they appear to be increased in many AD cases at all disease stages, already before the emergence of tau aggregates. In contrast, 18F-AV-1451 is a "disease stage marker", which is increased primarily in clinical stages of the disease, and is associated with both brain atrophy and cognitive dysfunction. Next, we studied whether the uptake of 18F-AV-1451 differs between early-onset AD (EOAD) and late-onset AD (LOAD). Comparing EOAD with controls resulted in significantly higher 18F-AV-1451 retention throughout the neocortex, while comparing LOAD with controls yielded a distinct pattern of higher 18F-AV-1451 retention predominantly confined to temporal lobe regions. When compared against each other, the EOAD group exhibited greater uptake than LOAD in prefrontal and premotor, as well as in inferior parietal cortex. These findings indicate that age constitutes an important contributor to Alzheimer's disease heterogeneity highlighting the potential of tau PET for capturing phenotypic variation across Alzheimer's disease patients. In patients with MAPT R406W mutations we found that the tau pathology starts in the hippocampus and adjacent temporal lobe regions, correlating with glucose hypometabolism in corresponding regions. Later in the disease, the basal ganglia and frontal lobe were affected. Post mortem examination of one case that had been examined with PET two weeks antemortem provided strong evidence that 18F-AV-1451 PET can be used to accurately quantify in vivo the regional distribution of neurofibrillary tangles. In cases with CBS we observed an asymmetry in the uptake of 18F-AV-1451 in the sensorymotor cortex, corticospinal tract and basal ganglia on the affected side, which is clearly different from the patterns observed in AD or other tauopathies. In patients with PSP we did not find any significant uptake in cortical regions, but increased uptake in the basal ganglia correlating with disease severity. However, age-dependent "off-target" binding of 18F-AV-1451 in the basal ganglia of many cases, including healthy controls, makes the clinical relevance of this finding less obvious, and we found no correlation with tau aggregates measured using immunohistochemistry post mortem. *Conclusions:* 18F-AV1451 PET can accurately determine the amount of tau aggregates found in AD as well as in MAPT R406W mutations carriers, which was confirmed using neuropathology. The diagnostic accuracy of 18F-AV-1451 for AD dementia is exceptionally high. The pattern of tau pathology differs between early- and late-onset AD. Patients with CBS exhibit a weak, yet specific, pattern of 18F-AV1451 uptake.

OC19: TOMMORROW: A TRIAL TO DELAY THE ONSET OF MCI DUE TO AD AND QUALIFY A UNIQUE GENETIC ALGORITHM BIOMARKER: STUDY UPDATE. Kathleen A. Welsh-Bohmer[1], Brenda L. Plassman[1], Carl Chiang[2], Meredith Culp[3], Patrick Harrigan[3], Janet O'Neil[3], Ryan Walter[3], Stephen Haneline[2], Julian Arbuckle[2], Shyama Brewster[2], Yuka Maruyama[2], Tom Swanson[2], Dominic Fitzsimmons[3], Alexandria S. Atkins[4], Sarah Powell[4], Richard Keefe[4], Craig Metz[2], Deborah Yarbrough[3], Daniel K. Burns[2], Ann M. Saunders[2], Ferenc Martenyi[3] for the TOMMORROW study investigators *((1) Department of Psychiatry & Neurology, Duke University, Durham NC, USA; (2) Zinfandel Pharmaceuticals, Inc., Chapel Hill NC, USA; (3) Takeda Development Center Americas, Inc., Deerfield, IL, USA; (4) NeuroCog Trials, Durham, NC, USA)*

Background: The TOMMORROW trial (NCT01931566) is a Phase 3 global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that is designed to accomplish two objectives simultaneously: 1) To qualify and determine the utility of a biomarker risk assignment algorithm (BRAA) based on apolipoprotein E (APOE) genotype, genetic variation at translocase of outer mitochondrial membrane 40 homolog (TOMM40), and age in predicting the near-term risk for development of mild cognitive impairment (MCI) due to Alzheimer's disease (AD), and 2) To evaluate the efficacy of pioglitazone 0.8 mg SR to delay the onset of MCI due to AD (MCI-AD) in cognitively normal subjects at high risk. A key secondary endpoint is cognitive decline from baseline, which uses a neuropsychological composite measure based on a broad neurocognitive test battery. *Methods:* Takeda Pharmaceuticals and Zinfandel Pharmaceuticals began design of TOMMORROW in 2010 with input from a neuropsychology advisory board, engaged to operationalize the primary endpoint event (MCI-AD) and to select a neuropsychological battery appropriate for use throughout the preclinical to MCI stages of AD. Genetic sampling for the BRAA was collected at screening. A small group of approximately 300 low-risk subjects meeting inclusion criteria was randomized to placebo; high-risk subjects were evenly randomized to either pioglitazone 0.8 mg SR or placebo. All subjects are followed at 6-month intervals over approximately 5 years, which is the estimated time needed for 202 events of incident MCI-AD or AD dementia to occur. Diagnoses of MCI-AD require confirmation across consecutive visits 6 months apart and are affirmed by an independent adjudication panel of dementia experts. *Results:* The study started screening potential subjects in August 2013, and enrollment was completed in December 2015. A total of 4856 individuals underwent baseline evaluations: there were 1362 baseline failures, resulting in a total of 3494 cognitively healthy subjects between 65 and 83 years of age (Clinical Dementia Rating Scale = 0) being randomized into the study. The study continues to follow all randomized participants every 6 months. Study procedures occur in the clinic, with project partners queried on site, in exceptional cases in the home, or by telephone. On April 3, 2017, the planned blinded operational futility analysis was conducted to assess the actual event accrual rate versus that modeled for the study design. Findings indicated that incident MCI-AD is broadly on target with projections for this point in the trial. This provides support that the study population has been enriched by the BRAA for subjects at near-term risk for development of MCI-AD. Early terminations have been staying within projections. To facilitate retention, the study has implemented a number of unique practices focused on maintaining an optimal "partnership" between the participants and the sites. The study continues to follow participants per the protocol, with a planned efficacy futility analysis expected to occur as early as Q4 of this year. *Conclusion:* Participants in the TOMMORROW study have now been followed for at least 1.5 years with detailed neuropsychological testing. The study, if it successfully passes the efficacy futility analysis, will continue to follow participants for at least another 2 years until the total number of events is achieved. If the low-dose pioglitazone proves effective at the trial conclusion, this finding would provide clinicians with a potential therapeutic avenue to delay MCI-AD symptoms within vulnerable patient groups. Further, if the genetic algorithm is validated within the TOMMORROW trial design, this would offer a strategy for identifying individuals at the higher imminent risk of developing symptomatic MCI-AD within a 3¬–5 year window. Regardless of the trial outcomes, the experience from the TOMMORROW study, with its comprehensive battery of neuropsychological tests, will provide valuable insights into the characteristics of emerging MCI-AD in high-risk populations. The results may also facilitate future efforts in designing efficient cognitive endpoints for subsequent studies along the pre-dementia AD continuum.

OC20: EMERGING PLASMA-BASED THERAPIES FOR AD. Montserrat Costa[1], Raquel Horrillo[1], Ana M Ortiz[1], Alba Pérez[1], Laura Núñez[2], Antonio Páez[2], Mercè Boada[3], Agustín Ruiz[3], Salvador Grancha[1] *((1) Research & Development, Grifols Bioscience Industrial Group, Parets del Vallès, Spain; (2) Clinical Operations Department. Grifols Bioscience Industrial Group, Sant Cugat del Vallès, Spain; (3) Memory Clinic of Fundació ACE. Institut Català de Neurociències Aplicades, Barcelona, Spain)*

Background: There is increasing interest in the therapeutic potential of plasma-based interventions for Alzheimer's disease (AD). A myriad of humoral factors are being studied as possible treatments for AD, including many known modulators of inflammation, oxidative stress and protein misfolding. A new approach directly applicable to clinical practice is plasma exchange with therapeutic albumin replacement (PE-A). Clinical trials using PE-A have been conducted for some time in AD patients. Grifols (Boada et al, 2009) first proposed it as a method of fostering brain amyloid clearance through peripheral sink mechanisms. A preliminary Phase I study showed that PE-A was able to induce alterations in the Aβ mobilization and that cognitive scores were more stable than expected. In a follow-up double blind Phase II RCT (NCT00742417), positive clinical outcomes were observed and cerebrospinal fluid (CSF) and plasma beta-amyloid protein 1–42 (Aβ1-42) levels were modified (Boada et al, 2017). Currently, a large scale Phase IIB/III study (AMBAR Trial, NCT01561053) to assess the efficacy of PE-A in patients with mild to moderate AD as well as to provide additional information on possible mechanisms of action of this intervention, is underway. *Methods:* Plasma and CSF samples of AD patients from the multicenter, randomized, patientand rater-blind, controlled Phase II RCT were analyzed with regard to albumin characterization in comparison to age-matched healthy subjects (controls), by means of different chromatographic, spectrometric and enzymatic techniques. *Results:* Different clinical and non-clinical results obtained along Phase II RCT, including Aβ mobilization will be reviewed. Importantly, the analysis of baseline samples evidenced molecular modifications in albumin from AD patients in comparison to age-matched healthy controls. Profound alterations in the redox state of CSF albumin and in the CSF to plasma ratio of reduced albumin were identified as well as differences in glycated albumin forms. The analysis of the above mentioned albumin modifications in samples collected along treatment showed some transient modifications linked to the treatment received based on PE-A. *Conclusions:* Albumin is the most prevalent protein in blood and CSF as well as the body's major extracellular anti-oxidant protein. Non-clinical studies provided new clues on the potential involvement of albumin in the outcome of the above mentioned Phase II RTC. The path to explore new targets and mechanisms of action of plasma-based therapies for AD is thus open.

OC21: COGNITIVE RUN-IN PERIODS FOR AMYLOID-POSITIVE ENRICHED SECONDARY PREVENTION TRIALS.
Andrew J. Aschenbrenner[1], Jason Hassenstab[1,2], Eric McDade[1], Guoqiao Wang[3], Tammie L.S. Benzinger[4], Randall J. Bateman[1], John C. Morris[1] *((1) Department of Neurology, Washington University in St. Louis; (2) Department of Psychological and Brain Sciences, Washington University in St. Louis; (3) Department of Biostatistics, Washington University in St. Louis; (4) Department of Radiology, Washington University in St. Louis)*

Background: The primary endpoint for Alzheimer's disease (AD) secondary prevention trials is a slowing in the rate of cognitive decline from baseline. In the preclinical stages of AD, declines in cognition are by definition subtle and many of the measures most sensitive to the earliest declines also demonstrate high levels of day to day variability and can have substantial retest effects. Thus, the degree to which the baseline cognitive assessment represents a reliable measure of the true abilities of participants is essential to accurately evaluate the effectiveness of therapies and can have significant impacts on statistical power. One method to ameliorate these sources of variability and increase power is to include additional cognitive assessments during a pre-randomization "run-in" period, which serves to stabilize estimates of subject-specific performance thereby increasing power. Several current secondary prevention efforts, including the European Prevention of Alzheimer's Dementia Consortium (EPAD), the Global Alzheimer's Platform (GAP), and the Dominantly-Inherited Alzheimer Network-Trials Unit (DIAN-TU), have affiliated cohorts that collect longitudinal clinical, cognitive, and biomarker data that can be used to establish a run-in period prior to randomization. We have previously reported that including a cognitive run-in period can increase power by 5-10% (Hassenstab et al., CTAD 2015), however these analyses included no biomarker information and therefore included individuals who are unlikely to be enrolled in AD secondary prevention trials. The aim of this study is to evaluate the utility of including "run-in" data from amyloid-positive (Aβ+, as determined by amyloid PET scans at baseline) older adults to determine if a cognitive run-in period enhances the statistical power of a trial, and if so, to determine the optimal parameters for the run-in period that result in increases in statistical power with minimal impacts on overall trial duration. *Methods:* Data from ongoing longitudinal studies of normal aging and dementia at the Knight Alzheimer's Disease Research Center at Washington University in St. Louis were used in these analyses. Participants were aged 65 and older at baseline and required to have at least three (and up to six) clinical and cognitive assessments administered at approximately yearly intervals as well as at least one amyloid PET scan (either Pittsburgh Compound B or Florbetapir). Established SUVR cutoff scores were used to eliminate individuals who did not have substantial amyloid accumulation, leaving 103 participants available for analysis. Linear mixed effects models were constructed to analyze the rate of decline on a cognitive composite score comprised of tests of episodic memory, processing speed, and executive function. From the six available time points, a four-year trial was simulated by using the participant's second visit as the randomization visit and the first visit as a pre-randomization run-in visit. Performance from the run-in assessment was included as a covariate in the mixed effects model. The first visit was never included as part of the simulated trial itself. Parameter estimates from this model were bootstrapped and fed through power analysis to determine the minimum sample size and confidence interval (CI) needed to detect a treatment effect of arbitrary magnitude with and without including the run-in period. Comparable analyses were conducted on three-year trials. Results are expressed as a proportional reduction in sample size necessary to detect a treatment effect after including the run-in data relative to a "no run-in data" control condition. *Results:* For a trial of amyloid-positive older adults with four years of active treatment, the inclusion of a one year pre-randomization run-in period reduced the required sample size to detect a 50% treatment effect with 80% power by 16% (bootstrapped CI = 12 to 21%). If the same trial was reduced to three years of active treatment, the sample size savings increased to 18% (CI = 9 to 26%). In all cases, the addition of run-in periods that increased the total duration of the trial reduced sample size requirements. However, as expected, if the total active treatment period (i.e., no run-in and 4 years active treatment) was equal to the run-in period plus the active treatment (i.e., 1 year run-in plus 3 years active treatment), including run-in conferred no benefit. Additional analyses will be presented that describe the optimal assessment frequency and length of run-in periods needed to maximize statistical power. *Conclusion:* Among participants who are most likely to be enrolled in secondary prevention AD clinical trials, including a one year cognitive run-in period can produce sample size savings of approximately 16-18% for a trial with 3 or 4 years of active treatment, respectively. These benefits were always outweighed by a longer active trial duration, suggesting that when possible, longer overall treatment durations are preferable to trials with run-in and shorter treatment duration. However, for trials that can readily utilize "trial-ready" cohort registries such as EPAD, GAP, and DIAN-TU, inclusion of run-in data markedly improves statistical power and may have several additional advantages including increasing participant engagement and compliance and reducing the influence of retest effects on cognitive outcomes. Funding: This research was supported by grants P50-AG05681, P01-AG03991 and P01-AG26276.

OC22: EIGEN COMBINATIONS OF COGNITION AND BIOMARKERS TO MINIMIZE THE SAMPLE SIZES IN PREVENTION TRIALS ON ALZHEIMER DISEASE.
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Background: Prevention trials in Alzheimer disease (AD) are routinely designed by powering the primary efficacy analysis on a cognitive endpoint, usually an equally weighted composite from several cognitive domains. The subtle annual cognitive progression among cognitively normal individuals at the preclinical stage of AD, however, implies that a huge sample size is likely required to power such trials. On the other hand, the rates of biomarker progression may be more pronounced and with lower variance of measurement at the preclinical stage of AD, and may jointly provide adequate power to prevention trials when optimally combined with cognitive endpoints. *Methods:* Longitudinal CSF samples and MRI and PET amyloid scans, as well as cognitive assessments over a mean follow-up period of 3 years (SD=1.12 yrs; range 1.01 to 6.25 years) were obtained from 69 cognitively normal (Clinical Dementia Rating [CDR] 0) individuals who were carriers of mutations in one of the three genes (the amyloid precursor protein, presenilin 1, and presenilin 2) from the Dominantly Inherited Alzheimer Network (DIAN), an international family-clustered registry of autosomal dominant

Alzheimer disease (ADAD). Bivariate random intercept and random slope models were used to jointly model the rates of longitudinal change on a cognitive composite and each of the main AD biomarkers: CSF β-Amyloid (1-42) (Abeta42), CSF Total-Tau (Tau), PET PIB mean cortical uptake, and MRI hippocampal volume. The cognitive composite was derived as the average of the 4 z-scores from the Mini Mental State Examination, Wechsler Adult Intelligence Scale Digit Symbol Substitution Test, Wechsler Memory Scale-Revised Logical Memory Delayed Recall, and DIAN Word List Delayed Recall. The estimated rates of changes, along with the estimated covariance matrix between them, were then used to estimate the optimum weights of the cognitive composite and the biomarker. The resulting eigen combination was further analyzed to estimate the rate of longitudinal change as well as the associated variation. These estimates were finally used to project the sample sizes required for the trial, which were also compared to results when only cognition was used in the power analyses. *Results:* At the time of baseline cognitive and biomarker assessments, the ADAD cohort had a mean age of 36.14 yrs (SD=9.23 yrs; range: 18 to 61 years). Compared to individuals' expected age of symptom onset, the baseline age was on average 11.52 years younger (the difference (i.e., individuals' age-expected age of onset) ranged from -30.2 yrs to 7.57 yrs). The estimated annual rate of change was -0.04286 (SE=0.01890, t=-2.27) for the cognitive composite, -15.0993 pg/mL (SE=6.0788 pg/mL, t=-2.48) for CSF Abeta42, 0.06378 (SE=0.01288, t=4.95) for mean cortical PIB uptake, 3.0781 pg/mL (SE=1.1222, t=2.74) for CSF total Tau, and -50.9468 mm^3 (SE=534.23mm^3, t=-0.10) for total hippocampal volume. When combining the cognitive composite with CSF Abeta42 on the z-scores, the estimated annual rate of change was -0.2443 (SE=0.06356, t=-3.84). When combining the cognitive composite with CSF Tau, the estimated annual rate of change was -0.1581 (SE=0.05086, t=-3.11). When combining the cognitive composite with MRI hippocampal volume, the estimated annual rate of change was -0.08001 (SE=0.03096, t=-2.58). When combining the cognitive composite with PET PIB mean cortical uptake, the estimated annual rate of change was –0.09979 (SE=0.02013, t=-4.96). Interestingly, in most cases, these optimum eigen combinations weigh more heavily on the cognition than on the biomarkers. For example, when the cognition and CSF Abeta42 were combined, the optimum weight for cognition is 2.5696186, whereas the weight for CSF Abeta is only 0.4388932. Assuming a future hypothetical prevention trial of 3 years in ADAD with annual assessments and a 1:1 sample size ratio between the active therapy and the placebo arms and 80% power, using the cognitive endpoint alone, 1506 subjects are needed to detect a 50% effect size (improvement on the rate of change as compared to the placebo). When the cognitive endpoint and CSF tau are combined, 348 subjects are needed to detect a 50% effect size. When the cognitive endpoint and CSF Abeta42 are combined, 210 subjects are needed to detect a 50% effect size. When the cognitive endpoint and MRI hippocampal volume are combined, 1064 subjects are needed to detect a 50% effect size. When the cognitive endpoint and PIB PET uptake are combined, 246 subjects are needed to detect a 50% effect size. *Conclusions:* Clinical and cognitive primary endpoints are routinely used to design prevention trials in AD, however, our results show that cognitive endpoints with biomarkers may provide more power for these trials. Utilizing the eigen combinations of cognition and well established CSF and imaging biomarkers dramatically reduce the required sample sizes of these trials, and increase feasibility. Acknowledgements: This study was funded by the National Institutes on Aging grants U19 AG032438, U01AG042791, R01AG046179, R56 AG053267, and 5P01AG003991, P50AG005681, and 2P01AG026276.

OC23: THE ALZHEIMER'S PREVENTION REGISTRY AND GENEMATCH: ACCELERATING RECRUITMENT AND ENROLLMENT INTO ALZHEIMER'S STUDIES. Jessica B. Langbaum, Nellie High, David Gordon, Jodie Nichols, Trisha Walsh, Eric M. Reiman, Pierre N. Tariot *(Banner Alzheimer's Institute, Phoenix, AZ, USA)*

Background: With heightened urgency, considerable effort, attention and funding have been focused on accelerating efforts to prevent and treat Alzheimer's disease (AD). As a result, a growing number of studies have been launched or are in various stages of planning, but a daunting challenge is finding enough participants to fill these studies. As the field shifts its emphasis from recruiting symptomatic patients for treatment studies to recruiting cognitively unimpaired healthy adults for prevention trials, it is imperative that we understand how to recruit, engage and retain large numbers study participants effectively and efficiently. This recruitment need is both new and challenging, since the prospective volunteers are not seeking care. The Alzheimer's Prevention Initiative (API) is a collaborative program conducting preclinical AD trials in people who, based on age and genetic makeup, are at elevated risk of developing AD symptoms. To support API as well as other studies, we developed the web-based Alzheimer's Prevention Registry ("Registry") and GeneMatch programs to provide resources to the AD scientific community, aiming to accelerate recruitment and enrollment into studies and to complement local efforts. *Methods:* Adults age 18+ are eligible to join the Registry at www.endALZnow.org. At enrollment, individuals provide their name, email address, zip/postal code and year of birth; after enrollment they provide additional demographic information at their convenience and discretion. GeneMatch is a US-based, trial-independent program of the Registry, performing APOE genotyping in US-based cognitively unimpaired individuals ages 55-75 in order to enrich referrals to prevention studies. Buccal swabs are sent to participants' homes or distributed at partner sites after online enrollment and consent at www.endALZnow.org/genematch. Although GeneMatch does not disclose APOE results to participants directly or inadvertently through invitations to studies, recruiting studies may require individuals to learn their results. A variety of local and online outreach and awareness tactics are used to expand enrollment into the Registry and GeneMatch programs. Enrollees in both programs receive email communication for engagement and retention purposes and are notified when study opportunities become available. A/B testing is used to refine messaging and improve website experience. *Results:* The Registry launched in May 2012; as of May 2017, over 272,000 have joined. Of the members who have provided optional demographic information, the mean age is 60.2 years (SD 12.2), 81% are female, 76% have a family history of AD/dementia, and 95% self-report being cognitively unimpaired. Approximately 32% of Registry members are actively engaged, defined as having opened a Registry-related email within the past 4-months; email open rates within the past twelve months of 35-50%, mean 43% (compared to the nonprofit healthcare industry average of 16%), email click rates were 3.3%-12.0%, mean 7.0% (compared to the industry average of 1.6%). As of May 2017, the Registry was actively recruiting for 36 AD studies. GeneMatch launched in pilot phase in November 2015, full launch was in August 2016. When GeneMatch was first launched participants were required to watch an informational video as part of their enrollment process, this was modified in November 2016 to allow participants to watch the video or read a bulleted summary of the video. This modification was associated with a 25% increase in enrollment completion for individuals who started the registration process. As of May 2017, more than 39,000 individuals have joined; 70% of enrollees completed their cheek swab kit within

90 days. Online advertising has been the most successful mechanism to increase enrollment into GeneMatch, followed by local community events and talks at partner sites. Approximately 4.2% of GeneMatch members age 55-59 are APOE ε4/ε4, compared to 3.6% and 2.8% in the 60-64 and 65-75 year age groups, respectively. In July 2016, GeneMatch began inviting a ratio of APOE4 homozygotes: non-homozygotes to the API Generation Study 1 as study sites became active in a given geographic area (the ratio is necessary so that the act of receiving an invitation to the study does not disclose APOE test results). As of May 2017, 728 GeneMatch members have been invited to participate in the API Generation Study 1, with acceptance rates within 90 days ranging from 50-60%. *Conclusion:* The Registry and GeneMatch are key elements of the API, facilitating enrollment into multiple studies. Both programs have been well-received and enrollment into each continues to increase. We are exploring novel approaches for increasing enrollment and engagement of enrollees in both programs, and collaborating with researchers and sponsors to help promote studies in their communities. We anticipate expanding the enrollment age range for GeneMatch to accommodate studies recruiting participants younger than age 55 or older than age 75.

OC24: AN EXAMINATION OF RATE OF DECLINE AS AN ALTERNATIVE TO CHANGE FROM BASELINE. Howard Mackey[1], Nan Hu[1], Michael Ahmadi[2], Yinghua Chen[2], Pierre Tariot[2], Eric M Reiman[2], Francisco Lopera[3], Kewei Chen[2], Ronald Thomas[4] *((1) Genentech, Inc., South San Francisco, CA, USA; (2) Banner Alzheimer's Institute, Phoenix, AZ, USA; (3) Universidad de Antioquia, Medellín, Colombia; (4) UC San Diego Department of Neurosciences, CA, USA)*

Backgrounds: Pivotal studies in Alzheimer's disease (AD) typically enroll hundreds to a thousand or more patients followed for at least 1.5 years. Resources required to execute such trials are considerable, which heightens the importance of efficiency in trial design and in the use of powerful statistical methods. The standard summary measure of efficacy in AD trials is a comparison of the change from baseline between the control and treatment groups at a specific landmark in time. Estimation is usually carried out using a Mixed Model for Repeated Measures (MMRM). While this approach has merits, the interpretability of this summary measure is limited to one specific point in time and does not summarize the treatment effect over the duration of the trial. In addition, alternative approaches may be more powerful in testing for treatment effects. *Methods:* We explore the rate of decline summary measure as an alternative to change from baseline. Approaches for testing the effect of treatment on the rate of decline have been described previously in AD (1–3). Here, we explore the use of a Random Coefficient Regression Model (RCRM) for hypothesis testing and estimation of a treatment's effect on rate of decline. The RCRM has been used in clinical trials in other disease settings leading to health authority approval (4). We investigate power comparisons between change from baseline via MMRM and rate of decline via RCRM under two important scenarios. *Results:* If rates of decline are constant during the course of a trial, a hypothesis test of the rate of decline via the RCRM approach is shown to be significantly more powerful than a hypothesis test of change from baseline via MMRM under certain scenarios. Power benefits are fueled by multiple sources and can be further boosted by optimization of measurement timing as well as from using data after the change from baseline landmark. Power improvements are similarly shown in an increasing rate of decline model. We further illustrate the potential benefits of the RCRM approach using longitudinal data from cognitively unimpaired 30–60 year old PSEN1 E280A mutation carriers from the world's largest autosomal dominant AD (ADAD) kindred with up to 20 years of follow-up (5). *Conclusion:* The rate of decline summary measure estimated via RCRM yields substantial improvements in power under a range of conditions and may be a viable alternative to MMRM in clinical trials of AD. (1) Doody RS et al. N Engl J Med 2014;370:311-21; (2) Thomas RG et al. Alzheimers Dement 2016;12:598-603; (3) Bateman RJ et al. Alzheimers Dement 2017;13:8–19; (4) Richeldi L et al. N Engl J Med. 2014;370:2071–82; (5) Silvia Rios-Romenets et al. AAIC 2017

OC25: THE SAFETY AND EFFICACY OF EDONERPIC (T-817) IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE. Lon S. Schneider[1], Ronald G. Thomas[2], James Brewer[2], Suzanne Hendrix[3], Robert Rissman[2], David Salmon[2], Hiroshi Kobayashi[4], Howard Feldman[2] for the ADCS TCAD group *((1) Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA; (2) University of California, San Diego, CA, USA; (3) Pentara Corporation, Salt Lake City, UT, USA; (4) Toyama Chemical, Ltd, Tokyo, Japan)*

Background: Edonerpic (T-817; 1-{3-[2-(1-benzothiophen-5-yl) ethoxy]propyl}azetidin-3-ol maleate, Toyama Chemical, Ltd) was developed as a neuroprotective agent that protects against Aβ42-induced toxicity and memory deficits. It promotes cortical and hippocampal neuron outgrowth, and preserves hippocampal synapses and spatial memory in tau transgenic mice. This may be through sigma receptor activation or through the inhibition of microglia CD33 receptor function (Quinti L, Forte AM, Kim DY, Griciuc A, Tanzi RE, 2017). An early phase 2a trial demonstrated safety, a trend for efficacy, especially in patients with MMSE less than 21 (Schneider et al 2012). The primary objective of this phase 2 trial was to assess the efficacy and safety of higher doses of edonerpic in mild to moderate Alzheimer's disease (NCT 02079909). *Methods:* Outpatients, ages 55 to 85, meeting criteria for probable AD, MMSE 12-22, taking stable doses of donepezil or rivastigmine, and who may or may not be taking memantine, were randomly assigned (1:1:1) to placebo, 224 mg, or 448 mg of T-817 once per day for 52 weeks. The primary outcomes were the ADAScog and ADCS-CGIC (CIBIC+) at week 52. Secondary outcomes were the MMSE, ADCS-ADL, FAQ, and NPI at week 52; and the outcomes at weeks 12, 24, 36, and 44. Biomarkers were MRI whole brain, lateral ventricular, and hippocampal volumes; and CSF Aβ40, 42, t-tau, and p-tau; and population pharmacokinetics. *Results:* The trial was conducted by the ADCS from June 2014 to December 2016 at 52 US sites.140 of 158 (88.6%) participants assigned to placebo, 117 of 166 (70.5%) to 224mg, and 120 of 158 (75.9%) to 448mg completed the trial. The LS mean ADAScog change was 7.9, 7.5, and 7.1 for the placebo, 224 mg, and 448mg groups, respectively. The difference between placebo and 448mg at week 52 was -0.8 (95% CI: -2.8, 1.1; P=0.3919). Mean ADCS-CGIC scores were 5.2, 5.2, and 5.3 with a maximum difference of 0.04 (95% CI: -0.19, 0.26; P=0.7588). There were no significant differences for the secondary outcomes. For exploratory biomarkers, p-tau was nominally significantly lower in the 448mg group vs. placebo (N=24 and N=18, P=0.0338); and hippocampal volumes decreased less in the 224mg group than placebo (N=79 and N=89; -0.27 vs. -0.39 mL, P=0.0106) but not in the 448mg group (N= 76; -0.31 vs. -0.39 mL, P=0.0996). Post hoc subgroup analyses suggested that shorter duration of illness and symptoms and the non-use of memantine were associated with better ADAScog outcomes. 4.4%, 13.9% and 14.6% participants receiving placebo, 224 mg, and 448 mg, respectively, discontinued because of adverse events. The most frequent AEs ≥ 5% were diarrhea (12.7%, 20.5%, 31.0%), nausea (3.8%, 7.8%, 5.7%). Infections, injuries, falls, agitation and anxiety were more common with placebo. *Conclusion:* In this phase 2 proof of concept trial edonerpic appeared

safe, tolerable, with the previously expected GI symptoms occurring early. There was no evidence for clinical effect in the protocol-specified primary and secondary outcomes. The potential effects of decreased CSF p-tau, hippocampal volumes, illness duration, and co-medications require further examination and confirmation

OC26: SAFETY OF AND TOLERABILITY OF GANTENERUMAB IN THE OPEN-LABEL EXTENSION OF SCARLET ROAD TRIAL, A GLOBAL STUDY IN PATIENTS WITH PRODROMAL DISEASE. Mirjana Andjelkovic[1], Danielle Abi-Saab[1], Nathalie Pross[1], Paul Delmar[1], Nicola Voyle[2], Michaela Mertes[1], Smiljana Ristic[1] *((1) Hoffman LaRoche, Basel, Switzerland; (2) Roche Products Limited, Welwyn, UK)*

Background: Gantenerumab is a fully human, anti-amyloid beta (Aβ) monoclonal antibody (mAb) that binds aggregated Aβ and promotes amyloid removal by Fc-gamma receptor mediated microglial phagocytosis. SCarlet RoAD (NCT01224106), was a multicenter, randomized, double-blind (DB), placebo-controlled, 2-year study which evaluated the effect of gantenerumab on cognition and function in a prodromal amnestic Alzheimer's disease (AD) population with confirmed amyloid pathology. Patients were randomized to monthly subcutaneous (SC) injections of placebo, or 105 mg or 225 mg gantenerumab, depending on their APOE4 genotype (patients with 2ε4 genotype could not receive 225 mg gantenerumab). Dosing in SCarlet RoAD was suspended in December 2014 following a pre-planned futility analysis. Gantenerumab was safe and well tolerated with amyloid-related imaging abnormalities (ARIA) and injection-site erythema being the most common adverse reactions. Although no treatment effect was detected on the clinical scores, a dose-dependent effect on cerebrospinal fluid biomarkers of neurodegeneration was observed and additional exploratory analyses showed an exposure-dependent effect on brain amyloid, and clinical benefit in patients predicted to progress at a faster rate. Based on these observations, SCarlet RoAD and another ongoing global study in mild patients (Marguerite RoAD; NCT02051608), were converted to open-label extensions (OLEs) with the primary objective to evaluate the safety and tolerability of higher doses of gantenerumab (up to 1200 mg SC every 4 weeks) administered at different titration schedules. Here, we present initial findings from the ongoing SCarlet RoAD OLE. *Methods:* The global DB study enrolled 799 patients and 797 were dosed. Subsequent to DB treatment suspension, patients entered a follow-up treatment-free period. Patients were eligible for a 3-year OLE if they had at least one follow-up visit, did not have recurrent vasogenic edemas (amyloid-related imaging abnormalities [ARIA]-E) during DB treatment, more than 4 and 5 cerebral microhemorrhage/superficial hemosiderosis (ARIA-H) at the start of the OLE on a 1.5 Tesla and 3 Tesla MRI scanner, respectively, or any serious medical condition potentially precluding patient's safe participation. The target dose of 1200 mg and the safety and efficacy of the titration schedules to target dose were modelled based on results from several studies with a similar mAb targeting aggregated Aβ. To minimize the incidence of MRI findings, the dose of open-label gantenerumab was increased gradually. Patients were assigned to a fast or slow titration scheme based on their APOE4 genotype and their last DB dose. An MRI was obtained prior to each up-titration to ensure absence of significant MRI findings including ARIA. In case of significant ARIA-E findings, dosing was temporarily withheld and monthly MRI monitoring was instated until ARIA resolution. Study treatment could be modified or discontinued based on the protocol-defined rules for ARIA-H count. *Results:* The study is still ongoing and the results are presented with the cut-off date of April 24, 2017. Out of 797 Patients who received DB treatment, 130 were enrolled in the OLE and dosed with open-label gantenerumab after a mean time of 80 weeks in the treatment-free follow-up period. The mean duration of previous DB treatment was ~105 weeks; 39 patients were previously on placebo, 48 on 105 mg gantenerumab and 43 on 225 mg gantenerumab. Demographics characteristics of OLE patients (age, gender, education, APOE genotype) were similar to the overall study population. From 130 patients in the OLE, 118 had at least one post-baseline MRI. Of these 118 patients, 75 received at least one 1200 mg dose and 47 had a post 1200 mg dose scan. Out of 118 patients, 25 (21.2%) had new ARIA-E on doses ranging from 105 to 1200 mg, compared with 10% (53 of 531 gantenerumab-treated patients) observed during the DB phase. As expected, a higher incidence of ARIA-E was observed at increased doses in the OLE. Seventeen patients with ARIA-E also had new ARIA-H. Most ARIA events were asymptomatic. Three patients discontinued due to ARIA-H as defined by the protocol. Review of the data in the OLE did not identify any new or unexpected findings for this population. As of April 24, 2017, most adverse events were of mild-to-moderate severity (87.1%) compared with 84.6% in patients on gantenerumab during the DB phase; approximately 16.5% of patients experienced a serious adverse event in the OLE compared with ~20% in the DB phase. *Conclusions:* In the ongoing SCarlet RoAD OLE, ARIA was seen to increase with higher doses but remained manageable with the implemented dosing algorithm. Severity and seriousness of adverse events was comparable between the DB phase and the Scarlet RoAD OLE. Overall, currently available data suggest the safety profile of gantenerumab at higher doses remains unchanged compared with the DB phase of the study.

OC27: THE EUROPEAN PREVENTION OF ALZHEIMER'S DEMENTIA (EPAD) AND AMYLOID IMAGING FOR PREVENTION OF ALZHEIMER'S DEMENTIA (AMYPAD) PROJECTS: COHORT READINESS FOR THE ADAPTIVE CLINICAL TRIAL PLATFORM. Craig Ritchie[1], Miia Kivipelto[2], Alina Soloman[2], Brian Tom[3], Jose Luis Molinuevo[4] *((1) Centre for Dementia Prevention, University of Edinburgh, UK; (2) Ageing Research Centre, Karolinska Institute, Sweden; (3) MRC Biostatistics Unit, University of Cambridge, UK; (4) Barcelona Beta Brain Research Centre, Spain)*

Introduction: Challenges in the development of disease modifying interventions for the secondary prevention of Alzheimer's dementia was a catalyst 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 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 and the AMYPAD Prognostic and Natural History Sub-Study. These projects will collectively create a readiness cohort for the Bayesian Adaptive Proof of Concept Phase 2 EPAD Clinical Trial. *Objectives:* The primary objective of the EPAD and AMYPAD projects is to deliver a readiness cohort for the embedded EPAD Proof of Concept trial and concurrently deliver very large amounts of longitudinal data from 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. *Discussion:* The EPAD LCS has recruited in the region of 500 research participants across several Trial Delivery Centres (TDC) in Europe. After being

identified from numerous aligned parent cohorts in Europe, potential research participants are contacted and invited to attend the local TDC. 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 be undertaken through the AMYPAD Prognostic and Natural History Study. Baseline data from EPAD LCS collected thus far will be presented indicating the amyloid status (through CSF analysis) of the population and which factors predict amyloid positivity and therein readiness for the EPAD PoC study. The PoC trial itself 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. As the initial interventions will target amyloid – we will present the factors which influence positive amyloid status in the EPAD LCS to date. The EPAD PoC uses a Bayesian Adaptive Clinical Trial design with well-informed simulations of the RBANS Primary Outcome driving a series of regular and influential evolutionary analysis of all trial data. These analyses and their influence on stopping an interventions progress or graduation to Phase 3 testing will be presented with particular emphasis on how this design improves the Phase 2 process for disease modifying drugs in Alzheimer's disease compared to the current sub-optimal methodologies. The IMI-AMYPAD Project will deliver two studies. The Diagnostic Utility Study and the Prognostic and Natural History Study. The latter is a sub-study of the EPAD LCS. It is considered that PET-Amyloid imaging is the gold standard for Alzheimer's disease presence in the preclinical and prodromal phase of this illness. Further improvements in this technology for accurate disease modeling and risk prediction will be achieved in the AMYPAD Prognostic and Natural History Study using approaches such as region of interest analyses, dynamic scanning and automated quantitative reading technology. These new techniques and there ability to improve disease modeling and trial design through improved subject stratification and selection will be presented. *Conclusions:* It is expected that 3,000 subjects in the EPAD LCS will undergo PET-Amyloid imaging with a significant proportion of these having longitudinal scanning and dynamic scanning. In concert with the data being collected in EPAD LCS, the EPAD/AMYPAD Collaboration will generate one of the largest data collections assembled for disease modeling in preclinical and prodromal Alzheimer's Dementia. The value of the EPAD PoC study on improving trial efficiency and effectiveness will ensure faster and better-informed delivery from Phase 2 to Phase 3 of numerous interventions for the secondary prevention of Alzheimer's Dementia. With significant progress being made through 2017 in EPAD LCS Recruitment and initiation of AMYPAD Prognostic and Natural History Study, the platform has delivered a state of readiness to accommodate the planned initiation of the EPAD PoC in 2018.

OC28: TOWARDS A NEW BIOMARKER BATTERY FOR DRUG DEVELOPMENT IN ALZHEIMER'S DISEASE. Régis Bordet[1], Claudio Babiloni[2], Pierre Payoux[3], David Bartrés-Faz[4], Catherine Cassé-Perot[5], Jill Richardson[6], Giovanni Frisoni[7], Olivier Blin[5] *((1) Department of Medical Pharmacology, University of Lille, France; (2) Department of Physiology and Pharmacology, University of Roma, Italy; (3) Department of Nuclear Medicine, University of Toulouse, France; (4) Department of Medicine, University of Barcelona, Spain; (5) Department of Medical Pharmacology, University of Aix-Marseille, France; (6) GSK, Stevenage, UK; (7) Department of Psychiatry, University of Geneva, Switzerland)*

Introduction: Cognitive disorders due to neurodegenerative diseases, especially Alzheimer's disease (AD), are one of the main medical burdens for the global economy with £350 billion invested each year. Until today the pharmacological therapy of Alzheimer's disease (AD) is limited to symptomatic temporary improvement or stabilization of cognitive performance and the reduction of neuropsychiatric symptoms of the disease, while an optimal treatment should associate both symptomatic and disease-modifying drugs. However, a recent study reported that out of the 244 compounds (413 clinical trials) for the care of AD between 2002 and 2012, only one was approved (Cummings, Morstorf, Zhong, Alzheimer's Res Ther. 2014). As a result, AD drug candidates have 99.6% of the failures rate, more than any disease area (81% for cancer). Following the failure of several late stages clinical studies in AD, the dramatic increase in costs associated with drug development together with the poor number of emerging drugs highlights how crucial it is to accelerate the findings aiming to bring new drugs to market. In this respect, optimization of the development process by integrating, at an early stage, reliable biomarkers able to predict clinical benefit in phase III clinical trials may help. The improvement of certain techniques such as neuroimaging (magnetic resonance imaging, MRI, and positron emission tomography, PET) and neurophysiological (quantitative electroencephalography, qEEG) methods has led to a more accurate assessment of the impact of new symptomatic and disease-modifying pharmacological treatments on brain structure and function in AD patients at prodromal and dementia stages. *Objective:* The conference will present the final results of the European Public-Private Alliance for the study of the biomarker of AD in 2010-2015, the IMI project entitled "PharmaCog" (Grant Agreement n°115009, www.pharmacog.org). The symposium will show the potential of an innovative multidimensional biomarker matrix that combines neuroimaging, neurophysiology (EEG), and biochemistry variables correlated to indexes of traditional and computerized neuropsychological tests (Deguil et al, Drug Discovery Today 2013). The biomarker matrix was tested in animals, healthy volunteers, and patients with prodromal AD. The "PharmaCog" project addressed to three central themes: 1) development of translational and reversible 'challenge' models in support of efficacy studies; 2) development and validation of pharmacodynamic biomarkers suitable to support the determination of efficacious exposure of drug; 3) development of biomarkers sensitive to early disease progression in prodromal AD patients with greater predictive value for stratification before patient selection in clinical trials and long-term assessment in disease-modifier development. *Discussion:* To assess the PharmaCog biomarkers battery in the development of symptomatic drugs, we tested the pharmacodynamics effect of the marketed drug donepezil in healthy volunteers in a double-blind, randomized, cross-over trial. The donepezil and placebo conditions differed in terms of the changes in delta/theta/alpha/beta inter-trial coherence (ITC) and event-related spectral perturbation (ERSP) of EEG activity in various regions of the scalp (especially the frontal electrodes) in good concordance with changes observed

in frontal regions in both fMRI and PET-FDG. To sensitize this approach, we have sophisticated the trials using challenge tests to induce transient cognitive impairment in healthy volunteers, through sleep deprivation, TMS or hypoxia. We will highlight the results obtained with sleep deprivation which induces a cognitive impairment measured through the N-back and working memory task with a relief induced by drugs specific or unspecific to AD in parallel to the improvement of EEG abnormalities. To test the interest of biomarker battery in term of patient selection and follow-up of cognitive decline, we have enrolled a cohort of 145 amnestic mild cognitive impairment (aMCI) patients that have been assessed by an extended neuropsychological battery. MRI, fMRI, and qEEG biomarkers were compared in aMCI patients positive vs. negative to CSF diagnostic markers of prodromal AD (e.g. Aβ42/p-tau) over 24 months (6-month follow-ups). Compared to the aMCI patients negative to the CSF diagnostic biomarker, those positive (possible prodromal AD) showed an altered matrix of MRI, fMRI, and qEEG biomarkers related to cognitive and clinical status. Furthermore, the aMCI patients positive to the CSF diagnostic biomarker exhibited a greater decline over time of cognitive functions (ADAScog) and that matrix of MRI, fMRI, and qEEG biomarkers. These results unveiled a matrix of biomarkers for the use for early detection and characterization of incipient AD. *Conclusions:* The PharmaCog biomarker matrix may be used to accelerate the AD drug development at all stages of the discovery and validation pathway. Its application may have a special impact at early stages of the pathway for improving the Go/No Go decision to continue the validation process to phase II and III. The PharmaCog biomarker matrix is presently used for testing a new drug for the relief of AD symptoms. Furthermore, we have been publishing those results in a special issue of a field journal as a preliminary step for the certification of the procedures by the regulatory European Medicines Agency.

OC29: ORY-2001 RATIONALE IN MILD TO MODERATE ALZHEIMER'S DISEASE. Roger Bullock, Cesar Molinero, Tamara Maes *(Oryzon Genomics S.A. Barcelona Spain)*

Background: Preclinical data in animal models for CNS disease suggest that epigenetics may play an important role in the development and loss of memory and cognition. Transcriptional regulation complexes for key genes in neural and glial functions often include HDAC1/2 and Lysine Specific Demethylase-1 (LSD1). ORY-2001 is a dual LSD1-MAOB inhibitor with good selectivity, ADME and PK properties that efficiently crosses the blood-brain barrier. In functional studies in SAMP-8 mice, the drug restores cognitive impairment and reduces expression of neuroinflammatory genes in the hippocampus. This is accompanied by changes in observed behaviours. Biological evidence of reduction in neuroinflammatory proteins alongside improvement in cognition and behaviour suggest ORY-2001 has a potential role in the treatment of AD. *Methods:* Following Phase 1 SAD and MAD studies showing good safety and tolerability in volunteers, ORY-2001 will now move to a six-month randomised, double-blind, phase IIa study to confirm these findings with two selected doses in people with biomarker confirmed mild to moderate AD. Secondary objectives will explore cognition (MMSE, ADAS-Cog), function (CDR-SB) and behaviour (NPI, HAM-D) to further explore the observations from the animal studies. *Results:* To date, oral ORY-2001 is well tolerated and shows no clinically significant changes in laboratory tests, vital signs, ECGs, physical findings, or adverse events in SAD cohorts up to 4 mg nor in MAD cohorts up to 2.5 mg. The first laboratory signs of hematopoietic impact were observed in the 2.5 mg cohort in the MAD. An additional cohort has now completed the safety profile and confirmed the dose selection. The pharmacokinetic profile demonstrates rapid oral absorption, relatively long half-life and approximate dose proportional exposure to ORY-2001. Dose-dependent LSD1 TE was demonstrated in peripheral PBMC samples in the SAD and MAD part of the study. *Conclusion:* The Phase I study provides detailed information that has allowed us to model the dose response in human vs preclinical species and to establish a safe administration scheme for longer term safety and efficacy studies of ORY-2001 in Phase II trials in neurodegeneration and neuro-inflammation. This is the first time a histone lysine demethylase has been targeted in clinical CNS disease and pioneers this epigenetic approach for the potential treatment of AD.

OC30: PLASMA AMYLOID LEVELS WITHIN THE ALZHEIMER'S PROCESS AND CORRELATIONS WITH CENTRAL BIOMARKERS; Olivier Hanon[1], Jean-Sébastien Vidal[1], Sylvain Lehmann[2], Stéphanie Bombois[3], Bernadette Allinquant[4], Marie Godard[1], Patrick Gelé[5], Christine Delmaire[3], Frédéric Blanc[6], S Schraen[5], Audrey Gabelle[7] and the BALTAZAR study group. *(1) Department of Gerontology, Broca Hospital, Paris, France; (2) Laboratoire de Protéomique Clinique, Department of Biochemistry, Saint Eloi Hospital, IRMB, inserm U1183, France; (3) CMRR de Lille, Department of Neurology, Lille, France; (4) Centre de Psychiatrie et Neurosciences, Université Paris Descartes, Paris, France ; (5) University of Lille Nord de France, Department of Biology and Pathology, Lille University Hospital, INSERM UMR 1172, 59037 Lille, France; (6) CMRR de Strasbourg, Department of Gerontology; Strasbourg, France; (7) CMRR de Montpellier, Department of Neurology; Inserm U1183, Montpellier, France.*

Backgrounds: Predictive value of plasma Aβ for Alzheimer disease (AD) diagnosis, for mild cognitive impairment (MCI) and for cognitive decline in at-risk AD population yields conflicting results. *Objectives:* The aim of this study was to (1) assess the plasma levels of amyloid Aβ42 and Aβ40 in a large clinically-based cohort of amnestic MCI (aMCI), non-amnestic MCI (naMCI) and AD patients and to (2) investigate the correlations between plasma Aβ42 and Aβ40 and CSF Aβ42, Tau, p-Tau, MRI and cognitive assessments. *Methods:* The BALTAZAR (Biomarker of AmyLoïd pepTide and AlZheimer's diseAse Risk) multicenter (23 memory centers) prospective study included 1040 participants from September 2010 to April 2015. They were classified as AD (n=501) according to international criteria, amnestic MCI (a MCI, n=417) and non-amnestic MCI (na MCI, n=122) according to Petersen's criteria. A comprehensive battery of cognitive tests was performed including MMSE, verbal fluency, FCSRT. Plasma and CSF samples were drawn the same day. All the measurements of plasma and CSF were centralized and analyses were performed blind to the participant's diagnosis and biomarker results. Plasma Aβ42 and Aβ40 were measured by xMAP technics, CSF biomarkers Aβ42, Tau and p-Tau by ELISA. The global and hippocampal atrophy were assessed by MRI and analysis was also centralized and blind to diagnosis and biomarker results. The design of the study enabled us to analyze these various biomarkers taking into account potential confounding factors such as vascular factors, BMI, disability, depression. Statistical analysis was performed with the R Core Team (2014). *Results:* Educational level differed between the 3 groups ($p<0.0001$) with a lower level for the AD participants. Women were more frequent in the naMCI group ($p=0.004$). No differences were observed for smoking status, BMI or comorbidities between the groups. The mean plasma Aβ1-42 and Aβ1-40 in the whole sample were 37.8 (11.6) pg/mL and 267 (73) pg/mL respectively. The levels of plasma Aβ1-42 and Aβ1-40 significantly decreased from naMCI,

aMCI to AD participants (for Aβ1-42: 39.7 (10.5) in naMCI; 38.2 (11.9) in aMCI and 36.9 (11.7) in AD (p=0.01); for Aβ1-40: 272 (52) in naMCI; 269 (68) in aMCI and 263 (80) in AD (p=0.04)). In the whole sample, plasma Aβ1-42 significantly correlated with age, MMSE, APOE ε4. Plasma Aβ1-42 correlated with all CSF biomarkers (Aβ42, Tau, p-Tau) in the whole sample and in MCI group (mainly in aMCI) but only correlated with CSF Aβ42 in AD. *Conclusion:* Plasma Aβ1-42 and Aβ1-40 levels significantly differed between AD and MCI groups and decreased from non-amnestic MCI, amnestic MCI to AD participants. Plasma Aβ1-42 correlated with CSF Aβ42 only in AD and with CSF Aβ42, Tau, p-Tau and p-Tau/Aβ42 ratio in MCI patients. Our findings highlighted the correlations between peripheral and brain amyloid metabolisms within the Alzheimer's process and support the relevance of plasma amyloid biomarkers in the diagnosis process even at an early stage of the disease

OC31: ONLINE CLINICAL RESEARCH: UPDATES AND INSIGHTS FROM THE BRAIN HEALTH REGISTRY. Shannon Finley[1], Diana Truran[1], Derek Flenniken[1,3], Juliet Fockler[1,3], Rachel L Nosheny[1,3], Monica Camacho[1,3], R Scott Mackin[1,2], Michael W Weiner[1,3] *((1) Center for Imaging of Neurodegenerative Diseases, San Francisco Veteran's Administration Medical Center, San Francisco, CA, USA; (2) UCSF Department of Psychiatry, San Francisco, CA, USA; (3) UCSF Department of Radiology and Biomedical Imaging, San Francisco, CA, USA)*

Background: The Brain Health Registry (BHR), is an online study for recruitment, screening, and longitudinal monitoring for neuroscience research including clinical trial recruitment as well as a platform for development of new online tools for assessment of cognition and function. Launched in April 2014, BHR has focused on registry growth to provide an enriched cohort for referrals to clinical trials, particularly in the field of Alzheimer's Disease (AD). This presentation focuses on updates and insights of the Brain Health Registry and will (1) review BHR's growth and clinical trial referral programs and (2) discuss how BHR addresses and adapts to ongoing needs in clinical trial recruitment. *Methods:* To grow the registry, multiple recruitment methods have been, and continue to be, utilized including word of mouth, earned media, and digital advertising. BHR worked with a public relations and digital advertising firm that introduced the BHR brand to a national audience through an appearance on the Today Show with BHR spokesperson B. Smith in March 2015. From there, BHR began to secure partnerships with collaborators, like the Global Alzheimer's Platform (GAP), which continued to grow the registry in areas where clinical trials are routinely conducted. Below we detail the different programs BHR has developed to facilitate AD clinical trial recruitment in order of implementation. Registry Referrals: BHR began referring registrants to clinical trials in 2014 and focused on sites where the largest concentration of participants resided – the San Francisco Bay Area. The program consists of querying the BHR database, selecting potentially qualified participants based on self-reported questionnaire responses, and inviting selected participants to contact a clinical trial site or give permission for a site to contact them. Once membership grew beyond the Bay Area, BHR began referring to trials located in Los Angeles, Providence, Boston, and Las Vegas. In 2015 BHR began to offer participant's data to collaborators through a data sharing consent form after multiple collaborators expressed an interest in BHR collected data. Direct to Site (DtS): Launched in 2016, interested persons are referred to clinical trial sites without requiring enrollment in BHR. DtS was created as some collaborators found more value in receiving a large volume of referrals without pre-screening through the Registry. Co-Enrollment Program: As BHR grew, collaborators voiced a need to follow their enrolled clinical trial participants longitudinally without burdening participants to physically return to their clinic. In 2016, BHR launched a co-enrollment program which enrolls participants from clinical studies in BHR for longitudinal monitoring and data sharing between the studies. Co-enrolled participants may be presented with a modified version of BHR, which can include modified questionnaires and cognitive tests, to suit the needs of the trial they enrolled in. (Note: Co-enrollment is further discussed in detail in another CTAD abstract titled "Enriching Clinical Trial Data through Co-enrollment with the Brain Health Registry" by Fockler J et al). Software as a Service (SaaS): 2016 also launched the SaaS program – where BHR recreates the internally created BHR platform for independent external use. This program focuses on providing BHR globally where the framework of BHR is implemented but outside researchers have full control over the content and use their local IRB. *Results:* Current enrollment is nearly 53,500 and growing both in United States and beyond. The oldest cohort recently began their 3 year timepoint with over 2000 returners thus far. Referral Programs: 15 unique studies are using Registry Referrals with over 1,700 BHR members referred to observational and treatment studies. 170 participants have been directly referred to clinical trial sites, bypassing enrollment in BHR. Co-Enrollment: 3 studies are using this program with more than 100 participants enrolled. Data Sharing: Over 1500 BHR participants have agreed to share their BHR data with collaborators either through the referral program or co-enrollment. SaaS: 2 partners are using this service – one in the Bay Area and one in the Netherlands with expansion to France projected for late 2017. *Conclusion:* The efforts described demonstrate the growth and continued learnings of BHR. While the original BHR Referral Programs continues to be successful, BHR has identified the need for more flexibility in referrals, like DtS. BHR introduced co-enrollment to meet the needs of researchers who want to longitudinal monitoring without requiring in-clinic visits, which is cost efficient and eases burden on participants. Lastly, the SaaS project has leveraged the internal BHR platform to give researchers full control of their registry - further accelerating online clinical trial recruitment and data collection. All programs have successfully shared data with multiple collaborators. BHR expects collaborative data sharing to increase as the BHR dataset grows and expands. Providing our rich dataset to outside investigators will help aid present research and future discovery. The success achieved in 3 years demonstrate BHR's value, efficiency, and flexibility. While BHR has met many challenges in creating an online research registry, we continue to evolve to meet the AD field's needs. BHR's goal remains to facilitate recruitment for clinical trials and we look forward to forging new collaborations and innovative directions. We gratefully acknowledge support for this project from Global Alzheimer's Platform, ADDF, Alzheimer's Association, Larry Hillblom Foundation, PCORI, The Mayo Foundation, NIH, California Department of Public Health, The Rosenberg Alzheimer's Project, The Ray and Dagmar Dolby Family Fund, Connie and Kevin Shanahan, and The Drew Foundation

OC32: BPN14770 PHOSPHODIESTERASE-4D NEGATIVE ALLOSTERIC MODULATOR FOR ALZHEIMER'S DEMENTIA: PRECLINICAL, PET IMAGING AND HUMAN PHASE 1 RESULTS. Mark Gurney[1], Chong Zhang[2], Ying Xu[2], James O'Donnell[2] PhD2, Masahiro Fujita[3], Robert Innis[3], Victor Pike[3], Sanjay Telu[3], Scott Reines[1] *((1) Tetra Discovery Partners, Inc. Grand Rapids, MI, USA; (2) School of Pharmacy and Pharmacological Sciences, University at Buffalo, Buffalo, NY, USA; (3) National Institute of Mental Health, Bethesda, MD, USA)*

Background: Early and late stages of memory formation are dependent upon cAMP signaling. In humans, genetic studies show that brain cAMP levels relevant to cognition are regulated by phosphodiesterase-4D (PDE4D). We have humanized the PDE4D gene in mice to study the effect of a PDE4D negative allosteric modulator, BPN14770, on early and late stages of memory. The selectivity of BPN14770 for PDE4D is due to a single amino difference in the drug binding site. This is a phenylalanine in PDE4D and a tyrosine in the other three PDE4 subtypes, PDE4A, B and C. BPN14770 inhibits PDE4D by binding to a key regulatory domain which it holds closed across the active site, thereby preventing hydrolysis of cAMP. The key phenylalanine is present only in primates. A tyrosine is present in PDE4D of other species, causing a sharp decrease in BPN14770 inhibitory potency. Humanizing the mouse PDE4D gene allowed us to compare the potency of BPN14770 in wild-type and humanized PDE4D mice, and thereby engagement of the PDE4D target, across a battery of cognitive and biochemical tests. In parallel, we studied the distribution of PDE4D in primate brain using a C-11 PET tracer, and explored the effect of BPN14770 on cognitive tasks in healthy, elderly human subjects in a multiple ascending dose Phase 1 clinical trial. *Methods:* The mouse PDE4D gene was humanized by knocking-into C57Bl6 embryonic stem cells a single nucleotide substitution that replaces PDE4D tyrosine571 by phenylalanine. This improves the 50% inhibitory concentration (IC50) of BPN14770 from 133 nM against recombinant mouse PDE4D enzyme to 4 nM against humanized mouse PDE4D Y571F enzyme. Humanized and wild-type mice were profiled in tests of working memory (novel object recognition, NOR, with 1 hour delay) and long-term memory (NOR with 24 hour delay) after single oral doses of BPN14770 or vehicle. Effects of BPN14770 on phosphorylation of CREB and levels of BDNF were assessed after 14 days of dosing by immunoblot. PET imaging studies were conducted in anesthetized rhesus monkeys with C-11 T1650, a selective PDE4D tracer. Preliminary cognitive benefit of BPN14770 was assessed in elderly human subjects (> 60 years of age) in an 8-day, multiple ascending dose study. 15 subjects were enrolled per cohort (10 active and 5 placebo). Cognitive assessments were performed using the CogState Global Battery at baseline (Predose Day 1) and 2 hours after dosing on Day 1, 3, 5 and 7 of the multi-day trial. *Results:* BPN14770 improved working and long-term memory in humanized PDE4D mice after single oral doses of 0.01 or 0.03 mg/kg, while the minimum effective dose in wild-type C57Bl6 littermate control mice was 1 mg/kg. There was no difference in the potency of rolipram (0.1 mg/kg), a reference PDE4 inhibitor not sensitive to the PDE4D tyrosine571 to phenylalanine mutation. After dosing for 14 days, BPN14770 at 0.03 mg/kg elevated pCREB and BDNF in humanized PDE4D mice. PET imaging of PDE4D distribution in anesthetized rhesus monkeys revealed specific binding in hippocampus, entorhinal cortex and prefrontal cortex that was displaceable by rolipram and BPN14770. In healthy elderly subjects, exposure to BPN14770 was dose-related, with terminal half-life of approximately 10 hours. Preliminary cognitive assessment suggested that BPN14770 oral doses of 10 and 20 mg bid improved complex attention/working memory and 24 hour delayed recall of verbal or visuospatial tasks. Analysis of the pooled standardized mean difference suggested improvement in the CogState working memory tasks (IDN, ONB), and the ISLT and GMLT with 24 hour delayed recall. Post-hoc pooling of the 10 and 20 mg bid dose groups with comparison against the intra-cohort placebo (20 active and 10 placebo), indicated an effect size in the ONB working memory task of 0.5 – 0.8 with p-values ranging from $p<0.05$ - <0.01. There were no adverse events related to gastrointestinal disturbance (nausea, vomiting or diarrhea). *Conclusions:* The humanized PDE4D mice provided a unique model in which BPN14770 engagement of the PDE4D target could be linked directly to improvement in early and late stages of memory as well as to biomarkers associated with activation of the cAMP-PKA-CREB pathway. The distribution of PDE4D in primate brain was highest in those regions known to be important for cognition, the hippocampus and the prefrontal cortex, which also are targets of Alzheimer's pathology. Preliminary assessment of BPN14770 cognitive benefit in elderly subjects was consistent with the proposed mechanism of action of the drug.

OC33: AMYLOID BETA STABLE ISOTOPE LABELING KINETICS AND CONCENTRATIONS OF HUMAN PLASMA DETECT CNS AMYLOIDOSIS. Vitaliy Ovod[1], Kara Ramsey[1], James Bollinger[1], Kwasi Mawuenyega[1], Terry Hicks[1], Theresa Schneider[1], Thomas Kasten[1], Wendy Sigurdson[1], Melissa Sullivan[1], Tamara Donahue[1], Katrina Paumier[1], David Holtzman[1,2,4], John Morris[1,4], Tammie Benzinger[2,3], Anne Fagan[1,2,4], Bruce Patterson[5], Randall Bateman[1,2,4] *((1) Department of Neurology, Washington University School of Medicine, St Louis, MO; (2) Hope Center for Neurological Disorders, Washington University School of Medicine, St Louis, MO; (3) Department of Radiology, Washington University School of Medicine, St Louis, MO; (4) Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St Louis, MO; (5) Department of Medicine, Washington University School of Medicine, St Louis, MO)*

Background: Blood biomarkers of Alzheimer's disease (AD) are essential for rapid and inexpensive screening of the hundreds of millions of people at risk for AD. There is substantial evidence implicating amyloid-beta (Aβ) in the molecular pathogenesis of AD1. Cerebrospinal fluid (CSF) Aβ is an established biomarker for detecting amyloidosis2 and risk of progression to dementia3. However, blood Aβ concentrations have correlated poorly with clinical AD4. Furthermore, Aβ amyloid binding positron emission tomography (PET) tracers have emerged as sensitive and specific signatures of amyloid deposition in the central nervous system (CNS)5. However, due to the invasiveness of CSF collection and the limited availability and cost of PET scans, there is an urgent need for a simpler, more practical Aβ biomarker for CNS amyloid deposition. To investigate a plasma-based Aβ biomarker, we adapted our previously reported Stable Isotope Label Kinetics (SILK) protocol6,7 to analyze the turnover kinetics and absolute amounts of Aβ 38, Aβ 40, and Aβ 42. *Methods:* In a prospective longitudinal biomarker trial design (NCT02021682) supported by an Alzheimer's Association Zenith award grant and NIH R01 study (NS065667), 41 SILK studies (>500 blood samples) were completed with either clinically diagnosed late onset sporadic AD or cognitively normal age-matched control participants at Washington University School of Medicine. All participants had Aβ amyloid imaging by PIB PET and/or CSF Aβ measures to detect CNS amyloidosis. Participants were given a bolus of 13C6- leucine label followed by blood sampling over 24 hours. Blood samples were immediately processed to plasma and analyzed in a blinded fashion. Aβ isoforms were immunoprecipitated with an anti-Aβ antibody and analyzed on a high resolution liquid chromatography

mass spectrometer6. *Results:* We found shorter half-life of Aβ38 than Aβ40 and Aβ42 in all participants, and the half-life of Aβ42 was significantly faster than Aβ40 in amyloid positive participants but not in amyloid negative participants. We found that the individual plasma Aβ42 concentrations and Aβ42/Aβ40 concentration ratios across all hours were significantly lower in participants with CNS amyloidosis. Further, an orthogonal approach of measuring Aβ42 kinetics in plasma found significant differences between individuals with CNS amyloidbeta amyloidosis vs. amyloid negative individuals as measured by PIB PET scans or CSF amyloid-beta, similar to previously seen in CSF. These findings regarding plasma Aβ42 concentrations and kinetics were similar to, but of lesser magnitude compared to measures in CSF7. *Conclusion:* Due to associations of differences in plasma Aβ between amyloid positive and negative participants, our findings support the hypothesis that blood Aβ interacts with and may be at least partially derived from the CNS. The results also suggest that blood-derived Aβ may be useful as a screening test for CNS Aβ amyloidosis. These findings will open new areas of research in the transport and clearance of Aβ in AD, including BBB mechanisms, and the start of blood tests for amyloidosis. Having a simple and inexpensive blood test for screening that could be adopted by the field is likely to lead to greatly accelerated clinical trials. Further, it will enable widespread treatment and prevention when effective therapeutics are developed. References: 1. Hardy J, Selkoe DJ. 2016. The amyloid hypothesis of Alzheimer's disease at 25 years.. EMBO Mol Med. 8(6):595-608. 2. Fagan AM, Mintun MA, Mach RH, Lee SY, Dence CS, Shah AR, LaRossa GN,Spinner ML, Klu nk WE, Mathis CA, et al. 2006. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Aβ42 in humans. Ann Neurol 59:512–519. 3. Vos SJB, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet neurology. 2013;12(10):957-965 4. Mayeux R, Schupf N. 2011. Blood-based biomarkers for Alzheimer's disease: plasma Aβ40 and Aβ42, and genetic variants. Neurobiol Aging. 32 Suppl 1:S10-9. 5. Klunk WE., 2011. Amyloid imaging as a biomarker for cerebral β-amyloidosis and risk prediction for Alzheimer dementia. Neurobiol Aging. 32 Suppl 1:S20-36. 6. Mawuenyega KG, Kasten T, Sigurdson W, Bateman RJ. 2013. Amyloid-beta isoform metabolism quantitation by stable isotope-labeled kinetics. Anal Biochem. 440(1):56-62. 7. Patterson BW, Elbert DL, Mawuenyega KG, Kasten T, Ovod V, Ma S, Xiong C, Chott R, Yarasheski K, Sigurdson W, Zhang L, Goate A, Benzinger T, Morris JC, Holtzman D, Bateman RJ. 2015. Age and amyloid effects on human central nervous system amyloid-beta kinetics. Ann Neurol. 78(3):439-53. Disclosures: RJB receives lab research funding from the National Institutes of Health, Alzheimer's Association, BrightFocus Foundation, Rainwater Foundation Tau Consortium, Association for Frontotemporal Degeneration, Barnes Jewish Hospital Foundation, the Cure Alzheimer's Fund and a Tau SILK Consortium (AbbVie, Biogen, and Eli Lilly and Co.). Funding for clinical trials not related to this research include the Alzheimer's Association, Eli Lilly and Co, Hoffman La-Roche, Janssen, Avid Radiopharmaceuticals, GHR Foundation, and an anonymous foundation. RJB also receives research funding from the DIAN Pharma Consortium (Abbvie, Amgen, AstraZeneca, Biogen, Eisai, Eli Lilly and Co, Hoffman La-Roche, Janssen, Pfizer, and Sanofi). RJB has received honoraria from Janssen and Pfizer as a speaker and from Merck and Pfizer as an Advisory Board member. RJB is a co-founder of C2N Diagnostics and receive royalty income based on technology licensed by Washington University to C2N Diagnostics. RJB receives income from C2N Diagnostics for serving on the scientific advisory board. Washington University, with RJB as co-inventor, has submitted the US nonprovisional patent application "Methods for Measuring the Metabolism of CNS Derived Biomolecules In Vivo" and provisional patent application "Plasma Based Methods for Detecting CNS Amyloid Deposition". DMH is a co-founder of C2N Diagnostics. Dr. Holtzman has served on/provided scientific advisory boards/consulting for Genentech, Eli Lilly, Proclara Biosciences, C2N Diagnostics, GlaxoSmithKline, AbbVie, Denali. The Holtzman lab receives research grants from the National Institutes of Health, Cure Alzheimer's Fund, Tau Consortium, Eli Lilly, the JPB Foundation, Denali, AbbVie, and C2N Diagnostics.

OC34: STEREOTYPICAL DATA-DRIVEN IMAGING BIOMARKER TRAJECTORIES ACROSS THE ALZHEIMER'S DISEASE SPECTRUM. Sergey Shcherbinin[1], Mark A. Mintun[2], Adam J. Schwarz[1], For the Alzheimer's Disease Neuroimaging Initiative[3] *((1) Eli Lilly and Company, Indianapolis, IN, USA; (2) Avid Radiopharmaceuticals, Inc., Philadelphia, PA, USA; (3) Data used in preparation of this abstract were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu))*

Background: The increasing use of both positron emission tomography (PET) and magnetic resonance imaging (MRI) measurements in Alzheimer's Disease (AD) clinical trials urges a quantitative understanding of the comparative behavior of these biomarkers, and their relationship to clinical instruments, at various stages of disease. One method for generating continuous, stereotypical, data-driven biomarker trajectories is based on the integration of averaged derivative graphs – relationships between annual rate of change and corresponding baseline values. This approach is straightforward in terms of both implementation and interpretation, is amenable to various datasets with relatively short follow-up periods, and does not incorporate any prior diagnostic information for data points contributing to derivative graphs. In the AD field, this approach has been used to study the PiB PET trajectory (Villain N et al, Brain, 2012, Jack CR et al, Neurology, 2013) and has begun to be extended to other biomarkers in the Australian Imaging Biomarkers and Lifestyle (AIBL) study (Villemagne VL, et al, Lancet Neurology, 2013). The goal of our project was to apply this methodology to the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset as a framework to model the stereotypical progression of different imaging biomarkers across the AD spectrum. *Methods:* We analyzed the dynamics of the composite florbetapir standardized uptake value ratio (FBP SUVR), composite fluorodeoxyglucose SUVR (FDG SUVR) and MRI-based hippocampal volume (HV) for N=224, N=309 and N=980, respectively, participants from the ADNI database. Cognitive decline was evaluated using the 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog13) index for N=1341 participants. For all considered subjects, 3+ longitudinal measurements obtained over 2-4 year follow-up periods were included in our analysis. Individual annualized rates of change were determined from the slope of a linear regression line fit to longitudinal measurements. For each characteristic Ai (i=1-4, indicating FBP SUVR, FDG SUVR, HV and ADAS-Cog13), we combined data for all participants into a consolidated rate vs. baseline scatterplot and generated an average continuous derivative graph using a locally weighted scatterplot smoothing (LOWESS). Importantly, the utilization of LOWESS processing allowed us to make no a priori assumptions regarding the shape of the derivative graphs. These graphs were further integrated over time using a 2nd order Runge-Kutta method resulting in four continuous long-term both trajectories Ai(t) and corresponding rates of change dAi/dt(t). For inter-measurement comparison, all investigated characteristics Ai were calibrated to the same 0 to 100 interval using different anchor points (ranged from means replicating the Centiloid approach to 10th/90th percentiles) in the CN amyloid negative (Aβ-) and AD Aβ+ groups. *Results:* For the four characteristics examined,

three different curve shapes were obtained. The derivative graph for FBP SUVR had an inverted U-shape and the corresponding trajectory of amyloid accumulation had a sigmoidal form. The FBP SUVR plateau was confirmed by the comparison between mean values and corresponding trajectory-derived annual rate for CN Aβ+ group (1.32 and 0.010/year) and AD Aβ+ group (1.45 and 0.006/year). Near-constant rates were observed for FDG SUVR and HV, resulting in near-linear trajectories: the moderate increase of trajectory-derived rate was found for both FDG SUVR (-0.02/year for CN Aβ+ group and -0.04/year for AD Aβ+ group) and HV (-121mm3/year for CN Aβ+ group and -171mm3/year for AD Aβ+ group). Unlike these three biomarkers, the average annual ADAS-Cog13 change grew as baseline values increased, resulting in an accelerated cognitive decline trajectory as AD progresses. While minimal average change (0.6/year) was found for CN Aβ+ group (mean ADAS-Cog13 value of 9.9), a more pronounced ADAS-Cog13 increase (4.7/year) was found for AD Aβ+ group (mean ADAS-Cog13 value of 31.5). Irrespective of the choice of anchor points, FBP SUVR became abnormal ahead of the other markers, FDG SUVR and HV trajectories were close in form and timing, and ADAS-Cog13 evidenced an accelerating trajectory. *Conclusions:* Our results are in reasonable agreement with previously published observations based on different datasets or applying different modeling techniques to ADNI data (Donohue MC et al, Alzheimer's & Dementia, 2014). They suggest that data-driven stereotypical trajectories may provide a meaningful insight on understanding of Alzheimer's Disease and design of both interventional and observational clinical trials. Indeed, use of the same modeling methodology for various biomarkers resulted in an internally-consistent and comprehensive (e.g. magnitudes and rates) continuous scheme of AD progression. An individualized staging may also benefit (Jack CR et al, The Lancet Neurology, 2011) from supplementing biomarker measurements by corresponding average rates obtained from stereotypical trajectories. Inter-subject variability, interrelations between measurements and noise in the scatterplot were not explicitly accounted for with this method and thus represent main limitations of this approach. Further validation of these findings using independent datasets and further optimization of methodology is warranted.

OC35: RAPID, REMOTE, AND REPEATABLE: SMARTPHONE-BASED "BURST" COGNITIVE ASSESSMENTS FOR GLOBAL AD PREVENTION TRIALS.

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Introduction: With acceptance that Alzheimer's disease (AD) biomarkers can be detected many years before clinical presentation of frank memory impairment there is a growing need to develop methods for capturing subtle cognitive changes in these populations. Ideally such methods will have greater levels of measurement precision and reliability than those used in conventional in-clinic cognitive assessments. The Ambulatory Research in Cognition Smartphone Application (ARC) is open-source and freely available for iOS and Android and was designed to achieve highly precise and reliable assessment of cognition in observational and treatment studies of preclinical AD. ARC utilizes smartphone technology to conduct very brief but frequent measurement of cognition in the same environments as those in which individuals perform cognitively demanding tasks in their everyday lives. Currently the ARC platform provides tests that measure episodic memory, working memory, and processing speed. Each test has been designed specifically to minimize the potential for cultural and linguistic bias. The ARC system has been designed for high frequency and repeated use without generating learning or practice effects. Hence it is optimized for use within a measurement burst experimental design, in which a "burst" of brief (20-60 seconds per test) cognitive tests are completed at random intervals several times per day over the course of one week. One study "visit" thus represents the average performance across seven days of assessments. In the current study, we evaluated the reliability and validity of ARC assessments in three cohorts: The Dominantly-Inherited Alzheimer Network (DIAN), the Knight Alzheimer's Disease Research Center (ADRC), and a community sample of healthy adults. *Methods:* Ninety-six participants were enrolled and completed seven consecutive days of ARC assessments. DIAN participants were cognitively normal mutation carriers (n=6) and non-carriers (n=4) who were 39.6 ±6.8 years old (yo), Knight ADRC participants (n=17) were cognitively normal and were 74.2 ±3.9 yo, and community-dwelling participants (n=69) were 38.2 ±10.8 yo. DIAN and Knight ADRC participants also completed in-clinic cognitive testing prior to completing one week of ARC assessments. ARC testing included four assessments per day for seven days, thus participants completed a maximum of 28 testing sessions. One testing session included three cognitive assessments: Symbols (a measure of processing speed, Grids (a visuospatial working memory measure), and Prices (an associate memory measure). Primary outcome measures were the average performance scores for each task across all sessions for each participant. Construct validity was assessed in DIAN and Knight ADRC participants by comparing ARC measures with standard in-clinic cognitive tests. Linear mixed effects models were used to calculate between-person reliability and within-person reliability. Between-person reliability assessed whether differences in scores observed reflect differences in performance between individuals, as opposed to other sources of variance. *Results:* Participants completed an average of 20.8 out of 28 ARC testing sessions (74.2%). The ARC app was tolerated well. 71% reported having little or no difficulty using the app, 64% preferred ARC testing over in-clinic testing, and only 9% reported privacy concerns. Slopes across the first four assessments revealed no evidence of a practice or learning effect. Performance on ARC measures was significantly associated with age in each cohort, with correlations ranging from 0.56 to 0.79 (note that higher mean scores on ARC measures indicate worse performance). In DIAN and Knight ADRC participants, in-clinic measures of episodic memory (Logical Memory, Paired Associates, Free and Cued Selective Reminding) were correlated with the ARC Prices test (Spearman's rho values -0.44 to -0.67, all ps <0.001). The ARC Grids test was associated with in-clinic measures of working memory including Trailmaking Test Part B (rho = 0.62), Digit Span Forward (rho = -0.52), Digit Span Backward (rho = -0.54), and Letter-Number Sequencing (rho = 0.33). In-clinic measures of processing speed were significantly correlated with the ARC Symbols test, including Digit-Symbol Substitution (rho = -0.72) and Trailmaking Test Part A (rho = 0.84). Between-person reliability estimates revealed expected patterns where reliability was highest for the average of seven days of assessments (Symbols = 0.98, Grids

= 0.90, and Prices = 0.88), suggesting excellent reliability for each ARC test. *Conclusions:* Our results demonstrate that rapid and highly repeatable assessments on smartphones are feasible, valid, highly reliable, and tolerated well in AD research populations. ARC measures correlate well with "gold standard" conventional clinical measures of cognition. The sensitivity to age of performance on ARC measures also provides early evidence for sensitivity to true differences in cognition. Within-person reliabilities were low as expected, suggesting that ARC measures successfully captured variation in test performance from occasion to occasion. Between-person reliabilities were excellent, ranging from 0.88-0.98, indicating that rapid and repeatable ambulatory cognitive assessments provide a level of reliability that far exceeds conventional in-clinic cognitive assessments. These findings are particularly relevant for AD prevention trials, where the high reliability and global adaptability of ARC assessments could considerably increase the statistical power of cognitive endpoint trials.Acknowledgements: Funding sources include an Anonymous Foundation, GHR Foundation, K23DK094982; NIH U01AG042791; NIH U19AG032438; NIH U19 AG032438, and NIH P01AG003991, NIH P50AG005681, NIH P01AG026276.

OC36: ASSOCIATING COGNITIVE FUNCTIONING PROFILES WITH AMYLOID STATUS IN ADNI2, WITH IMPLICATIONS FOR ADAPTIVE SCREENING FOR AMYLOID. Sarah J Carr[1], Judith Jaeger[2,3], Nancy Maserejian[4], Ahmed Enayatallah[4], Alan Lerner[1,5], Yanming Wang[6], Sheng Yang[7], Wenting Wang[4], Shijia Biang[4], Curtis Tatsuoka[1,5] and for the Alzheimer's Disease Neuroimaging Initiative* *((1) Department of Neurology, Case Western Reserve University, Cleveland, OH, USA; (2) CognitionMetrics, DE USA; (3) Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, NY USA; (4) Biogen, Cambridge, MA, USA; (5) Neurological Institute, University Hospitals Case Medical Center, Beachwood, OH USA; (6) Department of Radiology, Case Western Reserve University, Cleveland, OH USA; (7) Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, OH USA)*

Background: The aim of this study is to investigate how a range of cognitive functions is associated with the presence of amyloid deposition in the brain, considering age, sex and APOE genotype. This work lays a scientific foundation for the use of selective and tailored cognitive testing to help predict the presence of amyloid. Many treatments in development for Alzheimer's disease (AD) have amyloid as a target. Given the cost and access challenges of amyloid PET imaging, it is of interest to develop low cost, readily accessible and accurate non-imaging based methods of identifying patients with high probability of amyloid presence. Such screens could allow for more efficient utilization of AD-related health care resources. *Methods:* We use partially ordered classification models (posets) of neuropsychological (NP) test data to derive detailed profiles of cognitive functioning in the ADNI2 data. We considered episodic memory (four gradations of functioning), cognitive flexibility, verbal fluency, attention and perceptual motor speed. In poset models, profiles are discrete in the sense that for each of the functions, an individual is either at high or low functioning relative to the target population. The classification approach is Bayesian, so that posterior probability values of high functioning for each function are generated for every subject. We use these values as a basis for group comparison of cognitive functioning stratified by 1) amyloid status and age, 2) amyloid status, age, and APOE genotype, 3) amyloid status, age, APOE genotype and gender. We considered 3 age groups: < 65 years old, 65 up to 75, and >= 75 years old. APOE4 genotype was analyzed as the number of E4 alleles (0, 1, or 2). The sample in this cross-sectional analysis consisted of 644 ADNI2 participants: 255 cognitively normal, 389 with mild cognitive impairment (MCI), and 169 with early AD. This sample was 64.5% male and mean age = 74.8 years (SD = 7.5). The racial demographics were 93.1% Caucasian, 3.8% African American, 2.8% Asian and 0.3% American Indian or Alaskan Native. The average duration of education was 15.7 years (SD = 3.0). With the findings from the poset models, we develop a classification tree model for determining amyloid status that adaptively uses cognitive tests as needed, depending on age and APOE4 status. Given the general concern with over-fitting a classification tree to a specific data set, random forests methods, which rely on bootstrapping, were used as a comparison. *Results:* We see that patterns of cognitive differences emerge between amyloid groups depending on age, number of APOE4 alleles, and gender. The number of APOE4 alleles, in conjunction with age, seems to have a strong association on when specific cognitive differences arise. For APOE e4 allele carriers, relative episodic memory differences by amyloid status seem to emerge first in the earlier age groups (< 65 years old), followed by more widespread differences across other functions, such as verbal fluency, attention, and processing speed in older age groups. For APOE e4 non-carriers, differences by amyloid status mainly arise after 65 years old. Gender differences generally were not found, except in delayed recall (high level episodic memory), where women seem to retain higher functioning even when in the presence of amyloid. These results give guidance in developing feasible and relatively simple decision tree adaptive sequences that rely on age, APOE4 status, gender, and/or cognitive testing. Some interesting findings include: below 65 years old, it is possible that cognitive testing can be used in lieu of APOE genetic testing. Cognitive testing also appears to be particularly useful 1) when there is one APOE4 allele and age is 65 up to 75, and 2) when there are no APOE4 alleles and age is >= 75. Delayed recall tests are found to be more discriminatory in the younger age groups. Accuracy is approximately 70% or above in every branch in the tree that is developed. Random forests, stratified by age groups, were developed to compare variable selection and error rates. The cognitive tests selected in the classification tree correspondingly had relatively high variable importance values in the random forest approach, and out of bag error rates were around 70% or above as well. *Conclusion:* These findings help inform a potential role of cognitive testing in decision trees for detecting amyloid. Such decision trees may be able to efficiently and cost-effectively help identify patients as candidates for confirmatory amyloid PET imaging. Future work includes addressing the need to validate these findings in other data sets. *Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. Disclosures: Support for this work for the CWRU team (SC, AL, YW, SY and CT) and JJ was provided by Biogen. Authors AE, NM, WW, and SB were employees and shareholders of Biogen at the time this work was conducted.

OC37: ALZHEIMER'S DISEASE DEMENTIA AND THE LONG-TERM IMPACT ON CAREGIVER BURDEN – 36-MONTH RESULTS FROM GERAS. Catherine Reed[1], Mark Belger[1], J. Scott Andrews[2], Antje Tockhorn-Heidenreich[1] *((1) Eli Lilly and Company Limited, Windlesham, UK; (2) Eli Lilly and Company, Indianapolis, IN, USA)*

Background: There are inevitable health and quality of life consequences for caregivers of Alzheimer's disease (AD) patients, although these are not typically considered in economic evaluations of new treatments. Caregiver burden increases with AD dementia severity in cross-sectional studies and has been associated with time to institutionalisation. The few longitudinal studies in routine care of the impact of AD progression on caregivers have found burden to be affected by worsening functional ability and behavioural symptoms. Identification of drivers of caregiver burden could provide opportunities for interventions to benefit both caregivers and patients. *Methods:* GERAS is a 36-month European observational study of costs and caregiver outcomes associated with AD in France, Germany and the UK (the UK patients and caregivers participated in 18 months only). Patients with a diagnosis of probable AD and a Mini-Mental State Examination (MMSE) score ≤26 seen in routine care were enrolled between Oct 2010 – Sept 2011. Assessments at baseline and 6-month intervals collected measures of cognition (MMSE), functional ability (Alzheimer's Disease Cooperative Study – Activities of Daily Living - ADCS-ADL) (baseline, 18- and 36-months only), behavior (Neuropsychiatric Inventory - NPI), caregiver time and resource use (Resource Use in Dementia) and caregiver impact (Zarit Burden Inventory - ZBI). Linear models were run to identify which baseline factors were associated with change from baseline (CFB) in the Zarit burden score at 36 months. A further model included time dependent covariates at 18 months (CFB MMSE; CFB ADCS-ADL; CFB NPI). Variable selection methods were used to identify the important patient and caregiver factors for inclusion in the final models. The primary analyses were Mixed Method Repeated Measures (MMRM) models but as missing ZBI scores were associated with baseline characteristics, a sensitivity analysis where ZBI scores were imputed using Multiple Imputation (MI) was performed. *Results:* N=969 patients from the French and German GERAS cohorts were included in these analyses. Using baseline only variables, the primary model found that lower instrumental ADL abilities at baseline, higher number of years of education for the patient, younger caregivers and caregiver living with the patient were associated with faster increase in ZBI over 36 months. Including time dependent factors in a model showed that lower functional ability at baseline and a greater decline in function over 18 months are associated with an increase in caregiver burden at 36 months. Cognitive decline does not appear to affect the change in caregiver burden, while an increase in behavioural problems over 18 months are associated with a greater increase in caregiver burden at 36 months. In addition, a higher number of years of education for the patient and more patient co-morbidities were associated with faster increase in ZBI. Having an increasing number of caregivers in addition to the primary caregiver over 18 months was associated with a slower increase in caregiver burden. In the sensitivity analysis using MI, there was a minor difference in the results using baseline variables only, where the caregiver living with the patient was no longer significantly associated with greater increase in ZBI over 36 months. The MI model with time dependent variables replicated the findings of the primary analysis using MMRM. *Conclusion:* Decline in functional ability and behavioural symptoms over 18 months have a bigger impact on long-term informal caregiver burden than cognitive impairment. These results highlight the unique perspective of caregivers on the impact of AD and warrant their inclusion during evaluation of programs and interventions. Targeted support for caregivers and effective treatment options for patients could mitigate some of the impact of long-term informal caring. This study is sponsored and funded by Eli Lilly and Company Limited.

OC38: NEUROPROTECTIVE EFFECT OF A NEW PHOTOBIOMODULATION TECHNIQUE AGAINST AMYLOID AB25-35 PEPTIDE-INDUCED TOXICITY IN MICE. Guillaume J. Blivet[1], Johann Meunier[2], Francois J. Roman[2], Jacques Touchon[3,4] *((1) REGEnLIFE SAS, Montpellier, France; (2) Amylgen SAS, Montferrier-sur-Lez, France; (3) INSERM U1061, Montpellier, France; (4) Neurology Department, University of Montpellier, France)*

Background: Alzheimer's Disease (AD), the main cause of dementia, is a major public health problem because of the negative impact on patients and caregivers and the burden it creates for society. To date, a treatment able to slow or stop the progression of this pathology has yet to be identified and it appears that combination treatments engaging not only one but several targets are currently needed if we want to treat this complex neurodegenerative disorder. Photobiomodulation (PBM) has been used recently with encouraging results in animal studies. We present the results obtained with the application of a new device RGn500 combining photonic and magnetic emissions on the neurotoxic effects produced by Abeta 25-35 (Aβ25-35) oligomeric peptide central injection in mice. *Methods:* Aβ25-35 peptide induced toxicity: Male Swiss mice were injected intracerebro-venticularly with Aβ25-35 peptide or control scramble peptide. Seven days later, memory performances were evaluated with the Y-maze and the step through passive avoidance (STPA) tests before taking brain tissue samples for biochemical and immunohistochemical analyses. PBM treatment: RGn500n device was made with a near infrared (NIR) InAlGaAs laser (850nm) combined with a NIR LED (850nm) and a red LED (625nm). This photonic device is surrounded with a ring-shaped magnet creating a static magnetic field of 200mT. The photonic emissions were pulsed at a 10Hz frequency. Mice were manually restrained and the photonic emitters were applied at 1cm from the top of the head or the center of abdomen or both. Treatment was applied once a day for 7 days following the injection of Aβ25-35 peptide for a duration of 2.5, 5, 10 or 20 min. Protection against Aβ25-35 neurotoxicity was assessed first via a memory evaluation in two tests: spontaneous alternation performance in the Y-maze, an index of spatial working memory, and performance in the STPA test, an index of contextual long-term memory. Then, in the same animals, markers of inflammation, oxidative stress and cell integrity were measured in the brain as well as specific markers of AD (Aβ1-42 , pTau). *Results:* Our results clearly indicate that RGn500 treatment produced a neuroprotective effect in the Aβ25-35 mouse model after an application every day following peptide injection when the light beam was applied both on the head and on the abdomen and not when only the head or abdomen were irradiated. This protective effect was dependent on the time of application and a total reversal of deficits was obtained for 20 min of daily application. Protection against Aβ25-35 neurotoxicity was demonstrated both by memory restoration in the two tests that were investigated, Y-maze and STPA, and on the normalization of key markers of AD (Aβ1-42 , pTau), oxidative stress (lipid peroxidation), and cell integrity (Bax/Bcl2). Neuroinflammation was highly activated following Aβ25-35 injection and RGn500 treatment was able to fully reverse the elevation of TNFα as well as GFAP. In agreement with these biochemical measurements, immuno-histochemical observation of hippocampal slices showed that the activation of astrocytes and microglial cells was fully reversed by daily applications of RGn500. *Conclusion:* RGn500 displays therapeutic efficacy similar to other

pharmacological approaches evaluated in this model of AD. The efficacy of this treatment can be compared to what has been found in the same model by daily treatment with donepezil, one of the few compounds used in human, but also ibuprofen, an NSAID, a γ-secretase inhibitor (BMS299,897), a DYRK1A inhibitor (Leucittine L41), synthetic neurosteroids (ent-pregnenolone sulphate/ ent-DHEA) or sigma 1 receptor agonists (Anavex 2-73).

Late Breaking News

LB1: UTILIZING A PK/PD MODEL TO ENABLE DESIGN PRINCIPLES WITHIN THE GANTENERUMAB PHASE 3 GRADUATE PROGRAM. Gieschke[2], Daniel Serafin[2], Sylvie Retout[2], Paul Delmar[1], Mirjana Adjelkovic[1], Danielle Abi-Saab[1], Smiljana Milosavljevic-Ristic[1], Paulo Fontura[1], Carsten Hofmann[2] *((1) Roche Product Development, Neuroscience, Basel, Switzerland; (2) Roche Pharma Research and Early Development, Clinical Pharmacology and Bioanalytical R&D, Basel, Switzerland)*

Background: Gantenerumab is a fully human, anti-amyloid beta (Aβ) monoclonal antibody (mAb) that binds aggregated Aβ and promotes amyloid removal through Fc-gamma receptor mediated microglial phagocytosis. SCarlet RoAD (SR; NCT01224106) and Marguerite RoAD (MR; NCT02051608) evaluated monthly subcutaneous (SC) injections of gantenerumab up to 225 mg versus placebo on cognition and function in prodromal and mild Alzheimer's disease (AD), respectively. After a futility analysis in December 2014, SR dosing was suspended; MR recruitment stopped, and subjects in both studies entered an open label extension (OLE) in which we explored titration as well as safety and PK with higher doses of gantenerumab SC. Our analysis of the Scarlet Road data suggested an exposure related clinical effect (ADAS-Cog13) in a fast progressing group of patients (1). We used a combined approach of mathematical modeling techniques with actual clinical data from Scarlet Road and other monoclonal antibodies to estimate the dose of gantenerumab that would lead to a targeted PD effect (brain amyloid lowering by positron emission tomography [PET]). We are reporting in separate abstracts the safety profile of gantenerumab 1200 mg (2) as well as the effect of this dose on brain amyloid (3), both of which supported the validity of our model. *Methods:* In order to determine the best target dose above 225 mg in the absence of a formal dose-finding study, we constructed a PK-PET model. This model predicted that monthly SC doses of 1200 mg would result in composite amyloid PET SUVR reduction of around 20% at 1 year which we would expect to be associated with clinical benefit. To ensure an appropriate risk/benefit ratio at 1200 mg, our approach also included a PK-ARIA model prediction that utilized data from the lower dose gantenerumab study as well as publicly available data from other anti-Aβ monoclonal antibodies. Additionally, in our OLE we explored several different up-titration regimens designed based upon known risk factors for ARIA (dose, time on treatment, presence of ApoE4 allele). Throughout the OLE, MRI safety data were continuously added to the PK-ARIA model to optimize the dose-related safety prediction of the Phase 3 dosing regimen. *Results:* As of August 31 2017, N=381 patients have been enrolled in the OLE (N=373 received treatment). N= 247 had reached 1200 mg. PET SUVR relative to baseline decreased significantly (3) and fully confirmed the model-predicted percent of amyloid reduction. Safety information to date is indicative of an ARIA-E incidence well below the predicted incidence for a fixed 1200 mg dosing regimen without up-titration. Based on the integration of all the available information, we developed a single titration scheme for ApoE 4 allele carriers and non-carriers which enables the Phase 3 target dose while mitigating the increased risk of ARIA-E. *Conclusion:* Using clinical data from an earlier low-dose trial and PK-PD modeling, we established a target dose for our current Phase 3 studies that is approximately 5-fold higher than previously used. We explored this dose in the OLE of the previous trials and showed that, with the use of titration, we could mitigate the increased risk of ARIA despite the higher dose, and that the pharmacodynamic effect of the higher dose is within our targeted range. This approach to designing our currently underway Phase 3 studies maximizes benefit/risk ratio for patients regardless of ApoE genotype. 1. Retout et al. CTAD 2015; 2. Andjelkovic et al. CTAD 2017; 3. Klein et al. CTAD 2017

LB2: HIGHER DOSE GANTENERUMAB LEADS TO SIGNIFICANT REDUCTION IN AMYLOID PLAQUE BURDEN - RESULTS FOR THE MARGUERITE AND SCARLET ROAD OPEN LABEL EXTENSION STUDIES. Rachelle Doody[1], Ronald Gieschke[2], Daniel Serafin[2], Sylvie Retout[2], Paul Delmar[1], Mirjana Adjelkovic[1], Danielle Abi-Saab[1], Smiljana Milosavljevic-Ristic[1], Paulo Fontura[1], Carsten Hofmann[2] *((1) Roche Product Development, Neuroscience, Basel, Switzerland; (2) Roche Pharma Research and Early Development, Clinical Pharmacology and Bioanalytical R&D, Basel, Switzerland)*

Background: Gantenerumab (GANT) is a fully human, anti-amyloid beta (Aβ) monoclonal antibody (mAb) that binds aggregated Aβ and promotes amyloid removal by Fc-gamma receptor mediated microglial phagocytosis. Analyses of SCarlet RoAD (SR, NCT01224106), a randomized placebo controlled trial evaluating cognive and biomarker outcomes in GANT treated patients with prodromal AD, demonstrated a dose and time dependent amyloid plaque reduction. Mean standardized uptake value ratio (SUVR) reductions of up to 4.8% at 2 years for doses up to 225 mg sc q month were achieved. Following a pre-planned futility analysis, which demonstrated low likelihood to meet the study`s primary endpoint with doses applied (105 mg and 225 mg sc monthly), dosing was suspended in SR and both the SR and Marguerite RoAD (mild AD patients) (MR; NCT02051608) studies were converted to open label extension (OLE) to evaluate safety and efficacy of higher doses of ganterumab up to 1200 mg sc monthly. This work presents the amyloid PET results for a cohort of patients dosed at 1200 mg sc monthly in the OLE studies and followed longitudinally with florbetapir PET. *Methods:* Patients enrolled the SR and MR double-blind (DB) studies were eligible for participation in the OLE studies after ethics approval has been obtained and informed consent was signed. Based on modeled results of pharmakodynamic efficacy and safety from other mAb studies, patients were assigned to one of six different titration schedules (ranging from two to six months), all with a target top dose of 1200 mg sc per month. For patients enrolled in the PET substudy, change in amyloid burden was assessed by comparing florbetapir PET acquired at OLE baseline (OLE_BL) and OLE week 52 (OLE_WK52). To minimize patient burden, a new OLE_BL PET scan was not acquired if a patient already had a florbetapir scan from the DB period 12 months before first OLE dosing in SR, and prior to 9 months before OLE dosing in MR. Inclusion into the PET substudy required a positive visual read of the OLE_BL PET scan. Florbetapir PET scans were obtained as a 15 min (3x5 min) acquisition starting at 50 minutes post-injection and pre-processed as previously described1. The florbetapir global cortical signal was calculated as the volume-weighted, grey-matter masked average SUVR of five bilateral cortical regions based on the Automated Anatomical Labeling (AAL) template: anterior and posterior cingulate cortex, parietal, lateral temporal, and frontal cortex2 using sampled cerebellar cortex

as the reference region for intensity normalization. Percent change in SUVR was calculated as 100 *(SUVROLE_BL- SUVROLE_wk52)/ SUVROLE_BL, where SUVROLE_BL and SUVROLE_wk52 are the SUVr values computed at OLE baseline and week 52 PET visits respectively. For assessment of the significance of amyloid SUVR reduction, a SUVR cutpoint for amyloid positivity is obtained by transforming well-known 1.1 ADNI SUVR threshold reported using a whole cerebellum reference and a linear regression technique 3. Patients included into the analyses meeting criteria for high-dose PET analysis were all those who reached ≥ 900 mg doses for six or more months. Because of considerable differences in the titration schedules, time off dose between the DB and start of OLE dosing, and timing of the OLE baseline PET compared to the start of OLE dosing, analysis was split into three groups: patients from the MR DB placebo arm (MR-Pbo), from the MR DB on active gantenerumab treatement (MR-Gant) and patients from SR DB (SR). *Results:* Of the 81 patients initially enrolled in the OLE PET substudies, 40 patients (14 in MR-Pbo, 17 in MR-Gant, 9 in SR) met the criteria for high dose analysis by the cutoff date of August 31, 2017. Median times between the OLE_BL PET scan and start of OLE dosing were 10, 18 and 1.5 weeks for the MR-Pbo, MR-Gant and SR groups respectively. Median times between OLE_BL and OLE_WK52 PET scans were 62, 72 and 56 weeks for the three groups. The average number of 1200 mg doses received in each cohort in the high-dose analysis were 7.25, 9.91 and 5.875. Mean (SD) percent SUVR change seen in the three groups were -12.4 (9.0), -15.7 (7.3) and -7.3 (8.8). Overall, for patients meeting high dose criteria, approximately one third had amyloid levels below the cut point for amyloid positivity at the week 52 PET exam. *Conclusions:* The study showed significantly higher reductions of amyloid plaque are seen with the 1200 mg dosing regimen of gantenerumab compared to 105 or 225 mg dosing. Results in this ongoing study confirm the amyloid plaque removal component of the ganterumab mechanisms of action, and show that within a 6–12 month high-dose treatment period, approximately one third of subjects achieved below threshold PET SUVR signals based on quantitative measures. References: 1. Fleisher et al. Arch Neurol. 2011;68(11):1404–11; 2. Rowe et al. Lancet Neurol. 2008;7(2):129–35; 3. Landau et al. Nucl Med. 2015;56(4):567–74

LB3: EFFICACY AND SAFETY OF S 47445, A MODULATOR OF AMPA GLUTAMATERGIC RECEPTORS, IN PATIENTS SUFFERING FROM ALZHEIMER'S DISEASE AT MILD TO MODERATE STAGE WITH DEPRESSIVE SYMPTOMS.

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Background: Patients with Alzheimer's Disease (AD) present with memory impairment and other cognitive disorders leading to an alteration of functionality and dependence. These patients also present neuropsychiatric symptoms, which have a negative impact on cognition, functionality, quality of life and caregiver burden. In particular, depressive symptoms are frequently associated with AD, around 3 in every 4 AD patients developing depression over a period of 5 years. However, little is known about the course of these symptoms and their impact on cognition. S 47445 is a positive allosteric modulator of AMPA glutamateric receptors that demonstrated both procognitive and antidepressant-like properties in several animal models. S 47445 modulates synaptic plasticity by enhancing Long Term Potentiation and by increasing neurotrophic factors expression as BDNF. Based on these observations, S 47445 has emerged as a favourable candidate for the treatment of memory deficits, depressive symptoms and synaptic dysfunction associated with Alzheimer's disease. In healthy volunteers, S 47445 enhances functional connectivity between brain networks and increases glutamate concentration in posterior cingulate cortex (Ciuciu et al., in submission) and plasma BDNF. *Study design and main criteria:* The study was a 24-week international, randomized, double-blind, placebo-controlled phase II, 4-arm study in monotherapy followed by an optional 28-week extension period in co-administration with donepezil. The primary objective of this trial was to demonstrate the superiority of at least one dose of S 47445 versus placebo after 24 weeks of treatment on the 11-item ADAS-Cog total score (cognition). Other secondary endpoints include efficacy on functionality (DAD total score), depressive symptoms (CSDD), neuropsychiatric symptoms (NPI) and global clinical impression of change (CGIC) as well as safety criteria. Patients entering in the study fulfilled the following main selection criteria: Male or female out-patients, 65-85 years old, DSM-IV-TR criteria for Dementia of the Alzheimer's Type, MMSE total score between 15 and 24, National Institute of Mental Health (NIMH) provisional criteria for depression in AD (NIMH-dAD), Cornell Scale for Depression in Dementia (CSDD) total score ≥ 8. Patients at inclusion had no treatments for AD (acetylcholine esterase inhibitors and memantine) and any antidepressants or antipsychotics. Five hundred and twenty AD patients were included and randomized (1:1:1:1) to S 47445 (5, 15 or 50 mg/day) or placebo, 53 % were at a mild and 47% at a moderate stage of the disease. *Results:*At baseline, values of main scales were as follows (mean score ± SD): MMSE 19.7 ± 2.8, ADAS-Cog 11-item 23.6 ± 9, ADAS-Cog 13-item 34.9 ± 10.7, DAD 68 ± 18.6, CSDD 12 ± 3.5, NPI 12-item 22.4 ± 13.4 corresponding to a profile of AD patients with depressive symptoms. Baseline characteristics were comparable in the 4 arms. After 24 weeks of treatment, no significant differences between treatment groups and placebo were shown in either the primary or secondary outcomes, except a significant difference in the NPI total score with 5 mg (Δ -2.55, p=0.023). The highest difference observed for the primary endpoint, ADAS-Cog was Δ -0.90 (NS) with S 47445 15mg. Results were similar in mild or moderate patients. CSDD score notably improved (mean around -5 points) in all treatment groups and placebo over time. This improvement was observed all along the study and whatever the severity of the depressive symptoms. Patients presenting a higher score in depressive symptoms (CSDD ≥12) showed a better improvement in cognition than patients with less depressive symptoms, suggesting that improvement of depression leads to a better cognitive performance. NPI score also improved in all groups and all along the study, with a mean decrease of around 8 points from baseline in the placebo group. S 47445 at 15 and 50 mg do not differ from the placebo group, but there was a significant difference at 5 mg (p=0.023). In this group, items which improve the most were agitation, depression, anxiety, apathy, irritability and sleep disorders. More than 60% of patients at 5 mg/day experienced an improvement in all these symptoms. *Conclusion:* Given the procognitive and antidepressant properties of S 47445, a positive modulator of AMPA receptors, AD patients with depressive symptoms were selected in this study. S 47445 was safe and well tolerated but failed to improve cognition, depressive symptoms or functional ability in patients with AD and depressive symptoms. The slight improvement observed with S 47445 at the lower dose in neuropsychiatric symptoms does not allow the continuation of clinical development.

LB4: PHASE IIA STUDY RESULTS WITH THE GLUTAMINYLCYCLASE INHIBITOR PQ912 IN EARLY ALZHEIMER'S DISEASE. Philip Scheltens[1], Merja Hallikainen[2], Timo Grimmer[3], Thomas Duning[4], Alida A. Gouw[1,5], Alle Meije Wink[6], Paul Maruff[7], G. Caroline M. van Baal[8], Suzanne Bruins[9], Inge Lues[10], Charlotte E. Teunissen[11], Niels D. Prins[1] *((1) Alzheimer Centre and Department of Neurology, Amsterdam Neuroscience, VU University Medical Centre, Amsterdam, The Netherlands; (2) University of Eastern Finland, Institute of Clinical Medicine, Kuopio, Finland; (3) Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; (4) Department of Neurology, University of Münster, Münster, Germany; (5) Department of Clinical Neurophysiology and MEG Center, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, The Netherlands; (6) Department of Radiology, Nuclear Medicine and PET Research, Amsterdam Neuroscience, VU University Medical Centre, Amsterdam, The Netherlands; (7) Cogstate Ltd., Melbourne, Australia; (8) Julius Center for Health Sciences and Primary Care, UMC Utrecht, The Netherlands; (9) Julius Clinical, Zeist, The Netherlands; (10) Probiodrug AG, Halle, Germany; (11) Neurochemistry Laboratory and Biobank, Department of Clinical Chemistry, Amsterdam Neuroscience, VU University Medical Centre, Amsterdam, The Netherlands)*

Introduction: Most Aβ peptides deposited in Alzheimer's disease (AD) are truncated and modified post-translationally at the N-terminus. Among these modified species, pyroglutamyl-Aβ (pGlu-A β=N3pEAbeta) has been identified as particularly synapto- and neurotoxic. The formation of pyroglutamyl residues is catalyzed by the enzyme glutaminylcyclase (QC). The small molecule PQ912 targets the inhibition of QC resulting in a reduction of the formation of synapto- and neurotoxic pyro-Glu-Aβ and related oligomers. PQ912 has been investigated extensively in a Phase I MAD where it showed good tolerability and a dose dependent QC-inhibition in cerebrospinal fluid (CSF). In this first in-patient study (SAPHIR), a high dose of 800 mg bid achieving about 90% QC-occupancy was studied in treatment naïve early AD patients over 12 weeks to meet two objectives: to get a first impression of the frequency and types of safety and tolerability events (primary objective), and at the same time to test for early signals of efficacy (secondary exploratory objective). *Methods:* In the double blind SAPHIR study 120 patients were assigned randomly to receive placebo (n=60) or PQ912 (n=60). Treatment arms were equivalent for age, gender, disease severity and APOE4 status. Mean MMSE score at baseline was 25.5 (range 21-30). Statistical analysis of the endpoints were based on two-sided tests with a statistical significance set to $p< 0.05$, with adjustment for covariates. Multiplicity correction was not used. Results presented are for the Intention to treat (ITT) for the primary endpoints, and imputed ITT for all secondary endpoints (one exception is CSF, where the per protocol (PP) population is also used). *Results:* Safety and tolerability: No statistically significant differences were observed between treatment conditions for the number of patients experiencing an adverse event (PQ912 n=49, placebo n=45) and in the number of patients with a serious adverse event (PQ912 n=8; placebo n=5). The PQ912 treatment arm showed a higher discontinuation rate due to SAE or grade 3 adverse events compared to placebo (PQ912 n=6; placebo n=0, p=0.027). The number of patients non-adherent to randomized treatment for any reason was also higher in the PQ912 treatment arm (n=26) than in placebo (n= 2; $p<0.01$). Skin and gastrointestinal organ system related adverse events were more frequent in the PQ912 arm than in placebo and occurred most frequently in the first half of the treatment period. Dose reductions prescribed by the investigator were identical in the treatment and the placebo arm (both n=5). *Secondary exploratory endpoints:* Analysis of the CSF -molecular biomarkers showed QC inhibition (p=0.001), corresponding to a calculated target occupancy of 92%. CSF pGlu-Aβ oligomers decreased in the PQ912 treatment arm but increased in the placebo arm. This directional change demonstrates together with the significant QC enzyme inhibition a strong and robust target occupancy. There was a trend for reduction in the level of neurogranin, a marker of synaptic dysfunction in the ITT population in the PQ912 treatment arm compared to placebo (p=0.085 ITT), which became significant if 3 patients starting prohibited concomitant medication during the study were excluded (p=0.036). There was also a stronger reduction of YKL 40, a biomarker of inflammation, in the PQ912 treatment arm compared to placebo (p= 0.052 ITT). Analysis of eyes closed task free EEG oscillatory activity showed that global relative theta power (4 – 8 Hz) was significantly reduced in the PQ912 arm compared to placebo (p=0.002, Cohen's D=0.29, ITT, p=0,002, Cohen's D=0,38 PP). Slow wave theta activity is reported to increase with the onset and progression of AD. Analysis of neuropsychological outcomes showed stable performance for patients in the placebo arm with no statistical significant change between baseline and week 12. Compared to placebo, the PQ912 treatment arm was associated with meaningful improvements in working memory (One Card Back test p=0.05, Cohen's D = 0.23) and psychomotor function (Detection test, Cohen's D=0.21). Performance on the five other cognitive assessments, as well as on their aggregate scores, were not influenced by treatment with PQ912 for 12 weeks (Cohen`s D < 0.2). *Conclusion:* Lower tolerability in the PQ912 arm may require dose adaptation in further studies. The beneficial effects of PQ912 treatment on a working memory task, EEG theta power, and synaptic and inflammatory CSF markers suggest a direct effect of PQ912 on pGlu-Aβ with positive effects on synaptic function, even with a short treatment period. Together, these characteristics of the effect of PQ912 on AD are encouraging and provide a rationale for further studies of longer duration in this disease.

LB5: TARGETING TAU WITH RO7105705: PHASE I RESULTS AND DESIGN OF A PHASE II STUDY IN PRODROMAL-TO-MILD AD. Geoffrey A. Kerchner, Gai Ayalon, Mira Blendstrup, Flavia Brunstein, Priya Chandra, Akash Datwani, Reina N. Fuji, Paul Manser, Rajesh Menon, Sandra Sanabria Bohorquez, Edmond Teng, Michael Ward, Robby Weimer, Kristin R. Wildsmith, Corinne Foo-Atkins *(Genentech, Inc., a member of the Roche Group, South San Francisco, CA, USA)*

Background: RO7105705 is a humanized anti-tau monoclonal antibody in development for the treatment of Alzheimer's disease (AD) and other neurodegenerative diseases. RO7105705 binds specifically to tau and is intended to intercept tau in the extracellular space of the brain, thereby blocking cell-to-cell spread of tau pathology. No adverse effects related to administration of RO7105705 were observed in non-clinical safety studies, enabling a first-in-human study. *Methods:* The completed Phase I trial was a randomized, double-blind, placebo-controlled study conducted in healthy volunteers aged 18-80 years old, as well as in patients with a diagnosis of probable AD (by NIA-AA criteria) aged 50-80 years old, with a MMSE score of 16-28, a CDR global score of 0.5, 1, or 2, and a [18F]florbetapir PET scan positive by visual read for cerebral amyloid. The study was designed with a single-dose escalation stage in healthy volunteers, followed by a multiple-dose stage in healthy volunteers and in participants with AD, in which participants received study drug once weekly for four doses. RO7105705 was administered intravenously or subcutaneously. The primary objective was to evaluate the safety of single and multiple

doses of RO7105705 compared with placebo. The ongoing Phase II trial is a randomized, double-blind, placebo-controlled, parallel arm study conducted in patients aged 50-80 who meet NIA-AA criteria for probable AD dementia or MCI, with a MMSE score of 20-30, a CDR score of 0.5 or 1, evidence of amyloid pathology by PET or CSF, and evidence of episodic memory impairment by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) delayed memory index. Participants receive one of three active doses of RO7105705 or placebo for 68 weeks, followed by an optional open label extension. The primary endpoints include safety, tolerability, and change from baseline in CDR sum of boxes. Change from baseline in tau pathological burden, assessed by [18F]GTP1-PET imaging, is an important exploratory endpoint. *Results:* The Phase I study included 65 healthy volunteers and 10 participants with AD. RO7105705 was safe and well-tolerated at all doses administered. There were no dose limiting adverse events, no serious adverse events, no deaths, and no discontinuations due to an adverse event reported. Thirty-two participants (43%) experienced an adverse event, and all adverse events were non-serious Grade 1 or Grade 2. Nine participants (12%) experienced an adverse event reported as being related to study drug. Grade 1 injection site reaction was the only adverse event attributed to RO7105705 in >1 participant. A median terminal half-life of 32.3 days was observed after single intravenous doses. Plasma total tau increased with increasing doses of RO7105705, with a plateau observed at the higher doses. Participants with AD demonstrated a larger increase in plasma total tau after RO7105705 administration than healthy volunteers. *Conclusion:* RO7105705 appeared safe and well tolerated in a Phase I study of healthy volunteers and participants with AD. Plasma total tau concentration increased with increasing RO7105705 dose and was greater in participants with AD than in healthy volunteers, suggesting a pharmacodynamic signal. An ongoing Phase II study is designed to test both safety and efficacy of chronic RO7105705 therapy in participants with prodromal-to-mild AD.

LB6: PLASMA AB42/40 DETECTS EARLY STAGES OF AD IN THE AB255 STUDY AND CORRELATES WITH NEUROIMAGING AND CSF BIOMARKERS. Virginia Pérez-Grijalba[1], Judith Romero[1], Pedro Pesini[1], Leticia Sarasa[1], Itziar San-José[1], Javier Arbizu[2], Pablo Martínez-Lage[3], Lluis Tárraga[4], Agustín Ruiz[4], Mercè Boada[4], Manuel Sarasa1 and The AB255 Araclon Group[5] *((1) Araclon Biotech S.L., Zaragoza, Spain; (2) Clínica Universitaria de Pamplona, Pamplona, Spain; (3) Fundación CITA-Alzheimer, San Sebastián, Spain; (4) Fundació ACE. Barcelona Alzheimer Treatment and Research Center. Barcelona, Spain; (5) www.araclon.com)*

Background: Easily accessible biomarkers are needed for the early identification of individuals at risk of developing Alzheimer's disease (AD) in large population screening strategies and clinical trial recruitment. Neuroimaging and CSF biomarkers have become well-accepted biomarkers for AD, although their restricted availability, economic costs and invasiveness limit their utility in primary care clinical practice. On the other hand, more cost-effective and accessible tools, such as blood-based biomarkers, have shown limited consistency to date, with controversial results from different studies. The AB255 study was designed to evaluate Aβ blood-based biomarkers to identify MCI patients and predict progression to dementia. Additionally, in the present work we have assessed the agreement of total plasma Aβ42/40 (TP42/40) with multiple well established biomarkers of AD, such as Aβ-PET, FDG-PET and CSF biomarkers to prove its robustness as an AD biomarker. *Methods:* Total plasma Aβ42/40 ratio (TP42/40) was determined in 83 cognitively normal (CN) individuals and 145 subjects with (probable) amnesic mild cognitive impairment (aMCI) [1] from the AB255 Study, using ABtest kits (Araclon Biotech, Zaragoza, Spain). This population was followed for 24 months, with visits at baseline, 12 months and 24 months. All MCI participants underwent further classification based on a FDG-PET neuroimaging pattern suggestive, or not, of AD [2]. PiB-PET scans were carried out in 58 of the 228 participants, and CSF biomarkers (tTau, pTau, Aβ40 and Aβ42) were also determined in a different subpopulation of 43 individuals. The strength of the association of plasma TP42/40 with both CSF and PiB-PET biomarkers was evaluated using Spearman rank correlation. Generalized linear models were carried out to assess differences in TP42/40 levels between groups, and logistic regression was performed to evaluate the ability of TP42/40 to identify progression from MCI to AD. Every model was adjusted for age, education and APOE genotype. *Results:* Individuals with mild cognitive impairment showed significantly lower TP42/40 levels (p 0.028) than CN subjects in a consistent pattern during the whole follow-up. Additionally, the likelihood of progression to AD after 2 years was 2-fold higher in those aMCI participants with low TP42/40 levels at baseline (OR 2.4, CI 95% 1.2-5.0). Furthermore, TP42/40 ratio was also lower in MCI subjects with a FDG-PET suggestive of AD when compared to a negative FDG-PET pattern (p 0.003). There was a significant and inverse correlation between TP42/40 and PiB-PET levels (Spearman coefficient rs -0.464, p<0.001). Likewise, TP42/40 was concordant with the AD biomarker profile in CSF. A low TP42/40 ratio was associated with higher pTau (rs -0.329, p 0.031) and tTau (rs -0.314, p 0.040), as well as with lower Aβ42 levels (rs 0.549, p<0.001) in CSF. Furthermore, the levels of total Aβ42/40 ratio measured in plasma reflected those existing in CSF, showing a significant direct association (rs 0.407, p 0.008). *Conclusions:* These results show a robust and inverse association between the total plasma Aβ42/40 ratio and Alzheimer's disease. TP42/40 demonstrated value in the identification of individuals suffering a mild cognitive impairment, in the prediction of their progression to AD and in the detection of underlying AD pathology revealed by FDG-PET, PiB-PET and CSF biomarkers. Thus, TP42/40 was consistently associated with all the well-established indicators of AD, showing utility as a highly accessible biomarker in clinical trial enrichment and large population screening. References: [1] Espinosa A. et al., J Alzheimers Dis 2013; 34(3):769-80. [2] Arbizu J. et al., Eur J Nucl Med Mol Imaging 2013 Sep; 40(9):1394-405.

LB7: ADUCANUMAB 36-MONTH DATA FROM PRIME: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 1B STUDY IN PATIENTS WITH PRODROMAL OR MILD ALZHEIMER'S DISEASE. Samantha Budd Haeberlein[1], Sarah Gheuens[1], Tianle Chen[1], John O'Gorman[1], Philipp von Rosenstiel[1], Ping Chiao[1], Guanfang Wang[2], Christian von Hehn[1], LeAnne Skordos[1], Christoph Hock[3], Roger M Nitsch[3], Alfred Sandrock[1] *((1) Biogen, Cambridge, MA, USA; (2) Cytel, Cambridge, MA, USA; (3) Neurimmune, Schlieren-Zurich, and University of Zurich, Switzerland)*

Background: 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 or mild AD.1 Here, we report 36-month data for the fixed dose cohorts, 12 months of the placebo-controlled period and the first 24 months of the long term extension (LTE) period of PRIME. *Methods:* Patients included in this randomized, double-blind, placebo-controlled study (PRIME; NCT01677572) were aged 50-90 years, had a positive florbetapir positron emission tomography (PET) scan, and met clinical criteria for prodromal or mild AD.

During the double-blind, placebo controlled phase, patients received aducanumab or placebo once every 4 weeks for 52 weeks. In a staggered, parallel-group design, patients were randomized to fixed doses of aducanumab (1-10 mg/kg) stratified by apolipoprotein E4 (ApoE ε4) status (carrier/non-carrier). The study also included a dose titration cohort (not reported here; 36-month data for the titration cohort are not yet available). Patients meeting eligibility criteria at Week 56 were enrolled in the LTE, where all patients were assigned to receive aducanumab 3, 6, or 10 mg/kg. Dose assignments in the LTE were as follows: patients who had received placebo during the double-blind phase were assigned treatment to either aducanumab 3 mg/kg or a titration regimen of aducanumab 3 to 6 mg/kg (2 doses of 3 mg/kg followed by subsequent doses of 6 mg/kg) in the LTE. Patients who were randomized to receive aducanumab 1 mg/kg during the double-blind phase subsequently were assigned to receive aducanumab 3 mg/kg in the LTE. All other patients who received fixed doses of aducanumab (3, 6, or 10 mg/kg) during the double-blind phase continued at their original dose assignment or reduced dose. In the LTE, with the exception of safety, all endpoints were exploratory and included measurement of Aβ reduction using amyloid PET (as assessed by standard uptake value ratio) and change from baseline in the clinical endpoints Clinical Dementia Rating-Sum of Boxes (CDR-SB) scale and the MMSE. A mixed model for repeated measures was used for the analysis of change from baseline in amyloid PET, CDR-SB and MMSE. *Results:* Of 165 patients randomized and dosed in PRIME within the fixed-dose cohorts, 117 were dosed in the LTE and 77 completed treatment at Month 36. In patients treated up to 36 months, amyloid plaque as measured by PET continued to decrease in a dose- and time-dependent manner, with amyloid plaque levels in the 10 mg/kg fixed-dose treatment group reaching and remaining at a level considered below the quantitative cut-point that discriminates between a positive and negative scan.2 Decreases in brain amyloid plaque burden were also observed among patients switched from placebo to aducanumab in the LTE. CDR-SB and MMSE data suggest a clinical benefit in patients continuing aducanumab over 36 months. No new ARIA-E cases were observed during the first two years of the LTE in patients in the fixed-dose cohorts who continued on the same dose of aducanumab. One subject in the fixed-dose cohorts experienced recurrent ARIA-E after the first two years of the LTE. The incidence of ARIA-E in patients switching from placebo to aducanumab was consistent with the incidence reported in the placebo-controlled portion of the Phase 1b study. *Conclusions:* In this small population of patients from the fixed-dose cohorts treated up to 36 months, amyloid plaque, as measured by PET, continued to decrease in a dose- and time-dependent manner. Analyses of exploratory clinical endpoints CDR-SB and MMSE suggest a continued benefit on the rate of clinical decline during the third year of treatment. Recurring ARIA events were consistent with other ARIA events reported to date. No new safety signals were identified at 36 months. These data support further investigation of the clinical efficacy and safety 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. Landau SM, et al. Ann Neurol. 2012;72: 578–586.

LB8: POLYGENIC HAZARD SCORE: AN ENRICHMENT MARKER FOR ALZHEIMER'S ASSOCIATED AMYLOID AND TAU DEPOSITION. Chin Hong Tan[1], Chun Chieh Fan[2], Elizabeth C. Mormino[3], Leo P. Sugrue[1], Iris J. Broce[1], Christopher P. Hess[1], William P. Dillon[1], Luke W. Bonham[4], Jennifer S. Yokoyama[4], Celeste M. Karch[5], James B. Brewer[6,7], Gil D. Rabinovici[4], Bruce L. Miller[4], Gerard D. Schellenberg[8], Karolina Kauppi[7], Howard A. Feldman[6], Dominic Holland[6], Linda K. McEvoy[7], Bradley T. Hyman[9], Ole A. Andreassen[10], Anders M. Dale[2,6,7], Rahul S. Desikan[1,4] for the Alzheimer's Disease Neuroimaging Initiative) *((1) Department of Radiology and Biomedical Imaging, UCSF, San Francisco, CA, USA; (2) Department of Cognitive Science, UCSD, La Jolla, CA, USA; (3) Department of Neurology & Neurological Sciences, Stanford University, Stanford, CA, USA; (4) Department of Neurology, UCSF, San Francisco, CA, USA; (5) Department of Psychiatry, Washington University in St. Louis, St. Louis, MO, USA; (6) Department of Neurosciences, UCSD, La Jolla, CA, USA; (7) Department of Radiology, UCSD, La Jolla, CA, USA; (8) Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA; (9) Department of Neurology, MGH, Boston, MA, USA; (10) NORMENT Institute of Clinical Medicine, University of Oslo, Oslo, Norway)*

Backgrounds: There is an urgent need for identifying nondemented individuals at the highest risk of progressing to Alzheimer's disease (AD) dementia. Here, we evaluated whether a recently validated polygenic hazard score (PHS) can be integrated with known in vivo CSF or PET biomarkers of amyloid, and CSF tau pathology to prospectively predict cognitive and clinical decline in nondemented older individuals. *Methods:* We focused on 347 cognitive normal (CN) and 599 mild cognitively impaired (MCI) individuals. We evaluated enrichment in positive and negative predictive values of CSF or PET amyloid, and CSF tau as a function of PHS risk. We used linear mixed-effects (LME) analyses to examine if PHS and biomarker status in conjunction, best predict longitudinal cognitive and clinical progression. Using survival analysis we investigated whether a combination of PHS and biomarker positivity best predicts time to AD dementia progression. *Results:* In CN and MCI individuals, we found that amyloid and total tau positivity systematically varies as a function of PHS. For individuals in greater than the 50th percentile PHS, the positive predictive value for amyloid approached 100%. Similarly, for individuals in less than the 25th percentile PHS, the negative predictive value for total tau approached 85%. Beyond APOE, high PHS individuals with amyloid and tau pathology showed the steepest longitudinal cognitive decline and time to AD dementia progression. Among the CN subgroup, we similarly found that PHS was strongly associated with amyloid positivity and the combination of PHS and biomarker status significantly predicted longitudinal clinical progression. *Conclusion:* Among nondemented older individuals, PHS considerably improves the predictive value of amyloid, and tau biomarkers for evaluating longitudinal AD-associated cognitive and clinical decline. Beyond APOE, PHS may be useful in MCI and preclinical AD therapeutic trials to enrich for biomarker positive individuals at highest risk for short-term clinical progression.

LB9: AMYLIN TYPE PEPTIDES AS A NEW THERAPEUTIC AVENUE FOR ALZHEIMER'S DISEASE. Wendy Qiu[1,2] Haihao Zhu[3], Robert A. Stern[1], Qiushan Tao[3], Gustavo A. Mercier[4], Martin Farlow[5], Neil Kowall[1] *((1) Alzheimer's Disease Center; (2) Department of Psychiatry, Boston University School of Medicine, Boston, MA; (3) Department of Pharmacology, Boston University School of Medicine; (4) Department of Radiology, Boston University School of Medicine, Boston, MA, USA; (5) Alzheimer's Disease Center, Indiana University, Indianapolis, IN, USA)*

Backgrounds: Amylin is an important gut-brain axis hormone. Since amylin and amyloid-β peptide (Aβ) share similar β sheet secondary structure despite not having the same primary sequences, we hypothesized that the accumulation of Aβ in the brains of subjects with Alzheimer's disease (AD) might compete with amylin for binding to the amylin receptor (AmR). If true, adding exogenous amylin type peptides would compete with Aβ and reduce the AD pathological cascade, improving cognition and the amylin clinical analog, pramlintide, can be translated into humans for AD. *Methods:* First we used AD mouse models to detect the effects of amylin and its clinical analog, pramlintide, on AD pathology and behavior tests. Second, we conducted a pilot clinical trial with one injection of pramlintide in non-diabetic humans. *Results:* A 10-week course of peripheral treatment with human amylin significantly reduced multiple different markers associated with AD pathology, including reducing levels of phospho-tau, insoluble tau, two inflammatory markers (Iba1 and CD68), as well as cerebral Aβ. The treatment improves learning and memory in these mice. In the pilot clinical trial, none of the participants developed hypoglycemia after the injection of pramlintide. The pramlintide challenge induced a significant surge of Aβ and a decrease of total tau in the plasma of AD, but not in control participants. *Conclusions:* Amylin type peptide treatment reduces AD pathological cascade corresponding to improved cognition. Pramlintide, the diabetes drug and amylin analog, is safe even among participants who do not have diabetes and under fasting condition. The human data supports that pramlintide might exhibit utility as a therapeutic agent for AD and other neurodegenerative diseases.

LB10: INITIAL EXPERIENCE WITH PET IMAGING OF SYNAPTIC DENSITY (SV2A) IN ALZHEIMER'S DISEASE: A NEW BIOMARKER FOR CLINICAL TRIALS? Ming-Kai Chen[1], Adam P. Mecca[2], Mika Naganawa[1], Sjoerd J. Finnema[1], Takuya Toyonaga[1], Shu-fei Lin[1], Julia W. McDonald[2], Hannah R. Michalak[2], Nabeel B. Nabulsi[1], Yiyun Huang[1], Amy F. T. Arnsten[3], Richard E. Carson[1,4], Christopher H. van Dyck[2,3,5] *((1) Department of Radiology and Biomedical Imaging, Yale Positron Emission Tomography Center, Yale University, New Haven, CT, USA; (2) Department of Psychiatry, Yale University, New Haven, CT, USA; (3) Department of Neuroscience, Yale University, New Haven, CT, USA; (4) Department of Biomedical Engineering, Yale University, New Haven, CT, USA; (5) Department of Neurology, Yale University, New Haven, CT, USA)*

Backgrounds: The ability to measure synaptic density in vivo would accelerate the development of disease-modifying treatments for Alzheimer's disease (AD). Positron Emission Tomography (PET) imaging of glucose metabolism with 18F-fluorodeoxyglucose (18F-FDG) has been widely used to measure neuronal activity and to track the progression of AD. However, 18F-FDG PET is not a direct biomarker of synaptic density and may be affected by stimulation, medications, and blood glucose. Therefore, tracers for new molecular targets are needed to directly monitor synaptic density. One suitable target is the synaptic vesicle glycoprotein 2 (SV2), an essential vesicle membrane protein. One of its isoforms, SV2A, is ubiquitously present in presynaptic terminals and is involved in regulation of synaptic vesicle trafficking. Thus, SV2A imaging could provide a highly useful indicator of synaptic density in AD. We recently developed 11C-UCB-J (11C-APP311), a PET tracer for quantitative SV2A imaging in vivo and carried out the first-in-human studies (Finnema SJ, et al. Sci Transl Med. 2016;8:348). *Methods:* Here we compare SV2A density as measured by 11C-UCB-J in 10 participants with AD and 11 who were cognitively normal (CN). AD participants (72.9 ± 8.7 years, CDR=0.5–1.0, MMSE=24.1±4.8) were all confirmed Aβ+ by 11C-Pittsburgh Compound B (11C-PiB) PET and spanned the disease stages from amnestic Mild Cognitive Impairment (aMCI, n=5) to mild dementia (n=5). CN participants (72.7 ± 6.3 years, CDR=0, MMSE=29.3±1.2) were all confirmed Aβ– by 11C-PiB PET. Participants were scanned on the HRRT after bolus injection of 11C-UCB-J. Arterial blood samples were collected for measurements of radiometabolites and free fraction in 9 AD and 8 CN participants. Regional time-activity curves were analyzed with the 1-tissue (1T) compartment model (Finnema SJ, et al, J Cereb Blood Flow Metab. 2017) to estimate volume of distribution (VT). Using the centrum semiovale as a reference region, regional BPND values (VT ROI/ VT centrum semiovale – 1) were also estimated for the full sample. We hypothesized a reduction in hippocampal uptake, based on the early degeneration of entorhinal cortical cells projecting to hippocampus (via the perforant pathway) and evidence from postmortem studies of hippocampal SV2A reductions in AD. *Results:* AD participants—compared to CN participants—demonstrated significant reductions in hippocampal SV2A binding as assessed by 11C-UCB-J BPND ($p=0.005$, t-test) and VT ($p=0.011$). These reductions persisted after partial volume correction (BPND: $p=0.020$, VT: $p=0.056$). Exploratory analyses of other brain regions of interest and statistical parametric mapping (SPM) also revealed reductions in entorhinal cortex. Hippocampal SV2A binding was correlated with a composite episodic memory score in the overall sample. *Conclusion:* 11C-UCB-J PET may provide a direct measure of synaptic density in AD. Further study is needed to determine if the pattern of SV2A reductions in AD, as measured by 11C-UCB-J PET differs from that for 18F-FDG. SV2A PET imaging with 11C-UCB-J may hold promise as an in vivo biomarker and outcome measure for trials of disease-modifying therapies—particularly those that target the preservation and restoration of synapses in AD.

LB11: EARLY CHANGE IN RETINAL STRUCTURAL ANATOMY DURING THE PRECLINICAL STAGE OF ALZHEIMER'S DISEASE. Peter J. Snyder[1], Cláudia Y. Santos[2], Jessica Alber[1], Lenworth N. Johnson[3], Stuart Sinoff[4], Paul Maruff[5,6] *((1) Department of Neurology, Rhode Island Hospital & Alpert Medical School of Brown University, Providence, RI, USA; (2) Interdisciplinary Neuroscience Program, University of Rhode Island, Kingston, RI, USA; (3) Department of Ophthalmology, Rhode Island Hospital & Alpert Medical School of Brown University, Providence, RI, USA; (4) Department of Neurology, BayCare Medical Group, Clearwater, FL, USA; (5) Florey Institute of Neuroscience and Mental Health, University of Melbourne, Victoria, Australia; (6) Cogstate Ltd., Melbourne, Victoria, Australia)*

Background: Over the past two decades there have been dozens of papers published that explore retinal correlates of Alzheimer's disease (AD) with high-resolution optical methods, such as spectral domain optical coherence tomography (SD-OCT). This literature, consisting mostly of cross-sectional studies, has led to a variety of intriguing findings, but very few have sought to compare retinal anatomic differences to other direct biomarkers of AD (e.g., PET amyloid

imaging). Moreover, virtually no prior efforts have focused on retinal anatomic change(s) in the preclinical stage of AD. We have followed 56 individuals with significant risk for AD, and have measured change in all six retinal neuronal layers over 27 months, comparing any such retinal changes to PET amyloid neocortical binding. *Methods:* Fifty-six non-glaucomatous adults (mean age = 62.7 years), with 1st-degree family history for AD and subjective memory complaints, were recruited using inclusion/exclusion criteria described previously (Lim et al., 2015). All were cognitively healthy, and many were caretakers for a living parent with AD. Aβ status and APOE genotype were unknown at study entry and were not used to determine enrollment. All participants completed florbetapir Aβ PET scans, and SUVr threshold of 1.1 was used to discriminate between Aβ+ and Aβ- (MIMneuro software). Amyloid positivity was confirmed by consensus over-read by two radiologists who are board certified in nuclear medicine. Fifteen of 56 subjects were determined to be both Aβ positive and they all failed a micro-dose scopolamine "stress test" described by Snyder et al. (2014). Hence, these 15 individuals were determined to fall within the preclinical stage of AD.The Heidelberg SPECTRALIS SD-OCT system was used to acquire OCT scans of the optic nerve head and the macula (right and left eyes) at baseline and at the 27-month study visit. Outcome measures included volumes for the peripapillary retinal nerve fiber layer (pRNFL), macular RNFL (mRNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), outer nuclear layer (ONL), outer plexiform layer (OPL), and inner nuclear layer (INL). Volumes were obtained across the entire macular region extending 3.45 mm from the center of the fovea (except for the pRNFL, for which the centroid was positioned over the optic nerve head). Mean volumes (mm3) for each layer (right and left eyes averaged) were computed for both the baseline and the 27-month time points, and the differences were obtained to reflect change over time. Multicolor laser imaging was used to identify and exclude individuals with background diabetic retinopathy and multiple retinal microbleeds. *Results:* Considering each subject group separately, the change from baseline to 27 months in the total volume (mm3) of the mRNFL was significantly decreased for the preclinical AD group (0.032±0.003, p=0.002), and likewise the total volume was also decreased for the healthy control group (0.0190±0.003, p=0.03) as a result of normal aging. For both subject groups, these volume reductions were uniformly seen across the separable radial quadrants of the ETDRS circular grid. In comparing preclinical AD (N = 15) to healthy controls (N = 41), there was a significant between-groups difference for the mRNFL (p = .05) and a trend-level difference for the pRNFL (p=0.07). There were no observed between-groups differences for the other retinal layers, after accounting for expected effects of normal aging. A multivariate linear regression model, controlling for age and with total neocortical PET amyloid ligand binding (SUVr) entered as the dependent measure, was completed. Macular RNFL volume change, over the 27 month study interval, accounted for 10% of the variance in PET amyloid neocortical binding at the end of the study (Adj R2 = 0.106, $\varrho < 0.017$). By comparison, although main effects of aging were found for change in the other retinal layers, these volume reductions did not appear to be related to PET amyloid binding. *Conclusion:* To our knowledge this is a first attempt to explore within-subjects change in retinal cell layer structures in the preclinical stage of AD. Our findings, from this initial small study, suggest that a decrease in the mRNFL volume may possibly reflect the earliest detectable structural retinal changes in AD. The RNFL is principally composed of retinal-ganglion cell axons that course towards the optic nerve head and form the optic nerve. The macular region of the retina is known to suffer significant change in later stage AD, and postmortem histological studies have found prominent pathological alterations within the ganglion cell layer (containing the cell bodies for the myelinated axons within the RNFL), and a preferential loss of larger axons, in AD patients (Sadun et al., 1990; Blanks et al., 1996). These results suggest that early retinal anatomic change, associated with preclinical AD and neocortical amyloidosis, consists of RNFL retrograde axonal degeneration prior to ganglion cell layer loss in later stage disease. References: Lim YY, Maruff P, Schindler R, Ott BR, Salloway S, Yoo DC, Noto RB, Snyder PJ. (2015). Disruption of cholinergic neurotransmission exacerbates Aβ-related cognitive impairment in preclinical Alzheimer's disease. Neurobiology of Aging, 36(10), 2709-2715. Snyder PJ, Lim YY, Schindler R, Ott BR, Salloway S, Daiello L, et al. Microdosing of Scopolamine as a 'Cognitive Stress Test': Rationale and Test of a Very Low Dose in an At-Risk Cohort of Older Adults. Alzheimers Dement 2014;10:262–7.

LB12: ONLINE STUDY PARTNER-REPORTED SUBJECTIVE COGNITIVE DECLINE CAN HELP IDENTIFY POTENTIAL ALZHEIMER'S CLINICAL TRIAL PARTICIPANTS.

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Background: The goal of this study was to validate study partner-reported data collected online using the Brain Health Registry (BHR) to facilitate Alzheimer's clinical trials. Study partner-reported data is frequently used to assess cognitive and functional status in AD clinical research, including clinical trials, and can help identify older adults with cognitive decline, preclinical AD, mild cognitive impairment (MCI), and dementia due to AD. Therefore, development and validation of novel methods for efficiently collecting study partner data has the potential to accelerate AD drug development by improving AD trial screening and enrollment. In addition, online methods can be used in the future to efficiently screen for age-related cognitive decline and AD in various healthcare settings. *Methods:* Participants were enrolled in BHR, an online registry that collects longitudinal cognitive and health data using questionnaires and neuropsychological tests. All participants had a study partner enrolled in the BHR Caregiver and Study Partner Portal (CASPP), a novel tool through which study partners can separately enroll online and report on the participant's cognitive and functional status. BHR participants completed demographics, medical history, family medical history, and subjective memory concern (SMC) questionnaires, as well as online Cogstate Brief Battery (CBB); 67 also had known ApoE genotype. Study partners completed an online adaptation of the Everyday cognition scale (ECog), a measure of subjective cognitive decline (SCD) of the participant. We used multivariable linear and logistic regression to analyze associations between partner-reported ECog (partner-SCD) and either self- or study partner-reported diagnosis of MCI or dementia due to AD. Then, in order to determine the utility of study partner report for identifying AD clinical trail participants, we assigned participants to 4 likely diagnostic groups based on online CBB learning/memory scores, SMCs, and presence of AD risk factors (ApoE ε4 genotype, family history of AD). Participants were categorized as Cognitively-normal with low AD risk (LOW), or likely to be eligible for preclinical (PRE), prodromal (PRO), or dementia (DEM) trials. We then used multivariable models to measure associations between likely diagnostic group and partner-SCD. Finally, we compared the predictive value of study partner- versus self-report. We controlled for participant age, education, gender; and dyad relationship in all analyses. *Results:* Between June

2016-August 2017, 3690 participant-study partner dyads enrolled in the BHR and CASPP. Of those, 858 dyads included a participant age 55+ who completed medical and family history questionnaires. Participants had an average age of 66.0±6.8, average of 17.6±4.1 years education, 71% female, and 96% Caucasian. Study Partners had an average age of 62.5±11.4, average of 17.0±3.9 years education, 51% female, and 95% Caucasian. Dyads knew each other for an average of 32 years, 83% lived together, and 77% were spouses. (1) Prevalence of self- and study partner-reported diagnoses. We collect both self- and study-partner reported medical diagnoses of the participant. Fifty-six participants (7%) self report MCI, 9 (1%) self report AD, and 7 (0.8%) self report both MCI and AD. Study partner-reported diagnoses of the participant were 45 (5%) MCI, 7 (0.9%) AD, and 6 (0.7%) both MCI and AD. Agreement between self- and partner-report of diagnosis was 70% for MCI and 90% for AD, with study partners underreporting diagnosis compared to participants in both diagnostic categories. (2) Associations between partner-SCD and diagnosis. Partner-SCD was significantly associated with both self ($p<0.001$) and SP-reported ($p<0.001$) participant diagnosis. The association was significant for total ECog score, as well as all ECog sub-domain scores. Participant age was significantly associated with AD diagnosis. (3) Associations between partner-SCD and likely diagnostic group. Based on CBB score, SMCs, and AD risk factors, 66% of participants were classified as LOW, 39% PRE, 10% PRO, and 1% DEM. Partner-SCD significantly predicted likely diagnostic group. The association was significant for all ECog sub-domains ($p=0.008$) except memory ($p=0.297$). Age ($p<0.001$) and lower education ($p=0.002$) were also significantly associated with likely diagnostic group. In contrast to partner-SCD, self-report of SCD was associated with self-reported diagnosis ($p<0.001$), but not likely diagnostic group ($p=0.43$). *Conclusions:* We found significant associations between partner-SCD and participant diagnosis, consistent with previous in-clinic results showing that partner reported-SCD can predict diagnostic group in older adults. In our study, both self- and study partner-reported SCD were very good at predicting self-reported diagnosis, but only study partner-reported SCD could predict "likely diagnostic group", including older adults within the normal range of online CBB scores who have AD risk factors. This suggests that study partner-report may be uniquely valuable for identifying CN participants for preclinical trials. Overall, the results support the feasibility and construct validity of CASPP data, which has the potential to greatly facilitate AD clinical research. Future studies will examine the construct and predictive validity of CASPP data by analyzing associations between online study partner data and AD trial eligibility in cohorts with known clinical diagnosis and biomarker status.

LB13: THE ANTI-AB OLIGOMER DRUG CT1812 FOR ALZHEIMER'S: PHASE 1B/2A SAFETY TRIAL OUTCOMES. Lon S Schneider[1], Michael Grundman[2,3], Steven DeKosky [4], Roger Morgan[5], Robert Guttendorf[6], Michelle Higgin[7], Julie Pribyl[7], Kelsie Mozzoni[3], Nicholas J Izzo[3], Hank Safferstein[3], Celine Houser[3], Michael Woodward[8], Susan M. Catalano[3] *((1) Keck School of Medicine of USC, Los Angeles, CA, USA; (2) Global R&D Partners, LLC, San Diego, CA, USA; (3) Cognition Therapeutics, Inc., Pittsburgh, PA, USA; (4) McKnight Brain Institute, University of Florida, Gainesville, FL, USA; (5) MedSurgPI, LLC Raleigh, NC, USA; (6) Aclairo Pharmaceutical Development Group, Inc., Vienna, VA, USA; (7) PharmaDirections, Cary, NC, USA; (8) Memory and Wound Clinics, Austin Health, Melbourne, Australia)*

Introduction: CT1812 selectively displaces Aβ oligomers from synaptic receptor sites and clears them into the cerebrospinal fluid, restoring cognitive performance to normal in aged transgenic mouse models of AD. In prior clinical studies in volunteers (ClinicalTrials.gov NCT02570997), CT1812 appeared safe and well tolerated with multiple doses to 560 mg. CSF concentrations of CT1812 exceeded the minimum target concentrations expected to improve memory in AD patients. A probe study suggested lack of significant drug-drug interactions with P450 isozymes. To advance the clinical development of CT1812 we conducted a Phase 1b/2a multiple dose study in mild to moderate Alzheimer's patients to evaluate safety (ClinicalTrials.gov NCT02907567). *Objectives:* This was a multi-center, double-blind, placebo-controlled parallel-group study to evaluate the safety, tolerability and pharmacokinetics of CT1812) in mild to moderate Alzheimer's patients (MMSE 18-26). A total of 19 patients (N = 4 or 5 patients/group) were randomized to one of three doses of CT1812 (90, 280 and 560 mg) or placebo given once daily for 28 days. Primary outcomes were related to safety including the incidence of adverse events as well as clinical and laboratory assessments. Secondary and exploratory endpoints included plasma and CSF concentrations of CT1812, plasma and CSF biomarkers, and cognitive assessments including the Alzheimer's Disease Assessment Scale (ADAS-Cog 14), Controlled Word Association Test (COWAT) and Category Fluency Test (CFT). *Discussion:* 54 subjects were screened and 19 randomized, with 18 completing the 28 days of treatment. The first patient was randomized September 16, 2016, and the last patient completed August 24, 2017. Forty-four adverse events occurred in 16/19 participants. They included headache, post-LP headache, fatigue, lethargy, nausea, vomiting, diarrhea, and elevated alanine aminotransferase (ALT). Lymphocytopenia occurred in 4 participants, was transient, and resolved in all subjects by study completion. CT1812 in plasma at Day 28 showed a mean Cmax, Tmax, and T1/2 of 109 ng/mL, 1.0 hr, and 13.3 hr for the 90 mg/day dose; and 487 ng/mL, 1.5 hr, and 13.1 hr for the 280 mg/day dose; and 1626 ng/mL, 2.3 hr, and 11.0 hr for the 560 mg/day dose. Analyses of the exploratory clinical study outcomes are pending at this time and will be reported at CTAD. *Conclusions:* Outcomes indicate that CT1812 has an acceptable pharmacokinetic and safety profile to conduct additional clinical trials in AD patients. Additional planned trials include an indwelling lumbar catheter study to detect changes in Aβ oligomers in CSF, a PET study to assess synaptic density after six months of daily treatment, and a Phase 2 efficacy trial.

LB14: "PROXY ANTIGENS": A NEW, DEFINITIVE TOOL TO GUIDE SUCCESSFUL CLINICAL TRIALS. Reddy Moola[1], Ronald N. Zuckermann[2], William Shelander[1] *((1) Anven AlzdX Inc., Berkeley, California, USA; (2) Molecular Foundry, Lawrence Berkeley National Laboratory, Berkeley, California, USA)*

Background: Alzheimer's disease (AD) typically advances asymptomatically for years prior to initial diagnosis. Yet most candidate drugs appear to be marginally effective after cognitive impairment (often the first evidence of neurological damage) has presented. Therefore, cost effective and non-invasive tests for early detection of the disease are critical to design successful clinical trials and to assess risks in natural history studies. As neurodegeneration occurs in the brain of an AD patient, an activated immune response is believed to propagate disease-specific antibodies in the blood, which would lastingly present in the CSF and serum. These AD-specific antibodies could serve as definitive AD biomarkers if identification of such antibodies could be achieved. The goal of the current study was to design "synthetic mimics of protein antigens" to measure, probe, and monitor the immune response to AD in ways that were not previously possible. *Methods:* Systematically designed protein mimics with likely binding structures ("Feature Specific Molecules") were synthesized and exposed to whole sera of a mixed population

of Normal and AD-positive subjects. All molecules that did not bind to any antibodies generally present in the mixed sera were rejected from further study. The resulting "Focused Library" consists of only antibody-binding molecules (i.e. "proxy antigens"). Then the proxy antigens were used to perform two parallel screens on serum (n=12) from known AD-positive patients and from Normal Control subjects. Differentiating the two separate screens isolated a small subset of proxy antigen-antibody complexes consistently presenting in all AD case samples and in none of the Normal Controls. *Results:* Nine (9) proxy antigens demonstrated significant elevated signals in the AD subjects (intensity >20,000) in comparison to very low signals in the controls. Next, 50 serum samples were randomly selected from the AD cases (n=21) and controls (n=29) for further validation. These nine AD-specific proxy antigens clearly measure the presence or lack of AD antibodies in a blood sample. To test whether the measured signal from the AD proxy antigens could actually track the persistent progression of AD, we performed a sequential test of five (5) annual blood samples from known AD patients (n=15). Three of the AD proxy antigens were exposed to each of the annual blood samples. All three of the AD proxy antigens indicated consistent upward progression of measurements relative to age demonstrating that AD proxy antigens can quantifiably track and monitor progression of the state of AD antibodies in patients. Early detection has also been demonstrated in patient blood samples archived from one to five years prior to diagnosis of AD. *Conclusions:* To our knowledge, this study represents the first ever use of designed, synthetic mimics of protein antigens to extract disease specific antibodies. One high value application of AD-specific proxy antigens can profile and stratify clinical trial populations, i.e. differentiate and predict which subjects respond to a drug and which do not. Most importantly, retrospective analysis of archived blood samples from a past clinical trial can be used to unambiguously reassess subgroups of subjects and offer an enriched population for a guided prospective clinical trial. Additionally, our preliminary results suggest that a profile approach to measure disease states is a viable option for differential diagnosis between AD and non-AD neurological diseases. Additional analyses with larger samples of AD, PD, LBD and non-AD samples are underway. Disclosures: A patent is being filed on this work.

LB15: VALUE OF 18F-FLORBETABEN AMYLOID PET IN THE DIAGNOSTIC WORK-UP OF MOST COMPLEX PATIENTS WITH DEMENTIA IN FRANCE: A NATURALISTIC STUDY. Mathieu Ceccaldi[1], Thérèse Jonveaux[2], Antoine Verger[3], Pierre Krolak-Salmon[4], Claire Houzard[5], Olivier Godefroy[6], Trevor Shields[7], Audrey Perrotin[8], Rossella Gismondi[8], Santiago Bullich[9], Aleksandar Jovalekic[9], Nicola Raffa[10], Florence Pasquier[11], Franck Semah[12], Bruno Dubois[13], Marie Odile Habert[14], David Wallon[15], Mathieu Chastan[16], Pierre Payoux[17], NEUUS in AD study group; Andrew Stephens[19], Eric Guedj[18] *((1) AP-HM - Hôpital de la Timone, Neurology and Neuropsychology Department, and Aix Marseille University, Inserm, INS, Institut de Neurosciences des Systèmes, Marseille, France; (2) CHRU de Nancy - Hôpital Brabois, Geriatric Department, Vandoeuvre-les-Nancy, France; (3) INSERM U947, IADI, Nancy, France; (4) Clinical and Research Memory Center of Lyon, Hospices civils de Lyon, UCBL1, Inserm 1028, Lyon, France; (5) CHU Lyon, Nuclear Medicine Department, Lyon, France; (6) CHU Amiens Picardie - Hôpital Sud, Neurology Department, Amiens, France; (7) CHU Amiens Picardie - Hôpital Sud, Nuclear Medicine Department, Amiens, France; (8) Piramal Imaging, Medical Affairs, Berlin, Germany; (9) Piramal Imaging, Clinical Research and Development, Berlin, Germany; (10) Piramal Imaging, Market Access and HEOR, Berlin, Germany; (11) Inserm 1171, Université de Lille, CHU, DistAlz, Lille, France; (12) Univ. Lille, U1171, CHU Lille, Nuclear Medicine Department, Lille, France; (13) AP-HP - Hôpital Pitié Salpétrière, Memory and Alzheimer Disease Institute IM2A, Paris, France; (14) Laboratoire d'Imagerie Biomédicale, Sorbonne Universités, UPMC Univ Paris 06, Inserm U 1146, CNRS UMR 7371, Paris, France; (15) CHU de Rouen - Hôpital Charles Nicolle, Neurology Department, Rouen, France; (16) Centre Henri Becquerel, Nuclear Medicine Department, Rouen, France; (17) ToNIC, Toulouse NeuroImaging Center, Université de Toulouse, Inserm, UPS, France; (18) AP-HM - Hôpital de la Timone, Nuclear Medicine Department, and Aix-Marseille University, CERIMED, CNRS, INT, Institut de Neurosciences de la Timone, Marseille, France)*

Background: Alzheimer's Disease (AD) is not easily diagnosed, particularly in early onset of dementia and for mixed or atypical presentations. The current study investigates the naturalistic impact of florbetaben positron-emission tomography (PET) on diagnosis and management of mildly demented patients for whom the etiological diagnosis remains uncertain despite an exhaustive expert work-up. *Methods:* This multicenter open label study (ClinicalTrials.gov: NCT02681172) was performed at French tertiary memory clinics. Eligible patients were presenting with complex clinical situations (i.e., early-onset, atypical clinical profiles, suspected mixed etiological conditions, unexpected rate of progression) and had a preliminary uncertain diagnosis after a prior comprehensive workup. Because of the diagnostic uncertainty, cerebrospinal fluid (CSF) examination was planned in these patients but was not obtained or not considered helpful by the expert clinician for one of the following reasons: 1) lumbar puncture (LP) was refused by the patient; 2) LP was not feasible for medical reasons; or 3) results of CSF analysis were considered as non-contributory by the clinician. Therefore, this clinical trial was specifically designed to determine the potential impact of amyloid PET without interfering with the current standard practices of expert centers. Following an initial diagnosis, florbetaben PET was performed, and a confirmed or revised diagnosis was provided after scan result disclosure. PET images were visually assessed in each center by readers who had undergone appropriate training. *Results:* 205 patients (70.9±9.7 years, 103 male) were enrolled with evaluable PET scans; of these, 42.4% had a prior LP (87/205). 64.4% of scans (132/205) were rated amyloid-positive. Scan results led to changed

diagnosis in 66.8% of cases (137/205), particularly for negative scans (83.6% vs 57.6% of positive scans; p<0.0001). Improved diagnostic confidence was reported in 81.5% of cases (167/205; p<0.0001), with an overall significant average improvement of 30.2%. Changes in management were reported for 80.0% of patients (164/205), and considered as substantial in 50.7% (104/205) of patients (any change in initiation or withdrawal of medication, additional diagnostic tests, or referral to a new specialist). Withdrawal of medication was exclusively reported for amyloid-negative PET scans, whereas initiation of new medication was mainly reported following amyloid-positive PET scans. Subgroup analysis based on patients' eligibility revealed similar results independent of inclusion criteria. *Conclusion:* The results highlight the immediate clinical utility of amyloid PET imaging for patients with complex dementia presentations and high levels of diagnostic uncertainty in the context of the existing healthcare framework. Amyloid PET improves diagnostic and patient management parameters when a biomarker of amyloid pathology is recommended for differential diagnosis but CSF is not considered helpful because its results are inconclusive, or LP is contraindicated or refused.

LB16: ADUCANUMAB TITRATION DOSING REGIMEN: 24-MONTH ANALYSIS FROM PRIME, A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 1B STUDY IN PATIENTS WITH PRODROMAL OR MILD ALZHEIMER'S DISEASE. Philipp von Rosenstiel[1], Sarah Gheuens[1], Tianle Chen[1], John O'Gorman[1], Ping Chiao[1], Guanfang Wang[2], Christian von Hehn[1], LeAnne Skordos[1], Christoph Hock[3], Roger M Nitsch[3], Samantha Budd Haeberlein[1], Alfred Sandrock[1] *((1) Biogen, Cambridge, MA, USA; (2) Cytel, Cambridge, MA, USA; (3) Neurimmune, Schlieren-Zurich, and University of Zurich, Switzerland)*

Background: 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 or mild AD. Amyloid related imaging abnormalities-vasogenic edema (ARIA-E) were the main safety and tolerability findings in an interim analysis of PRIME; these were dose-dependent and more frequent in apolipoprotein E4 (ApoE ε4) carriers.1 A titration regimen was tested in ApoE ε4 carriers to explore the impact of titration on ARIA incidence. Here, we report 24-month data for both fixed-dose and titration cohorts, including 12 months from the placebo-controlled period and the first 12 months of the PRIME long term extension (LTE). *Methods:* Patients included in this randomized, double-blind, placebo-controlled study (PRIME; NCT01677572) were aged 50-90 years, had a positive florbetapir positron emission tomography (PET) scan, and met clinical criteria for prodromal or mild AD. During the double-blind, placebo controlled phase, patients received aducanumab or placebo once every 4 weeks for 52 weeks. In a staggered, parallel-group design, patients were randomized to fixed doses of aducanumab (1-10 mg/kg) stratified by ApoE ε4 status (carrier/non-carrier). 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. Patients meeting eligibility criteria at Week 56 were enrolled in the LTE, where all patients were assigned to receive aducanumab 3, 6, or 10 mg/kg. LTE dose assignments were as follows: patients initially randomized to the aducanumab titration regimen during the double-blind phase continued at their original dose assignment. By Week 110, average expected dose of the titration arm was 7.6 mg/kg. Patients who received placebo during the double-blind phase 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 randomized to aducanumab 1 mg/kg during the double-blind phase subsequently were assigned to receive aducanumab 3 mg/kg in the LTE. All other patients who had received fixed doses of aducanumab (3, 6, or 10 mg/kg) during the double-blind phase continued at their original dose assignment or a reduced dose. In the LTE, with the exception of safety, all endpoints were exploratory and included measurement of Aβ reduction using amyloid PET (as assessed by standard uptake value ratio) and change from baseline in the clinical endpoints Clinical Dementia Rating-Sum of Boxes (CDR-SB) scale and the MMSE. A mixed model for repeated measures was used for the 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 115 completed treatment at Month 24. Patients from the titration cohort who continued aducanumab treatment up to 24 months experienced a reduction in brain amyloid plaque burden, as measured by PET, which was consistent with the dose- and time-dependent results observed in fixed-dose cohorts. Decreases in brain amyloid plaque burden were also observed among placebo-treated patients who switched to aducanumab in the LTE. CDR-SB and MMSE data suggest a clinical benefit in patients continuing aducanumab over 24 months. Of the 185 patients dosed with aducanumab in PRIME, 46 patients experienced ARIA-E. There were no new cases of ARIA-E in patients who continued on the same dose of aducanumab. Four patients experienced more than one episode of ARIA-E over 24 months of treatment, with an additional 2 patients experiencing recurrent ARIA-E after the first year of the LTE. These recurrent events were consistent with other ARIA reported to date; they were typically asymptomatic, and most patients continued in the study. The incidence of ARIA-E in patients switching from placebo to aducanumab was consistent with that reported in the placebo-controlled portion of the study. *Conclusions:* In the small population of patients from the titration and fixed-dose cohorts who completed the first year of the LTE, amyloid plaque burden continued to decrease in a dose- and time- dependent manner. Analyses of exploratory clinical endpoints, CDR-SB and MMSE, in the titration cohort were consistent with the results from the fixed-dose cohorts and suggest a continued benefit on the rate of clinical decline during the second year of treatment. Recurrent ARIA events were consistent with other ARIA events reported to date. No new safety signals were identified at 24 months. These data support further investigation of the clinical efficacy and safety 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.

LB17: DIFFERENTIAL INHIBITION OF THE A-SECRETASE ADAM10 BY AB40 VARIANTS CONTAINING FAD MUTATIONS. Asa Hatami[1], Subrata Dutta[2], Alejandro Rodriguez[2], Patricia Spilman[1], Jevgenij Raskatov[2], Charles Glabe[3], Varghese John[1] *((1) Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles; (2) Department of Chemistry and Biochemistry, University of California, Santa Cruz; (3) Department of Molecular Biology and Biochemistry, University of California, Irvine)*

Background: The amyloid-beta (Aβ) peptide is produced following the sequential cleavage of the amyloid precursor protein (APP) by β- and γ-secretase. Aβ may then adopt oligomeric and fibrillar aggregation states with a wide range of conformations, some of which

may be implicated in Alzheimer's disease (AD). APP is also cleaved by the α-secretase ADAM10 to generate soluble APPα (sAPPα), which is neuroprotective, neurotrophic, and inhibits the β-cleavage of APP by the enzyme BACE1. We have previously shown that Aβ42 can inhibit ADAM10 activity (Spilman et al., J Alzheimers Dis, 2016). This may be a novel toxic mechanism of Aβ in AD pathogenesis, as the inhibition of ADAM10 results in decreased sAPPα levels while increasing the pool of membrane-associated APP susceptible to β-cleavage by BACE1 and could lead to a therapeutic approach devoid of the side effects such as ARIA seen with the current Abeta immunotherapy trials. The specific conformations of Aβ oligomers capable of inhibiting ADAM10 and the extent to which they reduce ADAM10 activity are as yet unknown. We have recently shown that Aβ peptides containing mutations associated with familial AD (FAD) (Hatami et al., J Biol Chem, 2017) adopt distinct conformations as recognized by a panel of amyloid conformation-specific monoclonal antibodies, and have a wide range of aggregation kinetics and sheet-stacking interactions in their fibrillar forms. *Methods:* We tested the abilities of 11 Aβ40 peptides containing FAD mutations to inhibit ADAM10 activity using a fluorogenic assay utilizing a short peptide cleaved by ADAM10. We also assessed the cleavage of a substrate comprising the C-terminal 125 amino acids of APP conjugated to maltose-binding protein (MBPC125) in a novel AlphaLISA assay wherein the cleavage of MBPC125 was measured by monitoring the interaction between an antibody against MBP and another antibody against the C-terminal portion of APP. We allowed the Aβ peptides to aggregate over a 10-day time course by resuspending the lyophilized peptide in 100 mM NaOH and then diluting the resuspended peptides to a concentration of 40 μM in 10 mM phosphate buffer pH 7.4. We assessed ADAM10 inhibition by monitoring the production of ADAM10 cleavage products over a 4-hour time course in the presence of the immediately resuspended peptides and peptides aggregated for 3 and 7 days. The conformational profiles and aggregation kinetics of the peptides were characterized using a panel of amyloid conformation-specific monoclonal antibodies by immunoblot. The peptides were further characterized in western blot experiments using selected antibodies. In order to determine the extent to which the inhibition of ADAM10 was due to a direct interaction of the peptide with the active site of the enzyme, we carried out liquid chromatography mass spectrometry to assess the relative proportions of intact to cleaved Aβ. *Results:* Aβ peptides containing mutations associated with FAD adopt different sets of amyloid conformations and have different aggregation kinetics, as determined using dot blots and western blots probed with a panel of amyloid conformation-specific monoclonal antibodies. In fact, the immunological profile of each peptide may be described by a fingerprint-like pattern of reactivity to the panel of antibodies. The distinct ensembles of amyloid conformations adopted by the Aβ variants during the aggregation time course differentially inhibited ADAM10 activity, as determined in both the fluorogenic and MBPC125 AlphaLISA assays. Most of the mutant peptides had more potent inhibitory activity than the wildtype peptide. Interestingly, there was a wide range of inhibitory activity ranging from ~10% to inhibitory activity exceeding that of the matrix metalloproteinase small molecule inhibitor marimastat. *Conclusion:* Our findings for the first time highlight a potential novel toxic mechanism associated with specific conformations of Aβ that warrant further investigation. Our approach may lead to the identification of specific amyloid conformations, which may be then be targeted immunologically to produce therapeutic benefit in AD without the complications associated with the targeting of amyloid conformations present in insoluble fibrillar aggregates of Aβ comprising amyloid plaques.

POSTERS

Theme: Clinical Trials Methodology

P1: JAPANESE ADNI: CLINICAL, NEUROIMAGING AND BIOMARKER PROFILES IN COMPARISON WITH ADNI.

Takeshi Iwatsubo[1], Atsushi Iwata[1], Kazushi Suzuki[1], Ryoko Ihara[1], Hiroyuki Arai[2], Kenji Ishii[3], Michio Senda[4], Kengo Ito[5], Takeshi Ikeuchi[6], Ryozo Kuwano[6], Hiroshi Matsuda[7], for the Japanese ADNI and Chung-Kai Sun[8], Laurel Beckett[9], Paul Aisen[8], Michael Donohue[8], for the ADNI *((1) The University of Tokyo, Tokyo, Japan; (2) Tohoku University, Sendai, Japan; (3) Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan; (4) Institute of Biomedical Research and Innovation, Kobe, Japan; (5) National Center for Geriatrics and Gerontology, Obu, Japan; (6) Niigata University, Niigata, Japan; (7) National Center for Neurology and Psychiatry, Kodaira, Japan; (8) Alzheimer Therapeutics Research Institute, University of Southern California, San Diego, CA, USA; (9) University of California, Davis, Sacramento, CA, USA)*

Backgrounds: The significance of neuroimaging and fluid biomarkers in the prediction of clinical progression during the very early stages of Alzheimer's disease (AD) is being demonstrated by the results of AD Neuroimaging Initiative (ADNI). We have conducted Japanese (J-) ADNI using almost identical protocols to ADNI's and compared the results, to ensure international harmonization in global clinical trials of disease-modifying drugs for AD. *Methods:* To characterize the clinical, neuroimaging and biomarker measures in subjects with normal cognition (CN), late amnestic mild cognitive impairment (MCI) or mild AD in the Japanese elderly population diagnosed using the same criteria with ADNI's, total of 537 subjects (154 CN, 234 late MCI, and 149 AD) from 38 clinical sites were enrolled at baseline and followed for 24-36 months using cognitive and functional measures used in ADNI, 1.5T structural MRI, FDG and 11C-PiB amyloid PET scans, blood and CSF sampling (assayed for Ab(1-42) and tau by Alzbio3) and APOE genotyping. These subjects were compared with 1004 ADNI participants with Ab biomarker data (400 CN, 355 late MCI, 249 AD). Rate of changes in representative cognitive composite measures were compared for amyloid-positive MCI and mild AD individuals between the J-ADNI and ADNI populations. J-ADNI data have been publicized from the National Bioscience Database Center, Japan (Research ID: hum0043.v1, 2016) and ADNI data were obtained from the ADNI database (http://adni.loni.usc.edu). *Results:* The subjects with late MCI in J-ADNI (total) progressed to dementia in 12 months at a rate of 26.3% per year, more rapidly than in ADNI (13.2%) (log-rank $p<0.001$). The percentages of APOE ε4-positive individuals in the total CN, MCI and AD in J-ADNI were 24.0, 52.1 and 59.6%, respectively, which were at similar levels to those in ADNI (28, 55 and 67%). Amyloid positivity rates in CN, MCI and AD in J-ADNI were 24, 67 and 93%, respectively, which were not significantly different from those in ADNI (34, 72 and 90%; borderline in CN: $p=0.137$). Three-year mean changes in MMSE (-1.23/y), CDR-SB (1.12/y) and ADAS-cog13 (2.9/y) in amyloid-positive MCI in J-ADNI were at similar levels to those in ADNI (-1.20/y, 0.73/y, 2.4/y, respectively), with significantly faster declines in MMSE at 6 and 12 months in J-ADNI. Two-year mean changes in MMSE (-1.65/y), CDR-SB (1.25/y) and ADAS-cog13 (2.9/y) in amyloid-positive mild AD in J-ADNI also were similar to those in ADNI (-2.2/y, 1.65/y, 3.9/y, respectively), whereas the baseline mean scores in CDR-SB (3.73) and ADAS- cog13 (27.4) in J-ADNI were significantly lower than those in ADNI (4.41 and 30.4, respectively), and these differences in mild AD were generally sustained during the

longitudinal follow-up. Functional Assessment Questionnaire in mild AD showed a similar trend of separation. In contrast, CN populations in J-ADNI and ADNI exhibited minimal movements in the cognitive scores. *Conclusion:* J-ADNI has successfully recruited cohorts of CN, subjects with late amnestic MCI and mild AD with generally comparable baseline characteristics and progression profiles with ADNI. The slightly faster trend of progression in MCI in a subset of measures (e.g., conversion to dementia and decline in MMSE within the 1st year), as well as milder cognitive scores and decline in mild AD of J-ADNI, may reflect (i) relatively narrower disease ranges (i.e, later in MCI and milder in AD) of individuals recruited in J-ADNI, (ii) a minor difference in the dividing line between late MCI and mild AD, with J-ADNI setting a slightly earlier cut-point, (iii) difference in educational length (slightly shorter in J-ADNI), (iii) ethnic differences, or combination of these factors. These results strongly support the successful bridging of clinical trial data between Japan and North America.

P2: PUTTING THE PGSA TO THE TEST: TIME TO PROGRESSION IN FIVE STUDIES WITH MCI PATIENTS.
Manfred Berres[1], Andreas U. Monsch[2], René Spiegel[3] *((1) RheinAhrCampus, Remagen, Germany; (2) Memory Clinic, University Center for Medicine of Aging, Felix Platter Hospital, Basel, Switzerland; (3) University Center for Medicine of Aging, Felix Platter Hospital, Basel, Switzerland)*

Background: The Placebo Group Simulation Approach (PGSA) represents an attempt to resolve three problems inherent to randomized, double-blind, placebo-controlled trials (RPCTs) in MCI patients: (1) Ethics - a number of patients in RPCTs will receive placebo, which may be problematic in long-term studies; (2) Selective study samples - some candidate patients decline participation once they are informed about the specifics of an RPCT; (3) Study logistics: Circumstances in RPCTs differ markedly from the situation in which treatments will be used in daily clinical practice. In contrast to RPCTs, studies using the PGSA provide experimental treatment to all participants and compare their outcomes with simulated outcomes that these participants might have achieved, had they been given placebo. Published simulation models (Alz Res & Ther 3:9-20; 2011) are based on anamnestic and neuropsychological data from MCI patients in the ADNI database. Attempts at validation of PGSA models were made using four longitudinal MCI datasets: One from the National Alzheimer's Coordination Center (NACC: Alz Dis Assoc Disord 21:249-258; 2007), one from a company-sponsored clinical trial with rivastigmine (RIVA; Lancet Neurol 6:501-512; 2007), one from a multicenter observation study performed in Germany (KND; Neurology 78:379-386; 2012), and one from a database collected at the University of Basel Memory Clinic (BSMC). It was found that the simulated cognitive outcome scores for these studies consistently overestimated the observed cognitive decline as reflected in the ADAScog and a neuropsychological battery. Hence, our attempts at validation of PGSA models revealed dissimilarities between neuropsychological test scores of different MCI study samples. To better understand these discrepancies, the rates of progression from MCI to AD in these studies were compared. *Methods:* Participants diagnosed as MCI at study entry were included in the analysis. In the RIVA trial, progression to AD was often ascertained in off-schedule visits, thus yielding the true time to progression. In the other studies, progression was usually ascertained at scheduled visits. For these patients progression is assumed to have happened halfway between the previous and the ascertaining visit. Univariate and multivariate Cox proportional hazard models with covariates age, gender and education were analyzed for each study separately and for all studies simultaneously. *Results:* Hazard ratios for age are distinctly positive ($p<0.0001$) in all studies except in ADNI, suggesting that age is a precipitating factor for progression to dementia in MCI subjects. The RIVA study has the largest hazard ratio (2.64 for 10 years older, 95% CI: 1.63-4.29). The hazard ratios per 10 years for BSMC (2.07, 95% CI: 1.65-2.61), KND (1.58, 95% CI: 1.30-1.92), and NACC (1.29, 95% CI: 1.20-1.38) are smaller. A preventive effect of education was only seen in KND (hazard ratio for 4 years: 0.71, 95% CI: 0.56-0.91). Gender had an effect in BSMC only (hazard ratio 1.57 for females, 95% CI: 1.10-2.24). Comparison of all studies in one model revealed a very small hazard ratio for progression in the RIVA sample compared to ADNI (0.151, 95% CI: 0.105-0.217). The hazard ratios of the other studies were close to 1 (NACC: 1.05, KND: 0.85, BSMC: 0.93). Adding interactions of age and education with studies confirmed the different effects of age in the other studies compared to ADNI. Interactions with education could not be shown. *Conclusions:* Comparing time to progression in five datasets did not fully explain why validation of PGSA models was not successful. While the distinctly lower progression rates in the RIVA data can explain the overestimation of cognitive decline in models derived from ADNI data, progression rates in the other studies were similar. Nevertheless, a relation between overestimation and progression rates can be presumed: Overestimation was only slight in NACC, where hazard ratio for progression is 1.05 (compared to ADNI), it was moderate in BSMC and KND, where hazard ratios are 0.93 and 0.85, respectively, and overestimation was highest in RIVA, with hazard ratio 0.15. The latter result suggests that the inclusion criteria for the RIVA study were different from those in the other studies. It also emerges from these analyses that MCI criteria need to be more uniformly defined for future clinical trials with potential disease-modifying anti-dementia drugs.

P3: THE IMPORTANCE OF CORRECT SPECIFICATION OF THE WITHIN-SUBJECT CORRELATION STRUCTURE IN SAMPLE SIZE CALCULATION AND POWER ANALYSIS FOR AN AD CLINICAL TRIAL UTILIZING MIXED EFFECTS REGRESSION ANALYSIS FOR OUTCOME ASSESSMENT.
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Backgrounds: Clinical trials and cohort studies in Alzheimer's disease often involve group comparisons of declining trends on neuropsychological measurements. The power and sample size analysis for a repeated measurement regression model requires a specification of within-subject correlation structure of the longitudinal outcome. Misspecification of this correlation structure may lead to insufficient power for a proposed study. In this simulation study, we compare the power of two commonly-used correlation structures, first order autoregressive (AR(1)) and spatial power (SP) models, of a longitudinal neuropsychological measurement model.. The "true values" for the simulated datasets were based on model estimation using the data collected by the Texas Alzheimer's Research and Care Consortium (TARCC). The sample size was fixed and the type I error rate was set at 0.05. *Methods:* TARCC enrolls subjects with MCI or AD and follows them annually to monitor cognitive changes. We used this data set to to examine the power for testing AD progression slope differences in MMSE scores when assuming an AR(1) versus SP correlation structure in a longitudinal regression model. We limited the observed dataset to approximately 700 subjects who had a baseline MMSE >= 20 and at least 3 observations. The model used abnormal level of HbA1c (defined as >= 6.0% of total hemoglobin)

as the exposure variable potentially associated with differential rate of decline on MMSE. We simulated 500 datasets for different effect sizes of abnormal HbA1c, ranging from -0.06 to – 0.2, and using first an AR(1) correlation matrix, then an SP structure. When generating datasets of SP correlation structure, we assumed the follow-up times followed a Poisson process with mean rate=1, that is to mimic our TARCC study design of one visit per year. . As "true values" for the simulated data sets, we specified a correlation between two outcomes measured one time unit apart as 0.846, and the standard deviation of each measurement as 5.8, as produced from modeling the TARCC data. The power for each method is defined as the proportion of rejecting the null hypothesis (slope difference between normal and abnormal HbA1c group=0) among 500 simulated datasets. *Results:* If the true correlation structure follows AR(1), using either AR(1) or SP as the outcome correlation structure would not change the power calculation for the various effect sizes. If the true correlation structure follows SP, using AR(1) would overpower the statistical test for significance of slope decline and hence lead to an incorrect sample size calculation. For example, our TARCC data analysis provided the AD progression as Mean MMSE at t years after new patient visit = 26 + (-0.42)*t + (-0.2)*(abnormal HbA1c group) + b* t*(abnormal HbA1c group), where b is the slope difference between two groups. If we choose b=-0.195 (effect size of 46.4% faster decline rate for the abnormal group) and keep all other coefficients unchanged, incorrectly assuming an AR(1) structure when the true structure is SP will give a power of 82%. However, if the correct SP structure is assumed, the power of the test is only 77%,with type I error rate=0.05. *Conclusion:* These simulation results demonstrate the importance of the within-subject correlation structure in modifying the power of a study that relies on mixed effects longitudinal regression to evaluate intervention or risk factor effects. If the true correlation structure cannot be inferred from the literature or the pilot data, it is recommended that several correlation structures should be considered for power analysis.

P4: JOIN DEMENTIA RESEARCH' IMPROVING DELIVERY OF CLINICAL TRIALS IN THE UK. Adam Smith *(Office of the NIHR National Director for Dementia Research, University College London, UK)*

Background: Launched in February 2015, Join Dementia Research (JDR) is a UK wide research register that supports members of the public, with and without dementia to volunteer to be matched to appropriate, ethically approved research studies, and contacted by approved researchers. JDR is funded by the UK government and delivered by the National Institute for Health Research (NIHR) in partnership with Alzheimer Scotland, Alzheimer's Research UK and Alzheimer's Society. The service is promoted through a range of channels including NHS healthcare services, charities, public champions, social media. And advertising. As part of registration, volunteers provide information about themselves and their health status. This information is used to match them to recruitment sites by study inclusion and exclusion criteria. The service achieved its objective of recruiting 6% of people to studies by a JDR in 2016. The overall government set ambition is to have 25% of people diagnosed with dementia in the year 2020 registered on JDR and 10% of people with dementia participating in a research study by 2020. Service / Programme: So far the service has attracted over 27,500 volunteers, and has recruited to over 6,000 people into more than 80 dementia studies, this includes all major commercial and non commercial drug trials run in the UK since 2015. Since July 2016 University College London has been working with Quintiles IMS and Biogen to test utilising JDR to recruit to the Engage Study via a centralised nurse led clinical screening service. Usually the recruiting sites would use JDR directly. However, this has a disadvantage in that staff are also working on other services, and have little time to properly utilise the register. Additionally volunteers are not always contactable during normal working hours. This new pilot service has screened over 2,600 volunteers, referred more than 150 volunteers to sites and supported recruitment of 15 people. Through this pilot we have demonstrating that a national register can substantially support recruitment to commercial trials, and that a centralised service working differently is more effective compared to decentralised use: 1. Service has been more cost effective, having averaged costing 30% lower than recruitment via other channels. 2. Volunteers are contacted at times when they are available including evenings and weekends, not just business house. 3. Volunteers has a choice of site, reducing DNAs, reducing travel costs and lost time. 4. Screen failure rates are lower due to giving more time for a comprehensive telephone screening. 5. More people can be screened, and passed to other potential studies if unsuitable. This service evaluation has extended to review additional benefits for volunteers. This is a summary of those identified: 1. Provides a way for people with dementia to express an interest in participating in research. Irrespective of where the live or research status of local services. 2. Ensures information on all research studies is more readily shared with the public, providing a better connection between academics, researchers and the people who the studies wish to help. 3. Provides researchers with data to improve research study feasibility tests, before studies are funded e.g. are there sufficient people in xxx area. 4. Improves chances of research studies being delivered on time, from a ready and willing potential participant list, in addition to other sources. 5. Ensures that the outcomes / benefits of research studies can be realised and acted upon more quickly. Summary: Join Dementia Research has had a positive effect on study recruitment in the UK. More than 25% of everyone recruited to the clinical trials in the UK was sourced via this new service last year. This is a service which is less than three years in being established. By working differently and centrally, it has successful support recruitment to the Biogen Engage Study with around 30% of volunteer being sourced via the service, costing less and reducing screen fail rates while also providing a better experience for trial participants.

P5: EVALUATION OF RAPID, ON-SITE APOE GENETIC TESTING FOR SUBJECT OUTREACH AND TRIAL RECRUITMENT. Sharon Cohen[1], Stephen G. Thein[2], Ian Cohen[1], Sophia Marie Pagtakhan[1], Fadi Franku[1] *((1) Toronto Memory Program, Toronto, ON, Canada; (2) Pacific Research Network, San Diego, CA, USA)*

Background: After age, polymorphisms in the APOE gene have been recognized as the second highest risk factor for Alzheimer's disease. For this reason, public awareness and interest in such testing has in-creased. In our study, two independent memory clinics investigated whether rapid APOE genotyping, in conjunction with a routine cognitive assessment, would be feasible in-house and the impact such testing may have on subject recruitment. *Methods:* The two memory clinics recruited subjects for a cognitive assessment which included a free APOE DNA test (Spartan Cube APOE; Spartan Bioscience, Inc). Using the Spartan system, buccal samples were collected, placed directly into the assay cartridge and analyzed by the device in 50 minutes. Op-erators in the clinics completed a questionnaire evaluating training and "ease-of-use" of the testing sys-tem. The clinics assessed the effect of on-site APOE testing on recruitment by comparing the impact of offering the genetic test to their previous recruitment approach that did not provide APOE testing. Clinic 1 ran a one-day advertisement in a local newspaper for 2 consecutive weeks which included the offer of APOE

genotyping and compared the response rate to past advertisements that did not include APOE test-ing. Clinic 2 had an information booth at a local "Walk for Memories" community event and recruited subjects to attend a memory screening session which included APOE genotyping, and compared partici-pant response to past community events offering memory screening alone. *Results*: A total of 9 clinic operators were trained and all found the test and workflow easy to perform. Clinic 1 found a 4.7-fold increase in response rate when advertisements included an offer of APOE test-ing versus previous advertisements without APOE testing (21 responses/week vs. 4.5 responses/week re-spectively). Clinic 2 had an information booth at the "Walk for Memories" event and recruited 80 sub-jects to attend memory screening with APOE testing, a 10-fold increase in participant response compared to past community events offering memory screening alone. *Conclusions:* The rapid APOE assay on the Spartan Cube was found to be a quick, non-invasive and easy-to-use test. When APOE testing was offered in conjunction with more traditional recruitment strate-gies, a substantially increased rate of participant response was achieved. These findings suggest that on-site APOE testing may be an effective adjunct to recruitment strategies for AD-related clinical trials.

P6: IMPLEMENTING A MEMORY CLINIC MODEL TO FACILITATE RECRUITMENT INTO EARLY PHASE CLINICAL TRIALS FOR MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE. Lovingly Park[1], Lev Gertsik[2], Zyanya Mendoza[2], Katrina Patrick[2], Darlene Gullaba[1], Airybelle Rodriguez[1], Stanford Jhee[1] *((1) PAREXEL International, Glendale, CA; (2) California Clinical Trials Medical Group, Glendale, CA, USA)*

Background: The recruitment challenges for MCI and AD subjects into clinical trials are well known, however this is particularly true for early phase studies. Currently, only 10-20% of all patients who are referred for research from the community are trial eligible (Grill and Karlawish, 2011). Due to the limited and specific study objectives in early phase study designs, these rates drop to approximately one patient every two months. Barriers to research recruitment are multi-factorial, involving patient centered factors, issues related to caregiver/study partner participation, and aspects related to the involvement of their treating physicians. We implemented a recruitment tool that represented a memory clinic model to address all three of these barriers. Our objective was to significantly facilitate recruitment into AD clinical trials by providing resources and education to patients, their treating physicians, and caregivers in the community. *Method:* A memory clinic paradigm was designed to address recruitment challenges for AD research. The primary goals were to increase research visibility and partnerships with local organizations and referring physicians. Members of the research team co-sponsored community outreach events with local organizations, thereby increasing awareness about the services of this memory clinic. Secondly, physician outreach was expanded to include those who were not previously amendable to clinical trial referrals. Finally, patients of the memory clinic were administered tailored cognitive tests free of charge in order to gauge their current level of functioning. These results were discussed with the patients and their caregivers. If the patients were interested in hearing more about possible research opportunities, they were referred to the early phase unit for a screening visit. *Results:* The data presented is from 2015 (prior to the memory clinic model), and 2016 to 2017 after the memory clinic model was implemented. Each year, there were 4 studies that required successful recruitment of patients who were clinically diagnosed with MCI and/or AD. In 2015, recruitment relied primarily on the existing database of 76 individuals. Only 1 new patient referral was provided and this person was subsequently enrolled in a research study. The memory clinic was initiated in February 2016 and has since evaluated approximately 102 individuals who were either referred through community outreach services targeting those with memory loss or their treating physicians. Mean age of the participants was 67.59 ± 11.29 and we found that new referrals for research participation significantly increased as a result of this new paradigm. In 2016, 12 patients diagnosed with MCI or AD per protocol, were referred to a research study and 3 were randomized. In 2017, 14 patients were referred and 7 were randomized. In addition the referral network increased over a 20 mile radius and a network of 30 referring physicians were established. Collaborations with national non-profit organizations also increased, thereby increasing public awareness about the importance of research participation in the development of new treatments for Alzheimer's Disease. *Conclusions:* In summary, community engagement and providing referring physicians with a clinical service improved recruitment significantly for our phase 1 unit. Moreover, the numbers presented in this abstract, do not include those who were seen as part of the memory clinic and referred to a non-AD study if they met criteria for other conditions or as a healthy volunteer. Resource education, staff training, and dedicated medical professionals can significantly improve awareness about clinical research participation provide additional participants over and above traditional recruitment methods and trial registry enrollment in a large urban area.

P7: AD CLINICAL TRIAL RECRUITMENT CAPACITY TO SCREEN DELIVERS FASTER RECRUITMENT. Roger Bullock[1], Mette G. Skaksen[2], Susanne B. Olesen[3], Aina S. Lihn[2], Ulla Schmidt[4], Hans Chr. Hoeck[1] *((1) Bioclinica Research Network, Stans NW, Switzerland; (2) Bioclinica Research Network, Aalborg, Denmark; (3) Bioclinica Research Network, Vejle, Denmark; (4) Bioclinica Research Network, Ballerup, Denmark)*

Backgrounds: Randomization rates in AD clinical trials are extremely challenging, averaging only about 0.5 participants randomized per study per month at each site. This rate needs to be improved upon if the search for new medicines is going to remain cost effective and new ideas such as trial ready registries are becoming the vogue. But do traditional methods still work? Maybe the attention to recruitment needs more time and focus; something which small clinical centers have less resource to provide, especially if not included in study costs. *Methods:* Bioclinica Research Network (BRN) sites in Denmark (Ballerup, Vejle, Aalborg) uses Facebook, posters and brochures, advertising in AD magazines, information meetings, social events and collaboration with primary care physicians and dementia nurses to find patients. They also have staff dedicated to filtering all the data collected and identifying prospective participants and approaching them personally. They are currently participating in a large multicenter, multi-national clinical trial of 'at-risk of AD' participants. This is known to be a traditionally difficult group to recruit, so BRN sought to benchmark their progress in Denmark at 19 weeks against the rest of the 150 sites performing the study. *Results:* At 19 weeks:

Sites	Randomization rate/month	In screening	% of target reached
Ballerup	2	14	52
Vejle	2.96	42	76
Aalborg	2	51	52
Total	2.32	107	60
Average of other 147 sites	0.15	N/a	6.25

Sites	Pre-screened	Screened	Randomized	Screen fail (%)	Screen fails	Target
Ballerup	944	140	9	83	117	17
Vejle	374	110	13	57	63	17
Aalborg	700	162	9	65	105	17
Total	2018	412	31	68	285	51
Global	2066	745	103	59	1218	1650

Conclusion: 1) Randomization rates at BRN sites are over four times the reported average for AD studies and 15 times above the average rate for other sites on this trial. 2) At this rate, the BRN sites will recruit to target in 31 weeks. The global study would reach target in 304 weeks. Future initiatives will demonstrate how much further dedicated patients recruit technology on a country / site level will be able to further increase randomizations rate. 3) BRN sites would shorten recruitment by more than 5 years providing significant cost savings and supporting faster results for a patient's population in high demand for effective medication. The opportunity costs alone of a successful study would pay for that study. 4) If the patients in screening at the 19-week point screen fail at 59%, another 43 patients can be potentially randomized; meaning the target will be exceeded by the end of the current screening period. 5) Traditional recruitment methods can attract large numbers of potential participants. 6) Screen fail rates are 7% higher than the other centers average, but less than the predicted screen fail rate for this study. 7) BRN has the capability and capacity to deliver complex AD studies at significantly faster rates than currently reported and accepted.

P8: CLINICAL AND PSYCHOMETRIC CHARACTERISTICS OF PARTICIPANTS WITH PRECLINICAL ALZHEIMER'S DISEASE IN JAPANESE ADNI. Ryoko Ihara, MD[1], Atsushi Iwata[1], Kazushi Suzuki[1], Takeshi Iwatsubo[1], Hiroyuki Arai[2], Kenji Ishii[3], Michio Senda[4], Kengo Ito[5], Takeshi Ikeuchi[6], Ryozo Kuwano[6], Hiroshi Matsuda[7], for the Japanese ADNI *((1) The University of Tokyo, Tokyo, Japan; (2) Tohoku University, Sendai, Japan; (3) Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan; (4) Institute of Biomedical Research and Innovation, Kobe, Japan; (5) National Center for Geriatrics and Gerontology, Obu, Japan; (6) Niigata University, Niigata, Japan; (7) National Center for Neurology and Psychiatry, Kodaira, Japan)*

Backgrounds: The Japanese ADNI (Alzheimer's Disease Neuroimaging Initiative) conducted between 2008 and 2014 included 3-year follow-up with intensive assessments of 154 cognitively normal individuals (CN). In recent years, presymptomatic phase of AD (i.e., preclinical AD) has gained increasing attention as a therapeutic target phase for AD disease modifying drugs. In order to evaluate characteristics of Japanese preclinical AD, we analyzed clinical and psychometric data of amyloid positive participants in comparison with amyloid negatives in cognitively normal participants in the Japanese ADNI. *Methods:* The entire dataset of the Japanese ADNI was downloaded from the National Bioscience Database Center (Tokyo, Japan). Positive amyloid status was defined as either having positive or equivocal amyloid accumulation on 11C-PiB or 11C-BF-227 amyloid PET by visual read or having cerebrospinal fluid (CSF) amyloid β1-42 (Aβ42) below cut-off value (333 pg/mL) at baseline assessment. Thus, negative amyloid status was defined as neither amyloid PET nor CSF showing amyloid accumulation. Positive tau status was defined as CSF p-tau greater than cut-off value (45 pg/mL) at baseline assessment. The cut-off values of CSF biomarkers were established by the Japanese ADNI biomarker core. As demographic data, age, sex, education, family history within the first-degree relatives, number of APOE ε4 alleles were compared between amyloid positive and amyloid negative participants. Baseline value and longitudinal data of Clinical Dementia Rating, MMSE, ADAS-cog, Neuropsychiatric Inventory Questionnaire, Functional Assessment Questionnaire logical memory, digit span, category fluency, trail making test, digit symbol substitution test, Boston naming test, clock drawing test, and clock copying test were compared between the two groups. In addition, demographic, clinical and psychometric data were also compared between tau positive and tau negative participants among the amyloid positives. Statistical analyses were performed on JMP software by chi-square test for categorical data, Man-Whitney U test for numerical data, linear mixed-effects regression model for longitudinal data. *Results:* Out of 154 CN, 82 participants underwent either amyloid PET or lumber puncture at baseline, and 17 participants (20.7%) and 65 participants (79.3%) were defined as amyloid positive and negative, respectively. Among the amyloid positive participants, 7 showed disagreement in amyloid status between amyloid PET and CSF. Mean age at baseline (68.1 years in amyloid positive, 67.8 years in amyloid negative), sex, education and family history were not statistically different between the groups. Amyloid positive participants carried larger number of APOE ε4 alleles (p=0.009). There were no significant differences in clinical scales and psychometric tests at baseline. CSF p-tau was significantly higher in amyloid positive participants (48.95 in amyloid positive vs 35.2 in amyloid negative, p=0.002). Linear regression model showed there was a statistical difference in longitudinal change only in MMSE (-0.35/y in amyloid positive vs +0.027/y in amyloid negative, p=0.03)). Although it didn't meet statistically significant differences, logical memory and trail making test also showed learning effect only in amyloid negative participants. Comparison between 5 tau positive and 7 tau negative participants (mean age at baseline, 67.8 years vs 67.7 years, respectively) showed no difference in demographic data but showed a trend toward worse decline in vegetable fluency score in tau positive participants (p=0.09). *Conclusion:* Our results suggest APOE status and longitudinal administration of MMSE would be a useful predictor to discriminate individuals with preclinical AD among the cognitively normal Japanese elderly. The largest symptomatic feature of preclinical AD may be deficits in learning effect in psychometric tests. The results support findings from previous studies including the North American ADNI. Although there was a limitation in sample size, tau positive amyloid positive participants (supposed preclinical AD stage 2 or 3) may have worse word retrieval function than individuals in tau negative amyloid positive participants (supposed preclinical AD stage 1). To draw explicit conclusions, a larger study on preclinical AD is needed. To support ongoing global clinical trials on preclinical AD, multimodal comparison of participants with preclinical AD between the Japanese ADNI and the North American ADNI is needed in the near future.

P9: A NOVEL MIXED EFFECTS MODEL TO SIMULTANEOUSLY ESTIMATE HOW THE BASELINE VALUE AND THE LONGITUDINAL CHANGE IN BIOMARKERS PREDICT THE CHANGE IN COGNITION IN DOMINANTLY INHERITED ALZHEIMER'S DISEASE. Guoqiao Wang, Chengjie Xiong, Eric M. McDade, Jason Hassenstab, Anne M. Fagan, Tammie L.S. Benzinger, John C. Morris, Andrew J. Aschenbrenner, Randall J. Bateman *(The Dominantly Inherited Alzheimer Network, Department of Neurology, Washington University School of Medicine, St. Louis, MO)*

Background: With the increase of pre-symptomatic Alzheimer disease (AD) trials comes a greater need to use AD biomarkers for enrollment, interim analysis, or as the primary outcome.

Consequently, understanding the association between AD biomarkers and early cognitive changes is of increasing importance to validate the legitimacy of using biomarkers as the primary outcome in prevention trials. Traditionally, the association between biomarkers and cognition has been investigated in two ways: (i) use of baseline biomarker values to predict the baseline cognition values or the change (also referred to as "slope") in cognition1 and (ii) use of longitudinal biomarker values to estimate the correlation in slopes between biomarkers and cognition2. However, few studies simultaneously use both the baseline and longitudinal biomarkers to predict change in cognition. Using both predictors in one model offers some advantages: (i) it estimates the significance of both the baseline value and the slope to predict cognition change simultaneously, (ii) provides a comparison of which predictor is relatively more informative, and (iii) leads to more accurate estimation since both predictors are adjusted for each other in the same model and each individual serves as its own control (eliminating potential confounders). *Methods:* We developed a novel general mixed effects model to simultaneously evaluate how the baseline value and the slope of various biomarkers predict the change in cognition using the Dominantly Inherited Alzheimer Network (DIAN) longitudinal observational study. The model simultaneously estimates the slope of the biomarker, the change in cognition predicted by the baseline biomarker, the change in cognition predicted by the biomarker slope, and the change in cognition not predicted by the biomarker baseline and slope. The biomarkers being investigated include: CSF Aβ42, Aβ-PET Pittsburgh compound B (PIB), MRI hippocampal volume, and cortical FDG-PET. The cognition test is a composite z-score of tests of episodic memory, processing speed, and executive function (more negative means worse cognition). Mutation carriers' cognitive composite decreases over time and thus is expected to have a negative slope over disease progression.

Table 1

The change in cognition predicted by the biomarker baseline and the biomarker slope for mutation carriers Biomarker

	Change in cognition predicted by the biomarker baseline, **mean (SE)**	Change in cognition predicted by the biomarker slope, **mean (SE)**	Change in cognition, **mean (SE)***	Change in biomarker, **mean (SE)**	Biomarker baseline **mean (SE)**
PiB PET	**-0.20 (0.04)** [p<0.0001]**	0.86 (0.60) [p=0.15]	0.22 (0.07) [p=0.002]	0.03 (0.01) [p<0.0001]	1.6 (0.03) [p<0.0001]
FDG PET	0.10 (0.17) [p=0.57]	**2.2 (0.89) [p=0.01]**	-0.23 (0.29) [p=0.42]	-0.004 (0.005) [p<0.37]	1.7 (0.01) [p<0.0001]
MRI hippocampal volume~	**0.06 (0.02) [p=0.0009]**	**1.1 (0.12) [p<0.0001]**	0.007 (0.02) [p=0.68]	-0.09 (0.02) [p<0.0001]	0.23 (0.06) [p<0.0001]
CSF Aβ42~	0.004 (0.1) [p=0.88]	-0.28 (0.24) [p=0.25]	-0.18 (0.03) [p<0.0001]	-0.1 (0.02) [p<0.0001]	0.21 (0.12) [p=0.07]

*This change is conditioned on the change in cognition predicted by the biomarker baseline and the change in cognition predicted by the biomarker slope.
**negative sign means 1 unit increase in biomarker will lead to a decrease in the rate of change in cognition.
~Both are standardized to have mean 0 and SD 1 for ease of computation and interpretation.

Results: Table 1 shows the results from the model predicting change in cognition from baseline and longitudinal biomarkers. First, as expected, PiB PET increased over time (.03), but more importantly, baseline PiB PET significantly predicted change in cognition (-.20) whereas the longitudinal change in PiB did not (.86). Furthermore, after accounting for the change predicted by both baseline and change in PiB PET, the residual change in cognition was positive (.22) suggesting that below a certain threshold of PiB cognitive change is minimum or slightly positive. In contrast, change in FDG PET predicted change in cognition (2.2) but the baseline value did not (.10). Both the baseline value and change in hippocampal volume predicted cognitive change, however the weight on the longitudinal predictor was noticeably larger than the baseline value suggesting relatively greater importance. Finally, although neither the baseline value nor the slope of Aβ42were related to change in cognition, results suggest that when the change in CSF Aβ42 is large (more reduction), the change in cognition is small (less negative). The lack of significance could be due to the small sample size. *Conclusion:* Our novel mixed effects model simultaneously evaluated/tested the predictability of biomarker baseline and slope on cognition change, and showed that for different biomarkers their predictability differed. Specifically, change in cognition was better predicted by baseline rather than change in PiB PET, while the rate of change was the better predictor for the remaining biomarkers. These results may provide insight for planning prevention trials such as which biomarker to use to identify the "right" trial cohort at enrollment and which biomarker to use at the interim analysis to determine whether a drug is hitting the target. Funding: The DIAN observational study is supported by grant U19 AG032438. Reference: 1 Wang, F. et al. Cerebral amyloidosis associated with cognitive decline in autosomal dominant Alzheimer disease. Neurology 85, 790-798 (2015). 2 Xiong, C. et al. Longitudinal relationships among biomarkers for Alzheimer disease in the Adult Children Study. Neurology 86, 1499-1506 (2016).

P10: AN EXAMINATION OF RATE OF DECLINE AS AN ALTERNATIVE TO CHANGE FROM BASELINE. Howard Mackey[1], Nan Hu[1], Michael Malek-Ahmadi[2], Yinghua Chen[2], Pierre Tariot[2], Eric M Reiman[2], Francisco Lopera[3], Kewei Chen[2], Ronald Thomas[4] *((1) Genentech, Inc., South San Francisco, CA, USA; (2) Banner Alzheimer's Institute, Phoenix, AZ, USA; (3) Universidad de Antioquia, Medellín, Colombia; (4) UC San Diego Department of Neurosciences, CA, USA)*

Backgrounds: Pivotal studies in Alzheimer's disease (AD) typically enroll hundreds to a thousand or more patients followed for at least 1.5 years. Resources required to execute such trials are considerable, which heightens the importance of efficiency in trial design and in the use of powerful statistical methods. The standard summary measure of efficacy in AD trials is a comparison of the change from baseline between the control and treatment groups at a specific landmark in time. Estimation is usually carried out using a Mixed Model for Repeated Measures (MMRM). While this approach has merits, the interpretability of this summary measure is limited to one specific point in time and does not summarize the treatment effect over the duration of the trial. In addition, alternative approaches may be more powerful in testing for treatment effects. *Methods:* We explore the rate of decline summary measure as an alternative to change from baseline. Approaches for testing the effect of treatment on the rate of decline have been described previously in AD (1–3). Here, we explore the use of a Random Coefficient Regression Model (RCRM) for hypothesis testing and estimation of a treatment's effect on rate of decline. The RCRM has been used in clinical trials in other disease settings leading to health authority approval (4). We investigate power comparisons between change from baseline via MMRM and rate of decline via RCRM under two important scenarios. *Results:* If rates of decline are constant during the course of a trial, a hypothesis test of the rate of decline via the RCRM approach is shown to be significantly more powerful than a hypothesis test of change from baseline via MMRM under certain scenarios. Power benefits are fueled by multiple sources and can be further boosted by optimization of measurement timing as well as from using data after the change from baseline landmark. Power improvements are similarly shown in an increasing rate of decline model. We further illustrate the potential benefits of the RCRM approach using longitudinal data from cognitively unimpaired 30–60 year old PSEN1 E280A mutation carriers from the world's largest autosomal dominant AD (ADAD) kindred with up to 20 years of follow-up (5). *Conclusion:* The rate of decline summary measure

estimated via RCRM yields substantial improvements in power under a range of conditions and may be a viable alternative to MMRM in clinical trials of AD. (1) Doody RS et al. N Engl J Med 2014;370:311-21; (2) Thomas RG et al. Alzheimers Dement 2016;12:598-603; (3) Bateman RJ et al. Alzheimers Dement 2017;13:8–19; (4) Richeldi L et al. N Engl J Med. 2014;370:2071–82; (5) Silvia Rios-Romenets et al. AAIC 2017

P11: METRIC COLLECTION FOR RESEARCH SITE OPTIMIZATION: GLOBAL ALZHEIMER'S PLATFORM EFFORTS TOWARD CREATING AN AD RESEARCH SITE DATABASE. Richard Mohs, Kate Zhong, John Dwyer, Jason Bork, Gabe Goldfeder *(Global Alzheimer's Platform, Washington, D.C., USA)*

Background: The importance of capturing clinical trial site performance metrics has long been known in the industry. That being said many sites find tracking these metrics extremely difficult (Getz, 2016). It is possible that some problems plaguing AD clinical trial development could be alleviated by better identification and remediation of site inefficiencies. Even when a site does capture its metrics it often does not know what to do with that data in a vacuum. The Global Alzheimer's platform (GAP) is a patient-centered, not-for-profit organization dedicated to speeding the delivery of innovative medicines to those in need by reducing the time and cost of Alzheimer's disease clinical trials. As part of the GAP mission we have created a network of 50 AD research sites. GAP will be striving to create a standardized system that all sites can use to report their metrics. This database will allow for unparalleled sharing of data and learning across AD research sites. GAP has the potential to create the largest knowledge base of AD clinical trial sites and site performance metrics in the world. *Methods:* The GAP network consists of 50 sites, 30 academic or institution affiliated and 20 private. GAP sites were selected for their quality and productivity based on recommendations from GAP pharma partners, key scientific advisers, and other existing sites. Each site filled out a detailed engagement survey to qualify to join GAP, many sites were also visited by GAP personnel to ensure quality and commitment of the site. As a prerequisite to joining GAP-Net, sites have to agree to report quarterly metrics to GAP. The first requested metrics were for the first quarter of 2016 and sent to 43 sites. Metrics ask to be tracked were in following areas: Study start-up: pre- and post-site selection (8 metrics) Recruitment (5 metrics), Execution (5 metrics). Sites were sent an Excel spreadsheet they were to fill in with requested information. The learnings from this process and initial data submitted will serve as backbone for information in this presentation. *Results:* Of the 43 sites for which metric data was requested, GAP received 30 reports back. Many sites reported being unable to report metrics as they had not been tracking them, and lacked a system to do so. Furthermore not all returned reports were filled out completely. Even given the missing sites there was a lot of data that can be learned from. As might be expected there was great variance in site metrics across many areas. The range of active studies at sites ranged from 2 to 33 with a mean of 13.1. Academic centers tended to have more active studies than private sites. These studies included observational, mild-moderate AD, MCI, and prevention trials. The average time between contract execution and first patient screened was 114 days, with commercial sites being slightly faster; surprisingly little difference was seen between commercial and academic sites in time between site selection and contract execution, with means of 271 and 246 respectively. The request prompted many sites to re-think or revamp their metric collection process as evidenced in comments to GAP. For example one site noted "As you will see, there are some definite holes in our data collection and I am working with our team to implement new strategies in an effort to better track our efforts" *Conclusion:* This initial project further bolsters GAP's belief in the value of creating such a robust AD clinical trial site metric database. Even with the preliminary data we see clear areas that can be approved across all sites, we can also give feedback to sites who were performing much lower than their peer sites. This collection effort also strongly suggests that sites would greatly benefit from a uniform system for which to track and report these metrics. GAP will be refining and adding to the metrics asked from sites, and is planning on developing a web-based system or platform for sites to report in to in a uniform and standardized way. Creating this AD clinical trial site database is an unprecedented effort in the world of AD research and can benefit the entire field greatly, but most importantly help advance the discovery of treatments for Alzheimer's disease.

P12: IN VITRO DEGRADATION OF B-AMYLOID FIBRILS BY MICROBIAL KERATINASES. Debananda Singh Ningthoujam *(DBT-State Biotech Hub (SBT Hub) & Microbial Biotechnology Research Laboratory (MBRL), Department of Biochemistry, Manipur University, Canchipur, Imphal)*

Background: Normal proteins, when misfolded, form insoluble aggregates or fibrils, resistant to proteolytic degradation. These fibrils are formed by proteins which may or may not be associated with diseases. Such fibrils are commonly formed by amyloid proteins, which share a common structural motif, known as cross β sheet structure. Deposition of these fibrils , usually called β-amyloid fibrils, causes neurodegenerative diseases such as Alzheimer's disease (AD). Some amyloid fibrils such as those formed by prions are infectious in nature. Microbial keratinases are reported to degrade prions and prion-like structures. Since prions have structural similarities with β-amyloid fibrils, we tested microbial keratinases, purified in our lab, for their possible activity on β-amyloid fibrils. *Methods and findings:* Lysozyme is a model system for generating β-amyloid fibrils. We prepared β-amyloid fibrils by treating HEWL lysozyme with 8M Urea for 48 h at 55°C. Generation of β-amyloid fibrils was confirmed by the appearance of a fibrous precipitate, immunoblotting with anti β-amyloid antibody, HPLC, and Congo Red Absorption spectroscopy. Two keratinases, Ker1 and Ker2, were purified from an indigenous actinomycete strain Amycolatopsis sp. MBRL 40 using Q-sepharose Column Chromatography. Ker1 and Ker2 were incubated with β-amyloid fibrils of lysozyme and their activity on β-amyloid fibrils was monitored. Similar activity was also monitored with Ker1 reconstituted in neutral or cationic liposomes. Soluble Ker1 or Ker1 reconstituted in liposomes degraded β-amyloid fibrils of lysozyme after 24 h incubation at 40°C as evidenced by loss of fibrous precipitate of β-amyloid fibrils, loss of signal when immunoblotted with anti β-amyloid antibody, and changes in the HPLC peaks and Congo Red Absorption spectra when compared to the peaks and spectra obtained with untreated β-amyloid fibrils. Ker 2 was found to be less potent than Ker1. *Conclusions:* Various therapeutic agents for AD are currently under clinical trials. These drugs inhibit the activity of acetylcholinesterase or inhibit the formation of Aβ plaques and their downstream effects. Such agents could be antioxidants, Ca++ channel antagonists, non-steroidal anti-inflammatory drugs, iron chelators, hypolipidemic compounds or vaccines containing anti-Aβ antibodies. These candidate drugs, however, suffer from various adverse side effects, and they don't benefit globally in cognition and behavior. Keratinases can be prospective molecules for possible drug development against AD and other neurodegenerative diseases. Our results indicate that Amycolatopsis sp. MBRL 40 keratinases, esp. Ker1, hold promise for possible development of therapeutic agents for AD and related neurodegenerative diseases.

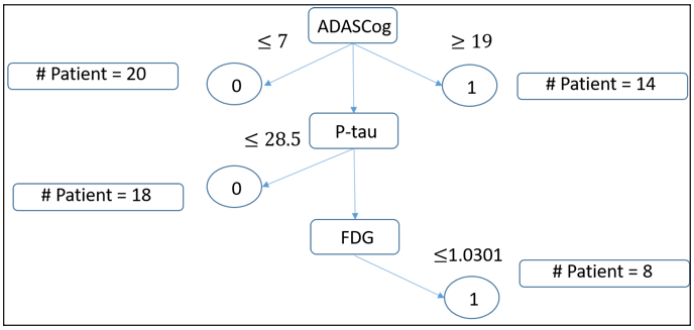
P13: A LIKELIHOOD-BASED PREDICTION OF ALZHEIMER'S DEMENTIA USING BIOMARKERS: APPLICATIONS FOR CLINICAL TRIALS. Igor Yakushev[1], Felix Müller-Sarnowski[2], Bing Si[3], Jing Li[3], Timo Grimmer[2] *((1) Dept. of Nuclear Medicine, Technical University of Munich; (2) Dept. of Psychiatry and Psychotherapy, Technical University of Munich; (3) Dept. of Industrial Engineering, Arizona State University*

Backgrounds: Amyloid-positive subjects with mild cognitive impairment (MCI) bear a high risk of developing dementia due to Alzheimer's disease (AD). However, only a proportion of them progress to dementia within a clinically relevant period. Thus, an NIA-AA workgroup recommended usage of biomarkers to increase the likelihood of AD pathology in patients with MCI. Among these biomarkers are atrophy on magnetic resonance imaging (MRI), glucose hypometabolism on positron emission tomography (PET) and increased tau protein levels in cerebrospinal fluid (CSF). It is still unclear, however, how to deal with a range of available biomarkers in the context of clinical trials. Specifically, such questions as which biomarkers should be tested for, if a few, in what order, and the place of neuropsychological testing in the diagnostic sequence have remained unresolved so far. In the present paper, we propose an algorithm that considers all available information and produces an optimal sequence of the biomarkers in dependence on a pre-defined likelihood of progression to dementia. *Methods:* We searched the Alzheimer's disease neuroimaging initiative database for subjects with MCI, for whom baseline neuropsychological, CSF examinations, structural MRI and PET with fluorodeoxyglucose (FDG), as well as a clinical follow-up were available. Included were 144 patients with MCI and probable beta-amyloid (Aβ) pathology defined as reduced CSF Aβ42. Exactly a half of them progressed to dementia due to AD within 2 years; they are referred to as converters thereafter. The proposed algorithm splits each variable (biomarker) into three sections: low risk, indiscriminate, and high risk. Herewith, high risk means a high likelihood of progression to AD dementia within 2 years. The likelihood is pre-defined by the user according to trial or diagnostic needs. High and low risk cut-offs for a given biomarker are searched iteratively. Then, the algorithm is re-applied to a second biomarker, but only on subjects classified as indiscriminate by the first biomarker. Thereby, a tree-like diagnostic sequence is generated. *Results:* In analogy with previous findings Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) was chosen as starting point. Subsequently, the algorithm searched which biomarker should be tested for as 2nd, 3rd, and potentially 4th, to reach the highest cross-validated positive predictive value (PPV). At a 90 % (pre-defined) likelihood, the algorithm produced ADAS-cog followed by p-Tau and FDG-PET as the optimal diagnostic sequence. From the whole sample of 144 subjects 22 were identified as high-risk converters. Among them, 14 were disclosed by ADAS-cog, 8 by FDG-PET. CSF p-tau was included exclusively due to its negative predictive power (figure). When the likelihood of progression was set at 95 % 14 high risk converters with a cross-validated PPV of 91 % were identified. At any level of likelihood, the proposed algorithm identified at least twice as many high risk converters as were predicted by any logistic regression model with all available variables. *Conclusion:* Our results demonstrate that testing for a few biomarkers (including neuropsychological tests) allows identification of more high risk converters than identified by any biomarker alone. The sequence of biomarkers to be tested for varies with the likelihood of progression to dementia. In the proposed algorithm, this likelihood can be pre-selected by the user. In any case, the algorithm provides a meaningful trade-off between the reliability of an early, biomarker-supported diagnosis and a sample size for a clinical trial. The starting variable (biomarker) can be chosen by the user as well. Thus, potential restrictions in a recruitment process, e.g. unavailability of FDG-PET, can be accounted for. In conclusion, the proposed algorithm integrates biomarker information in a flexible, user-friendly fashion and hence can serve a useful tool for clinical trials in the field of AD and beyond.

High-risk converters are noted as 1. Twenty two high-risk converters are selected by ADAS-cog, followed by CSF p-tau and FDG-PET. Inclusion of MRI did not improve the results; it is therefore not included in this tree.

Figure

Tree for selecting converters with the likelihood of progression to dementia of 90 %



P14: A RANDOMIZED PLACEBO-CONTROLLED CROSS-OVER TRIAL INVESTIGATING NABILONE AS A TREATMENT FOR AGITATION IN PATIENTS WITH ADVANCED AD: STUDY PROTOCOL. Myuri Ruthirakuhan[1,2,3], Nathan Herrmann[1,2,3], Eleenor H. Abraham[1,3], Chelsea Sherman[1,2,3], Nicolaas Paul L.G. Verhoeff[2,4], Alex Kiss[1], Sandra E. Black[1,2], Ana C. Andreazza[2], Krista L. Lanctot[1,2,3] *((1) Sunnybrook Research Institute, Toronto, ON, Canada; (2) University of Toronto, Toronto, ON, Canada; (3) Neuropsychopharmacology Research Group, Toronto, ON, Canada; (4) Baycrest Health Sciences, Toronto, ON, Canada)*

Background: Current pharmacological interventions for the management of agitation in Alzheimer's disease (AD) have modest benefits and high risk-profiles, spurring the search for new medications. With the availability of synthetic cannabinoids (CB), such as nabilone, the therapeutic potential of the endocannabinoid system (ECS) can now be investigated. The ECS may be a rational target to treat agitation in AD as it has been shown to modulate neuropsychiatric symptoms, as well as pain and weight. We describe a randomized placebo-controlled cross-over trial investigating the safety and efficacy of nabilone in the treatment of agitation, as well as pain and weight loss in patients with moderate-to-severe AD. *Methods:* This is an ongoing double-blind, randomized placebo controlled cross-over trial comparing 6 weeks of nabilone (target dose: 1-2 mg) to 6 weeks of placebo, with a 1-week washout preceding each treatment phase. While nabilone has a short half-life (2 hours), that of its active metabolites is 35 hours, suggesting a wash-out period of 1 week. The recruitment goal is to randomize 40 patients. The primary outcome is agitation, as measured by the Cohen-Mansfield Agitation Inventory (CMAI). The secondary outcomes includes behaviour (Neuropsychiatric Inventory (NPI)-NH), cognition (standardized Mini Mental Status Exam (sMMSE) and Severe Impairment Battery (SIB)) and global impression (Clinician's Global Impression of Change (CGI-C)). Exploratory outcomes include pain (Pain Assessment in Advanced AD (PAIN-AD)), nutritional status (Mini-Nutritional Assessment-Short Form (MNA-SF)), and safety. Pairwise t-tests

between the screening visit and the baseline (BL) of phase 1, and between the BLs of phase 1 and 2 were completed to investigate the role of placebo and cross-over effects, respectively on the primary, secondary, and exploratory outcomes. *Results:* To date, 31 participants (mean±SD age=87±10, CMAI=67.6±118.1, NPI-NH total=33.8±15.4, NPI-NH agitation subscore=7.1±7, sMMSE=7.1±7, SIB=36.8±29.7, PAIN-AD=2.9±1.5, MNA-SF=8.2±2.5, 73.3% male) have been randomized. In phase 1 and 2 of the study, 77% and 76% of participants received the maximum target dose of 2mg/ placebo, respectively. In phase 1 of the study, 61% of participants had a reduction in CMAI total score, while this was the case for 74% of participants in phase 2. With regards to our primary outcome, CMAI total score, there were no significant placebo ($t(29)=-1.26$, $p=0.22$) or carry-over ($t(23)=0.88$, $p=0.39$) effects identified. However, compared to screen, the mean CMAI verbal/aggressive subscore was significantly lower at the BL of phase 1 ($t(29)=-2.13$, $p=0.04$). There were no significant placebo or cross-over effects identified with the NPI-NH total, NPI-NH subscale items, sMMSE, PAIN-AD and MNA-SF scores (all, $p>0.05$). *Conclusions:* Our target dose has been relatively well tolerated as most participants received a maximum dose. A 6-week study duration per phase seems appropriate as we were able to detect an overall reduction in CMAI scores in most of our participants. Limitations of a cross-over RCT include the potential for treatment-order and carry-over effects. Currently we are unable to investigate treatment-order effects as we are blinded to treatment allocation. However, based on interim blinded results, there are currently no carry-over effects. There may be potential placebo-effects as indicated by reduced verbal aggression during the placebo run-in phase of our trial. As such, the inclusion of a placebo-run in may be advantageous in the design of a double-blind randomized placebo-controlled trial.

P15: ENRICHING CLINICAL TRIAL DATA THROUGH CO-ENROLLMENT WITH THE BRAIN HEALTH REGISTRY.

Juliet Fockler[1,2], Rachel L Nosheny[1,2], Diana Truran[1], Shannon Finley[1], Monica Camacho[1], Derek Flenniken[1], Aaron Ulbricht[1], R Scott Mackin[1,3], Gil Rabinovici[4], Michael W Weiner[1,2] *((1) Center for Imaging of Neurodegenerative Diseases, San Francisco Veteran's Administration Medical Center, San Francisco, CA, USA; (2) UCSF Department of Radiology and Biomedical Imaging, San Francisco, CA, USA; (3) UCSF Department of Psychiatry, San Francisco, CA, USA; (4) UCSF Department of Neurology, San Francisco, CA, USA)*

Background: The high cost of clinical research including randomized controlled trials (RCT) is a major obstacle in the development of effective treatments for Alzheimer's disease (AD) and other dementias. The necessity to bring participants into clinic repeatedly to gain longitudinal data is a major cost. Additionally, in almost all cases, the research participants are no longer followed after the completion of the study. There is a need for a more affordable alternative where participants can be followed longitudinally without the cost and staff burden of repeated in-clinic visits. To meet this need, the Brain Health Registry (BHR) offers collaborating scientists a way to enrich their current datasets by following their research participants via co-enrollment, a mechanism in which research participants who are currently enrolled in clinical studies including RCTs, or who are newly enrolling in such studies, also join the BHR allowing supplemental data to be obtained. The BHR is a University of California, San Francisco (UCSF) Institutional Review Board (IRB) approved online research study where participants can register, provide consent, answer questionnaires about health, lifestyle, cognition, medications and family history, and complete cognitive tests. See CTAD abstract entitled "Online Clinical Research: Updates and Insights from the Brain Health Registry" by Finley et al. for more details on BHR overall. *Methods:* BHR collects extensive information including self-report data on demographics, medications, family medical history, mood, diet, sleep, exercise patterns, and lifestyle through questionnaires. BHR also uses three online neuropsychological tests (NPTs) to collect information about cognitive functioning. Participants are invited to return bi-annually to complete follow-up questionnaires and retake cognitive tests. Collaborators who wish to co-enroll their clinical cohorts in BHR can request this standard experience, or create a customized experience by selecting which questionnaires and NPTs are given to the participants. Visit frequency and the content and schedule of all participant communications can can also be tailored to the needs of the specific study. For the current co-enrollment studies, new participants were invited to join BHR by email. These invitation emails included information about the collaboration, a co-enrollment code, and a link to a study-specific BHR registration page. The co-enrollment codes are unique to each participant and are used as the key for identifying and sharing data between the BHR and the collaborator without exchange of PII. In some cases, prior to the invitation email being sent, the collaborator also provided additional information about the BHR through various recruitment methods such as phone calls to participants, and printed materials provided by mail or during in-clinic visits. All communications and content may be customized by including the collaborator study name and logo. To link the data between the studies, participants signed a consent to share their BHR data with the collaborator once enrolled in the BHR. The collaborator also included the use of and data sharing to the BHR in their consent and HIPPA, if needed. *Results:* Since January 2017, the BHR has two co-enrollment studies with the Alzheimer's Disease Neuroimaging Initiative (ADNI) Study (PI: Michael Weiner), and Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) Study (PI: Gil Rabinovici). To date, across the two projects, 113 participants have been co-enrolled into the BHR. The average age is 75 with a SD of 4.6. 40% are female and 9% are non-Caucasian. 46 also have a study partner enrolled in BHR through the Caregiver and Study Partner Portal. Compared to the general BHR older adult cohort, the co-enrollment cohort is enriched in participants with memory complaints and diagnosed memory problems. For example, in the BHR-IDEAS co-enrollment study, 43% of co-enrolled participants self-report MCI diagnosis, compared to 4% of older adults in BHR; and 34% of co-enrolled participants self-report AD, compared to 1% of older adults in BHR. Both co-enrollment studies are now in the process of linking online cognitive data with in-clinic data including MRI and PET images, genetics, cognitive tests, CSF and blood biomarkers. *Conclusion:* Co-enrollment with the Brain Health Registry offers clinical trials an innovative way to enrich their datasets and maintain contact with study participants. The preliminary results demonstrate proof of concept that the BHR and interested collaborators can co-enroll participants into both research studies. Although both current co-enrollment studies are observational studies, the same approach can be used with clinical trials. Co-enrollment studies of impaired clinical cohorts also offer a unique opportunity to involve those with memory complaints, MCI, and AD in online research. The study data collected will be linked to create a more enriched dataset. Furthermore, BHR is able to maintain contact and collect longitudinal data after the studies have ended. These enriched datasets can be used for analysis, papers and presentations, and to inform future research projects. Finally, since all BHR visits are completed at-home, at the convenience of the participants, it is an easy, effective, low-cost approach to gathering longitudinal data.

P16: OUTCOMES AND LENGTH OF PHARMACOTHERAPY TRIALS ON ALZHEIMER'S DISEASE. Enea Traini, Michele Moruzzi, Francesco Amenta *(Centre for Clinical Research, Telemedicine and Telepharmacy, University of Camerino, Camerino)*

Backgrounds: Alzheimer disease (AD) is a progressive neurodegenerative condition, characterized by neuronal deterioration and cognitive decline. During the years, numerous drug therapies were proposed and tested to alleviate cognitive dysfunction and behavioral problems occurring in AD. Overall, clinical pharmacotherapy trials were limited to an elapse of time shorter than the average lifetime of an AD patient that some studies indicate in 7.1 years after diagnosis. This study has assessed the relationships between the length of pharmacotherapy trials and their outcomes. *Methods:* Articles on AD clinical trials published from January 2007 to February 2017 were considered. The selection of the analyzed has considered the pharmacological trials and the time of observation for completing them. The search included two main sources of research libraries: PubMed and Cochrane Library using the entries "Alzheimer's disease" "Alzheimer's disease clinical trials/pharmacological trials" as keywords. *Results:* We found 62 articles fulfilling the inclusion criteria, most of them were made using Cholinesterase Inhibitors as drugs. The average length the studies was 15.5 months, ranging from 1.5 to 110 months. Results are interesting even difficult to interpreter, as some drugs showed efficacy in shorter trials and lack efficacy in longer ones. On the other hands, some other drugs were more efficient in the longer than in the shorter times. *Conclusion:* The findings suggest that studies that did not find positive results had an observation time too short to sort the expected effects of treatment. On the other hand, prolonging observation for long times may come to show a «flattening» of the effects. These differences may depend from the drugs used. Long periods of study obviously increase the costs of a clinical trial, but it is desirable in the design phase, to have trials lasting for a reasonable elapse of time to demonstrate drug efficacy over time if any.

P17: ELECTROPHYSIOLOGY OF THE GABA AND CHOLINERGIC SYSTEMS IN HEALTHY ELDERLY SUBJECTS. Kristinn Johnsen[1], Peter Draxler[1], Gísli Johannesson[1], Magnus Johannsson[1], Thorkell Gudmundsson[2], Jon Snaedal[2] *((1) Research and Development, MentisCura, Reykjavík, Iceland; (2) Geriatrics, Landspitali University Hospital, Reykjavík, Iceland)*

Backgrounds: One of the main challenges in central nerve system (CNS) related drug development is to demonstrate target engagement in humans. An indirect method to demonstrate target engagement is to monitor functional modality which is sensitive to the activity of the neurotransmitter systems related to the target. Electrophysiology as recorded by electroencephalography (EEG) has been demonstrated to be sensitive to the level of activity of various neurotransmitter systems. This has been demonstrated in drug challenge studies targeting specific neurotransmitter systems by monitoring the changes in quantitative EEG features by administration of the compound. In the present work, we demonstrate how data collected from challenge studies can be analyzed to demonstrate target engagement, and how to relate the response to the activity of different brain networks. Networks considered are the default mode network, as well as networks relating to acetylcholine depletion and cognitive control. The connection is made by studying cross channel cross frequency coherence related measures. *Methods:* The underlying data used for the study was collected from 110 elderly subjects recruited into a 2-visit study. In each visit the subjects underwent drug challenge. EEG recordings were collected pre-challenge and post-challenge at a time overlapping the top of the PK-curve for the compound. During the first visit subjects were challenged with scopolamine which is a muscarinic antagonist which acts by blocking the muscarinic acetylcholine receptors, 101 subjects finished the challenge. During the second visit subjects were challenged with benzodiazepine which affects the neurotransmitter gamma-aminobutyric acid (GABA) at the GABAA receptor, 42 subjects conclude the second visit. The EEG recordings were performed using 19 electrodes placed according to the standard 10-20 system. The electrodes were placed at positions: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz. The recording took place while the subject was at rest with eyes closed for a duration 150 seconds. The resulting data was analyzed by considering the cross channel cross frequency variance (CCFV) of the signals, for all electrode pair combinations. For each pair the principal components evaluated from the combined pre-challenge and post-challenge data was analyzed. The receiver operator characteristic curve (ROC) was then evaluated for separation of the pre-and post-data for each of the principal components. The pairs strongly influenced by the challenges were then identified by considering the area under curve (AUC) of the ROC. These pairs were then related to brain networks which have been described in the literature. *Results:* For the cholinergic system, we found that local gamma oscillations couple to gamma oscillations in other areas of the cortex through low frequency alpha and theta oscillations driven by cholinergic activity. The cholinergic activity mapped out in this manner correlates strongly with the default mode network. The network revealed by this analysis for the GABA system strongly connect the frontal regions with the temporal regions and coincides strongly with network previously identified to relate to cognitive control. *Conclusion:* The present study demonstrates how a combination of challenge studies for compounds and in depth analysis of the networks revealed by the challenge can be applied to demonstrate that engagement of the compound takes place. Furthermore, it also demonstrates how the networks can be related to known functional brain networks potentially bringing insight into the effect of the compound studied. We have demonstrated this for scopolamine and benzodiazepine opening a virtual window into the activity of the cholinergic- and GABA-systems. This methodology can potentially be applied to study other compounds with well know properties yielding further insight into other functional networks and neurotransmitter systems, as well as being a potential method to study the influence of candidate drugs on these networks and systems.

P18: IDENTIFYING ELEVATED RATES OF CDR SCORING ERRORS: THE COGNITIVE-FUNCTIONAL DIFFERENCE SCORE. Christopher Weber[1], Selam Negash[1], Michael Ropacki[1], Christopher Randolph[1,2] *((1) MedAvante, Inc.; (2) Loyola University Medical Center)*

Background: The Clinical Dementia Rating scale (CDR) is a subjectively rated clinician-reported outcome measure, used as a sole primary endpoint in clinical trials of early symptomatic Alzheimer's disease (AD), as a key secondary endpoint that contributes to diagnostic classification in prevention trials for time-to event analyses, and as a co-primary endpoint in some trials of mild to moderate dementia due to AD1. Scoring the CDR can be challenging, particularly in mild disease; rater administration and scoring errors are common. The goal of this study was to identify a CDR quality metric based upon internal patterns of domain scores that could be used to identify atypical patterns that might be indicative of scoring errors. *Methods:* 10,283 CDR assessments, with CDR sum of boxes (CDR-SB) ranging from 0.5 to 5, from eleven ongoing industry-sponsored clinical trials in Alzheimer's disease, including prevention, prodromal, and mild-moderate dementia were collated for analyses.

This CDR-SB range was chosen to restrict the focus of the study to mild disease, where the scoring is typically more challenging2. All CDR assessments were centrally reviewed by trained and calibrated clinicians. A preliminary pattern analysis revealed an expected pattern of elevations in scores (more impairment) on the three cognitive domains (Memory, Orientation, Judgment & Problem-Solving) that preceded and remained above elevations in the three functional domains (Community Affairs, Home & Hobbies, and Personal Care) with increasing CDR-SB scores. We decided therefore to construct a single score that would reflect the relationship of the cognitive domains to the functional domains. This was done by taking the mean of the cognitive domains for each CDR assessment and subtracting the mean of the functional domains. Our hypothesis was that this score, referred to as the cognitive-functional difference (CFD) score should be positive in the vast majority of cases, and that negative scores might be associated with increased scoring errors. To test this hypothesis, the CFD scores for each assessment were calculated from site rater scores, and errors as detected by central review were examined for both "typical" (positive) CFD scores, and "atypical" (0 or negative) CFD scores. *Results:* For the overall sample, 89.2% of the CFD scores were positive (N=9,167), and 10.8% were at or below 0. In order to further explore the pattern of positive and negative CFD scores as a function of overall CDR-SB, assessments were clustered into CDR-SB categories of 1,2,3,4, and 5, with half-step scores being included in the next higher full-step score (e.g., a CDR-SB of 3.5 would be included with CDR-SBs of 4). The percentage of positive CFD scores across these 5 steps ranged from 85% to 92%, with no discernible pattern of change as a function of overall CDR-SB. Error rates were significantly higher in the atypical group compared to typical, $F(1,10,281) = 142.3$, $p < .0001$. At each CDR-SB level, the atypical group had significantly higher errors compared to typical, (p-values <.0001). Comparison of clinician reviewer scores revealed that in atypical CFD scores with at least one error (n=181), clinician reviewers improved (i.e., shifted CFD closer to a typical score) in 94% of the assessments. *Conclusion:* Because the CDR is utilized as a sole primary endpoint in trials of early symptomatic AD, and is a critical outcome measure in trials at other stages of disease, including prevention trials, and its scoring can be challenging, particularly in mild disease, there is a need to identify CDR administrations within clinical trials that have an increased probability of scoring errors to maintain data integrity and improve signal detection. This study demonstrated that it is feasible to identify "atypical" patterns of domain scoring within the milder range of disease severity that are indicative of elevated rates of scoring errors. This allows us to add a trigger to central review algorithms based entirely upon the internal pattern of domain scores. Further work is needed to identify potential atypical patterns in more advanced disease, and to potentially exploring more sophisticated data analytic approaches to explore internal score patterns in this and other scales that reflect an increased probability of scoring errors. References: 1. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr. 1997;9 Suppl 1:173-6; discussion 177-8. PubMed PMID: 9447441. 2. Tractenberg RE, Schafer K, Morris JC. (2001). Interobserver disagreements on clinical dementia rating assessment: interpretation and implications for training. Alzheimer Dis Assoc Disord. 2001 Jul-Sep;15(3):155-61. PMID: 11522933

P19: STUDY DESIGN AND PROTOCOL OF THE NOLAN TRIAL: A RANDOMIZED CONTROLLED TRIAL OF A NUTRITIONAL BLEND TO PREVENT COGNITIVE DECLINE IN OLDER ADULTS. Claudie Hooper[1], Sophie Guyonnet[1,2], Corina Boschat[3], Julie Hudry[3], Sandrine Andrieu [2,4], Jeronen Schmitt[3,5], Bruno Vellas[1] *((1) Gérontopôle, Department of Geriatrics, CHU Toulouse, Purpan University Hospital, Toulouse, France; (2) UMR1027, Université de Toulouse, UPS, INSERM, Toulouse, France; (3) Nestlé Research Center, Vers-chez-les-Blanc, Switzerland; (4) Department of Epidemiology and Public Health, CHU Toulouse, Toulouse, France; (5) Center of Human Psychopharmacology, Swinburne University of Technology, Melbourne, Australia)*

Background: Nutrition is an attractive target for the management of cognitive aging in the elderly population (1,2). However, randomized controlled trials (RCTs) of nutritional interventions have yielded mixed results (1–5). One reason for this might be that the administration of nutrients in isolation is of little effect for the holistic nutritional requirements associated with cognitive aging considering the complex interplay of mediators associated with this process. Thus, we propose that a blend of nutrients might be more beneficial for the management of cognitive aging as evidenced by preliminary experiments in elderly cats (6). *Methods:* The Nolan trial was designed to assess the efficacy of a multi-component nutritional supplementation on change in cognitive function over 48 months in older adults with subjective memory complaints (SMC), but without dementia. The supplement was designed to target multiple cell signalling pathways associated with cognitive aging and is composed of omega 3 polyunsaturated fatty acids, B vitamins, choline, vitamin D, vitamin C, vitamin E, selenium and citrulline. Subjects (n= 2080) aged 70 years and older with SMC will be enrolled by 20+ memory clinics across France. Subjects will be randomized to the nutritional intervention or placebo. Participants will undergo clinical and biological assessments at baseline, 6, 12, 24, 36 and 48 months. The primary endpoint of the study is the change from baseline to 48 months in the MAPT Preclinical Alzheimer Cognitive Composite (MAPT-PACC) score. Secondary outcome measures include other neuropsychological cognitive measures, the assessment of quality of life and physical function. Neuroimaging will be employed to evaluate the impact of the intervention on brain connectivity, brain atrophy, white matter integrity, and cerebral blood flow. Furthermore, effects of the nutritional intervention on plasma biomarkers will be assessed including brain derived neurotrophic factor, β-amyloid, tau, homocysteine and biomarkers of inflammation and oxidative stress. *Results:* The Nolan trial is currently in the recruitment phase. *Discussion:* The Nolan trial is currently the largest and longest trial in which a nutritional blend is used in attempt to help/maintain cognitive function in the elderly. This nutritional intervention if proven effective will play an important role in understanding how nutrition can affect cognitive aging. In addition to evaluating the effect of the nutrient blend, the study is set up to yield a wealth of new scientific insights in the field of cognitive aging. This includes identification of modulating factors for rate and magnitude of cognitive decline, mechanistic insights in the process of cognitive decline, and development of predictive and sensitive measures to diagnose and investigate at risk populations. References: 1. Oulhaj A, Jernerén F, Refsum H, Smith AD, de Jager CA. J Alzheimers Dis JAD. 2016;50(2):547–57. 2. Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, Basun H, Faxén-Irving G, Garlind A, et al. Arch Neurol. 2006 Oct;63(10):1402–8. 3. van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, Olderikkert MGM, et al. Neurology. 2008 Aug 5;71(6):430–8. 4. Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. Am J Clin Nutr. 2010 Jun;91(6):1725–

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P20: VALIDATING TRIAL POWER IN PRESENCE OF NON-RANDOM DROPOUTS USING DISEASE SIMULATION. Ali Tafazzoli, Peter L. Quon, Sean Stern, Anuraag Kansal *(Evidera, Bethesda, MD, USA)*

Background: Clinical trial simulation (CTS) is increasingly being used for designing more efficient clinical trials. Trials in Alzheimer's disease (AD) may benefit from this approach given the challenges of variability in cognitive measures and large sample sizes and long trial durations required. One example in which simulation may be valuable is understanding how the power of a trial may vary if attrition is dependent on disease progression. This may occur due to challenges in retention of patients with more advanced disease (as seen in ADNI) or, conversely, loss of patients with large treatment response. Trial powering frequently accounts for treatment effect and patient attrition independent of each other, but disease simulation can evaluate potential outcomes when they interact. The objective of this study is to understand whether the power of a trial is influenced by non-random dropouts that may depend on the degree of disease progression. *Methods:* This study relied on the Alzheimer's Disease Archimedes Condition-Event (AD ACE) simulator, which is a disease simulator that predicts the progression of AD in terms of multiple interacting trajectories for key biomarkers and cognition, behavior, function, and dependence markers. In particular, it is constructed using predictive equations for rate of change in cerebrospinal fluid (CSF) amyloid-beta, CSF t-tau, FDG-PET, hippocampal volume, MMSE, CDR-SB, ADAS-Cog, and NPI derived from statistical analyses of ADNI. The AD ACE is used to simulate the disease progression of a large pool of subjects with and without a treatment. The CTS engine then samples patients from this pool in accordance with the trial design and inclusion / exclusion criteria. In addition, patient behavior, such as missed visits or early loss to follow are applied in the CTS. In this study, disease progression in patients with prodromal AD with and without a hypothetical amyloid-targeting treatment was simulated in the AD ACE (sample size of 2,000 patients and mean MMSE of 27). These patients were then analyzed in CTS to compare the effects of modeling a random dropout rate to a dropout rate conditioned on decline in MMSE. The simulated trial followed patients for 24 months and dropout rates were assumed to be similar to those observed in recent AD clinical trials: 10% after excluding reasons of adverse events, death, protocol violation, and abnormal lab/ECG. Two scenarios were tested for dropouts – one in which patients were lost to follow up with an equal probability after every patient visit and a second in which patients were more likely to be lost to follow up with sudden change in their disease severity (a risk of dropout was applied to patients once a decline in MMSE of 2.5 was observed between two visits; this probability increased based on patients AD severity). *Results:* The results suggested a 71% and 73% probability of success for the trial under the random dropout scenario and the scenario of dropouts associated with disease severity, respectively. A successful trial replication was defined to be one in which the primary endpoint (ADAS-cog) showed a difference between the treatment and placebo arms that met statistical significance at the $p < 0.05$ threshold. *Conclusion:* CTS results suggest that the change in power associated with dropouts associated with disease severity is relatively modest. This study demonstrates how disease simulation can be applied as a verification or means of refining results from statistical methods when designing clinical trials.

P21: ACCOUNTING FOR BASELINE PROGNOSTIC VARIABLES AND PATIENT DROP-OUT IN THE ANALYSIS OF LONGITUDINAL OUTCOMES WITHIN RANDOMIZED TRIALS FOR ALZHEIMER'S DISEASE. Elizabeth Colantuoni[1], Michael Rosenblum[1], Jon Steingrimsson[1], Aidan McDermott[1], Arnold Bakker[2], Michela Gallagher[3,4] *((1) Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD USA; (2) Department of Psychiatry and Behavioral Sciences, Johns Hopkins Medical School, Baltimore, MD USA; (3) AgeneBio, Inc. Baltimore, MD USA; (4) Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD USA)*

Background: Consider a two arm regulatory trial where the primary outcome is measured at baseline and several fixed follow-up times. The primary endpoint is the change in the primary outcome from baseline to the final follow-up and the average treatment effect is the difference in the mean change comparing the treatment and control arm. Assume that a set of potentially prognostic baseline variables are collected and patient drop-out is expected. To estimate the average treatment effect, the mixed model for repeated measurement (MMRM) is the standard statistical approach. However, novel targeted minimum loss estimators (TMLE) proposed by Van der Laan and Gruber in 2012 can be applied to this setting and may offer gains in efficiency relative to MMRM. *Methods:* We use data from the completed Alzheimer's Disease Cooperative Study (ADCS) to simulate hypothetical clinical trials for a drug that reduces the decline in cognitive impairment among persons with amnestic subtype mild cognitive impairment. We compare the key statistical properties (such as Type I error control, mean square error and power) of MMRM and TMLE for estimating the average treatment effect when varying the prognostic ability of the baseline variables and the models generating patient drop-out. *Results:* It is customary to include the baseline value of the primary outcome and any stratification variables used for randomization in the MMRM model. However, including additional a priori selected baseline variables that are prognostic for the primary outcome can provide substantial precisions gains for estimation of the average treatment effect. Under certain models that generate patient drop-out, the MMRM and TMLE have similar statistical properties. *Conclusion:* In future trials with similar patients as those in the ADCS, adjusting for prognostic baseline variables will substantially improve the precision to estimate the average treatment effect. Specification of the statistical approach should include careful consideration of the possible mechanisms that generate patient drop-out.

P22: AN OPEN-SOURCE IMPLEMENTATION OF DATA STANDARDS FOR ALZHEIMER'S DISEASE CLINICAL TRIALS. Chung-Kai Sun, Michael Donohue, Karin Ernstrom, Yanxin Jiang, ZeyunLu, Paul Aisen, Rema Raman *(Alzheimer Therapeutics Research Institute, University of Southern California, San Diego, CA, USA)*

Background: In multi-center clinical trials, study data are frequently exchanged among teams to generate reports and analysis that facilitate and monitor study progress. Data standards provide an efficient and effective way to decouple data capture, data transformation, quality control and report generating processes to expedite the clinical data process for drug discovery. In 2014, the Food and Drug Administration (FDA) released a guidance document regarding the electronic submission of clinical trial data in standardized data format, for example Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM). This guidance also specifies that all studies starting after December 2016 must adopt these

data standards for submission. We propose a scalable implementation of these data standards for Alzheimer's Disease clinical trials using open-source, literate programming tools for data management and documentation. *Methods:* The Alzheimer's Therapeutic Research Institute (ATRI) conducts collaborative, multicenter clinical trials in AD utilizing open-source tools for data capture, data integration, data sharing and statistical analysis. The ATRI Biostatistics team has implemented a workflow to achieve CDISC compliant data and scalable code for generating study reports and analyses using the R statistical programming language. This workflow establishes a process for mapping and exporting data to SDTM standards for studies managed by the Institute. Our approach adopts CDISC standards to make the research data process a metadata-driven process from data collection to submission. We integrate code, documentation, and data into study specific R packages and utilize the latest contributed R packages for literate programming (knitr, rmarkdown) and data management (tidyverse) to eliminate discrepancies that commonly exist between code and documentation, and create efficient workflows. Git repositories are used to ensure efficient collaboration, change control, and version control. *Results:* The workflow was tested in two studies currently being managed at the Institute. Our approach simplifies peer review process for validation, generates documentation for reference, and can be applied across similar studies within the Institute. With the standardized data as the foundation, we are able to modularize study reports and analysis using knitr and rmarkdown. The functions, scripts, documentations, validation rules, raw data and standardized data are organized into a comprehensive study R package which ensures reproducibility, traceability,transparency and scalability. *Conclusion:* Preliminary implementation of this workflow demonstrates the need for a hybrid approach. Our approach can accommodate any data capture system. The metadata-driven process characterized by CDISC standards ensures reproducibility, traceability, transparency, and scalability of the flow the clinical trial data, reports, and analysis.

P23: LONGITUDINAL IMPACT OF AUDIO REVIEW ON DATA QUALITY. Todd M. Solomon[1,2], Jordan M. Barbone[1], Sarah M. Karas[1], H. Todd Feaster[1] *((1) Bracket, Wayne, PA, USA; (2) Boston University School of Medicine, Boston, MA, USA)*

Background: Data quality programs that reduce rater error are important to clinical trials, especially those in Alzheimer's disease (1). Given the high failure rate in AD drug development over the past 10+ years (2), ensuring optimal data quality is paramount. Prior research has shown that employing enhanced electronic versions of the ADAS-Cog and MMSE in Alzheimer's disease (AD) clinical trials significantly reduces rater error rates compared to when paper versions of these scales are used (3,4). Further, the addition of audio review of scale assessments has been shown to uncover additional errors that cannot be identified by review of the eScale data alone (5). While audio review of scale administration has become more ubiquitous, little data has been reported on how the use of audio impacts rater performance longitudinally. In this preliminary analysis, we evaluated the impact of audio review on rater performance across two time points to determine if remediation of administration issues resulted in subsequent improvement in administration. *Methods:* MMSE ratings were evaluated from a multi-national AD clinical trial. Raters were trained and certified on the proper scale administration and scoring. Initial submissions of scale data from the electronic scales administered to each subject were reviewed along with the corresponding audio. *Results:* One hundred percent of MMSE ratings were reviewed at both Screening and Baseline visits for both data and administrative errors. In total, 2718 MMSE reviews were completed, 1753 at Screening and 953 and Baseline. A total of 13% (n = 356) MMSE's contained an administrative error of which 273 were flagged at Screening and 83 at Baseline. Notably, for those subjects who had the same MMSE rater at both Screening and Baseline, < 2% (n = 14) made an administrative error longitudinally for the same subject. *Conlusions:* The use of electronic versions of scales that are enhanced beyond their respective paper-pencil versions and coupled with an in-study data quality have proven to reduce rater error. Adding audio reviews of scale administrations enables detection of additional administrative errors that are not apparent on data review alone. Longitudinal analysis indicates that raters, who have their initial administrative mistakes remediated, tend to significantly improve at their next administration.

P24: UTILIZING AUDIO REVIEW TO IMPROVE ADCS-ADL DATA QUALITY. Todd M. Solomon[1,2], H. Todd Feaster[1], Jordan M. Barbone[1], David S. Miller[1] *((1) Bracket, Wayne, PA, USA; (2) Boston University School of Medicine, Boston, MA, USA)*

Background: Data quality programs that reduce rater error are vital to clinical trials, especially those in Alzheimer's disease (1). Given the high failure rate in AD drug development over the past 10+ years (2), ensuring optimal data quality is paramount. One potential means of addressing data quality in global AD trials is the implementation of an enhanced and validated electronic version of standard scales (3) such as the ADCS-ADL, MMSE and ADAS-Cog coupled with a tailored in-study data quality program. Further, the use audio recording of scale administration allows for additional review of both standardization and quality of collected data. However, the use of audio recording, particularly when assessing caregiver interview scales such as the ADCS-ADL in Alzheimer's disease clinical trials is not yet wide spread. *Methods:* This analysis evaluated the results from two multi-national AD clinical trials. Both studies utilized a standardized electronic version of the ADCS-ADL (eADL). Each program also employed a comprehensive surveillance program in which rater performance on the scale was assessed by a calibrated clinician. Only one of the studies employed review of an audio recording of the ADCS-ADL interview in addition to the standard review of the item level data. *Results:* Out of the 1346 ADCS-ADL's reviewed in the program without additional audio review, only 2 (<1%) total errors were identified. In contrast, out of the 3733 ADCS-ADL's reviewed for the program with corresponding audio, 233 (6%) errors were identified. Results demonstrated the program which employed the additional audio reviewed exposed significantly more errors related to either scoring or administration of the ADCS-ADL. *Conclusions:* It is essential that any and all methodologies that could maximize data quality in AD clinical trials be considered. The implementation of an in-study data quality program has proven to reduce rater error. Adding audio reviews of scale administrations enables detection of additional errors that are not apparent on data review alone. As the ADCS-ADL is often utilized as a Co-Primary outcome, even a modest reduction in error rate and improvement in standardization could prove beneficial. References: 1. Miller, DS, McNamara, C, Samuelson, P, Mulder, D and Young, A. Is an In-Study Surveillance Program Effective at Reducing Error Rates for Both Experienced and Novice Raters? Poster Presentation at the 7th Annual International Society for CNS Clinical Trials and Methodology (ISCTM) Scientific Meeting Washington, DC on February 21-23, 2011; 2.Cummings JL, Morstorf T and Zhong K (2014). Alzheimer's disease drug development pipeline: few candidates, frequent failures. Alzheimers Res Ther, 6(4), 37; 3. Solomon, T.M., Feaster, T., & Miller, D. (2016, July). Initial Pilot Validation of an Electronic Alzheimer's Disease Assessment Scale – Cognitive Subscale (eADAS-Cog): Rationale & Methods. Presentation at the Alzheimer's Association International Conference, Toronto, CA

P25: THE INFLUENCE OF A MOBILITY TRAINING PROGRAM ON GAIT PERFORMANCE AMONG HEALTHY COGNITIVE ELDERLY PEOPLE AND PEOPLE WITH MCI. Carine Federspiel[1,2], Elisabeth Bourkel[1], Jean-Paul Steinmetz[1,2] *((1) Centre for memory and mobility, Luxembourg; (2) ZithaSenior, Research&Development, Luxembourg)*

Backgrounds: Gait performance (i.e., velocity and gait variability) is an indicator of an older adult's mobility capacities. General mobility training contributes to improving gait performance and thus reducing the risk of falling. In this study, the effect of mobility training among cognitive healthy elderly people and people having MCI are compared, taking into account that cognitive deficits often are linked to mobility deficits. *Methods:* The participants (N = 60, age range = 70-87 years) partook in a 12-week mobility training program which focused on the training of general mobility, coordination, balance, gait stability, endurance, torso muscles, spine flexibility and muscular strength. The training groups, which were attended twice a week, had different intensity levels with a maximum of eight participants. The subjects were assigned to the groups according to their respective mobility capacities, independent of their respective cognitive capacities. According to their MMSE-Scores, the participants were divided into (1) cognitive healthy older adults and people showing MCI (Cut-off score: under 27 points). The participant's gait velocity and gait variability was measured before and after the training program. Gait performance was assessed with an instrumented walkway system (GAITRite) measuring averaged temporal and spatial gait parameters. The participants completed three walks with different instructions: (1) normal walk, (2) dual-task (walking while counting backwards) and (3) dual-task (walking while completing a word fluency task). *Results:* Velocity as well as gait variability (stride length and time) before and after the training program in both groups were analyzed and compared. We expect to find an improvement of gait performance in both healthy elderly people and people with MCI, with less impact in the second group as cognitive deficits may influence the effect of the training. *Conclusion:* The discussion of the findings focuses on the necessity of introducing structured mobility training programs for both older healthy adults and people with MCI.

Theme: Clinical trials : results

P26: LONGITUDINAL COGNITIVE AND FUNCTIONAL CHANGES ARE INFLUENCED BY EDUCATIONAL HISTORY IN THE J-ADNI MCI INDIVIDUALS. Atsushi Iwata[1], Takeshi Iwatsubo[2], Kazushi Suzuki[1], Ryoko Ihara[2], Hiroyuki Arai[3], Kenji Ishii[4], Michio Senda[5], Kengo Ito[6], Takeshi Ikeuchi[7], Ryozo Kuwano[7], Hiroshi Matsuda[8] for the Japanese ADNI *((2) Department of Neuropathology, The University of Tokyo, Tokyo, Japan; (3) Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan (4) Diagnostic Neuroimaging Research, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan; (5) Department of Molecular Imaging, Institute of Biomedical Research and Innovation, Kobe, Japan (6) Department of Clinical and Experimental Neuroimaging, National Center for Geriatrics and Gerontology, Obu, Japan; (7) Brain Research Institute, Niigata University, Niigata, Japan; (8) Integrative Brain Imaging Center, National Center for Neurology and Psychiatry, Kodaira, Japan*

Background: Successful completion of the Japanese ADNI (Alzheimer's disease Neuroimaging Initiative) project resulted in a dataset of clinical and cognitive evaluation of 537 subjects including 154 CN (cognitive normal), 234 late MCI (mild cognitive impairment), and 149 AD. This dataset allows us to precisely analyze the longitudinal progression of Japanese subjects in terms of clinical status and cognitive function. When designing a clinical trial for AD, enrolling an appropriate population is one of the key components so that during the trial period, cognitive or clinical decline of the placebo population should be adequate enough to evaluate the effect of the drug. It is well known that individual cognitive reserve serves as a buffer to have resistance to AD pathology; i.e. synaptic, neuronal losses, and cortical atrophy. The true nature of this cognitive reserve is still unknown, but it is considered to have wide variation among individuals that could be attributed to genetic or epigenetic factors. One of the components of the reserve is one's educational history. In order to evaluate the effect of educational history on longitudinal clinical and cognitive functional change, we analyzed the result of MCI and AD subject in J-ADNI data set. *Method:* We accessed the National Bioscience Database Center, Japan (Research ID: hum0043.v1, 2016) to obtain the entire J-ADNI dataset. We classified the subjects into three categories in terms of educational history according to the enrollment criteria of late MCI and AD of J-ADNI study; i.e. Low educational history (L) as 0 to 9 years of education, mid educational history (M) as 10-15, and high educational history (H) as >=16 years respectively and analyzed longitudinal change from the baseline visit of clinical evaluation and cognitive function including CDR-SOB, CDR-global, ADAS-cog, MMSE, clock drawing test, category fluency, digit span, digit symbol, trail making test A and B, WMS-R logical IA, IIA, NPI-Q, and FAQ. Statistical analysis was performed by chi-square test, linear regression analysis, analysis of variance, or analysis of covariance on JMP software. *Results:* The number of the patients and female/male ratio in each sub-group were not significantly different. In AD, none of the scales analyzed was significantly different among three different educational history groups during the entire follow-up period. In MCI subjects, there were significantly different worsening patterns of CDR-SOB (L:1.027/yr (95% CI 0.9334 to 1.121), M:1.368/yr (1.178 to 1.558). H: 0.6556/yr (0.4187 to 0.8925)), CDR-global (L:0.1336/yr (0.0811 to 0.1861)), M:0.1607/yr (0.1084 to 0.2131). H: 0.0476/yr (0.0149 to 0.0803), ADAS-cog (L:1.087/yr (0.1041 to 2.069), M:2.315/yr (1.619 to 3.012). H: 1.294/yr (0.5698 to 2.019)), MMSE (L: -1.135/yr (-1.718 to 0.5526), M:-1.642/yr (-1.851 to 1.434). H: -0.6048/yr (-0.9665 to 0.2430)), NPI-Q (L:0.8884/yr (0.4918 to 1.285 95% CI), M:0.8770/yr (0.6837 to 1.070). H: 0.6288/yr (0.4343 to 0.8233)), and FAQ (L:3.115/yr (2.482 to 3.747 95% CI), M:3.512/yr (3.296 to 3.729). H: 1.963/yr (1.324 to 2.601)) among three groups. Highly educated groups tend to have less worsening. Since late MCI in J-ADNI study is composed of individuals with multiple pathological background, we further analyzed these scales using amyloid positivity data from PET and/or CSF analysis. There were 117 MCI subjects with amyloid data including 40 negatives and 77 positives. Since the number of subjects was not enough to draw statistical conclusions, the trend still remained even after stratification by amyloid positivity. *Conclusion:* In J-ADNI late MCI subjects, educational history significantly affected the change of cognitive or clinical evaluation, whereas there was no effect on AD subjects. Subjects in highly educated groups supposedly have more cognitive reserve compared to low educated individuals that helped them from worsening during mildly affected period; however, progression of the disease process damaged their function so badly that the reserve effect was no longer effective for protecting them from worsening during mild dementia period. In order to design effective clinical trial in the Japanese population, considering the subjects' educational history could be an important issue.

P27: A RANDOMIZED PLACEBO-CONTROLLED CROSS-OVER TRIAL INVESTIGATING NABILONE AS A TREATMENT FOR AGITATION IN PATIENTS WITH ADVANCED AD: STUDY PROTOCOL. Myuri Ruthirakuhan[1,2,3], Nathan Herrmann[1,2,3], Eleenor H. Abraham[1,3], Chelsea Sherman[1,2,3], Nicolaas Paul L.G. Verhoeff[2,4], Alex Kiss[1], Sandra E. Black[1,2], Ana C. Andreazza[2], Krista L. Lanctot *((1) Sunnybrook Research Institute, Toronto, ON, Canada; (2) University of Toronto, Toronto, ON, Canada; (3) Neuropsychopharmacology Research Group, Toronto, ON, Canada; (4) Baycrest Health Sciences, Toronto, ON, Canada)*

Background: Current pharmacological interventions for the management of agitation in Alzheimer's disease (AD) have modest benefits and high risk-profiles, spurring the search for new medications. With the availability of synthetic cannabinoids (CB), such as nabilone, the therapeutic potential of the endocannabinoid system (ECS) can now be investigated. The ECS may be a rational target to treat agitation in AD as it has been shown to modulate neuropsychiatric symptoms, as well as pain and weight. We describe a randomized placebo-controlled cross-over trial investigating the safety and efficacy of nabilone in the treatment of agitation, as well as pain and weight loss in patients with moderate-to-severe AD. *Methods:* This is an ongoing double-blind, randomized placebo controlled cross-over trial comparing 6 weeks of nabilone (target dose: 1-2 mg) to 6 weeks of placebo, with a 1-week washout preceding each treatment phase. While nabilone has a short half-life (2 hours), that of its active metabolites is 35 hours, suggesting a wash-out period of 1 week. The recruitment goal is to randomize 40 patients. The primary outcome is agitation, as measured by the Cohen-Mansfield Agitation Inventory (CMAI). The secondary outcomes includes behaviour (Neuropsychiatric Inventory (NPI)-NH), cognition (standardized Mini Mental Status Exam (sMMSE) and Severe Impairment Battery (SIB)) and global impression (Clinician's Global Impression of Change (CGI-C)). Exploratory outcomes include pain (Pain Assessment in Advanced AD (PAIN-AD)), nutritional status (Mini-Nutritional Assessment-Short Form (MNA-SF)), and safety. Pairwise t-tests between the screening visit and the baseline (BL) of phase 1, and between the BLs of phase 1 and 2 were completed to investigate the role of placebo and cross-over effects, respectively on the primary, secondary, and exploratory outcomes. *Results:* To date, 31 participants (mean±SD age=87±10, CMAI=67.6±118.1, NPI-NH total=33.8±15.4, NPI-NH agitation subscore=7.1±7, sMMSE=7.1±7, SIB=36.8±29.7, PAIN-AD=2.9±1.5, MNA-SF=8.2±2.5, 73.3% male) have been randomized. In phase 1 and 2 of the study, 77% and 76% of participants received the maximum target dose of 2mg/placebo, respectively. In phase 1 of the study, 61% of participants had a reduction in CMAI total score, while this was the case for 74% of participants in phase 2. With regards to our primary outcome, CMAI total score, there were no significant placebo ($t(29)=-1.26$, $p=0.22$) or carry-over ($t(23)=0.88$, $p=0.39$) effects identified. However, compared to screen, the mean CMAI verbal/aggressive subscore was significantly lower at the BL of phase 1 ($t(29)=-2.13$, $p=0.04$). There were no significant placebo or cross-over effects identified with the NPI-NH total, NPI-NH subscale items, sMMSE, PAIN-AD and MNA-SF scores (all, $p>0.05$). *Conclusions:* Our target dose has been relatively well tolerated as most participants received a maximum dose. A 6-week study duration per phase seems appropriate as we were able to detect an overall reduction in CMAI scores in most of our participants. Limitations of a cross-over RCT include the potential for treatment-order and carry-over effects. Currently we are unable to investigate treatment-order effects as we are blinded to treatment allocation. However, based on interim blinded results, there are currently no carry-over effects. There may be potential placebo-effects as indicated by reduced verbal aggression during the placebo run-in phase of our trial. As such, the inclusion of a placebo-run in may be advantageous in the design of a double-blind randomized placebo-controlled trial.

P28: OC47 BPN14770 PHOSPHODIESTERASE-4D NEGATIVE ALLOSTERIC MODULATOR FOR ALZHEIMER'S DEMENTIA: PRECLINICAL, PET IMAGING AND HUMAN PHASE 1 RESULTS. Mark Gurney[1], Chong Zhang[2], Ying Xu[2], James O'Donnell[2], Masahiro Fujita[3], Robert Innis[3], Scott Reines[1] *((1) Tetra Discovery Partners, Inc. Grand Rapids, MI, USA; (2) School of Pharmacy and Pharmacological Sciences, University at Buffalo, Buffalo, NY, US; (3) National Institute of Mental Health, Bethesda, MD, USA)*

Background: Early and late stages of memory formation are dependent upon cAMP signaling. In humans, genetic studies show that brain cAMP levels relevant to cognition are regulated by phosphodiesterase-4D (PDE4D). We have humanized the PDE4D gene in mice to study the effect of a PDE4D negative allosteric modulator, BPN14770, on early and late stages of memory. The selectivity of BPN14770 for PDE4D is due to a single amino difference in the drug binding site. This is a phenylalanine in PDE4D and a tyrosine in the other three PDE4 subtypes, PDE4A, B and C. BPN14770 inhibits PDE4D by binding to a key regulatory domain which it holds closed across the active site, thereby preventing hydrolysis of cAMP. The key phenylalanine is present only in primates. A tyrosine is present in PDE4D of other species, causing a sharp decrease in BPN14770 inhibitory potency. Humanizing the mouse PDE4D gene allowed us to compare the potency of BPN14770 in wild-type and humanized PDE4D mice, and thereby engagement of the PDE4D target, across a battery of cognitive and biochemical tests. In parallel, we studied the distribution of PDE4D in primate brain using a C-11 PET tracer, and explored the effect of BPN14770 on cognitive tasks in healthy, elderly human subjects in a multiple ascending dose Phase 1 clinical trial. *Methods:* The mouse PDE4D gene was humanized by knocking-into C57Bl6 embryonic stem cells a single nucleotide substitution that replaces PDE4D tyrosine571 by phenylalanine. This improves the 50% inhibitory concentration (IC50) of BPN14770 from 133 nM against recombinant mouse PDE4D enzyme to 4 nM against humanized mouse PDE4D Y571F enzyme. Humanized and wild-type mice were profiled in tests of working memory (novel object recognition, NOR, with 1 hour delay) and long-term memory (NOR with 24 hour delay) after single oral doses of BPN14770 or vehicle. Effects of BPN14770 on phosphorylation of CREB and levels of BDNF were assessed after 14 days of dosing by immunoblot. PET imaging studies were conducted in anesthetized rhesus monkeys with C-11 T1650, a selective PDE4D tracer. Preliminary cognitive benefit of BPN14770 was assessed in elderly human subjects (> 60 years of age) in an 8-day, multiple ascending dose study. 15 subjects were enrolled per cohort (10 active and 5 placebo). Cognitive assessments were performed using the CogState Global Battery at baseline (Predose Day 1) and 2 hours after dosing on Day 1, 3, 5 and 7 of the multi-day trial. *Results:* BPN14770 improved working and long-term memory in humanized PDE4D mice after single oral doses of 0.01 or 0.03 mg/kg, while the minimum effective dose in wild-type C57Bl6 littermate control mice was 1 mg/kg. There was no difference in the potency of rolipram (0.1 mg/kg), a reference PDE4 inhibitor not sensitive to the PDE4D tyrosine571 to phenylalanine mutation. After dosing for 14 days, BPN14770 at 0.03 mg/kg elevated pCREB and BDNF in humanized PDE4D mice. PET imaging of PDE4D distribution in anesthetized rhesus monkeys

revealed specific binding in hippocampus, entorhinal cortex and prefrontal cortex that was displaceable by rolipram and BPN14770. In healthy elderly subjects, exposure to BPN14770 was dose-related, with terminal half-life of approximately 10 hours. Preliminary cognitive assessment suggested that BPN14770 oral doses of 10 and 20 mg bid improved complex attention/working memory and 24 hour delayed recall of verbal or visuospatial tasks. Analysis of the pooled standardized mean difference suggested improvement in the CogState working memory tasks (IDN, ONB), and the ISLT and GMLT with 24 hour delayed recall. Post-hoc pooling of the 10 and 20 mg bid dose groups with comparison against the intra-cohort placebo (20 active and 10 placebo), indicated an effect size in the ONB working memory task of 0.5 – 0.8 with p-values ranging from $p<0.05$ - <0.01. There were no adverse events related to gastrointestinal disturbance (nausea, vomiting or diarrhea). *Conclusions:* The humanized PDE4D mice provided a unique model in which BPN14770 engagement of the PDE4D target could be linked directly to improvement in early and late stages of memory as well as to biomarkers associated with activation of the cAMP-PKA-CREB pathway. The distribution of PDE4D in primate brain was highest in those regions known to be important for cognition, the hippocampus and the prefrontal cortex, which also are targets of Alzheimer's pathology. Preliminary assessment of BPN14770 cognitive benefit in elderly subjects was consistent with the proposed mechanism of action of the drug.

P29: SUSTAINED CLINICAL EFFECTS OF TRAMIPROSATE IN APOE4/4 HOMOZYGOUS PATIENTS WITH ALZHEIMER'S DISEASE OVER 130 WEEKS: RESULTS OF PHASE 3 EXTENSION STUDY. S. Abushakra[1], A. Porsteinsson[2], C. Sadowsky[3], B. Vellas[4], S. Gauthier[5], A. Power[1], L. Shen[6], P. Wang[6], J.A. Hey[1], M. Tolar[1] *((1) Alzheon, Inc., Boston, MA, USA; (2) University of Rochester, Rochester, NY; (3) Palm Beach Neurology, Florida USA; (4) University of Toulouse, Toulouse, France; (5) McGill University, Montreal, Canada; (6) Pharmapace Inc., San Diego, CA US*

Background: ALZ-801 is in development as an oral AD treatment with disease modification potential. ALZ-801 is a pro-drug of tramiprosate that provides improved pharmacokinetics and GI tolerability. Tramiprosate, the active agent in ALZ-801, inhibits the aggregation of beta amyloid (Aβ) monomers into toxic, soluble Aβ oligomers through a recently reported enveloping molecular mechanism of action (Kocis et al. 2017). In transgenic CRND8 mice tramiprosate reduced amyloid plaque and soluble Aβ42 in brain (Gervais et al. 2007). In a 12-week study in AD patients, tramiprosate showed a dose-dependent decrease in soluble Aβ42 in CSF, with up to 70% reduction at 150mg BID (Aisen et al. 2006). On this basis, tramiprosate was evaluated in two global Phase 3 studies, one in North America (NA study), and the other in Western Europe (EU study). The NA study did not show efficacy in the overall Mild to Moderate AD study population, and therefore the EU study was terminated. Recent re-analyses of the NA dataset based on APOE4 genotype showed positive effects of tramiprosate in APOE4/4 homozygotes at 150mg BID (Abushakra et al. 2016), with larger effects in the Mild subgroup of patients (Abushakra et al. 2017). The NA study had a safety extension of up to an additional 52 weeks of treatment (Study 017). We evaluated efficacy and safety of tramiprosate in APOE4/4 homozygotes in the Extension Study. *Methods:* The NA Study was a randomized, double-blind, placebo-controlled parallel-arm multi-center study of 78-weeks duration, and enrolled 1,053 AD patients (MMSE range 16-26) to either placebo, 100mg BID, or 150mg BID. The NA placebo-controlled study included 148 APOE4/4 subjects. ADAS-cog11 and CDR-SB were the co-primary efficacy outcomes. Subjects who completed this study were offered enrollment into the blinded extension study for up to 52 weeks of treatment, where all subjects received 150mg BID after a titration period. All subjects and sites remained blinded to treatment assignment in the placebo-controlled phase. Efficacy was analyzed in APOE4 subgroups as described previously for the placebo-controlled study (Abushakra et al. 2016). Changes in ADAS-cog and CDR-SB from original baseline up to 130 weeks were analyzed using a mixed effects model with repeated measures (MMRM). *Results:* 735 subjects completed the 78-week NA study and enrolled in the Extension Study. 104 subjects were APOE4/4 homozygotes: 43, 33 and 28 from the original placebo, low and high-dose groups respectively; and 27, 25, 18 completed a total of 130 weeks on study drug. The baseline demographics of the 3 dose arms were similar at the start of the Extension Study. Mean baseline MMSE were: 21.6, 21.3, and 21.0 for placebo, low and high dose arms respectively. The 150mg-150mg group showed significantly larger ADAS-cog benefits at both 104 and 130 weeks compared to the placebo-150mg group. On ADAS-cog, the differences in the change from baseline at Week 78, Week 104 and Week 130 were: 2.4 ($p=0.12$), 3.3 ($p=0.04$), and 3.9 ($p=0.03$); the effects were smaller for the 100mg-150mg group. For CDR-SB, the differences in the change from baseline at Week 78, Week 104 and Week 130 were: 0.7 ($p=0.22$), 0.9 ($p=0.12$), and 1.0 ($p=0.09$) for the 150mg-150mg group; the 100mg-150mg group showed no difference from the placebo-150mg group. For the 150mg-150mg group, ADAS-cog effect showed a trend to increase with time. In the Mild AD subgroup of APOE4/4 homozygotes (MMSE 22-26), the positive effects at the 150mg-150mg group were larger for both ADAS-cog and CDR-SB. Across all 735 patients, which included 471 who received active drug for up to 130 weeks, the most common TEAE were falls, nausea, urinary tract infection, diarrhea, and decreased weight. The safety profile in the 115 APOE4/4 homozygotes was similar. *Conclusions:* Reanalysis of two prior tramiprosate studies showed promising efficacy in the APOE4/4 homozygous patients with Mild and Moderate AD over 78 weeks. We further analyzed the efficacy analysis of the APOE4/4 homozygotes subgroup over an additional 52 weeks in the Extension Study. In APOE4/4 patients, tramiprosate 150mg BID exhibited sustained cognitive and functional benefits over 2.5 years, compared to the "delayed start" group who initially received placebo. The differences between the two treatment groups increased with time in the Extension Study. These results suggest potential disease modifying effects of tramiprosate, consistent with its molecular mechanism inhibiting formation of amyloid oligomers. The safety profile remained favorable with no new toxicities observed at exposures up to 2.5 years. This profile of sustained efficacy and favorable long-term safety supports further development of ALZ-801, an optimized prodrug of tramiprosate, in an upcoming confirmatory study in APOE4/4 homozygous AD patients.

P30: EFFECT OF MILD OR MODERATE HEPATIC IMPAIRMENT ON THE CLEARANCE OF AZELIRAGON. Ann Gooch[1], Aaron H Burstein[1], Scott J Brantley[2], Michael J Lamson[2], Imogene Dunn[1], Larry D Altstiel[1] *((1) vTv Therapeutics, High Point, NC, USA; (2) Nuventra Pharma Sciences, Inc, Durham, NC, USA)*

Background: Azeliragon is an oral antagonist of the Receptor for Advanced Glycation Endproducts (RAGE) currently being evaluated in a pivotal Phase 3 study for mild Alzheimer's disease (AD). Azeliragon is metabolized by hepatic enzymes prior to elimination. The present study evaluated the pharmacokinetics (PK), safety and tolerability of azeliragon in subjects with mild or moderate hepatic impairment compared to healthy subjects. *Methods:* This study was an, open-label, single-dose, parallel design trial in which 8 subjects with mild hepatic impairment (Child-Pugh category A), 8 subjects with moderate hepatic impairment (Child-Pugh category B), and 8

healthy subjects received a single 15 mg dose of azeliragon. Four of the healthy volunteers were matched for age (±5 years), weight (± 10 kg), and gender (1:1) with four of the subjects with mild hepatic impairment. Similarly, four of the healthy volunteers were matched with four of the subjects with moderate hepatic impairment. Subjects were admitted on Day -1 and remained confined until Day 5. Blood samples for plasma concentrations of azeliragon and metabolites of interest were collected prior to and for 984 hours (41 days) following dosing. Noncompartmental PK parameters were estimated from azeliragon plasma concentrations. *Results:* Azeliragon PK parameter values in subjects with varying degrees of hepatic impairment were similar to those in healthy subjects with normal hepatic function Results from the analysis of variance on azeliragon PK parameter values (geometric least squares means, ratios and 90% confidence intervals) are summarized in the table below.

PK Parameter	Hepatic Impairment Group	Test (Impaired)*	Reference (Normal)*	Ratio of Geometric Means Impaired/Normal% (90% CI)
Cmax (ng/mL)	Mild	1.77	1.72	103% (74.78, 142.59)
	Moderate	2.29	1.72	133% (96.48, 183.96)
AUC0-∞ (ng.h/mL)	Mild	304	302	101% (52.37, 193.66)
	Moderate	261	302	86.5% (44.99, 166.35)
AUClast (ng.h/mL)	Mild	451	474	95.3% (51.32, 176.53)
	Moderate	500	474	105% (53.6, 207.42)

*geometric least squares mean.

PK parameter values for the M2 and M3 metabolites were similar and/or lower between mild / moderate hepatic impairment subjects and subjects with normal hepatic function. M1 metabolite concentrations were generally below limits of quantitation and did not permit pharmacokinetic analyses. No deaths, treatment-related SAEs, discontinuations due to treatment-related AEs, or clinically significant changes in laboratory parameters, vital signs or ECGs were reported. *Conclusions:* No clinically important effect of hepatic impairment on Cmax, AUC0-∞ or AUClast was observed in subjects with mild or moderate hepatic impairment. Therefore, it is expected that no dose adjustments will be required when administering azeliragon to patients with mild or moderate hepatic impairment.

P31: EFFECT OF CYP2C8 AND CYP3A4 INHIBITION AND CYP INDUCTION ON THE PHARMACOKINETICS OF AZELIRAGON. Aaron H Burstein, PharmD[1], Michael J Lamson[2], Mark Sale[2], Scott J Brantley[2], Ann Gooch[1], Imogene Dunn[1], Larry D Altstiel[1] *((1) vTv Therapeutics, High Point, NC, USA; (2) Nuventra Pharma Sciences, Inc, Durham, NC, USA)*

Background: Azeliragon is an oral antagonist of the Receptor for Advanced Glycation Endproducts (RAGE) currently being evaluated in a pivotal Phase 3 study for mild Alzheimer's disease (AD). Enzyme phenotyping suggested CYP2C8 and CYP3A4 were the predominant enzymes responsible for the metabolism of azeliragon. The present study evaluated the effect of CYP2C8 and CYP3A4 inhibition and CYP induction on the pharmacokinetics of azeliragon and its major metabolites (M1, M2, M3). *Methods:* This study was a randomized, open-label, multiple-dose, parallel design, single center study with three cohorts conducted separately. In each cohort six subjects received azeliragon alone 15 mg/d x 6 days followed by 5 mg/d x 9 days and 18 subjects received the same azeliragon dose in combination with the CYP inhibiting/inducing medication administered as follows:

Cohort	Enzyme Inhibitor / Inducer	Dosing Regimen
1	Gemfibrozil (CY2C8 inhibitor)	600mg q12h x 15 days
2	Nefazodone (CYP3A4 inhibitor)	100mg q12h x 7 days, 200mg q12h x 8 days
3	Rifampin (CYP inducer)	300 mg q12h x 22 days (Day -7 to Day 15)

Subjects were admitted to the clinical research unit on Day -1 and remained confined until Day 16. Subsequent assessments through Day 70 were obtained on an outpatient basis. Blood samples were collected for determination of azeliragon, M1, M2 and M3 concentrations prior to and serially for 70 days following Day 1 azeliragon dosing. Plasma concentration data were analyzed using standard non-compartmental analysis (NCA) techniques to determine Day 15 Cmax, Cmin and AUC0-τ. Due to the long half-life of azeliragon and the possibility that azeliragon plasma concentrations in the presence of CYP inhibitors may not have reached steady state by Day 15, population pharmacokinetic modeling was performed and results compared with the NCA results. The effect of CYP inhibition and induction on azeliragon, M1, M2 and M3 pharmacokinetics were analyzed using a mixed effect model, with treatment as a fixed effect and subject as a random effect. Geometric mean ratio and 90% confidence intervals for the ratio (CYP inhibitor or inducer + azeliragon / azeliragon alone) of the log transformed Day 15 exposure parameters (Cmax, Cmin, and AUC0-τ) were estimated. Safety and tolerability were evaluated by spontaneous AE reporting, physical examination, clinical laboratory evaluations, ECGs and vital signs. *Results:* 75 subjects were enrolled in the study. Mean age was 30.2 (range 18-45) years. Subjects were predominantly male (73/75; 97.3%) and mostly Black or African American (41/75; 55%) or White (28/75; 37%). Co-administration of azeliragon and gemfibrozil resulted in a modest (19%) decrease in azeliragon exposure (90% CI: 0.62, 1.07). Nefazodone slightly (6-8%) increased azeliragon exposure (90% CI: 0.82, 1.41). Co-administration with rifampin slightly (approximately 15%) reduced azeliragon exposure (90% CI: 0.65, 1.12). For the pharmacologically active M1 metabolite, co-administration with gemfibrozil or nefazodone produced an approximate 20% decrease in exposure (90% CI: 0.57, 1.18). Rifampin co-administration resulted in a slight increase in M1 exposure of approximately 14-16% (90% CI: 0.82, 1.62). For the non- pharmacologically active M2 metabolite co-administration with gemfibrozil decreased exposure by approximately 26% (90% CI: 0.53, 1.03). Nefazodone modestly decreased M2 exposure by approximately 31% (90% CI: 0.5, 0.95). The effect of co-administration with rifampin produced a slight decrease in M2 exposure by approximately 20% (90% CI: 0.58, 1.12). For the non-pharmacologically active M3 metabolite, co-administration with gemfibrozil increased exposure approximately 360-392% (CI 2.15, 6.67). Co-administration with nefazodone produced an approximate 30% decrease in M3 exposure (90% CI: 0.4, 1.23). Rifampin co-administration resulted in a slight decrease in M3 exposure of approximately 20% (90% CI: 0.47, 1.52). The results of the population pharmacokinetics analysis were largely consistent with the noncompartmental analysis indicating steady state had been achieved by Day 15 for azeliragon, M1 and M2. Simulations predicted M3 would achieve steady state by Day 336 with 10-fold increased exposure following administration of azeliragon + gemfibrozil compared to azeliragon alone. No deaths, serious adverse events, discontinuations due to treatment related AEs or tolerability concerns were identified in this study. *Conclusions:* Overall azeliragon exposure was not significantly changed in the presence of CYP2C8 / 3A4 inhibitors or CYP inducer. Slight changes in exposure, unlikely to be clinically significant, were observed for azeliragon M1 and M2 metabolites, with the non-pharmacologically active M3 metabolite exhibiting a 4-10 fold increase. Together, these data are consistent with the presence of multiple elimination pathways for azeliragon which reduces the magnitude of a clinically relevant drug-drug interaction and supports a recommendation for no requirement for azeliragon dose adjustment when co-administered with CYP3A4 inhibitors or CYP inducers. Co-administration with strong CYP2C8 inhibitors is not supported at this time.

P32: THE PLASMA FOR ALZHEIMER SYMPTOM AMELIORATION (PLASMA) STUDY. Sharon J. Sha[1], Gayle K. Deutsch[1], Lu Tian[2], Kara Richardson[3], Maria Coburn[3], Jennifer Guadioso[1], Tatiana Marcal[4], Ethan Solomon[5], Athanasia Boumis[1], Anthony Bett[3], Steven P. Braithwaite[6], Sam Jackson[6], Karoly Nikolich[6], Darby Stephens[1], Geoffrey A. Kerchner[1], Tony Wyss-Coray[1,6] *((1) Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA; (2) Department of Health Research and Policy, Stanford University, Stanford, CA, USA; (3) Department of Neurosurgery, Stanford University, Stanford, CA, USA; (4) Department of Pediatrics, Stanford University, Stanford, CA, USA Endocrinology; (5) Alzheimer's Therapeutic Research Institute, University of Southern California, Los Angeles, CA, USE; (6) Alkahest, San Carlos CA, USA)*

Background: Plasma obtained from young mice has been demonstrated in aged mice to restore memory and to stimulate synaptic plasticity in the hippocampus. Whether these findings translate to man is unknown as the effects of plasma on cognitive function have not yet been studied in aged humans or in patients with Alzheimer's disease (AD). The primary objective of this study was to assess the safety, tolerability and feasibility of infusions of plasma from 18-30-year-old donors in patients with mild to moderate AD. Secondary objectives were to determine the effect of plasma infusions on cognition, functional ability, and mood. Evaluation of potential effects on functional connectivity in the default mode network and the identification of plasma components associated with aging and Alzheimer's disease were exploratory endpoints. *Methods:* Patients with mild to moderate AD were recruited for a safety, tolerability and feasibility study of infusions of young plasma in humans. Nine subjects were enrolled and randomized to treatment under a double-blind crossover protocol with four once-weekly infusions of either ~250mL of plasma from 18 to 30-year-old male donors or saline, followed by a 6-week washout and then crossover to four once-weekly infusions of the alternate treatment. An additional 9 subjects were enrolled and treated under an open label amendment with four once-weekly infusions of ~250mL of plasma from male donors aged 18-30. As part of this study, patients and/or informants were administered the ADAS-Cog 13-item version, Trail Making Test Part A (TMTA) and Part B (TMTB), Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI-Q), Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), the Functional Activities Questionnaire (FAQ) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) prior to infusions, after the fourth infusion, and after the eighth infusion (when applicable). All analyses were carried out in the R programing language and environment. Safety measures were compared between baseline and 4-week post-treatment timepoints using paired nonparametric rank tests. For each cognitive and functional measure, we performed a linear mixed-effects regression analysis of both the crossover and open-label patients. The linear mixed-effect regression model also takes into account performance at baseline, repeated measures, and missing data. *Results:* Results describing the primary endpoints of safety, tolerability and feasibility will be presented and analyzed. Results describing the secondary and exploratory endpoints will be presented and analyzed. *Conclusion:* Conclusions will be presented.

P33: FUNDAMANT: A 72-WEEK PHASE 1 FOLLOW-UP STUDY OF AADVAC1, AN ACTIVE VACCINE AGAINST TAU PATHOLOGY. Petr Novak[1], Matej Ondrus[1], Stanislav Katina[1], Norbert Zilka[1], Eva Kontsekova[1] *((1) AXON Neuroscience CRM Services SE, Bratislava, Slovakia; (2) AXON Neuroscience R&D Services SE, Bratislava, Slovakia)*

Introduction: Neurofibrillary pathology composed of tau protein is a main correlate of cognitive impairment and disease progression in Alzheimer's disease (AD). We have developed an active vaccine - AADvac1 - against pathological tau protein, which was previously investigated in a 24-week first-in-man study. The present article details findings from the 72-week follow-up study. *Objectives:* The study's primary objective was to evaluate safety and immunogenicity of AADvac1. Cognition was assessed in an exploratory fashion via MMSE, the ADAS-Cog11, Category Fluency Test and Controlled Oral Word Association Test. Possible predictors of the development of the immune response were explored through flow cytometry. Results: We did a phase 1, 72-week open label study of AADvac1 (EudraCT 2013-004499-36, NCT02031198) in patients with mild-to-moderate AD who have previously completed the 24-week first-in-man study of AADvac1 (EudraCT 2012-003916-29, NCT01850238). A total of 26 patients took part in the study; there were 6 drop-outs. 20 patients completed the study. 7 SAEs were reported, none of them related to treatment. The most common adverse events were injection site reactions following administration. No other safety signals emerged in any assessments. No cases of meningoencephalitis or vasogenic edema were observed following administration. The IgG immune response persisted over the vaccination-free 24-week periods, with geometric mean antibody titers settling at 18-25% of peak values. Booster doses reinstated previous antibody levels. Patient sera recognized pathological tau protein from PSP, CBS, and AD brains. Exploratory analysis found that the decline in patient cognition was lower in patients with higher antibody titers, especially in the subgroup of patients positive for AD biomarkers. *Conclusions:* AADvac1 has displayed a favorable safety and immunogenicity profile in this study. Findings from cognitive assessment indicate that high antibody titers should be maintained in patients. Further trials are necessary to corroborate the safety assessment and to confirm efficacy of AADvac1. AADvac1 was applied in study weeks 0, 4, 8, 12, 16, 20, and subsequently in weeks 48 and 72.The patient serum used for staining was collected prior to vaccination, and after 6 doses of AADvac1.

Figure 1

Antibody response over time

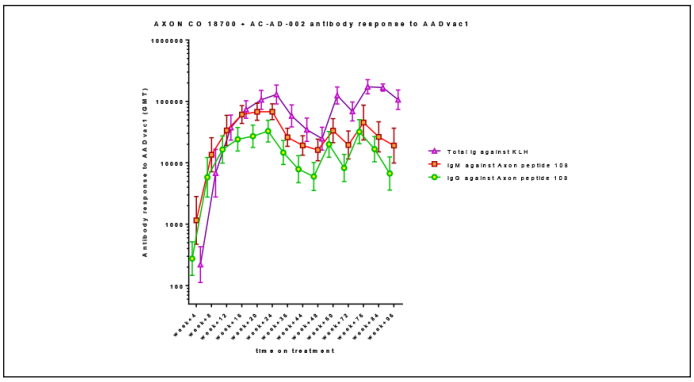
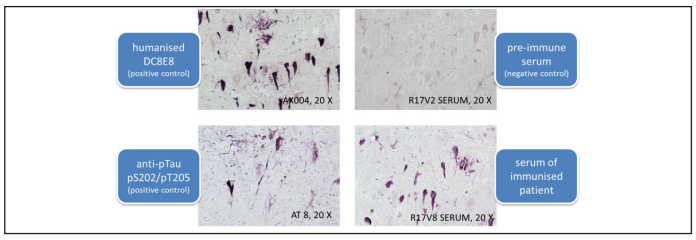


Figure 2
Antibodies recognise Alzheimer pathology in AD brains



P34: OPEN-LABEL EXTENSION STUDY OF IDALOPIRDINE AS ADJUNCTIVE TO DONEPEZIL FOR THE TREATMENT OF MILD-MODERATE ALZHEIMER'S DISEASE. Lutz Frölich[1], Jose Luis Molinuevo[2], Alireza Atri[3,4], Clive Ballard[5], Neli Boneva[6], Marie Aavang Geist[6], Anna Bladström[6], Jeffrey L. Cummings[7], Pierre N. Tariot[8] *((1) Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany; (2) Alzheimer´s disease and other cognitive disorders unit, Neurology Service, ICN Hospital Clinic i Universitari and Pasqual Maragall Foundation, Barcelona, Spain; (3) Ray Dolby Brain Health Center, California Pacific Medical Center, San Francisco, CA, USA; (4) Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; (5) University of Exeter Medical School, Exeter, UK; (6) H. Lundbeck A/S, Valby, Denmark; (7) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; (8) Banner Alzheimer's Institute, Phoenix, AZ, USA)*

Background: Idalopirdine is a novel, selective, 5-HT6 receptor antagonist tested as adjunctive to acetylcholinesterase-inhibitors (AChEIs) for the treatment of mild-moderate Alzheimer's disease (AD). This abstract provides baseline data for patients enrolled in the ongoing interventional, multi-national, multi-site, open-label extension study in patients with mild-moderate AD, projected to be finalized in September 2017 (NCT02079246). The open-label extension study is part of the Phase III idalopirdine development program. The study recruited patients from two 24-week, double-blind, parallel group, placebo-controlled, multi-national, multi-center, fixed-dose (10, 30, and 60 mg QD) studies of idalopirdine as adjunctive to donepezil in patients aged ≥50 years with mild-moderate AD (MMSE 12-22) (hereafter referred to as the "lead-in studies") (NCT01955161; NCT02006641). *Methods:* The ongoing open-label extension study consists of a 28-week open-label treatment period with idalopirdine 60 mg/day as adjunctive to donepezil (10 mg/day). All patients who rolled over to the open-label extension study were treated with idalopirdine 60 mg/day. A down-titration to 30 mg/day was allowed, based on tolerability. Following the 28-week treatment period, a subsample of 100 patients who, as per investigator judgement, required initiation of treatment with memantine, entered a 6-month open-label treatment period with memantine (concomitant with idalopirdine and donepezil), extending the total treatment duration up to 18 months. The primary objective of the open-label treatment period is to evaluate the long-term safety and tolerability of idalopirdine as adjunctive to donepezil in patients with AD. The primary objective of the open-label treatment period with memantine is to evaluate the safety and tolerability of concomitant treatment with idalopirdine, memantine and donepezil in patients with AD. *Results:* The roll-over to the extension study from the lead-in studies was high (90.9%). A similar proportion of patients assigned to idalopirdine (91.1%) or placebo (90.6%) in the lead-in studies were enrolled in the extension study. The 1463 patients enrolled in the extension study were 63% female. At baseline of the extension study, patients had a mean Mini-Mental State Examination (MMSE) total score of 17.8±4.2 and 17.9±4.0 from the two respective lead-in studies. At baseline of the lead-in studies, the patients who rolled-over to the extension study had a mean age of 73.7±8.2, 11.4 years of education, a median time since AD diagnosis of 1.5 years, and a median duration of current donepezil treatment of 2.0 years. The distribution of MMSE strata at baseline of the lead-in studies was 42% and 58% on 19-22 and 12-18, respectively. Approximately 60% of all patients enrolled in the open-label extension study were ApoE-4 carriers. *Conclusion:* The patient population in this open-label extension study is representative of patients diagnosed clinically with mild-moderate AD. The roll-over rate from the lead-in studies to the extension study was high. This open-label extension study will provide long-term safety and tolerability data for idalopirdine in AD patients treated for up to 18 months, including a cohort with safety and tolerability data of concomitant treatment with idalopirdine, memantine, and donepezil.

P35: A KETOGENIC SUPPLEMENT IMPROVES BRAIN ENERGY METABOLISM AND COGNITION IN MILD COGNITIVE IMPAIRMENT: PRELIMINARY RESULTS OF A 6-MONTH RANDOMIZED CONTROLLED STUDY WITH NEUROIMAGING (BENEFIC TRIAL). Etienne Croteau[1,2], Christian-Alexandre Castellano[1], Melanie Fortier[1], Francis Langlois[1], Tamas Fulop[1,3], Stephen Cunnane[1,3] *((1) Research Center on Aging, CIUSSSE – CHUS, Sherbrooke, QC, Canada; (2) Pharmacology-Physiology department, FMSS, University of Sherbrooke, QC, Canada; (3) Medicine department, FMSS, University of Sherbrooke, QC, Canada)*

Backgrounds: In addition to the cognitive changes and memory loss, an Alzheimer-like glucose hypometabolic pattern in several brain regions is observed in mild cognitive impairment (MCI). Brain uptake of ketones, i.e. acetoacetate (AcAc) and β-hydroxybutyrate, which are the main alternative energy substrate to glucose for the brain, is normal in Alzheimer's disease (Castellano et al. J Alzheimers Dis 2015) and MCI (Croteau et al. Exp Geront 2017). Ketogenic interventions reportedly have a modest therapeutic benefit in MCI (Krikorian et al. Neurobiol Aging 2012) and in Alzheimer's disease (Reger et al. Neurobiol Aging 2004; Henderson et al. Nutr Metab 2009; Newport et al Alzheimers Dement 2015). Little is known about how a ketogenic intervention changes brain energy metabolism in MCI. *Methods:* In this placebo-controlled randomized study (BENEFIC trial), participants with MCI received 30 g/day of a ketogenic medium chain triglyceride supplement (MCT) or a matching placebo (Placebo). Brain uptake of acetoacetate (CMRacac) and glucose (CMRglu) - both before and after the 6-month intervention was quantified by PET-MR neuroimaging. A full cognitive assessment was done pre- and post-intervention. This ongoing trial is registered with ClinicalTrials.gov (NCT02551419). *Results:* To date, twenty-three participants (74 ± 6 y) have completed the study. After 6 months, the MCT group (N=11) showed 2.2 fold increase in plasma AcAc compared to baseline (0.33 ± 0.13 vs.0.15 ± 0.05 mM; $p = 0.004$). Post-intervention, this group also had a 93-97% increase in global CMRacac and CMRketones (0.83 ± 0.38 vs. 0.43 ± 0.23 µmol/100 g/min and 2.14 ± 0.65 vs. 1.09 ± 0.64 µmol/100 g/min, respectively; all $p \leq 0.013$), whereas global CMRglu was unchanged (28.1 ± 3.3 µmol/100 g/min; $p = 0.095$). The Placebo group (N=12) did not have any difference pre- to post-intervention in CMRglu or CMRacac (all $p \geq 0.19$). In the cognitive evaluation, shorter completion time on the Trail making Number-Letter switching test was related to higher global CMRacac ($r = -0.46$; $p = 0.015$). The same significant inverse relation was observed between the number of failed at the Boston Naming test and plasma AcAc ($r = -0.44$; $p = 0.025$). A moderate positive relation was also found between performance on a verbal fluency test and the increase

in CMRacac (r= 0.53; p = 0.005). About 80% of the participants completed the 6 month intervention and were protocol-compliant. *Conclusions:* These preliminary results (still in progress) demonstrate for the first time that a ketogenic MCT supplement would sustain about 7.5% of total brain energy metabolism in MCI, specifically by increasing brain ketone uptake and utilization while maintaining brain glucose metabolism. The increase in plasma and brain AcAc observed in this study was associated with significant improvement in several cognitive domains (processing speed, executive function and language). A placebo-controlled MCT intervention at 30 g/day for 6 months is well tolerated and feasible in MCI. Acknowledgements: Excellent help from Christine Brodeur-Dubreuil, Éric Lavallée, Sebastien Tremblay and the clinical PET and MRI group. Financial support provided by the Alzheimer's Association USA.

P36: MRI FINDINGS IN THE OPEN LABEL EXTENSION OF THE MARGUERITE ROAD STUDY IN PATIENTS WITH MILD ALZHEIMER'S DISEASE. Danielle Abi-Saab[1], Mirjana Andjelkovic[1], Nathalie Pross[1], Paul Delmar[1], Nicola Voyle[2], Nelli Esau[1], Smiljana Ristic[1] *((1) Hoffman LaRoche, Basel, Switzerland; (2) Roche Products Limited, Welwyn, UK)*

Background: Gantenerumab is a fully human, anti-amyloid beta (Aβ) monoclonal antibody (mAb) that binds aggregated Aβ and promotes amyloid removal by Fc-gamma receptor mediated microglial phagocytosis. In previous studies, gantenerumab was found to be safe and well tolerated and as with other similar mAb, has been associated with amyloid-related imaging abnormalities (ARIA) consisting of MRI changes representing either vasogenic edemas (ARIA-E) or cerebral microhemorrhage/superficial hemosiderosis (ARIA-H). Marguerite RoAD (MR; NCT02051608), a phase III randomized, double-blind, placebo-controlled, efficacy and safety study of gantenerumab in patients with mild Alzheimer's disease (AD), randomized patients to monthly subcutaneous injections of either placebo or gantenerumab starting at 105 mg for 24 weeks, followed by 225 mg. Following a pre-planned futility analysis of another study of gantenerumab in prodromal AD (SCarlet RoAD; NCT01224106), that showed no effect of the current doses (105 mg and 225 mg) on clinical outcome measures, recruitment in the MR study was halted and the study was converted into an open label extension (OLE). The purpose of the OLE was to evaluate the safety of higher doses of gantenerumab (up to 1200 mg) using different titration schedules. *Methods:* The safety and efficacy of the target dose of 1200 mg, and the titration schedules to target dose, were modelled based on results from several studies with similar mAb targeting aggregated Aβ. Subjects actively enrolled in the MR study were eligible to participate in the OLE after signing the informed consent. Depending on their APOE4 genotype (carrier vs. non-carrier) and their treatment during the double-blind phase (gantenerumab vs. placebo), patients were assigned different titration schedules: for example, non-carriers previously on 225 mg of gantenerumab were assigned the fastest titration schedule (2 months) whereas the carriers previously on placebo or 105 mg of gantenerumab were assigned the slowest titration schedule (6 months). An MRI was obtained prior to each dose up-titration to ensure absence of significant MRI findings including ARIA. In case of significant ARIA-E findings, dosing was temporarily withheld and monthly MRI monitoring was instated until ARIA resolution. *Results:* Three hundred and eighty-nine patients with mild AD were enrolled in the double-blind phase. Overall, the percentage of patients with ARIA-E in the double blind phase was 10.9 on gantenerumab vs. 1.5 on placebo. The percentage of patients with ARIA-H was 13.5 on gantenerumab vs. 9.8 on placebo. The OLE study is ongoing and as of 24 April 2017, 191 patients had enrolled in the OLE and 164 had at least one post-baseline MRI. Of these 164 patients, 133 had received at least one dose of 1200 mg, and 90 had a post 1200 mg dose MRI. Out of 164 patients, 29 had a new ARIA-H with eight having an ARIA-H without an ARIA-E, and 41 had a new ARIA-E. Overall, the incidence of new ARIA-E increased with the dose and ranged from 1.7% at 225 mg to 16.7 % at 1200 mg. The rate of ARIA-H was 17.7%. Of note, at the time of the data cut, not all patients had an MRI scan at 1200 mg. The majority of ARIA events were asymptomatic, non-serious, of mild-to-moderate severity, and consisted of non-specific symptoms: headache, visual disturbance, confusion. Eleven patients discontinued due to ARIA-H as defined by protocol rules and one subject discontinued due to ARIA-E. *Conclusion:* In this ongoing study, the incidence of ARIA was seen to increase with higher doses and overall incidence was 25% as of April 2017. The majority of ARIA were asymptomatic and when present, symptoms were mostly non-serious. MRI findings were managed by monthly MRI monitoring and with dosing algorithms as defined by the protocol. Overall, the safety profile of gantenerumab at higher doses remains unchanged.

P37: THREE YEARS OF TREATMENT OF THE TRIAL ON THE ASSOCIATION BETWEEN A CHOLINESTERASE INHIBITOR AND CHOLINE ALPHOSCERATE IN ALZHEIMER'S DISEASE: INTERIM RESULTS. Enea Traini[1], Anna Carotenuto[1,2], Angiola M Fasanaro[2], Valentino Manzo[2], Francesco Amenta[1] *((1) Centre for Clinical Research, Telemedicine and Telepharmacy, University of Camerino, Camerino; (2) Alzheimer Evaluation Unit, National Hospital, "A. Cardarelli", Naples, Italy)*

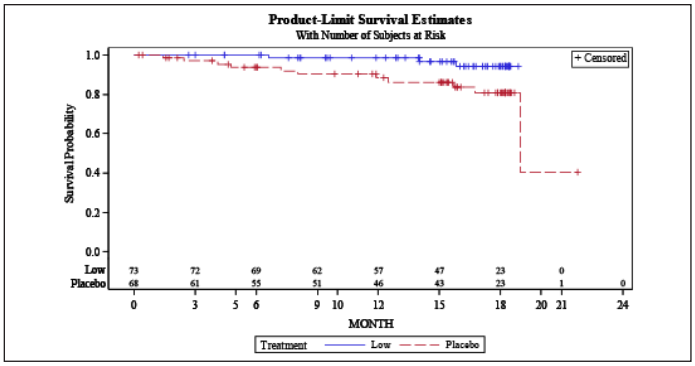
Background: Cholinergic precursors have represented the first approach to counter cognitive impairment occurring in adult onset dementia disorders. ASCOMALVA [Effect of association between a cholinesterase inhibitor (ChE-I) and choline alphoscerate on cognitive deficits in AD associated with cerebrovascular injury] is a double-blind, controlled, randomized clinical trial investigating if the ChE-I donepezil and choline alphoscerate in combination are more effective that donepezil alone. The trial investigates the effects of association between the cholinesterase inhibitor (ChEI) donepezil and choline alphoscerate on Alzheimer's disease (AD) with cerebrovascular impairment over a 48 months period. *Methods:* Patients with mild to moderate AD suffering from ischemic brain damage documented by neuroimaging were recruited. They were randomly allotted to an active treatment group [donepezil (10 mg/day) + choline alphoscerate(1,200 mg/day)] or to a reference treatment group [donepezil (10 mg/day) + placebo]. Cognitive decline was assessed by Mini Mental State Evaluation, Alzheimer's Disease Assessment Scale Cognitive subscale, Frontal Assessment Battery and Trail Making Test A and B. Functional activities were explored by Basic and Instrumental Activities of Daily Living tests. The patient's behavioral profile and the distress of the caregiver were examined by the Neuropsychiatric Inventory. *Results:* At this point patients have reached the 36 months endpoint. The interim results after three years of treatment show, in the reference group, a global time-dependent worsening of different parameters evaluated. In the treatment group the cognitive decline is slowed down, behavioral disorders (particularly mood disorders such apathy, agitation and depression) are decreased and the caregiver's distress is reduced. Stratifying the data based on the cognitive performances at baseline, it is observed that the groups most benefiting from the slowdown in regression are those with lower cognition, in which the difference between the two treatments is more pronounced. *Conclusions:* These results suggest that association of choline alphoscerate to the ChEI treatment may represent an option to prolong beneficial effects of cholinergic therapies in Alzheimer's disease with concomitant ischemic cerebrovascular injury.

P38: SAFETY AND EFFICACY RESULTS FROM PHASE 2 PILOT TRIAL OF GM-CSF/LEUKINE® IN MILD-TO-MODERATE AD. Huntington Potter[1,2], Jonathan H. Woodcock[1,2], Timothy Boyd[1,2], Stefan H. Sillau[2], Brianne M. Bettcher[1,2,3], Joseph Daniels[1], Kate Heffernan[1], H. Gray[1,2] *((1) Rocky Mountain Alzheimer's Disease Center, Department of Neurology, University of Colorado School of Medicine, Aurora, CO, USA; (2) Crnic Institute for Down Syndrome, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; (3) Department of Neurosurgery, University of Colorado School of Medicine, Aurora, CO, USA)*

Introduction: Rheumatoid arthritis (RA) patients have a reduced risk of developing 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 μg GM-CSF reduced AD pathology by greater than 50% and completely reversed the cognitive impairment of transgenic AD mice. 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. *Objectives:* In order to determine whether Leukine® administration is safe in AD subjects and whether Leukine® has an effect on cognition and amyloid load, we are conducting a Phase 2 pilot trial of Leukine® in mild-to-moderate AD subjects. Leukine® is administered at 250 μg/m2/day SC for 5 days/week for three weeks with follow-up visits at 45 and 90 days. Neurological and neuropsychological assessments are carried out at baseline, at end of treatment, and at follow-up visits. MRIs are performed at baseline and at end of treatment. Amyvid® PET imaging of amyloid is carried out at baseline and at first follow up. *Results and Discussion:* Interim analyses of 11 subjects treated with Leukine® and 9 subjects treated with placebo 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, Activities of Daily Living, and Delayed Word Recall score showed improvement in the Leukine® group relative to the placebo group by repeated measures mixed model analysis and/or permutation T-tests ($p<0.05$). The differences became non-significant by the follow-up visits. PiB PET imaging is ongoing. *Conclusions:* These results, although preliminary and based on a small number of subjects, indicate that completing the three-week trial and initiating our Alzheimer's Association "Part the Cloud"-funded 24-week trial of GM-CSF/ Leukine® in subjects with mild-to-moderate AD are warranted. We will report on the further progress of both trials, including the effect of Leukine® using Amyvid® PET imaging to assess amyloid load.

P39: ANALYSIS OF TREATMENT EMERGENT ADVERSE EVENT INCIDENCES IN PHASE 2 STUDY OF AZELIRAGON REVEAL POTENTIAL ATTENUATION OF PSYCHIATRIC SYSTEM ORGAN CLASS (SOC) ADVERSE EVENTS AND EXPECTED DRUG EFFECTS IN GASTROINTESTINAL SOC. Imogene Dunn, Aaron H Burstein, Larry D Altstiel *(vTv Therapeutics, High Point, NC, USA)*

Background: Azeliragon is an oral antagonist of the Receptor for Advanced Glycation Endproducts (RAGE) currently being evaluated in a pivotal Phase 3 study for mild Alzheimer's disease (AD). A phase 2 study evaluated the efficacy and routine safety and tolerability of azeliragon in subjects with mild-to-moderate AD (baseline MMSE 14 through 26). The ongoing azeliragon phase 3 study in mild AD includes patients with entry MMSE of 21 through 26. Routine statistical methodologies for the analysis of treatment-emergent adverse events (TEAEs) includes incidence comparisons based on proportions of patients reporting at least one TEAE and also survival methodologies applied to time to first report of a TEAE. Native MedDRA hierarchy levels, including the system organ class (SOC) and high level group terms (HLGT), are used. *Methods:* The phase 2 study was a randomized, double-blind, placebo-controlled, 18-month study in mild-to-moderate AD investigating effects of once daily oral treatment with azeliragon. Statistical analysis of all reported TEAEs includes the initial comparison of TEAE incidence overall (any TEAE) followed by analysis of TEAEs by SOC, and, where nominal significance is observed, analysis proceeds to HLGTs of interest. Populations of analysis included all randomized patients (mild-to-moderate; baseline MMSE 14 through 26) and the subpopulation of mild AD (baseline MMSE of 21 or more). *Results:* Comparisons of placebo-treated patients with patients treated with 5 mg/d azeliragon revealed two SOCs with nominal p-values less than 5% in either population of analysis: GI disorders (p=0.04) and psychiatric disorders (p=0.04). All other SOCs showed no remarkable disparity between treatment groups in incidences of reported TEAEs in both populations of analysis. Analysis of the profiles of TEAEs in the GI disorders SOC showed greater incidence in the group treated with 5 mg/d azeliragon relative to placebo. This result is supported by time-to-event analysis, consistent with prior studies showing GI effects following treatment with azeliragon. MedDRA HLGTs, in decreasing order of frequency, were gastrointestinal motility and defecation conditions (17% azeliragon; 9% placebo), gastrointestinal signs and symptoms (17% azeliragon; 9% placebo), and salivary gland conditions (16% azeliragon; 14% placebo). Analysis of the profiles of TEAEs in the psychiatric disorders SOC showed decreased incidence from the group treated with 5mg/d azeliragon relative to placebo (p=0.04) and time-to-event analysis, consistent with attenuation of signs and symptoms of AD for TEAEs classified by MedDRA in this SOC. MedDRA HLGTs, in decreasing order of frequency, were anxiety disorders and symptoms (6% azeliragon; 15% placebo; Fisher's exact test (FET) p=0.02) and depressed mood disorders and disturbances (9% azeliragon; 13% placebo; FET ns). Kaplan-Meier curves are shown below for TEAE anxiety disorders for the mild AD subpopulation treated with 5 mg/d of azeliragon or placebo: The Kaplan-Meier curves for both the subpopulation of mild AD patients and the total population of mild-to-moderate AD patients show favorable profiles for subjects treated with azeliragon relative to placebo with nominal statistical significance for all treated patients (N=263; logrank p=0.03) and for mild AD patients (N=141; logrank p=0.02). *Conclusions:* Statistical analysis of TEAEs reveal results consistent with attenuation



of TEAEs associated with AD that are classified by MedDRA in the psychiatric disorders SOC. Statistical analysis of TEAEs also show expected association of tolerability TEAEs classified in the GI Disorders SOC. Comparison of TEAEs in other SOCs revealed no remarkable delineation.

P40: TREATMENT WITH PXT-864 SHOWED STABILISATION OF COGNITIVE DISABILITY IN MILD ALZHEIMER'S DISEASE AFTER 36 WEEKS. Jacques Touchon[1], Pierre-Jean Ousset[2], Florence Pasquier[3], Claude Guériot[4], Philippe Robert[5], Sophie Auriacombe[6], Jean-Marc Orgogozo[6], Jacques Hugon[7], Peter Schmitt[8], Anne-Claire Coyne[8], Rodolphe Hajj[8], René Goedkoop[8] *((1) Memory Research Resource Center for Alzheimer's disease, University Hospital Montpellier, France; (2) Alzheimer's Disease Clinical Research Centre, Gérontopôle, Toulouse University Hospital, France; (3) Memory Clinic, University Hospital Lille, France; (4) Memory Research Resource Center for Alzheimer's disease, University Hospital La Timone, Marseille, France; (5) Memory Center CHU -EA CobTeK, University of Nice Sophia Antipolis, Nice, France; (6) Memory Research Resource Center for Alzheimer's disease, University Hospital Pellegrin, Bordeaux, France; (7) Memory Clinical Center CMRR Paris Nord Ile-de-France, Saint Louis-Lariboisiere, Fernand Widal Hospital, AP-HP, Paris, France; (8) Pharnext SA, Issy-les-Moulineaux, France)*

Background: PXT864 is a fixed low dose combination of baclofen (GABAB receptor agonist) and acamprosate (glutamatergic modulator), that is predicted to act by restoring inhibitory and excitatory imbalances present in Alzheimer's disease (AD). PXT864 restored cognitive ability in amyloid-ß intoxicated animals and prevented scopolamine-induced amnesia (Chumakov et al. 2015) in rodents and humans. This formed the rationale to conduct a multicentre, 36-week single-blind, explorative study of 3 doses of PXT864 in 45 anti-dementia treatment-naïve patients with mild AD. *Methods:* The study was conducted in 7 french investigational sites of the "Centres Mémoire de Ressources et de Recherche (CMRR)". Patients (>60 years and of either sex), with progressive decline in cognition for at least 6 months and a MMSE score of 20-26, and without major or severe depressive disease were eligible to participate in the PLEODIAL study. A MRI diagnosis of hippocampal atrophy excluding other causes of dementia was required. The 3 doses of PXT864 were assigned centrally to assure an even distrubition of 15 patients per dose. PXT864 was administered orally (2x/day) and concomitant donepezil (5 mg/day) was allowed from week 24 onward. After the first 4 weeks of PXT864 treatment, patients received placebo for 4 weeks and continued with the initially assigned PXT864 dose for the remaining 28 weeks. Patients and independent neuropsychologist raters were blind to assigned study treatment throughout the study. The efficacy of PXT864 alone was assessed through cognitive and behavioural tests for the per protocol dataset. Change from baseline ADAS-Cog11 scores were compared to published historical placebo-treated patients with mild AD (Thomas et al., 2016). *Results:* Thirty-six patients out of 45 patients (mean age 73.9±6.1 years (range 60-88), 56.8% female) completed the study. Twenty-three patients were treated with PXT864 alone (n=3 in dose group 1 (D1), n=8 in D2 and n=12 in D3) for 36 weeks. Nine patients received concomitant donepezil at 5 mg/D for 12 consecutive weeks during the last 12 weeks of the study (7 in Dose 1, 1 each in Dose 2 and 3). Treatment was safe and well-tolerated. No statistically significant change from baseline ADAS-Cog11 was observed for any PXT864 dose after 36 weeks. At week 36, 10 patients (43.5%) had stable (<0.2 point increase) or improved ADASCog11. The mean change from baseline ADAS-Cog11 was significantly improved for D2 and D3 PXT864 alone vs historical placebo at W36 ($p<0.002$ and $p<0.014$, respectively). The mean CDR-SB was significantly improved for all PXT864 treated patients vs historical control ($p<0.007$). *Conclusion:* The excellent safety and tolerability of PXT864 was confirmed in patients with mild AD at the end of the 36-week study. The stabilising effect of PXT864 on cognitive ability from this explorative study suggests a promising efficacy of PXT864, to be further evaluated in future studies.

P41: PHASE 1 STUDY OF A NOVEL HUMANIZED ANTI-AMYLOID BETA (AB) AGGREGATES SPECIFIC ANTIBODY KHK6640 IN ALZHEIMER'S DISEASE. Marc Cantillon[1], Louisa Wilson[2], Eri Ohta[1], Niels Prins[3], Niels Andreasen[4], Katsuyoshi Tsukii[1] *((1) Kyowa Kirin Pharmaceutical Development, Inc., USA; (2) Kyowa Kirin Pharmaceutical Development, Ltd., UK; (3) VUmc Alzheimer Center, Netherlands; (4) Karolinska University Hospital, Sweden)*

Background: KHK6640 is a novel humanized anti-Aβ aggregates specific antibody. KHK6640 and/or the mouse parent antibody showed high potency in showing cognitive improvement in several rodent Alzheimer's disease (AD) models including Aβ-injection mouse model or APPxPS2 transgenic mice. KHK6640 showed favorable safety and pharmacokinetic profiles in preclinical studies, warranting clinical studies in human. This study was a first-in-human study to investigate the safety and tolerability of KHK6640 in AD patients in Europe. Also, pharmacokinetics and exploratory pharmacodynamics were investigated. *Methods:* This was a phase 1 double-blind, placebo-controlled, single- (SAD) and multiple-ascending-dose (MAD) safety/pharmacokinetic study in AD (NCT02127476). Eligible subjects were 55 years and older with prodromal or mild/moderate AD (CDR of 0.5, 1, or 2; MMSE > 16), having a cognitive impairment and CSF Aβ < 600 pg/mL and Tau > 300 pg/mL at screening. Procedures included exploratory pharmacodynamics, cerebrospinal fluid/plasma biomarkers, and standard cognitive testing. Enrollment completed in the Netherlands, Sweden, Finland, Belgium, and Serbia. Single ascending doses (randomized 8:2/cohort) of KHK6640 1, 3, 10, or 20 mg/kg or placebo (intravenous [IV]), or KHK6640 0.3 mg/kg or placebo (subcutaneous [SC]) were administered for the SAD phase. Subjects could be re-randomized to continue into the MAD phase with an additional 5 doses at 28-day intervals. *Results:* A total of 57 unique subjects received single/multiple doses of treatment. Only 6 subjects (SAD cohorts 1, 2 and 4), did not continue into MAD, 1 subject started MAD but withdrew prior to being confirmed as eligible for multiple dosing; 7 replacement subjects were enrolled into MAD cohorts 1, 2 and 4. KHK6640 was well tolerated with no dose-limiting toxicities. A Safety Review Committee reviewed blinded laboratory results and adverse events (AEs) prior to dose escalation. No amyloid-related imaging abnormalities (ARIA E) were reported and only 4 subjects had changes from screening microhemorrhages. Two subjects discontinued study drug due to unrelated serious AEs (traffic accident and pancreatic mass). One subject experienced a related serious AE (Cohort 1, third MAD dose; mild hypotension, 90/60 mmHg). Overall, 69.6% and 82.4% of SAD and MAD subjects, respectively, experienced at least one AE during the study. Of these, 23.9% and 17.7% of SAD and MAD subjects, respectively, experienced AEs that were considered by the investigators to be related to study drug. Frequently reported related AEs included headache (5.9%) and feeling hot (6.5%). Other related AEs occurred in one subject each. Dosing has completed and subjects are in safety follow up. *Conclusions:* Blinded safety results support KHK6640 safety after SAD/MAD IV and SC administration for 1 dose followed by 5 doses at 28-day intervals, with no ARIA-E and low dropout rates.

P42: A SINGLE DOSE STUDY OF A NOVEL HUMANIZED ANTI-AMYLOID BETA (AB) AGGREGATE SPECIFIC ANTIBODY KHK6640 IN JAPANESE PATIENTS WITH ALZHEIMER'S DISEASE. Hiroyuki Shimada[1], Kenichiro Sugiyama[2], Yoshiumi Ouchi[2], Katsuyoshi Tsukii[3] *((1) Osaka city university hospital, Osaka, Japan; (2) Kyowa Hakko Kirin Co., Ltd., Japan; (3) Kyowa Kirin Pharmaceutical Development, Inc., USA)*

Background: KHK6640 is a novel humanized anti-Aβ aggregates specific antibody. KHK6640 and/or the mouse parent antibody showed high potency in showing cognitive improvement in several rodent Alzheimer's disease (AD) models including Aβ-injection mouse model or APPxPS2 transgenic mice. KHK6640 showed favorable safety and pharmacokinetics profiles in preclinical studies, warranting clinical studies in human. This study was a single dose study to investigate the safety as a primary objective in Japanese patients with AD. *Methods:* KHK6640 was investigated in this phase 1 double-blind, placebo-controlled, single-ascending-dose (SAD) study (NCT02377713) for its safety and tolerability after single intravenous (IV) dose in Japanese patients with mild to moderate AD (CDR of 1, or 2; 17≤MMSE≤26). Safety was evaluated by incidence of treatment-emergent adverse events (TEAEs) and their nature laboratory values, physiological values, 12-lead electrocardiogram and brain magnetic resonance imaging (MRI). The secondary objective was to investigate the pharmacokinetics and immunogenicity of KHK6640. Also the exploratory efficacy of KHK6640 was investigated. Subjects were randomized 4:1/cohort of KHK6640 1, 3, 10 or 20 mg/kg or placebo. *Results:* A total of 20 unique subjects received a single dose of treatment. KHK6640 was overall well tolerated and there were no death and no discontinuation due to TEAEs in this study. Overall, two serious adverse events (SAEs) were observed, one in 1 mg/kg was vomiting (Non-drug related) and the other in 20 mg/kg was lacunar infarction (possibly drug-related). These events were temporary and recoverable. Regarding as amyloid-related imaging abnormalities (ARIA), no ARIA-edema/effusion (ARIA-E) were observed. Two subjects from 10 mg/kg and 20 mg/kg in each developed the microhemorrhage, those were considered not related to study drug. Pharmacokinetics of KHK6640 showed linear between 1 and 20 mg/kg. A range of average serum half life (t1/2) of each cohort was from 14.0 to 15.9 days. None of the 16 subjects who received KHK6640 were positive for anti-KHK6640 antibodies at any of the time points after drug administration. *Conclusions:* A single intravenous infusion of KHK6640 in Japanese patients with mild to moderate AD was well-tolerated with no dose-limiting toxicities. A multiple dose study with Japanese AD patients is under investigation (NCT03093519).

Theme: Clinical trials : imaging

P43: FRANCE ADOPTS A 3D DIAGNOSIS STRATEGY FOR ITS NATIONAL ALZHEIMER DATABANK – AN OPTIMIZATION OF PATIENT SELECTION FOR CLINICAL TRIALS. Pierre Krolak-Salmon[1], Philippe Robert[2], Eric Assemat[3], Claudine Berr[4,8], Mathieu Ceccaldi[5], Bruno Dubois[6], Stephane Epelbaum[6], Bruno Vellas[7], Audrey Gabelle[8] *((1) Clinical and Research Memory Centre of Lyon, Hospices civils de Lyon, University Lyon 1, INSERM U1028, UMR CNRS 5292, Lyon, France; (2) Clinical and Research Memory Centre of Nice, France; (3) Memory Clinic Alpes Nord, France; (4) Inserm U1061, University of Montpellier, 34093 Montpellier, France; (5) Clinical and Research Memory Centre of Marseille, France; (6) Clinical and Research Memory Centre of Paris Pitié-Salpêtrière, France; (7) Clinical and Research Memory Centre of Toulouse, France; (8) Clinical and Research Memory Centre of Montpellier, France)*

The diagnosis Alzheimer's disease and related diseases (ADRD) has been for a long time associated to dementia, but the concept of "Mild Cognitive Impairment" (MCI) has allowed focusing on earlier stages of the different diseases. Now, a preclinical or a "Subjective Cognitive Decline" stage may be even considered. After a period of discrimination between MCI and Alzheimer's disease (AD) that was associated to dementia in the definition, it has been widely admitted that ADRD should be considered not only at the dementia stage, but also at the MCI stage. So the syndrome MCI has evolved towards the "stage" MCI. That is clearly proposed by the DSM 5 introducing the concept of minor and major neurocognitive disorder (NCD). Another confusing period in the scientific history of ADRD is represented by the mixing of aetiologies like AD and clinical syndromes like Primary Progressive Aphasia (PPA) or Posterior cortical Atrophy/Benson's syndrome (PCA). It has been now clearly disclosed that clinico-radiological syndromes related to focal atrophy may be related to different types of underlying lesions. Since 2009, the French National Alzheimer dataBank (BNA) collects data from all memory centers throughout the country. The first version of the database considered different diagnosis situations derived from ICD 10 classification including MCI, dementia, ADRD, focal syndromes like PPA or PCA. A new version has been proposed in 2017 aiming at disentangling 3 clear dimensions in the diagnosis process, i.e. 1- the stage (isolated cognitive complaint, minor NCD, major NCD), 2- the predominant clinical presentation (amnesic, dyexecutive, aphasia, visual, apraxia, diffuse), 3- the underlying presumed aetiology and/or lesions (AD, CVD, FTLD, LBD, mood disorders for example). A pilot study - phase 1 - has submitted different prototypical clinical cases to the physician community and shown a high inter individual reproducibility. The phase 2 has also collecting between January and April 2017, 13 515 cases coded with the two successive diagnosis approaches, i.e. the ICD 10 and the 3D diagnoses. Of particular interest, 37,7% of minor NCD have been previously classified as "dementia", whereas 21,5 % of major NCD have been classified as "cognitive disorder without dementia". 65% of patients with presumed AD presented with an amnestic syndrome, and 18,6% with a dysexecutive one. These proportions do not differ with biomarkers enrich the cases. This formal 3D diagnosis strategy appears to clarify the classification of French cases in the national databank, and provides a unique opportunity to better explain recent scientific and conceptual considerations regarding ADRD, and to optimize selection of patients for clinical trials.

P44: DIVERGENT TOPOLOGICAL NETWORKS OF GREY AND WHITE MATTER IN ALZHEIMER'S DISEASE: A DIFFUSION KURTOSIS IMAGING ANALYSIS. Jun Xu[1], Hongying Zhang [2], Jiaxing Cheng [1] *((1) Neurology Department, Northern Jiangsu People's Hospital, Yangzhou University, Yangzhou, China; (2) Radiology Department, Northern Jiangsu People's Hospital, Yangzhou University, Yangzhou, China)*

Background: Alzheimer's disease (AD) is the most frequent neurodegenerative disorder causing cognitive impairment, disabilities and finally death in aged people. Graph theory speculates that human brain is constructed of complex networks and provides a powerful approach to quantitative analysis of the organization of network connectivity. In recent years, different imaging modalities have revealed structural and functional connectivity disruptions between anatomically distinct brain regions in patients with AD and showed discrepant results. *Objective:* To construct diffusion networks using a new technology called diffusion kurtosis imaging and apply them to investigate the changes of networks in AD patients and the association with cognitive performance. *Methods:* Brain networks of 21 AD patients and 19 healthy controls were constructed by correlation matrices of 90 regions and analyzed using graph theoretical approaches. Overall network efficiency was assessed by measures of local (clustering coefficient, local efficiency) and global (shortest paths, global efficiency) connectivity. Cognitive scores were related to network measures. *Results:* There were no significant differences in age (p= 0.07) and gender (p=0.8) between AD patients and controls. For the neuropsychological tests, there were significant differences in MMSE and MOCA scores between the two groups ($p<0.05$). We found that the brains of both AD patients and controls had prominent small-world network properties. AD brains presented with significant increased shortest paths and decreased global efficiency for fiber number (all $p< 0.05$), however, decreased shortest paths and increased global efficiency for all the diffusion metrics of mean kurtosis, axial kurtosis, radial kurtosis, mean diffusivity, axial diffusivity, radial diffusivity, fractional anisotropy and axial diffusivity in the white matter networks, which suggested that the small-world architecture of diffusion networks were significantly altered in AD patients. To identify the hub regions, we examined normalized nodal betweenness centrality for the mean kurtosis metric in the grey matter networks. Compared to the controls, less hub regions were observed in thalamus and paralimbic system in AD patients, which were most involved in default mode. We next examined the relationship of the network metrics (small-world and efficiency metrics) with cognitive performance. Partial correlation analysis with age and gender as confounding covariates were separately performed for AD group. The results showed that kurtosis metrics had closer ties with cognitive functions than tensor metrics, particularly for fiber number, mean kurtosis and axial kurtosis metrics. In addition, AD patients showed increased correlations in a set of paired cortical regions involved in the parietal and fronto-temporal cortices including supramarginal gyrus, inferior temporal gyrus, superior temporal gyrus, middle frontal gyrus and cingulate regions. *Conclusions:* DKI could be used to construct diffusion brain networks. We found small-world characteristic DKI networks in both AD patients and normal subjects. The divergent features demonstrated in AD brains probably imply a dedifferentiation tendency in AD patients. In addition, AD patients showed reduced nodal centrality predominantly in the default mode network areas. Finally, the disruptions of kurtosis networks in AD were significantly related to cognitive performance. Our results suggest that diffusion kurtosis networks provide a novel approach to understanding pathogenic mechanisms in neurodegenerative diseases.

P45: IMPACT OF TWO DISTINCT MRI PARALLEL IMAGING IMPLEMENTATIONS ON HIPPOCAMPAL VOLUME ESTIMATES OBTAINED FROM TWO METHODOLOGICALLY DIFFERENT METHODS. Oliver Peters[1], Per Suppa[2,3], Catharina Lange[3], Ralph Buchert[4], Lothar Spies[2], Isabella Heuser [1] *((1) Department of Psychiatry, Charité, Berlin, Germany; (2) jung diagnostics GmbH, Hamburg, Germany; (3) Department of Nuclear Medicine, Charité, Berlin, Germany; (4) Department of Nuclear Medicine, University Medical Center Hamburg-Eppendorf, Germany)*

Background: Parallel MR imaging techniques offer the opportunity to reduce scan time in order to minimize the risk of motion artifacts and to increase patient throughput. Two parallel imaging techniques can be distinguished: generalized autocalibrating partially parallel acquisition (GRAPPA) and sensitivity encoding (SENSE). Scan time is reduced by undersampling the k-space in either the phase-encoding direction (2D imaging) or in both, the phase-encoding and the partition-encoding direction (3D imaging). Whereas GRAPPA works on the undersampled k-space data to restore the non-sampled k-space information, SENSE uses the aliased images to unfold each pixel/voxel to receive the final unaliased image. However, the reduction of scan time is associated with decreased signal-to-noise-ratio which might directly influence automatic segmentation of the hippocampus for hippocampal volumetry. The objective of this study was to assess the impact of parallel imaging on hippocampal volumetry by two widely used fully automatic methods: FSL-FIRST (FIRST-HV) and an SPM-based approach (SPM-HV) [1, 2]. *Methods:* All ADNI2 MCI subjects with non-accelerated and accelerated 3T scan within the same imaging session were identified. The spreadsheet provided by the ADNI repository (Mayo (Jack Lab) – ADNI GO/2 MRI QC [ADNIGO,2]) was used for this purpose. This resulted in a total of 412 subjects. Raw DICOM files for 408 of these 412 subjects were available from the ADNI homepage. Test-retest stability was quantitatively characterized by the signed difference in hippocampus volume between the non-accelerated and the accelerated scan in mm3. The bias (offset) of the signed difference measure was tested against a zero-centered distribution using the Wilcoxon signed rank test. The difference between the variances of FIRST-HV and SPM-HV as well as for the parallel imaging techniques applied for data acquisition was tested for statistical significance using the Pitman-Morgan test. Results were regarded as significant for a p value below 0.05. *Results:* For a total of 388 subjects both scans (non-accelerated and accelerated) passed visual quality control of the segmentation results from both FIRST-HV and SPM-HV. In case of FIRST-HV, the signed difference measure revealed a slightly larger hippocampus volume from the accelerated compared to the non-accelerated scan: 12.88 ± 245.52 mm3. The offset was not statistically different from a zero-centered distribution (p=0.1156). In case of SPM-HV, the mean hippocampus volume obtained from the non-accelerated scan was larger by on average 36.88 ± 207.62 mm3. The offset was found to be statistically different from a zero-centered distribution ($p<0.001$). The Pitman-Morgan test revealed a significant difference between the variances of the signed measure obtained from FIRST-HV and SPM-HV (p=0.001). The comparison of both methods applied for parallel acquisition (i.e. SENSE vs. GRAPPA) revealed a significant offset for the signed difference measure with respect to a zero-centered distribution for the GRAPPA technique compared to the SENSE technique for FIRST-HV (0 ± 0.26 mm3; p=0.9245 and -0.02 ± 0.24 mm3; p=0.0375 for SENSE and GRAPPA, respectively). No significant difference between the variances of the signed measures obtained from both parallel imaging techniques were found according to the Pitman-Morgan test (p=0.1529). For SPM-HV, the signed

difference measure showed a significant difference to a zero-centered-distribution for GRAPPA (0.06 ± 0.12 mm3; p<0.001) but not for SENSE (0 ± 0.28 mm3; p=0.5357). In addition, the variance for the signed measure obtained from SENSE was statistically larger than the one obtained from GRAPPA (p<0.001). *Conclusion:* Parallel imaging is a valuable technique to reduce MR scan time. However, decreased signal-to-noise ratio associated with scan time reduction can have an impact on the estimates of hippocampus volume obtained by fully automated methods. The effect of parallel imaging on hippocampus volume estimates varies both, between different volumetry methods and between different parallel imaging techniques. Although the effects are rather small, it is recommended not to mix methodology within a clinical trial in order to avoid increasing variability and, as a consequence, decreasing statistical power. References: [1] Patenaude B, Smith SM, Kennedy DN, Jenkinson M (2011) A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 56, 907-922. [2] Opfer R, Suppa P, Kepp T, Spies L, Schippling S und Huppertz HJ (2016) Atlas based brain volumetry: how to distinguish regional volume changes due to biological or physiological e f f e c t s from inherent noise of the methodology. Magn Reson Imaging 34:45-461.

P46: MRI MARKERS OF NEURODEGENERATION IN PRECLINICAL ALZHEIMER'S DISEASE. Adam J. Schwarz[1], Michael G. Case[1], Peter F. Castelluccio[1], AnnCatherine M. Downing[1], John R. Sims[1], James B. Brewer[2], Anja Soldan[3], Corrine A. Pettigrew[3], Marilyn Albert[3] *((1) Eli Lilly and Company, Indianapolis, IN, USA; (2) University of California, San Diego, CA, USA; (3) Johns Hopkins University, Baltimore, MD, USA)*

Backgrounds: The lexicon surrounding individuals in the earliest stages of Alzheimer's disease (AD) pathology is complex and continues to evolve. An A/T/N biomarker research classification has been proposed to describe the pathology commonly seen in patients with AD and to address the lack of alignment between the current clinical diagnostic classifications. Volumetric MRI (vMRI) is currently the only neurodegeneration biomarker proposed with sufficient global availability and standardization to be uniformly used as an "N+" marker in a large clinical trial setting. This report summarizes the evaluation of vMRI metrics and cut-points in two longitudinal datasets of cognitively normal individuals to evaluate "N+" classification, and the utility of vMRI markers in multivariate models to predict faster progressors in this population. *Methods:* Data from the ADNI and BIOCARD studies were used. In ADNI, baseline values of three metrics reflecting temporal lobe atrophy were assessed: hippocampal volume (HV), hippocampal occupancy fraction (HOC) and a composite measure of anterior temporal lobe cortical thickness (ATL-CT). For comparison, "global" atrophy measures (whole brain volume, cortical volume, and ventricular volume) were also assessed. Each of these was corrected for age, gender, and/or intracranial volume, if a significant dependence on that variable was found in an amyloid-negative, cognitively normal (CN) control group. The test group comprised amyloid-positive participants in the ADNI CN and subjective memory concerns (SMC) diagnostic categories. The control group comprised amyloid-negative CN subjects from the ADNI study. Cognitive outcome measures included MMSE, ADAS-Cog13, CDR-SB, FAQ, AVLT-DR, WMS-LMD, API ADAD, and ADCS PACC v2. The relationship of these markers to amyloidosis was assessed in a cross-sectional linear model across disease stages in ADNI with diagnostic category, amyloid status and category by amyloid status interaction as predictors. Their performance as "N+" markers and the dependence on cut-point were assessed by evaluating cognitive decline in "N+" and "N-" groups, defined by cut-points ranging from approximately -2 to +2 standard deviations above the mean of the control group. The utility of these metrics as continuous measures to predict cognitive decline was evaluated in multivariate mixed models with the vMRI variable alongside ApoE status, age, gender, and baseline cognition as predictors of change in clinical scales out to 4 years post-baseline. Depending on the number of subjects with available data, sample size ranged from approximately 150 at baseline to approximately 60 at 48 months. In the BIOCARD study, analogous multivariate models were run to examine the performance of three measures of temporal lobe atrophy: HV, ATL-CT, and a BIOCARD composite metric comprising of HV, amygdala and entorhinal cortex volume. Models were run on all participants with the relevant available measures, with sample sizes ranging from 105-260 at baseline, and MMSE and CVLT-DR as cognitive outcome measures. No triage by amyloid level or status was applied. BIOCARD subjects were cognitively normal at baseline (mean age ~57 years). Follow-up duration was 12 years on average, extending as far as 20 years in some participants. *Results:* In cross-sectional analyses on ADNI data, ATL-CT decreased strongly across diagnostic categories in amyloid-positive but not notably in amyloid-negative individuals (group x amyloid interaction, p<0.0001). In contrast, both hippocampal atrophy measures markedly decreased in more advanced diagnostic categories, for both amyloid-positive and -negative individuals (weaker group x amyloid interaction, p=0.05). Performance of the studied vMRI metrics, dichotomized as "N+" markers, was variable in the ADNI sample. For some, but not all, combinations of vMRI metric, clinical endpoint and follow-up time, the enriched "N+" population evidenced a more rapid decline than the excluded "N-" population, but there was no consistent dependence on cut-point. As continuous baseline predictors in multivariate models, in the ADNI sample vMRI markers of temporal lobe atrophy were more strongly associated with clinical decline than measures of "global" atrophy. In both ADNI and BIOCARD samples, the strength of association was dependent on the clinical outcome measure. For example, in the ADNI sample, HV was significantly associated with decline in CDR-SB, WMS-LMD and ADCS-PACC; in the BIOCARD sample, HV was significantly associated with decline in CVLT-DR. *Conclusion:* Baseline vMRI metrics of temporal lobe atrophy were variably associated with subsequent clinical decline in two "preclinical AD" population samples. Although a significant association was observed in many cases, the effectiveness with which an enriched, more rapidly declining subpopulation is identified would seem to depend on the instrument used to measure that decline. In the ADNI sample, values of cortical thickness in more advanced stages were preferentially associated with amyloidosis, possibly reflecting the mediating influence of tau pathology in the anterior temporal lobe.

P47: FDA QUALIFICATION OF INTRACRANIAL ADJUSTED HIPPOCAMPAL VOLUMETRIC MAGNETIC RESONANCE IMAGING (ICV-HV VMRI) AS A PROGNOSTIC BIOMARKER FOR PRE-DEMENTIA CLINICAL TRIALS FOR ALZHEIMER DISEASE THERAPEUTICS. Daniela J. Conrado[1], Klaus Romero[1], Derek L. Hill[2], Patricia Cole[3], Dawn Matthews[4], Gerald Novak[5], Volker D. Kern[1], Robin Wolz[2], Richard Meibach[6], Jackson Burton[1], Brian Corrigan[7], Timothy Nicholas[7], Danny Chen[7], Julie Stone[8], Vikram Sinha[8], Brian Willis[9], Wenping Wang[6], Stephen P. Arnerić[1] *((1) Critical Path Institute, Tucson, AZ, USA; (2) IXICO, London, United Kingdom; (3) Advisor, MA, USA; (4) ADMDX, Chicago, IL, USA; (5) Janssen Pharmaceutics (J&J), Titusville, NJ, USA; (6) Advisor, NJ, USA; (7) Pfizer Inc, Groton, CT, USA; (8) Merck, West Point, PA, USA; (9) Eli Lilly, Indianapolis, IN, USA)*

Background: Interest in identifying, evaluating, and qualifying innovative imaging technologies for use as Drug Development Tools is growing. In 2011, the European Medicines Agency (EMA) concluded that low hippocampal volume, measured by vMRI and considered as a dichotomized variable (presence of low volume), appears to help enriching recruitment into clinical trials aimed at studying drugs that potentially slow the progression of the pre-dementia stage of Alzheimer disease AD [1]. In 2016, the U.S. Food and Drug Administration (FDA) qualified Total Kidney Volume (TKV) as its first clinical imaging biomarker [2]. The Coalition Against Major Diseases (CAMD), a consortium within the Critical Path Institute is using a model-informed approach to pursue regulatory qualification of ICV-HV vMRI as a prognostic enrichment biomarker for pre-dementia clinical trials. The work herein describes the pathway to submit an ICV-HV vMRI qualification dossier to FDA in late 2017. *Methods:* Face-to-face meetings have been held with the FDA to finalize the context-of-use statement for ICV-HV vMRI as a prognostic enrichment biomarker, as well as the statistical analysis plan. The Alzheimer's Disease Neuroimaging Initiative (ADNI)-1 and ADNI-2 observational studies, and the Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon (InDDEx) clinical trial were standardized to the Clinical Data Interchange Standards Consortium (CDISC) AD therapeutic-area standards. *Results:* Context-of-Use Target Population for Use: Patients with aMCI. Clinical symptoms of aMCI are defined for this purpose as MMSE scores between 24-30 (inclusive), a memory complaint, objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia (ADNI criteria). Stage of Drug Development for Use: Phase II and III stages of clinical drug development in pre-dementia, including proof-of-concept, dose-ranging, early efficacy and safety clinical studies through clinical trials for registration of a therapy for pre-dementia. Intended Application: Clinical trial enrichment for pre-dementia Phase II and Phase III studies, based on the prognostic imaging biomarker ICV-HV as a predictor of disease progression. Data and Endpoint: Integrated, individual-level, longitudinal, CDISC-standardized dataset consisting of approximately 800 pre-dementia subjects from the ADNI-1, ADNI-2 and InDDEx studies. The vMRI images have been reprocessed with ICV-HV vMRI determined using LEAP™ and FreeSurfer™ algorithms. The model endpoint is the Clinical Dementia Rating Scale Sum-of-Boxes (CDR-SB), as per FDA feedback. Statistical Analysis: The trajectory of CDR-SB over time will be described by a mixed-effects statistical model, which allows the differentiation of sources of variability. Along with ICV-HV, sex, baseline disease severity, baseline age, and apolipoprotein E genotype will be included as covariates. Utility of ICV-HV vMRI enrichment will be compared between both algorithms. Enrichment utility will be determined by several analysis outputs, including whether simulated biomarker-enriched trials have increased statistical power to demonstrate a disease-modifying drug effect. *Conclusions:* 1. Further exploration of imaging technologies for prognostic biomarker purposes should be encouraged. 2. Having frequent dialogue with regulators is critical to shape the development, validation, and clinical relevance of Drug Development Tools. 3. Model-informed enrichment analyses can streamline the pathway towards regulatory biomarker qualification. 4. If ICV-HV vMRI enrichment utility is confirmed, its qualification with the FDA will increase the efficiency of clinical trial design and pre-dementia drug development programs for AD in the United States. References: [1] Qualification opinion of low hippocampal volume (atrophy) by MRI for use in regulatory clinical trials – in pre-dementia stage of Alzheimer's disease. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2011/10/WC500116264.pdf; [2] Qualification of Biomarker: Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease. Available at: https://www.fda.gov/downloads/%20Drugs/Guidances/UCM458483.pdf

P48: CEREBRAL ATROPHY IN ALZHEIMER'S DISEASE PATIENTS: EFFECT OF COMBINED THERAPY BETWEEN THE CHOLINESTERASE INHIBITOR DONEPEZIL AND THE CHOLINERGIC PRECURSOR, CHOLINE ALPHOSCERATE. Enea Traini[1], Anna Carotenuto[1,2], Angiola Maria Fasanaro[2], Francesco Amenta[1] *((1) Centre for Clinical Research, Telemedicine and Telepharmacy, University of Camerino, Camerino; (2) Alzheimer Evaluation Unit, National Hospital, "A. Cardarelli", Naples, Italy)*

Background: Cerebral atrophy is a common feature of neurodegenerative disorders. This is true also for Alzheimer's disease (AD) in which with loss of gyri and sulci in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus has reported. *Methods:* Participants of the ASCOMALVA [Effect of association between a cholinesterase inhibitor (ChE-I) and choline alphoscerate on cognitive deficits in AD associated with cerebrovascular injury] trial underwent yearly MRI for diagnostic purposes. In 56 patients who achieved three years of therapy, MRI were analyzed by voxel morphometry techniques to assess if addition of choline alphoscerate to standard treatment with donepezil had an effect on volume loss typical of AD brain. *Results:* After three years of treatment, reference group (treated with the cholinesterase inhibitors donepezil only) showed a greater atrophy of the gray matter and white matter with a concomitant increase of the volume of the ventriculi and space of the cerebrospinal fluid, compared to the group treated with donepezil plus choline alphoscerate. The areas affected by the atrophy were the frontal and temporal lobes, hippocampus and basal ganglia. The volume loss was more limited in patients treated with donepezil plus the cholinergic precursor choline alphoscerate. These morphological data are also confirmed by neuropsycological assessment done along the course of the trial. *Conclusion:* These findings have shown that cholinergic precursor loading strategy with choline alphoscerate associated to cholinesterase inhibition with donepezil counters to some extent the atrophy occurring in some brain areas of AD patients. The observation of a parallel improvement of cognitive and functional tests in patients treated with choline alphoscerate plus donepezil versus donepezil alone suggests that morphological changes observed may have functional relevance.

P49: CEREBRAL HYPOPERFUSION IS NOT ASSOCIATED WITH AN INCREASE IN B-AMYLOID PATHOLOGY. Ruben Smith[1,2], Sebastian Palmqvist[1,2], Hanna Ljung[2,3], Tobias Cronberg[2,3], Danielle van Westen[4], and Oskar Hansson[1,5] *((1) Lund University, Clinical Memory Research Unit, Dept. of Clinical Sciences Malmö, Malmö, Sweden; (2) Skåne University Hospital, Dept. of Neurology, Lund, Sweden; (3) Lund University, Skane University Hospital, Department of Clinical Sciences, Neurology, Lund, Sweden; (4) Lund University, Skane University Hospital, Department of Clinical Sciences Lund, Diagnostic radiology, Lund, Sweden; (5) Skåne University Hospital, Memory clinic, Malmö, Sweden)*

Background: It has been hypothesised from animal studies that cerebral hypoperfusion promotes the development of Alzheimer's Disease pathology by induction of transcription factors that cause β-amyloid deposition. Data from human subjects supporting this hypothesis are missing. We therefore studied whether longstanding cerebral hypoperfusion is associated with Alzheimer's Disease pathology in non-demented humans. *Methods*: Patients with a diagnosis of stenosis or occlusion of precerebral arteries, seen at the Department of Neurology, Skåne University Hospital, Sweden Jan 2012 - May 2014 were assessed for participation in the study. Inclusion criteria were occlusion or near occlusion (non-continuous blood flow) of one of the internal carotid arteries or a significant stenosis of one of the middle cerebral arteries resulting in a unilateral decrease in cerebral perfusion. Eleven patients fulfilled the criteria and were included in the study. Cerebral blood flow was assessed using MRI (regional Cerebral Blood Flow (rCBF) and Mean Transit Time (MTT)) or CT-perfusion and the patients underwent 18F-Flutemetamol PET to assess the regional deposition of amyloid in the brain. A subset of patients (n=5) underwent tau (18F-AV-1451) PET. *Results:* Subjects were non-demented with a median age of 69 years (range 51–83). The median time of known artery occlusion was 22 months (range 9–258). The blood flow in the analysed hypoperfused regions was 84% of the blood flow in the contralateral side of the brain (interquartile range, IQR, 66-90; p<0.01). The median Mean Transit Time (MTT) was 135% of the time in the contralateral side (IQR 115-202; p<0.01). We found no effect on regional amyloid or tau deposition in the hypoperfused versus the more normally perfused side of the brain. The median 18F-flutemetamol standardized uptake value ratio (SUVR) was 1.35 (IQR 1.32-1.40) in the hypoperfused region versus 1.32 (IQR 1.28-1.46) in the normal region (p=0.97). Similarly, the median 18F-AV-1451 SUVR was 1.09 (IQR 1.08-1.11) in the hypoperfused region versus 1.12 (IQR 1.09-1.13) in the normal region (p=0.44). We further examined ratios of cortex/white matter retention in both hypoperfused and normal regions to account for a potential error introduced by reduced perfusion leading to reduced delivery of radiotracer to the hypoperfused regions and falsely low results in these regions. Using these ratios we again found no differences in amyloid or tau deposition (18F-Flutemetamol hypoperfused versus normal: 0.68 (IQR 0.62-0.70) versus 0.66 (0.63-0.70), p = 0.90; 18F-AV-1451 hypoperfused versus normal: 0.91 (IQR 0.88-1.06) versus 0.96 (IQR 0.91-1.06), p = 0.19). We next correlated the ratio of the 18F-Flutemetamol cortex (Ctx)/white matter (Wm) ratios (i.e. (Ctx Hypo/Wm Hypo)/(Ctx Normal/Wm Normal)) to the blood flow measurements (rCBF, MTT). We found no significant correlation between these two measures, again indicating that a more severe blood flow reduction is not coupled to increased β-amyloid deposition. Further, correlating the ratio above to time with arterial occlusion did not result in a significant correlation, indicating that an increased time with an arterial occlusion is not associated to an increased amyloid deposition in affected areas. *Conclusion:* Our results suggest that longstanding cerebral hypoperfusion in humans, caused by large vessel disease, does not result in accumulation of β-amyloid fibrils or tau aggregates.

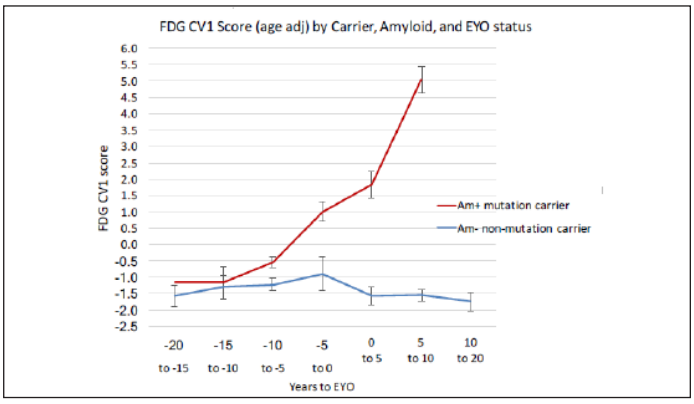
P50: OPTIMIZED DETECTION OF DISEASE AND TREATMENT EFFECT IN PRECLINICAL AND PRODROMAL AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE WITH IMAGING BIOMARKERS. Dawn C Matthews, Ana S Lukic, Randolph D Andrews, Miles N Wernick, Stephen C Strother, Tammie L S Benzinger *(Dominantly Inherited Alzheimer Network)*

Background: The Dominantly Inherited Alzheimer Network (DIAN) has provided a valuable early onset cohort characterized with multi-modality imaging and other data in which symptom onset can be predicted from parental age of onset. DIAN-TU has extended this to study disease prevention potential using different treatment mechanisms. It is anticipated that findings from these early onset studies will provide insight to disease progression and treatment response in late onset populations. Imaging biomarkers have the potential to detect and measure longitudinal changes in pathology and neurodegeneration. However, particularly in early disease, accumulation levels and rates of change in pathology and neurodegeneration are subtle. Univariate measurement approaches are challenged by signal variability, image noise, and the inability to capture network effects. Advances in multivariate machine learning may optimize image signal detection for use in DIAN trials and for translation to trials of late onset AD. Our work focused on the development and application of Alzheimer's disease progression classifiers in the DIAN population using machine learning and structural MRI, FDG PET, and amyloid PET image data to detect neurodegenerative and pathological changes. We examined classifier performance with regard to prediction of symptom onset and correlation with clinical progression, and relationships to amyloid PET, CSF Abeta42, tau, and p-tau. *Methods:* Disease progression classifiers were developed separately and in combination using structural MRI, FDG PET, and amyloid PET data from 170 DIAN subjects (age 38±9.9 years). For each classifier, nine training classes were defined based upon mutation carrier status, amyloid load, and estimated years to onset (range -25 (pre) to +21 years EYO). Regional volumetric and cortical thickness values derived using Freesurfer were used as inputs for the structural MRI classifier. FDG SUVRs measured using the Freesurfer masks were used as inputs for the FDG classifier. Principal Component Analysis was applied for feature reduction, followed by Canonical Variates Analysis, with model parameters optimized through intensive iterative split half resampling of the data set, measurement of reproducibility and prediction, and determination of a robust consensus pattern. Pattern expression was quantified for each scan as a numeric CV score. Age effects were examined and incorporated as a covariate. Leave One Out testing was performed to validate performance. In addition, 274 independent DIAN subjects were evaluated on a cross-sectional basis and 74 independent subjects having 2 or more serial scans available were evaluated longitudinally with respect to score vs. time relative to EYO. Scores were examined in 5 year bins for strata consisting amyloid negative (Am-) non-mutation carriers (mean PiB PET SUVR 1.06 ± 0.06), mutation carriers with a negative PiB SUVR (1.18 ± 0.10), and mutation carriers with a positive PiB SUVR (1.67 ± 0.28). Correlations with clinical endpoints and tau progression were assessed. *Results:* The FDG, MRI, and combined FDG/MRI classifiers each produced a primary pattern of neurodegeneration that was increasingly expressed (reflected by increasing CV score) in mutation carriers from amyloid negative (A-) status through A+ symptomatic stages of disease. A- non-carriers remained stable in score throughout the pre- and post-

EYO timeframe. A+ mutation carriers began to differ crosssectionally from A- non-carriers in FDG CV score at 10 years pre-EYO (Fig. 1) and showed longitudinal increases in pattern expression as early as 13 years pre-EYO. MRI classification detected progression at approximately 5 years prior to symptom onset and also showed longitudinal progression. Regions common to both patterns included neurodegeneration in precuneus, posterior cingulate, hippocampus, and temporo-parietal cortices, and preservation in pre- and postcentral gyrus, brainstem, and cerebellum. Cognitive endpoints MMSE and CDR-sb showed steep rates of worsening coinciding approximately with the predicted EYO (based upon parental onset), and correlated with neurodegenerative pattern expression in Am+ mutation carriers (MMSE vs. FDG CV1: R-squared = 0.63). CSF Abeta and Tau values differed between all three amyloid PET strata, in that the Am- PET mutation carriers had lower, and decreasing, CSF Abeta42 levels, concomitant with greater, and increasing, levels of CSF tau, than Am- non-mutation carriers, tracking at approximately half the level of those in the Am+ category. The neurodegenerative imaging patterns showed progressive change in the Am+ PET group but were stable in the Am- PET carrier group. This was consistent with findings in late onset AD, where we have found primary progression patterns to associate with tau beyond Braak stages I-III, but change in medial temporal subregions associated with earlier stages. *Conclusions:* Image classifiers developed using machine learning can provide highly sensitive measures of disease progression in preclinical and prodromal AD as demonstrated in the DIAN data. Functional imaging using FDG PET shows the greatest sensitivity in early years while also tracking progression post-EYO, but structural measures are also sensitive. These initial results suggest that use of imaging biomarkers with multivariate classification analysis can aid in the detection of early disease progression, prediction of clinical trajectory and statistically powered detection of treatment effect upon pathology and neurodegeneration.

Figure 1

FDG classifier scores for Am- non-mutation carriers as compared to Am+ mutation carriers (cross sectional data, independent test subjects)



P51: COGNITIVE FUNCTION AND PREVALENCE OF AMYLOID PATHOLOGY IN FRAIL ADULTS - THE COGFRAIL STUDY. S. Sourdet, G. Soriano, Z. Steinmeyer, J. Delrieu, P.J. Ousset, B. Vellas *(Gérontopôle, Centre Hospitalier Universitaire de Toulouse, Toulouse, France)*

Background: A number of cross-sectional and longitudinal studies have demonstrated an association between physical frailty and cognitive impairment. Many mechanisms have been suggested to explain the presence of cognitive impairment in frail subjects, such as cardiovascular risk, hormonal disturbances, chronic inflammation or nutrition. Another hypothesis is that cognitive impairment in frail patient may be due to Alzheimer's disease (AD). Converging epidemiological studies have shown an association between frailty and incident clinical Alzheimer's disease (AD). Further supporting the link between frailty and AD, a recent neuropathological study found that physical frailty in the years immediately prior to death was associated with age-related neuropathology, including AD, in patients with and without dementia. However, the link between frailty and amyloid deposition has to date never been studied in vivo. Moreover, cognitive functioning is often not assessed in frail and pre-frail older individuals, likely hindering the early diagnosis of AD in frail and pre-frail subjects. Given the complex medical profile and poor physical functioning of frail and pre-frail patients, cognitive impairment goes often undetected in this population. We previously observed that among over 1000 individuals referred by their physician to the Toulouse Geriatric Frailty Clinic for a frailty assessment, 51.1% had MCI (CDR=0.5) and 14.9% had dementia according to the Clinical Dementia Rating (CDR) scale (CDR >=1). The current study seeks to examine the prevalence of amyloid pathology, among patients referred to the Toulouse Geriatric Frailty Clinic presenting an objective memory impairment. We also aim to fully characterize the clinical progression of frail cognitively impaired patients presenting AD pathology vs those who also present a cognitive impairment but do not have AD pathology. *Methods:* This is a 2 years longitudinal study recruiting 345 frail and pre-frail individuals, aged 70 years and older, and presenting an objective memory impairment (CDR=0.5 or CDR=1). Frailty is defined using Fried criteria. Participants who are robust (0 Fried criteria), dependant (ADL<4), with major deterioration in global cognitive function (MMSE<20), with severe visual or auditory difficulties (which may interfere with the completion of neuropsychological and functional assessments), or a severe clinical or psychological condition, will be excluded. The main objective of the study is to evaluate the prevalence of amyloid pathology as determined by Amyloid PET (Positron Emission Tomography) among participants. The evaluation of the amyloid load will be performed by visual analysis: this charge will be dichotomized as present (amyloid +), or absent (amyloid -). Secondary objectives are to compare the cognitive performance, neuropsychiatric profile, and physical function at baseline, 1 and 2 years, according to the amyloid status (amyloid + or amyloid -). Participants will be recruited at the Toulouse Frailty Clinic, France, and followed-up every 6 months (with cognitive, physical and nutritional evaluation), during 2 years. Amyloid PET will be performed within 2 months of inclusion. *Results:* Recruitment for the COGFRAIL study started January 2, 2017. Twenty four participants have been included by then. The amyloid PET was performed in 12 participants, and 2 subjects realised their first six-month follow-up visit. *Conclusion:* The results of the study will help characterize the cognitive decline in frail and pre-frail patients, with important implications for the detection, management and ultimately prevention of neurocognitive disorders among frail old individuals. This may in turn enable a more effective prevention of disability and dependence in the old population. If mechanistic frailty-cognitive decline links are established, these results may also help optimize the early identification of patients with or even at risk of AD-dementia by taking into account physical parameters that are not conventionally looked at in AD, such as frailty parameters (e.g. gait speed) or muscle composition. Such an outcome might also open a window to novel prevention and treatment strategies in AD. Finally, a high prevalence rate of amyloid deposition, in frail and pre-frail patients may reveal a novel target population for clinical trials in AD.

P52: HIPPOCAMPAL VOLUME IS WEAKLY ASSOCIATED WITH AMYLOID BETA LEVELS IN ASYMPTOMATIC INDIVIDUALS AT RISK FOR ALZHEIMER'S DISEASE: FINDINGS FROM THE CHARIOT-PRO SUB-STUDY. Derrek P. Hibar[1], Ziad Saad[1], Hartmuth Kolb[1], Gerald Novak[2], Nzeera Ketter[2], Nandini Raghavan[2], Chi Udeh-Momoh[3], Nina Mansoor[3], Michael Ropacki[4], Sherry Meeh[2], Robert Perneczky[3], Steve Einstein[2], Gary Romano[2], Lefkos Middleton[3] *((1) Janssen Neuroscience LLC, California, USA; (2) Janssen Neuroscience LLC, New Jersey, USA; (3) Neuroepidemiology and Ageing Research, Imperial College London, London, UK; (4) MedAvante Inc., New Jersey, USA)*

Background: The CHARIOT-PRO Sub-Study (CPSS) is an ongoing, longitudinal cohort study (LCS) of cognitively normal adults (aged 60-85 years) with a target enrollment of 500 subjects. Approximately 50% of enrolled subjects will have elevated amyloid beta levels (as measured by CSF assay and/or PET scan during a screening phase). Subjects ultimately enrolled in the study will be followed-up every 3 months for up to 3.5 years and receive comprehensive cognitive testing. A longitudinal study of patients with elevated amyloid beta levels without observed cognitive deficits can provide invaluable information about the early stages of Alzheimer's disease (AD). Amyloid beta is a key component of the pathophysiology of AD (Hardy and Selkoe, 2002) but the exact trajectory of the disease and the sequence of brain changes leading to a diagnosis are still poorly understood (Jack Jr. et al., 2010). Amyloid deposits are thought to precede hippocampal neurodegeneration and believed to be among the earliest detectable biomarkers of AD progression (Jack Jr. et al, 2013). This study tested the hypothesis that lower hippocampal volume would be associated with higher levels of amyloid beta in the brains of cognitively normal subjects. This was further tested using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI2GO; Weiner et al., 2015). *Methods:* To date, a total of 310 cognitively normal subjects (mean age 72.8 years; 144 males) have received high-resolution 3T MRI and combined CT/PET scans with one of three amyloid PET tracers (florbetapir, florbetaben, flutemetamol) as part of the CPSS screening. Each attenuation-corrected PET image was rigid-body registered to its corresponding MRI scan in native-space. Cortical regions of interest (including hippocampal volume) were defined using the FreeSurfer image processing pipeline (v5.3). Amyloid load was estimated from a composite of average tracer uptake (SUVR) from frontal, temporal, parietal, anterior cingulate, posterior cingulate and precuneus cortical regions using whole cerebellum as an uptake reference region (Landau et al., 2013). Composite SUVR and hippocampal volumes from 218 cognitively normal subjects (mean age 72.8 years; 101 males) from the ADNI2GO study were also estimated using similar processing procedures. We tested the association between amyloid load and hippocampal volume using multiple linear regression with covariates for age, sex, intracranial volume (ICV), and a 3-level factor for tracer type. The latter covariate was not used with ADNI2GO replication tests as only one tracer was used. Tests of association were performed for left and right hippocampal volume separately. All P-values presented are for two-sided tests and are reported uncorrected for multiple comparisons. Nominal significance was set at $P \leq 0.05$ and significance at Bonferroni FWER of 5% (Psign $\leq 0.05/2$ or 0.025 to account for left and right hippocampus comparisons). *Results:* We found evidence of a weak, nominally significant negative association between right hippocampal volume and amyloid load in CPSS (partial Pearson's rpartial=-0.116; P=0.0432) but not in the left hippocampus (rpartial=-0.0812; P=0.156). In ADNI2GO, the negative association was highly significant (P<1x10-11) for both hemispheres when subjects of all cognitive levels (normal, MCI, and AD) were included. However negative associations were no longer significant when the analysis was restricted to cognitively normal subjects (left hippocampus rpartial=-0.0582; P=0.396 and right rpartial=-0.0748; P=0.275) [Figure 1-A]. Negative associations were also not significant when analysis was restricted to subjects with elevated amyloid beta levels (SUVR > 1.1) in both CPSS and ADNI2GO subjects [Figure 1-B]. Age and ICV covariates were significant in all models. No interactions were significant between tracer and amyloid load. *Discussion:* Based on these current findings, negative associations between hippocampal volume and level of amyloid beta deposits in the brain is weak at best in cognitively normal populations. In the CPSS LCS, only the right hippocampus volume showed nominally significant evidence of a negative association with amyloid beta levels. There were no significant associations in the ADNI2GO dataset for cognitively normal subjects. We also investigated whether an association of hippocampal volume with SUVR was present for subjects with elevated amyloid levels. However, when restricting our analyses to subjects with SUVR > 1.1, negative associations did not reach significance for either study. Analysis of the ADNI2GO study indicates that associations between hippocampal volume and level of amyloid beta become significant in MCI and AD stages. References: Weiner, Michael W., et al. Alzheimer's & Dementia 11.7 (2015): 865-884. Hardy J, Selkoe DJ. Science. 2002; 297:353–356. Jack Jr, Clifford R., et al. Lancet Neurology 12.2 (2013): 207. Jack Jr, Clifford R., et al. Lancet Neurology 9.1 (2010): 119-128. Landau, Susan M., et al. Journal of Nuclear Medicine 54.1 (2013): 70-77.

Figure 1-A

Relationship between amyloid beta levels (SUVr) and hippocampal volume in the ADNI2GO healthy control population. Neither left nor right hippocampal volume showed evidence of association with amyloid beta levels. Data from CPSS are not shown in order to maintain blinding in the ongoing study

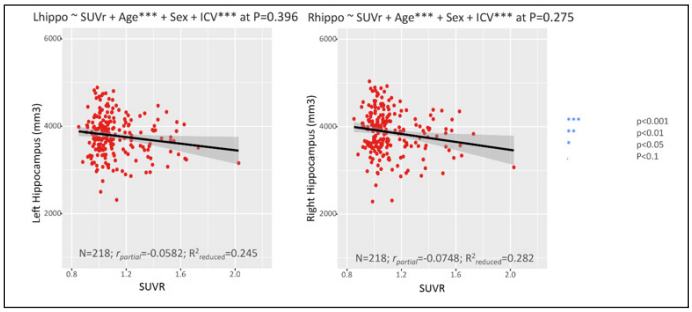


Figure 1-B

Summary of association tests between hippocampal volume and amyloid beta levels in cognitively normal subjects (CDR=0) and cognitively normal subjetcs with high amyloid levels (SUVR > 1.1) in CPSS and ADNI2GO

	CPSS	ADNI2GO
Cognitively Normal (CDR=0)	Left: $r_{partial}$=-0.0812; P=0.156; N=310 Right: $r_{partial}$ = -0.116 P=0.0432; N=310	Left: $r_{partial}$=-0.0582; P=0.396; N=218 Right: $r_{partial}$=-0.0748; P=0.275; N=218
Cog. Normal+High SUVR (>1.1)	Left: $r_{partial}$=-0.145; P=0.149; N=112 Right: $r_{partial}$=-0.177; P=0.0714; N=112	Left: $r_{partial}$=-0.120; P=0.307; N=77 Right: $r_{partial}$=-0.0828; P=0.483; N=77

P53: IMPACT ON SAMPLE SIZE AND SCREENING USING AMYLOID VISUAL READ VERSUS QUANTITATIVE VALUES FOR INCLUSION. Donald G. McLaren[1], Felix Carbonell[1], Alex P. Zijdenbos[1], Barry J. Bedell[1,2] *((1) Biospective Inc., Montreal, Quebec, Canada; (2) McGill University, Montreal, Quebec, Canada)*

Background: It is well-known that anti-amyloid therapeutics will only benefit individuals harboring β-amyloid. As a result, anti-

amyloid therapeutic intervention trials typically only enroll amyloid-positive subjects based on the visual read of amyloid PET scans. However, this strategy limits the potential pool of patients who could be prescribed a successful therapeutic and increases the number of patients needing to be screened for clinical trial enrollment. Furthermore, visual reads may not identify the optimal study population for all clinical trial endpoints. In the present study, we determined the optimal proportion of individuals that should enrolled in a study to minimize the sample size per arm needed to detect a halt of regional amyloid standard uptake value ratio (SUVR) change. The optimal proportion and sample size per arm were compared against inclusion based on an amyloid positive visual read. *Methods:* We analyzed repeated amyloid PET scans from 142 cognitively normal (CN) subjects, 116 early MCI (eMCI) patients, and 115 late MCI (lMCI) patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. [18F]Florbetapir PET and 3D T1-weighted MRI scans were processed through Biospective's PIANO™ pipeline. SUVR values were calculated using the whole cerebellum as a reference region. Longitudinal change in amyloid burden was computed for the Frontal Cortex, Default Mode Network (DMN), Anterior Cingulate Cortex, a standard amyloid cortical composite region, the Striatum, and our previously defined Statistical ROI (statROI) that maximally separates individuals into low and high amyloid burden[1]. Using multiple amyloid SUVR cut-points, individuals were repeatedly separated into low and high amyloid burdens. For each cut-point, the longitudinal change and effect sizes were computed in for high amyloid burden individuals. We report the proportion of high amyloid individuals, the longitudinal SUVR change, and the sample size per arm needed to detect a halting of amyloid accumulation (e.g. to detect a significant effect at 80% power assuming the placebo group is similar to ADNI and the drug group has no increase in amyloid burden) in a 104-week study period based on the optimal quantitative cut-point. The proportions and sample size estimates are compared to those achieved based on visual reads. *Results:* We found that 19% of CN individuals, 38% of eMCI patients, and 59% of lMCI patients in our samples were amyloid positive based on visual reads. The annual SUVR changes (± s.d.) in amyloid positive individuals for the statROI were 0.0772±0.1379, 0.0374±0.1305, and 0.0015±0.1293 for each group, respectively. The corresponding sample sizes per arm needed to detect a halt of amyloid accumulation are 52, 193, and >10,000 for each group, respectively. Results when using quantitative SUVR cut-points are illustrated using the statROI. 53% of CN individuals, 70% of eMCI patients, and 69% of lMCI patients were classified as having high amyloid based on their SUVR in the statROI. The annual SUVR changes (±s.d.) in high amyloid individuals for the statROI were 0.0487±0.1032, 0.0308±0.1095, and 0.0129±0.1322 for each group, respectively. The corresponding sample sizes per arm needed to detect a halt of amyloid accumulation are 72, 200, and 1,650 for each group, respectively. *Conclusions:* Several conclusions can be drawn from the present analysis. First, there is a trade-off between percentage of individuals that would pass amyloid screening and sample size estimates for clinical trials. In all three groups, the number of people enrolled in a study using the optimal quantitative cut-point increased. In CN and eMCI subjects, the sample size estimates marginally increased (72 vs 52 in CN; 200 vs 193 in eMCI). The increase in sample size estimates was less when using the optimal DMN for the cut-point and amyloid change in the statROI as the end point in CN (56 vs 52) and eliminated in eMCI (183 vs 193). In lMCI, where the rate of amyloid accumulation slows in amyloid positive subjects, the sample size estimates are smaller with the optimal quantitative SUVR cut-point. Overall, these results indicate that quantitative SUVR cut-points are beneficial for clinical trial enrollment and amyloid change clinical trial end points. The other ROIs tested generally showed similar behavior, but further work is needed to identify the optimal ROI for inclusion and the optimal ROI to be used as an end point. Second, the number of subjects needing to be screened dramatically decreases. As an example, 136 CN individuals would need to be screened to find 72 individuals that are above the quantitative statROI cut-point; whereas 273 CN individuals would need to be screened to find 52 that were amyloid positive. Third, the results also indicate that for trials with impaired populations (e.g. lMCI), the therapeutic would need to do more than halt (i.e. must reduce) amyloid accumulation to show a significant effect with reasonable sample sizes. Finally, this approach could be utilized to determine the quantitative amyloid cut-points for any clinical trial endpoint (e.g. CDR Sum-of-Boxes).

References: [1]Carbonell et al. J. Nucl. Med., 56:1351-1358, 2015.

P54: AUTOMATED VOXEL-BASED TAU PET QUANTITATION IN EARLY ALZHEIMER'S DISEASE: ASSOCIATION OF HIPPOCAMPUS MASKED SUVR WITH BASELINE COGNITION.

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Background: There is considerable interest in novel approaches that accurately reflect disease activity at the earliest stage and location of neurodegeneration, and that correspond well to clinical outcome, with a particular goal of predicting and measuring response to tau-directed therapies in early Alzheimer's disease (AD). Initial attempts to derive such measures using fixed anatomical or composite regions of interest and/or z-score based approaches have so far been met with mixed success, and/or are hampered by the additional need to incorporate prior knowledge of Amyloid positivity status. Pontecorvo et al. (Brain 2017) reported promising results in a [18F]Flortaucipir PET cohort analysis. Of note, SUVR calculated from subsections of the hippocampus appear more useful for group discrimination than a composite neocortical SUVR. We have previously developed a fully automated PET quantitation method for calculating voxel-based-SUVR using PET in conjunction with MRI, for improved localization of deposition, and enhanced performance for identifying subjects with early disease (Mikhno et al., AAIC 2015; HAI 2016). The aim of our present study was to investigate the association of voxel-based (hippocampus-masked) Tau quantitation with baseline memory, and its ability to differentiate MCI non-converter subjects from early AD subjects. *Methods:* Thirty subjects with MCI or AD were included from the ADNI cohort and divided into two groups: 18 MCI non-converters (4-5 years of MCI follow-up) and 12 predominantly early AD subjects (Tau scan acquired before, or within one year of conversion event in 8/12 subjects; we also included 4 subjects with moderate AD due to limited data at time of abstract submission). Their corresponding [18F]Flortaucipir PET, T1 MRI scans, and MMSE scores (at the time of PET) were also obtained. A hippocampus mask was derived from the T1 MRI using fast (GPU-accelerated) hippocampus segmentation, as previously described (Mikhno et al., HAI 2016) and validated against the EADC/ADNI harmonized protocol (HarP). Voxel-wise SUVR maps (75-105 min, cerebellum reference) were partial volume corrected and transformed into MNI space. Optimal voxels within the hippocampus that discriminated non-converter and early AD groups were determined based on a voxel-wise t-score cluster analysis. Voxel-based-SUVRs were obtained from the hippocampus voxels for each subject in a leave-one-out analysis. Association between the hippocampus voxel-based- SUVR and MMSE was assessed with Pearson's correlation. *Results:* Receiver operating characteristic area under the curve (AUC) for group

separation was 0.79 (two-tailed t-test for group differences: p=0.013). Voxel-based-SUVR was strongly correlated with baseline MMSE ($r = -0.60$, $p < 0.001$). *Conclusion:* Preliminary results demonstrate that voxel-based-SUVR separates groups independent of prior knowledge of Amyloid positivity status, and more importantly, showed a stronger correlation with baseline MMSE than reported to date by other investigators, as it relates to either Tau PET quantitation, or Amyloid PET quantitation. Use of an integrated quantitative measure may have potentially important applications in disease understanding and trial enrichment, or prediction and monitoring of tau-directed treatment response.

P55: INTER AND INTRA PET SCANNER VARIABILITY IN MULTI-CENTER CLINICAL TRIALS USING THE HOFFMAN PHANTOM. Katarzyna Adamczuk[1], Beth Gorman[2], Maureen Runkle[2], Nicolas Pannetier[1], David Scott[1], Joyce Suhy[1] *((1) Bioclinica, Newark, CA, USA; (2) Bioclinica, Philadelphia, PA, USA)*

Background: The majority of Alzheimer's disease clinical trials last between two to six years. During this time, participating imaging facilities may experience minor to major changes, including scanner upgrades, software updates or hardware replacements. Changes to the equipment affect the stability of quantitative measurement. Specifically, these changes can bias longitudinal studies when the effect on quantitative measurement is similar in magnitude to the effect of prospective therapy. It is therefore recommended to perform longitudinal studies on the same scanner with minimal expected changes throughout the entire study period. The main objective of this work is to measure scanner performance using the Hoffman phantom and to estimate inter and intra PET scanner variability. *Methods:* Hoffman phantom scans were acquired on several different models for each of three vendors to give a flavor of current scanner/model variability. Each vendor group consisted of two scanners of the same model at different locations and three other scanner models. Models were ranked from oldest to newest and most sophisticated. Models were matched within vendor for attenuation, scatter and random corrections, dynamic acquisition and iterative reconstruction. Variance was estimated at three levels: intra model, inter models, and between vendors. Hoffman phantoms were prepared by thoroughly mixing 0.5-0.6 mCi 18F-FDG solution in the phantom, and imaging immediately using the same 4 x 5 min acquisition. For phantom analysis, a 20 min portion of the scan was averaged and co-registered to the digital gold standard. Because the physical Hoffman phantom slice thickness is slightly variable, a scaling term was used in the co-registration process. Once co-registered, effective spatial resolution was determined by fitting in-plane and axial Gaussian smoothing parameters to best match the digital model to the test phantom data [1]. Intensity of the test data was normalized to the gold standard using a volume of interest specified in regions of pure grey matter, which represent the highest signal intensity in the phantom. Once co-registered, smoothed and intensity normalized, a difference image was computed. Additionally, standard uptake value ratios (SUVR) were computed and compared for the digital and test datasets using a modified AAL atlas to define regions in the frontal, temporal, cingulate, occipital, parietal, and precuneus areas, normalized to whole cerebellum. The difference image and normalized Hoffman data allow computation of visual and quantitative metrics such as scanner spatial resolution, axial uniformity, grey to white matter contrast and accuracy of SUVR calculations. *Results:* Scanner resolution differed within and between models. Axial resolution improved along with newer version of scanner model, more substantially in vendor 2 and 3, and subtly in vendor 1. In plane resolution also improved along with newer version of scanner model, more substantial improvement was observed for vendor 2 and subtle improvement for vendor 1 and 3. SUVR values differed between models of all three vendors. Intra model SUVR were largest in vendor 3, moderate in vendor 2, and minimal in vendor 1. All three vendors showed similar pattern of uptake with lowest SUVR in parietal and highest in cingulate cortex. Ranges of SUVR values were 0.85-0.92 for vendor 1, 0.87-0.90 for vendor 2, and 0.74-0.84 for vendor 3. No intra or inter differences were observed in models for vendor 1 and 2 in the ratio between intensity of grey matter in test image compared to that in the smoothed reference image (all within 10% variation from the reference image); for vendor 3, differences were observed between one of the models and three others. The white matter ratio of intensity between test and reference image showed higher variance throughout all slices; no inter or intra differences were observed in models of vendor 1; higher variance in white mater ratios was observed in newer model of vendor 2 compared to older models, likely reflecting higher sensitivity; differences were detected inter models of vendor 3 but not intra model. Three out of five models of vendor 1 showed similar magnitude in the absolute difference between intensity of grey and white matter in test image compared to this in the smoothed reference image; vendor 2 consistently across models had higher absolute difference in grey matter than in white matter, more so in two models than in other three; vendor 3 as well had higher absolute difference in grey matter compared with white matter in all models except for one. *Conclusion:* Results indicate that even within the same scanner model some differences can be expected. Care must be taken when considering potential scanner change and compatibility of both scanner should be carefully analyzed. References: 1. Joshi A, et al. Reducing between scanner differences in multi-center PET studies. Neuroimage 2009;46:154–9

Theme: Clinical trials : biomarkers including plasma

P56: DEVELOPMENT OF COMPUTATIONAL TOOLS TO IMPROVE THE DESIGN OF CLINICAL TRIALS OF POSSIBLE THERAPIES FOR ALZHEIMER'S DISEASE. Christoforos Hadjichrysanthou[1], Alison Ower[1], Stephanie Evans[1], Kevin McRae-McKee[1], Mei Mei Wong[1], Frank de Wolf[1,2], Roy M. Anderson[1] *((1) Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London, London, United Kingdom; (2) Janssen Prevention Center, Leiden, The Netherlands)*

Background: Drugs are urgently needed for the treatment of Alzheimer's disease (AD). Over 98 percent of clinical trials of AD drug candidates have failed or been discontinued. This failure rate of AD clinical trials is far higher than that of trials in other therapy areas, and information on the reasons of trial failure or discontinuation is limited. Mathematical, computational and statistical tools can be employed to investigate why AD clinical trials fail, to improve the design of trials of potential treatments and to enhance the chances of success. *Methods:* Based on the analysis of a number of longitudinal observational studies, including ADNI and NACC, we developed a stochastic mathematical model to predict the development and progression of AD. In particular, we developed a Markov model to describe the movement of individuals through a finite sequence of distinct health and disease states over time. Using mathematical and statistical techniques we estimated covariate effects of various risk factors and investigated several measurable surrogate markers, focusing on the construction of the trajectories of Aβ1-42 in CSF, t-tau in CSF, MMSE score, ADAS-Cog score, and Hippocampal Volume, as well as the correlation between these markers. We used this modelling framework to simulate hypothetical AD clinical

trials and assess the effect of candidate treatments when they are administered at different stages of disease development. *Results:* We developed a clinical trial simulation tool that can predict the results in the actual AD clinical trial and facilitate the evaluation of potential treatments against Alzheimer's disease. The output of simulations suggests that a high variance in any given measurement might be the dominant cause of trial failure. The detection of the true efficacy of a treatment given at a late stage of disease can be more challenging, even if the treatment has high efficacy. Developing the trajectories of biochemical (CSF Aβ1-42 and t-tau), neuro-psychological (MMSE and ADAS-Cog) and MRI (Hippocampal Volume) markers, we also showed that the incubation period of Alzheimer's disease is likely to be up to 25 years. These results can facilitate the detection of early stages of AD development, before the occurrence of any symptoms, and thus enable a better choice of the sample of patients that should participate in a clinical trial. *Conclusions:* Mathematical modelling of AD progression and the development of clinical trial simulations are essential tools for exploring the reasons why a clinical trial can fail and for the improvement of the design of expensive clinical trials. The high variance in the measurement of diagnostic markers may be one of the most important reasons for the high failure rate of clinical trials of potential treatments against AD. The development of sensitive clinical assessment tools and the reduction of the variance of currently employed measures will thus improve trial design, facilitate detecting a signal in the trial, shorten the trial times for detecting an effect and reduce the number of patients enrolled. In addition, the long incubation period of AD and the inefficiency of treatments of high efficacy when they are administered at late stages of the disease demonstrate the need of accurate identification of measurable surrogate markers to detect earlier stages of AD development and the administration of treatments early on in the disease development, even at the asymptomatic stage.

P57: PIB-PET AS A STANDARD FOR EVALUATING THE CLINICAL ACCURACY OF DIAGNOSING THE CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE WITH PLASMA BIOMARKERS. Che-Chuan Yang[1], Ming-Jang Chiu[2], Ta-Fu Chen[2], Shieh-Yueh Yang[1] *((1) MagQu Co., Ltd., New Taipei City 231, Taiwan; (2) Department of Neurology, National Taiwan University of Hospital, College of Medicine, National Taiwan University, Taipei 100, Taiwan)*

Backgrounds: Recent advances in quantifying plasma beta-amyloid (Aβ) and total tau protein (T-Tau) with immunomagnetic reduction (IMR) technology provided the possibility of an early or preclinical diagnosis of Alzheimer's disease. Latest findings of two parameters, plasma Aβ1-42/Aβ1-40 and Aβ1-42xT-Tau, showed a high accuracy (>80%) for a clinical diagnosis of AD according to NIA-AA 2011 criteria and guidelines. Amyloid PET imaging is also a biomarker-based tool, which is widely used for early and preclinical diagnosis. But little evidence is available to underline a correlation between plasma biomarkers and amyloid PET imaging. *Methods:* 19 elderly control participants, 16 participants with MCI due to AD, and 19 AD patients, were diagnosed according to NIA-AA 2011 guidelines and enrolled for measuring plasma Aβ1-40, Aβ1-42 and T-Tau proteins. All participants received 11C-labeled Pittsburgh compound B PET (PiB-PET) scans. A cutoff value to define PET-positive or PET-negative group was determined by conducting a binary analysis of total standard uptake value ratios (SUVR-total) in the frontal, parietal, temporal lobes, ACC and the precuneus. The cut-off value for differentiating PET-positive from PET-negative in terms of SUVR-total was set at 7.0. *Results:* By using the SUVR-total value of 7.0 as a diagnostic standard, 94.7% of older controls turned out to be PET-negative, 56.3% of 16 subjects with MCI due to AD were PET-positive, and 84.2% of AD patients were PET-positive. Through ROC-curve analysis, the cut-off value of plasma Aβ1-42/Aβ1-40 ratio to discriminate PET-positive from PET-negative subjects was found to be 0.370, corresponding to 80.8% and 78.4 % for sensitivity and specificity respectively. The area under curve was 0.868. *Conclusion:* We demonstrated plasma biomarkers show high correlation with amyloyd PET (PiB-PET) image in this study when diagnosing Alzheimer's disease. The accuracy is over 80% by using plasma Ab1-42/Ab1-40 ratio as a parameter against amyloid PET diagnosis. Plasma biomarkers is promising to be the first step in a multiple process to screen preclinical AD instead of CSF biomarkers.

P58: A CROSS-VALIDATION STUDY ON PLASMA BIOMARKER DETECTION IN CLINICAL PRACTICE FOR DIAGNOSING ALZHEIMER'S DISEASE. Ming-Jang Chiu[1], Ta-Fu Chen[1], Chaur-Jong Hu[2], Sui-Hing Yan[3], Yu Sun[4], Bing-Hsien Liu[5], Yun-Tsui Chang[5], Che-Chuan Yang[5], Shieh-Yueh Yang[5] *((1) Department of Neurology, National Taiwan University of Hospital, College of Medicine, National Taiwan University, Taipei 100, Taiwan; (2) Department of Neurology, Taipei Medical University Shuang-Ho Hospital, New Taipei City 235, Taiwan; (3) Department of Neurology, Renai Branch, Taipei City Hospital, Taipei 106, Taiwan; (4) Department of Neurology, En Chu Kong Hospital, New Taipei City 237, Taiwan; (5) MagQu Co., Ltd., New Taipei City 231, Taiwan)*

Background: In order to verify the assay of plasma -amyloid (A) and tau protein for diagnosing Alzheimer's disease (AD), a cross-sectional study of recruiting two independent cohorts was conductted. *Method:* The first cohort (or referred to as the original cohort), included 96 healthy controls, 24 patients with mild cognitive impairment (MCI) due to AD, and 60 AD patients, was enrolled. The clinical diagnosis of each subject was based on the 2011 NIA-AA guidelines, along with a blind assay of plasma A and tau protein using immunomagnetic reduction. We discriminated healthy controls and patients through ROC analysis, cut-off values, sensitivities, specificities, and area under the curve (AUC) in terms of these plasma biomarkers. To validate the use of these plasma biomarkers in diagnosing AD, the second cohort (or referred to as the validation cohort) included 134 healthy controls, 34 patients with MCI due to AD, and 74 AD patients, was recruited at four hospitals. All subjects had a clinical diagnosis according to 2011 NIA-AA guidelines, and were assayed blindly for plasma A and tau protein. By applying biomarkers cut-off values from the original cohort to the validation cohort, the positive percent agreement, negative percent agreement, and overall percent agreement (or accuracy) for discriminating healthy controls form MCI-due-to-AD patients, or differentiating MCI-due-to AD patients from AD patients were refined. *Results:* It was found that the concentration product of A1-42 and tau protein in plasma, which cut-off value was 455.49 (pg/ml)2, showed the highest accuracy (> 80%) to discriminate healthy controls from MCI due to AD. Moreover, by applying the cut-off value 642.58 (pg/ml)2 with the concentration product of A1-42 and tau protein in plasma to differentiate MCI due to AD from AD, the accuracy was also higher than 80%. *Conclusion:* These results underline the high correlation between plasma biomarker assay and clinical diagnosis according to 2011 NIA-AA guidelines. Instead of using individual biomarkers, the concentration product of A1-42 and tau protein in plasma would be highly relevant and a highly-accurate (>80%) parameter for diagnosing AD in routine clinical practice.

P59: BRAIN ABCA-1 ACTIVITY AND APOE LIPIDATION ARE REDUCED IN APOE4 AND WITH COGNITIVE IMPAIRMENT. H.N. Yassine[1], V. Rawati[1], A. Boehm-Cagan[2], A. N. Fonteh[3], J. Johansson[4], J. Bielicki[5], H. C. Chui, D. M. MichaelsonI[6], M. G. Harrington[3] *((1) USC, Los Angeles, CA; (2) Tel Aviv Univ., Herzilya, Israel; (3) Huntington Med. Res. Inst., Pasadena, CA; (4) Artery Therapeut., San Ramon, CA; (5) UC Berkeley, Berkley, CA; (6) Tel-Aviv Univ., Tel-Aviv, Israel)*

Introduction: ApoE4 genotype is the strongest genetic risk factor for developing Alzheimer's disease (AD). *Objectives:* Our objective is to demonstrate that importance of brain ABCA-1 activity and ApoE hypolipidation as a mechanistic biomarker for AD. Complementary rodent and human studies were employed to assess the role of ApoE lipidation and ABCA-1 activity in AD pathology. *Discussion:* First, a cohort of 4-months old female mice (n=6-8 per group, ApoE4 vs ApoE3 TR mice) was treated with either PBS or CS-6253 (20mg/kg/48h) for 6 weeks. Treatment was associated with an increase in percentage of larger brain ApoE4 particles, decrease in intraneuronal Abeta and tau, enhanced synaptic functions (VGLUT1), and improved cognition. Second, cerebrospinal fluid (CSF) samples from 59 older individuals with and without cognitive impairment were analyzed for ApoE particle size using native PAGE. ABCA-1 function of CSF was assessed using ABCA-1 mediated cholesterol efflux capacity assay. Lipidation profile of ApoE and ABCA-1 cholesterol efflux capacity were assessed before and after treatment with the ABCA-1 agonist CS-6253 ex vivo. CSF ApoE was resolved in four distinct bands by electrophoresis α0 (>669 KDa), α1 (600 KDa), α2 (440 KDa) and α3 (232-140 KDa). CSF from ApoE4/4 individuals (n=4) had reduced capacity to induce cholesterol efflux compared to CSF from ApoE3/3 individuals (n=31). CS-6253 was able to increase ABCA-1 mediated cholesterol efflux capacity of CSF from both ApoE3/3 and ApoE4/4 individuals ($p<0.01$). However, the increase in ABCA-1 activity was less in ApoE4/4 compared with ApoE3/3 containing CSF (31.45% vs 68.03%, n=3, $p<0.005$). The relative ratio of α0 and α1 (larger) ApoE bands in CSF were significantly lower in ApoE3/4 (n=25, $p<0.05$), and ApoE4/4 (n=4, $P<0.001$) compared to ApoE3/3 (n=29). ApoE lipidation and ABCA-1 activity were reduced in CSF of cognitively impaired individuals compared with cognitively normal participants. *Conclusions:* Compared with ApoE3, brain ApoE4 in mice and CSF ApoE4 in humans demonstrate lower ABCA-1 activity and smaller ApoE particles suggesting hypolipidation of ApoE4. The lower ABCA-1 and ApoE hypolipidation are mechanistic biomarkers associated with ApoE4 and cognitive impairment. Inducing brain ABCA-1 activity is viable target for drug development in AD.

P60: ANALYSIS OF MACULAR THICKNESS AND RETINAL NERVE FIBER LAYER BY USING OF SPECTRUM DOMAIN-OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS WITH ALZHEIMER'S DISEASE AND AMNESTIC MILD COGNITIVE IMPAIRMENT, Kyung-Hoon Shin[1], Do-Gyun Kim[2], Bon D Ku[3] *((1) Department of Ophthalmology, Kim's Eye's Hospital, Konyang University, South Korea; (2) Department of Ophthalmology, Myongji Hospital, Seonam University College of Medicine, South Korea; (3) Department of Neurology, International St. Mary's Hospital Institute for Translational & Clinical Research College of Medicine Catholic Kwandong University, South Korea)*

Background: Spectrum Domain-Optical Coherence Tomography (SD-OCT) is a non-invasive technology that acquires cross-sectional images of retinal structures allowing neural fundus integrity assessment. Moreover, recent advances in OCT technology, have allowed sectional evaluation of the macula, enabling the assessment not only of whole retinal measurements but also divided sectional retinal assessment. Macular thickness and retinal nerve fiber layer (RNFL) thickness measured by an SD-OCT have been used as a indicator of Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI). However which portion of retinal RNFL is the most sensitive area among normal control, aMCI and AD is not clear yet. The purpose of this study is to demonstrate that RNFL thickness is a useful indicator and which portion of reninal RNFL is the most sensitive area among normal control. *Methods:* In a cross-sectional study we consecutively recruited 53 patients with AD, 58 with aMCI, and 54 normal controls. AD-OCT was performed in all of them to measure circumpapillary macular thickness in the 9 sectors (fovea, temporal outer superior outer, nasal outer, inferior outer, temporal inner, superior inner, nasal inner, inferior inner). We made 4 RNFL quadrant area as following: superior (superior outer+superior inner), inferior (inferior outer+ inferior inner), nasal (nasal outer + nasal inner), temporal (temporal outer + temporal inner). We also evaluated the correlation of the RNFL thickness and MMSE score and disease duration of the patients. *Results:* Average macular thickness and 9 sectors of RFNL thickness were not significant among the group in our patients. In quadrant analysis, however superior quadrant RNFL thickness showed significant differences among groups(109.98±12.01 um, 106.83±10.05 um 101.25±11.90 um in normal control, aMCI and AD respectively, $p<0.01$). The RNFL thinning of the superior quadrant showed a significant correlation with MMSE score($r=0.555$, $p<0.01$) and AD duration($r=-0.528$, $p<0.01$). *Conclusion:* The superior quadrant RNFL thickness is the most sensitive among the group and as well as we know this is not reported before. This finding could suggest superior quadrant retinal RNFL by SD-OCT could be a useful marker of AD and a MCI for early detection and monitoring of disease progression. Also distinct correlation of RNFL thinning in superior quadrant and MMSE score and disease duration can imply that the severity of dementia can be inferred from RNFL thickness in superior quadrant.

P61: LEVELS OF CEREBROSPINAL FLUID BIOMARKERS TOTAL TAU AND PHOSPHORYLATED TAU DO NOT PREDICT SURVIVAL TIME AFTER DIAGNOSIS OF ALZHEIMER'S DISEASE – AN 18-YEAR FOLLOW-UP. Carina Wattmo[1], Kaj Blennow[2], Lennart Minthon[1], Oskar Hansson[1] *((1) Clinical Memory Research Unit, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden; (2) Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy, University of Gothenburg, Mölndal, Sweden)*

Background: The pathological process in Alzheimer's disease (AD) probably starts decades before the onset of symptoms and the clinical AD diagnosis. In patients with AD, the level of cerebrospinal fluid (CSF) amyloid-β1-42 (Aβ42) is usually lower, and the levels of total tau (T-tau) and phosphorylated tau (P-tau) higher than in healthy elderly people. However, the cutoffs differ between studies and the predictive values are too low to diagnose AD using only CSF biomarkers. Several previous reports have shown that the levels of T-tau and P-tau become pathological later in the course of AD compared with Aβ42, yet it is unclear if higher levels of tau shorten the individuals' life expectancy after diagnosis. The current study aims to investigate whether pathological levels of T-tau and/or P-tau can predict survival in AD. *Methods:* The Swedish Alzheimer Treatment Study (SATS) is a prospective, observational, multicenter study for the longitudinal assessment of cholinesterase inhibitor treatment in a routine clinical setting. This presentation includes all 151 participants clinically diagnosed with AD, who underwent a lumbar puncture.

Patients were evaluated regarding cognitive and functional abilities at baseline (time of diagnosis) and semi-annually over 3 years. Socio-demographic characteristics, concomitant medications and the date of death were recorded. CSF was collected in polypropylene tubes, stored at –80 °C and analyzed after the clinical follow-up of the study was completed. The levels of T-tau, P-tau phosphorylated at Thr181 and Aβ42 were determined using xMAP technology. Pathological levels of CSF biomarkers were defined as: T-tau >100 ng/ml, P-tau >51 ng/ml and Aβ42 <209 ng/ml. Cox proportional hazards regression was used to determine the patient characteristics that affected mortality. Potential predictors were investigated, including sex, age at baseline, apolipoprotein E (APOE) ε4 carrier status, years of education, the clinician's estimated duration of AD, cognitive and functional abilities at baseline, the number of concomitant medications, and levels of CSF biomarkers. *Results:* The number and frequency of SATS participants with pathological CSF biomarkers were: T-tau, n=18 (12%); P-tau, n=14 (9%); and both T-tau and P-tau, n=46 (31%). All 151 individuals had pathological Aβ42. The group with normal T-tau and P-tau (n=73, 48%) had a higher education level, mean (95% confidence interval [CI]) 10.2 (9.5–10.8) vs. 9.1 (8.7–9.6) years, p=0.013; better cognitive ability at baseline, Mini-Mental State Examination, 22.8 (21.9–23.8) vs. 20.6 (19.5–21.6) points, p=0.002; and higher level of Aβ42 124 (118–129) vs. 117 (113–120) ng/ml, p=0.034, compared to patients with pathological T-tau and/or P-tau. No difference between the two groups was detected regarding the other aforementioned characteristics. After 18 years of follow-up, 139 of the 151 participants (92%) had died; their mean (95% CI) lifespan after diagnosis was 6.7 (6.2–7.3) years. No linear associations were found between survival time and Aβ42 (r = –0.005, p=0.957), T-tau (r = –0.127, p=0.135), or P-tau (r = –0.020, p=0.816). In a Kaplan–Meier analysis with pairwise Log-rank tests, the individuals with normal tau levels showed a longer life expectancy than those with pathological T-tau (p=0.044) and P-tau (p=0.025), but not if both tau biomarkers were pathological (p=0.439). However, using a one-way analysis of variance (ANOVA), the mean lifespan did not differ among the four groups: normal T-tau and P-tau, 7.0 (6.1–7.9) years; pathological T-tau, 5.6 (4.5–6.7) years; pathological P-tau, 5.9 (4.4–7.4) years; and both pathological T-tau and P-tau, 7.1 (6.1–8.1) years, p=0.276. The interaction effect of normal/pathological levels of tau with presence/absence of the APOE ε4 allele did not affect the participants' survival time in a Kaplan–Meier analysis, p=0.100, or in an ANOVA, p=0.451. In addition, no significant linear relationships were observed between life expectancy after AD diagnosis and any of the CSF biomarkers in the APOE ε4 non-carrier or in the ε4 carrier groups. Patients with the highest quartile and quintile of T-tau (≥126 and ≥129 ng/ml) and P-tau (≥65 and ≥70 ng/ml), respectively, were also examined; their lifespan did not differ from the other individuals. The actual continuous values of the CSF biomarkers or dichotomously coded normal/pathological, respectively, were not significant in Cox regression models adjusted for the above-mentioned predictors. *Conclusion:* Mortality in AD is complex and depends on many factors e.g., demographic and clinical. In this clinical-practice-based long-term study, almost half of the participants with AD had normal levels of tau. We found no clear results that the levels of T-tau and/or P-tau affect survival after diagnosis in AD. This observation does not support the theory that these patients have a more advanced disease. However, the individuals with pathological levels of tau had fewer years of education and worse cognitive status indicating a lower cognitive reserve capacity, which might influence life expectancy. These findings might be useful when considering new diagnostic criteria and when interpreting outcomes from future clinical trials of potentially disease-modifying AD therapies.

P62: AN AMYLOID BLOOD BIOMARKER FOR PRECLINICAL ALZHEIMER'S DISEASE. Klaus Gerwert, Andreas Nabers, Julia Lange, Jonas Schartner, Jörn Güldenhaupt *(Department of Biophysics, Ruhr-University Bochum, Germany)*

Background: Today, clinical diagnosis of Alzheimer's disease (AD) occurs too late when brain damage is already irreversible. However, emerging evidence suggests that AD could be treated in its preclinical stages. Therefore, a reliable, non-invasive blood based biomarker for the detection of preclinical AD stages is generally believed to be crucial for future therapy. *Methods:* Here, the secondary structure distribution of the Aβ peptide from blood plasma was identified as meaningful blood biomarker [1-4]. The secondary structure distribution of the Aβ peptide fraction was measured by an immuno-infrared-sensor [1,2]. The sensor detects the conformation sensitive amide I band of the total Aß fraction within the respective body fluid [3,4]. In addition, the immuno-infrared-sensor can also be applied to unravel the effect of potential drug candidates [5] on Aß or Tau aggregates. The refolding of CSF Aß from the pathogenic to the non-toxic state due to congo red was analyzed label-free. The same refolding experiment was performed with Tau from CSF and methylene blue [6]. *Results:* Using the immuno-infrared-sensor severe AD cases and disease controls were discriminated with a sensitivity of 94 % and a specificity of 88 % for CSF analyses. Within this study, the amide I maxima significantly correlated with neurochemical biomarkers [3]. On the other hand, the immuno-infrared-sensor also enabled for the identification of preclinical AD stages based on blood plasma analyses years before clinical symptoms appear. These results are obtained in a prospective follow-up cohort study. Participants at baseline were cognitively unimpaired and clinically assigned as healthy. In addition, the amide I maxima could be correlated with the PET signal for the first time [4]. Using the immuno-Infrared-Sensor for unraveling the drug intervention of congo red on the Aβ secondary structure we observed a secondary structure change from the pathogenic form to mostly monomeric isoforms upon congo red application. Furthermore, a similar effect was observed for methylene blue on the Tau protein secondary structure [6]. *Conclusion:* The secondary structure distribution of the total Aβ peptide fraction provides a blood biomarker, which is indicative already for preclinical AD stages [4]. The presented immuno-infrared-sensor method represents a promising, simple, robust, and label-free diagnostic tool for blood analysis in order to screen potential participants for clinical trials in very early stages. Moreover, the sensor can be applied to study the refolding efficacy of potential drug candidates on misfolded Aß and Tau. [1] Gerwert, Wiltfang, Ollesch, Nabers, Schartner, Kötting, "Biosensor for Conformation and Secondary Structure Analysis", 2015, WO 2015/121339 A1. [2] Nabers, Ollesch, Schartner, Kötting, Genius, Haußmann, Klafki, Wiltfang, Gerwert, "An infrared sensor analysing label-free the secondary structure of the Abeta peptide in presence of complex fluids", Biophotonics, 9(3): 224-234, 2016. [3] Nabers, Ollesch, Schartner, Kötting, Genius, Hafermann, Klafki, Gerwert, Wiltfang, "Amyloid-ß-Secondary Structure Distribution in Cer-ebrospinal Fluid and Blood Measured by an Immuno-IR-Sensor: A Biomarker Candidate for Alzheimer's Disease", Analytical Chemistry, 88(5): 2755-2762, 2016. [4] Perna, Nabers, Lange, Mons, Schartner, Güldenhaupt, Saum, Janelidze, Holleczek, Rujescu, Hansson, Gerwert, Brenner, " Amyloid Blood Biomarker Detects Preclinical Alzheimer's Disease, submitted. [5] Gerwert, Nabers, Schartner, "Method for Preselection of Drugs for Protein Misfolding Diseases", 2016, EP 16199792.9. [6] Schartner, Nabers, Budde, Lange, Hoeck, Wiltfang, Kötting, Gerwert, "An ATR-FTIR-Sensor Unraveling the Drug Intervention of Methylene Blue, Congo Red, and Berberine on Human Tau and Aβ", ACS Medicinal Chemistry Letters, accepted.

P63: EFFECTS OF APOE ε4 ON NEUROIMAGING, BIOMARKERS AND CLINICAL CHARACTERISTICS OF PRODROMAL ALZHEIMER'S DISEASE. Niklas Mattsson[1,2,3], Oscar Eriksson[1], Olof Lindberg[1], Michael Schöll[1,4], Björn Lampinen[5], Markus Nilsson[6], Philip S. Insel[1,7,8], Ronald Lautner[9,10], Olof Strandberg[1], Danielle van Westen[6], Henrik Zetterberg[9,10,11], Kaj Blennow[9,10], Sebastian Palmqvist[1,3], Erik Stomrud[1,2], Oskar Hansson[1,2] *((1) Clinical Memory Research Unit, Faculty of Medicine, Lund University, Lund, Sweden; (2) Memory Clinic, Skåne University Hospital, Malmö, Sweden; (3) Department of Neurology, Skåne University Hospital, Lund, Sweden; (4) MedTech West and the Department of Psychiatry and Neurochemistry, University of Gothenburg, Sweden; (5) Clinical Sciences Lund, Medical Radiation Physics, Lund University, Lund, Sweden; (6) Lund University, Skane University Hospital, Department of Clinical Sciences Lund, Diagnostic Radiology, Lund, Sweden; (7) Center for Imaging of Neurodegenerative Diseases, Department of Veterans Affairs Medical Center, San Francisco, CA, USA; (8) Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA; (9) Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; (10) Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden; (11) Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK)*

Background: APOE ε4 is a major genetic risk factor for Alzheimer's disease (AD), but around 40 % of AD patients lack APOE ε4. It is unclear how APOE ε4 affects AD pathophysiology, particularly during the prodromal disease stage. *Methods:* We studied 152 prodromal AD patients from the Swedish BioFINDER cohort (44 APOE ε4-negative and 108 APOE ε4-positive, matched for age and sex). *Results:* APOE ε4 was not associated with baseline global cognition or memory, or with cortical Aβ load. However, APOE ε4-negative prodromal AD patients had more impaired baseline executive function, more rapid progression of global cognitive decline, higher cerebrospinal fluid levels of Aβ-peptides and neuronal injury biomarkers, more white matter pathology and other signs of vascular burden, and more cortical atrophy compared to APOE ε4-positive patients. APOE ε4 only had minor effects on cortical tau retention, measured by 18F-AV-1451 positron emission tomography in 39 AD patients (whereof 15 APOE ε4-negative). *Conclusion:* We conclude that AD is heterogenic with multiple APOE ε4-dependent differences, which are present already at the prodromal stage of the disease.

P64: LOW TOTAL AB42/40 PLASMA RATIO IN MCI PATIENTS IS ASSOCIATED WITH A FDG-PET PATTERN SUGGESTIVE OF AD AND PREDICTS PROGRESSION TO DEMENTIA. Virginia Pérez-Grijalba[1], Judith Romero[1], Pedro Pesini[1], Leticia Sarasa[1], Itziar San-José[1], Javier Arbizu[2], Pablo Martínez-Lage[3], Lluis Tárraga[4], Agustín Ruiz[4], Mercè Boada[4], Manuel Sarasa[1] and The AB255 Araclon Group[5] *((1) Araclon Biotech S.L., Zaragoza, Spain; (2) Clínica Universitaria de Pamplona, Pamplona, Spain; (3) Fundación CITA-Alzheimer, San Sebastián, Spain; (4) Fundació ACE. Barcelona Alzheimer Treatment and Research Center. Barcelona, Spain; (5) www.araclon.com)*

Background: Early stages of Alzheimer's disease (AD) are increasingly being targeted for potential disease-modifying therapeutic interventions. Consequently, success of clinical trials depends on the ability to accurately classify individuals and predict their likelihood of future decline. Although beta-amyloid (Aβ) peptide levels both in cerebrospinal fluid (CSF) and amyloid imaging are well-accepted biomarkers for AD, a minimally invasive blood-based biomarker reflective of brain processes would be a useful tool to enrich anti-amyloid targeting clinical trials with people at prodromal stages of AD, as well as to assess target-engagement and disease progression monitoring. The aim of this work was to evaluate the potential of highly accessible plasma Aβ biomarkers in identifying early stages of AD and predicting cognitive decline within the AB255 study. *Methods:* The AB255 study comprised 228 subjects, including 83 cognitively normal individuals (CN) and 145 subjects with (probable) amnesic mild cognitive impairment (aMCI) [1], stratified by their FDG-PET neuroimaging pattern as suggestive (positive) or not (negative) of aMCI due to AD [2]. Individuals were followed-up during 2 years, with visits at baseline, 12 and 24 months. The ratio of total plasma Aβ42/40 (TP42/40) was assessed using ABtest kits (Araclon Biotech, Zaragoza, Spain) for each participant. Comparisons of TP42/40 ratio among diagnostic groups were carried out using generalized linear models (GLM) and logistic regression. A multivariate Cox proportional hazard model was performed to estimate the relationship of baseline TP42/40 with the progression of MCIs to AD. All the models were adjusted for age, education and APOE4 genotype. Additionally, CSF Aβ40 and Aβ42 levels were also determined with ABtest in a subset of 62 patients. The association between plasma and CSF Aβ42/40 ratios was assessed by Pearson correlation. *Results:* TP42/40 ratio was significantly lower in MCI with regard to CN subjects (GLM coefficient -13.45, p0.028). Moreover, MCI subjects showing a FDG-PET pattern suggestive of AD had even lower ratio than the MCI group with a negative FDG-PET (GLM coefficient -16.05, p0.003). This inverse association was consistently found in every time-point of the follow-up. In terms of progression from MCI to AD, 52.4% of MCI subjects with low TP42/40 ratio (below the median of the population) at baseline progressed to AD after 24 months, whereas only 28.8% with high TP42/40 ratio did. For these individuals with low TP42/40 ratio, the likelihood of being a MCI-progressor was 2-fold higher than remaining as a MCI-stable (OR 2.4, CI 95% 1.17-4.95, p0.017) and 3-fold higher than remaining as a CN (OR 3.01, CI 95% 1.46-7.04, p0.004) after follow-up. Low TP42/40 ratio at baseline implied an increase of ≈70% in the risk of conversion to AD (HR 1.687, CI 95% 1.058-2.691, p0.028). In addition, we found a significant positive correlation between plasma TP42/40 ratio and the Aβ42/40 ratio in CSF (Spearman coefficient rs 0.428, p0.005). *Conclusion:* These data further validate our previous results on the inverse association of plasma TP42/40 ratio and neuroimaging markers of cortical pathology, and are congruent with those reported from large studies such as Framingham, Rotterdam, and the 3-City Study. The results demonstrate that plasma TP42/40 ratio is able to detect the stage of mild cognitive impairment, and discriminates among subjects diagnosed as aMCI with a FDG-PET pattern suggestive or not of AD. Moreover, low plasma TP42/40 ratio appears as predictive of cognitive decline from MCI to AD in 2 years. Thus, TP42/40 ratio could be a useful cost-effective biomarker to predict progression to AD in early stages of the disease, with value as a tool for target-engagement, patient stratification, and monitoring in clinical trials. References: [1] Espinosa A. et al., J Alzheimers Dis 2013; 34(3):769-80. [2] Arbizu J. et al., Eur J Nucl Med Mol Imaging 2013 Sep; 40(9):1394-405.

P65: BETA AMYLOID ANTI-OLIGOMER ACTION OF ALZ-801 AND CLINICAL DOSE TRANSLATION ANALYSES SUPPORT CONFIRMATORY PHASE 3 PROGRAM IN ALZHEIMER'S DISEASE. J.A. Hey[1], P. Kocis[1], S. Abushakra[1], J. Yu[1], A. Power[1], K. Blennow[2], M. Tolar[1] *((1) Alzheon Inc., Framingham, MA, USA; (2) University of Gothenburg, Molndal, Sweden)*

Background: Beta amyloid (Aß) oligomers play a critical role in the pathogenesis of Alzheimer's disease (AD), and represent a promising target for drug development. Tramiprosate is a small-molecule Aß anti-aggregation agent that was previously evaluated in Phase 3 clinical trials of Mild and Moderate AD but did not meet the primary efficacy endpoints in the overall study population. A pre-specified subgroup analysis revealed robust, clinically meaningful cognitive and functional effects in APOE4/4 homozygous patients with Mild AD (Abushakra 2016, 2017). To advance this important efficacy attribute and to further improve its pharmaceutical properties, we have developed ALZ-801 a clinical stage prodrug of tramiprosate with substantially improved pharmaceutical properties for treatment of Alzheimer's disease (AD). Here we characterize a multi-ligand enveloping effect of tramiprosate on Aβ42, which stabilizes Aβ monomers, and underpins anti-aggregation activity (Kocis et al. 2017). To select the ALZ-801 dose for the pivotal clinical trials of ALZ-801, we performed an integrated analysis that links tramiprosate exposures in the brain and its clinical effects in prior trials, to the anti-Aβ oligomer effect. Bridging human pharmacokinetic studies between tramiprosate and ALZ-801 are presented. *Methods:* Ion mobility mass spectrometry. To address the high conformational flexibility of Aß42 and characterize its interaction with tramiprosate, we used ion mobility mass spectrometry (IMS MS), using Waters Synapt G2-quadrupole time of flight mass spectrometer (Q-TOF MS) with traveling wave ion mobility. IMS MS is a technique capable of separating molecular ions based on their size and conformation and can characterize the stoichiometry of ligand-protein complexes. Nuclear magnetic resonance; To determine how tramiprosate binds to the target we used two-dimensional heteronuclear multiple quantum correlation nuclear magnetic resonance spectroscopy (2D 1H-15N HMQC NMR) of uniformly 15N-labeled Aß42 peptide (in 90% H2O/10% D2O sodium phosphate buffer, pH 7.4 at 37°C). The NMR experiments were conducted at 800 MHz on a Bruker AVANCE II spectrometer using a 5mm HCN cryogenic probe. 2D1H-15N SOFAST-HMQC software with 3919 Watergate was used. Molecular dynamics; To characterize the structure of Aß42 alone and with different levels of excess tramiprosate, we conducted a series of all atom molecular dynamics simulations. All molecular modeling was performed using the Schrödinger suite. Molecular dynamics simulations were run using Desmond on GeForce GTX Titan Black GPU cards. To describe the large conformational changes observed in these simulations, we performed a principal component (PC) analysis of the free energy surface. Human pharmacokinetic analyses, CSF Aß42 measures, and pharmacokinetic-pharmacodynamic (PK-PD) translation Plasma and CSF concentrations of tramiprosate at 78 weeks in the previous Phase 3 studies were determined in frozen samples using a validated LC-MS/MS method. The steady-state drug level in the brain was projected based on the brain/plasma drug exposure relationship from animals to humans. The CSF Aß42 concentrations in AD patients in the tramiprosate Phase 2 trial were measured by ELISA, and were used in the PK-PD analyses. *Results:* We observed a multi-ligand interaction of tramiprosate with monomeric Aß42, which differs from traditional 1:1 binding. This results in the stabilization of Aß42 monomers and inhibition of oligomer formation and elongation, as demonstrated by IMS MS and molecular dynamics. Using NMR spectroscopy and molecular dynamics, we also showed that tramiprosate bound to Lys16, Lys28 and Asp23, the key amino acid side chains of Aß42 that are responsible for both conformational seed formation and neurotoxicity. The projected molar excess of tramiprosate versus Aß42 in humans using the dose effective in APOE4/4 homozygotes (150mg BID) aligns with the molecular stoichiometry of the interaction providing a clear clinical translation of the mechanism of action. *Conclusions:* Aβ oligomers are considered a key driver of synaptic dysfunction and toxicity in AD. In summary, we have identified the molecular mechanism that may underlie the observed clinical efficacy of tramiprosate in APOE4/4 homozygous AD patients. In addition, the integrated application of the molecular methodologies (i.e., IMS MS, NMR, and thermodynamics analysis) shows that it is possible to modulate and control the Aß42 conformational dynamics landscape by a small molecule, and cause the Aß42 peptide to alter its conformation, leading to a clinically relevant anti-aggregation action. The 265mg dose of ALZ-801 determined from the preclinical to clinical translational PK/PD analyses is projected to provide tramiprosate plasma exposure that is bioequivalent to the clinically effective dose in completed Phase 3 studies, and to fully inhibit Aß42 oligomer formation in brain. This ALZ-801 dose will be evaluated in a confirmatory pivotal program in APOE4/4 homozygous AD patients. Furthermore, the novel enveloping mechanism of action of tramiprosate described herein has potential utility in the discovery of disease-modifying therapies for AD and related neurodegenerative disorders caused by misfolded, prion-like proteins.

P66: ELECSYS CSF BIOMARKERS PREDICT CLINICAL AND COGNITIVE OUTCOMES. Chengjie Xiong[1,2,3,4], Dean Coble[1,2], Julia D. Gray[2,3], Elizabeth Grant[1,2], Lena McCue[1,2], John C. Morris[2,3], Jason Hassenstab[2,3], Richard Batrla[5], Udo Eichenlaub[6], Katharina Zink[6], Sandra Rutz[6], Marian Quan[7], Anne M. Fagan[2,3] *((1) Division of Biostatistics, Washington University School of Medicine, St. Louis, MO, USA; (2) Knight Alzheimer Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA; (3) Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA; (4) Department of Mathematics, Washington University, St. Louis, MO, USA; (5) Roche Diagnostics International, Rotkreuz, Switzerland; (6) Roche Diagnostics GmbH, Penzberg, Germany; (7) Roche Diagnostics Operations, Indianapolis, IN, USA)*

Background: The design of prevention trials in Alzheimer disease (AD) requires biomarkers that can identify individuals at high risk of developing AD dementia. It is thus crucial to assess the ability of CSF biomarkers, including Aβ42 , Tau, and Ptau, to predict subsequent clinical and cognitive outcomes. *Methods:* CSF samples were obtained from 362 cognitively normal (Clinical Dementia Rating [CDR] 0) elderly individuals (≥65 years at baseline) who were research participants at the Washington University Knight Alzheimer Disease Research Center and had follow-up longitudinal clinical and cognitive assessments after the CSF collection (mean follow-up=4.63 yrs, SD=3.13 yrs). Samples were analyzed with the Elecsys® β-Amyloid (1-42) (Abeta42), Elecsys Total-Tau (tTau) and Elecsys Phospho-Tau (181P) (pTau) automated immunoassays (Roche Diagnostics). Cox proportional hazards models were used to assess the ability of the CSF biomarkers, as well as combinations of these, to predict subsequent progression of dementia, as operationalized by a CDR>0. General linear mixed effects models were used to assess how the CSF biomarkers predict the subsequent rates of changes in CDR sum-of-boxes (CDR-SB), a more quantitative measure of cognitive and functional decline, as well as performance on the Mini-Mental State Examination (MMSE) and on several composites of

neuropsychological outcomes. *Results:* At the time of CSF collection, the cohort had a mean age of 72.98 y (SD=5.70 y). 84 individuals subsequently received a CDR>0. After adjusting for age at CSF collection, APOE4 genotype status, sex, education, and family history of AD, lower values of CSF Abeta42 were significantly associated with higher risk of CDR progression (hazard ratio [HR] for every 100 pg/mL increase of Abeta42=0.940, 95% CI =[0.908, 0.974], p=0.0005). Values of CSF tTau or pTau on their own were not significantly associated with higher risk of CDR progression (tTau, p=0.4018; pTau, p=0.2156). However, higher values of the ratio between tTau and Abeta42 were significantly associated with higher risk of CDR progression (HR for every one unit increase of the tTau and Abeta42 ratio=4.212; 95% CI=[1.630, 10.885], p= 0.0030). Higher values of the ratio between pTau and Abeta42 were also significantly associated with higher risk of CDR progression (HR for every one unit increase of the pTau and Abeta42 ratio=135021.0; 95% CI=[49.517, 3.6817E8], p= 0.0034). For each biomarker, a cutoff was determined by a ROC curve analysis maximizing the Youden index for the outcome CDR 0 versus CDR>0 in the larger Knight ADRC cohort that also included individuals with CDR>0 at the time of CSF collection. Cut-offs for Aβ42 are dependent on pre-analytical handling of samples. The determined cut-offs are therefore specific for the current study and the pre-analytics. For individuals with low CSF Abeta42 at baseline (<=1043 pg/mL), the longitudinal rates of change in CDR-SB, MMSE, episodic memory composite, visuospatial composite, and a global cognitive composite were all significantly worsening, whereas, for others with high CSF Abeta42 (>1043 pg/mL), none of the rates of change was different from 0 (with the exception of CDR-SB, p=0.0284). The longitudinal rates of changes in these same clinical and cognitive outcomes were not significantly different between individuals with and without a high CSF tTau (>239 pg/mL) or pTau (>21.7 pg/mL). Finally, the longitudinal rates of change for the same outcomes among individuals who had a high ratio of CSF tTau and Abeta42 (>0.24) were all significantly different from the corresponding rates of change among individuals who had a low ratio of CSF tTau and Abeta42 (<=0.24), with the former worsening over time. Similar results were also obtained when comparing the longitudinal rates of change among individuals with a high (>0.02) or low (<=0.02) ratio of CSF pTau and Abeta42. *Conclusions:* Results support the utility of Elecsys CSF biomarker values, obtained with highly automated assays, in identifying cognitively normal individuals at high risk of developing AD dementia and worsening rates of cognitive decline. Further studies are needed to explore the utility of CSF biomarkers as primary efficacy endpoints in prevention trials by correlating the longitudinal rate of biomarker changes with that of the cognitive outcomes. Acknowledgements: This study was funded by the National Institutes on Aging 5P01AG003991, P50AG005681, and 2P01AG026276, and by Roche Diagnostics.

P67: THE EVALUATION OF NOVEL MONOCLONAL ANTIBODIES TARGETING DIFFERENT FORMS OF NEUROFILAMENT LIGHT IN BRAIN AND CSF. Ann De Vos[1], Dirk Jacobs[1], Nele Dewit[1], Carola Schipke[2], Oliver Peters[2], Eugeen Vanmechelen[1] *((1) ADx NeuroSciences N.V., Gent, Belgium; (2) Charité-Universitätsmedzin Berlin, Memory Clinic at the ECRC, Berlin, Germany)*

Background: Neurofilament light (NF-L) in cerebrospinal fluid (CSF) is a promising biomarker for a number of neurodegenerative conditions. CSF NF-L can discriminate Parkinson's disease from other Parkinsonian disorders, while it correlates well with disease severity in Frontotemporal lobe dementia. In Alzheimer's Disease (AD), CSF NF-L, in contrast to CSF tau, is an Aβ-independent neurodegenerative biomarker. However, some questions remain, especially in the AD field. A potential added value of CSF NF-L, as compared to CSF tau/P-tau, in early MCI to AD diagnosis has not yet been fully established. Furthermore, since the majority of the studies is based on one NF-L immuno-assay with an unique pair of monoclonal antibodies (mAbs), one may wonder whether quantification of other forms or fragments from NF-L might be clinically more informative. *Methods:* The aim of the current study was to develop novel NF-L specific mAbs and to design an immuno-assay to explore the role of CSF NF-L in differentiating depression from MCI-AD, in parallel with the well-known ELISA by Uman Diagnostics. The new mAbs were raised using bovine purified NF-L, as well as custom-made synthetic peptides mapping the ROD-domain of NF-L. *Results:* The affinity of the novel mAbs, which is in the low nM or subnM range, was determined by biolayer interferometry using synthetic peptides. Specificity was defined on various purified NF-M and NF-H proteins and the mAbs were found to be highly NF-L specific. Two clones, i.e. 1F7 and 15H7, were selected to design a novel ELISA format, as well as to set up hybrid ELISA formats combining these new mAbs with the Uman mAbs. Using these different formats on human brain extracts, we clearly observed correlations in NF-L levels, indicative for the detection of the same forms of NF-L by a subset of the mAbs. Yet, not all combinations of NF-L mAbs resulted in correlating data in the brain extracts, thus different NF-L forms might be captured. We next performed an explorative CSF study including diagnostic groups of patients suffering from depression and AD, next to cognitively healthy persons. While CSF NF-L was significantly increased in AD compared to depression, there was no correlation between the CSF NF-L levels measured with the 1F7-15H7 assay and the concentrations quantified with the Uman assay. This observation was in line with the findings in brain tissue and suggests different forms being captured in CSF as well. *Conclusion:* Novel high-affine mAbs were generated that are specific for NF-L and can be used to design various immuno-assays. Currently we are transferring combinations of NF-L mAbs on the SiMoA instrument to improve the analytical sensitivity of the immuno-assays and to further explore differences and similarities between the different NF-L mAb combinations. While this work is ongoing, and will be presented, this could offer novel insights in the clinical value of different NF-L forms.

P68: DETECTION OF BETA AMYLOID IN THE OCULAR LENS. PRELIMINARY RESULTS EVALUATING A CORRELATION WITH PET AMYLOID SCANS (PET) IN SUBJECTS WITH MILD COGNITIVE IMPAIRMENT (MCI) AND MILD ALZHEIMER'S DISEASE (AD). Joyce E. Myers[1], Charles Kerbage[1], Dennis Nilan[1], John Loewy[2], Julie Blasbalg[1], Daniel R. Vlock[1], Teresa Villena[3], Carl Sadowsky[3] *((1) Cognoptix Inc., Concord, MA USA; (2) DataForeThought, Winchester, MA USA; (3) Premiere Research Institute, West Palm Beach, FL USA)*

Background: The Sapphire II System is a fluorescence ligand eye scanning (FLES) diagnostic technology consisting of a medical imaging agent, Aftobetin-HCl, and a florescence detection device that can detect β-amyloid in the ocular lens. In preclinical models of AD and Down Syndrome, this pathology develops prior to amyloid deposition in the brain, suggesting it may be an early biomarker of risk for the development of AD. In a previous study, Sapphire II was able to discriminate in 20 subjects with a clinical diagnosis of AD from 20 healthy age-matched controls with significant statistical significance ($p < 0.001$) and sensitivity and specificity of 85% and 95%, respectively. No serious or unanticipated adverse device effects were reported during that study. The current study is exploring the

correlation between Sapphire II and PET amyloid at early stages in subjects with MCI and AD. *Methods:* This is an open-label study to evaluate the Sapphire II system to detect β-amyloid in subjects with normal cognition (CN), MCI, and AD. A total of 45-105 subjects will be enrolled in the study. MCI and AD subjects must meet the follow criteria: aged 55-90 years old inclusive; able to provide informed consent; have a reported memory concern verified by study partner; capable of cooperating for the duration of the study with procedures and assessments; Magnetic Resonance Imaging (MRI) Scan within 9 months with a Modified Hachinski Score < 4, no evidence of infection, infarction (ischemic or hemorrhagic), or other focal lesions; Geriatric Depression Scale (GDS) score of < 6; Neuropsychiatric Inventory (NPI) total score < 10 and < 4 in any NPI domain; sufficient vision in at least one eye and hearing to participate in cognitive testing. MCI subjects must also meet the following: National Institute on Aging-Alzheimer's Association (NIA-AA) core clinical criteria for Mild Cognitive Impairment due to AD; Clinical Dementia Rating Scale Score (CDR) of 0.5 (memory box score must = 0.5); Mini-Mental State Exam (MMSE) score of > 24; abnormal memory function on education adjusted Wechsler Memory Scale Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) - Revised (16 years: < 11; 8-15 years: < 9; 0-7 years: < 6); absence of dementia: no significant impairment in cognitive functioning or Activities of Daily Living (AODLs) – Functional Assessment Questionnaire (FAQ) score of < 6. AD subjects must: meets National Institute on Aging-Alzheimer's Association (NIA-AA) core clinical criteria for probable AD dementia; CDR between 0.5 or 1; MMSE score between 20 to 26 (inclusive); abnormal memory function on education adjusted Wechsler Memory Scale Logical Memory II subscale - (Delayed Paragraph Recall, Paragraph A only) - Revised (16 years: < 8; 8-15 years: < 4; 0-7 years: < 2); Functional Assessment Questionnaire (FAQ) score of > 6. Following screening of subjects, those who qualify for the study will be given consent undergo a baseline (pre-ointment administration) Sapphire II measurement and receive then 3 ointment administrations 1.5- 2 hours apart. Subjects will return to clinic 24 hours (+/- 2 hours) and 28 hours (+/-30 minutes) and 48 hours (+/- 2 hours) after the first administration of ointment for a Sapphire II measurement. 7-10 days following the Sapphire II measurement, subjects will return for a follow up safety assessment, including ophthalmic examination. Subjects will undergo an amyloid PET scan if they have not had a positive PET amyloid scan in last 3 years. CN subjects will not receive a PET scan. All subjects who successfully complete the Sapphire II testing will be asked to return for the following visits to assess repeatability. Repeatability testing is optional and will require a separate consent. *Results:* To date 15 subjects have been evaluated. Ointment administration has been well tolerated and no untoward reactions have been noted. It is planned to enroll up to 105 subjects. Estimation of diagnostic accuracy of the Sapphire II system will be performed based on the baseline (prior to ointment administration) fluorescent uptake values (FUV) and at 24, 28, and 48 hours following first ointment administration. Statistical estimation of agreement between Sapphire II and PET will be based on the findings of estimates of sensitivity and specificity pairs, likelihood ratio of positive and negative result pairs and Receiver Operating Characteristic (ROC) analysis along with confidence intervals. *Conclusions:* The Sapphire II system offers the ability to detect β-amyloid in the ocular lens. Correlation of Sapphire II system with PET amyloid scans will be presented. Those results will permit utilization of Sapphire II as a cost effective and safe screening method in MCI and AD subjects.

P69: CONVERSION PREVALENCE AMONG PRE-DEMENTIA AD PATIENTS AND RISK FACTORS. Beatrice Blanc[2,3], Nicolas Pelletier[1,2], Clotilde Biscarrat[1], Pauline Martinasso[1], Samantha Galluzzi[4], Moira Marizzoni4, Jorge Jovicich[4,6], Giovanni B. Frisoni[4,5], Gianluidgi Forloni[7], Diego Albani[7], Jill Richardson[8], Lucilla Parnetti[9], Magda Tsolaki[10], Flavio Nobili[11], David Bartrez-Faz[12], Mira Didic[13], Peter Schoenknecht[14], Pierre Payoux[14], Andrea Soricelli[16], Paolo M Rossini[17], Pieter Jelle Visser[18], Regis Bordet[19], Ute Fiedler[20], Olivier Blin[21], Joëlle Micallef[22], Laura Lanteaume[22], Nathalie Sambuchi[23], Isabelle Muraccioli[23], Elizabeth Jouve[22], Bernard Michel[23], Nathalie Compagnone[1,2,3] *((1) ICDD, Diagnostic Dept Gemenos, France; (2) Lab Alzheimer's Neuroimaging & Epidemiology, IRCCS Fatebenefratelli, Brescia, Italy; (3) University Hospitals and University of Geneva, Geneva, Switzerland; (4) Center for Mind/Brain Sciences, University of Trento, Trento, Italy; (5) Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy; (6) Neurosciences Therapeutic Area, GlaxoSmithKline R&D, Stevenage, UK; (7) Clinica Neurologica, Università di Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy; (8) Third Neurologic Clinic, Medical School, G. Papanikolaou Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; (9) Clinical Neurology, Department of Neurosciences, Rehabilitation, Ophthalmology and Maternal-Fetal Medicine, University of Genoa, Genoa, Italy; (10) Department of Psychiatry and Clinical Psychobiology, Faculty of Medicine, University of Barcelona and Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalunya, Spain; (11) Service de Neurologie et Neuropsychologie, APHM Hôpital Timone Adultes, Marseille, France; (12) Department of Psychiatry and Psychotherapy, University of Leipzig, Leipzig, Germany; (13) Dept. Medecine Nucléaire, CHU de Toulouse, Toulouse, France; (14) SDN Istituto di Ricerca Diagnostica e Nucleare, Naples, Italy; (15) Department of Gerontology, Neurosciences & Orthopedics, Catholic University, Rome, Italy; (16) Department of Neurology, Alzheimer Centre, VU Medical Centre, Amsterdam, the Netherlands; (17) University of Lille, Inserm, CHU Lille, U1171 - Degenerative and Vascular Cognitive Disorders, Lille, France; (18) Department of Psychiatry and Psychotherapy, Faculty of Medicine, LVR-Hospital Essen, University of Duisburg-Essen, Essen, Germany; (19) Pharmacol. and Pharmacovigilance, Aix-Marseille Univ., Marseille, France; (20) Service de neurologie et neuropsychologie, CHU la Timone, Marseille, France; (21) Service de neurologie comportementale, Hôpital Sainte Marguerite, Marseille, France; (22) Service d'Evaluation Médical, Hôpital de la Conception, Marseille France)*

Background: The development of disease-modifying therapeutics for Alzheimer's disease (AD) is hampered by the lack of validated biomarkers identifying disease progression at pre-dementia stages. Guidelines for AD diagnosis include markers measuring Amyloid status, Tau protein phosphorylation and neurodegeneration or neuronal injury markers along with the determination of the cognitive decline rate through batteries of neuropsychological tests. Less invasive and more cost-effective tests are needed. ADFlag® is a blood test intending to recognize AD pre-dementia stages. We have previously shown validation results obtained in a multi-cohort, multi-centric setting in Europe. ADFlag® is a scale of 1-5 based on immunologic profiling of circulating blood cells & plasma associated with disease progression as measured by neurological testing including memory assessments, verbal fluency assessments and general cognitive scales. Moreover, in the Pharmacog cohort, the ADFlag® scale correlated with amyloid load in CSF samples. Having an ADFlag® score above 2 at baseline significantly increased the likelihood that conversion to dementia occurred within the 24 months of follow up

in the Pharmacog study (OR=4.11, chi sq=0.0030). *Methods:* The "Alzpredict" trial and the "Pharmacog" trial patients were used in the present study. The Alzpredict trial is a monocentric ongoing longitudinal trial in which 147 memory-clinic patients were enrolled at baseline. Diagnostics included normal, SCI, MCI and AD patients. The Pharmacog trial is a multi-centric cohort, which enrolled 147 MCI patients at baseline. We measured the ADFlag® score in the Alzpredict and Pharmacog patients. In the Pharmacog cohort, we previously showed that having an ADFlag® score above 2 at baseline significantly increased the likelihood that conversion to dementia occurred within the 24 months of follow up in the Pharmacog study (OR=4.11, chi sq=0.0030). We now used a multivariate regression analysis stratified by age, presence of ApoE4 allele and ADFlag® scale on both cohorts to determine the odd ratio for conversion to AD. *Results:* 338 patients were analyzed. Overall, the prevalence of conversion within the two cohorts was 21.53% for a maximal follow-up period of 36 months. Converters were 73.66+/-7.99 years of age, similar to the age of non-converters, 50% had an ApoE4 allele (NS), 47.62% were amyloid positive (NS), and 63.16% scored 4 on the ADFlag® scale (p=0.0081). We found that scoring 4 on the ADFlag® scale significantly increased the odds for conversion by 4.00-fold compared to patients scoring 1 (p=0.0035) and 6.36-fold compared to patients scoring 3 on the ADFlag® scale (p=0.0030). A generalized regression predictive model confirmed the association between conversion into AD and scoring 4 on the ADFlag® scale. The positive predictive value for ADFlag® scores corrected by Age, presence of ApoE4 allele and Amyloid beta status was 0.84. The studies have been approved by the appropriate institutional and/or national research ethics Committees. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

P70: SEX-SPECIFIC CHANGES IN LEVELS OF CIRCULATING BRAIN-ENRICHED MICRORNAS DURING NORMAL AGING AND DIFFERENT STAGES OF ALZHEIMER'S DISEASE. Kira Sheinerman[1], Anne Fagan[2], Elizabeth Grant[2], Aabhas Mathur[3], Debra Kessler[3], Beth Shaz[3], Jon Toledo[4], David Wolk[4], John Trojanowski[4], Vladimir Tsivinsky[1], Samuil Umansky[1] *((1) DiamiR Biosciences, Monmouth Junction, NJ, USA; (2) Neurology Department, Washington University in St. Louis, MO, USA; (3) New York Blood Center, New York, NY USA; (4) Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA)*

Background: Cell-free microRNAs detectable in the blood plasma are potential novel biomarkers of brain disorders, including Alzheimer's (AD) and other neurodegenerative diseases (ND). microRNAs are short, non-coding nucleic acids whose levels change in disease; some microRNAs are specific to or enriched in the brain and can cross blood-brain barrier. Our previous studies indicate that the ratios of plasma levels of microRNAs enriched in specific regions of the brain and present in synapses could serve as potential biomarkers for detection of presymptomatic AD, mild cognitive impairment and AD dementia, and differentiation of AD from other NDs. Here we investigated microRNA biomarkers in cohorts stratified by sex to determine its impact on the biomarker sensitivity and specificity. *Methods:* The plasma levels of 18-38 pre-selected brain-enriched and inflammation-associated microRNAs were quantified using qRT-PCR in samples collected at The New York Blood Center (cognitively normal participants in five age groups, 26-35 to 66-75 year old, n=140); the Washington University Alzheimer's Disease Research Center (early mild cognitive impairment, control (Clinical Dementia Rating, CDR 0-1), n=59; cognitively normal (CDR 0) participants, who progressed/not-progressed to CDR>0 within 12 years after plasma collection, n=84); the Alzheimer's Disease Center at the University of Pennsylvania (AD dementia, control, n=100). "microRNA pair" approach (Aging 2013, 5:925) was used for data normalization. *Results:* Age-dependent changes in plasma concentrations of brain-enriched microRNAs (miR-132 and miR-134 families) differ strongly in cognitively normal male and female study participants. The analysis of sex-stratified cohorts increased accuracy of microRNA biomarker classifiers in differentiation of early mild cognitive impairment from control (accuracy:AUC (Area Under ROC Curve) improved from 0.85:0.92 to 0.93:0.96/0.93:0.96 for male/female participants), prediction of progression of cognitively normal participants to CDR>0 (0.75:0.79 to 0.85:0.88/0.84:0.86), and differentiation of AD dementia from control (0.92:0.98 to 0.98:1.0/0.94:0.99). *Conclusions:* Here we report that the levels of circulating brain-enriched microRNAs change differently with age in males and females and present data suggesting that sex-specific analysis improves accuracy of plasma microRNA classifiers for AD diagnosis at different stages. Larger clinical studies in heterogeneous populations are needed to further assess these findings.

P71: EUROPEAN VALIDATION OF THE PLM-SCALE, A CEREBROSPINAL FLUID BIOLOGICAL SCALE FOR POSITIVE ALZHEIMER'S DISEASE DIAGNOSIS. Audrey Gabelle[1], Sebastiaan Engelborgh[2], Koen Poesen[3], Panos Alexopoulos[4], Martin Vynhalek[5], Julien Dumurgier[6], Vincent De la Sayette[7], Susanna Schraen[8], Stéphanie Bombois[9], Mathilde Sauvée[10], Jean-Louis Laplanche[11], Jakub Hort[5], J. Hugon[6], F. Pasquier[9], Alzheimer's Disease Neuroimaging Initative, Sylvain Lehmann[12], Claire Paquet[6] *((1) Memory Resources and Research Center of Montpellier, Department of Neurology, CHU Gui de Chauliac; and Montpellier University and IRMB, Inserm UM1183, Montpellier, France; (2) University of Antwerp (UA), Belgium; (3) Laboratorium voor Moleculair Neurobiomarker Onderzoek O&N II Herestraat 49 - bus 1022, 3000 Leuven; (4) Department of Psychiatry and Psychotherapy, Technische Universität, München; Department of Psychiatry and Psychotherapy, Universität Rostock, Rostock , Germany; (5) Memory Clinic, Department of Neurology, Charles University, 2nd Faculty of Medicine and Motol University Hospital, Czech Republic; International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic; (6) CMRR, Paris Nord Ile-de-France; C.P., J.H. Inserm U839 ; Paris 7- Faculté de médecine Xavier Bichat, France ; (7) CMRR de Caen, France; (8) University of Lille Nord de France, Department of Biology and Pathology, Lille University Hospital, INSERM UMR 1172, 59037 Lille, France; (9) CMRR de Lille, Department of Neurology, University of Lille Nord de France, France; (10) CMRR de Grenoble, Department of Neurology, Grenoble, France; (11) Laboratoire de Biochimie Lariboisière-Fernand Widal Hospital, APHP, University Paris 7-Denis Diderot, University Paris Descartes, Paris, France; (12) Laboratoire de Protéomique clinique, Laboratoire de Biochimie and IRMB, Inserm UM1183 and Montpellier University, Montpellier, France)*

Introduction: The development, validation and comparison of biomarkers for Alzheimer's disease (AD) represented a major topic in neurosciences. The biomarkers are dedicated to early diagnosis, to predict cognitive decline, and for the patients' follow-up. To use them necessitates however to control pre-analytics biases which could be achieved thanks to standardization procedures. To facilitate the interpretation of multivariate CSF data and its routine use for clinicians, different tools could be used such as sensitivity/specificity

with area under the curve, logistic regressions such as of logarithmic transformed values of Aβ42 and p-tau and gender parameter. Recently, we developed a valuable and intuitive scale that have the major advantage to be used independently of CSF AD biomarkers cut-off that is known to be a large debate for clinical implementation. This scale, named PLM, is based on the three commonly used cerebrospinal fluid (CSF) biomarkers: amyloid β peptides, tau and p-tau proteins. This scale is defined to classify patients with specific probabilities that memory impairment or dementia is due to Alzheimer's disease (AD). *Objective:* The purpose of our study was to validate this scale in a large European memory centers and in a subgroup of neuropathological confirmation cases in order to extend the use of the PLM-scale in routine and in clinical trials. *Results:* We tested the predictive PLM scale based on the number (from 0 to 3) of pathological CSF biomarkers in a large multisite European memory centers (2344 participants; 1001 AD vs 1343 non-AD). The predictive value for AD of this scale were for class 0: 6.1%, class 1: 27.3%, class 2: 63.1% and for class 3: 87.0%. In addition, this scale had significantly more patients correctly classified than a categorisation based on logistic regression (net reclassification index (NRI) at 27.4%). We validated this scale on 183 cases with neuropathological confirmation, and PLM scale performed better (AUC=0.706) than Aβ, Tau or other logistic regression model. *Conclusion:* The PLM scale is simple and efficient, this enabled us to facilitate the interpretation in routine use without cut-off limitation of multivariate CSF data. The PLM scale could be used for stratification of patients in clinical research programs and trials

P72: ELECSYS® TOTAL-TAU CSF AND ELECSYS® PHOSPHO-TAU (181P) CSF: NOVEL, FULLY AUTOMATED IMMUNOASSAYS FOR RAPID AND ACCURATE QUANTITATION OF CSF BIOMARKERS FOR CLINICAL USE. Valeria Lifke, Ekaterina Manuilova, Christian Knop, Tobias Selle, Werner Kraus, Tobias Oelschlaegel, Lars Hillringhaus *(Roche Diagnostics GmbH, Penzberg, Germany)*

Background: Currently, diagnosis of neurodegenerative diseases is largely based on clinical symptoms. Recently however, amyloid-beta 1-42, total tau and phosphorylated (181P) tau levels in cerebrospinal fluid (CSF) have been identified as promising diagnostic biomarkers, and have been implicated in a number of neurodegenerative disorders, including for example the differential diagnosis of dementia. Technically robust and reliable tests are required for the broad utilization of CSF biomarkers in clinical trials and routine clinical practice. Here, we report for the first time, the results from the verification and validation of two novel, fully automated immunoassays for use in clinical diagnosis: Elecsys® Total-Tau CSF (tTau) and Elecsys® Phospho-Tau (181P) CSF (pTau) assays, both of which have been developed at Roche and will be marketed soon. *Methods:* tTau and pTau assays are fully automated quantitative immunoassays and were performed on the cobas e 601 and the cobas e 411 analysers (throughput, 170 and 86 tests/hour, respectively). For this analysis, four separate lots of the final assays were produced and evaluated for analytical performance, according to the CLSI guidelines (see Table for full methods). Reagent and sample stability were also evaluated (data not shown). *Results:* Analytical sensitivity. Limit of quantitation (LoQ) values for tTau and pTau assays were calculated as the lowest concentration within the pre-specified precision range (% coefficient of variance [CV] = 20) and were found to be 62.6 pg/mL and 3.90 pg/mL, respectively. Linearity: Linearity was demonstrated throughout the entire measuring range for tTau assay: 80–1300 pg/mL and for pTau assay: 8–120 pg/mL, across 13 dilution series and three different reagent lots. Precision: Repeatability (within-run precision) CVs for the tTau assay varied from 0.7%–1.7% and intermediate (within-laboratory) precision ranged from 0.8%–4.0%. Between-instrument (intermodule) precision CVs were 1.6%–3.1%. Repeatability for the pTau assay varied from 0.7%–2.3%, intermediate precision ranged from 1.0%–3.2%, and between-instrument CVs were 0.9%–2.6%. Lot-to-lot comparability: Pearson's correlation coefficients ranged from 0.980–1.000. The intercept and slope fitted using Passing-Bablok regression varied from 10.4–12.0 and 0.958–0.966, respectively, across all three reagent lots. Proportional bias between all lots was <1% in the medical decision area. Interference by endogenous compounds and drugs: No interference was observed with all tested endogenous substances. Recovery of tTau and pTau compared with a non-spiked reference sample was within ±10% of the expected value. Performance matched the pre-specified acceptable values. INNOTEST® comparison: The Pearson correlation coefficients between tTau/pTau assays and the INNOTEST® hTAU Ag/ INNOTEST® Phospho-Tau (181P) were 0.982 and 0.985, respectively. Platform comparability: Excellent platform comparability was observed between the cobas e 601 (mid-scale instrument) and cobas e 411 (small-scale instrument). *Conclusion:* The outstanding technical performance of both tTau and pTau assays demonstrated in this analysis support their use to determine CSF pTau and tTau in clinical trials and in routine clinical decision-making, in a broad spectrum of neurodegenerative disorders.

P73: CONCORDANCE OF THE ELECSYS® B-AMYLOID (1-42) (ABETA42) CEREBROSPINAL FLUID (CSF), TOTAL-TAU CSF (TTAU) AND PHOSPHO-TAU (181P) CSF (PTAU) IMMUNOASSAYS WITH AMYLOID-PET, AND THEIR ASSOCIATION WITH CLINICAL PROGRESSION OF ALZHEIMER'S DISEASE. Leslie M. Shaw[1], Kaj Blennow[2], Niklas Mattsson[3], John Seibyl[4], Michal Figurski[1], John Q. Trojanowski[1], Katharina Buck[5], Christina Rabe[5], Udo Eichenlaub[6], Sandra Rutz[6], Monika Widmann[7], Maryline Simon[8], Oskar Hansson[3] *((1) Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, PA, USA; (2) Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; (3) Clinical Memory Research Unit, Lund University, Malmö, Sweden; (4) Institute for Neurodegenerative Disorders, New Haven, CT, USA; (5) Genentech, South San Francisco, USA; (6) Roche Diagnostics GmbH, Penzberg, Germany; (7) Roche Diagnostics, Mannheim, Germany; (8) Roche Diagnostics, Rotkreuz, Switzerland)*

Background: The accumulation of plaques composed of amyloid beta peptides, tau protein neurofibrillary tangles, and resulting neuronal and synaptic degeneration, are hallmark pathologies of Alzheimer's disease (AD). Early diagnosis of AD is important to achieve the maximum benefit from therapeutic intervention; currently, diagnosis is largely based on clinical symptoms alone. Appropriate biomarkers could increase the accuracy of AD diagnosis and enable intervention at an earlier disease stage. Amyloid-PET is the only FDA-approved imaging method used as a reliable biomarker for the presence of amyloid plaque in the brain, but it has a number of disadvantages including high cost. An alternative approach for AD diagnosis and monitoring of disease progression could be the measurement of cerebrospinal fluid (CSF) biomarkers, such as Abeta42 and tau proteins. This study aimed to evaluate: the concordance of CSF biomarkers, namely Abeta42 and the ratios tTau/Abeta42 and pTau/Abeta42 measured by Elecsys® CSF immunoassays, with established amyloid-PET; and to further assess whether these biomarkers can be used to predict cognitive decline in the following years. *Methods:* CSF samples from the Swedish

BioFINDER study population (n=277; a prospective study including patients with mild cognitive impairment [MCI] and subjective cognitive decline) were used to assess the concordance of Abeta42, tTau/Abeta42, and pTau/Abeta42 with amyloid-PET images and derive cut-off values for these CSF biomarkers. Samples from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (n=646; including patients with subjective memory complaints, MCI, and AD) were used to validate the concordance that was shown in the BioFINDER samples. CSF concentrations of Abeta42, tTau, and pTau were measured using the Elecsys® CSF immunoassays on a cobas e 601 analyzer at different sites for BioFINDER and ADNI samples. In BioFINDER, receiver operating characteristic (ROC) analyses were conducted to assess the concordance of the CSF biomarkers with visual read amyloid-PET and determine cut-offs for each CSF biomarker that optimized concordance. As CSF sample handling differed between both studies and Abeta42 is known to be affected by pre-analytical factors, a cut-off value adjustment factor was determined in order to transfer the cut-off values defined in BioFINDER to the ADNI cohort. We assessed the performance of the adjusted pre-defined cut-offs independently in the ADNI cohort for concordance with visual read amyloid-PET using baseline CSF samples. Standard uptake value ratio (SUVR)-based classification was also evaluated. A second analysis in patients with MCI assessed the ability of CSF biomarker status, as defined by the PET-optimized cut-offs, to predict clinical progression based on the change from baseline in the Clinical Dementia Rating Sum of Boxes (CDR-SB) score over 24 months. A multivariable mixed-effects modeling approach was used, adjusting for age, sex, Apolipoprotein E4 genotype status, education, and baseline CDR-SB score. *Results:* Good concordance between CSF and PET was observed in the BioFinder cohort with superior performance of the ratios compared to Abeta42 alone. The Abeta42 cut-off value based on concordance with amyloid-PET imaging was determined to be 1100 pg/mL in BioFINDER, and the tTau/Abeta42 and pTau/Abeta42 ratio cut-offs were 0.26 and 0.022, respectively. In the ADNI cohort, CSF biomarkers showed good concordance with amyloid-PET imaging, with high positive percent agreement (PPA, sensitivity), negative percent agreement (NPA, specificity) and overall percent agreement (OPA) across all biomarkers (Table). Again, the ratios showed superior performance compared with using Abeta42 alone.

Table

Positive percent agreement (PPA), negative percent agreement (NPA), overall percent agreement (OPA) values of the adjusted ADNI CSF biomarker cut-off values with PET imaging

CSF biomarker	PET method	PPA, % (95% CI)	NPA, % (95% CI)	OPA, % (95% CI)
Abeta42	Visual read	84 (79–87)	85 (81–89)	84 (81–87)
	SUVR	79 (75–83)	84 (80–88)	81 (78–84)
tTau/Abeta42 ratio	Visual read	85 (81–89)	94 (91–96)	89 (87–91)
	SUVR	81 (76–85)	94 (91–96)	87 (84–89)
pTau/Abeta42 ratio	Visual read	88 (84–91)	93 (89–95)	90 (88–92)
	SUVR	85 (81–88)	94 (90–96)	89 (86–91)
CI, confidence interval				

Comparison of the CSF-PET concordance with the PET-inter-reader performance demonstrated a similar concordance between and within methods (biomarker ratios to visual PET OPA, 89–90%; inter-reader OPA, 91–97%), indicating that methods (CSF and PET) could be interchangeably used. There was also a high level of agreement between the SUVR and visual read (OPA, 92%). Analysis of clinical progression in the ADNI MCI population (n=398) showed a significant difference between biomarker-negative and biomarker-positive groups in terms of the change in CDR-SB score after 24 months; the biomarker-negative group remained stable with a mean change in CDR-SB score <0.5. *Conclusion:* The Elecsys® immunoassays have shown technical advantages compared with other CSF assays and are now clinically validated. In this study, we took a first step towards transferring AD CSF cut-off values between two independent cohorts, which importantly showed close agreement, despite population discrepancies between cohorts and the use of different pre-analytical handling procedures for each dataset. A high concordance was observed between the Elecsys® CSF Abeta42 immunoassay and amyloid-PET, and there was a superior concordance based on tau/Abeta42 ratios compared with Abeta42 alone. Patients classified into biomarker positive and negative groups also showed significantly different rates of progression over 24 months, with patients classified as negative remaining generally stable. This new evidence highlights a potential role for the Elecsys® CSF biomarker assays (fully automated assays that are technically superior with better reproducibility compared with previously used research platforms) in guiding the management of patients with suspected AD.

P74: CRENEZUMAB PHARMACOKINETIC-PHARMACODYNAMIC ANALYSIS TO DESCRIBE THE INCREASE IN TOTAL PLASMA AMYLOID BETA (AB) FOLLOWING TREATMENT IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE. Kenta Yoshida[1], Anita Moein[1], Tobias Bittner[2], Lee Honigberg[1], Jin Y Jin[1], Angelica Quartino[1] *((1) Genentech, Inc., a member of the Roche Group, South San Francisco, CA, USA; (2) F. Hoffman-La Roche AG, Basel, Switzerland)*

Background: Crenezumab is a monoclonal anti-amyloid beta (Aβ) immunoglobulin G4 antibody that is currently being developed for the treatment of Alzheimer's disease (AD). While crenezumab binds with highest affinity to Aβ oligomers, the form of Aβ hypothesized to mediate neurotoxicity in AD, it also binds to Aβ monomers. This monomer binding is observed as a rise in plasma Aβ following crenezumab administration. The aim of this analysis is to describe the pharmacokinetics (PK), plasma pharmacodynamics (PD) and the PK-PD relationship between serum crenezumab and monomeric plasma Aβ. *Methods:* Crenezumab serum concentrations and plasma Aβ40 and Aβ42 levels were measured in a phase Ib study evaluating the safety, tolerability and PK of escalating doses of crenezumab (30 mg/kg, 45 mg/kg, 60 mg/kg and 120 mg/kg intravenously every 4 weeks [q4wk IV]) in mild to moderate AD patients. A total of 2110 samples from 75 patients were analyzed using non-linear mixed-effects modeling using NONMEM 7.3. A target mediated drug disposition (TMDD) model was used to describe the observed serum concentrations of crenezumab, plasma concentrations of Aβ40 and Aβ42 and the PK-PD relationship. *Results:* Crenezumab serum PK displays biphasic disposition with an approximate half-life of 25 days. Steady-state concentrations were achieved within 13 weeks, with modest accumulation (~1.5-fold). Crenezumab serum PK appears to increase proportional to dose at the dose range tested, as demonstrated by the proportional increase in the PK parameters Cpeak and AUCinf, following the first administered dose. The observed serum concentrations at 60 mg/kg q4wk IV were consistent with projected exposures based on historical data (1) i.e. four-fold higher than following the 15 mg/kg dose. Total plasma Aβ40 and Aβ42 significantly increased following administration of crenezumab and reached peak response at 7–14 days post-dose. Total plasma Aβ levels increased in a dose-dependent manner; however, the increase was less

than dose-proportional. The PK-PD analysis showed that the plasma PD effect reached a plateau of approximately 29 nM for Aβ40 and 2.4 nM for Aβ42 at crenezumab serum concentrations of approximately 6,000 nM. The TMDD model reproduced observed profiles of serum crenezumab and total plasma Ab40 and Ab42. In serum, crenezumab was in a huge excess compared to total plasma Aβ; more than 100-fold and 1,000-fold higher than Aβ40 and Aβ42, respectively. As such, circulating crenezumab was predominantly unbound. On the other hand, Aβ in plasma was predominantly bound. Simulations using the model illustrated that the peak reduction in free Aβ was similar among simulated dose levels of 30 to 120 mg/kg q4wk IV, whereas a more sustained reduction in free Aβ levels is expected with higher doses. *Conclusion:* Crenezumab serum PK appears dose-proportional within the doses tested (30–120 mg/kg q4wk IV) and were consistent with projected exposures based on historical data (1). Total plasma Ab40 and Ab42 significantly increased following dosing with crenezumab. The PK-PD relationship was nonlinear and reached a plateau at the 120 mg/kg q4wk IV dose. A TMDD model described the observed data well, and provided insights into the time-course of total, bound and free crenezumab and plasma Aβ. References: 1. Polhamus D et al. CTAD 2016

P75: HGF IS ASSOCIATED WITH DECREASED SUBCORTICAL GRAY MATTER AND HIPPOCAMPAL VOLUMES ON MRI IN YOUNG AND MIDDLE-AGED ADULTS. Mekala R. Raman[1,2], Jayandra J. Himali[1,2,3], Sarah C. Conner[2,3],Charles DeCarli[5], Ramachandran S. Vasan[2,5], Alexa Beiser[1,2,3], Sudha Seshadri[1,2], Claudia L. Satizabal[1,2] *((1) Department of Neurology, Boston University School of Medicine, Boston, MA; (2) Framingham Heart Study, Framingham, MA; (3) Department of Biostatistics, Boston University School of Public Health, Boston, MA; (4) Department of Medicine, Boston University School of Medicine, Boston, MA; (5) Department of Neurology, University of California, Davis School of Medicine, Sacramento, CA)*

Background: Hepatocyte growth factor (HGF) is expressed in the brain and promotes neurogenesis, angiogenesis, and healing of vascular injury, among many other functions. HGF levels are elevated in neurons, astrocytes, and cerebrospinal fluid (CSF) of Alzheimer's disease (AD) patients, and higher levels are associated with an increased risk of stroke and its risk factors. Although the pleiotropic functions of HGF in the central nervous system recommend it as a potential therapeutic target for AD, more research is needed to elucidate the underlying mechanisms on brain health, and to this date, its associations with MRI markers of brain aging have not been explored. To fill this gap, this study investigated the associations of circulating HGF levels with MRI markers of early brain aging in young and middle-aged adults in the Framingham Heart Study. *Methods:* Participants in the third generation of the Framingham Heart Study without stroke, large cerebral brain infarcts, and other neurological disorders that might confound measures of brain structure, who had brain MRI and serum HGF measurements were included (n=1877, age 46±8). No participants had dementia. Mean interval between blood draw and MRI was 1.5±0.77 years. MRI volumetric measurements of cortical and subcortical gray matter, white matter, white matter hyperintensity, and cerebrospinal fluid were regressed into total intracranial volumes to account for differences in head sizes and the residuals from each of these models were then standardized and used as the outcome measures. HGF was natural log transformed to normalize the distribution and then standardized. In a first model, all analyses were adjusted for age, sex, and time between blood draw and MRI; a second model additionally adjusted for waist-to-hip ratio, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, and prevalent cardiovascular disease. *Results:* In the first model, higher HGF levels were associated with lower subcortical gray matter (Estimate by standard deviation units ± se=-0.06±0.02, p=0.010) and hippocampal volumes (-0.07±0.03, p=0.039) and with higher CSF volume (0.10±0.02, p<0.0001). After adjusting for vascular risk factors, only the association between HGF levels and CSF volume was significant (0.08±0.03, p<0.0001). *Conclusion:* Our results suggest that higher levels of HGF are associated with subcortical gray matter and hippocampal atrophy, corresponding with increased CSF volume, in young and middle-aged adults. The hippocampus is a key structure that is affected early in AD and subcortical gray matter structures are susceptible to small vessel disease. Increased HGF levels might indicate ongoing neuronal repair and vascular injury response due to AD or cerebral small vessel disease. Since associations with smaller subcortical gray matter and hippocampal volumes did not remain significant after adjusting for vascular risk factors, it is possible that the relationship between HGF and brain structural changes is occurring through prevalent vascular disease. While currently there is interest in testing whether HGF is an effective therapeutic target in AD, future work will help to elucidate whether HGF treatment acts on AD neurodegenerative pathways, on co-occurring vascular risk factors, or both. We plan to expand our findings by exploring associations between HGF and cognitive function in this cohort.

P76: CSF AND GENETIC BIOMARKERS IN MCI AND AD SUBJECTS IN J-ADNI FOR PREDICTING FUTURE OUTCOME. Kazushi Suzuki[1], Ryoko Ihara[1], Atsushi Iwata[1], Takeshi Iwatsubo[1], Hiroyuki Arai[2], Kenji Ishii[3], Michio Senda[4], Kengo Ito[5], Takeshi Ikeuchi[6], Ryozo Kuwano[6], Hiroshi Matsuda[7], for the Japanese ADNI *((1) The University of Tokyo, Tokyo, Japan; (2) Tohoku University, Sendai, Japan; (3) Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan; (4) Institute of Biomedical Research and Innovation, Kobe, Japan; (5) National Center for Geriatrics and Gerontology, Obu, Japan; (6) Niigata University, Niigata, Japan; (7) National Center for Neurology and Psychiatry, Kodaira, Japan)*

Background: The successful completion of the Japanese ADNI (J-ADNI) project resulted in a longitudinal dataset of Japanese normal control (NC), late mild cognitive impairment (MCI), and Alzheimer's dementia (AD) subjects. This is the first large dataset consisted of precise clinical and cognitive evaluation on the Japanese population. Since Japan is one of the most aged country among all others, J-ADNI dataset can serve as a model for other aging society. Moreover, this dataset can be also a representative for the east Asian population. The result of clinical and cognitive evaluation can be affected by the subjects' genetic, cultural and most of all the linguistic background. Thus, obtaining longitudinal data among different ethnic population is one of the key component to successful global clinical trials. Prediction of cognitive or functional decline by biomarkers is important for subject selection in AD clinical trials. By utilizing data from MCI and AD of J-ADNI, we analyzed the association between genetic biomarker (the number of APOE4 allele), amyloid biomarkers (positivity of C11-PiB or 11C-BF-227 by amyloid PET, CSF Aβ1-42), neurodegenerative biomarkers (CSF total tau (t-tau), phosphorylated tau (p-tau)) and clinical/ cognitive outcome. *Method:* The dataset of the J-ADNI (Research ID: hum0043.v1, 2016) was obtained from the National Bioscience Database Center (Tokyo, Japan). From J-ADNI dataset, 82 cognitively normal, 117 MCI, and 85 AD subjects were selected according to the availability of amyloid PET imaging data or CSF biomarker data at baseline visit. Cognitive function and clinical outcome were evaluated by Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and Clinical Dementia Rating-sum

of boxes (CDR-SB), respectively. Statistical analysis was performed by chi-square test for categorical data, correlation analysis, one-way/ANOVA or t-test for numerical data using JMP software. Data were shown in average value unless otherwise indicated. Missing values are excluded in each analysis. *Results:* Among 117 MCI subjects, 56 converted to AD during the 3-year follow-up period, 52 stayed at MCI and 9 reverted to NC. Comparison of CSF biomarker measurements at baseline between the converters and non-converters showed significantly lower Aβ1-42 levels (290.6 pg/ml vs 383.6 pg/ml, p=0.0009) and significantly higher t-tau and p-tau levels (132.7 pg/ml vs 103.0 pg/ml, p=0.0072 and 69.5 vs 50.9, p=0.0001, respectively) in converters. The correlation between Aβ1-42, t-tau and p-tau at baseline and decline in CDR-SB and ADAS-cog during the 3-year follow-up was highest with the increase in CDR-SB vs p-tau (correlation coefficient = 0.39), as well as with the increase in ADAS-cog vs Aβ1-42 (correlation coefficient = - 0.40). The association between amyloid PET positivity and conversion to dementia was examined in 73 MCI cases with PET data. Twenty-four out of the 45 subjects (53%) in the amyloid positive group converted to dementia, whereas 5 out of the 28 amyloid negative cases (18%) to dementia (P = 0.0026, OR = 5.25). The influence of the number of APOE4 alleles on future conversion to dementia was examined. Twenty-seven out of 48 MCI (56%) with one APOE4 allele, 7 out of 8 (88%) with two APOE4 alleles (88%) converted to AD, whereas 22 (42%) among 52 without APOE4 allele converted (p = 0.04). The correlation between levels of Aβ1-42, t-tau, p-tau, decline in CDR-SB, and ADAS-cog during the 2-year follow-up in 55 AD subjects with available CSF biomarkers at baseline was also examined. P-tau showed the highest correlation with the decline in CDR-SB (correlation coefficient: 0.25). The relationship between the number of APOE4 alleles and the worsening in ADAS-cog in AD subjects showed an unexpected tendency of ADAS-cog decline as the number of APOE4 alleles increased. *Conclusion:* Assessment of CSF biomarkers at the MCI stage may be useful in predicting the progression to dementia in the Japanese population. The amyloid PET positivity and APOE genotype also were useful as predictors of subsequent disease progression. In contrast, there was no clear correlation between disease progression and CSF/genetic biomarkers in AD. This result well coincides with the previous dataset from the western population, suggesting the presence of very little ethnic differences for clinical and cognitive decline in MCI and AD population.

P77: CONCORDANCE BETWEEN IN VIVO AMYLOID IMAGING AND CSF AD BIOMARKERS MEASURED BY THE AUTOMATED LUMIPULSE G ASSAY PLATFORM.

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Background: Biomarkers of Alzheimer disease (AD) brain pathology are increasingly used in trials of potential disease-modifying therapies for purposes of screening, target engagement, and outcome measures. Furthermore, by definition, such biomarkers are required for prevention trials targeting asymptomatic individuals who are in the preclinical stages of the disease. Due to methodological limitations of current cerebrospinal fluid (CSF) assays, automated platforms are being developed to hopefully provide better analytical performance. To assess the ability of one such automated assay to identify individuals with underlying AD pathology, we evaluated the correspondence between CSF β-amyloid 1-42 measured with the automated Lumipulse® G β-Amyloid 1-42 assay, the manual INNOTEST® β-AMYLOID (1-42) ELISA, and in vivo β-amyloid positron emission tomography (PET) imaging. *Methods:* One hundred ninety-eight CSF samples from a convenience cohort of research volunteers at the Knight Alzheimer Disease Research Center at Washington University who had undergone PET imaging with Pittsburgh Compound B (PIB) within 12 months of CSF collection were analyzed by the automated Lumipulse G β-Amyloid 1-42 assay and the manual INNOTEST® β-AMYLOID(1-42) and INNOTEST® β-AMYLOID(1-40) ELISAs (Fujirebio Europe). Samples were selected that spanned a wide range of associated cortical PIB PET measures, without reference to participant demographics or clinical status. For both platforms, analytes were measured from the same sample aliquot (initial freeze/thaw) on the same day. Values for Aβ1–40, Aβ1–42 and their ratios that corresponded best to PIB positivity (mean cortical PIB standardized uptake value ratio with partial volume correction [SUVR] >1.42) were determined using receiver operating characteristic (ROC) analyses. Cut-off values with the highest Youden index were established for each analyte (and their corresponding ratios), and agreement measures at these cut-offs were determined using area under the ROC curve (AUC) analyses. *Results:* Values for Aβ 1–42 obtained with the Lumipulse and INNOTEST assays were positively correlated (Pearson r = 0.8633, p<0.001), although the measured INNOTEST values were lower compared to Lumipulse (slope = 0.52 ± 0.02, Y-intercept [INNOTEST] = 185.3pg/mL; X-intercept [Lumipulse] = -356.0pg/mL). Within-sample reproducibility of a common pooled CSF quality control (QC) sample was high for all three assays (% coefficients of variation [%CV]: Lumipulse Aβ1–42 [3.9%, n=5]; INNOTEST Aβ1–42 [5.4%, n=6]; INNOTEST Aβ1–40 [9.8%, n=7]). As expected, the Aβ1–42 values discriminated PIB-positive (n=50) from PIB-negative (n=148) individuals better than Aβ1–40 values (Lumipulse Aβ1–42 AUC=0.83 [95% CI, 0.77-0.89]; INNOTEST Aβ1–42 AUC=0.88 [0.83-0.94]; INNOTEST Aβ1–40 AUC=0.57 [0.48-0.67]). Both Lumipulse and INNOTEST Aβ1–42 values, when put in a ratio with INNOTEST Aβ1–40, outperformed each single Aβ1–42 analyte value in discriminating PIB-positivity from PIB-negativity (Lumipulse Aβ1–42/INNOTEST Aβ1–40 AUC = 0.91 [0.85-0.96]; INNOTEST Aβ1–42/INNOTEST Aβ1–40 AUC = 0.88 [0.82-0.94]), with increases in both sensitivity and specificity (sensitivities/specificities ranging from 0.78-0.84/0.75-0.84, respectively, for Aβ1–42 alone and 0.82-0.88/0.85-0.88, respectively, for the Aβ1–42/Aβ 1–40 ratios). *Conclusions:* The automated Lumipulse G β-Amyloid 1-42 assay discriminated PIB-positive from PIB-negative individuals with moderate to high sensitivity and specificity, as did the manual INNOTEST ELISA platform. These preliminary findings suggest that automated platforms may offer benefits (speed; less reliance on personnel) in assaying CSF biomarkers of AD. When put in ratio with INNOTEST Aβ1–40, ratios of CSF Aβ1–42 levels derived from both assay platforms outperformed Aβ1–42 alone in discriminating amyloid PET status, with higher sensitivity and specificity than the individual Aβ1–42 values on their own. These ratios may be useful for identifying individuals with amyloid pathology for enrollment in clinical trials of disease-modifying therapies. Acknowledgements: This study was funded by the National Institutes on Aging 5P01AG003991, P50AG005681, and 2P01AG026276, and by Fujirebio Diagnostics.

Theme: Clinical trials : cognitive and functional endpoints

P78: SHORT-TERM REPEAT COGNITIVE TESTING AND ITS RELATIONSHIP TO HIPPOCAMPAL VOLUMES IN OLDER ADULTS. Kevin Duff[1], Jeff Anderson[2], Atul Mallik[2], Kayla R. Suhrie[1], Bonnie C. Allred Dalley[1], Taylor J. Atkinson[1], John M. Hoffman[2,3] *((1) Center for Alzheimer's Care, Imaging and Research, Department of Neurology, University of Utah, Salt Lake City, UT, USA; (2) Department of Radiology, University of Utah, Salt Lake City, UT, USA; (3) Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA)*

Background: Practice effects, which are improvements in cognitive test scores due to repeated exposure to testing materials, may provide information about Alzheimer's disease pathology, which could be useful for clinical trials enrichment. The current study sought to add to the limited literature on short-term practice effects on cognitive tests and their relationship to neuroimaging biomarkers. *Methods:* Twenty-five, non-demented older adults (8 cognitively intact, 17 with mild cognitive impairment) received magnetic resonance imaging and two testing sessions across one week to determine practice effects on seven neuropsychological test scores. A series of correlations examined if bilateral hippocampal volume was associated with baseline, one-week, or practice effects scores on these tests. A series of stepwise multiple regression models next examined which of the three test scores best predicted hippocampal volumes. *Results:* In the correlation analysis, baseline scores on 5 of the 7 tests were significantly associated with hippocampal volumes, one week scores were significantly related for 7 of the 7 tests, and practice effects scores were significantly correlated for 4 of the 7 tests. In the stepwise regression models, 5 of the 7 tests indicated that one-week scores best predicted hippocampal volumes. For the other 2 models, baseline score and practice effects score each best predicted hippocampal volume. *Conclusions:* These results add to the growing body of evidence suggesting that short-term repeat testing is related to neuroimaging biomarkers of Alzheimer's disease and may serve as a screening tool for clinical practice and to enrich samples for research trials.

P79: DEVELOPMENT AND VALIDATION OF A SHORT VERSION OF THE AMSTERDAM IADL QUESTIONNAIRE: A POTENTIAL FUNCTIONAL OUTCOME MEASURE FOR CLINICAL TRIALS. Roos J Jutten[1], Carel FW Peeters[2], Sophie MJ Leijdesdorff[3], Pieter Jelle Visser[1,4], Andrea B Maier[5,6], Caroline B Terwee[1], Philip Scheltens[1], Sietske AM Sikkes[1,2] *((1) Alzheimer Center, Department of Neurology, VU University Medical Center, Amsterdam Neuroscience, Amsterdam, The Netherlands; (2) Department of Epidemiology & Biostatistics, Amsterdam Public Health research institute, VU University Medical Center, Amsterdam, The Netherlands; (3) Alzheimer Center Rotterdam, Erasmus Medical Center, Rotterdam, The Netherlands; (4) Alzheimer Center, School for Mental Health and Neuroscience, University Medical Center Maastricht, The Netherlands; (5) MOVE Research Institute Amsterdam, Department of Human Movement Sciences, VU University of Amsterdam, The Netherlands; (6) Department of Medicine and Aged Care, Royal Melbourne Hospital, University of Melbourne, Australia)*

Background: Functional assessment plays a pivotal role in dementia clinical trials, particularly in the evaluation of therapies targeted at Alzheimer's disease (AD). There is a need for a psychometrically strong measure that is able to detect functional changes in the early stages of AD. Previously, the Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q) was developed: a 70-item informant-based tool with good psychometric properties regarding reliability, validity and sensitivity to changes over time. However, a drawback of the A-IADL-Q is its length, resulting in an administration time of 20-25 minutes. To facilitate its administration and implementation on a wider scale, we aimed to design a short and more concise version of the A-IADL-Q whilst preserving its psychometric quality. *Methods:* We included a total of 1355 subjects from three Dutch memory-clinics (consecutive patients, n=1251) and a cognitively healthy cohort (Amsterdam site of the European Medical Information Framework preclinAD cohort, n=104). Informants of subjects completed the A-IADL-Q on a tablet computer. Additionally, 33 international experts rated all A-IADL-Q items on their necessity for inclusion in the short version, using a visual analogue scale ranging from 0 (not necessary at all) to 100 (very necessary). We randomly split the total subject sample into a training (n=677) and validation set (n=678). Using the training set, we selected the most informative items based on a stepwise procedure combining missing data, Item Response Theory characteristics and comments from informants and experts. To confirm the quality of the short version, we subsequently investigated missing data patterns, IRT characteristics and experts' ratings in the validation set. In this validation set, we also calculated internal consistency of the short version and concordance between sum-scores derived from the short and original version. To assess the construct validity of the novel short version, we examined concordance between the short version scores and Mini-Mental State Examination (MMSE) and Disability Assessment for Dementia (DAD) scores. We evaluated interpretability of the short version scores by investigating whether IADL scores differed between diagnostic groups across the dementia spectrum. *Results:* The total study sample consisted of subjects with normal cognition (NC, n=104), Subjective Cognitive Decline (SCD, n=219), Mild Cognitive Impairment (MCI, n=138), AD dementia (n=413) and dementia other than AD (non-AD dementia, n=235). The remaining 246 subjects had other neurological or psychiatric diagnoses (Other group). Overall, subjects' age ranged from 27 to 94 (M=65.7, SD=9.7) and 44% (n=607) were female. The training and validation sets did not differ with respect to age, sex and distribution of the diagnostic groups. We ultimately selected 30 items for the short version, providing information on the entire spectrum of IADL functioning. All retained items had less than 60% missing responses in the validation set and received moderate to high expert ratings (M=70.2, SD=8.3). This short version showed high internal consistency (McDonald's Omega=.98) and high concordance with the original version (Kendall's W=.97). Concordance with the MMSE (Kendall's W=.72) and DAD (Kendall's W=.87) scores were also high. A Kruskal-Wallis test indicated that the mean IADL score ranks of the diagnostic groups indeed differed ($\chi 2$ =187.01, df = 5, p <.001). Pairwise comparisons with Bonferroni correction for multiple testing indicated the following differences: (1) NC versus all other groups (all corrected p-values < .001); (2) SCD versus AD dementia, non-AD dementia and Other group (all corrected p-values <.001); and (3) MCI versus AD dementia (corrected p-value = .002). *Conclusion:* The A-IADL-Q Short Version (A-IADL-Q-SV) consists of 30 items: we thereby reduced its administration time by approximately 10 minutes. We showed that, although significantly shorter, the A-IADL-Q-SV has maintained the psychometric quality of the original version. We demonstrated adequate measurement precision along the entire spectrum of IADL functioning. Short version scores were in high concordance with original A-IADL-Q scores, MMSE and DAD scores, supporting the construct validity of the A-IADL-Q-SV. We also found that this short version could differentiate between various

diagnostic groups with respect to IADL impairment. Our findings suggest that the A-IADL-Q-SV can already detect functional changes in the earliest stages of AD, such as SCD and MCI. Hence, we expect the short version to be a promising functional outcome measure for contemporary clinical trials focused on early stages of AD.

P80: EXPANDING THE BRIEF ASSESSMENT OF COGNITION (BAC-APP) FOR ASSESSMENT OF COGNITION IN AGING: PRELIMINARY NORMATIVE DATA AND SENSITIVITY TO SUBJECTIVE COGNITIVE DECLINE.

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Background: The Brief Assessment of Cognition (BACS) is a pen-and-paper cognitive assessment used in hundreds of research studies and clinical trials. A tablet-based version of the BACS, the BAC App, has been developed to allow standardized presentation of task instructions and stimuli, audio-recording of responses, and automatized scoring and data management. To extend use of the BAC App for assessment of cognition in aging and early detection of Mild Cognitive Impairment due to Alzheimer's disease (MCI-AD), additional tests of episodic verbal memory and visuospatial working memory were developed and incorporated. Collection of census-matched normative data in 650 healthy individuals is currently underway. We describe preliminary findings comparing normative performance of young (<55) and older (≥55) healthy adults, as well as performance of individuals with subjective cognitive complaints. *Methods:* Tasks were designed in compliance with guidance for objective psychometric tests (Ferris et al., 1997) and to enable tablet-assisted administration, automatic scoring, and data management in compliance with 21 CRF Part 11 requirements. Ongoing data collection is rapid and will be substantially larger at the time of presentation. Data currently includes 149 participants, including 63 healthy young adults (YA, <55 years), 76 healthy older adults (OA, ≥55 years), and 10 individuals with subjective cognitive decline. Participants with subjective cognitive decline were classified as such based on total scores of ≥ 4 on the self-reported Mail-In Function Cognitive Screening Instrument (MCSFI). *Results:* Means and standard deviations are presented for YAs, healthy OAs and OAs with subjective cognitive decline. Healthy OAs underperformed YAs on BAC App endpoints including verbal learning, verbal fluency, symbol coding, and token motor test ($p<.01$ for all), highlighting the importance of age-matched normative data collection. Although delayed recall did not reliably differ between healthy YAs (mean=9.01, SD=3.02) and healthy OAs (mean=8.38, SD=3.26), OAs with subjective complaints performed well below their normative counterparts (mean=4.25, SD=2.99). Visuospatial working memory performances were significantly poorer in healthy OAs as compared to YAs ($p<.01$), and preliminary data suggest even poorer performance in OAs with subjective decline. *Conclusion:* Preliminary findings suggest the BAC App is sensitive to age-related changes in cognition, and show potential sensitivity to differences between healthy OAs and those with subjective cognitive decline. Enhancement of the BAC App with additional measures of episodic memory and visuospatial working memory shows potential for increasing the utility of the measure in clinical trials for early MCI-AD.

P81: EXTRACTING DIGITAL BIOMARKERS OF SLEEP FROM 3-AXIS ACCELEROMETRY USING DEEP LEARNING.

Robin Wolz[1,2], Janet Munro[1], Ricardo Guerrero[1,2], Derek Hill[1], Yves Dauvilliers[3] *((1) IXICO Plc, London, UK; (2) Imperial College London, London, UK; (3) Sleep Unit, Department Neurology, Centre Hospitalier Universitaire, Montpellier, INSERM 1061, France)*

Background: Poor sleep quality is both a risk factor and a symptom of many neurological conditions, including Alzheimer's disease. While the gold standard for sleep assessment is polysomnography (PSG), the increasing availability of wearable sensor technology offers more practical ways of collecting "digital biomarkers" to identify risk patterns and behaviors in clinical trials and daily life. Correct interpretation of the actigraphy data is essential including clinical contextualization, for example taking into account age and neurodegenerative disorders. Advanced data analytics allows to learn highly complex movement patterns from training data, potentially allowing more accurate extraction of digital biomarkers compared to traditional analysis methods. *Methods:* Overnight PSG with simultaneous 3-axis accelerometry was undertaken on 22 elderly subjects from a community study in the Centre Hospitalier Universitaire, Montpellier (age: 85.7±3.7, 15 female, 7 male). All subjects wore two Axivity devices (http://axivity.com/) side by side on the same (non-dominant) wrist during the PSG night. "Deep Learning" techniques were used to build a convolutional neural network to predict sleep / wake status from accelerometry based on the PSG reference in a leave-one-out approach on the 22 datasets. Accuracy for correct sleep / wake classification, as well as an overall sleep efficiency measurement (time asleep / time in bed), were compared between the developed algorithm (referred to as Deep Learning Sleep - DLS) and two standard algorithms employed in current wearable devices: the ESS algorithm (Borazio 2014, Int. Conf. Health Inf.) that is provided with the Axivity device as well as the widely used Cole-Kripke algorithm (Cole 1992, Sleep). A test:re-test analysis was performed for 17 subjects that had usable data from both devices during the PSG night (in the remaining subjects, devices were not deployed correctly or the data was corrupted and not usable). *Results:* Comparing DLS with the two standard algorithms, Figure 1 shows sensitivity and specificity for detecting sleep and awake phases. Cole-Kripke provides significantly better mean sensitivity than DLS (91% compared to 80%, $p<0.05$). However, mean specificity with Cole-Kripke is substantially lower than with DLS (42% compared to 69%, $p<0.001$). Mean specificity of DLS is significantly improved from ESS (69% compared to 53%, $p<0.05$). All other comparisons are not significantly different at $p=0.05$. Figure 2 shows scatter plots for estimated sleep efficiency as compared to PSG together with Pearson correlation coefficients and 95% confidence intervals. DLS shows improved accuracy in classifying sleep / awake status, most dramatically witnessed in a significant reduction of false positive prediction of sleep. This leads to a substantially reduced error between predicted and true sleep efficiency (as measured through PSG) compared to standard algorithms. The test:re-rest analysis from the two devices worn simultaneously showed an average unsigned difference in estimated sleep efficiency of 3.1%, 6.6% and 5.2% for the Cole-Kripke, ESS and DLS algorithms respectively. *Conclusions:* The presented results show the potential of Deep Learning techniques to identify "digital biomarkers" from wearable sensor data. The developed DLS algorithm, outperformed traditional analysis techniques currently employed in commercially available devices. In elderly subjects periods of quiet (not-moving) wakefulness are common during the night; the standard actigraphy algorithms frequently incorrectly interpret these periods as sleep. Good agreement with PSG and an acceptable test:re-test performance gives an initial

positive result for the application of actigraphy-derived sleep metrics in elderly populations as a digital biomarker. Customized algorithms using advanced data analytics have the potential to outperform off-the shelf algorithms in detecting sleep disturbances.

Figure 1

Sensitivity and specificity to detect sleep with Cole-Kripke algorithm (left), ESS algorithm (middle) and DLS algorithm (right)

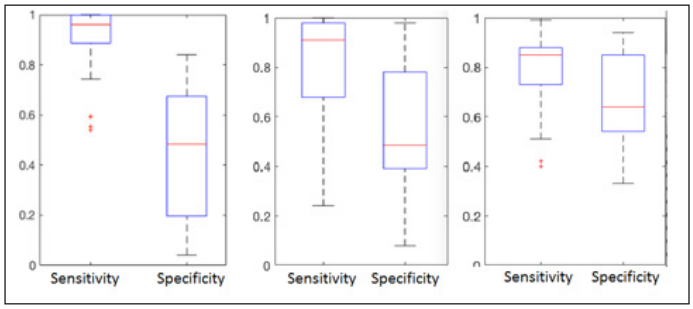
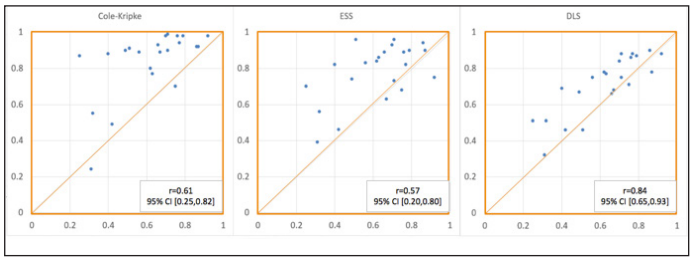


Figure 2

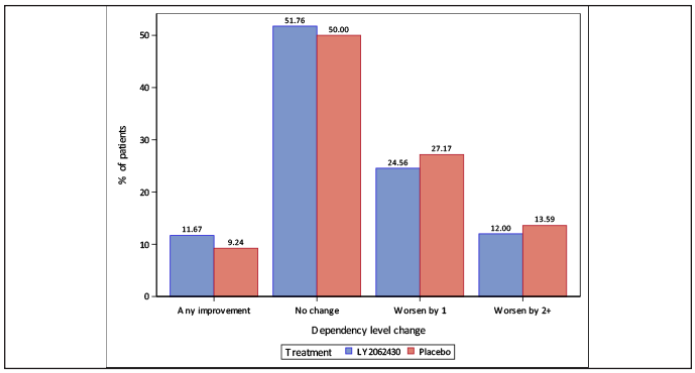
Sleep efficiency determined by the Cole-Kripke algorithm (left), the ESS algorithm (middle) and DLS algorithm (right) and comparison to PSG



P82: ASSESSING THE POTENTIAL OF PATIENT DEPENDENCE LEVELS AS A TREATMENT OUTCOME – INSIGHTS FROM EXPEDITION 3. Daniel E. Ball, J. Scott Andrews, Wenyu Ye, Ann M. Hake, Helen M. Hochstetler, Brandy R. Matthews, Kristin K. Wrobleski *(Eli Lilly and Company, Indianapolis, IN, Research funding provided by Eli Lilly and Company, Indianapolis, IN)*

Background: In addition to cognitive primary outcomes in clinical trials for Alzheimer's disease (AD), reliable measures are needed to characterize the everyday impact of the disease and potential new treatments. Historically, institutionalization was considered a relevant endpoint, but its applicability is confounded by factors including finances, insurance, caregiver availability, and the temporal association between stage of disease and likelihood of institutionalization. Researchers have proposed that considering levels of dependence, with institutionalization (or its equivalent care needs) as one end of the severity spectrum, is more informative and allows for an understanding of impact across the spectrum of disease (Stern et. al., 1994). An approach to transforming continuous functional scale scores into discrete levels of dependence was examined previously in longitudinal observational studies, with preliminary results suggesting acceptable validity and progression in dependence level over time (Kahle-Wrobleski et al., 2017). This initial work was done to inform the analysis plan for characterizing treatment effects in Phase 3 clinical trials. Although the results of the EXPEDITION 3 (EXP3) clinical trial were negative, there was a small, nonsignificant effect on cognition and a small significant effect on Activities of Daily Living (ADL) for both instrumental (iADL) and basic (bADL) components (Honig et al., CTAD 2016). We conducted additional analyses to explore changes in dependence levels across the trial population and potential differences on dependence level by treatment to inform how dependence levels may be incorporated into future clinical trials. *Methods:* The source of data was the EXP3 clinical trial, which evaluated solanezumab compared to placebo among 2129 individuals with mild AD dementia and confirmed amyloid pathology. The ADCS-ADL was collected to assess performance of ADLs at randomization and Weeks 12, 28, 40, 52, 64, 80, and at time of discontinuation if before Week 80. ADL item scores were used to map individuals into one of six dependence levels (0 to 5), as previously described in Kahle-Wrobleski et al., (2015). Level 0 – No iADL/bADL impairment; Level 1 – Some supervision needed on isolated iADLs; Level 2 – Supervision on multiple iADLs or loss of at least 1 household activity; Level 3 – Supervision on all types of iADLs or homebound; Level 4 – Supervision on some bADLs; and Level 5 – Impaired transfer or complete incontinence. Dependence levels were compared at baseline and 80 weeks to assess changes among those with data at both time points (n=1806) and in a cohort that used last observation carried forward (LOCF) to impute a value for those individuals with missing data at Week 80 (n=2122) by Cochran-Mantel-Haenszel Test. *Results:* There were 1806 (solanezumab 908 vs. placebo 898) individuals with data available at both baseline and 80 weeks. At baseline, Level 2 was most common, and the overall dependence distribution (0 to 5) was 4.2, 13.4, 60.7, 16.7, 4.7, and 0.4%, respectively. At Week 80, Level 2 remained the most common dependence level, and the overall dependence distribution (0 to 5) was 2.5, 7.4, 49.3, 24.4, 14.0, and 2.3%, respectively. Overall, 50.9% stayed at the same dependence level, 10.5% improved, and 38.7% worsened. Comparing solanezumab to placebo with respect to dependence changes: Stayed the same (51.8% vs. 50.0%), any improvement (11.7% vs. 9.2%), worsened one level (24.6% vs. 27.2%), and worsened two or more levels (12.0% vs. 13.6%) with p=0.032 (see figure). The distribution in the imputation cohort (n=2122; solanezumab 1055 vs. placebo 1067) was similar to the cohort with complete data. Overall, 51.5% stayed at the same dependence level, 9.9% improved, and 38.6% worsened. Comparing solanezumab to placebo with respect to dependence changes: Stayed the same (52.7% vs. 50.2%), any improvement (11.1% vs. 8.8%), worsened one level (23.7% vs. 27.2%), worsened two or more levels (12.5% vs. 13.8%) with p=0.020. *Conclusion:* The use of dependence levels to categorize patients according to equivalent care needs demonstrated a reasonable ability to discriminate among individuals with mild AD dementia over 80 weeks. Although more than 70% of individuals remained in the middle two levels at Week 80, more than one-third of individuals worsened by one or more dependence level. This suggests that it should be possible to detect progression to higher levels of dependence in similar cohorts with longer follow-up. Changes in dependence levels were observed over 80 weeks with slightly less worsening among the solanezumab cohort. Results show statistical significance among the cohort with complete data and among the larger LOCF cohort. Analysis of dependence level changes in clinical trials of disease-modifying agents shows promise to detect differences between cohorts, even when the treatment effect is small. Disease-modifying treatments with greater efficacy than solanezumab demonstrated in EXP3 may yield less progression in dependence, though confirmation in future studies will be necessary. In addition to demonstrating appropriate validity as an outcome measure, dependence levels may be a useful input to Health Economic models evaluating the value of AD interventions.

Figure



P83: MAXIMUM WALKING SPEED, PHYSICAL ACTIVITY, AND AD BIOMARKERS: RESULTS FROM THE HARVARD AGING BRAIN STUDY. Dylan R. Kirn[1], Rachel Buckley[1,3,4,5], Bernard Hanseeuw[1], Hannah M. Klein[1], Dorene M. Rentz[1,2], Reisa A. Sperling[1,2,3], Keith A. Johnson[1,2,3] *((1) Department of Neurology, Massachusetts General Hospital, Boston, MA, USA; (2) Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA; (3) Harvard Medical School, Boston, MA USA; (4) Florey Institutes of Neuroscience and Mental Health, Melbourne, Australia; (5) Melbourne School of Psychological Science, University of Melbourne, Australia)*

Background: The relationship between physical function and physical activity (PA) and neuroimaging markers of Alzheimer's disease (AD) pathology remains unclear. Recent evidence from post-mortem studies suggest that AD pathology, namely, β-amyloid (Aβ) plaques and neurofibrillary tau tangles, may not only influence decline in cognition, but physical functioning as well. In addition, PA reduces the risk for dementia onset, though there is no consensus regarding the mechanism driving this relationship. This study examines the longitudinal relationship between baseline neuroimaging AD biomarkers, and changes in maximum walking speed (MWS) and self-reported PA in clinically normal older adults. We focused on neuroimaging markers of Aβ, tau and glucose metabolism using positron emission tomography (PET), paying particular attention to AD regions of interest and also the striatal region, which is disrupted early in neurodegenerative movement disorders, such as Parkinson's disease. *Methods:* 299 clinically normal older adults (Age=73.3±6.8 years, 59.1% female) were followed over a period of approximately six years (median number of visits = 4). Aβ (n=299), tau (n=147) and striatal glucose metabolism (n=299) were measured with PET using 11C Pittsburgh compound B (PIB), 18F-Flortaucipir (T807/AV1451), and 18F-fluorodeoxyglucose (FDG), respectively. A smaller sample was available for Flortaucipir-PET, as this tracer was introduced later in the study. A global measure of neocortical Aβ PiB-PET were represented by a summary distribution volume ratio (DVR) of frontal, lateral temporal, and retrosplenial (FLR) tracer uptake. These regions have been previously published by our group as an aggregate of AD regions of interest. Posterior cingulate glucose metabolism was used as the FDG-PET AD region of interest. Striatal Aβ and FDG was measured with a composite of caudate and putamen regions in both PET measures. For tau, we analyzed the inferiortemporal (IT) and entorhinal cortical (EC) tau as AD regions of interest. All measures were referenced to cerebellar grey cortex, and partial volume corrected (PVC). PA was collected using the self-reported Community Healthy Activities Model Program for Seniors (CHAMPS). MWS was collected using a 15-ft course, where subjects were instructed to walk to the end of the course, pivot, and return as quickly as possible. Time to complete the walk was converted to meters per second (m/s). First, we examined cross-sectional relationships between MWS, PA, and AD biomarkers. We subsequently analyzed longitudinal relationships. MWS was collected each year over the six-year period, and so linear mixed models were conducted to determine the association between baseline AD biomarkers and change in MWS over time, after adjusting for age, sex, and BMI. Self-reported PA, on the other hand, was collected at two time points (baseline and at the fourth year); as such, change slopes were extracted from a PA-by-time linear mixed model. Subsequently, we ran linear regressions to determine whether these PA change slopes were related to baseline AD biomarkers, after adjusting for age, sex, and BMI. *Results:* At baseline, we observed a significant correlation between MWS and PA ($r(277)=0.19$, $p=0.003$). Cross-sectionally, no relationships were observed with MWS and baseline neuroimaging AD biomarkers including global Aβ ($\beta=0.03$, $p=0.6$), striatal Aβ ($\beta=0.05$, $p=0.3$), or IT/EC tau ($\beta=0.0$, $p=0.9$; $\beta=0.0$, $p=0.9$, respectively). A significant cross-sectional relationship was observed between MWS and glucose metabolism in the posterior cingulate ($\beta=0.14$, $p=0.008$), and striatum ($\beta=0.15$, $p<0.001$). No significant relationships were observed cross-sectionally between PA and global Aβ, striatal Aβ, IT/EC tau, glucose metabolism in the posterior cingulate or striatum. Longitudinally, no statistically significant relationships were observed between longitudinal MWS and baseline AD biomarkers when examined in fully adjusted models. We found declining self-reported PA to be independently associated with higher levels of baseline global Aβ ($\beta=-0.17$, $p=0.01$) and baseline striatal Aβ ($\beta=-0.16$, $p=0.02$). In addition, declining PA was related to elevated levels of baseline EC tau ($\beta=-0.20$, $p=0.04$), though the relationship with baseline IT region was trend level ($\beta=-0.18$, $p=0.06$). No relationship was observed between changes in PA and baseline glucose metabolism in the posterior cingulate ($\beta=-0.02$, $p=0.60$) or striatum ($\beta=-0.03$, $p=0.75$). *Conclusion:* This is the first study to examine the relationship between baseline Aβ, tau, and glucose metabolism and changes in both PA and MWS in clinically normal older adults. While higher MWS was related to greater glucose metabolism, PA did not exhibit relationships with AD biomarkers at the cross-section. By contrast, we found small but significant relationships between increasing levels of baseline Aβ (global and striatal) and entorhinal tau, and declines in self-reported PA. These findings suggest that changes in self-reported PA may serve as a meaningful functional outcome in clinically-normal older adults.

P84: PROVIDING CULTURALLY SENSITIVE TRAINING AND MONITORING TO CLINICIANS ADMINISTERING FUNCTIONAL ASSESSMENTS IN DEMENTIA GLOBAL TRIALS. Magdalena Perez[1], Julie Marsh[1], Chris Brady[1], Patricia Belchior[2], Isabelle Gelinas[3], Christelle Giroudet[4], Caroline Anfray[4], Shuhong Zhao[1] *((1) inVentiv Health, Somerset, New Jersey, United States; (2) Centre de Recherche Institut Universitaire de Geriatrie de Montreal, McGill University, Montreal, Quebec, Canada; (3) Centre de Recherche Interdisciplinaire en Readaptation du Montreal, McGill University; (4) MAPI, Lyon, France)*

Background: Functional performance is usually defined in the literature as the ability to perform activities of daily living (ADLs). It includes basic ADLs, activities that are part of our daily habits and we usually perform them automatically, such as eating or brushing teeth and instrumental ADLs (IADLs), more complex activities that are usually crucial for independent living, such as managing finances or preparing meals. Many studies have compared ADL and IADL performance in normal aging, mild cognitive impairment and dementia and it is well established that there is a continuum of functional decline. For this reason, functional performance is often a

co-primary outcome in Alzheimer's disease (AD) trials, though it is challenging to measure in global trials. Most of the functional decline experienced in the early stages of dementia goes unnoticed because it is perceived as decline associated with normal aging, thus, a great window of opportunity for early intervention is being missed. Another important issue in measuring functional performance is that unlike other outcome measures collected in AD trials (i.e., measurements of cognition), functional performance is highly influenced by the societal and cultural background of patients. As a result, the ADLs and IADLs that are evaluated within a functional assessment scale may vary across countries, which should be taken into consideration when clinicians are trained to administer these scales in global AD trials. This study hypothesized that in order to maximize the validity and reliability of the data collected, clinicians should be provided with standardized culturally sensitive scale training and central review of their administration of theses scales. This hypothesis was explored by examining the efficacy of a culturally sensitive training program by evaluating the clinicians' performance on a knowledge test and their performance on their first in-study administration of the functional assessment. *Methods:* A total of 345 clinicians from 17 countries participating in 2 AD clinical trials were qualified to participate in a culturally sensitive training program on a functional assessment scale; the Disability Assessment for Dementia (DAD). The training program included a didactic session that reviewed the standard DAD administration and scoring guidelines and included culturally sensitive techniques tailored to account for the diversity across the participating countries. These techniques involved providing clinicians with interview skills training to ask the DAD items that tend to be more personal/sensitive and ways to explain the structure of the questionnaire. Next, clinicians were required to complete a culturally neutral evaluation exercise where they rated a written vignette illustrating the caregiver responses to the DAD items. The didactic presentation and exercise were both translated by MAPI into the clinicians' native language to maximize their understanding of the material. Once clinicians successfully completed the training program, they were then asked to audio-record their first in-study administration of the DAD and submit it for review by a cultural expert from their respective countries. A total of 133 audio-recorded administrations were reviewed and rated on Rating Adherence (RAd) and Rating Accuracy (RAc) on a 4-point scale: 0=Unsatisfactory; 1=Fair; 2=Good, and 3=Excellent. *Results:* Clinicians performance on the training program was evaluated by examining 1) the degree of clinician agreement with the expert panel criterion scores on the DAD vignette using the Mean Difference Inter-rater Score (MDIS) analysis and 2) the degree of inter-rater reliability (IRR) on the scores they provided for this vignette using Gwen's AC1 index. The MDIS result was 0.08 showing that the clinicians rated very similarly to the expert panel criterion scores. Inter-rater reliability (IRR) results showed that 83% of the clinicians had substantial to almost perfect agreement among themselves. Clinician's performance on the audio-review program was evaluated by examining the group's mean on RAd and RAc and determining if an overall country difference existed on these measures. A pairwise comparison of RAd to RAc indicated that clinicians performed significantly better on RAc (M=2.86) than RAd (M =2.16). Results of an ANOVA performed to examine country effect indicated that there was no overall significant country effect for either RAd or RAc. *Conclusions:* In order to maximize reliability of study data in global clinical trials, training on functional assessments requires a standard approach that incorporates culturally-sensitive components. Clinicians rated very reliably in relation to the criterion scores of the vignette exercise indicating a solid understanding of the DAD's scoring rules. This understanding was further demonstrated in the inter-rater agreement on the vignette exercise indicating that clinicians were harmonized on how they applied the DAD guidelines. Audio review of clinician's first in-study DAD administration indicated that clinicians applied the scoring rules very strictly, but may have slightly deviated from the administration guidelines lowering their RAd score, but not to a degree that it would comprise the validity of the assessment. Lastly, there were no country differences on how clinicians performed on RAd and RAc indicating that clinicians were globally harmonized on how they conducted and scored the DAD.

P85: GAINING EFFICIENCIES IN PREVENTION TRIAL DESIGN: SAMPLE SIZE PROJECTIONS ACROSS CATEGORICAL AND CONTINUOUS COGNITIVE ENDPOINTS. Rebecca L. Koscik[1], Erin M. Jonaitis[1], Bruce P. Hermann[1,2] , Lindsay R. Clark[1,3], Cindy M. Carlsson[1,3], Sterling C. Johnson[1,3] *((1) Wisconsin Alzheimer's Institute, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; (2) Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; (3) Geriatric Research Education and Clinical Center, Wm. S. Middleton Veterans Hospital, USA, Madison WI USA)*

Background: By the time AD is diagnosed, brain pathologies including amyloid, tau, or neurodegeneration are present along with significant cognitive deficits in domains such as memory and executive function. Early intervention holds promise for preventing or delaying the cognitive declines and functional impairments associated with AD. Designing cost-effective AD prevention studies requires careful consideration of study entry criteria and outcome selection. The aim of this study is to compare sample size requirements needed to have 80% power to detect meaningful differences for different cognitive outcomes and cognitive status entry criteria for two-armed intervention/prevention studies designed to improve cognitive outcomes. *Methods:* Sample size projections are based on data from the Wisconsin Registry for Alzheimer's Prevention (WRAP). WRAP is a longitudinal study of cognition designed to identify midlife health and lifestyle predictors of AD. For this study, participants with at least 3 study visits who were free of neuropsychological disorders at baseline and free of clinical cognitive impairment were included (n=1084; 69% women; mean(sd) baseline age and follow-up years= 54.1(6.5), 9.6(2.2)). After each study visit, a review process is used to determine current cognitive status (unimpaired/cognitively normal, preclinical/early Mild Cognitive Impairment (eMCI), clinical MCI, or AD). Binary outcomes for the sample size projections included progression to a worse level of impairment or reversion from eMCI to unimpaired. Continuous outcomes were calculated as visit-to-visit change on nine individual tests scores (3 each for the domains: immediate memory, delayed memory, and executive function) and four composite scores (each of the 3 domains just listed plus a global composite of the average change across the nine scores). To facilitate comparisons across individual tests and composites, individual test change scores were standardized to a mean(sd) of 100(15) and were calculated such that lower scores represented greater decline. We began by determining sample sizes needed to detect a 25% improvement in each outcome type (e.g., reduction in progression to more impaired cognitive status or improvement in reversion to unimpaired when starting out eMCI; α=.05, power=.80). Given that a 25% improvement in continuous outcomes was equivalent to extremely large Cohen's d (>2), we present sample sizes needed to have 80% power to detect small, medium and large effects sizes (i.e., Cohen's d of .2, .5, and .8) for continuous change outcomes. *Results:* 1) Binary outcomes: After adjusting for baseline age and follow-up years, eMCI predicted increased risk of progression to a clinical status at a later visit (OR(95%CI)=5.9(2.9-11.9)). 6.5% of

people aged 59-65 progressed to a worse level of impairment over 4 years. 52.2% who were eMCI at one visit reverted to unimpaired at the subsequent visit approximately 2 years later. To detect a 25% reduction in 4-year progression in impairment for persons in this age range and eMCI at worst at study entry, a total of approximately 3288 participants would be needed for a two-group study (α=.05, power=.80). To detect a 25% improvement from eMCI to unimpaired in a sample that was eMCI at study entry, 221 total participants would be needed. 2) Continuous change outcomes: Sample sizes needed to have 80% power to detect small, medium and large effect sizes for change outcomes ranged from totals of 50 (large effect size) to 784 (small effect size). Average change for the standardized change scores was 100 for both individual tests and composite scores. Composite scores, however, resulted in much lower standard deviations than the sd=15 for the individual scores (~35% lower for 3-test composites and ~52% lower for 9-test composite). Because of the reduced variability, a Cohen's d of .8 corresponds to a between-group difference of 5.7 for the composite score and 12 for a single test score. In other words, when using a composite score, the same sample size will yield adequate power to detect smaller absolute between-group differences. *Conclusion:* Interventions that prevent or delay the onset of AD are critically needed. Focusing early intervention studies on people who meet criteria for eMCI at study entry may be an effective approach since this group is at increased risk of progressing to clinical levels of cognitive impairment. Given the low rate of progression to clinical statuses over a 3-4 year window, however, powering to detect improvements in the rate of reversion to unimpaired will be more feasible than powering to detect reductions in progression to clinical statuses. Composite measures of change have smaller variance than their contributing scores resulting in greater power to detect the same amount of visit-to-visit change. Use of the preclinical MCI construct or composite measures of change in study design hold promise to reduce sample size requirements, making studies more cost-effective to run and recruitment more feasible.

P86: LONGITUDINAL DATA MODELING: AN APPROACH TO ENABLE THE PREDICTION OF BIOMARKER TRAJECTORIES FOR ALZHEIMER'S DISEASE. Meemansa Sood[1,2], Sven Hodapp[1], Anandhi Iyappan[1,2], Marc Jacobs[1], Martin Hofmann-Apitius[1,2] *((1) Department of Bioinformatics, Fraunhofer Institute for Algorithms and Scientific Computing, Sankt Augustin 53754, Germany; (2) Rheinische Friedrich-Wilhelms-Universität Bonn, Bonn-Aachen International Center for IT, Dahlmannstrasse 2, 53113 Bonn, Germany)*

Backgrounds: Neurodegenerative Diseases are characterized by their long incubation period and their unknown aetiology. The analysis of temporal aspects of disease initiation and progression is further complicated by the fact that almost all studies on Alzheimer's disease (AD) have only a very limited observation time range. Often, cross-sectional studies are designed to avoid the need to follow patients over longer time span. The lack of follow-up data, however, makes the validation of prediction models very difficult. Integration of heterogeneous information in a longitudinal model of disease offers a promising route to overcome some of the limitations inherent to cross-sectional data. In particular, the abstraction that comes with longitudinal modeling fundamentally improves our understanding of clinical trial data and it allows us to identify subtype-specific, stratifying biomarker trajectories. Alzheimer's disease Neuroimaging Initiative (ADNI) was designed to develop clinical, genetic and biochemical biomarkers from longitudinal studies related to clinical trials on a longitudinal basis. ADNI is the longest longitudinal study going on till date and provides a platform to build a longitudinal model for different biomarkers. *Methods:* We have used a linear mixed modeling approach to develop a longitudinal model for AD. A linear mixed model (LMM) comes into play when the values in the data are not independent of each other. It takes fixed effects and random effects into consideration. Fixed effects are expected to have a systematic and predictable influence on the data while random effect is assumed to have a non-systematic, or unpredictable effect. The data we deal with here is in longitudinal format, which means one subject is measured over a certain number of months/years. A random effect is added for each subject to deal with this type of situation, because the individual differences can be modeled by assuming different intercepts for each subject. This LMM is further applied to predict trends of sub-populations over various stages of the disease. The disease indicators are an essential component of the LMM, which help to predict the prognosis of the disease. These disease indicators also known as predictors enable the prediction of a particular value of a biomarker at a specific time point. We have also designed an algorithm, which follows a re-sampling approach to derive clinical data from the literature. This algorithm enables the conversion of unstructured data present in the scientific literature to a structured format. A comparative analysis was further performed on this cohort of structured data and the ADNI data to determine the accuracy and the reliability of the re-sampling approach. *Results:* The longitudinal model developed helps to predict the values of biomarkers from diverse set of predictors. The combination of fixed and random effect predictors are found to have a significant effect on the biomarkers. Fixed effects such as the repetitive time point of measurement and the gender of the subject play an important role in the prediction of brain volumes such as hippocampal and ventricle volume and cerebrospinal fluid biomarkers such as Abeta. These predicted values further assist in the generation of the trajectories for separate stages of the disease over longitudinal time points of measurement. Our re-sampling approach enables the integration of literature data with ADNI data. This approach proved to be valuable as it enables a comparison of literature data with the ADNI trajectories. The pattern of biomarker trajectories along the progression of disease in both data sets were observed to be similar. However, the algorithm underlying this approach needs to be made robust so that it could be extended to the diverse set of literature data available. *Conclusion:* We need longitudinal modeling, data representation, prediction and simulation capabilities to derive informative patterns for diseases like AD. We need to limit the analysis on individual cohorts and lay our main focus on making different clinical studies comparable. In future, the comparative analysis on various studies can be done on the basis of the biomarker trajectories developed from the LMM. It is noteworthy that our approach will be also used for the generative creation of virtual patient cohorts that mimic the distribution of variables in AD studies.

Theme: Cognitive assessment and clinical trials

P87: USE OF THE CVLT-II AS A PRE-SCREENING TOOL TO REDUCE SCREEN FAILS IN MCI CLINICAL TRIALS. Marieke Cajal, Lauren Trottier, Katherine Kruczek, Pamela Voccia1, Craig Curtis, Ira Goodman *(Compass Research – Bioclinica, Orlando, FL, USA)*

Backgrounds: Over the last few years, the Alzheimer's Disease (AD) clinical trial landscape has progressively shifted to include Mild Cognitive Impairment (MCI) as a focus of study. With the rise of early detection tools such as amyloid PET scans and amyloid cerebrospinal fluid detection, potential therapeutics can be evaluated in MCI subjects, with the belief that they are more likely to have an impact in that population. Selecting appropriate subjects with

MCI due to AD has introduced several challenges resulting in an increasing complexity of clinical trials and a surge in screen failure rates. A common screen fail reason is failure to meet MCI criteria on cognitive testing scales. The use of cognitive testing for inclusion into MCI trials is becoming the standard in order to exclude subjects with cognitive changes associated with normal aging as well as to identify those subjects most likely to have increased amyloid burden and/or most likely to demonstrate progressive cognitive impairment over the course of the study. In an effort to reduce the number of screen failures on cognitive testing, some research sites have instituted a mandatory pre-screen for all MCI and AD subjects. The pre-screening process includes subject and caregiver interviews in addition to brief cognitive testing. There are several challenges in selecting cognitive assessments to use at pre-screen. First, those assessments should be distinct from those used in the study so as to not impact study results. Second, administration time needs to be brief in order to accommodate for high pre-screening volume and minimize subject and site burden. Third, they must reliably distinguish between normal aging and MCI due to AD by predicting performance on common assessments utilized for inclusion in MCI trials. The California Verbal Learning Test-Second Edition - Short Form (CVLT-II-SF) meets the criteria of distinctiveness and brevity of administration. The CVLT-II-SF is a brief test of verbal memory and assesses for learning, immediate and delayed free recall, immediate and delayed cued recall, and recognition of words. The test takes approximately 30 minutes to administer, including a 15-minute delay. The correlation between the CVLT-II-SF at pre-screen and several common screening scales was assessed. *Methods:* The CVLT-II-SF was systematically administered at pre-screen to potential subjects at two large research site in Orlando and The Villages for 4 months, and screening scores were collected on all pre-screened subjects who subsequently decided to participate in a clinical trial. A total of 51 pre-screened subjects signed consent for a clinical trial and completed associated screening scales. The most commonly used screening scales at the site were the Mini–Mental State Examination (MMSE), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Free and Cued Selective Reminding Test (FCSRT), and the International Shopping List Test (ISLT). The MMSE was performed on 43 subjects, the RBANS on 15, the FCSRT on 9, and the ILST on 8. As inclusion criteria for MCI or AD studies typically tend to use indicators of memory performance after delay, only the Delayed Memory Index (DMI) and its subtests were analyzed from the RBANS, and only the Free Recall, Delayed Cued Recall, and Cueing Index were analyzed from the FCSRT. Both the Immediate Recall and Delayed Recall were used from the ISLT. Subjects' raw scores were converted to Z-scores prior to analysis. Correlations were assessed between the tests and subtests noted above and the delayed memory components of the CVLT-II-SF. In particular, the Long-Delay Free Recall (LDF), Long-Delay Cued Recall (LDC), Long-Delay Recognition Hits (LDR_Hit), and Long-Delay Recognition False-Positives (LDR_FP) were used in this study. The inverse of the LDR_FP Z-score was used for consistent interpretation of lower scores to indicate worse performance. *Results:* The CVLT-II-SF was affordable and easy to administer in the pre-screening context. No correlation was observed between the CVLT-II-SF subtests and the ISLT scores, although the small sample size likely impacted the results; more data will need to be collected to assess the relationship between these assessments. A moderate correlation was found between the CVLT-II-SF and the MMSE Total Score (LDF and LDC r = 0.53, LDR_FP r = 0.63). The CVLT-II-SF LDF and LDC strongly correlated with all delayed memory scores on the FCSRT (r = 0.7) as well as with the RBANS List Recall (r = 0.62 and 0.63 respectively), Story Recall (r = 0.64 and 0.58), and Figure Recall (r = 0.55 and 0.62). *Conclusion:* The CVLT-II-SF can successfully be used as a pre-screening tool to help predict performance on the RBANS and FCSRT, which may reduce the rate of screen failures in MCI trials. The results demonstrate the efficacy of the CVLT-II as a pre-screening measure. Data on the CVLT-II-SF will continue to be collected in order to further assess its predictive performance on common assessments used for inclusion in MCI trials.

P88: ENRICHING PARTICIPANT ELIGIBILITY FOR EARLY AD CLINICAL TRIALS THROUGH COMPUTERIZED PRE-SCREENING FOR EPISODIC MEMORY DEFICIT. Kenton Zavitz, Rosemary Abbott, Francesca Cormack, Pasquale Dente, Jennifer H Barnett *(Cambridge Cognition, Cambridge, UK)*

Background: Prodromal AD is defined through a combination of subtle cognitive decline and the presence of AD biomarkers. Identifying such patients is important in successfully implementing clinical trials of disease modifying drugs. However, subjective cognitive problems are poor predictors of both objectively measured cognitive decline and the presence of AD biomarkers in CSF or amyloid PET imaging. Both CSF screening through lumber puncture and PET imaging are costly, invasive and difficult to scale. Pre-screening on objective cognitive tests has the potential to increase the proportion of trial participants who will meet the inclusion criteria at screening and minimise costly screen failures. Prior research has established that scores on the CANTAB Paired Associates Learning (PAL) task of episodic memory correlate with both AD biomarkers and other measures of cognitive impairment. The PAL test can be delivered online, enabling large scale screening. Here we summarise data on the use of PAL to enhance various samples for specific trial requirements, such as biomarker positive participants or deficits in other cognitive screening tasks (e.g. CERAD list learning, Clinical Dementia Rating Scale (CDR), and Mini-mental state examination (MMSE)). *Methods:* Data are reviewed from a number of different studies using CANTAB PAL, demonstrating the correlations, sensitivity and specificity for biomarkers (AB1-42,Tau) and impairment on other cognitive tests commonly used as inclusion criteria for clinical trials in prodromal AD subjects. Samples range from large epidemiological study (n=1700) to a mixed population sample (n=211). Data are analysed using Pearson correlation coefficients, ROC curves, demographically adjusted logistic regression, and subject scores relative to quantile bands of normative (PAL) data. Estimates for improving sample selection were based on the age-specific probability of biomarker positivity in the general population. *Results:* The correlation between PAL and other measures of memory ranged from -.65 to -0.81. Logistic regression models, which included weightings for demographic characteristics showed excellent ability to discriminate participants with a deficit in memory tasks with an area under the curve of 0.89 to 0.96. A complementary approach using normative comparisons based on 1,700 individuals over 50 years of age, also showed good discrimination in distinguishing patients with and without memory problems on other cognitive measures. Enrichment for beta amyloid positivity showed that as the level of impairment on the PAL task increases, the number of subjects that require CSF sampling (or amyloid PET imaging) to identify cerebral amyloid positivity is reduced. The percentage reduction is a trade-off between sensitivity and specificity (maximizing true positives and minimizing false negatives) and can be tailored to meet specific trial requirements, such as for more impaired (MCI) versus less impaired ('asymptomatic at risk for AD') populations. *Conclusions:* PAL is a brief, computerised test which can be used to pre-screen subjects and identify those with episodic memory deficits early in the recruitment process, to enrich samples for biomarker positive subjects. This task can be used at home as a web-based

assessment as well as in-clinic, potentially reducing trial costs, screen failure rates, site and patient burden, by targeting subjects with a high probability of meeting screening criteria.

P89: AN OBJECTIVE CLINICAL VOCABULARY FOR THE TEMPORAL UNFOLDING OF AD BIOMARKERS: STAGES OF OBJECTIVE MEMORY IMPAIRMENT. Ellen Grober[1], Amy E. Veroff[2] *((1) Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA; (2) Consultant, Bethesda, Maryland, USA)*

Background: In clinical trials, to screen for preclinical AD in asymptomatic older adults using biomarkers is expensive (amyloid or Tau PET) or invasive (CSF assessment of amyloid and Tau biomarkers) and is unsuitable for large-scale population-based intervention. In addition, the rate of clinical decline in the presence of cerebral amyloid is highly variable, affected by known (e.g. ApoE4 carriage) and unknown factors. Furthermore, the revised system for classifying biomarker trajectories is agnostic with regard to the order in which these biomarkers emerge. An objective clinical vocabulary for understanding the temporal unfolding of AD biomarkers in the revised classification system is needed (Jack et al, 2016). The Stages of Objective Memory Impairment (SOMI) reliably identifies points of transition in the emergence of episodic memory impairment using performance on the picture version of the Free and Cued Selective Reminding Test with Immediate Recall (pFCSRT+IR) (Grober et al, 2016). The SOMI system includes four sequential pre-dementia stages of declining episodic memory, and one clinical dementia stage (Table 1). It was based on the extensive literature mapping FCSRT performance to clinical outcomes and biological markers, and change in rates of free and total recall decline in longitudinal preclinical data. *Methods:* The SOMI was used to distinguish at cross-section 1344 participants from the EAS (age=77.2; education=13.5) who remained dementia-free from 141 participants (age=79.5; education=12.3) who developed AD over five years of follow-up. pFCSRT+IR performance from the final wave of the controls and the diagnostic wave of the AD cases was assigned to a SOMI stage using the FR and TR cut-scores in the Table 1. Based on the notion that impairment of total recall on the FCSRT+IR defines the typical clinical phenotype of AD, the assessments with impaired TR (SOMI stages 2b and 3) were considered positive for dementia (Dubois et al, 2016). *Results:* The sensitivity and specificity of the SOMI system for distinguishing persons with incipient AD from dementia-free persons was estimated by sorting into their respective SOMI stages the diagnostic assessment of the AD cases and the last assessment of the controls (Table 2). At the last assessment, conducted about five years from their baseline visit, 20% of the controls were diagnosed with an MCI subtype. Sensitivity was 81% (114/141) when the 16% (22/141) of the AD assessments that were not were not classified by the SOMI system were considered misses. Specificity was 86% (1169/1366) when the 9% (126/1366) of the unclassified assessments from the controls were considered false alarms. *Conclusion:* The SOMI system provides a clinical vocabulary for describing the severity of episodic memory impairment in preclinical AD that can be used alongside the latest iteration of a classification scheme for AD biomarkers that divides the seven major anti-mortem AD biomarkers into three binary classes based on the pathophysiology that each biomarker measures: Aß biomarker (A: amyloid PET or CSF Aß 42), tau pathology biomarker (T: CSF p-tau or tau PET) or neurodegeneration or neuronal injury (N: CSF t-tau, FDG PET, structural MRI). The last column of Table 1 shows the hypothesized association of each SOMI stage with the A, T, and N biomarkers largely based biomarker associations with FCRT performance summarized in Table 1. The absence of FR or TR impairment in SOMI 0 may indicate the absence of any biomarker abnormality. A positive Aß marker at this stage would not be surprising given the presence of amyloid deposition up to 20 years before clinical dementia. Impaired FR and intact TR in SOMI 1 is presumed to reflect amyloid deposition and absence of tau pathology or neurodegeneration. The status of tau pathology is uncertain in the first prodromal stage (SOMI 2a) when TR is still intact but FR has declined further and executive dysfunction accelerates. Tau pathology is abnormal in the second prodromal stage (SOMI 2b) when TR is impaired. Evidence of neurodegeneration may be present at this stage as well. At SOMI 3, all three biomarkers are predicted to be present. Whether or not the expected associations between SOMI stages and the three classes of biomarkers are observed in future studies, the SOMI system provides needed clinical vocabulary for understanding the temporal trajectory of AD biomarkers. For completed or ongoing MCI/prodromal/early AD clinical trials using the FCSRT with brain amyloidosis as the biomarker inclusion criterion, applying the SOMI stages to the data retrospectively may help in the interpretation of existing clinical trial data where amyloidosis was used for subject selection. In addition, for measuring efficacy in early AD clinical trials there is increased interest in the use of the sum of FR plus TR to be sensitive to both the earliest signs of episodic memory impairment and to change across a wide range of severity of impairment as participants decline (Coley et al, 2016).

P90: OBJECT AND SCENE MEMORY ARE DIFFERENTIALLY ASSOCIATED WITH CSF MARKERS OF ALZHEIMER'S DISEASE AND MRI VOLUMETRY. David Berron[1,2], Hartmut Schütze[1], Arturo Cardenas-Blanco[2], Klaus Fliessbach[4,5], Michael Wagner[4,5], Annika Spottke[5], Martin Reuter[5,17,18], Stefan Teipel[6,7], Katharina Bürger[9,10], Schneider, Anja[4,5], Oliver Peters[11,12], Peter Nestor[2], Josef Priller[11,12], Jens Wiltfang[13,14], Christoph Laske[15,16], Frank Jessen[4,8], Emrah Düzel[1,2,3], and the DELCODE consortium *((1) Institute of Cognitive Neurology and Dementia Research, Otto von Guericke University Magdeburg, Germany; (2) German Center for Neurodegenerative Diseases Magdeburg, Germany; (3) Institute of Cognitive Neuroscience, University College London, United Kingdom; (4) Department of Psychiatry, University Hospital Bonn, Bonn, Germany; (5) German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; (6) Department of Psychosomatic Medicine, University Medicine Rostock, Rostock, Germany; (7) German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany; (8) Department of Psychiatry, University of Cologne, Cologne, Germany; (9) Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilians-Universität (LMU), Munich, Germany; (10) German Center for Neurodegenerative Diseases (DZNE), Munich, Germany; (11) Department of Psychiatry, Charité-Universitätsmedizin Berlin, Berlin, Germany; (12) German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany; (13) Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany; (14) German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany; (15) Department of Psychiatry and Psychotherapy, Eberhard Karls University, Tübingen, Germany; (16) German Center for Neurodegenerative Diseases (DZNE), Tübingen, German; (17) Department of Radiology, Harvard Medical School, Boston, USA; (18) Computer Science and Artificial Intelligence Lab, Massachusetts Institute of Technology, Cambridge, USA)*

Background: Alzheimer's Disease (AD) is characterized by progressive tau-pathology in perirhinal and entorhinal cortices (ErC), hippocampus, parahippocampal cortex and the retrosplenial/posterior

cingulate region (RS/PCC). The latter also shows early amyloid plaque accumulation. While these regions form a network for complex objects-in-scene memories, there is a segregation of object memory into a perirhinal-entorhinal and scene-layout memory into a RS/PCC-parahippocampal-entorhinal pathway. Here we investigated whether complex objects-in-scene memory, as opposed to isolated object or scene-layout memory is correlated with CSF levels of Aß42 and phospho-tau and MR volume and thickness measures. In addition, we investigated whether the same cognitive tasks can be performed using mobile smartphone-based versions. *Methods:* 204 participants (cognitively healthy, subjective memory complaints, mild cognitive impairment or early AD) of the DELCODE study of the DZNE performed a complex scene recognition memory task. CSF samples were available from 80 participants. 78 participants also performed a second task on mnemonic discrimination of objects (in the absence of scenes) or scenes (in the absence of objects). Of these 28 CSF samples were available. MR thickness measures were obtained from T1 and T2-weighted images using Freesurfer 6. We also tested whether mobile smartphone-based versions of the tasks yield similar results compared to in-lab test sessions. *Results:* Objects-in-scene recognition memory correlated with PCC and hippocampal volume, Aß42, phospho-tau and their ratio. Isolated object and scene discrimination correlated with hippocampal volume and ErC thickness. A scene-minus-object difference score correlated with Aß42 levels indicating that decreasing levels of Aß42 were associated with selective decline of scene discrimination. When considering only healthy older adults, object discrimination relatively selectively correlated with hippocampal volume (N=57), left entorhinal thickness and with phospho-tau levels (N=19). *Conclusion:* These data suggest that complex object-in-scene recognition captures variance caused by both tau and amyloid pathology. A domain-specific breakdown, however, indicates that tau-related variance tends to be captured by object discrimination whereas amyloid pathology is captured by scene discrimination performance. The findings are compatible with the possibility that object and scene discrimination track different stages of disease progression in AD. Longitudinal trajectories obtained via a smartphone-based application including both tasks will shed light on the detailed time course of object and scene memory decline in the same subjects.

P91: EFFECTIVENESS OF RATER TRAINING AND DATA SURVEILLANCE IN ALZHEIMER 'S DISEASE (AD) CLINICAL TRIALS. Rolana Avrumson, MS[1], Melissa A. Carbo[2], Henry J. Riordan[2], Michael F. Murphy, M.D., PhD2, Neal R. Cutler[1] *(1) Worldwide Clinical Trials, Beverly Hills, CA; (2) Worldwide Clinical Trials, King of Prussia, PA)*

Background: Literature examining the reasons for an increasing number of failed clinical trials in AD in recent years has emphasized the necessity for high quality ratings which can influence the reliability of study outcomes and therefore the overall success of clinical trials. Rater variability is a significant source of unpredictability and assessments that are repeatedly administered such as the ADAS-Cog or MMSE are subject to both practice effects and increased variability due to subject responses, idiosyncratic administration, scoring interpretations and errors, as well as various biases. However, evidence suggests that across various experience levels rater performance tends to significantly improve with re-training and feedback. Overall rater proficiency increases and fewer scoring deviations are identified following intervention, thereby reducing rater variability or drift (the tendency to deviate from standardized scale administration and scoring conventions). The Federal Drug Administration (FDA; 2014), European Medicines Agency (EMA; 2014) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR; 2014) all provide clear recommendations regarding the effectiveness and applicability of rater training and training both at the start of a study, along with ongoing data surveillance are frequently utilized by drug development teams to help ensure the accuracy of scale administration and scoring, and that all patients meet appropriate patient eligibility criteria. The current study examines the utility of rater training and ongoing data surveillance to identify rater drift and reduce data variability across two AD clinical trials. *Method:* Data from two separate clinical trials evaluating the effects of verum versus placebo across a broad spectrum of AD patients (from mild to severe) was evaluated. Trained and credentialed site raters submitted all screening diagnostic and symptom severity scales to independent, expert clinicians for clinical review. These independent clinicians reviewed source documentation and data flags to detect rater errors based on deviations from standardized scale administration and scoring conventions at screening, baseline and during several time points during the study. *Results:* Data was acquired from 56 raters across 46 US centers over 285 subject screening visits. Results indicate that of the 285 screening source documents monitored by independent, expert clinicians, 67% of the source documentation submitted included either clinical scoring or administration errors. Importantly, results suggest a downward trend in scoring and administration errors over the course of the trial after ongoing feedback, remediation, and refresher trainings, with a 20% reduction in overall error rates. Of note there was no significant difference in the number or type of errors between studies, or between patient severities, nor assessment type. *Conclusion:* Though a direct causal relationship cannot be inferred without a control group that did not receive rater training and ongoing surveillance, results suggest that expert clinical feedback regarding rater scale scoring and administration competency can reduce errors significantly and potentially reduce rater drift and variability. An assessment of various rater training methodologies (investigator meeting, on site, web-based) prior to study start and ongoing data surveillance methodology (source document or data flag reviews) will be made in an effort to determine which methodology leads to the greatest reduction in error variance and rater drift providing the best chances of signal detection.

P92: DIAGNOSTIC VALUE OF A COGNITIVE BATTERY FOR ASSESSING COGNITIVE DECLINE. A. Nidos[1], D. Kasselimis[2], K. Zavitz[3], F. Cormack[3] *((1) Neurological Clinic – Department of Neuropsychology, Metropolitan Hospital; (2) 1st Neurology Department, National and Kapodistrian University of Athens; (3) Cambridge Cognition)*

Background: Early diagnosis of progressive cognitive decline is a crucial issue for clinicians involved in assessment of elderly individuals. A thorough neuropsychological examination is usually a costly and time-consuming procedure, hence the need for sensitive, accurate, and brief batteries is obvious. The aim of the present study is to explore the clinical-diagnostic value of a brief neuropsychological battery for dementia, consisting of fully automated computerized tasks and classical neuropsychological measures of memory and language. *Methods:* 82 memory clinic patients (55 women), aged 42–91 years (mean=71.73, sd=9.87) underwent a formal neuropsychological evaluation in five cognitive domains: attention and concentration, memory, language, visuospatial abilities and executive functions. Patients received a clinical diagnosis based on the following: clinical history (plus caregiver interview), neurological examination, radiologic-laboratory examinations, where available, (EEG, brain MRI-CT, blood work), and formal neuropsychological assessment. The clinical diagnosis served as a gold standard for the

classification of the patients on the study groups. For the purpose of this study, 65 patients were included in the final sample: 24 diagnosed with Alzheimer's Disease (AD), 14 diagnosed with Mild Cognitive Impairment (MCI), and 27 well-worried subjects with no present concern (NC). The measures used were CANTAB Insight, the Memory Impairment Screen (MIS; Buschke et al., 1999), the short forms of the Boston Naming Test (BNT; Kaplan, Goodglass, and Weintraub, 1983) and the Peabody Picture Vocabulary Test – Revised (PPVT-R; Dunn and Dunn, 1981), both standardized in Greek (Simos, Kasselimis, and Mouzaki, 2011a, 2011b), the Comprehension of Instructions in Greek (CIG; Simos, Kasselimis, Potagas, & Evdokimidis, 2014), and the Controlled Oral Word Fluency (COWF; Kosmidis, Vlahou, Panagiotaki, & Kiosseoglou, 2004). Subjects were classified into three study groups, based on the clinical diagnosis (gold standard) described earlier. The relative discriminating value of each CANTAB Insight test, verbal memory (MIS) and language (CIG, BNT, PPVT, semantic fluency) was initially assessed though discriminant function analysis. Age and education were also inserted in the function by entry. We then computed sensitivity and specificity indices for the composite CANTAB Insight, verbal memory and language score (canonical variable), obtained on the basis of the discriminant equation using the ROC procedure. Analyses were performed with IBM Statistical Package for Social Sciences v. 19.0 and MedCalc. *Results:* The discriminant function was significant, Wilk's $\lambda(11) = 0.211$, $p<0.001$, with two out of eleven measures (CANTAB Paired Associates Learning and MIS) included in the canonical function having loadings > 0.40. Individual scores on the canonical variable ensured a global correct classification rate of 100%. Area under the ROC curve (AUC) was 100% ($p<0.0001$) suggesting good differentiation between the patient groups using the composite score. *Conclusion:* Early identification of MCI patients, as well as differential diagnosis between MCI, AD, and subjective memory complaints in the absence of pathology, is considered to be among the most crucial goals in the field of clinical neuropsychology. However, time and cost constraints often pose severe difficulties to a comprehensive examination of a broad spectrum of cognitive functions. In this context, our findings clearly demonstrate that a brief battery of tests can be of great clinical utility, with regard to discriminating pathological memory cognitive decline. References: Buschke, H., Kuslansky, G., Katz, M., Stewart, W. F., Sliwinski, M. J., Eckholdt, H. M., & Lipton, R. B. (1999). Screening for dementia with the memory impairment screen. Neurology, 52(2), 231-231. Dunn, L. M. and Dunn, E. S. 1981. Peabody Picture Vocabulary Test – Revised, Circle Pines, MN: American Guidance Service. Kaplan, E., Goodglass, H. and Weintraub, S. 1983. Boston Naming Test, Philadelphia: Lea & Febiger. Kosmidis, M. H., Vlahou, C. H., Panagiotaki, P., & Kiosseoglou, G. (2004). The verbal fluency task in the greek population: Normative data, and clustering and switching strategies. Journal of the International Neuropsychological Society,10(2), 164-172. Simos, P. G., Kasselimis, D., & Mouzaki, A. (2011a). Age, gender, and education effects on vocabulary measures in greek. Aphasiology, 25(4), 475-491. Simos, P. G., Kasselimis, D., & Mouzaki, A. (2011b). Effects of demographic variables and health status on brief vocabulary measures in greek. Aphasiology, 25(4), 492-504. Simos, P. G., Kasselimis, D., Potagas, C., & Evdokimidis, I. (2014). Verbal comprehension ability in aphasia: Demographic and lexical knowledge effects. Behavioural Neurology, 2014.

Theme: Behavioral disorders and clinical trials

P93: LUMATEPERONE (ITI-007), A NOVEL DRUG IN DEVELOPMENT FOR THE TREATMENT OF AGITATION IN PATIENTS WITH DEMENTIA, INCLUDING ALZHEIMER'S DISEASE: RATIONALE AND CLINICAL TRIAL DESIGN.

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Background: It has been estimated that over 47 million people worldwide are living with dementia. In the US alone, approximately 5.5 million patients suffer from Alzheimer's disease. While clinical criteria for Alzheimer's disease mostly focus on the related cognitive deficits, it is often the behavioral symptoms that are most troublesome for caregivers and lead to poor quality of life for patients and institutionalization. These symptoms include agitation (including aggression), depression, sleep disorders, and psychosis. Studies suggest that approximately 60% of patients with Alzheimer's disease experience agitation. There are no currently approved treatments for agitation and aggression in this patient population. Certain medications are prescribed off-label to manage these behavioral symptoms. These medications are frequently ineffective and associated with deleterious side effects, including those leading to falls and fractures, and increased mortality. Lumateperone (ITI-007) is a first-in-class, investigational new drug that simultaneously modulates serotonergic, dopaminergic, and glutamatergic neurotransmission, with differing pharmacology depending on dose. At low doses lumateperone is a potent 5-HT2A receptor antagonist. As the dose is increased lumateperone shows dose-related mesolimbic/mesocortical dopamine phosphoprotein modulation (DPPM) with activity as a pre-synaptic partial agonist and post-synaptic antagonist at D2 receptors, a SERT inhibitor and an indirect glutamate (NMDA and AMPA) enhancer downstream from dopamine D1 receptor activation. Taken together, these unique pharmacological features predict improved nighttime sleep with restored circadian rhythm and reduction in agitation and aggression at lower doses, and antipsychotic and antidepressant efficacy at higher doses. Furthermore, efficient dopaminergic modulation with relatively low striatal D2 receptor occupancy as well as a lack of affinity for off-target muscarinic and histaminergic receptors confer a favorable side effect profile. *Methods:* Lumateperone has been evaluated in randomized, double-blind, placebo-controlled clinical trials across a wide range of doses. Low doses of lumateperone were evaluated in patients with primary insomnia in a randomized, double-blind, single dose cross-over design study. Multiple ascending doses of lumateperone were evaluated in healthy geriatric volunteers in a randomized, double-blind, placebo-controlled study. Repeated doses of lumateperone administered once every evening orally were evaluated for safety in a randomized, double-blind, placebo controlled study in elderly patients with dementia. In late stage clinical trials, lumateperone was evaluated for efficacy to reduce psychosis as measured by the Positive and Negative Syndrome Scale (PANSS) in patients with acute schizophrenia. Safety and tolerability were also assessed. *Results:* In a Phase 2 trial in patients with primary insomnia, ITI-007 (1 – 10 mg) demonstrated a dose-related increase in deep slow wave sleep, decrease in wake after sleep onset, and increase in total sleep time with no next-day hang-over effects. In patients with dementia, ITI-007 9 mg was safe, well-tolerated, and improved measures of cognition. A safety and tolerability study in healthy elderly subjects showed that low doses of ITI-007 (7.5, 15.0 and 30 mg, QAM for 7 days) were safe and well-tolerated and showed no clinically significant impact on the extrapyramidal and endocrine systems, nor cardiac function.

Additionally, in elderly patients with dementia, ITI-007 9 mg was safe and well tolerated. In these patients, lumateperone also improved measurements of cognition. In two late-stage schizophrenia studies ITI-007 60 mg met the primary endpoint and demonstrated efficacy with statistically significant superiority over placebo at Day 28 as measured by the PANSS total score. Across all schizophrenia studies to date, lumateperone has been well-tolerated with a safety profile similar to placebo. In two studies that included risperidone as an active control, lumateperone demonstrated statistically significant safety advantages over risperidone. on key safety and tolerability parameters including glucose, lipids and weight gain. Lumateperone is also in phase 3 clinical development for bipolar depression. A late-stage clinical trial for the treatment of behavioral disturbances in dementia is ongoing. The rationale for therapeutic utility of low doses lumateperone in patients with dementia will be presented along with the clinical trial design. This rationale is based on previous data evaluating lumateperone in patients with primary insomnia as well as the safety, tolerability and cognitive data from study ITI-007-200 in elderly healthy subjects as well as patients with dementia. The low-dose strategy and the rationale for future development of lumateperone for the treatment of behavioral disturbances in patients with dementia will be discussed. *Conclusion:* Lumateperone represents a potentially important and novel therapeutic advancement in the treatment of a broad array of behavioral symptoms associated with dementia and related disorders. Not only is there evidence to suggest improvements in sleep, cognition, learning and behavioral disturbances, but lumateperone's favorable safety and tolerability profile in particular, would make it an important novel and safe treatment option for this patient population.

P94: ALZHEIMER'S DISEASE COOPERATIVE STUDY (ADCS) MULTICENTER TRAIL: PRAZOSIN FOR AGITATION IN ALZHEIMER'S DISEASE (PEACE-AD).
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Background: Disruptive agitation (irritability, anger outbursts, uncooperativeness with basic care, and pressured motor activity) is a major source of distress to patients and caregivers, and is a common precipitant of long-term care placement. High central nervous system (CNS) noradrenergic responsiveness of the alpha-1 adrenoreceptor (AR) in Alzheimer's disease (AD) may contribute to the pathophysiology of disruptive agitation. Prazosin, a CNS active alpha-1 AR antagonist, was shown to be beneficial for reducing disruptive agitation in a single site pilot randomized controlled trial. This led to the Alzheimer's Disease Cooperative Study (ADCS) undertaking a large, multi-center trial of prazosin for treatment of disruptive agitation in Alzheimer's patients residing in the long-term care setting. *Methods:* This study will be performed in approximately 20 long-term care facilities. One hundred eighty-six participants with AD complicated by frequent disruptive agitation will be randomized to prazosin or placebo (2:1 randomization ratio) for a total of 12 weeks. Prazosin (or an equal number of placebo capsules) will be titrated using flexible dose titration to a maximum dose of 4 mg midmorning and 6 mg at bedtime. Rescue lorazepam at a dose of 0.5 mg will be allowed for up to a total of 21 days. Wrist actigraphy will be performed at a subset of study sites. Adverse events as well as supine or sitting blood pressure (BP) and heart rate (HR) and orthostatic BP and HR will be monitored. The primary outcome measure will be the ADCS-Clinical Global Impression of Change-Agitation, a modification of the ADCS-CGIC to specifically target disruptive agitated behaviors. The key secondary outcome measure will be the Neuropsychiatric Inventory-Nursing Home (NPI-NH) version. Additional secondary outcome measures will include the ADCS-Activities of Daily Living (severe dementia version), the Severe Impairment Battery-8 item version, total mg of rescue lorazepam administered, and total number of study days completed. Exploratory outcomes will include analysis of the NPI-NH Agitation/Aggression, Anxiety, Disinhibition, Irritability/Lability, and Aberrant Motor Behavior items, and actigraphic measures of activity and sleep. *Conclusion:* Enrollment will begin in fall, 2017, and the study will extend for 18 months. This multi-center study is funded by the National Institute on Aging via the Alzheimer's Disease Cooperative Study.

P95: NEUROPSYCHIATRIC SYMPTOMS AND THE RISK OF CONVERSION TO DEMENTIA AMONG MCI SUBJECTS.
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Backgrounds: Neuropsychiatric Symptoms (NPS) are common in dementia and pre-dementia syndromes such as Mild Cognitive Impairment (MCI). The objective was this work was to investigate NPS and the risk of conversion to dementia Alzheimer's disease (AD) type among subjects with MCI. *Methods:* We prospectively followed 96 participants with MCI without dementia (MMSE≥24 and CDR=0.5, memory impairment RAVLT<1DS) enrolled in the Research Of biomarkerS in Alzheimer's diseaSe (ROSAS) cohort for 4 years. Conversion to dementia was defined as the change of CDR total score from 0.5 to ≥1, reviewed by an expert consensus panel based on published criteria, after reviewing neurologic, cognitive, and other pertinent data. NPS were determined using the Neuropsychiatric Inventory (NPI) 12-items. This study analyzed prognostic value of each NPI item and 4 clusters of NPS (apathy, psychosis, affective and hyperactivity) for prediction of conversion. A Cox proportional hazard model was used and Hazard Ratios (HRs) and 95% confidence intervals (CIs) were estimated with time dependent variable (each NPI item or each cluster) to compare the incidence of conversion taking into account the presence of the considered NPS or cluster. *Results:* agitation/aggression, delusions and aberrant motor behavior, significantly increased the risk of dementia among MCI participants (HR= 3.8; 95%CI= 1.8-7.9; HR= 13.9; 95%CI= 4.1-47.5; HR= 3.8; 95%CI= 1.6-9.2, respectively). Psychosis and Hyperactivity clusters were also predictors of conversion (HR= 14.0; 95%CI= 4.4-44.5; HR= 2.0; 95%CI= 1.1-3.7, respectively). Affective and apathy clusters were not associated with increased risk of conversion to dementia AD type. *Conclusion:* Presence of delusions, agitation/aggression and aberrant motor behavior in a heterogeneous group of MCI are predictor of cognitive decline progression in MCI and of conversion to dementia AD type. Further biomarkers studies should examine the associations of the presence of these NPS with the underlying neurobiological process driving the conversion to dementia among MCI patients.

P96: NATURAL HISTORY, EPIDEMIOLOGY, NEUROBIOLOGY, BURDEN, AND UNMET NEEDS OF AGITATION IN ALZHEIMER'S DISEASE: WHERE ARE WE NOW? A SYSTEMATIC REVIEW. M Chuidian[1], F Waterman[1], S Bird[2], A De Jong-Laird[3], R Baker[4], T Megerian[1] *((1) Avanir Pharmaceuticals Inc, Aliso Viejo, CA; (2) Xcenda, Palm Harbor, Fl; (3) Otsuka Pharmaceutical Europe Ltd. (OPEL), Gallions, Wexham Springs; (4) Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC), Princeton, NJ)*

Background: Agitation is among the most common neuropsychiatric symptom (NPS) in patients with Alzheimer's disease (AD) and is a significant burden to patients, caregivers, and the healthcare system. Although a provisional definition of agitation in AD has been published, inconsistencies in the interpretation and diagnosis of symptoms are common, and a wide range of prevalence rates have been reported. While published guidelines suggest non-pharmacologic intervention as the preferred first line treatment option for the management for agitation in AD, differences in the use and reported effectiveness of these interventions exist. Moreover, according to published reports, the off-label use of pharmacologic therapies demonstrates modest and inconsistent effectiveness, particularly in patients with severe symptoms, and is associated with safety and tolerability issues. A clear and comprehensive understanding of current evidence would help guide research efforts and provide additional information needed to adequately address the unmet needs for optimal management of agitation in AD patients. A targeted systematic literature review was conducted to gain a better understanding of the existing evidence and to inform an evidence gap analysis around the definition of agitation in AD, natural history, neurobiology, burden of illness, and unmet treatment needs. *Methods:* MEDLINE, via PubMed, EMBASE, and Cochrane library as well as abstracts from relevant conferences were searched to identify studies addressing the epidemiology (specifically prevalence), natural history (including predictors of disease progression), neurobiology, biomarkers, and burden (including caregiver burden) of agitation in AD. Randomized clinical trials (RCTs), observational studies, meta-analyses, systematic literature reviews (SLR), and case series/reports published in English between January 2000 and December 2016 were included. An initial reviewer assessed the abstracts of the retrieved citations for relevance based on inclusion and exclusion criteria. A second reviewer evaluated the preliminary screening results for accuracy. Extraction of relevant data from the full-text of included articles was conducted by the second reviewer. Data were organized by categories of interest (eg, epidemiology, pathophysiology) to assist in the identification of common themes or similar threads of data and information. A quality assessment (QA) of included publications was conducted by 2 independent reviewers using various QA tools, depending on the study design (eg, PRISMA for systematic literature reviews, Jaded Scale for RCTs). Furthermore, a review of relevant treatment guidelines as well as existing SLRs was completed to identify supplemental information and to ensure that all relevant data were captured. Finally, based on the findings from the literature review and QA, a gap analysis was conducted to determine where additional information or better quality data are needed. *Results:* Analyses of the findings are ongoing. The results will be presented at the 2017 Clinical Trials on Alzheimer's Disease (CTAD) meeting in Boston, MA.

Theme: Health economics and clinical trials

P97: COST OF ILLNESS AND ECONOMIC BURDEN OF EARLY ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW. Richard Lawson[1], Weiguang Xue[2], Adam Lloyd[2], Christina-Jane Crossman-Barnes[3], Rebekah Fong[3] *((1) AstraZeneca, US; (2) QuintilesIMS, UK; (3) University of East Anglia, UK)*

Background: The economic burden of early Alzheimer's disease (AD) is less well understood than for late stage disease. A systematic review of the literature was conducted to identify existing information on the costs of early AD in Europe and the United States (US). *Methods:* The search included cost of illness studies published in Medline, Embase, and EconLit in 2006-2016. Eligible studies had to report direct or indirect costs including informal care and work loss for patients with a diagnosis of mild cognitive impairment (MCI) due to AD, mild AD, moderate AD, or severe AD. Annual costs per patient were inflated to 2015 and non-US studies were converted to US dollars using purchasing power parities. *Results:* A total of 19 studies met the inclusion criteria: costs of early AD (MCI and mild AD) were reported in 17 studies (4 MCI and 13 mild AD) across 6 countries (Germany, France, United Kingdom, Spain, Sweden and US). Disease staging was most commonly defined according to ranges of the Mini-Mental State Examination or the Clinical Dementia Rating Scale. The mean annual per patient total cost was $11,220 (range between studies $6,627 to $20,605) for MCI and $27,209 ($13,910 to $53,746) for mild AD. Indirect costs including a high proportion associated with caregiving represented approximately 52% of the total cost burden of early AD. By comparison, the mean annual per patient total cost was $60,722 (range between studies $27,778 to $168,554) for severe AD. *Conclusion:* The economic burden of early AD is substantial, with a large proportion of costs borne by caregivers and patients. This burden increases as patients progress to severe AD. Further research in early AD, especially MCI, is warranted due to the limited number of published studies.

P98: CHALLENGES IN OPTIMISING REAL WORLD EVIDENCE FOR ALZHEIMER'S DISEASE. Catherine Reed[1], Frederic de Reydet de Vulpillieres[2], John Gallacher[3] and the ROADMAP consortium *((1) Eli Lilly and Company Limited, Windlesham, UK; (2)Novartis Pharma AG, Basel, Switzerland; (3) University of Oxford, UK)*

Background: Innovative treatments currently in development for patients with Alzheimer's disease (AD) are needed to address the economic, caregiver and societal impact. Challenges exist with evaluating early disease interventions in a slowly progressive disorder within current health technology assessment and payer systems. Real world evidence (RWE) integrates available population health records and patient outcome data, eliciting indicators to provide an enriched clinical and health policy decision-making environment. RWE potentially better informs regulators (on effectiveness and safety), payers and healthcare providers (cost effectiveness), industry (pricing and manufacturing), and scientists (mechanisms and diagnostic/treatment pathways) to accelerate decision-making on new and existing treatments. The aim of ROADMAP is to deliver a series of data integration methods and tools for patient outcomes, developed and tested through pilot projects, which are scalable and transferable, and which will provide the foundation for a future Europe-wide RWE platform on AD. In parallel, we will develop tools for stakeholder engagement, understanding the ELSI context and the health economic impact of a RWE approach in AD. In doing so, ROADMAP aims to create the conditions for an open collaboration among stakeholders

that yields consensual, efficient uses of such RWE platform for the ultimate benefit of AD patients and their caregivers. *Methods:* ROADMAP brings together data infrastructures that can access cohorts and EHRs across Europe. A data pyramid approach is used to integrate data differing in modality and provenance, conceptualising trials and cohorts as structured studies nested within a less well defined but wider population-based data-space. Evidence from national/regional EHR databases is supplemented with patient and population outcomes, and overlaid with cohort and trials data to derive models. This approach makes explicit the relationships and limitations of each data type, informing triangulation between highly focussed, question-specific evidence from trials, detailed etiologic inference from cohorts, self-report data from patients, and population-based EHR data. From this, models of disease progression can be developed and hypotheses on effectiveness, cost and impact can be tested. It also provides the context for a new generation of trials and population studies that will integrate regulatory and patient perspectives, reduce and spread risk between stakeholders, and reduce cost. *Results:* Diverse national database and registry data are available to ROADMAP including primary care, hospital, mental health and specialist registers. The data corpus is drawn from 7 EU Member States (Denmark, France, Netherlands, Spain, Sweden, UK) and involves 75 national databases and clinical registries ($\sum n \approx 80M$), >40 cohorts ($\sum \approx 2M$), several studies using wearables and smart devices ($\sum n \approx 100K$), and 4 dementia relevant trials ($n \approx 50K$). ROADMAP is built around established technologies that facilitate rapid and secure data acquisition, access and analysis. We will leverage technologies and methods developed in the IMI project EMIF, in particular for data source fingerprinting/cataloguing, EHR data extraction and integration across diverse sources and countries, semantic harmonisation and analysis. For cohort analyses the DPUK integrated informatics environment enables rapid and secure cross-cohort analysis. This platform uses the UK Secure e-Research Platform (UKSeRP), which DPUK has adapted to deliver a dementia dedicated data safe-haven, allowing the analysis of sensitive cohort data alongside the integration of EHR and other national database records. Results will become available over the next 2 years and include proposals for further advancement in RWE applications. *Conclusions:* As the significance of a precision medicine approach to health funding grows, new models are needed that integrate all the available evidence in AD to identify which treatments work for which patient. ROADMAP is unique in its approach, bringing together a wide range of academic and industry experts, using cutting edge tools and infrastructure with an unprecedented depth and breadth of data, which will lay a foundation for the design and development of RWE research. Funding: This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 116020 ("ROADMAP"). This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

P99: DEPENDENCE SCALE TO ASSESS THE COST-CONSEQUENCES OF ALZHEIMER'S DISEASE TREATMENTS. Joshua A. Roth[1], Joshua T. Cohen[2], Peter J. Neumann[2], Carolyn W. Zhu[3], Yaakov Stern[4] Sean D. Sullivan[5] *((1) Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; (2) Center for the Evaluation of Value and Risk in Health, Tufts Medical Center, Boston, MA, USA; (3) Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; (4) Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA; (5) Department of Pharmacy, University of Washington, Seattle, WA, USA)*

Background: Healthcare payers must compare the value of alternative Alzheimer's Disease (AD) treatments, but existing modeling frameworks are limited in that they are based primarily on progressive decline in cognitive function and delay to institutionalization. Clinical endpoints may not be relevant to decision makers trying to gauge the impact and/or value of these treatments. The Dependence Scale (DS) directly measures the level of assistance AD patients require and is associated with AD progression (across cognitive, functional and behavioral domains). It has been shown to measure related but distinct aspects of disability in AD encompassing patients' cognition and function and can provide a bridge between measures of clinical efficacy and value in a single transparent measure. It has been shown to be associated with direct medical and non-medical expenditures in both cross-sectional and longitudinal studies. Nonetheless, there are no established frameworks to project the cost-consequences of new AD treatments based on changes in DS. The objectives of this study were to: 1) develop a DS-based cost-consequences framework to fill this gap in comparative and cost effectiveness research methods, and 2) to examine the plausible range of cost impacts of new AD treatments vs. current standard care using the framework. *Methods:* We developed a state-transition simulation model that projects long-term costs of AD care based on changes in DS for cohorts initiating treatment at an average age of 70. The model relates DS to cost using findings from Zhu et al. (2015) and Stern et al. (2016). The relationship between DS and mortality can be switched on or off, allowing analysis with no effect of treatment on survival or a linear relationship between DS and mortality, respectively. Additionally, caregiver time costs can be switched on or off to allow evaluation of costs from societal or payer perspectives, respectively. Outcomes include AD progression, life years, and costs related to medication, inpatient and outpatient care, and informal caregiver time. The model can be structured to allow evaluation of new treatments in a cohort including all levels of AD severity (mild, moderate, severe) or can be stratified to evaluate effects in individual AD severity sub-groups. To explore the range of potential cost-consequences related to new AD treatments, we evaluated three hypothetical oral agents for mild AD (baseline DS=3, baseline MMSE=21-26) over 5-year and lifetime horizons. Treatment #1 was assumed to result in 20% improvements in DS (vs. baseline) for the initial 48 weeks it is taken (i.e. disease-modifying effect), and then halves the rate of DS progression (vs. standard care) thereafter. Treatment #2 was assumed to halve the rate of DS progression (vs. standard care) for the entire time it is taken. Treatment #3 was assumed to reduce the rate of DS progression by 20% (vs. standard care) for the entire time it is taken. Across analyses, we took a payer perspective, discounted cost results at 3% per year, assumed that treatment was discontinued at a DS≥10, and assumed that treatment doesn't impact mortality. Our analyses do not incorporate any cost for the new treatments in order to focus results on disease-related cost-consequences. *Results:* Over a lifetime

(mean survival of 6.1 years), monthly AD progression averaged 0.045, 0.019, 0.023, and 0.036 DS points for standard care, treatment #1, treatment #2, and treatment #3, respectively. The standard treatment was expected to result in a total cost of $33,100 and $55,200 over 5-year and lifetime horizons, with the largest proportion (37%) attributable to inpatient care. Treatments #1, #2, and #3 all reduced total costs by $600 (vs. standard care) over a 5-year time horizon as there was limited time for substantial DS differences to emerge based on treatment effects. Over a lifetime horizon, Treatments #1, #2, and #3 decreased total costs by $5,300, $4,800, and $1,900 (vs. standard care) with the biggest cost offsets of $3,200, $2,900, and $1,200 coming from reduced inpatient care, respectively. *Conclusion:* Our DS-based modeling framework provides a new approach to evaluating the long-term cost-consequences of alternative AD strategies using an increasingly common trial endpoint that aggregates the cognitive, functional, and behavioral symptom progression into a single metric and is associated with AD disease cost. Our findings suggest that new AD treatments that reduce the rate of DS progression are likely to reduce overall costs vs. current standard care, and that the greatest cost reduction is likely to be in inpatient care among the cost categories explored in our scenarios.

Theme: Epidemiology and clinical trials

P100: PREVALENCE AND PROGRESSION OF PRECLINICAL AND PRODROMAL AD AMONG NON-DEMENTED PERSONS IN A POPULATION-BASED SETTING. Rosebud O. Roberts[1,2], Jeremiah A. Aakre[3], Walter K. Kremers[3], Maria Vassilaki[1], Michelle M. Mielke[1,2], David S. Knopman[2], Yonas E. Geda[1,4], Preciosa Coloma[5], Barbara Schauble[6], Val J. Lowe[7], Clifford R. Jack Jr.[7], Ronald C. Petersen[1,2] *((1) Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Rochester, MN; (2) Department of Neurology, Mayo Clinic, Rochester, MN; (3) Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN; (4) Departments of Psychiatry and Psychology and Neurology, Mayo Clinic, Scottsdale, AZ; (5) Real World Data Science, F. Hoffman-La Roche Ltd, Basel, Switzerland; (6) Medical Affairs, F. Hoffmann-La Roche Ltd, Basel, Switzerland; (7) Department of Radiology, Mayo Clinic, Rochester, MN)*

Background: Amyloid accumulation, the hallmark of Alzheimer's disease (AD) pathology, starts decades before the onset of clinical symptoms of AD dementia. This suggests that non-demented persons in the population may have the asymptomatic phase of AD (preclinical AD) or the symptomatic pre-dementia phase of AD (mild cognitive impairment [MCI] due to AD or prodromal AD). The objective of this study was to estimate the prevalence of preclinical AD and prodromal AD in a defined population, and to assess their related outcomes during follow-up. *Methods:* Participants enrolled in the population-based Mayo Clinic Study of Aging were evaluated at baseline and during follow-up to assess cognitive status (cognitively unimpaired [CU], MCI (amnestic [aMCI], nonamnestic [naMCI]), AD dementia) and measures of cognitive performance. Participants underwent PIB PET imaging at baseline to assess brain amyloidosis (A+, PIB PET SUVR >1.42). Preclinical AD was defined as CU amyloid positive (CU A+) and prodromal AD was defined as aMCI amyloid positive (aMCI A+). The frequencies of brain amyloidosis among non-demented participants (preclinical AD, CU A-, prodromal AD, aMCI A-, naMCI A+ and naMCI A-) were estimated and adjusted for non-participation in the MCSA at recruitment and for non-participation in PIB PET imaging among participants in the MCSA. Frequency estimates were then standardized to the Olmsted County, MN 2010 population by age and sex to assess the prevalence of amyloid positivity in the population. Proportional hazards models were used to estimate the risk of progression from preclinical AD to amnestic MCI (aMCI), prodromal AD to AD dementia, preclinical or prodromal AD to AD dementia, and from any A+ (i.e. including naMCI A+) to AD dementia and reported as hazard ratio (HR) and 95% confidence intervals [95% CI]), adjusting for sex and education, with age as the time variable (basic model), and for several vascular risk factors, and APOE ε4 allele (fully adjusted models). *Results:* Among 1,668 non-demented persons (mean [SD] age, 71.3 (9.9); range, 50-89 years), the overall (men and women) prevalence (95% CI) of preclinical AD was 17.9% (15.9, 20.0), and increased with age from 2.8 (0.5, 5.0) at ages 50-59 years to 41.3% (33.4, 49.2) at ages 80-89 years. The overall prevalence of prodromal AD was 3.3% (2.3, 4.3) and increased with age from 0% at 50-59 years to 13.6% (7.7, 19.6) at ages 80-89 years. The prevalence of prodromal AD was similar in men, 3.1% (1.6, 4.5) and in women 3.5% (2.0, 4.9). The hazard ratio (HR, 95% CI) estimates of progression were as follows: preclinical AD (vs. CU A-) to aMCI, 2.34 (1.55, 3.52); prodromal AD (vs. aMCI A-) to AD dementia, 1.48 (0.73, 3.02); preclinical or prodromal AD (vs. CU A- and aMCI A-) to AD dementia, 3.77 (2.03, 7.02). These estimates remained significant and essentially unchanged with further adjustments for vascular risk factors, coronary artery disease, stroke and depression. When APOE ε4 allele was included in the multivariable models predicting AD dementia, an ε4 allele was associated with an increased HR of AD dementia, and the strength of the associations of preclinical or prodromal AD with AD dementia were reduced. Specifically, the HR of AD in ε4 carriers was 2.92 (1.47, 5.77) in models for prodromal AD vs. aMCI A- (estimates declined to null: 0.96 (0.45, 2.06); association of ε4 with AD was 2.73 (1.58, 4.72) in models for preclinical or prodromal AD to AD dementia (estimates declined to: 2.73 (1.42, 5.22). Persons with preclinical AD or with prodromal AD had steep declines in cognitive performance assessed by global cognitive z-scores and memory domain z-scores during follow-up. *Conclusion:* The prevalence of preclinical AD and prodromal AD from a non-demented population-based sample are essential for accurately projecting estimates of the future population burden of AD dementia, planning AD prevention trials, and planning resources and care for the elderly. The elevated risk of progression from preclinical AD to aMCI and from prodromal AD to AD dementia suggest an urgent need for effective interventions that may reduce progression in persons at increased risk.

P101: LIPOPHILIC VERSUS HYDROPHILIC STATIN EXPOSURE AND POST-MORTEM NEUROPATHOLOGICAL FINDINGS IN THE NACC AUTOPSY COHORT. Aaron M. Koenig[1], Jing Qian[2], Rebecca A. Betensky[3], Steven E. Arnold[1] *((1) Department of Neurology, Massachusetts General Hospital, Boston, MA, USA; (2) Department of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA, USA; (3) Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA)*

Background: In addition to their systemic lipid-lowering effects, HMG-CoA reductase inhibitors ("statins") may promote brain health through pleiotropic processes that include antioxidant and anti-inflammatory pathways, as well as potential modulation of Aβ and/or tau metabolism in the brain. Despite promising preclinical findings, studies of statins in humans have been decidedly mixed as to whether these agents have preventative or ameliorative effects in neurodegenerative disease, partly because statins have, to this point, been treated as a homogeneous species (thus failing to acknowledge that individual agents are unique with respect to their

lipophilicity and ability to penetrate the blood-brain barrier). In the current report, we describe data highlighting the relationship between statin exposure and neuropathological outcomes in the National Alzheimer's Coordinating Center (NACC) autopsy cohort, with a focus on statin biochemical properties. We hypothesized that degree of post-mortem neuropathology would be less severe in tissue derived from individuals treated with blood-brain barrier-penetrant lipophilic statins as compared to hydrophilic statins. On the other hand, we hypothesized that degree of cerebrovascular pathology would not differ between lipophilic and hydrophilic statin users. *Methods:* We conducted a secondary analysis of NACC clinical and neuropathological data, designed to examine the relationship between lipophilic and hydrophilic statin exposure and post-mortem neuropathological findings. Statins were classified based on octanol:water partition coefficient, with higher coefficients indicating greater lipophilicity. Lipophilic agents included simvastatin, pitavastatin, fluvastatin, and atorvastatin, and hydrophilic agents included rosuvastatin and pravastatin. NACC participants with available autopsy data were identified (n=4286). Demographic and neuropathological characteristics were summarized using means and percentages, and statin exposure was quantified by length (number of years) and type (hydrophilic, lipophilic, both). For binary responses (or multilevel ordinal response) conditional logistic regression (or adjacent categories logit model), matching on (or adjusting for) length of follow-up in NACC (0-2 years, 2-4 years, 4-6 years, 6-8 years, and 8+ years) was performed. While controlling for ApoE status, gender, age at death, and medical comorbidity index, relationships between neurodegenerative pathology (Braak Stage, CERAD score, severity of cerebral amyloid angiopathy, presence/absence of Lewy Body pathology, presence/absence of subcortical arteriosclerotic leukoencephalopathy, and presence/absence of FTLD pathology), cerebrovascular pathology (large vessel atherosclerosis, infarcts/lacunes, microinfarcts, hemorrhages/microbleeds, and arteriosclerosis) and statin exposure (lipophilic/hydrophilic/both/none) were examined. *Results:* We examined 4286 cases from the NACC autopsy cohort. Of these, 41.0% (n=1757) were from individuals who had been exposed to statins, including 34.7% (n=1488) exposed only to lipophilic agents, 4.2% exposed only to hydrophilic agents (n=181), and 2.1% exposed to both (n=88). Mean age at NACC entry did not differ significantly between groups (p=0.18), though mean age at death did differ significantly (p=0.002). Groups were similar in terms of education (p=0.06) and racial composition (p=0.16), though differed significantly in gender composition (p<0.001), extent of medical comorbidity (p<0.001), CDR-SOB at NACC entry (p=0.03), and ApoE4 status (p=0.02). In terms of the relationship between post-mortem neurodegenerative pathologies and statin exposure: holding other factors constant, the odds of having a high Braak stage (5/6) versus moderate Braak stage (3/4/5) was found to change 0.998 times (95% CI: 0.959, 1.037) with every 1 year increase in lipophilic statin exposure, as compared to 1.060 times (95% CI: 0.954, 1.178) with every 1 year increase in hydrophilic statin exposure, suggesting no difference between the groups. This was similarly the case for CERAD score, severity of cerebral amyloid angiopathy, presence/absence of Lewy Body pathology, presence/absence of subcortical arteriosclerotic leukoencephalopathy, and presence/absence of FTLD pathology. In terms of the relationship between post-mortem cerebrovascular pathologies and statin exposure: holding other factors constant, the odds of having more severe large vessel atherosclerosis (i.e. Circle of Willis) was found to change 0.969 times (95% CI: 0.928, 1.012) with every 1 year increase in lipophilic statin exposure, as compared to 0.977 times (95% CI: 0.869, 1.099) with every 1 year increase in hydrophilic statin exposure, again suggesting no difference between the groups. This was similarly the case for the presence of infarcts/lacunes, microinfarcts, hemorrhages/microbleeds, and arteriosclerosis. *Conclusion:* While investigations into the relationship between statin exposure and risk for neurodegeneration remains a well-traveled path, it is critical that we address key shortcomings of studies to date, particularly as to whether statins with different biochemical properties (and thus blood-brain barrier permeability) exert differential effects on neurodegenerative and cerebrovascular pathobiology. In the present study, a clear association could not be established between exposure to lipophilic versus hydrophilic statin species and risk for developing neurodegenerative or cerebrovascular pathology. As a next step, we will attempt to replicate our results in another large, well-characterized autopsy dataset to determine if these findings are consistent across populations.

P102: THE LONGITUDINAL ASSOCIATION OF GLYCEMIC CONTROL BASED ON GLYCEMIC TARGET OF THE JDS/JGS JOINT COMMITTEE WITH COGNITIVE AND ADL DECLINE IN PATIENTS WITH MCI AND AD.

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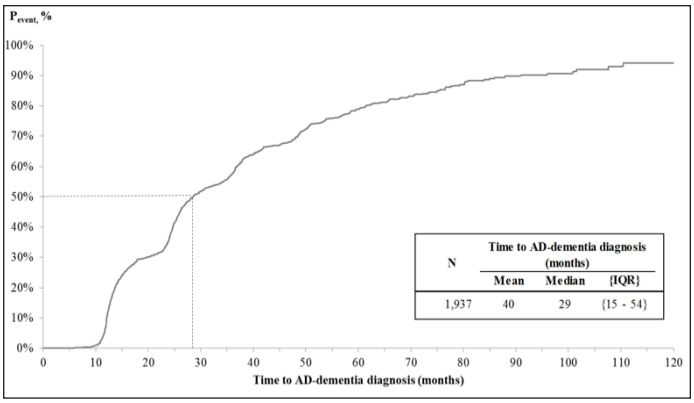
Backgrounds: In recent years, several studies from western countries showed the prevalence and incidence of dementia is decreasing. In Japan, however, prevalence of dementia is still increased, and is expected to increase further with increasing population of diabetic elderly. Therefore, prevention of dementia in elderly with diabetes is the urgent challenge. Recently, "Glycemic Targets for Elderly Patients with Diabetes" was introduced by the Japan Diabetes Society (JDS)/Japan Geriatrics Society (JGS) Joint Committee. According to this report, glycemic target (HbA1c) is to be determined by taking into account the patient's background characteristics and health status, and patients are classified into three categories: Category I (intact cognitive function and activity of daily living [ADL]); Category II (MCI to mild dementia or impairment of instrumental ADL); and Category III (moderate or severe dementia, or impairment of basic ADL, or presence of multiple comorbidities). In these three categories, the upper limit and the lower limit of the glycemic target (HbA1c) are specified to prevent several diabetic complications and comorbidities. The aim of this study was to examine the longitudinal effects of glycemic control based on the glycemic target recommended by the JDS/JGS joint committee on dementia prevention and care. *Methods:* The subjects were 156 MCI and 295 AD patients who attended the Memory Clinic of the National Center for Geriatrics and Gerontology of Japan during from October 2010 to February 2016 (mean age ± SD: 78.3 ± 5.1, female: 75.2%). At baseline, information on age, sex, education and use of medications were obtained from clinical charts. We assessed cognitive function and behavioral and psychiatric symptoms of dementia by using Mini-Mental State Examination (MMSE) and dementia behavioral disturbance scale (DBD), respectively. Basic ADL, instrumental ADL and physical performance were evaluated by using Barthel Index, Lawton Index, and timed up and go test (TUG), respectively. MMSE and Barthel Index were assessed at baseline and 2nd visit. The presence of diabetes was defined as (1) a self-reported previous diagnosis by medical doctors, (2) the use of anti-diabetic medication,

(3) HbA1c concentration of 6.5% or more. In analyses, we assigned subjects into two categories: Category II (MCI to mild AD [MMSE ≥ 21] or impairment of instrumental ADL); and Category III (moderate or severe AD [MMSE < 21] or impairment of basic ADL). In each category, subjects with diabetes were divided into three glycemic control groups (good control, hyperglycemic, and hypoglycemic) according to the glycemic target suggested by the JDS/JGS joint committee. Multivariable linear mixed models were used to examine the associations of the three glycemic control groups (no diabetes group is reference group for these analyses) with cognitive and ADL decline over time in each category. Each model included visit time, glycemic control groups, visit time*glycemic control groups interaction and controlled for age, sex, education, diagnosis, DBD, TUG and use of anti-dementia drug. *Results:* Out of 451 subjects, 146 subjects (32.4%) had diabetes. We assigned 246 patients into the Category II (no diabetes group, n = 178; good control group, n = 32; hyperglycemic group, n = 25; hypoglycemic group, n =11) and 205 patients into the Category III (no diabetes group, n = 127; good control group, n = 51; hyperglycemic group, n = 13; hypoglycemic group, n =14). At baseline, there were no difference in MMSE and Barthel Index among glycemic control groups in both Category II and III. In Category II (mean follow-up period; 429.56 ± 148.41 days), the mean changes in MMSE and Barthel Index over 2nd visit time were -1.20 ± 3.22 and -1.74 ± 4.52, respectively. Multivariate linear mixed model demonstrated that hyperglycemic group showed faster ADL decline over 2nd visit time (visit time*hyperglycemic group; β = -3.09 ± 0.90, p = 0.001) compared to no diabetes group. Although it was not statistically significant, hyperglycemic group tended to show faster cognitive decline over 2nd visit time (visit time*hyperglycemic group; β = -1.24 ± 0.68, p = 0.066). In Category III (mean follow-up period; 447.27 ± 175.09 days), the mean changes in MMSE and Barthel Index over 2nd visit time were -1.03 ± 3.47 and -3.94 ± 11.29, respectively. Multivariate linear mixed model demonstrated that hypoglycemic group showed faster ADL decline over 2nd visit time (visit time*hypoglycemic group; β = -11.5 ± 3.36, p = 0.001) compared to no diabetes group. *Conclusion:* Poor glycemic control, hyperglycemia in Category II and hypoglycemic group in Category III, based on the glycemic targets of the JDS/JGS was significantly associated faster ADL decline in patients with MCI and AD. In addition to the treatment for dementia, optimal glycemic control by taking into account the patient's background characteristics and health status is necessary for prevention for ADL decline, in other words, progression of dementia.

P103: CLINICAL ATTRIBUTES AND DISEASE PROGRESSION AMONG PATIENTS WITH MILD COGNITIVE IMPAIRMENT ASSOCIATED WITH ALZHEIMER'S DISEASE: FINDINGS FROM THE NATIONAL ALZHEIMER'S COORDINATING CENTER. J. Scott Andrews[1], Urvi Desai[2], Noam Y. Kirson[2], Miriam Zichlin[2], Sophie Schonfeld[2], Daniel E. Ball[1], Colin Green[3] *((1) Eli Lilly and Company, Indianapolis, IN; (2) Analysis Group, Inc., Boston, MA; (3) University of Exeter, Exeter, UK)*

Background: Clinical criteria for identifying mild cognitive impairment (MCI) believed to be due to Alzheimer's disease (AD) etiology have evolved over time, and there remains considerable variation in diagnosis in clinical practice. A better understanding of clinical attributes and disease progression among patients with MCI due to AD (MCI-AD) in a real-world setting could contribute to the design of clinical trials evaluating interventions to improve the prognosis for these patients. This study assessed the characteristics of patients with MCI-AD and evaluated the time from a diagnosis of MCI-AD to a diagnosis of dementia due to AD (AD-dementia) among patients visiting 35 past and present Alzheimer's Disease Centers (ADC) across the United States. *Methods:* Patients with at least one record with MCI diagnosis and concurrent or subsequent record indicating primary etiology of AD (per clinician's assessment) between September 2005 and September 2016 were selected from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). Patients were required to have no evidence of normal cognition after the first visit with MCI-AD or other specific primary dementia etiologies (e.g., vascular dementia) at any time. Additionally, patients were required to have at least one visit to an ADC after initial MCI-AD diagnosis. Patient demographics and comorbidity profiles at the time of MCI-AD diagnosis, as well as clinical characteristics at the time of MCI-AD and AD-dementia diagnoses were described. In addition, rates of progression to AD-dementia among MCI-AD patients were estimated using Kaplan-Meier survival analyses. Patients were censored at the last observed visit to an ADC. *Results:* A total of 4,498 patients in the NACC dataset had an MCI-AD diagnosis, of which, 1,937 (43%) met all selection criteria and were included in the final analytic sample. The average age of the MCI-AD cohort at the time of diagnosis was 76 years and 48% of the patients were male. On average, patients had 3 ADC visits after the initial MCI-AD diagnosis. Approximately half of the patients had hypertension and/or hypercholesterolemia, and 36% had depression at the time of MCI-AD diagnosis. The mean Global Clinical Dementia Rating (CDR) score at the time of MCI-AD diagnosis was 0.5, the mean Mini Mental State Examination (MMSE) score was 26.6, and the mean Neuropsychiatric Inventory Questionnaire (NPI-Q) score was 2.4. Nearly 70% of patients were able to live independently, 29% required some assistance with complex activities, and 2% required some assistance with basic activities; the mean Functional Assessment Questionnaire (FAQ) score was 4.1. Kaplan-Meier analyses found median time to AD-dementia diagnosis of 29 months (Figure 1). At the time of AD-dementia diagnosis, the mean Global CDR score was 0.8, the mean MMSE score was 23.4, the mean NPI-Q score was 3.9, and the mean FAQ score was 11.9. Only 29% of the patients were able to live independently at the time of AD-dementia diagnosis; 56% required assistance with complex activities, 12% required assistance with basic activities, and 2% were completely dependent. *Conclusion:* Within the NACC dataset, the clinical attributes of patients with MCI-AD at the time of diagnosis were consistent with the National Institute of Aging-Alzheimer's Association as well as the American Psychiatric Association guidelines for MCI-AD diagnosis. Half of the patients with MCI-AD received an AD-dementia diagnosis within 2.5 years of the MCI-AD diagnosis, suggesting an average annual conversion rate of approximately 25%. At the time of initial AD-dementia diagnosis, most patients had a mild form of dementia (as indicated by CDR and MMSE scores) marked by some noticeable but mild neuropsychiatric symptoms and having difficulty in performing complex activities of daily living. These findings provide insight regarding changes observed between an MCI-AD diagnosis and diagnosis of AD-dementia for several key clinical trial measures.

Figure 1
Kaplan-Meier Time from First Visit with MCI-AD to First Visit with AD-Dementia Diagnosis (N=1,937)



Abbreviations: MCI=mild cognitive impairment; AD=Alzheimer's disease; P=probability; IQR=interquartile range; ADC=Alzheimer's disease center. Note: Patients were censored at their last visit to an ADC.

P104: THE ASSOCIATION BETWEEN BODY MASS INDEX AND COGNITIVE DECLINE IN PATIENTS WITH SMALL VESSEL DISEASE -PRELIMINARY STUDY. Hae-Eun Shin, Seong-Hoon Kim, Si Baek Lee, Jung-Wook Park *(The Catholic University of Korea, Uijeongbu, South Korea)*

Background: Obesity in middle age might increase the risk of dementia in old age. The potential underlying mechanisms linking higher body mass index (BMI) to dementia may include direct effect of adiposity as well as indirect effects such as vascular risk factors and cerebrovascular disease. We investigated the association of BMI with cognitive decline according to the severity of the small vessel disease. *Methods:* We recruited 92 individuals who visited complain of the cognitive decline. All subjects were assessed with Seoul Neuropsychological Screening Battery (SNSB) to evaluate their cognitive functions and checked their BMI. Severity of the small vessel disease was categorized in three groups by clinical white matter rating scale using their FLAIR images of brain MRI. We calculated the correlation coefficient of BMI on the cognition in each small vessel disease groups. *Results:* Mean age of the individuals were 73.05±7.19 and mean BMI was 24.39±3.13. According to BMI, overweight (25-29.9 Kg/m2) and obese (≥30 Kg/m2) individuals tend to low p-value of the MMSE score, but it was not significant. Total 77 individuals were performed brain MRI and the number of patients in each small vessel disease scale was follows: 44 hand a minimal, 18 hand a moderate and 15 had a severe. In each subgroup of small vessel disease, we did not find the correlation between BMI and their cognition. *Conclusions:* This study did not demonstrate the association between BMI and cognitive decline under the severity of small vessel disease. These findings suggest that the possible another mechanism of the influence of BMI to dementia as well as vascular risk factors is exist. However, more caution is needed because there is a need for more research with larger sample and further study is needed to evaluate by dementia subtypes.

P105: NUTRITIONAL STATUS IN PATIENTS WITH MCI, AD AND DLB AND ITS CLINICAL MEANING FOR DEMENTIA PREVENTION AND CARE. Ai Kimura[1,2,3], Takashi Sakurai[1,3], Taiki Sugimoto[1,2,4,5], Kazuya Kitamori[6], Naoki Saji[1], Shumpei Niida[2], Kenji Toba[1] *((1) Center for Comprehensive Care and Research on Memory Disorders, National Center for Geriatrics and Gerontology, Obu, Japan; (2) Medical Genome Center, National Center for Geriatrics and Gerontology, Obu, Japan; (3) Department of Cognitive and Behavioral Science, Nagoya University Graduate School of Medicine, Nagoya, Japan; (4) Department of Community Health Sciences, Kobe University, Graduate School of Health Sciences, Kobe, Japan; (5) Japan Society for the Promotion of Science, Tokyo, Japan; (6) College of Human Life and Environment, Kinjo Gakuin University, Nagoya, Japan)*

Background: With aging of the world's population, the prevalence of dementia is increased. Since no basic medical treatment of Alzheimer's disease (AD) is established at present, intervention for prevention of AD is crucial. Although multi-domain intervention of diet, exercise, cognitive training, and social activities from early phase of dementia would be a successful strategy, there are little data on diet especially in mild cognitive impairment (MCI) and early-stage AD. In this study, we aimed to clarify the nutritional status at various types and stages of cognitive impairment (MCI, AD and dementia with Lewy bodies: DLB). In addition, some studies showed the association between nutritional status and behavioral and psychological symptoms of dementia (BPSD) as well as cognitive decline in patients with moderate to severe AD. We aimed to examine the relationship between nutritional status and BPSD in MCI and early-stage AD. *Methods:* The subjects were 1324 female outpatients who attended the Memory Clinic at the National Center for Geriatrics & Gerontology of Japan and were diagnosed with cognitive normal (CN, n=157), MCI (n=290), AD (n=807), or DLB (n=70) during the period from September 2010 to January 2015. Since it is well known that there are gender differences in nutritional status (e.g. body composition, serum levels of 25-hydroxyvitamin D [25-(OH)D]) and manifestation of BPSD, we focused on female patients who aged 65-89 years in this study. Information on age, years of education, and living situation were obtained from the clinical charts. Nutritional status was assessed by using Mini Nutritional Assessment-Short Form (MNA-SF; well-nourished: 14-12, at risk of malnutrition: 11-8, malnutrition: 7-0). We also measured body mass index (BMI) and body composition (amount of body fat mass, muscle mass and fat-free mass) with bioelectrical impedance analysis. Serum levels of albumin, total protein, 25OHD, folate and total homocysteine were assessed. BPSD was assessed by caregivers using the Dementia Behavior Disturbance Scale (DBD). Other confounding variables of nutritional status including cognitive status (Mini-Mental State Examination; MMSE), basic/instrumental activities of daily living (Barthel Index: BI/Lawton Index: LI), depressive mood (Geriatric Depressive Scale-15: GDS), vitality (Vitality Index: VI), comorbidities, and polypharmacy were assessed. We compared nutritional status of subjects at various cognitive stages by using multinomial logistic regression analyses (CN is the reference group for these analyses). In the second place, in order to examine the association between nutritional status and BPSD in patients with MCI or early-stage AD, we focused on 590 patients (MCI; n=272, early-stage AD; n=318) who had a MMSE score of 21 or more. We assigned subjects into two groups according to individual MNA-SF score (well-nourished group: 14-12, at risk and malnutrition group: 11-0). Since the DBD consist of 28 subitems, factor analysis (principal factor method and promax rotation) was carried out and 6 factors were extracted as follow: 1) Verbal aggressiveness/Emotional disinhibition, 2) Motor aggressiveness, 3) Behavior disturbance,

4) Memory impairment/Apathy, 5) Incontinence, and 6) Sexual disinhibition. The differences in total DBD score and factor scores between well-nourished group and at risk and malnutrition group were analyzed by using analysis of covariance (ANCOVA) adjusted for age, education, polypharmacy, comorbidities, living situation, BI, LI, GDS, VI and MMSE. *Results:* The patients with MCI, AD, and DLB had lower MNA-SF score and the prevalence of at risk of malnutrition and malnutrition were higher than CN (at risk of malnutrition: CN: 35.7%, MCI: 46.6%, AD: 54.5%, DLB: 67.1%, malnutrition: 5.1%, 6.2%, 11.0%, 15.7%). Regarding breakdown of MNA-SF, "food intake decline" (1.9±0.2 vs. 1.8±0.4 / 1.7±0.5 / 1.6±0.6; p<.001), "weight loss" (2.3±0.9 vs. 2.1±1.0 / 2.1±1.0 / 2.0±0.9; p=.011) and "neuropsychological problems" (1.9±0.4 vs. 1.7±0.4 / 1.4±0.6 / 1.1±0.5; p<.001) were lower in MCI, AD, and DLB. AD and DLB patients had significantly lower amount of fat (15.3±6.5kg, 14.7±6.3kg, 13.6±6.4kg, 13.1±5.8kg; p=.001), muscle mass (35.3±3.2kg, 34.3±3.5kg, 33.1±3.6kg, 32.5±2.8kg; p<.001), and fat-free mass (33.4±2.9kg, 32.4±3.3kg, 31.4±3.3kg, 30.8±2.6kg; p<.001) than CN, but BMI was not different. Moreover, AD and DLB patients showed the lower serum level of 25(OH)D than CN (26.3±5.7ng/dl, 23.5±8.2ng/dl, 21.8±7.3ng/dl, 16.7±6.5ng/dl; p<.001), although there were no differences in other biochemical data. For the second purpose, we focused on 590 subjects with MCI or early-stage AD, and we assigned 247 patients into well-nourished group and 343 patients into at risk and malnutrition group. At risk and malnutrition group showed higher score of DBD than well-nourished group (well-nourished group vs. at risk and malnutrition group = 9.5±7.3 vs. 12.8±9.1, p<.001). In multivariate analyses, ANCOVA showed that nutritional status was significantly associated with total DBD score (F[1, 577]=8.518, p=0.004), Verbal aggressiveness/ Emotional disinhibition, (F[1, 577]=6.111, p=.014), and Memory impairment/Apathy (F[1, 577]=14.953, p<.001) after adjusted for confounding factors. *Conclusions:* Nutritional problems, especially decreased muscle and fat mass, food intake, and 25(OH)D, appeared to be increased from early phase of dementia. Our results suggest that the multidomain interventions including exercise and diet therapy from early phase of dementia are necessary.

P106: OPTIMIZING DIETARY INTERVENTION STUDIES OF MODIFIABLE RISK FACTORS AND COMORBIDITIES FOR LATE ONSET ALZHEIMER'S DISEASE. Feng-Yen Li[1], Ann Lam[1,2] *((1) Physicians Committee for Responsible Medicine, Washington, DC, USA; (2) Green Neuroscience Laboratory, Neurolinx Research Institute, San Diego, CA, USA)*

Background: Late-onset Alzheimer's disease (LOAD) is the most common form of dementia and is associated with number of lifestyle risk factors. Without effective prevention or interventions LOAD's prevalence is expected to triple by 2050. Despite decades of research involving hundreds of experimental drug trials, largely based on animal models, there are no disease-modifying drug treatments to date. However, epidemiological studies and the recent success of non-pharmacological clinical trials like the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study suggest that modifying lifestyle factors could be an effective strategy to help reverse the current disease trends. Dietary patterns are a highly understudied modifiable risk factor in LOAD and even when nutrition studies are conducted many dementia clinical trials focus on testing the benefits of isolated single component nutrients rather than the effects of overall dietary patterns. Yet, the efficacy of interventions which alter dietary patterns, from the Mediterranean diet to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, suggest immense therapeutic potential in optimizing this non-pharmacological prevention or reversal strategy for cognitive impairment. Adding to the compelling case for focused investment to improve dietary intervention studies is the fact that unhealthy dietary trends in the modern era have coincided with the prevalence of LOAD and associated comorbidities over the last several decades. LOAD is often associated with chronic diseases of metabolic, vascular, and inflammatory derangements, thus developing strategies to address these risk factors which have been shown to be remediated by dietary changes may serve as a powerful therapeutic intervention for the disease. *Methods:* For proof-of-principle of the value comprehensive dietary interventions, we analyzed the peer-reviewed literature on modifiable risk factors of LOAD that induce metabolic, vascular, and inflammatory dysfunction. Surveying epidemiological and ecological studies conducted worldwide, we searched for statistically significant ($p < 0.05$) associations and correlations between Alzheimer's disease prevalence and temporal related changes in dietary components or food supplies and consumption. We also assessed the epidemiological evidence on specific food types conferring significant protective or detrimental effects on cognition. Based on these data we hypothesized a plant-based dietary intervention would be effective for countering some of the major underlying, modifiable risks of LOAD. We also gathered data from human clinical trials that tested the efficacy of plant-based dietary interventions to reverse the diet-related, modifiable risk factors or comorbidities associated with LOAD or provide specific cognitive benefits with statistical significance ($p < 0.05$). Based on this evidence, we propose a study design for a comprehensive dietary intervention to modify risk factors and comorbidities of LOAD. *Results:* From both ecological and epidemiological studies worldwide, increasing consumption of animal-derived food products was strongly associated with the increase of LOAD. In contrast, multiple prospective and retrospective cohort studies showed that plant-based foods significantly reduced dementia risk. With the exception of vitamin D and B12 deficiency, a whole plant-based diet was found in clinical trials to be effective for reversing many lifestyle-related risk factors of LOAD. These factors include cardiovascular disease, type 2 diabetes, hypertension, obesity, depression, hypercholesterolemia, elevated saturated fats, hyperhomocysteinemia, low vitamin levels (B6, folate, A, C, E), and elevated levels of inflammatory markers. Epidemiological and empirical evidence also suggest that eliminating animal-derived products including fish from the diet could reduce accumulation of heavy metals and other chemicals -- another risk factor of LOAD. A number of anti-inflammatory plant-derived foods were also found to promote better memory and/or cognition including curcumin/tumeric, cumin seeds, omega-3, water hyssop, and gingko biloba. *Conclusions:* Epidemiological evidence presents a strong case for dietary patterns as a driving or modulating factor of neurovascular inflammation and metabolic dysregulation which are increasingly implicated in the etiology of LOAD. Human clinical trials on the efficacy of plant-based diets to modulate comorbidities and risk factors of LOAD support changes to dietary patterns as a potentially effective prevention strategy for LOAD. However, these indications must be tested within well controlled settings within prodromal LOAD populations. Thus we propose assessing the efficacy of a dietary intervention program composing of a whole food plant-based diet complemented with evidence-based neuroprotective plant-based supplements for preventing or reversing LOAD in randomized controlled trials.

P107: IS THE TIME RIGHT TO CAPITALISE ON EMERGENCE OF LIFETIME AND LIFESTYLE ALZHEIMER'S DISEASE RELATED FACTORS AS DETERMINANTS OF PRE-DISEASE NEUROCOGNITIVE PERFORMANCE? CROSS-SECTIONAL EVIDENCE FROM THE CHARIOT PRO MAIN STUDY. Chinedu T Udeh-Momoh, PhD[1], Bowen Su[1], Geraint J Price[1], David Muller[1], Darina Bassil[1], Catherine Robb[1], Heather Ward[1], Michael T. Ropacki[3,4,5] Robert Perneczky[1,2], Ioanna Tzoulaki[1], Lefkos T Middleton[1] *((1) Imperial College London, London, United Kingdom; (2) Ludwig-Maximilians-Universität, Munich, Germany; (3) Janssen Research and Development, Fremont, CA, USA; (4) Loma Linda University School of Medicine, Loma Linda, CA, USA; (5) MedAvante, Inc., Hamilton, NJ, USA)*

Background: The aetiology of Alzheimer's disease (AD), thought to result from complex interactions over time between genetic, other biological and environmental factors, remains poorly understood. Epidemiological evidence has linked several lifestyle exposures and lifetime experiences to a delayed onset of cognitive impairment attributable to AD (Norton et al. 2014; Bellou et al. 2016). Furthermore, the 2-years results of the multidomain lifestyle intervention FINGER trial, simultaneously targeting multiple lifestyle paradigms suggest benefits for the preservation of cogntive function in high risk individuals (Ngandu et al. 2015). Here we present novel evidence for construct validity of multi-factorial composites encompassing established protective factors that may contribute to delaying onset of AD-dementia symptoms. Our study aims to: (a) identify latent components that describe the structure of epidemiological factors associated with AD prevention; and b) evaluate the discriminative utility of the weighted component scores for distinguishing between differing cognitive abilities within a cohort of healthy individuals, over the age of 60. *Methods:* 987 healthy elderly individuals, aged 60-85, with no history of cognitive deficits, were screened for the CHARIOT PRO: a prospective cohort study. Established protective factors linked to AD prevention, namely demographic (age, gender, socioeconomic status – high level of household income and of occupational attainment, cohabitation status, lack of family history of dementia, multilingualism); biological (non-carriage of APOEε4 allele – major AD genetic risk determinant); cognitive (high premorbid intelligence, high educational attainment and complex mental activities) and lifestyle (physical and social activities, and good sleep quality) were collected at study entry. We used multiple linear regression analyses (adjusted for age, gender, ethnicity, BMI, depression and Type II diabetes) to identify predictors of higher cognitive abilities as determined by performance in a well-validated multi-domain cognitive evaluation – the Repeatable Battery for Assessment of Neuropsychological Status (RBANS). Age-adjusted total index scores calculated from the RBANS tests provided a suitable outcome measure of neurocognitive abilities. Variables were subjected to a principal components analysis (PCA) to determine the best factor loading within agnostically-derived PCA components. Weighted component scores calculated as latent constructs were assessed by multilevel mixed regression methods to evaluate validity of the generated scores as predictors of cognitive performance. *Results:* Amongst our deeply-phenotyped cohort [mean age: 68.5 years+/- 2.31, 67% female], 25% were APOEε4 allele carriers, 17% obese (BMI>30), 7% current smokers and 7% diabetic. Univariate analyses adjusted for age and gender highlighted educational and occupational attainment, income, mid-life and current participation in physical, social and complex mental activities, and IQ, non or ex - smoker, lack of hypertension, hypercholesterolemia or CVD diagnoses as significantly associated with better cognitive performance. Using the principal components extraction method, we identified four independent hypothesised variable clusters of the investigated protective factors. Component I comprised current and mid-life participation in complex mental activities. Factors typically associated with lifetime cognitive and socioeconomic status, namely education, IQ, income and occupation loaded on Component II. Component III factors consisted of current and mid-life participation in physical and social activities, while vascular health determinants i.e. smoking, diagnosis of CVD, hypertension and hypercholesterolemia clustered within the Component IV. Multivariate linear regression analyses adjusted for aforementioned medical, psychological and demographic covariates revealed significant associations between high neurocognitive test performance and mid-life physical activity, non-smoking status, managerial and professional type occupations, high premorbid IQ as well as education level to at least high school completion. Further evaluation of the data revealed significant associations for factors associated with component I – [Coefficient= 1.33; $p<0.001$; 95%CI: 0.89 -1.76], and component II - [Coefficient= 0.67; $p<0.001$; 95%CI: 0.53 - 0.80], with higher neurocognitive test scores. Adjustment for APOEε4 allele status indicated a genotype-independent effect of the protective composites in relation to prediction of RBANS test scores. Additional exploratory analyses showed a positive association between mid-life physical/social activities and cognitive performance - [Coefficient= 2.06; $p=0.002$; 95%CI: 0.77 - 3.35]) in APOEε4 carriers only. *Conclusion:* Our data provide evidence to suggest that factors typically featured as indicators of cognitive reserve (CR), including greater participation in physical/social-type activities during mid-life, seem to be associated with higher neurocognitive performance, as measured using the multi-domain RBANS test in pre-symptomatic individuals. In light of our findings and other recent publications, the time may be ripe for a critical re-consideration of study designs for future observational or interventional pre-clinical AD trials to take into account risk and protective scores and profiles. Promoting the use of a consistent risk and protective factor composite across studies may also provide a reliable reference tool to control for influencers of cognitive changes in longitudinal studies of ageing and dementia.

P108: CLINICAL TRIAL RECRUITMENT RATE FROM A PATIENT DATABASE IN AN ACADEMIC GERIATRIC CENTER. Daniel G. Gámez Treviño, Blanca I. González García, Patricia A. Guerrero Garza, Ricardo Salinas Martínez *(Geriatric Services, "Dr. Jose Eleuterio González" University Hospital, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, México)*

Introduction: Interest in populations with Alzheimer's disease has increased in the last decades due to the epidemiological growth of this clinical condition. In Mexico, 800,000 individuals suffer from dementia and a cross sectional survey published by the 10/66 Dementia Research Group1 from community based sites showed a rate of MCI in Mexican communities of from 3.8 to 6.3% with variations according to age groups (Sosa et al 2012)1. Considering that treatments that are currently available for these conditions are only partially effective, participating in clinical trials is a reasonable option for these individuals. Latin-America has participated in AD projects since 1980, such as the Francisco Loperena research team in Antioquia Colombia, Argentinean groups participating in the Neuroimagine initiative of AD (WW-ADNI), and an international effort to validate biomarkers for advanced AD (Snyder et al 2016). Brasil, Argentina, Chile and Mexico participate regularly in Clinical trials for AD since 20032. This has followed the interest shown by the pharmacological industry in this geographic area. Over time

almost all of these centers have been growing responding to the increased demand that Alzheimer's disease clinical trials have shown. Despite perceived cultural and institutional barriers, recruitment issues identified in other studies examining rates of eligibility found that only 10 to 27% of AD patients fulfill inclusion and trial eligibility criteria 3. This report looks into our experience selecting patients from an on-going data base. As a country, Mexico has several issues to take in consideration such as population's educational level, unwillingness to participate, lack of mobility due to adults living alone, etc. We focused our efforts on developing a data base from our memory clinic reports. This work shows how the prescreening data collected over three years has resulted in patient recruitment in AD and MCD clinical trials. *Methods:* This is a descriptive observational retrospective study from the data base of the Geriatric Services research unit at the "Dr. José Eleuterio González" University Hospital in Monterrey, México. 1,560 patients were followed through their medical outpatient assessment in the last 3 years. A prevalence of 16% probable Alzheimer's disease diagnosis and 5% of MCI diagnosis was found. 138 patients (8.8%) that fulfilled prescreening criteria for AD clinical trials during their geriatric evaluation were selected. The statistical analysis was carried out using SPSS 21 Inc.

Theme: Clinical Trials: Animal Models

P109: NANODELIVERY OF CEREBROLYSIN REDUCES PHOSPHORYLATED TAU AND PROSTAGLANDIN METABOLITE F-2 ISOPROSTANE IN CSF AND BRAIN IN ALZHEIMER'S DISEASE. NOVEL THERAPEUTIC STRATEGIES USING NANOMEDICINE. Aruna Sharma[1], José V Lafuente[2], Dafin F Muresanu[3], Rudy J Castellani[4], Mark A Smith[5], Ranjana Patnaik[6], Z Ryan Tian[7], Asya Ozkizilcik[7], Herbert Mössler[8], Hari S Sharma[1] *((1) International Experimental CNS Injury & Repair (IECNSIR), Laboratory of Cerebrovascular Research, Dept. of Surgical Sciences, Anesthesiology & Intensive Care Medicine, Uppsala University Hospital, Uppsala University, Uppsala, Sweden; (2) Dept of Neurosciences, University of Basque Country, Bilbao, Spain; (3) Dept. Clinical Neurosciences, University of Medicine & Pharmacy, Cluj-Napoca, Romania; a''RoNeuro'' Institute for Neurological Research and Diagnostic, 37 Mircea Eliade Street, 400364, Cluj-Napoca, Romania; (4) University of Maryland, Dept. of Pathology, Baltimore, MD, USA; (5) Case Western Reserve Medical University, Dept. of Pathology, Cleveland, OH, USA; (6) School of Biomedical Engineering, Dept. of Biomaterials, Indian Institute of technology, Banaras Hindu University, Varanasi, India; (7) Dept. Chemistry & Biochemistry & bBiomedical Engineering, University of Arkansas, Fayetteville, AR, USA; (8) Ever NeuroPharma, Oberburgau, Austria)*

Background: Alzheimer's Disease (AD) affecting millions of people World Wide every year for which no suitable therapeutic measures are still available. Thus, exploration of novel therapeutic strategies to improve the functional parameters of the victims for a better healthcare and quality of life is urgently needed. It appears that severe oxidative stress caused by a variety of internal factors and altered metabolism of enzymes could results in vascular, neuronal and glial cell damages in the brain leading to progression of AD brain pathology. Increased levels of lipid peroxidation and phosphorylation of tau (p-tau) protein occurs in the CSF and plasma of AD patients. Elevated levels of prostaglandin metabolite F-2 isoprostane (ISP) in CSF and plasma further confirm oxidative stress in AD. The levels of tau and ISP correlate well with the accumulation of amyloid beta protein (AbP) in AD brains. Thus, novel therapeutic strategies to reduce these elements may have potential neuroprotective effects in AD. In this investigation we examined the influence of cerebrolysin-a balanced composition of several neurotrophic factors and active peptide fragments on oxidative stress induced in an animal model of amyloid beta protein (AbP) infusion in rats. Furthermore, nanodelivery of cerebrolysin using TiO2-nanowires or PLGA-nanoparticles labeled drug was examined on p-tau and ISP levels in CSF and brain of AD rats. The brain pathology following AD e.g., blood-brain barrier (BBB) leakage to proetins, edema formation and neuronal, glial and axonal changes was also investigated. *Methods:* Experiments were carried out on Male Sprague Dawley rats (250-300 g, Age 30 to 35 weeks). AD like symptoms was produced by intraventricularly (i.c.v.) administration of AbP (1-40) in the left lateral ventricle in a dose of 250 ng/10 μl once daily for 4 weeks. Control group received physiological saline (0.9% NaCl) instead of AbP infusion. After 30 days of the 1st AbP or saline infusion, the rats were examined for blood-brain barrier (BBB) disturbances to endogenous/exogenous protein tracers, brain edema formation, AbP deposits and brain pathology comprising, neuronal, glial and axonal changes using standard procedures. In addition, separate group of rats received nanowired cerebrolysin (NWCBL 25μl, i.c.v.) or PLGA-nanoparticles labeled cerebrolysin (PLGA-CBL 25 μl, i.c.v.) under identical conditions after 1 week of AbP infusion daily for 2 weeks. In all these cerebrolysin treated animals with or without nanodelivery, brain pathology and behavioral functions were analyzed using standard protocol. Furthermore, in these AD rats untreated or treated with NWCBL or PLGA-CBL, p-tau and ISP in the CSF collected from cisterna magna and brain tissues obtained from cerebral cortex, hippocampus and cerebellum was measured using commercial ELISA kit according to standard protocol. *Results:* Our observations showed marked AD like symptoms in untreated AbP infusion group as described earlier. Thus, AbP deposits in the cortex and in hippocampus, neuronal damage and cell death, activation of astrocytes as seen using glial fibrillary acidic protein (GFAP) immunoreactivity, loss of myelin basic protein (MBP) and increase in albumin immunoreaction were prominent in AbP administered group as compared to saline treated rats. Breakdown of the BBB to Evans blue albumin or radioiodine ([131]-I) and edema formation was much more pronounced in several brain areas following AbP infusion. The behavioral disturbances on Rota Rod performances and inclined plane angle tests were significantly deteriorated along with the ability to retrieve platform in water maze tests in AbP infused rats as compared to saline treated control group. Our results further showed a 2-fold increase in p-tau in CSF and 3-to 4-fold in the cortex, hippocampus and cerebellum from control group (CSF 35±5 pg/ml, Brain 5±2 ng/g) in AbP infused rats as compared to saline control group. Likewise, ISP was elevated 1.5 fold in CSF and 2-fold in the AD brain from control (CSF 45±6 pg/ml, Brain 0.56±0.03 pg/mg). NWCBL or PLGA-CBL administration significantly reduces the elevation of both p-tau and ISP in AD brain by 40 to 60 % and reduced brain pathology. Interestingly, NWCBL resulted in profound superior reduction in p-tau and ISP levels by 85 to 90% and thwarted AD brain pathology as compared to PLGA-CBL under identical condition. The BBB breakdown, edema formation and brain pathology as well as behavioural dysfunction were also reduced significantly by NWCBL or PLGA-CBL in AD. However, NWCBL has the most superior effects in reducing brain pathology and behavioral dysfunction in AD as compared to PLGA-CBL nanodelivery. *Conclusions:* These results are the first to indicate that NWCBL has superior effects in reducing oxidative stress in AD as compared to PLGA-CBL nanodelivery. Furthermore, oxidative stress plays key roles in AD brain pathology, not reported earlier. *Supported by grants from the Air Force Office of Scientific Research (EOARD, London, UK), and Air Force Material Command, USAF, under grant number FA8655-05-1-3065; supported by Grants from the

Alzheimer's Association (IIRG-09- 132087), the National Institutes of Health (R01 AG028679) and the Dr. Robert M. Kohrman Memorial Fund (MAS, RJC); Swedish Medical Research Council (Nr 2710-HSS), Göran Gustafsson Foundation, Stockholm, Sweden (HSS), Astra Zeneca, Mölndal, Sweden (HSS/AS), The University Grants Commission, New Delhi, India (HSS/AS), Ministry of Science & Technology, Govt. of India (HSS/AS), Indian Medical Research Council, New Delhi, India (HSS/AS) and India-EU Co-operation Program (RP/AS/HSS) and IT 794/13 (JVL), Government of Basque Country and UFI 11/32 (JVL) University of Basque Country, Spain, & Society for Neuroprotection and Neuroplasticity (SSNN), Romania.

P110: NANODELIVERY OF CEREBROLYSIN POTENTIATES HISTAMINE ANTIBODIES AND HISTAMINERGIC H3 AND H4 RECEPTOR MODULATION INDUCED REDUCTION IN BRAIN PATHOLOGIES IN ALZHEIMER'S DISEASE. Hari Shanker Sharma[1], José V Lafuente[2], Dafin F Mureasanu[3], Rudy J Castellani[4], Mark A Smith[5], Ranjana Patnaik[6], Z Ryan Tian[7], Asya Ozkizilcik[7], Stephen D Skaper[8], Herbert Mössler[9], Aruna Sharma[1]
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Background: Alzheimer's disease (AD) inflicts over 40 millions people aged 65 and older Worldwide and roughly 5 million Americans are living with the disease that involves huge burden on the society and families as well. Thus, exploration of novel therapeutic measures is needed to contain the disease and improve the quality of life of the victims. Increasing evidences suggest that histamine is involved in the pathogenesis of Alzheimer's disease (AD). Decrease of histamine concentration in several brain areas are seen in postmortem studies on human AD cases. Also, increased levels on histamine in plasma and in some areas of the brain are seen in Alzheimer's dementia brain. However, the precise mechanism of histamine induced AD pathology is not well known. Since histamine induces breakdown of the blood-bran barrier (BBB) in several brain areas and activated astrocytes and microglia causing disturbances in brain microenvironment, it is quite likely that the amine could play critical roles in AD pathology. Few studies indicate an involvement of H3 receptors are involved in cognitive and memory functions and H4 histamine receptors stimulation affects neuronal functions. Thus, it would be interesting to see whether drugs blocking the H3 receptors and/or stimulating H4 receptors may have some beneficial effects in AD induced brain pathology. In present investigation we examined the influence of one potent histamine H3 receptor inverse agonist BF 2649 hydrochloride and one selective H3 receptors antagonist with partial H4 agonist properties Clobenpropit dihydrobromide in our rats model of AbP induced AD like brain pathology. Furtehrmore, to prove an effective role of histamine in AD pathology we used monoclonal histamine antibodies infusion intracerebroventricularly (i.c.v.) to test the hypothesis. *Methods:* AD like pathology was produced in rats by administering AbP (1-40) intraventricularly (i.c.v.) in the left lateral ventricle (250 ng/10 μl) once daily for 4 weeks. Control rats received saline. In separate group of rats either BF 2649 (1 mg/kg, i.p.) or Clobenpropit (1 mg/kg, i.p.) once daily was administered 3 weeks after the 1st AbP administration and continued for 1 week. After 30 days of the 1st AbP infusion, the rats were examined for BBB breakdown, edema, neuronal, glial injuries and AbP deposits in their brain. In separate group of rats monoclonal histamine antibodies (Monoclonal Mouse anti-Histamine antibody, Abcam #ab5836, 1:20 in phosphate buffer saline, 20 μl) was co-administered with AbP under identical conditions, once daily for 30 days. In addition, in separate group of rats, TiO2-nanowired TiO2-nanowired delivery of cerebrolysin-a multimodal drug comprising a balanced composition of several neurotrophic factors and active peptide fragments administered (2.5 ml/kg, i.v.) after 1 week of AbP infusion for 3 weeks under identical conditions. In all such treated and untreated groups blood-brain barrier (BBB), brain edema and cellular injuries were examined using standard protocol. *Results:* Our results showed that histamine antibody treatment as well as BF 2649 (1 mg/kg, i.p.) or Clobenpropit (1 mg/kg, i.p.) administration was able to significantly reduce AbP deposits in the brain along with neuronal damage and glial activation. Interestingly, the breakdown of the BBB to Evans blue albumin and radioiodine in cortex, hippocampus, hypothalamus and cerebellum was significantly reduced in drug treated group as compared to control. Clobenpropit showed superior effects than BF2649 in reducing brain pathology in AD. However, when these drugs or histamine antibodies when administered 2 weeks after the onset of AbP for 2 weeks, the magnitude of neuroprotection was severely diminished. This suggests that blocjade of histamine action by antibodies or histamine receptor modulation could reduce AD pathology in a narrow therapeutic window. Since TiO2-nanowired delivery of cerebrolysin-a multimodal drug comprising a balanced composition of several neurotrophic factors and active peptide fragments administered (2.5 ml/kg, i.v.) after 1 week of AbP infusion for 3 weeks also induced neuroprotection, in this investigation we studied the co-administration of cerebrolysin and histaminergic drugs in our AD model on brain pathology. Our results further showed a significant reduction in AbP deposits in the brain along with neuronal damage and glial activation. Breakdown of the BBB and brain edema formation was also absent in these treated AD rats. Interestingly, a combination of cerebrolysin and Clobenpropit showed superior effects in reducing brain pathology in AD. Taken together, Taken together our observations are the first to show that blockade histamine action by antibodies or drug induced H3 receptors blockade and/or stimulation of H4 receptors are beneficial for the treatment of AD pathology. Furtehrmore, cerebrolysin treatment potentiate the neuroprotective effects ofhistamine antibodies and H3 receptor blocker or stimulation of H4 receptors in AD pathology even initiated 2 weeks after AbP infusion, not reported earlier. *Supported by grants from the Air Force Office of Scientific Research (EOARD, London, UK), and Air Force Material Command, USAF, under grant number FA8655-05-1-3065; supported by Grants from the Alzheimer's Association (IIRG-09- 132087), the National Institutes of Health (R01 AG028679) and the Dr. Robert M. Kohrman Memorial Fund (MAS, RJC); Swedish Medical Research Council (Nr 2710-HSS), Göran Gustafsson Foundation, Stockholm, Sweden (HSS), Astra Zeneca, Mölndal, Sweden (HSS/AS), The University Grants Commission, New Delhi, India (HSS/AS), Ministry of Science & Technology, Govt. of India (HSS/AS), Indian Medical Research Council, New Delhi, India (HSS/AS) and India-EU Co-operation Program (RP/AS/HSS) and IT 794/13 (JVL), Government of Basque Country and UFI 11/32 (JVL) University of Basque Country, Spain, & Society for Neuroprotection and Neuroplasticity (SSNN), Romania.

P111: CAN THE USE OF APPROVED IMAGING COMPOUNDS ALSO BE USED A THERAPY IN ALZHEIMER'S DEMENTIA. James Fontanesi[1], Daniel B Michael[1], Alaa Hanna[1], Michael Maddens[1], Prakesh Chinaiyan[1], Giovanni Fontanesi[2], Thomas Wilson[1], Alvaro Martinez[3], Katie Buelow[1], Barbara Pruetz[1], George D Wilson[1] *((1) William Beaumont Health Systems; (2) Oakland University; (3) 21st Century Oncology)*

Introduction: For over 5 years our research group has investigated the use of various external beam radiation schedules on a well known mouse model to determine in radiation may play a role in the treatment of Alzheimer's Dementia (AD). This effort is based on the knowledge that low dose irradiation has been used in non CNS settings of amyloidosis with excellent and durable responses. However external beam irradiation is non discriminatory and can affect non amyloid bearing areas of the brain. Because of this concerns have arisen regarding potential side effect . Last year we presented data regarding our use of a FDA approved imaging compound (Amyvid used in the diagnosis od AD. We realized that the annihilation event that led to the images was within the range of energies that could be effective in the treatment of amyloid , which we believe is the triggering event in the eventual development of symptoms associated with AD. We report here on our initial experience with various doses of that compound and its effectiveness on amyloid plaque reduction. *Methods:* We use the murine model APPswe,PSEN1dE9/85Dbo for our experiments . Its characteristics are well reported and produce in our breeding colonies consistent results. We used 3 -5 month old animals for our trial which was institutionally approved. We selected 4 dose levels for tail injection. They were: 1) 1000 uCi in 5 month old animals; 2) 500 uCi in 5 month old animals; 3) 500 uCi in 3 month old animals; 4) 500 uCi x 2 separated by 1 month in 5 month old animals. Following injection all animals were sacrificed within 1 month and stained for amyloid ; We had control animal data to compare with these animals 3 separate individuals did visual counting and then the slides were subject to evaluation Definiens Tissue Studio Image analysis. There was minimal differences between the human counters and computer analysis in terms of number of residual plaques identified. *Results*: Analysis of all data : Manual counting. The data below shows the average number of plaques per brain (3 sections counted by three different people) using manual counting. Statistical analysis shows that 1000uCi dose has significantly less plaques than the 500uCi (treated at 5 months) p=0.081 as well as the 500uCi treated a 3 months (p=0.014). The split dose 500uCi has significantly less plaques than the 500uCi treated at 3 months (p=0.0154) but not the 500uCi treated at 5 months(p=0.055) The other comparisons are not significantly different. Analysis of all data : Definiens counting. The data below shows the average number of plaques per brain using the automated Definiens counting. Statistical analysis shows that 1000uCi dose has significantly less plaques than the 500uCi treated at 5 months (p=0.0005) but not the 500uCi treated a 3 months (p=0.26). The split dose 500uCi has significantly less plaques than the 500uCi treated at 5 months (p=0.0002) and the 500uCi treated at 5 months (p=0.0488). The other comparisons are not significantly different. *Conclusions:* We believe that this is the first time that an imaging compound that works by use of an annihilation event with an energy capable of affecting amyloid deposits has been shown to have the potential for it to be used as a therapeutic agent that would target only the amyloid thus sparing non affected cells in the CNS , thus minimizing potential side effects that can be seen with external beam irradiation. We plan to look at use of this potential in both younger and older animals' and will report on those results separately

P112: INHIBITION OF CASPASE-1 AS A NOVEL TREATMENT AGAINST AGE-DEPENDENT COGNITIVE DECLINE AND ALZHEIMER DISEASE. Andrea C. LeBlanc[1,2], Joseph Flores[1] *((1) Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada; (2) Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada)*

Background: Active cysteinyl protease Caspase-6 (Casp6) is highly abundant in neuritic plaques, neuropil threads, and neurofibrillary tangles in sporadic and familial forms of Alzheimer disease (AD). Furthermore, active Casp6 is observed in the entorhinal cortex of aged individuals with no clinical cognitive impairment and the levels of Casp6 are inversely correlated with episodic and semantic memory performance. Expression of a self-activated form of human Casp6 in the CA1 of the mouse induces age-dependent spatial and episodic memory impairment, neuroinflammation, and neurodegeneration, in the absence of other AD pathologies. In CNS primary human neurons, Casp6 cleaves several proteins that contribute to AD pathology. Casp6 activation increases the production of amyloid beta peptide (Aβ), cleaves several cytoskeletal or cytoskeletal associated proteins including Tau and alpha-tubulin, and cleaves valosin containing protein resulting in the accumulation of misfolded proteins normally degraded by the proteasome. In addition, several synaptic proteins are substrates of Casp6 indicating that Casp6 may alter neuronal function. Activation of Casp6 in these human neurons causes axonal degeneration. These results suggest that inhibition of Casp6 could be a novel early treatment against age-dependent cognitive impairment and AD. Unfortunately, there are currently no selective Casp6 inhibitors to assess this hypothesis. However, Casp6 is activated by Caspase-1 (Casp1), the interleukin 1 beta-converting enzyme (Il-1-ß), via the neuronal inflammasome Nlrp1, which is increased by 20-25 fold in AD. This suggests that a neuron-specific inflammatory cascade initiates the activation of Casp6 and the subsequence neurodegeneration in aging and AD. Therefore, we propose that inhibition of Nlrp1, Casp1, or Casp6 could prevent neurodegeneration and cognitive decline in AD. Here, we assess a previously developed Casp1 inhibitor against cognitive deficits and AD-like pathologies in a transgenic mouse familial AD model. *Methods:* A transgenic mutant amyloid precursor protein (APP) AD mouse model was treated before or at the onset of memory impairment symptoms with a Casp1 inhibitor. A protocol was established to assess the effect of the treatment and the subsequent removal of the inhibitor. Episodic and spatial memories were measured with the novel object recognition test and with the Barnes maze, respectively, at baseline, after treatments and after washout of the inhibitor. Mice brains were analysed biochemically and histologically for amyloid plaque load, APP levels, Aβ levels, synaptophysin levels, Il-1ß, Iba1-positive microglial numbers and morphological subtypes, and GFAP-positive astroglial inflammation. *Results:* Given pre-symptomatically, the Casp1 inhibitor delayed the appearance of AD-like memory impairment and pathologies by 4-5 months in the transgenic mouse model. Given at the onset of symptoms, the Casp1 inhibitor reversed memory impairment and prevented the progression of AD-like pathology in the brain of the transgenic mice. *Conclusions:* These results validate the implication of Casp1 activation in mutant amyloid precursor protein-mediated cognitive deficits and pathologies, and provide in vivo proof of concept for the use of a Casp1 inhibitor against AD cognitive deficits and pathologies.

P113: COMBINATION RADIATION TECHNIQUES MAY PLAY A ROLE IN THE TREATMENT OF ALZHIEMER'S DEMENTIA. James Fontanesi[1], Daniel B Michael[1], Michael Maddens[1], Alaa Hanna[1], Thomas G Wilson[1], Giovanni Fontanesi[2], Prakesh Chinaiyan[1], Alvaro Martinez[3], Katie Buelow[1], George D Wilson[1] *((1) William Beaumont Health Systems; (2) Oakland University, Rocheste, Mi, USA; (3) 21st Century Oncology, Farmington Hills, Mi, USA)*

Introduction: Our group has been investigation both external beam irradiation and "target" therapy in an effort to determine their potential roles in the treatment of Alzheimer's Dementia (AD). Our previous animal experiments utilized 4 – 6 month old mice and demonstrated significant plaque reduction with various external beam doses and various doses of targeted therapy. We based our research based on multiple peer reviewed articles documenting early and durable response using low dose irradiation in non CNS sites. We decided to look at combination therapy in older animals (10-11 month old) to determine if could replicate our previously reported data and to investigate the novel combination of External Beam irradiation with a targeted agent. *Methods:* We have been using a well characterized model, the APPswe, PSEN1dE9/85Dbo/J mouse. We choose to use Amyvid as our targeted agent as it FDA approved and the annihilation event has an energy that we considered in the range of effectiveness for treatment of non CNS amyloid. Four groups were involved: 1) Control animals who received no treatment; 2) Hemi brain irradiation (5 x 200 cGy); 3) Hemi brain irradiation plus depleted Amyvid 8 weeks after treatment. We used this due to the fact that in an earlier experiment we injected 24 hour old Amyvid to determine if it might have a immunologic effect , which it did show. 4) Hemi brain irradiation plus 500 uCi "hot" Amyvid 8 weeks after treatment; We chose hemi brain irradiation to allow for a "control" side in the treatment groups. The animals were then sacrificed 5-6 days after Amyvid injection. There were rapidly dissected , fixed in formalin immunostained for AB plaques using standard methods. Images were captured using an Aperio Slidescanner. The slides were then analyzed by 3 independent reviewers and by Definiens Tissue Studio Imaging software. Plaque counts were compared using the Student's T test. This investigation was IRB approved and animals were maintained according to SFN guidelines. *Results:* The un-irradiated brains had equal number of plaques in both hemispheres where as the irradiation alone animals had an 18% reduction in plaques on the irradiated side. The addition of either Hot or Cold Amyvid to hemi brain irradiation reduced the overall plaque burden and eliminated the differential between the hemispheres. Of particular interest was the combination of External Beam and the hot Amyvid. It resulted in a statistically significant difference when compared to non treated animals ($p=0.00038$). *Conclusion:* These results, although with a modest number of animals ,clearly show that the combination of low dose irradiation plus Amyvid results in impressive reduction in plaques . We plan to continue our investigations into these combination therapy in younger mice (10-12 week olds) in an effort to determine if earlier intervention may prolong time to development of macroscopic plaques

Theme: New therapies and clinical trials

P114: A NOVEL APPROACH TO THE THERAPY OF ALZHEIMER'S DISEASE BASED ON PEPTIDE NANOLIPOSOME INHIBITORS OF AB AND TAU AGGREGATION. David Allsop[1,2], Mark Taylor[1,2], Nigel Fullwood[1], Maria Michael[1], Anthony Aggidis[1], 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)*

Introduction: Considerable advances have been made over the last 30 years in understanding the neuropathology, biochemistry and genetics of Alzheimer's disease (AD). Disappointingly, there are only five approved drugs that treat the symptoms of AD. Many of the new drugs in development aim to modify the disease process itself, by impacting one or more of the many wide-ranging brain changes that AD causes. Many disease modifying drugs have failed in clinical trials. These drugs have been targeted mainly at Aβ and consist of inhibitors of β-secretase or γ-secretase, which block Aβ production, or immunotherapy based on antibodies to Aβ, which results in clearance of plaque amyloid from the brain. These drugs have run into various problems including mechanism-based side effects (e.g. secretase inhibitors) and vasogenic oedema and micro-haemorrhages in the brain (the immunotherapy approach). Moreover, these drugs were probably given too late during the course of AD, when damage to the brain is likely to be irreversible. There have been relatively few selective and potent inhibitors of Aβ and/or tau aggregation in clinical trials. *Methods:* Our proposed therapeutic candidates consist of modified peptides that inhibit the aggregation of either Aβ or tau attached covalently to the surface of nanoliposomes which are composed of cholesterol and sphingomyelin. They also contain a PEGylated lipid which has a maleimide group for covalent linkage to a thiol group (cysteine residue) on the peptide. The external surface of these liposomes is therefore decorated with multiple copies of the peptide. The peptide developed against Aβ aggregation is retro-inverted (D-amino acids, with sequence reversal) and so is stable against proteolysis [1]. This retro-inverted peptide is linked to a 'TAT' sequence for targeting to the brain and for intracellular drug delivery [2]. Similar types of peptide-liposome system are under development for the inhibition of tau and combination inhibition of Aβ/tau aggregation. *Results:* Our inhibitory peptides bind with high affinity to Aβ and prevent its assembly into oligomers and fibrils, as demonstrated by several different in vitro and in vivo experimental systems [1-4]. Very low concentrations of the inhibitory peptide are required to reduce the aggregation of Aβ when the peptide inhibitor is attached to liposomes [3]. The peptide-liposomes rescue cultured neuronal cells from the toxic effects of pre-aggregated Aβ, cross a BBB cell model, enter the brains of normal C57/BL6 mice, and protect against memory loss in the APPSWE transgenic mouse model [3]. The peptide-liposomes also reduce amyloid plaque load by ~30% when injected peripherally (once per day, over 21 days) into transgenic APPSWE/PS1ΔE9 mice, or into APPSWE mice. Electron microscope studies show that the liposome-peptide captures Aβ and binds to the free ends of Aβ fibrils, apparently terminating fibril growth [4]. The peptides have no effect on cytochrome P450 drug metabolizing enzymes, and the peptide-liposomes are non-toxic to cultured cells. In the case of the tau-directed peptides, they inhibit the formation of tau fibrils in an in vitro aggregation assay and have the potential to be developed along similar lines to the Aβ inhibitors. *Conclusions:* Secretase inhibitors for Aβ, and immunotherapy for Aβ and tau, are already in the advanced stages of development/clinical trials. Our

approach is different to this and specifically targets the very early stages of aggregation of these molecules. Multiple inhibitory peptides attached to the liposome surface create a potent, multivalent inhibitor that can cross the BBB and prevent oligomer and fibril formation. In the case of Aβ, we have shown that our peptide-liposomes are potent inhibitors of oligomer formation, and this is seldom clear for other drugs. Moreover, our peptide-liposomes hide from the immune system, and so should not invoke an undesirable pro-inflammatory response. Liposomes can be derivatized with multiple different peptides so that they are directed against more than one therapeutic target. Importantly, there is increasing recognition that combination therapies may be warranted to address the complex biology of AD and our development allows for Aβ or tau peptide inhibitors alone or in combination to be attached to the surface of the same population of liposomes, resulting in a therapeutic with dual action against plaques and tangles. If the development of our inhibitory peptides, either attached independently to different liposomes or in combination, are successful, we must rethink and revise the FDA and EMA guidance on developing drugs for early stage AD. [1] Taylor M., et al. (2010) Biochemistry 49, 3261–3272; [2] Parthsarathy V., et al. (2013) PLoS ONE 2013;8(1): e54769; [3]. Gregori M., et al. (2017) Nanomed: Nanotech. Biol. Med. 13, 723-732; [4]. Sherer M., et al. (2015) Journal of Physics: Conference Series 644, 012040, 10.1088/1742-6596/644/1/012040.

P115: ALZHEIMER'S DISEASE DRUG DEVELOPMENT PIPELINE: 2017. Jeffrey Cummings[1], Garam Lee[1], Travis Mortsdorf[2], Aaron Ritter[1], Kate Zhong[3] *((1) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; (2) Touro University Nevada, Henderson, NV, USA; (3) Global Alzheimer Platform, Washington, D.C., USA)*

Background: There is an urgent need to develop new treatments for Alzheimer's disease (AD) and to understand the drug development process for new AD therapies. *Methods:* We assessed the agents in the AD pipeline as documented in clinicaltrials.gov for phase I, phase II, and phase III as of 1/5/2017. *Results:* There are 105 agents in the AD treatment development pipeline, of which 25 agents are in 29 trials in phase I, 52 agents are in 68 trials in phase II, and 28 agents are in 42 trials in phase III. Seventy percent of drugs in the AD pipeline are disease-modifying therapies (DMTs). Fourteen percent are symptomatic cognitive enhancers, and 13% are symptomatic agents addressing neuropsychiatric and behavioral changes (2% have undisclosed mechanisms). Most trials are sponsored by the biopharmaceutical industry. Trials include patients with preclinical AD (cognitively normal with biomarker evidence of AD), prodromal AD (mild cognitive symptoms and biomarker evidence of AD), and AD dementia. Biomarkers are included in many drug development programs particularly those for DMTs. Thirteen of 46 phase II DMT trials have amyloid imaging as an entry criterion, and 10 of 28 phase III trials incorporate amyloid imaging for diagnosis and entry. A large number of participants are needed for AD clinical trials; in total, 53,089 participants are required for trials spanning preclinical AD to AD dementia. When compared with the 2016 pipeline, there are eight new agents in phase I, 16 in phase II, and five in phase III. *Conclusion:* The AD drug development pipeline has 105 agents divided among phase I, phase II, and phase III. The trials include a wide range of clinical trial populations, many mechanisms of action, and require a substantial number of clinical trial participants. Biomarkers are increasingly used in patient identification and as outcome measures, particularly in trials of DMTs.

P116: THE INFLUENCE OF A MOBILITY TRAINING PROGRAM ON GAIT PERFORMANCE AMONG HEALTHY COGNITIVE ELDERLY PEOPLE AND PEOPLE WITH MCI. Carine Federspiel[1,2], Elisabeth Bourkel[1], Jean-Paul Steinmetz[1,2] *((1) Centre for memory and mobility, Luxembourg; (2) ZithaSenior, Research&Development, Luxembourg)*

Backgrounds: Gait performance (i.e., velocity and gait variability) is an indicator of an older adult's mobility capacities. General mobility training contributes to improving gait performance and thus reducing the risk of falling. In this study, the effect of mobility training among cognitive healthy elderly people and people having MCI are compared, taking into account that cognitive deficits often are linked to mobility deficits. *Methods:* The participants (N = 60, age range = 70-87 years) partook in a 12-week mobility training program which focused on the training of general mobility, coordination, balance, gait stability, endurance, torso muscles, spine flexibility and muscular strength. The training groups, which were attended twice a week, had different intensity levels with a maximum of eight participants. The subjects were assigned to the groups according to their respective mobility capacities, independent of their respective cognitive capacities. According to their MMSE-Scores, the participants were divided into (1) cognitive healthy older adults and people showing MCI (Cut-off score: under 27 points). The participant's gait velocity and gait variability was measured before and after the training program. Gait performance was assessed with an instrumented walkway system (GAITRite) measuring averaged temporal and spatial gait parameters. The participants completed three walks with different instructions: (1) normal walk, (2) dual-task (walking while counting backwards) and (3) dual-task (walking while completing a word fluency task). *Results:* Velocity as well as gait variability (stride length and time) before and after the training program in both groups were analyzed and compared. We expect to find an improvement of gait performance in both healthy elderly people and people with MCI, with less impact in the second group as cognitive deficits may influence the effect of the training. *Conclusion*: The discussion of the findings focuses on the necessity of introducing structured mobility training programs for both older healthy adults and people with MCI.

P117: PRE-CLINICAL AND FIRST CLINICAL DATA OF AN ORALLY AVAILABLE AMYLOID BETA OLIGOMER ELIMINATING COMPOUND THAT ENHANCES COGNITION AND IMPEDES NEURODEGENERATION IN VARIOUS ALZHEIMER'S DISEASE MOUSE MODELS. Dieter Willbold[1,2], Janine Kutzsche[2], Manfred Windisch[3], Dagmar Jürgens[2] *((1) Institut für Physikalische Biologie, Heinrich-Heine-Universität, Düsseldorf, Germany; (2) Institute of Complex Systems, ICS-6: Structural Biochemistry, Research Centre Jülich, Jülich, Germany; (3) Neuroscios, Graz, Austria)*

Backgrounds: Several lines of evidence suggest a central role of amyloid-β-peptide (Aβ) in the pathogenesis of Alzheimer's disease (AD). More than Aβ fibrils, small soluble and prion-like propagating Aβ oligomers are suspected to be the major toxic species responsible for disease development and progression. Therefore, elimination of these Aβ oligomers is our principal objective for therapy of AD. *Methods:* Previously, we have identified the fully D-enantiomeric peptide D3 by mirror image phage display selection and showed that it was able to specifically eliminate Aβ oligomers and convert them into non-toxic species. D3 was able to reduce plaque load in transgenic AD mouse models, and improved cognition even after oral application [1]. More recently, we developed derivatives of D3 with improved properties during a lead optimization strategy that focused primarily

on the Aβ oligomer elimination efficiency. We used our newly developed Aβ-QIAD (quantitative determination of interference with Aβ aggregate size distribution) to quantitatively measure Aβ oligomer elimination efficiency and thus target engagement [2]. Morris water maze and novel object recognition experiments in several transgenic mouse models were used to measure cognition enhancement of the D3 derivatives. SHIRPA and Rotarod assays were used to follow neurodegeneration in the TBA2.1 mouse model and its inhibition by our compounds. *Results:* As expected from D-peptides, D3 and its derivatives showed superior pharmacokinetic properties, such as long half-lives and high oral bioavailability [3, 4]. The here presented compound was able specifically and efficiently eliminate Aβ oligomers and are able to enhance cognition and impede neurodegeneration even in old animals with full-blown pathology and even when orally applied. We will present pre-clinical data on safety and toxicity of the most promising compound. Also, we will present the first clinical data on safety and tolerability. *Conclusion:* The D3 derivative is a highly promising new-in-class compound for causal and disease modifying treatment of Alzheimer's disease with a new mechanism of action. [1] Funke et al., ACS Chem. Neurosci. 1, 639-648 (2010). [2] Brener et al., Sci. Rep. 5, 13222 (2015). [3] Jiang et al., PLoS One 10, e0128553 (2015). [4] Leithold et al., Pharm Res. 33, 33(2):328-336 (2016)

P118: INFORMED CONSENT ENSURING ACCESS TO ANONYMIZED PATIENT-LEVEL DATA AND BIOSPECIMEN IS CRITICAL TO ACCELERATING INNOVATIVE ALZHEIMER DISEASE TREATMENTS. Stephen P. Arnerić[1], Penny A. Dacks[2], Ann Marie Hake[3], James Hendrix[4], Monica Moreno[1], Lisa A. Gold[5], Dagmar Theis[6], Mark F. Gordon[7], Volker D. Kern[1], George Vradenburg[8] *((1) Critical Path Institute, Tucson, AZ, USA; (2) American Epilepsy Society, Chicago, IL, USA (3) Eli Lilly and Company, Indianapolis, IN, USA; (4) Alzheimer's Association, Chicago, IL, USA; (5) Merck, West Point, PA, USA; (6) Boehringer-Ingelheim, Vienna, Austria; (7) Advisor, CT, USA); (8) USAgainstAlzheimer's, Washington, DC, USA)*

Background: Informed Consent Forms (ICFs) are a central requirement of clinical research in the USA, intended to ensure that prospective participants understand the risks and benefits of the study and the purpose of the research before they agree to participate. This goal has become very involved as ICFs have evolved into lengthy and technical forms designed to protect both the patients and the sponsors of the research study. Many ICFs do not discuss secondary research purposes or corresponding data sharing, leaving the research participant uninformed and data/samples may be lost in storage or are destroyed after the study has concluded. ICFs that restrict the distribution of data and samples have been an impediment to advancing Alzheimer disease (AD) understandings and treatments. An addendum to the ICF template that highlights the choice of expanded data and biospecimen sharing was recently developed by the Coalition Against Major Diseases (CAMD). CAMD is one of fourteen public-private-partnerships of the Critical Path Institute, dedicated to delivering on the vision of the U.S. Food and Drug Administration's (FDA) Critical Path Initiative. CAMD convenes diverse stakeholders (academia, non-profit patient-advocacy or research foundations, industry, and regulatory agencies) to collaboratively create tools and methods to advance new treatments for various stages of Alzheimer disease and related neurodegenerative diseases. Many projects rely on the sharing of data or samples and, in some cases, could not be accomplished because ICFs had been used that did not include provisions addressing potential data sharing. At the same time, CAMD members from non-profit and for-profit entities strongly maintain the need to use data and samples in a manner consistent with the participant's consent. *Methods:* CAMD assembled a working group of individuals from industry, patient advocacy, and information technology backgrounds to draft addenda that would enable broader responsible data sharing. Because ICFs are often criticized as lengthy (e.g., 15-40 pages), technical, and difficult to understand, the addenda were designed for clarity and brevity with direct oversight from patient communication experts at the Alzheimer's Association. A key objective was to create concise (<2 pages) language that ensures future data and sample sharing, and complies with patient privacy protection according to applicable U.S. law. Recognizing that AD is progressive and informed consent forms are intended for the patient, it was vital to incorporate input from individuals living in the early stage of the disease and their care partners. To that end, the draft was presented for review to the Alzheimer's Association Early-Stage Advisory Group (AA-ESAG), and to their care partners, to establish the understandability and relevance. *Results:* Two key findings: 1) Patients with dementia and care partners were "shocked" that their data and samples are not broadly shared; 2) With diverse feedback, concise addenda (to be presented) were created to enable data and sample sharing both within, and outside, future sponsored studies. Two documents were created: a more complete addendum containing the key elements of informed consent that would enable future data and sample sharing, and an abbreviated version. Both documents are intended to augment pre-existing ICFs. Essential features include: • The research purposes were intentionally not restricted to any single disease due to the many situations where data and samples collected for one disease may be useful to another. • Data and samples will not be sold for profit. This concern was reiterated as an important concern by the AA-ESAG members and care partners. • Specific examples of groups with whom a study team may share data and samples, with reassurance that these groups will have oversight committees to supervise the ethical use of the data and samples. • Potential benefits and risks, in particular, the fact that anonymity cannot be guaranteed. *Conclusions:* Data and sample sharing from clinical research is being increasingly recognized, with some leading groups describing it as an ethical obligation to the participants who may have put themselves at risk in interventional clinical trials. With technological advances over the past 50 years, the data and samples collected in one study can often be used for secondary research purposes, reducing the costs, time, and patient-burden needed to develop effective therapies. Increasing the access of valuable anonymized patient-level clinical trial data has the potential to inform the foundational and regulatory science required to deliver innovative treatments for AD.

P119: NOVEL STRATEGIES AGAINST ALZHEIMER'S DISEASE USING INDUCED HUMAN NEURONAL PROGENITORS AND NEURONAL CELLS. Ying Lei[1], Gang Li[1], Ying Chen[2], Ge Gao[2], Jian Zhao[1] *((1) GMP Center of Stem Cell Engineering, Translational Medical Center for Stem Cell Therapy, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China; (2) IxCell Biotechnology Co., Ltd, Shanghai, China)*

Backgrounds: Alzheimer's Disease (AD) has brought heavy burdens to both family and society. Till now there is not any effective prevention or disease-modifying therapy available yet. Focusing on neural progenitor cells (NPC) is a new direction of therapeutic strategies for AD. In our previous work, we reported that human neural progenitors and neurons can be induced from fibroblasts with a small set of small-molecule compounds. Based on this unique technology, we are systematically inducing iPSC, iNPC and iN from patients suffered from AD. Furthermore, we would use these induced human neuronal cells to explore the pathogenesis as well as the underlying molecular mechanism. And these human disease-modeling

cell lines can also be used to access the efficacy of treatment as well as explore novel therapeutic strategies. This work may shed some light on the therapeutic area of AD. *Methods:* This project aimed to compare human NPC preparation methods systematically, and then achieve the clinical criterion required by the National Guideline. We tried to obtain the human NPC with different strategies, somatic cell reprogramming and chemical induced trans-differentiation for example. After comparing the characteristic of self-renewal and differentiation in vitro, we would establish a safe, effective, repeatable human NPC preparation system. At the same time, we would differentiate NPCs into NCs, and establish a disease specific human NPC/NC model to explore the mechanism of disease development and evaluate clinical medicines. *Results:* In the first period of work, we have generated over 30 iPSC lines from AD and healthy volunteers, and roughly established the human NPC preparation system. The characterization of iPSC and NPC lines has been done. *Conclusion:* As planned, we are generating iPSC, iNPC and iN from patients who suffered from AD. At the same time, we are also exploring their applications in mechanism research, clinical study and drug development. Perspectives of this work: 1. Comparison of iNPCs generated by different strategies. 2. Difference between iNPCs from young adults, old healthy adults and patients. 3. Re-investigation of drugs using the iNPCs. 4. Novel drug screening or evaluation models. 5. Potential cell therapy resources.

P120: A SOCIAL SECURITY NETWORK TO PREVENT SENIORS' COGNITIVE DECLINE AND FRAILTY IN SOUTHERN FRANCE. Michel Noguès[1], Valérie Bruguière[1], Justine Millot-Keurinck[1], Jacques Touchon[2] *((1) Caisse Assurance Retraite et Santé Au Travail (Carsat) Languedoc-Roussillon, Montpellier, France; (2) Centre Hospitalier Universitaire (CHU), Montpellier, France)*

Backgrounds: Frailty could be associated with higher risk of developing dementia (Bilotta C, 2010; Gray SL, 2013) and covers several fields: biophysical, psychological and cognitive, social and environmental. Studies (FINGER, MAPT) have demonstrated that multidomain interventions had a positive impact on cognition. Through a global approach, the French Retirement and Occupational Health Insurance Agency of Languedoc-Roussillon (Carsat LR) supports frailty prevention by targeting psycho-social and environmental components. Over 80% of the population of the Languedoc Roussillon has a pension from the Carsat LR, representing more than 500,000 beneficiaries. Among them, more than 1000 elderly people have been welcomed and accompanied since 2014 through the "concerted service window", an innovative device supporting prevention pathways. *Methods:* The Concerted service window targets retirees and pre retirees at risk of frailty, advising and orienting them towards appropriate services. This experimental project is held within the French Proximity Autonomy Plan, a joint initiative from the Public Health & Retirement Insurances, aiming at coordinating their actions for the screening of people at risk of frailty. People are identified either through the IRV's Frailty Observatory (geographical information system), or by diverse partners (hospitals, prevention centres, associations). Then, they are invited to meet with a prevention case manager. This one conducts a face-to-face (or telephone) 45 min interview with a 32-question multidimensional grid, which was built upon to the EIP-AHA questionnaire (Bousquet, 2015), based on the WHODAS, WHOQOL and EQ5D. This grid is composed of 9 thematic items allowing the evaluation of cognition, mobility, personal care, relationship support, activities of daily life, social interaction, quality of life, resources and nutrition. Concerning cognition, one question relates to memory problems. From this global needs approach, personal advice concerning rights and health access are then formulated. If necessary, orientation is proposed towards adequate social protection organisations competent services. When a health checkup is necessary, people are oriented toward a health prevention centre. Regular follow-up is provided at least during 6 months to all the individuals who benefited from prevention recommendations, with the help of a simplified 4 sections - 20-question grid (somatic, cognition, psychosocial, nutrition). *Results:* In terms of profile, 57% are women, 61% live alone, 88% are between 60 and 70 years old and 40% declare having forgone medical care. The data analysis from the health prevention centres show that main advice relates to lifestyle: nutrition (50%) and physical activities. In the medical field, the main recommendations concern visual and hearing tests, cancer screening, biological tests, and vaccinations. A psychological risk is detected in nearly 50% of people. This is confirmed by the interviews made by the Carsat, which supports the establishment in 2017 of focus groups on two recurring topics, grief and illness. Among the workshops offered by the Carsat, sophrology workshop is the most requested by the beneficiaries, with a positive impact both on mental and physical health. It helps people to relax and to restore enthusiasm to go out of the house and meet up with other people. Concerning memory complaint, 50% of seniors (n=500) didn't answer that question. Among respondents, more than 25% declare memory problems. Among them 66% declare a slower walking speed in the last 3 months, 26% have fallen in the last 3 months and 40% declare being regularly sad or melancholic. Only 13% wish to participate to a memory workshop. An evaluation at 6 months (Narbonne, 9 cases) with the 20-question grid shows a reduction in the difficulties identified, on the four axes (somatic, cognition, psychosocial, nutrition). Even if more cases are needed, this tends to prove the relevance of a global approach to tackle frailty in all its dimensions. *Conclusion:* Further studies and analysis are needed to demonstrate how a simple tool could allow evaluating multidomain interventions for populations at risk of socio-environmental frailty. Even if clinical trials have proven results on high socio economic level population, the main issue is to find the right methodology to reach the more isolated, older and vulnerable ones. Carsat is experiencing a new home-support solution based on a digital tablet. This solution proposes prevention messages but also information about the workshops of Carsat's partners. A liaison book, games and news are integrated in this tool, participating to maintain cognitive functions. It also includes a test which allows a diagnosis of the risks of frailty. It is based on a self-administered questionnaire on three axes: social life, functional abilities and health environment. Depending on the outcome, people can benefit from personalized advice or participate to a health prevention workshop.

P121: P38A KINASE INHIBITION APPEARS TO LEAD TO REDUCTION IN AMYLOID-BETA GENERATION IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE. Philip Scheltens[1], Niels Prins[1], Adriaan Lammertsma[2], Maqsood Yaqub[2], Hui-May Chu[3], Bart van Berckel[2], John Alam[4] *((1) Department of Neurology and Alzheimers Center, VU University Medical Center; and the Alzheimers Research Center (ARC), Amsterdam, NL; (2) Department of Radiology & Nuclear Medicine, VU University Medical Center, Amsterdam, NL; (3) Anoixis Corporation, Natick, MA, USA; (4) EIP Pharma LLC, Cambridge, MA, USA)*

Backgrounds: In 6- and 12-week duration clinical studies in patients with early AD, neflamapimod (selective oral inhibitor of p38α) led to within-subject improvement in episodic memory function (CTAD, 2016; AAIC, 2017). In addition, in the 12-week study, neflamapimod led to a reduction in [11C]PiB BPND, indicating a reduction in amyloid load. The purpose of the present report was

to compare the [11C]PiB results with more commonly used semi-quantitative measure SUVr with the gold standard BPND. In addition, a biologic model is proposed by which neflamapimod may be acting to reduce amyloid-plaques, based on the emerging role of p38α in generating amyloidbeta production from neurons. *Methods:* Fifteen patients (ages 60 to 85) with MCI due to AD or mild AD (MMSE 20-28) had dynamic PET scans at baseline and after 12 weeks of twice-daily neflamapimod treatment at either 40 mg (n=8) or 125 mg (n=7). Patients at baseline had elevated brain amyloid plaque load by visual inspection of [11C]PiB PET scans. Brain amyloid load was measured quantitatively and semi-quantitatively using dynamic [11C]PiB PET scans with BPND (Yaqub, 2008) and SUVr as outcome measures, respectively, in which SUVr was based on the ratio of cortex to cerebellum uptake for the interval from 60 to 90 minutes after injection of [11C]PiB. *Results:* In the BPND analysis reported previously there were no main group level effects, though in a predefined responder analysis (>7% reduction in BPND) there were 3 responders at week 12 (-11.6%, -11.9%, and -40.5%, respectively) in the 40 mg group, and one (-7.7%) in the 125 mg group. Similarly, in the SUVr analysis there were no significant group level treatment effects, with mean±s.e.m. SUVr60–90 in the 40 mg dose group at baseline being 2.17±0.09 and 2.08±0.15 at week 12; and in the 125 mg dose group SUVr at baseline was 1.76±0.11 and 1.85±0.12 at week 12. However, within the 40 mg dose group three of eight subjects (37.5%) were responders with baseline and week 12 SUVr being 1.77 and1.48 (-0.29, 16% reduction), 2.0 and 1.56 (-0.42, 21.8% reduction), and 2.07 and 1.76 (-0.311, 15% reduction), respectively. There were no responders by change in SUVr in the 125 mg dose group (note: the responder in that group by BPND analysis only had 1.1% reduction in the SUVr analysis). Also, as in the BPND analysis, there was a significant inverse correlation (p=0.04) between baseline SUVr and % reduction in SUVr from baseline to week 12, with all 3 responders being below the median SUVr at baseline. Estimated average brain tissue concentration based on pharmacokinetic modeling was 27 nM (range 25-30 nM) in the 40 mg dose group and 44 nM (range 34-68 nM) in the 125 mg dose group. Both dose groups are predicted to exceed the 50% inhibitory concentration (IC50) for p38α of 5-10 nM, but only the 125 mg dose group is predicted to achieve the 40-50 nM IC50 to block the pro-inflammatory effect of p38 activation (Alam, 2015), an effect that is dependent on both p38α and p38β. *Conclusion:* Both quantitative (BPND) and semi-quantitative (SUVr) approaches support a drug effect on brain amyloid plaques, though BPND appears to be more sensitive to drug effect. From a mechanistic point of view, the original scientific premise for conducting this study was that p38α inhibition within microglia would increase clearance of brain amyloid plaques. However, during our actual clinical study a novel rationale emerged from preclinical studies, in which neuronal p38α through modulating autophagy-lysosome protein degradation could impact amyloid plaque load, as genetic knockout of neuronal p38α in transgenic mice led to reduced amyloid beta generation and amyloid pathology (Schnöder, 2016; Alam & Scheper, 2016, Colié et al, 2017). In general, the present results are more consistent with impacting neuronal p38α-mediated amyloid-beta generation. First, a direct effect on amyloid plaque clearance might be expected to have a homogenous, and dose-responsive effect. Instead, the heterogeneous response on amyloid plaque levels within the active 40 mg dose group is more readily explained by a model in which there is an underlying homogenous effect on amyloid beta generation due to a direct pharmacological effect on the neuron, but only patients with efficient endogenous clearance would demonstrate reduction in brain amyloid plaque load by PET scans. Consistent with this hypothesis, the responders were all patients with lower levels of baseline brain amyloid plaque load, as these would be the patients, who were expected to have higher endogenous amyloid plaque clearance levels at study entry. Moreover, this model also potentially provides an explanation for the inverted dose-response as an expected anti-inflammatory activity of neflamapimod at the higher dose level of 125 could be offsetting the effect on amyloid plaque production at the lower dose by decreasing microglia mediated amyloid plaque clearance.

P122: ACD678, A NOVEL GAMMA-SECRETASE MODULATOR FOR THE TREATMENT OF ALZHEIMER DISEASE. Bengt Winblad[1], Johan Lundkvist[2], Helena Karlström[1], Magnus Halldin[2], Johan Sandin[2], Gunnar Nordvall[2] *((1) Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division of Neurogeriatrics, Karolinska Institutet, Huddinge, Sweden; (2) AlzeCure Pharma AB, Hälsovägen 7, Huddinge, Sweden)*

*Background:*The process of Aβ amyloidosis plays a pivotal role in the onset of Alzheimer Disease (AD) and starts decades prior to clinical symptoms. To this end anti-amyloidogenic therapies have been tested in AD without clinically meaningful effect. It is conceivable that an Aβ targeting drug would be most beneficial initiated during the preclinical phase, ie at the earlier stages of Aβ amyloidosis. As such, the therapy needs to be well tolerated while still effective. Aβ is a family of postproteolytical peptides, varying from 31 to 43 amino acids in length, and is generated as the result of γ-secretase mediated processing of amyloid precursor protein, APP. Aβ42 is particularly prone to aggregate and is also the primary Aβ component of amyloid plaques, whereas shorter Aβ peptides are less amyloidogenic and have also been suggested to inhibit Aβ42 amyloidosis. Gamma-secretase modulators (GSMs) are an emerging class of anti-amyloidogenic agents that exhibit several key features making them suitable for the treatment of preclinical AD: 1) they target amyloidogenic Aβ42 production while stimulating Aβ37 and 38, and 2) they modulate but do not affect total γ-secretase activity, a property that is of central importance from a safety perspective. In this study we describe a novel GSM, ACD678, which is the result of many years of drug discovery and medicinal chemistry efforts. ACD678 shows an excellent in vivo potency, a favorable pharmacological and pharmacokinetic profile, and is currently in late preclinical development for the treatment of early Alzheimer Disease. *Methods:* In vitro pharmacology: The impact of ACD678 on Aβ production was explored in HEK/APPSwe cells and analyzed with MSD Aβ triplex assay and a custom-made ELISA for Aβ37. HEK293 cell lines overexpressing five different γ-secretase substrates including Notch, ErbB2 and EphA4 were exposed to ACD678 and analyzed for γ-secretase mediated cleavage using a luciferase reporter gene assay. In vivo pharmacology: Wild type mice were administered with different doses of ACD678. Six hours post administration, the experiment was terminated and the brains were recovered for Aβanalysis using commercial ELISA methods. DMPK: Solubility, adsorption, pharmacokinetics, brain/plasma distribution and CYP activity were assessed using conventional assays and methods. *Results*: ACD678 shows a potent low nM inhibition of Aβ40 and 42 and induction of Aβ37 and 38 in HEK/APPSwe cells. ACD678 shows good CNS exposure, a suitable PK profile and reduces brain Aβ42 levels with 50%. Moreover, ACD678 does not affect the general turnover of any of the five gamma secretase substrates explored. *Conclusions:* ACD678 is a novel GSM that displays excellent Aβ modulatory activity in vitro and in vivo. GSM ACD678 does not affect the general turnover of γ-secretase substrates and initial toxicology data supports further development of ACD678 as a novel treatment of early Alzheimer Disease.

P123: DEMONSTRATION OF BLOOD-BRAIN-BARRIER (BBB) PENETRATION AND BRAIN TARGET ENGAGEMENT FOR NEFLAMAPIMOD (P38A KINASE INHIBITOR) IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE (AD). John Alam[1], Charlotte Teunissen[2] *((1) EIP Pharma LLC, Cambridge, MA, USA; (2) Department of Clinical Chemistry, VU University Medical Center, Amsterdam, NL)*

Backgrounds: Synaptic dysfunction is considered a major therapeutic target for Alzheimer's disease (AD). In pre-clinical studies the alpha isoform of the stress-activated kinase p38 (p38α) within neurons is implicated in amyloid-beta and inflammation-induced synaptic dysfunction (Li, 2011; Tong, 2012; Watterson 2013; Pietro, 2015; Sandersen, 2016). Neuronal p38α also plays a critical role in dysregulated autophagy (Alam & Scheper, 2016). Further, genetic knockout of neuronal p38α activity leads to both reduced synaptic dysfunction and amyloid beta-generation (Colié, 2017).P38 otherwise is traditionally considered as an inflammation target as it is involved in the regulation of cytokine production and cytokine signaling, though the anti-inflammatory effects occur at higher doses than the pro-cognitive effects (Alam, 2015). Neflamapimod (previously code-named VX-745) is a highly selective oral inhibitor of p38α kinase-activity, which in preclinical studies demonstrated brain tissue drug-concentrations that were 2-fold higher than in plasma and significant pharmacological activity in the brain (CTAD, 2014; Alam, 2015). In addition, 6- and 12-week duration clinical studies in patients with early AD demonstrated within-subject improvement in episodic memory function (CTAD, 2016); consistent with the potential for reversing synaptic dysfunction derived from preclinical studies. In this abstract, we report on additional analyses from the 6- week duration clinical study that (1) demonstrates BBB penetration through correlating preclinical plasma:brain:cerebrospinal fluid (CSF) drug concentration relationships with clinical plasma:CSF ratios, and (2) target engagement in the brain through analysis of downstream effects of p38α association with reduced cerebrospinal fluid (CSF) biomarkers. *Methods:* Patients with MCI due to AD or mild AD received 40 mg (n=7) or 125 mg neflamapomid (n=1) twice daily for 42 days. Patients at baseline had MMSE scores of 21-27 inclusive, amnestic presentation, and positive FDG-PET scan. Indwelling CSF catheter placed at baseline, and again on Day 41; and CSF collected 6 times over 24 hours at both time-points. Interleukin-8 (IL-8) and amyloid-beta (Aβ) peptides results measured by MSD ELISA platform were available for all timepoints; and total tau and phospho-tau were measured by Innotest assay at one time-point (24- hours post-catheter insertion) at baseline and end-of-dosing. Time-matched plasma and CSF drug-concentrations were obtained on days 1 and 41 at 3- and 6-hrs post-dosing. *Results:* Prior to the clinical study, extensive pharmacokinetic studies in dogs indicated brain tissue concentrations of neflamapimod are consistently ~2-fold higher than in plasma, while only low CSF concentrations were seen (~7% of that in plasma). In the current clinical study, 12 of the 32 post-dosing CSF samples contained drug-concentrations above the lower limit-of-quantitation in the assay utilized; and in those samples the drug-concentrations were 6.2% (+/-0.1%) that in plasma samples obtained simultaneously; suggesting BBB penetration in humans is similar to that in dogs, and therefore implying brain tissue concentrations are two-fold higher than plasma in humans as well. When analyzed as a group there were no significant changes from baseline to Day 41 in any of the CSF parameters. However, individual plasma drug-concentrations (average of morning predosing plasma drug-concentration on Day 41 and Day 42) were inversely correlated (i.e reduced with increasing plasma drug-concentration) to % change from baseline to Day 41 in CSF-IL-8 levels (p=0.03; r2=-.65) and strongly positively correlated (i.e. increased with increasing plasma drug-concentration) to CSF-Aβ38 (p=0.001; r2=0.9), CSF-Aβ40 (p=0.04, r2=0.59), CSF-tau (p=0.04, r2=0.61) and CSF-p-tau (p=0.06; r2=0.53). No correlation was evident to CSF-Aβ42. In order to determine whether the drug-concentration effects are consistent with the in-vitro potency (IC50) of neflamapimod of approximately 25 nM for IL-1β induced IL-8 production (Alam, 2015), the plasma drug-concentration were multiplied by two to obtain an estimated brain tissue concentration. Reductions in CSF IL-8 and increases in CSF-Aβ38/40 or CSF-tau or p-tau levels were only evident among the four subjects with estimated brain tissue concentrations >25 nM. *Conclusion:* Neflamapimod is BBB-penetrant in humans, likely achieving brain tissue concentrations approximately two-fold higher than in the blood. Further, as reduction in IL-8 production is a well-known pharmacological effect of inhibiting p38α (Cuenda, 2007; Cuadrado, 2010), the plasma drug-concentration dependent suppression of CSF IL-8 levels in a manner that is consistent with neflamapimod's in vitro potency provides evidence of target engagement of p38α in the brain (i.e. inhibition of p38α kinase activity). With regard to the apparent effects on CSFAβ and tau/p-tau, there are no effects described yet of p38α that would lead to increases in these measures. However, p38α is known to activate innate immune responses (e.g. microglia) within the brain (Bachtetter, 2010), responses that have been implicated in the clearance of Aβ and tau from the interstitial space (Mandrekar, 2009; Yoon, 2012; Zuroff, 2017; Luo, 2015). Therefore, the plasma drug-concentration dependent increase in the AD biomarkers CSF-Aβ(38/40) and tau/p-tau may be additional, though indirect evidence of target engagement as from mechanism standpoint it is likely to be the result of inhibition of mic microglial/immune system activation resulting from p38α inhibition.

P124: ACD855, DEVELOPMENT OF A POSITIVE MODULATOR OF NEUROTROPHIN SIGNALING FOR THE TREATMENT OF ALZHEIMER'S DISEASE. Pontus Forsell[1,2], Gunnar Nordvall[1,2], Johan Lundkvist[1,2], Magnus Halldin[1,2], Märta Dahlström[1,3], Maria Eriksdotter[3,4], Johan Sandin[1,2] *((1) AlzeCure Foundation, Karolinska Institutet Science Park, Huddinge, Sweden; (2) AlzeCure Pharma AB, Huddinge, Sweden; (3) Dept of Neurobiology, Care Sciences and Society, Karolinska Institutet, Sweden; (4) Dept Geriatric Medicine, Karolinska university hospital, Huddinge, Sweden)*

Background: Neurotrophins are a class of structurally related proteins that regulate neuronal function, survival, differentiation and plasticity. The neurotrophin family includes nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin 3 (NT3) and neurotrophin 4/5 (NT4/5). Synapse loss is an early pathological signature of Alzheimer's disease (AD) and a number of studies suggest that synapse loss is the best neuroanatomical correlate to cognitive decline in the disease. A large body of pathological and mechanistic evidence suggests that loss of NGF signaling contributes significantly to the dysfunction of basal forebrain cholinergic neurons during the course of AD. Impairments in formation and retrieval of episodic memory observed in AD patients have been reported to be partly due to this cholinergic dysfunction. Substantial evidence shows that NGF plays a key role in supporting the cholinergic neurons of the basal forebrain system. There are also numerous studies performed in animal models suggesting that increased BDNF signaling mediate improved synaptic plasticity during pathological conditions. The important role of BDNF in maintaining normal neurological function in man is also becoming clearer. The BDNF gene has a single nucleotide polymorphism rs6265 (Val66Met) causing a substitution at position 66 from a valine (Val) to a methionine (Met), which leads

to a reduction of extracellular BDNF levels. This BDNF Val66Met polymorphism has been demonstrated to affect the anatomy of hippocampus and prefrontal cortex in normal individuals and also to moderate episodic memory, hippocampal function and hippocampal volume in patients with either sporadic or familial Alzheimer's disease. Thus, Val66Met-BDNF is to date the only non-amyloid genetic factor known to affect the progression of AD. The strong genetic linkage between BDNF signaling and familial and sporadic AD, strongly support and validate the development of stimulators of neurotrophin signaling as novel and promising therapeutic strategies for AD. We have identified ACD855 as an in vivo active positive modulator of neurotrophin signaling. ACD855 has passed toxicology- and safety pharmacology studies necessary for further development. Taken together, these observations strongly suggest that ACD855 has a straightforward avenue to clinical testing in man. *Methods:* We have through a high throughput screening effort identified several chemical series, including ACD855, as positive modulators of NGF/TrkA- and BDNF/TrkB-signaling. These chemical series were expanded with considerable medicinal chemistry efforts and structure activity relationship was obtained for each chemical series. Representative compounds in each series were characterized in native systems and functional assays including ERK phosphorylation in mouse primary cortical neurons and in ex vivo long term potentiation (LTP) assay in rat brain slices. ACD855 was further investigated using Western blot analysis of ERK phosphorylation in rat hippocampi and in different in vivo models, i.e. scopolamine or MK-801 induced memory impairment in the passive avoidance model and in forced swim test. *Results:* Several chemical series, including ACD855, were discovered as positive modulators of NGF/TrkA- and BDNF/TrkB-signaling in a cell-based assay for positive modulation of NGF and BDNF signaling. Secondary screens in primary neurons and rat brain slices confirmed their activity as positive modulators of BDNF signaling. Our lead compound ACD855, has very low agonistic properties but potentiate BDNF-induced phosphorylation of ERK in primary cortical neurons. ACD855 also increases the maintenance of LTP in rat brain slices as measured by ex vivo electrophysiology. Interestingly, peripheral administration of ACD855 results in increased levels of ERK-phosphorylation in the hippocampus, as compared to vehicle-treated animals. Furthermore, we have demonstrated that ACD855 is active in several preclinical animals models. ACD855 can significantly and almost fully reverse scopolamine or MK-801 induced memory impairment in mice in the passive avoidance model in a TrkB-dependent manner. Combined these data demonstrate a nice correlation and translation between the in vitro and in vivo assays and suggest that ACD855 is a TrkB-dependent cognitive enhancer. Next we compared the activity of ACD855 to an acetylcholine esterase inhibitor (physostigmine). Interestingly, ACD855 was shown to be additive to physostigmine in the scopolamine-induced memory impairment paradigm. To further explore the potential of ACD855 as a BDNF enhancer, we explored its activity in a model of depression. ACD855 showed similar efficacy as Fluoxetine, a well-established anti-depressant, in the forced swim test. *Conclusion:* ACD855 is a positive modulator of Trk-signaling and as such, it targets key neuronal mechanisms. We have identified ACD855, as a synaptic enhancer and potentially a new symptomatic therapy for Alzheimer's disease. Indeed, ACD855 stimulates BDNF signaling, a genetically validated mechanism in AD, in different cellular and functional contexts in vitro as well as in multiple behavioral paradigms in vivo. The observation that ACD855 acts in an additive manner to physostigmine and is equipotent to fluoxetine in different behavioral paradigms, suggest a broad applicability of ACD855 for CNS disorders. The positive results in several assays/models, including general safety pharmacology and toxicological studies are very encouraging and the results supports further development of ACD855 for the treatment of AD. Thus, ACD855 is ideally suited as a symptomatic treatment for Alzheimer's disease either as a stand-alone therapy or as a combination therapy. Active pharmaceutical ingredient is available and we have initiated pharmaceutical development. The first clinical studies are planned to start during 2018.

P125: PHARMACOKINETICS AND DELIVERY TO THE BRAIN IN RATS OF P8, A PEPTIDE DRUG CANDIDATE FOR THE TREATMENT OF ALZHEIMER'S DISEASE. Nazneen N. Dewji[1,2], S. Jonathan Singer[1,3], Leah Hanson[4], William Frey[4], Bruce Morimoto[5], David Johnson[6], Daniel Dolan[6], Marc R. Azar[7] *((1) Cenna Biosciences Inc., La Jolla, CA, USA; (2) Department of Medicine, UC San Diego, La Jolla, CA, USA; (3) Division of Biological Sciences, UC San Diego, La Jolla, CA, USA; (4) Health Partners Institute, St. Paul, MN, USA; (5) Celerion Inc., USA; (6) MicroConstants, San Diego, CA, USA; (7) Behavioral Pharma, La Jolla, CA, USA)*

Background: Our previous work (Plos One, 2015) offered the potential for a new, early and effective approach for the treatment of Alzheimers disease (AD), by a strategy that does not target the secretases. We showed first that a family of peptides containing the DEEEDEEL sequence (P6, P7 and P8) and another independent peptide (P4), all derived from the amino terminus of PS-1 are each capable of markedly reducing the production of total Aß and of Aß 40 and 42 in vitro and in mThy1-hAPP Tg mice. Second, we showed using biolayer interferometry for those peptides that were effective in reducing Aß, of a strong, specific and biologically relevant binding with the ectodomain of human APP. This binding was further confirmed by confocal microscopy for cell-surface-expressed APP in fibroblasts. Finally, we demonstrated that the reduction of Aß by the peptides did not affect the catalytic activities of ß- or γ-secretase, or the level of APP. Critical to the development of any therapeutic for AD is the requirement that it can be delivered to the brain. We report here two studies that demonstrate that our lead candidate, P8, can be delivered to the rat brain. The first shows the delivery and distribution of radiolabeled P8 in the rat brain. The second shows the pharmacokinetics (PK) of P8 in rat plasma and CSF following a single dose of P8 by intravenous (IV), intranasal (IN) and subcutaneous (SC) administration. *Methods:* Male Sprague-Dawley rats were used in all the studies. Radiolabel distribution study: 3H-P8 was administered IV or IN to anesthetized animals over 18 minutes. Blood was drawn at 10, 20 and 30 minutes after administration. Brain and body tissues were dissected and processed for scintillation counting. Bioanalytical method development: Rat plasma: P8 was precipitated from samples after addition of formic acid in acetonitrile:methanol and separated by HPLC using a 50 x 2.1-mm, 5 µm Onyx monolithic C18 column. The compounds were ionized using electrospray in the positive ionization mode and detection was accomplished by a tandem quadrupole mass spectrometer (Xevo TQS, Waters, Milford, MA). The parent > daughter mass transition from 1007.55 > 876.35 was monitored for P8. The peak areas of P8 were fitted to a log-transformed linear equation. Rat CSF: The method was as described for plasma. PK Study: P8 in PBS was administered via 3 routes: IV, SC and IN. Blood was sampled from 0-165 minutes and CSF was sampled from 0-180 minutess from the onset of administration. P8 Treatment: IV and SC administration of P8 occurred in one minute intervals. For IN, P8 was administered in a volume of 60 μl over18 min. Calculations: PK analyses were performed using noncompartmental analysis (Models 200) in a validated WinNonlin Professional 6.3 computer program. *Results:* Delivery to the brain of 3H-P8 and radiolabel distribution. 3H-P8 administered by IN and IV modes reached the CNS quickly. With IV administration, 3H-P8 reached the brain at slightly higher

concentrations (56 – 104 nM) than IN (36 – 103 nM) and was present in all parts of the brain, suggesting that it could be delivered to the brain via the blood. Plasma and CSF Pharmacokinetics of P8. In order to ascertain that the radiolabel in the brain indeed represented intact P8 and was not due to leaching or fragmented peptide, we first developed an HPLC/MS/MS method for the determination of P8 concentrations in rat plasma and CSF. The plasma calibration curve had a range of 1.00 to 100 ng/mL and the CSF calibration curve had a range of 0.500 to 50.0 ng/mL. We next carried out PK analysis of P8 in plasma and CSF in rats following single IV, IN and SC doses of P8. Following IV dosing, the mean area-under-the-curve (AUC)(0-inf) in plasma was 679,000 ng·min/mL with a mean clearance of 17.6 mL/min/kg and a mean T1/2 of 21.9 minutes. In CSF the mean AUC(0-inf) was 3,270 ng·min/mL. Following IN dosing, the AUC(0-inf) was 10,700 and 330 ng·h/mL with a mean Cmax of 197 and 12.4 ng/mL and a mean Tmax of 5.00 and 26.7 minutes for plasma and CSF respectively. Following SC dosing, the mean AUC(0-inf) was 439,000 and 2,750 ng·min/mL with a mean Cmax of 5,390 and 19.8 ng/mL and a mean Tmax of 25.0 and 43.3 minutes for plasma and CSF respectively. The mean absolute bioavailability of P8 was 65.2% and 2.82% following SC and IN dosing, respectively. The results indicated that P8 has greater absorption following SC dosing compared to IN. *Conclusions:* 1. P8 can be delivered to the brain, CSF and plasma of rats by IV, IN and SC administration, as detected by two separate methods. 2. SC administration gave greater absorption of P8 compared to IN and is the delivery method of choice for the further development of P8 as a clinical candidate.

P126: THE ABCA-1 AGONIST CS6253 THAT REVERSES APOE4-DRIVEN ALZHEIMER'S DISEASE BRAIN PHENOTYPE AND COGNITION DECLINE LOWERS PLASMA NEUROFILAMENT-LIGHT CONCENTRATIONS. Jan O Johansson[1], Anat Boehm-Cagan[2], Henrik Zetterberg[3,4,5,6], Kaj Blennow[3,4], John K. Bielicki[7], Daniel M. Michaelson[2] *((1) Artery Therapeutics, Inc., San Ramon, CA; (2) Tel Aviv University, Tel Aviv, Israel; (3) Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Aacademy at the University of Gothenburg, Mölndal, Sweden; (4) Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; (5) Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK; (6) UK Dementia Research Institute, London, UK; (7) UC Berkeley, Berkley, CA)*

Background: Having plasma biomarkers that describe neurodegeneration enables faster and more precise development of therapeutic modalities. We have recently shown that the ATB Binding Cassette A1 (ABCA1) agonist CS6253 reverses apoE4-driven AD in targeted replacement (TR) mice in a process involving ABCA1 facilitated apoE lipidation, reversal of conventional brain phenotype variables as P-tau, Aβ42 and glutaminergic receptor (VGlut1) density. Concomitantly brain and plasma apoJ/clusterin were significantly lowered by CS6253 treatment. Plasma neurofilament light (NFL) originates from the cytoskeleton of neurons and is associated with AD diagnosis and with cognitive, biochemical, and imaging hallmarks of the disease. Plasma NFL has therefore been proposed as a blood-based biomarker for neurodegeneration in dementias (Mattsson et al. JAMA Neuro 2017). We hypothesized that CS6253 treatment would lower NFL in apoE TR mice. *Methods:* Plasma from male and female ApoE4 and apoE3 TR mice 4.5 months old that had been treated with PBS-control or CS6253 20mg/kg/q2d for 6 weeks were analyzed for plasma NFL concentrations. Plasma NFL concentrations were measured using an NFL kit (NF-light; UmanDiagnostics), transferred onto the ultrasensitive single-molecule array platform using a home brew kit (Simoa Homebrew Assay Development Kit; Quanterix Corporation). Calibrators were run in duplicates and obvious outlier calibrator replicates were masked before curve fitting. Samples were run in singlicates with a 4 fold dilution. Results were compensated for the dilution. Two QC levels were run in duplicates in the beginning and the end of each run. For QC with concentration 12.4 pg/mL, repeatability was 17.7 %. For QC with concentration 167.7 pg/mL, repeatability was 18.8 %. LLOQ = 6.7 pg/mL. *Results:* Plasma NFL results obtained showed a non-Gaussian distribution. CS6253 treatment vs. control (n=16/group) resulted in a 31% reduced plasma NFL level ($p<0.05$, Mann-Whitney), i.e. 79(38) pg/mL vs. 55 (30) pg/mL. Plasma NFL reduction was seen in both apoE4 and apoE3 TR mice. The apoE4 mice displayed a 61% reduction in VGlut1 concentrations in hippocampus suggesting neuron cell reduction. *Conclusions:* The ABCA1 agonist CS6253 that has shown reversal of apoE4 driven AD in apoE TR mice lowers plasma NFL concentrations. The sensitive SIMOA technology assessment of plasma NFL has potential to support translational development of dementia therapeutics.

P127: NOVEL MODULATORS OF MOLECULAR CHAPERONE NETWORK FOR THE TREATMENT OF ALZHEIMER DISEASE. Pavel Pavlov, Bengt Winblad, Rajnish Kumar *(Karolinska Institutet, Dept of Neuroscience and Society, Div of Neurogeriatrics, Huddinge, Sweden)*

Background: Most of the neurodegenerative diseases can be classified as proteinopathies or protein misfolding disorders with intra- or extracellular aggregation of certain proteins or peptides observed in affected brain areas. Molecular chaperones Hsp90 and Hsp70 are primarily responsible for maintenance of intracellular protein homeostasis including protein folding, transport and degradation. Hsp90 interacts with tau protein in vitro and in vivo. Hsp90 co-chaperone FKBP51 has been found to play an important role in metabolism of tau. Down-regulation of FKBP51 gene in cell lines or its deletion in the mice resulted in reduction of tau intracellular levels. It has been suggested that strategies aimed at attenuating FKBP51 levels or its interaction with Hsp90 have the potential to be therapeutically relevant for AD and other tauopathies. *Methods:* Using available crystal structure of FKBP51 and in silico docking we have developed molecules disrupting Hsp90-FKBP51 interactions at sub-micromolar concentrations. These molecules have been tested in neuronal cell culture for the ability to decrease total as well as phospho-tau levels in the cells. Cell viability was measured with MTT assay and mitochondrial membrane potential was measured using fluorescent probes TMRM and JC-1. *Results:* Treatment of cultured neurons for 24 hours with these modulating compounds leads to decrease of total tau levels within the cells. Moreover we have also found increased MTT signal due to improved mitochondrial function as evidenced by increase in mitochondrial membrane potential. *Conclusions:* Our results confirm previous findings regarding the role of FKBP51 in tau metabolism. Developed molecules represent a novel class of tau based therapeutics, and have good potential for further development.

P128: CEREBRAL ENERGY DEFICIT IN MILD TO MODERATE ALZHEIMER'S DISEASE: STRATEGIES TO INCREASE BRAIN FUEL SUPPLY. Christian-Alexandre Castellano[1], Etienne Croteau[1,2], Melanie Fortier[1], Christian Bocti[1,3], Tamas Fulop[1,3], Guy Lacombe[1,3], Nancy Paquet[4], Isabelle Dionne[1,5], Stephen Cunnane[1,3] *((1) Research Center on Aging, CIUSSSE – CHUS, Sherbrooke, QC, Canada; (2) Pharmacology-Physiology department, FMSS, University of Sherbrooke, QC, Canada; (3) Medicine department, FMSS, University of Sherbrooke, QC, Canada; (4) Nuclear medicine department, FMSS, University of Sherbrooke, QC, Canada; (5) Faculty of physical education and sports, University of Sherbrooke, QC, Canada)*

Background: Alzheimer's disease (AD) is characterized by brain glucose hypometabolism (Castellano et al. J Alzheimers Dis 2015). Fat-derived brain fuels such ketones (acetoacetate) have been proposed as an alternative fuel to compensate for the brain energy deficit widely observed in AD (Cunnane et al Front Mol Neurosci 2016). We have developed brain ketone PET-MR neuroimaging to assess brain energy supply in AD. We report here two strategies that could be effective ways to improve brain energy supply, both of which stimulate brain ketone uptake and metabolism. *Methods:* Participants with mild to moderate AD (72 ± 8 y) were offered the opportunity to participate in a study that provided either a ketogenic supplement (providing 30 g/day of medium chain triglycerides) for one month (N=8; in progress), or a supervised physical exercise program involving walking on a treadmill (15-40 minutes per session, 3 days/week) for 3 months (N=10). Quantitative measurement of the cerebral metabolic rate of glucose and acetoacetate (CMRglu and CMRacac, respectively; both μmol/100 g/min) using PET and MR neuroimaging were done before and at the end of the two interventions. Both trials are registered with ClinicalTrials.gov (NCT02709356 and NCT02708485). *Results:* Compared to baseline, plasma acetoacetate increased by 158% in the ketogenic supplement group and by 146% in the Walking group (both $p < 0.05$). Post-intervention, global and regional CMRacac increased by 2-3 fold in both groups (all $p < 0.05$), whereas global and regional CMRglu remained unchanged (all $p \geq 0.10$). Of note, the blood-to-brain acetoacetate influx rate constant increased by 66% ($p = 0.03$) only in the Walking group. *Conclusions:* These results demonstrate that individual lifestyle interventions such as a ketogenic supplement or a supervised walking program improve brain ketone metabolism while maintaining brain glucose metabolism in AD. These results demonstrate the utility of brain ketone and glucose PET to assess interventions that may improve brain energy supply. These two strategies suggest the potential complementarity of combining both a ketogenic and physical activity intervention to optimize brain energy since the ketogenic supplement increased brain ketone availability while the physical exercise increased both plasma ketones and the brain's capacity to take up ketones. *Acknowledgements:* Excellent help from Christine Brodeur-Dubreuil, Eric Lavallee, Sebastien Tremblay and the clinical PET and MRI group. Financial support from Sojecci 2, FRQS, and University of Sherbrooke research chair (SCC).

P129: PHARMACOKINETIC AND TARGET ENGAGEMENT (TE) ANALYSIS OF BIIB076 IN CYNOMOLGUS MONKEYS. Weiping Chen, Julie Czerkowicz, Qin Wang, Danielle Graham

Background: BIIB076 (6C5 huIgG1/λ) is a human monoclonal antibody with the potential to be a disease-modifying treatment for mild to moderate Alzheimer's disease (AD). BIIB076 binds human tau in AD brain homogenate and CSF. In addition, BIIB076 binds with subnanomolar affinity to cynomolgus monkey tau. The primary objective of these experiments was to determine the pharmacokinetic and target engagement potential of BIIB076 in cynomolgus monkey cerebrospinal fluid (CSF) and interstitial fluid (ISF). *Objectives:* Measure BIIB076 drug levels and target engagement endpoints in cynomolgus serum, CSF, and ISF following a single administration of drug. *Methodology:* For the PK studies, an anti-id immunoassay (ELISA) incorporating anti-human antibodies were used to measure drug levels in serum CSF and ISF. For CSF and ISF target engagement, a highly sensitive bead-based immunoassay was developed to measure free tau. *Results:* BIIB076 shows pharmacokinetic (PK) properties typical of a monoclonal human IgG1 antibody. In cynomolgus monkey CSF, BIIB076 half-life is approximately 2-3 weeks and concentrations reach maximal levels at ~2-3 days. Once steady state concentrations are achieved the drug concentration in CSF and ISF is proportional. In CSF, free tau levels decrease roughly 24 hr post drug administration, while total tau levels remain unchanged. In ISF, we observed a reduction in both free and total tau. *Conclusion:* These data confirm that BIIB076 has a PK profile similar to most monoclonal human IgG1 antibodies and provide additional information related to the distribution of tau and drug concentrations throughout the fluid compartment in the CNS.

Late Breaking News

Theme: Clinical trials methodology

LBP1: NOW I REMEMBER! (THAT I'M IN ANOTHER STUDY): DUPLICATE SUBJECTS IN CLINICAL TRIALS OF ALZHEIMER'S DISEASE. Thomas Shiovitz[1,2], Brittany Fox[1], Chelsea Steinmetz[1], Sabrina Schoneberg[1] *((1) CTSdatabase LLC, Sherman Oaks, CA, USA; (2) California Neuroscience Research, Sherman Oaks, CA, USA)*

Background: Duplicate and Professional subjects are a documented problem in CNS clinical trials, comprising up to 10% of screens in studies of major depressive disorder (MDD) and schizophrenia. Little, however, has been described regarding the frequency and impact of duplicate subjects in studies of Alzheimer's Disease (AD). While most schizophrenia and depression subjects are professional subjects – i.e. they do it to collect stipends – it is postulated that subjects with Early AD may do it primarily to increase the chances of getting effective treatment rather than for money. In any case, even a small number of these subjects can adversely affect the accuracy of safety and efficacy signals. *Methods:* A search of CTSdatabase from January 1st 2012 to August 31st 2017 was conducted to determine the frequency of prescreens for memory relative to other indications, whether these subjects presented to unique sites within the timeframe studied and whether they changed indications across sites. A case history of a subject who was simultaneously enrolled in schizophrenia and Early AD studies will be presented. *Results:* 829 of 36,410 subjects (2.3%) entered into CTSdatabase prescreened for a memory indication. Of these, 80 subjects (9.7%) attempted to screen at one or more unique site during the 5.7 year time period. Surprisingly, 75% of these (60 subjects) presented for an indication other than memory loss, most commonly depression (20 subjects) and schizophrenia (7 subjects). *Conclusion:* Duplicate subjects are likely a small but significant problem in studies of AD. Longer studies (> 12 mos) may increase the risk of duplicate enrollment as subjects and their study partners note further cognitive decline and will do whatever is necessary to get treatment for their condition. Use of a subject registry, such as CTSdatabase, may allow duplicate and professional subjects to be identified. Once identified, steps can be taken to mitigate their confounding effects on AD studies.

LBP2: ALZHEIMER'S DISEASE SHOULD WE JUMP, SINK OR SWIM THROUGH PHASE 2? HOW DO DIFFERENT EARLY PHASE DESIGNS ADDRESS ALZHEIMER'S ISSUES?
Trevor Smart *(Eli Lilly, Windlesham, Surrey, United Kingdom)*

Background: Alzheimer's disease (AD) is a key unmet medical need and the search is still on for disease modifying compounds. There are many issues unique to AD that need addressing in early phase development (up to Phase 3): • Cognitive decline takes a long time, so for a proof of concept study, it needs to be a long study to be able to identify a reduction in the decline or the treatment difference will be small requiring large sample sizes. • What population should we be treating, those later in progressing have a more rapid decline, but we may be too late to treat these patients, or do we choose patients with a much earlier diagnosis, but the progression is slower and hence a longer study is required. • Can we use other endpoints, such as biomarkers instead of cognition for study endpoints? How with small studies can we gain enough confidence that the compound works before going to Phase 3? *Method:* Different Phase 2 designs are compared under different scenarios and assumptions to illustrate the pros and cons of different sample sizes, the use of biomarkers or cognitive endpoints and different decision rules. Our prior belief in a compound is dependent on many aspects including whether the mechanism of action has already been shown to work. This is used to establish a prior distribution, which is used in conjunction with the power function of a study design to estimate the proportion of the prior distribution that we would expect to go forward into Phase 3 and the proportion we would expect to stop prior to Phase 3. These distributions are used to estimate parameters used to compare designs. *Results:* Phase 2 studies with cognitive endpoints are more informative than pharmaco dynamic mechanistic biomarker studies. In most situations, even though these studies take longer than the biomarker studies, the benefits of gaining information on cognition outweigh the additional time it takes to run the study. Combining both the biomarker with cognitive endpoints in the decision rules increases the overall probability of Phase 3 success. *Conclusion:* Phase 2 studies assessing cognition and establishing a proof of concept can improve the probability of phase 3 success. With little evidence of successful mechanisms, if we were to continue until a phase 3 success is achieved, on average fewer patients would be used in an overall shorter time, if phase 2 cognition studies are used. The level of confidence in a mechanism of action can influence the design approach and therefore a standard phase 2 design used for all compounds may be inappropriate.

LBP3: LOW PET SCREEN FAILURE RATE IN THE UB-311 PHASE 2A STUDY ENRICHED FOR APOE E4 CARRIERS WITH MILD COGNITIVE DEFICIT.
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Background: Given that cognitive impairment and loss of function in older people can reflect a myriad of CNS disruptions, it is important to confirm the presence of Aβ deposition for subject screening in disease modification clinical trials in Alzheimer's disease (AD). Aβ positron emission tomography (PET) imaging allows evaluation of AD neuropathology in vivo and provides a biomarker for disease-modification. UB-311, is an immunotherapeutic vaccine, comprised of Aβ1-14-targeting peptide immunogens (B-cell epitopes) linked with one of two synthetic helper T-cell peptide epitopes (UBITh®) and is currently in a phase IIa study (V203-AD, NCT02551809). In the V203-AD study, 43 subjects with mild AD were enrolled and Florbetapir (18F-AV-45) PET was performed for patient selection and tracking of amyloid deposition. Visual and quantitative SUVR assessments were compared to evaluate accuracy and efficiency for subject selection. The aim of this presentation is to demonstrate that for clinical trials amyloid PET imaging can be used efficiently to screen for AD among older patients with mild cognitive dysfunction. *Methods:* V203-AD 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. 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). 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 reviewers 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. For the confirmatory quantitative read an SUVR threshold of 1.1 was used. *Results:* 66 subjects signed the informed consent for screening with 43 subjects ultimately satisfying study inclusion/exclusion criteria (overall screen fail rate = 34.8%). Twelve subjects failed to enter the second stage of screening for florbetapir PET scans due to either positive serology for hepatitis B virus [6 subjects], unqualified MMSE scores [2 subjects], brain abnormality [2 subjects], caregiver issue [1 subject], and prohibited medications [1 subject]. Among the 54 subjects selected for PET scanning, 11 subjects (20.4%) were screen failures due to negative PET scan [10 subjects] and voluntary consent withdrawal [1 subject]. Of the 43 enrolled mild AD subjects, the ratio of male to female was 1:3, the mean (SD) MMSE score is 22.5 (2.14) and 35 subjects (81.4%) carried at least one ApoE ε4 allele. Visual PET reads were used for enrolling the 43 subjects with concordance sought between 2 readers for questionable cases. A subsequent quantitative analysis of the PET data revealed a mean SVUR (SD) of 1.33 (0.11) for the 43 subjects enrolled. The quantitative analysis revealed that two subjects, selected as PET positive by the visual read, had SUVR values of 1.03 and 1.09, which were slightly below the traditional 1.1 SUVR cutoff. Overall, the agreement between visual and quantitative assessments was high. The mean (SD) MMSE score was 22.51 (2.14) for amyloid positive subjects and 23.1 (2.23) for amyloid negative subjects. *Conclusion:* Compared to other AD immunotherapeutic clinical trials using amyloid PET scans, those subjects who progressed to the PET scan screen in the V203-AD study had a low PET screen failure rate of 18.5%. There was good consistency (94.4%) between the visual and quantitative PET scan reads for determining Aβ positive or negative cases. Of the 43 enrolled amyloid PET positive subjects in V203-AD study, 81% were ApoE ε4 carriers. Screening for both APOE ε4 status and amyloid PET imaging may thus provide an accurate and efficient method to identify mild subjects for disease modification trials in AD. The lower amyloid burden (SUVR = 1.33) in the V203-AD study as compared to the Aducanumab Ph1b study (SUVR = 1.44) may provide a more ideal population for an immunotherapy trial.

LBP4: THE BRAIN HEALTH REGISTRY-IDEAS STUDY: EVALUATING THE FEASIBILITY OF INTERNET-BASED DATA COLLECTION IN COGNITIVELY IMPAIRED OLDER ADULTS. Monica R Camacho[1,2], Rachel L Nosheny[1,2], Shannon Finley[1], Derek Flenniken[1,2], Juliet Fockler[1,2], R Scott Mackin[1,3], Diana Truran-Sacrey[1], Aaron Ulbricht[1,3], J Wesson Ashford[4,5], Curtis B Ashford[6], Gil Rabinovici MD[7], James Hendrix[8], Maria Carrillo[8], Michael W Weiner[1,2] *((1) Center for Imaging of Neurodegenerative Diseases, San Francisco Veteran's Administration Medical Center, San Francisco, CA, USA; (2) UCSF Department of Radiology and Biomedical Imaging, San Francisco, CA, USA; (3) UCSF Department of Psychiatry, San Francisco, CA, USA; (4) Stanford Department of Psychiatry & Behavior Science, Palo Alto, CA, USA; (5) Palo Alto Veteran's Administration Medical Center, Palo Alto, CA, USA; (6) MemTrax, Inc, Redwood City, CA, USA; (7) UCSF Department of Neurology, San Francisco, CA, USA; (8) Alzheimer's Association, Chicago, IL, USA)*

Background: The Imaging Dementia - Evidence for Amyloid Scanning Study (IDEAS) aims to follow over 18,000 Medicare patients age 65+ with objectively confirmed cognitive impairment by a dementia expert to determine the clinical utility of amyloid imaging on patient management and health outcomes. While the IDEAS study is highly impactful to the field of Alzheimer's disease (AD), it does not include direct assessment of patients' cognition or daily function. The Brain Health Registry (BHR), an online registry with over 55,000 participants age 18+, is used to collect longitudinal cognitive, functional, and health data from IDEAS patients and care partners, that will be linked to IDEAS data, including amyloid status and clinical diagnosis. This study evaluated the feasibility of collecting online data from IDEAS participants using BHR. *Methods:* We analyzed cognitive, functional, and health data from participants with and without cognitive impairments, who co-enrolled in BHR-IDEAS between April and August 2017, or enrolled in BHR from the public between December 2013 and August 2017. We considered completion of: (1) An online battery of self-report questionnaires, which includes Everyday Cognition Scale (ECog), family AD history, Geriatric Depression Scale (GDS), head injury and concussion history, medical history, medication stability, Patient Health Questionnaire (PHQ-9), and the short-form health survey (SF-36); and (2) MemTrax, an online, continuous recognition test that measures episodic memory, inhibition, and reaction time. The BHR-IDEAS protocol includes MemTrax and a shortened BHR questionnaire battery due to concerns over participant burden in a cognitively impaired cohort. We compared procedure completion rates and reasons for non-completion between: (1) BHR-IDEAS and BHR participants age 65+ who self-reported AD or MCI diagnosis; (2) BHR participants age 65+ identified as cognitively normal (CN) because they did not self-report AD/MCI diagnosis, and had no self-reported subjective memory complaints; and (3) BHR-IDEAS participants suspected to have other memory impairment (OMI) because they did not self-report AD/MCI diagnosis. *Results:* Of the 916 IDEAS patients who were invited, 318 (35%) enrolled in BHR-IDEAS. 27 BHR-IDEAS participants self-reported AD (8%), 98 self-reported MCI (31%), and 8 reported neither AD or MCI (OMI, 3%). In addition, data were obtained from 17,736 BHR participants age 65+: 42 self-reported AD (0.24%), 909 self-reported MCI (5%), and 5708 considered CN (32%). In BHR-IDEAS, a lower percentage of AD participants completed all available questionnaires (30%) compared to MCI (36%), and OMI participants (38%). In BHR, a lower percentage of AD participants completed all available questionnaires (43%) compared to MCI (60%), though AD participants had the same completion rate as CN (43%). In BHR-IDEAS, 93% of AD participants completed MemTrax, while 95% of MCI and 100% of OMI participants completed the test. In BHR, 81% of AD, 75% of MCI, and 80% of CN participants completed MemTrax. *Conclusion:* In only 4 months of recruitment, over 300 IDEAS participants with confirmed memory impairment enrolled in BHR and completed online procedures, including a neuropsychological test. These results demonstrate that it is possible to efficiently collect online data from a large group of cognitively impaired participants. Contrary to concerns about cognitively impaired cohorts having lower completion rates for a self-administered, online neuropsychological test, BHR-IDEAS participants completed MemTrax at higher rates than older, cognitively normal BHR participants. This may have occurred because BHR-IDEAS participants are "treatment seeking", while BHR participants are not. Moreover, BHR-IDEAS participants completed MemTrax at higher rates than older BHR participants who self-reported MCI/AD diagnosis. This is a surprising finding in light of the fact that general BHR enrollment is likely to have a selection bias for those with more mild MCI/AD compared to BHR-IDEAS. Although BHR-IDEAS participants had fewer questionnaires in their protocol, they completed questionnaires at lower rates than older CN and impaired participants in BHR, suggesting that participant burden may be rate limiting in populations with more cognitive impairment. In the future, we plan to reexamine procedure completion rates comparing groups identified by clinical diagnosis from linked IDEAS data. Future validation studies are also necessary to determine the utility of online data obtained in an unsupervised setting.

LBP5: FRAILTY AND BIOLOGICAL AGEING MAY IMPACT THE EXTERNAL VALIDITY OF RANDOMIZED CONTROLLED TRIALS ON ALZHEIMER'S DISEASE. Alessandro Trebbastoni[1], Marco Canevelli[1], Federica Quarata[1], Fabrizia D'Antonio[1], Matteo Cesari[2,3], Giuseppe Bruno[1], Carlo de Lena[1] *((1) Department of Neurology and Psychiatry, "Sapienza" University of Rome, Italy; (2) Gérontopôle, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; (3) Université de Toulouse III Paul Sabatier, Toulouse, France)*

Background: To date, the external validity of randomized controlled trials (RCTs) on Alzheimer's disease (AD) has been assessed only considering monodimensional variables. Nevertheless, looking at isolated and single characteristics cannot guarantee a sufficient level of appreciation of the AD patients' complexity. The only way to understand whether the two worlds (i.e., research and clinics) deal with the same type of patients is to adopt multidimensional approaches more holistically reflecting the biological age of the individual. In the present study, we compared measures of frailty/biological aging (assessed by a Frailty Index, FI) of a sample of patients with AD resulted eligible and subsequently included in phase III RCTs compared to patients referring to the same clinical service, but not considered for inclusion. *Methods:* We collected the clinical and sociodemographic characteristics of two groups of AD patients. The first group, the "RCTs sample", included 23 individuals with an amyloid pathology biomarker positivity (i.e., probable AD dementia with evidence of the AD pathophysiological process-NIA-AA criteria) enrolled in two Phase III RCTs, both exploring the efficacy and safety/tolerability of passive immunization interventions against amyloid. The second group was composed by 23 subjects of randomly selected, age- and MMSE-matched patients with a diagnosis of probable AD dementia (NIA-AA criteria), not studied with biomarkers and not participating to any RCT. Both the groups had to meet the following inclusion criteria: 1) age between 55 and 90 years; 2) Mini-Mental State Examination (MMSE) score ranging between 20 and 26; 3) Modified Hachinski Ischemia Scale score of ≤4; 4) MRI scan with no

findings inconsistent with a diagnosis of AD; 5) absence of concurrent serious or unstable illnesses. A FI was retrospectively generated from the variables available in the clinical charts by computing 28 age-related deficits (including signs, symptoms, adjudicated diagnoses, disabilities). Each item included in the FI was coded so that a value of 0 indicated the absence of the deficit and a value of 1 its presence. The FI was calculated as the ratio between the number of deficits presented by the individual and the number of considered deficits (i.e., 28). Thus, the FI potentially ranged between 0 (no deficit) and 1 (all deficits). Univariate analyses were conducted to compare the baseline data between the "RCT sample" and the "real world sample". Spearman's correlations were used to assess the strength and direction of the relationship between age and FI. *Results:* The "RCTs sample" and the "real world sample" were found to be statistically similar for all the considered sociodemographic and clinical variables. Nevertheless, the "real world sample" was found to be significantly frailer compared to the "RCT sample", as indicated by higher FI scores (0.28 [SD 0.1] vs. 0.17 [SD 0.1]; $p<0.001$, respectively). Moreover, when assessing the relationship between FI and age, we found that the correlation was almost null in the "RCT sample" (Spearman's $r=0.01$; $p=0.98$), while it was statistically significant in the "real world sample" ($r=0.49$; $p=0.02$). *Conclusion:* The application of too rigid designs may result in the poor representativeness of RCT samples. It may even imply the study of a condition biologically different from that observed in the "real world". The adoption of multidimensional measures capable to capture the individual's biological age may facilitate evaluating the external validity of clinical studies, implicitly improving the interpretation of the results and their translation in the clinical arena.

LBP6: CLINICAL TRIAL DESIGN OF THE CREAD STUDIES: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP PHASE 3 STUDIES TO EVALUATE THE EFFICACY AND SAFETY OF CRENEZUMAB IN PATIENTS WITH PRODROMAL TO MILD ALZHEIMER'S DISEASE. Helen Lin[1], Janice Smith[2], Laurie Millar[2], Kaycee M. Sink[1], Jillian Smith[2], Andres Schneider[3], Reina Fuji[1], Angelica Quartino[1], Howard Mackey[1], Michael Rabbia[4], Susan Yule[3], Susanne Ostrowitzki[1], Paulo Fontoura[3], Rachelle Doody[1,3] *((1) Genentech, Inc., South San Francisco, USA; (2) Roche Products Ltd, Welwyn Garden City, UK; (3) F. Hoffmann-La Roche Ltd, Basel, Switzerland; (4) Roche Innovation Center New York, New York, NY)*

Background: Crenezumab is a humanized anti-amyloid-beta (Aβ) monoclonal IgG4 antibody in development for the treatment of Alzheimer's disease (AD). Crenezumab binds monomeric and aggregated forms of amyloid β, with highest affinity for oligomers, a form hypothesized to mediate neurotoxicity. Its IgG4 backbone reduces effector function and its lack of detectable binding to vascular amyloid are hypothesized to lower the amyloid-related imaging abnormalities (ARIA) risk. Crenezumab was evaluated in Phase 2 studies in over 500 patients with mild-to-moderate AD treated for 18 months. Although the co-primary endpoints (ADAS-Cog12 and CDR-SB) were not met (ABBY study), pre-planned and post-hoc exploratory analyses together suggested that treatment with crenezumab compared to placebo may be associated with increasing effects in favour of the crenezumab group on both endpoints in progressively milder subsets of AD patients and at the higher dose tested (15 mg/kg IV q4w). In Phase 2, only a single case of asymptomatic ARIA-E was reported and ARIA-H was balanced between the crenezumab and placebo-treated arms. These data suggested that a higher dose used in patients at an earlier disease stage may have greater efficacy potential. Subsequently, a Phase 1b study investigated the safety and tolerability of crenezumab dosed up to 120 mg/kg IV q4w. The efficacy signal in Phase 2 and favorable safety data at higher doses enabled initiation of Phase 3 Crenezumab in Alzheimer's Disease (CREAD) studies with 4-fold higher dose (60 mg/kg) than used in the Phase 2 studies. *Methods:* Two nearly identical global, randomized, double-blind, placebo-controlled, parallel-group Phase 3 studies (CREAD and CREAD2) are testing the efficacy and safety of crenezumab (60 mg/kg) in patients with prodromal to mild AD. Each study is being conducted in approximately 250 centers across 30 countries, with approximately 750 patients randomized 1:1 to placebo or crenezumab 60 mg/kg monthly i.v. treatment arms. Eligible patients are 50-85 years old, have a clinical diagnosis of probable or prodromal AD according to the NIA-AA diagnostic criteria, an MMSE score of ≥ 22, a CDR-global score of 0.5 or 1, Free and Cued Selective Reminding Test (FCSRT) immediate free recall ≤27 and cueing index ≤0.67, and confirmed evidence of cerebral amyloid pathology. FCSRT is used to enrich the population in patients with amnestic deficits and greater likelihood of progression over 2 years. The primary endpoint of this study is change in the CDR-SB score at 2 years and the key secondary outcome is ADAS-Cog-13. Sub-studies explore treatment effects on CSF biomarkers as well as amyloid- and tau-PET. MRI examinations are used to monitor safety and measure volumetric changes. An independent data monitoring committee regularly reviews study data for safety. *Results:* N/A. *Conclusion:* Building on key learnings from Phase 2, these Phase 3 studies have been designed to investigate the clinical efficacy of a 4-fold higher dose of crenezumab in patients with prodromal to mild AD, and to test whether efficacy can be obtained without the associated increase in safety findings that have been described with other passive immunotherapies in AD.

LBP7: UTILIZING MACHINE LEARNING TO ENABLE IMPROVED COHORT SELECTION FOR ALZHEIMER'S DISEASE CLINICAL TRIALS. Mallory Busso[1], Emmanuel Fuentes[1], Christopher Buckley[2], Rabia Ahmad[2], Christopher Foley[2], Jan Wolber[2] *((1) GE Healthcare, Life Sciences, San Ramon, USA; (2) GE Healthcare, Life Sciences, Core Imaging, Amersham, UK)*

Background: Bringing disease modifying drugs (DMD) to market for Alzheimer's disease (AD) is extremely complex due to the heterogeneity of the disease and the need for large and lengthy clinical trials. A principle confounder of efficacy in DMD is the selection of appropriate subjects. More sensitive screening and stratification tools are required to identify subjects suited for a given cohort and endpoint. Providing predictive models based on the optimal combination of clinical and imaging biomarkers has strong potential in improving the selection process. *Methods:* A machine learning-based analytical approach that facilitates the identification of appropriate subjects based on their specific imaging, genetic, psychometric, and demographic data was used to determine optimal stratification of clinical trial subjects with mild cognitive impairment (MCI). The approach encompassed the application of machine-learned models in series or individually to exclude patients lacking appropriate biomarkers, progression rate, or both. Specifically, a four-stage approach can be applied: 1) application of standard trial screening through psychometric testing, collection of subject demographics, and acquisition of an MRI: 2) utilization of a machine-learned model predicting the probability of the subject being Beta-amyloid (Aβ) positive; 3) acquisition of an amyloid PET image; 4) utilization of a machine learned model for predicting the probability of subject conversion to AD in the timeframe of the clinical trial. Alternatively, each model can be used on its own to customize the selection process as needed. In this way, subjects that would not benefit from the DMD of question do not have to be subjected to unnecessary testing,

clinical trial expenses can be dramatically reduced, and overall trial efficiency can be improved. *Results:* Two models were built to meet the needs of clinical trial cohort enhancement: a model predicting Aβ status and a model predicting Fast Progressing MCI subjects where fast progressing subjects are defined as those who converted to probable AD (pAD) status within a 36-month time frame. These models were learned on a phase III clinical trial dataset containing 232 MCI subjects with 87 Aβ positive subjects and 81 subjects having converted to AD within 36 months after the baseline imaging exam. The primary objective of this phase III clinical trial was to compare pAD conversion of MCI subjects with normal and abnormal [18F]flutemetamol uptake. The longitudinal tracking of subjects conversion status to pAD makes this an ideal dataset for model learning purposes.The Aβ Positivity model showed the potential to improve trial efficiency of selecting Aβ positive subjects by 43% with a model accuracy of 79% and specificity of 85% where improvement in trial efficiency is measured as positive predictive value (PPV) of the model compared to the original inclusion of Aβ positive subjects. The Fast Progressing MCI model showed an improvement of selecting fast progressing MCI subjects by 24% with an accuracy of 86% and specificity of 92% where improvement in trial efficiency is measured as PPV of the model compared to subjects that were identified as being Aβ positive through amyloid PET imaging alone. Whilst reporting model performance metrics produced through cross validation is a valid approach for presenting machine learned results it is important to know that these can be applied to independent datasets and are not only specific to the learning dataset. To evaluate this capability, the Aβ Positivity model was rebuilt using features common to both the phase III dataset and the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing (AIBL) dataset. The AIBL validation for Aβ positivity with n=551 yielded an accuracy score of 75% with a specificity of 87% demonstrating extrapolation to other populations and disease states due to inclusion of healthy and AD subjects in the AIBL dataset. *Conclusions:* The use of machine learning for screening and stratification of subjects in a clinical trial may increase the probability of success of showing drug efficacy and the rate at which efficacious disease modifying drug therapies become available. The model performance demonstrated suggests that inclusion efficiency may be improved by 50% or more. Further, the validation of the Aβ Positivity model with the AIBL dataset demonstrates the feasibility of extending a model learned on one population to a different population as well as the ability to extend the positivity risk scores learned on MCI subjects only to both healthy and AD subjects. Future work will focus on continuing to refine the methods outlined here to separate distinct subgroups of disease progression such as non-memory complainers, memory complainers, early MCI, late MCI, and probable AD allows for trial participants to be selectively chosen in such a way as to meet the distinct needs of each trial in which the models are utilized.

LBP8: DOES THE LENGTH OF TIME TO CLINICAL TRIAL SITE ACTIVATION RELATE TO SCREENING PERFORMANCE? Sarah Walter, Devon Gessert, Elizabeth Shaffer-Bacareza, Karin Ernstrom, Rema Raman, Paul Aisen *(Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA)*

Background: The Alzheimer's Therapeutic Research Institute (ATRI) was founded in 2015 with the mission of improving treatment for Alzheimer's. ATRI is currently conducting and coordinating 12 clinical studies in collaboration with the NIH, industry, as well as public-private partnerships. Site activation timelines and screening rates are two critical variables influencing the total duration of a clinical trial. As the field of Alzheimer's Disease Clinical research expands into studies with greater complexity, activation requirements for performance Sites have become more extensive and burdensome, thus drawing out activation and enrollment timelines. When the startup of a study is slower than expected, groups coordinating trials face difficult decisions such as, when to add sites, how many sites to add, and whether to drop sites that are moving slowly through activation. Dropping a site is a difficult decision because of the amount of resources already invested by the coordinating center and locally at that Site. Understanding whether assumptions can be made about screening rates based on time to activation, would present a significant advantage to a study team trying to decide how best to complete the study within budget and on time. This past summer, ATRI has been working on assessing the nature of these data on existing studies to develop approaches and models that allow greater confidence in projecting screening rates and making these critical decisions. For this project, we hypothesized that the sites quickest to activate will have higher screening rates for the study. *Methods:* We used data from two recent studies coordinated by ATRI where screening has recently completed (2016-2017). The studies (called Study 1 and Study 2), while different, were representative of trials coordinated by ATRI in terms of time to activation; requiring the certification of cognitive raters, both PET and MRI certifications, as well as the usual requirements of local Institutional Review Board (IRB) approval, and an executed contract. In regard to screening criteria, Study 1 was screening for a preclinical AD population with a target screening rate of 8-10 per site per month, while Study 2 was screening for a mild to moderate AD population with a target screening rate of 1 per site per month. For these analyses, the studies were analyzed separately. The time to activation is the number of days between the date the Investigator Initiation Packet (protocol, consent template etc.) was distributed and the Site activation date. Screening performance was assessed by calculating the monthly screening rate over the period of activation. The association between the two variables was analyzed using Spearman's correlation. In both studies, additional sites («rescue sites») that committed to rapid activation and high screening rates were added in order to bring up total enrollment numbers. To control for the possible differential impact of these «rescue sites», these sites were excluded from the second analysis. *Results:* In Study 1, we saw a small inverse correlation (n=67, rho = -0.3, p=0.014) between the length of time to activation and screening rates. Sites that took longer to be activated were less likely to achieve the highest screening rates. In Study 2, we found a moderate correlation (n=22, rho = 0.495, p=0.019), that showed a reverse association. Sites with shortest time to activation had lower screening rates than sites that took longer. Sensitivity analyses removing the «rescue sites» showed identical results in both study datasets. *Conclusion:* Our preliminary analyses showed mixed results, with small negative (Study 1) and moderate positive (Study 2) correlations between time to site activation and site-specific screening rates. In the case of sites with the shortest activation timelines, the lower screening rates may be due to extending recruitment efforts and resources over a longer duration or sites having a maximum threshold of screens they were able to manage. It may also be that sites that take longer to activate are better prepared for screening activities, resulting in higher screening rates. In subsequent work, we will continue to examine which factors contribute to screening rates, and develop methodology to best model site activation and screening rates for the next generation of clinical trials. These results may be due to the complex interaction between a number of factors influencing activation and screening rates not considered in these analyses.

LBP9: NEXT GENERATION OF CLINICAL DEVELOPMENT: APPLYING PATIENT-CENTERED INSIGHTS TO ACCELERATE PATIENT RECRUITMENT FOR ALZHEIMER'S DISEASE CLINICAL TRIALS. Olga Uspenskaya-Cadoz[1], Kenneth Stanley[2], Natalia Balko[3], Sadiq Lula[3], Sam Khinda[2], Milena Kanova[2] Penny Randall[1], Lynne Hughes[2] *((1) QuintilesIMS Central Nervous System Center of Excellence; (2) QuintilesIMS Project Leadership Unit; (3) QuintilesIMS Analytics Center of Excellence)*

Background: Although the prevalence of Alzheimer's disease (AD) is nearly 44M people worldwide, the industry struggles with slow recruitment of patients with AD across the disease spectrum. Particularly in early stages of the illness, patients are sometimes still unaware of their diagnosis and thus, are difficult to reach for a clinical trial.The urgent need to accelerate AD drug development in order to bring efficacious therapies to patients and the ever expanding AD development pipeline calls for the identification, enrolment and management of tens of thousands of patients. Traditional approaches to reach AD patients have relied heavily on contracting with AD investigators, who would mine their site/practice databases to identify potential subjects. More innovative approaches are clearly needed in Alzheimer's clinical development to accelerate recruitment and accelerate the introduction of new therapies to the market. We have explored the potential impact on AD patient recruitment combining deep operational experience in the execution of large scale AD trials with patient-centered data and advanced analytics. Enabling clinical trial teams to identify opportunities for expanding AD investigator site networks and thus to increase the pool of potential AD trial candidates available to sites would be a major development in this increasingly competitive trials arena. Patient-centered data and advanced analytics appear to be promising approaches in supporting AD clinical trial execution at different stages, including trial feasibility, planning, and site identification providing valuable support with country and site-tailored recruitment strategies. *Methods:* A cross-functional team was assembled to evaluate how to leverage the available data sources to inform AD trial management. This group included team members with deep expertise in AD studies and program management (experienced AD program managers, therapeutic and medical strategy leaders, patient recruitment and site identification specialists) together with data scientists; input from AD key opinion leaders and investigator sites was also taken into consideration by the working group. This group collaborated to evaluate how to combine trial characteristics data, country and site level trial performance data (using both previously completed and ongoing trials) with hospital, physician, prescription, patient, and demographic data to improve site selection and AD trial delivery. The following patient-centric data sources were included in the analysis: Country-specific claims databases (PharMetrics Plus; Programme de Médicalisation des Systèmes d'Information (PMSI); and Health Insurance Review and Assessment Service (HIRA)), pharmacy audit data (Hospital Pharmacy Audit; and Xponent), publically available data (diagnostic capabilities by facility), location-based information (elderly care homes; elderly care centers; and long term care facilities), age demographic data by region, and client relation management databases (OneKey; HCOS; and UNIDB). *Results:* Consolidated data review facilitates the identification of: a) Geographic areas that are either underserved with investigator trial sites, or; b) Locations with the potential to expand trial offerings either through a strategic approach to investigator site selection or further development of existing investigator sites. The data provided evidence to improve patient recruitment opportunities and implementation of site-specific tailored recruitment strategies. Through our analyses we found that the data can be a powerful tool to implement better recruitment and advertising campaigns. This is accomplished by analysing the data to identify specific markets with higher incidence of the target population and/or through targeted outreach programs to specific locations where the desired populations are known to be present – e.g. nursing homes, diagnostic and elderly care centers. The development of improved physician referral techniques and increasing the AD site pool is possible due to the availability of these databases. Health Care Providers (HCPs) with high potential to refer the target population and within reasonable proximity to a study site can be identified using these data. The team then worked to develop processes to define how to engage the HCPs, how to educate these HCPs on the value of trial participation, and how to support and manage logistics associated with referral of the potential participants to the investigator study site. Pilot programs are underway to confirm the validity of this approach. *Conclusion:* The big data mining capabilities enable the opportunity to expand investigator site networks and improve patient recruitment rates in AD trials on a global basis. Patient-centered data analytics allow improved decision-making on where to locate specific trials by considering site workload and access to the target patient population. The use of these databases have been the catalyst for building out targeted patient referral networks capable of improving trial participation rates while better geo-targeting of recruitment advertising campaigns has been accomplished.

LBP10: EXPERIMENTAL DESIGN ON A BUDGET FOR SPARSE LINEAR MODELS: APPLICATIONS TO COGNITIVE PATTERNS IN PRECLINICAL ALZHEIMER'S DISEASE. Daniel J. Belongia[1], Sathya N. Ravi[1], Rebecca Koscik[1], Erin Jonaitis[1], Sterling C. Johnson[1,2], Vikas Singh[1] *((1) University of Wisconsin - Madison; (2) William S. Middleton Memorial Veterans Hospital)*

Backgrounds: An optimal approach to experimental design for prevention trials will involve consideration of the sample size required to detect the hypothesized effect (i.e. a power analysis), as well as a consideration of which subjects to choose in order to attain a statistically robust model. Here, we focus on the second of those two considerations in the context of AD-related research and clinical trials. Specifically, we assume that we have preliminary, inexpensive neuropsychological evaluations from potential trial subjects during two or more lead-in visits. From this data, we would like to identify subjects, both with and without predicted cognitive decline, to participate in a more invasive or expensive study, such as a study involving CSF assays or amyloid or tau molecular imaging. These chosen subjects can be thought of as an "enriched" sample. To identify these participants, we use a machine learning algorithm that selects subjects in such a way that the model produced by the reduced data set will best approximate the full model that would have been produced if all subjects had been included. This algorithm was previously shown to be effective with Region-of-Interest summaries from PET images of subjects with AD. Now, the objective is to identify subjects for imaging based on neuropsychological evaluations. This method can be used to easily identify candidates for clinical trials in a way that improves upon participant self-selection or variance-based selection methods. *Methods:* The experimental design (ED) subject selection algorithm consists of two equivalent formulations that operate on the premise that we have already identified the sample size (B) of our study, and now we wish to identify specific subjects in a way that optimizes the information content of the selected sample. Each algorithm also contains an additional term that enforces similarity between the "reduced" and full model. We apply these formulations to a linear model that is created from neuropsychological test scores of up to 770 middle-aged and elderly subjects in the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort. Specifically, we

use the ED formulations to select a subset B of the full 770 subjects, a small portion of whom will have mild cognitive impairment, and evaluate our selection by comparing a model created with the reduced subset to a model created with the full set. We repeat this for a wide range of budget values B, and for comparison, we also create models whose subjects were chosen using random selection and a "smarter" subject selection algorithm. For each of the budgeted and full data sets, we compute a linear model with LASSO. Our covariates, shown in Table 1, include cognitive test scores from 2 visits; the dependent variable is a test score from a third visit, which effectively predicts cognitive improvement or decline. The "model" that LASSO creates is a series of coefficients that represent the relationship between the input values; if a particular covariate is not important in predicting the dependent variable, we expect the coefficient to be 0. The models created from the full and budgeted data sets can therefore be compared by examining feature selection and sign consistency of the chosen features. *Results:* Use of the ED formulations to create budgeted models resulted in improved similarity to the full model when compared to participant self-selection (modeled here as random selection of subjects), as well as a sorted selection algorithm, for a variety of budget sizes and number of model features. Figure 1 shows the error in feature selection, calculated as the fraction of covariates that LASSO identified as important in the reduced model that were also considered important in the full model. The figure demonstrates that selecting subjects using the ED algorithm, instead of random selection, results in a population sample that better approximates the full population by 10-20%, even for budget sizes that are about 1/3 of the full sample. Other metrics, including sign inconsistency and model similarity as a function of number of features selected, suggest similar improvements. The choice of dependent variable impacts the degree of similarity between the ED selected models and the full models, but the ED selection method never underperforms by more than several percentage points as compared to the other selection methods. Importantly, the subjects chosen by the formulations are consistent, so additional subjects could be added to an already budget-constrained study without dramatically impacting the validity of the chosen subset. *Conclusions:* We showed that the use of either formulation of a novel subject selection algorithm results in a budgeted model that approximates the full model better than random selection or a variance-based method. The budgeted model closely resembles the full model even for small budget sizes (1/3 the full population). When applied to a clinical trial, this method can be used to inexpensively identify subjects that constitute a full range of expected cognitive stability and decline.

LBP11: RATIONALE, DESIGN AND PROGRESS OF ALZHEIMER'S PREVENTION INITIATIVE TRIALS.
Pierre N. Tariot, Jessica B. Langbaum, Eric M. Banner *(Alzheimer's Institute, Phoenix, AZ, USA)*

Background: In 2010, Banner Alzheimer's Institute launched the Alzheimer's Prevention Initiative (API) to: a) conduct trials of potentially AD-modifying treatments in cognitively unimpaired people who, based on their age and genetic background, are at high imminent risk of AD symptom onset (i.e., have "preclinical" AD); b) develop new cognitive outcomes; c) asses treatments' theragnostic, predictive, and prognostic utilities; d) help establish the regulatory approval pathway needed for the field to test other preclinical AD treatments; e) provide more informative tests of the amyloid hypothesis than trials in clinical or later preclinical (e.g., amyloid-positive only) stages of AD; e) provide large prevention registries as shared resources for enrollment into these and other trials; and f) establish data and sample sharing plans to help advance the field. *Methods:* We launched several potentially label-enabling placebo-controlled trials designed to systematically address each of these aims in addition to trial-specific aims: their design and progress will be described along with lessons learned. *Results:* The first API trial, studying crenezumab vs placebo, is being conducted in partnership with the Neurosciences Group of Antioquia in Colombia and Roche in cognitively unimpaired people age 30-60 from families afflicted with the autosomal dominant PS1 E280A mutation causing early-onset AD. It is closed to enrollment: recruitment of the sample of 252 relied on the API Colombia Registry, with over 1,100 mutation carriers identified. The ongoing second and third API studies, Generation Study 1 and Generation Study 2, are being conducted globally in partnership with Novartis and Amgen. The Generation studies enroll 60-75 year old cognitively unimpaired participants: APOE4 homozygotes in Generation Study 1; APOE homozygotes as well as APOE heterozygotes with elevated brain amyloid in Generation 2. US enrollment in the Generation Program is supported in part by the Alzheimer's Prevention Registry (www.endALZnow.org), numbering about 280,000, and its associated GeneMatch program, through which volunteers (about 42,000 enrolled thus far) can opt to have APOE genotyping to help match them to preclinical trials. Enrollment methods in the Generation Program vary considerably by country, with a planned total sample size of more than 3300 randomized participants. *Conclusions:* The first three API trials aim to enroll a total of over 3,500 cognitively unimpaired people who are particularly high risk of developing symptoms of AD. We started with a trial in persons at virtually certain risk and have subsequently launched trials in people at high but not certain risk. We have grappled with and will discuss challenges inherent in this type of research, such as identifying and enrolling people at elevated risk, risk disclosure, discerning how to measure change in cognition in people without clinical manifestations, obtaining funding, assuring Health Authority approval, and whether/how to offer trials to people with limited education. Finally, in an effort to maintain momentum in addressing this critical public health need, we have several other API trials in various stages of preparation, designed to further address the aims of our program.

LBP12: GRAPH IMPUTATION TECHNIQUES FOR ESTIMATING AMYLOID POSITIVITY FROM LONGITUDINAL COGNITIVE AND MRI MEASUREMENTS FOR EFFICIENT SECONDARY PREVENTION TRIALS.
Tuan Dinh, Sathya Ravi, WonHwa Kim, Nagesh Adluru, Rebecca Koscik, Cynthia Carlsson, Sterling C. Johnson, Vikas Singh *(University of Wisconsin--Madison, WI, USA)*

Background: Cerebrospinal fluid (CSF) measures including AB42 and Tau are known to be important biomarkers for Alzheimer Disease (AD) research including secondary prevention trials. Assay values that denote amyloid and tau positivity may be utilized as enrollment criteria. Efficient screening methods are needed to identify participants who may be biomarker positive so that lumbar puncture procedures are performed only on people who are most likely to exhibit positivity. This will lead to significant cost savings and avoid unnecessary lumbar punctures. *Methods:* Given longitudinal imaging (159 attributes extracted from deformations in the temporal, cingular, hippocampal and amygdalar ROIs from the AAL atlas) and cognitive data (27 attributes including age and 12 pairs of slopes and intercepts of linear regression model of participant visits) on 147 prospective, non-demented participants from an existing longitudinal observational AD-risk study, and given existing CSF measurements on a small subset of these participants (50%), we present a novel graph theoretic/harmonic analysis approach for imputation --- that is, estimating how likely the individuals who do not have CSF

measurements would become amyloid positive. Our method utilizes the high-dimensional relative rankings between the full suite of longitudinal measurements of each pair of individuals and constructs a "graph" using these pairwise relationships. Via Fourier analysis, we set up a recovery (or imputation) problem to predict a binary class (+1 means likely amyloid positive and -1 means not amyloid positive) for all individuals whose CSF measurements are unavailable. While the recovery problem is solved in continuous space, we finally classify the individuals as positive or negative based on predefined thresholds. For evaluation, we compare our proposed model with linear regression, lasso regression, random forest and support vector machine (SVM) and show significant improvements over all other alternatives. *Results:* Recovery is evaluated using Relative Root Mean Square Error (Relative RMSE) and classification is evaluated by precision score (fraction of correctly classified instances over positive classified instances). Table 1 shows our graph completion model achieves a relatively low error for AB42 prediction in comparison with other baselines. Table 2 shows that our method gets very high precision, recall and accuracy when classifying AB42 using longitudinal cognitive data alone. Overall, graph-completion model provides the best prediction among currently available methods. *Conclusion:* We present an effective method to predict amyloid positivity from a small subset of training data where longitudinal cognitive and imaging data are available. Our main contribution is a mathematical framework for imputation and the insight into the relationship between CSF and the suite of longitudinal cognitive and tensor based morphometry measurements. 1. ROI: region of interest; 2. AAL: automated anatomical labeling; 3. Precision: fraction of relevant instances among the retrieved instances; 4. Recall: fraction of relevant instances that have been retrieved over the total amount of relevant instances; 5. Accuracy: fraction of correctly retrieved instances over the total amount of instances

Table 1
Relative RMSE of 5 models on AB42 over 3 datasets

Model	Cognitive	Cognitive + Genetic	Cognitive + ROI
Linear Regression	96.1	99.75	88.33
Lasso	33.35	33.2	32.65
Random Forest	24.3	23.59	23.5
SVM	23.9	23.73	23.97
Graph Completion	19.97	19.51	20.26

Table 2
Classification scores of graph-completion on AB42 using cognitive dataset (unit: %)

Metrics	AB42
Precision	85.85
Recall	99.17
Accuracy	85.24

Theme: Clinical Trials Results

LBP25: A STUDY TO EVALUATE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF AD-35 TABLETS TAKEN ORALLY IN HEALTHY CHINESE SUBJECTS. Cuibai Wei, Jianping Jia, Tingting Li, Wei Wang, Tingting Hou, Xiu Wang, Hui Xu *(Department of Neurology, Xuan Wu Hospital, Capital Medical University, Beijing, P.R. China)*

Backgrounds: Alzheimer's disease is a progressive neurodegenerative disease characterized by gradual loss of cognitive and memory functions, a variety of neuropsychiatric symptoms and behavioral disorders. It's the most common cause of dementia. AD-35 is a new drug for the treatment of Alzheimer's disease which has important clinical significance. In this study we evaluated the safety, tolerance and pharmacokinetic characteristics of single oral AD-35 tablets in healthy Chinese subjects, so as to provide the basis for the later clinical trials. *Methods:* Thirty-six healthy subjects were enrolled in the single-dose, randomized, double-blinded, placebo-controlled, dose-escalation trial and divided into three dose groups: 40mg, 60mg and 90mg. The study was conducted from low to high dose, and the next dose was performed only after the safety and tolerability were confirmed favorable. Safety and tolerability of AD-35 Tablets taken orally in the subjects were assessed by vital signs, ECG, laboratory parameters and adverse events. Harmacokinetic studies were performed simultaneously on three dose groups. *Results:* All of the thirty-six subjects (40mg: 10mg cases, 60mg: 10 cases, 90mg: 10 cases, placebo group: 6 cases) had completed the study and no cases off. There was no statistically significant difference among the groups about study time, the treatment time and the vital signs. No abnormality before and after the physical examination was found. A total of 5 adverse events associated with the study drugs were reported in 2 subjects in 40mg group, the incidence was 20.00%. 60mg group did not occur anyone. In 90mg group, 8 adverse events were reported in 7 subjects, the incidence was 70.00%. 1 subject was reported once in placebo group, the incidence was 16.67%. The difference of incidence among the groups has statistically significant analyzed by Fisher direct probability method. No serious adverse events were observed in each group. The main pharmacokinetic parameters of the three dose groups were: Cmax: 318 ± 41, 490 ± 118, 743 ± 110 ng / mL; AUC0 ~ t: 5.83 ± 0.96, 9.26 ± 2.85, 15.10 ± 2.72 h * ug / mL; AUC0 ~ ∞: 6.13 ± 1.05, 9.71±3.07, 16.00 ±3.05 h * ug / mL; t1/2: 23.70 ± 5.30, 20.70 ± 2.95, 24.40 ± 3.56 h; Tmax: 1.7 ± 0.632, 2.0 ± 0.466, 2.0 ± 0.408h. *Conclusion:* The research data of AD35 tablets showed that in different dose groups, Cmax, AUC0 ~ t and AUC0 ~ ∞ were consistent with the trend of dose change, while the mean value of other main pharmacokinetic parameters were roughly the same. The elimination of AD35 tablets in vivo is in compliance with linear pharmacokinetic characteristics. Healthy Chinese subjects taken orally with AD35 tablets 40 to 90 mg were safety and tolerance.

LBP26: THE USE OF TRANSDERMAL RIVASTIGMINE IN THE TREATMENT OF ALZHEIMER'S DISEASE. Gustavo Alves Andrade dos Santos *(SENAC University Center, São Paulo, Brazil)*

The development of Alzheimer's disease is marked by gradual or progressive deterioration of the intellectual function, with a marked decline in the ability to perform daily activities and to deal with changes in personality and behavior, with memory impairment, fatigue, visual and spatial deficits And impairment of the ability to make calculations and abstractions. Currently there are two categories of drugs to treat patients with dementia: anticholinesterases, which try

to replace a substance called Acetylcholine, mediator of memory; And antiglutamatergics, which decrease calcium overload. Rivastigmine tartrate has been shown to be an effective inhibitor of the carbamate-type acetylcholinesterase enzyme and, even without further studies, facilitates cholinergic neurotransmission by delaying the degradation of acetylcholine released by functionally intact cholinergic neurons. Rivastigmine has a pseudo-irreversible mechanism of inhibition, because in the interaction of the enzyme with Rivastigmine, which occurs in the synaptic cleft, the formation of a phenolic cleavage product with minimal pharmacological activity and rapid excretion occurs, in addition to a carbamylated complex with Enzyme, which prevents the hydrolysis of acetylcholine, by competitive and long-term, but reversible inhibition. For the present study, 40 volunteers of both genders, all with diagnosed Alzheimer's dementia, were evaluated. Rivastigmine showed beneficial effects on cognitive manifestations for treatments over 2 years in patients diagnosed with AD, when compared with placebo. Both the oral form and the transdermal form of the drug tartrate Rivastigmine were statistically similar with respect to the cognition of patients after 180 days of treatment. Both the oral form and the transdermal form presented biochemical values relative to the levels of acetylcholinesterase equal, being That no significant statistical differences were found that could refer to a possible follow-up of the dementia with this test. Acetylcholine levels also showed statistically relevant elevation during the period of the experiment, in transdermal form.

LBP27: NILVAD: A PHASE III CLINICAL TRIAL OF NILVADIPINE IN MILD TO MODERATE ALZHEIMER'S DISEASE - RESULTS OF SUBGROUP ANALYSES. Michael Mullan[1], Laila Abdullah[1], Fiona Crawford[1], Ricardo Segurado[2], Suzanne Hendrix[3], Brian Lawlor[4], The NILVAD consortium. *((1) Archer Pharmaceuticals, Sarasota, FL, USA; (2) University College Dublin, Dublin, Ireland; (3) Pentara Corporation, Salt Lake City, UT, USA; (4) Trinity College Dublin, Dublin, Ireland)*

Background: NILVAD is an investigator driven phase III clinical trial of nilvadipine in mild to moderate Alzheimer's disease (AD). Nilvadipine, a dihyropyridine calcium channel blocker, is a licensed antihypertensive and is being repurposed for AD based on clinical and basic science evidence for its potential as a disease-modifying agent in AD. *Methods:* 511 subjects with mild to moderate AD were recruited across 23 sites in 9 different European countries. Subjects received 8 mg over encapsulated nilvadipine or matching placebo over a period of 18 months. The sponsor of the trial was St. James's Hospital, Dublin. Academic trial units were used to monitor the trial in each country. The primary outcome measures were the Alzheimer's Disease Assessment Scale Cognitive (ADAS-Cog) and the Clinical Dementia Rating Scale sum of boxes (CDR-sb) and the Disability assessment for Dementia (DAD) was a secondary outcome measure. The secondary analysis included examination of subgroups by baseline MMSE scores. *Results:* Nilvadipine was well tolerated with the only adverse event occurring more frequently on nilvadipine than placebo being peripheral edema. The pre-specified primary analyses failed to show any treatment benefits for nilvadipine on the co-primary or secondary outcomes in the total population of mild to moderate AD patients. However, stratification of the total study population by the baseline MMSE scores showed that individuals with higher MMSE scores who were treated with nilvadipine showed less decline on ADAS-Cog scores over the 78-week period compared to placebo treated individuals. *Conclusion:* These subgroup analyses suggest that nilvadipine may have cognitive benefits for individuals in the earliest (and potentially, preclinical) stages of AD. Further studies focused on such individuals are required to confirm these findings.

LBP28: BIOMARKER OUTCOMES FROM THE PHASE 1B/2A SAFETY TRIAL OF THE ANTI-AB OLIGOMER DRUG CT1812 IN ALZHEIMER'S PATIENTS. Susan M. Catalano[11], Lon S Schneider[3], Steven DeKosky[4], Roger Morgan[5], Courtney Rehak[1], Kelsie Mozzoni[1], Nicholas J Izzo[1], Michael Grundman[1,2], Michael Schirm[7], Rudolf Guilbaud[7], Mark Watson[7], Daniel Chelsky[7] *((1) Cognition Therapeutics Inc., Pittsburgh, PA, USA; (2) Global R&D Partners, LLC, San Diego, California USA; (3) Keck School of Medicine of USC, Los Angeles, CA, USA; (4) McKnight Brain Institute, University of Florida, Gainesville, FL, USA; (5) MedSurgPI, LLC Raleigh, North Carolina, USA; (6) Aclairo Pharmaceutical Development Group, Inc, Vienna, VA, USA; (7) Caprion Biosciences, Inc., Montreal, Canada)*

Background: CT1812 is the only therapeutic candidate demonstrated to displace Aβ oligomers from synaptic receptor sites and clear them from the brain into the cerebrospinal fluid, restoring normal cognitive performance in aged transgenic mouse models of AD. Chronic treatment of aged transgenic mice with efficacious doses of CT1812 significantly reduces inflammatory protein expression in CSF, and normalizes Alzheimer's disease-related protein expression in CSF and plasma as measured by LC/MSMS. CT1812 appears safe and well tolerated with multiple doses up to 560 mg/day in healthy elderly volunteers (ClinicalTrials.gov NCT02570997). To further the clinical development of CT1812, we completed a clinical trial in mild to moderate Alzheimer's patients to evaluate protein biomarkers as well as safety (ClinicalTrials.gov NCT02907567). *Methods:* A multi-center, double-blind, placebo-controlled parallel group trial was performed to evaluate the safety, tolerability and pharmacokinetics of three doses of CT1812 (90, 280 and 560 mg) or placebo (N = 4 or 5 patients/group) given once daily for 28 days to Alzheimer's patients (MMSE 18-26). Plasma and CSF protein expression were measured by LC/MSMS in samples drawn prior to dosing (Day 0) and at end of dosing (Day 28) and were compared within each patient and between dosing groups. *Results:* LC/MSMS analysis resulted in the identification and relative quantitation of 915 CSF proteins and 1400 plasma proteins across all subjects. Changes in expression of specific proteins were observed in both CSF and plasma following treatment with study drug. Multiple proteins were upregulated in the CSF in response to drug. These include proteins previously linked to AD and proteins involved in axon guidance/CNS development, all of which could be expected to increase with disease reversion. The relationship between protein function and disease, and association with therapeutic target receptor pathways will be reported in detail, along with additional CSF outcomes including Aβ 40, 42 tau and p-tau). *Conclusions:* Treatment of Alzheimer's patients with study drug once daily for 28 days results in protein expression changes in plasma and CSF as measured by LC/MSMS. Along with safety and clinical outcomes, the protein expression outcomes will help guide the future development of CT1812. Additional trials include an indwelling lumbar catheter study to detect changes in Aβ oligomers in CSF, a PET study to assess synaptic density after treatment with CT1812 and a Phase 2 six-month efficacy trial.

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LBP29: UB-311 ACTIVE VACCINE GENERATES TITERS SPECIFIC FOR AB OLIGOMERS AND FIBRILS WITHOUT EVIDENCE OF ARIA-E OR ENCEPHALOPATHY IN A COMPLETED PHASE 1 AND AN ONGOING PHASE 2A STUDY IN ALZHEIMER'S DISEASE. Ajay. Verma[1], Paul Maruff[2], A. Schembri[2], P. N. Wang[3], M. J. Chiu[4], C. C. Huang[5], C.C. Chang[6], H. C. Chen[1], P. Chan[g1], C. Y. Wang[1] *((1) United Neuroscience, Inc. Hauppauge, NY, USA; (2) Cogstate Limited, Melbourne, Victoria, Australia; (3) Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan; (4) Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan; (5) Department of Neurology, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; (6) Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan)*

Background: UB-311 is an active vaccine targeting the Aβ1-14 epitope. An open label Phase I (Ph1) study in patients with mild to moderate Alzheimer's Disease (AD) has been completed, and over 50% of patients with mild AD have completed the Week 52 visit of a 78 week, placebo controlled Phase IIa (Ph2a) study. Vaccine therapies are challenged by low responder rates and titer levels, particularly in elderly subjects. Prior Aβ immunotherapy efforts also suggest targeting aggregated Aβ oligomers and fibrils yields better clinical outcomes than targeting soluble Aβ monomers. We therefore evaluated immune response rates and titer specificity against amyloid species in subjects who had completed the Ph1 study. Aβ immunotherapy has also been associated with acute adverse CNS events such as ARIA-E and or encephalopathy. We conducted CNS safety monitoring using serial MRI scans and cognitive assessment to identify any acute CNS changes in the Ph1 and Ph2a studies. Here we report on the nature of Aβ species targeted by induced antibodies from subjects in the Ph1 study and report the number of events of ARIA-E and acute clinically meaningful cognitive decline observed to date in both studies. *Methods:* Antibody titer responses from the Ph1 study were evaluated using an ELISA against Aβ1-28. Pharmacokinetics of induced antibodies was evaluated using area-under-curve (AUC) analysis of all individuals by age. For specificity assessment of titers against Aβ species we generated dot blots using α-monomers, β-monomers/dimers, β-oligomers and β-fibril forms of Aβ and probed these with individual and pooled patient serum samples via dot blot analysis. We also evaluated the ability of induced human titers to stain aggregated forms of Aβ by immunohistochemistry using post mortem tissue sections from AD brains. MRIs from all subjects who received drug or placebo were obtained at baseline and Week 24 in the Ph1 study and at baseline and every 3 months following vaccination in the Ph2a trial. All images were inspected by a board-certified neuro-radiologist for evidence of ARIA-E. Acute clinically meaningful decline in cognition was defined to have occurred when the ADAS-cog composite score (derived from scores on the Information, Orientation and Memory subtests) had declined by 1.65 standard deviations between adjacent visits. The Ph1 sample consisted of 19 adults aged between 51 and 78 years (M=64.00, SD=8.25; 52.6% females), 47.4% mild AD and 52.6% Moderate AD. At the time of analysis (September 2017), the Ph2a sample included 43 adults with mild AD aged between 60 and 86 years (M=72.60, SD=6.93; 74.4% females) with MMSE scores ranging between 20 and 26 (M=22.51, SD=2.14) and the CDR-SB score ranging between 0.5 and 1.0. *Results:* UB-311 elicited anti-Aβ antibody titers in all subjects in the Ph1 study with no evidence of immunosenescence. Vaccine induced antibodies were highly specific for the β-oligomer and β-fibril species and recognized aggregated Aβ pathology on AD brain tissue sections. For the Ph1 study, no incidence of treatment induced ARIA-E was observed from 19 post-vaccination MRI reads. For the 25 subjects who have completed the Week 52 assessment in the Ph2a trial, no incidences of treatment induced ARIA-E were detected from 175 post-vaccination MRI reads. In the Ph1 study, acute clinically meaningful cognitive decline was observed in 1 of the 19 subjects (5.3%) at the Week 16 assessment and in no subjects from the week 16 to week 24 assessments. Review of this case by the study safety group identified that the subject suffered a respiratory infection near the time of assessment but had no other neurological issues. In the Ph2a study, acute clinically meaningful decline was observed in 2 of 37 (4.7%) subjects at Week 28 and in no cases from Week 24 to Week 52 in the 25 subjects completing the 52 Week assessment at the time of this analysis. Data for the Ph2a study are still blinded but review of these cases of clinically important decline by the study safety group identified no signs of an adverse CNS event. *Conclusion:* UB-311 generates antibody titers in elderly patients specific for oligomers and fibrils without evidence of ARIA-E or encephalopathy. Treatment with UB-311 for 52 weeks of treatment appears to be safe.

LBP30: MULTIPARAMETER ANALYZES OF PROGRESSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DEMENTIA: A 10 YEAR LONG-TERM FOLLOW-UP STUDY. Oliver Peters[1], Dominik Diesing [1], Stefan Klöppel[2], Johannes Kornhuber[3], Roberto Goya[4], Jens Wiltfang[4] Isabella Heuser[1] *((1) Department of Psychiatry, Charité, Berlin, Germany; (2) Department of Psychiatry, Bern, Switzerland; (3) Department of Psychiatry, Erlangen, Germany; (4) Department of Psychiatry, Göttingen, Germany)*

Background: Most recent observational studies investigating the progression from prodromal stages of Alzheimer´s disease to dementia are relying on short-term follow up data (i.e. < 3 years). Long-term follow up studies of patients presenting with mild cognitive impairment (MCI) at baseline have been rarely performed so far. Here, we clinically followed up on average 10 years after baseline a cohort of MCI patients well characterized at baseline by a comprehensive data set comprising an extensive neuropsychological test battery, cerebrospinal fluid (CSF)-biomarker (i.e. t-Tau and A-beta species) and MRI-volumetry (i.e. hippocampal volume). *Methods:* MCI patients (n = 48) recruited within the framework of the German Dementia Competence Network (DCN) were reexamined. MCI at baseline was defined as CDR (Clinical Dementia Rating) = 0.5 and SD < -1 in any CERAD subdomain (Consortium to Establish a Registry for Alzheimer's Disease). Conversion to AD was defined by a worsening in CDR between baseline and follow-up ≥ 0.5. Prediction capability of a priori defined single biomarkers was calculated using a support vector machine and bootstrapping (0.632). ROC (receiver operating curves) were generated and AUC (area under the curve) values of best single predictors and best two to four parameter combinations with best predictive accuracy for MCI to AD conversion were computed. *Results*: Within a decade after baseline a total of 25 (52,1%) MCI remained stable versus 23 (47,9%) who progressed to dementia and fulfilled the NINCDS-ADRDA criteria for AD at follow-up. The mean follow up time was 10.48 years. For prediction of progression from MCI to AD the ratio tTau/Amyloid-beta-42 was identified as the best single predictor (AUC = 0.701), followed by Bayer Activities of Daily Living (BADL) (AUC = 0.663), Ratio amyloid-beta-42/40 (AUC = 0.638), Delayed Logical Memory subtest from the CERAD test battery (AUC = 0.587), CDR-SB (AUC = 0.565) and hippocampal volume (AUC = 0.558). In further analyzes allowing more than one parameter the combination of tTau/Aß42 ratio and BADL reached an AUC of 0.795. In a three parameter model the highest AUC value was detected for tTau/Aß42 ratio, CDR-SB and BADL (AUC = 0.819) and finally in a four parameter model

APOE4, tTau/Aß42 ratio, BADL and CDR-SB (AUC = 0.821) were found to be best predicting parameters. *Conclusion:* Only long-term follow up studies in MCI are able to detect with reasonable certainty eventual AD progressors and stabile MCI. In our study we found about 50% of participants to be AD progressors and 50% stabile MCI. After analyzing multiple parameters, we concluded that the CSF biomarker ratio tTau/Aß42 is the most relevant factor predicting disease progression from MCI to AD in the long run.

LBP31: SINGLE ASCENDING DOSE PHASE I CLINICAL TRIAL OF PTI-125 IN HEALTHY VOLUNTEERS. Lindsay H. Burns[1], George J. Atiee[2], Michael Marsman[1], Nadav Friedmann[1] *((1) Pain Therapeutics, Inc., Austin, TX; (2) Worldwide Clinical Trials, San Antonio, TX)*

Background: PTI-125 is a novel small molecule drug candidate to treat Alzheimer's disease (AD). PTI-125 preferentially binds and reverses an altered conformation of the scaffolding protein filamin A (FLNA) that is present in AD brain (Wang et al., 2017). PTI-125 binds altered FLNA in AD brain with femtomolar affinity and control FLNA with a 100-fold lower, picomolar affinity. Altered FLNA links to both the α7 nicotinic acetylcholine receptor (α7nAChR) and toll-like receptor 4 (TLR4) to enable α7nAChR-mediated Aβ42-induced tau phosphorylation and TLR4-mediated inflammatory cytokine release. PTI-125's restoration of FLNA's normal conformation prevents the aberrant FLNA linkages to both receptors and the resultant tau hyperphosphorylation and neuroinflammation. In triple transgenic AD mice (22 mg/kg/day, equivalent to 105 mg for a 60-Kg person) and/or in postmortem human AD brain (1 nM), therapeutic effects included (1) reduced tau hyperphosphorylation, (2) reduced TNFα, IL-1β and IL-6 brain levels, (3) reduced Aβ42 – α7nAChR complexes (4) improved function of α7nAChR, NMDAR and insulin receptors, (5) improved synaptic plasticity, evidenced by activity-dependent expression of Arc, the master synaptic plasticity regulator, (6) reduced Aβ42 deposits and neurofibrillary lesions, and (7) improved cognitive/behavioral assessments. No-observable-adverse-effect-levels (NOAELs) in 28-day toxicity studies were 500 mg/kg/day in rat and 100 mg/kg/day in dog. These preclinical data suggest that PTI-125 will provide some cognitive recovery as well as slow disease progression. *Methods:* Following IRB approval, we conducted a double-blind, placebo-controlled Single Ascending Dose Phase I clinical trial in 24 healthy volunteers, age 18-45. PTI-125 was administered orally at doses of 50, 100 and 200 mg. Each dose cohort consisted of 6 active and 2 placebo subjects. PTI-125 was administered as an oral dosing solution in an ORA Sweet SF vehicle for taste-masking to maintain blinding. The study followed a sentinel design, with one active and one placebo subject dosed first, followed by the full dose cohort after Data and Safety Monitoring Board (DSMB) review of 24-h safety assessments. Blood draws for laboratory testing were conducted pre-dose and 24 h post-dose. PK blood draws occurred at 13 timepoints from 20 min through 72 h. Orthostatic vital signs were taken pre-dose and at 12 timepoints from 10 min through 72 h. Electrocardiograms (ECGs) were conducted at all vital sign timepoints except 10 min. A physical exam was conducted at 72 h prior to discharge. All safety assessments were repeated at a 7-day follow-up visit. *Results:* PTI-125 was well tolerated at 50 and 100 mg. The 200-mg cohort is ongoing. PK of the 50-mg cohort showed PTI-125 to be rapidly absorbed with the following mean PK values: Tmax 1.56 h; Cmax 327 ng/mL; AUClast 2170 h*ng/mL; and T1/2 6.05 h. *Conclusions:* PTI-125 appears safe and well tolerated in an anticipated therapeutic dose range. PK parameters were consistent with preclinical studies. Supported by NIA grant AG056166.

LBP32: MULTIPLE ASCENDING DOSE STUDY OF THE TAU-DIRECTED MONOCLONAL ANTIBODY BIIB092 IN PATIENTS WITH PROGRESSIVE SUPRANUCLEAR PALSY. Irfan Qureshi[1], Michael Grundman[2] Giridhar Tirucherai[1], Clifford Bechtold[1], Michael Ahlijanian[1], Gerry Kolaitis[1], Lawrence I. Golbe[3], Lawrence S. Honig[4], Stuart Isaacson[5], Murray Grossman[6], Nikolaus R. McFarland[7], Irene Litvan[8], David S. Geldmacher[9], Tao Xie[10], Yvette Bordelon[11], Paul Tuite[12], Padraig O'Suilleabhain[13], Theresa Zesiewicz[14], Adam Boxer[15] *((1) Bristol-Myers Squibb, Lawrenceville, NJ, USA and Wallingford, CT, USA; (2) Global R&D Partners, LLC, San Diego, CA, USA; (3) Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA; (4) Columbia University Medical Center, New York, NY, USA; (5) Boca Raton Institute for Neurodegenerative Disorders, Boca Raton, FL, USA; (6) University of Pennsylvania, Philadelphia, PA, USA; (7) University of Florida, Gainesville, FL, USA; (8) University of California, San Diego, CA, USA; (9) University of Alabama at Birmingham, Birmingham, AL, USA; (10) University of Chicago, Chicago, IL, USA; (11) University of California, Los Angeles, CA, USA; (12) University of Minnesota, Minneapolis, MN, USA; (13) University of Texas Southwestern Medical Center, Dallas, TX, USA; (14) University of South Florida, Tampa, FL, USAl (15) University of California, San Francisco, CA, USA)*

Introduction: BIIB092 (formerly known as BMS-986168) is a humanized monoclonal antibody that recognizes human extracellular tau (eTau), a series of N-terminal tau protein fragments. In transgenic mouse models of tauopathy, the murine analog of BIIB092 lowered free eTau concentrations in cerebrospinal fluid (CSF) and limited tau pathology. In a previous phase I trial, single doses of BIIB092 (up to 4200 mg) suppressed free eTau in the CSF of healthy subjects and were safe and well tolerated. Based on preclinical and phase I data, this multiple ascending dose study was designed to evaluate the safety profile of BMS-986168 and the ability to reduce free eTau in the CSF of patients with progressive supranuclear palsy (PSP). *Objectives:* This was a randomized, double-blind, placebo-controlled, multiple ascending dose trial of 48 patients with PSP. The main study objective was to assess the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects of BIIB092 on eTau after intravenous (IV) infusions every 4 weeks (Q4W) in patients with PSP. Three ascending dose panels (150 mg, 700 mg, and 2100 mg) comprising8 patients per panel, were administered IV infusions of BIIB092 (6 patients) or placebo (2 patients) Q4W for 12 weeks; an additional 24 patients were treated with BIIB092 at a dose of 2100 mg (18 patients) or placebo (6 patients) administered Q4W for 12 weeks. All patients were also offered the opportunity to participate in an open-label extension study. Safety assessments and serum and CSF samples were collected over the 12 weeks. PK parameters (in serum and CSF) and absolute and percent change from baseline in PD measures (concentrations of CSF free eTau) were evaluated. *Discussion:* Patients' mean age was 67.4 ± 5.5 years; 54.2% were female. Concentrations of BIIB092 in serum and CSF increased with dose. The percentages of patients experiencing adverse events (AEs) were similar in the BIIB092 and placebo groups (~75%). Most AEs were mild and unrelated to test article. There were no deaths or discontinuations due to AEs. CSF and serum exposures increased with dose and significant reductions of CSF free eTau were observed with all BIIB092 doses used in the study. Mean suppression of CSF free eTau was approximately 90–96% (Day 29) and 91–97% (Day 85) at doses ranging from 150 mg to 2100 mg. *Conclusion:* Administration of multiple doses of BIIB092 was safe and well tolerated at doses up to 2100 mg in patients with PSP. The robust suppression of CSF free eTau concentrations in this study is consistent with target

engagement in the CSF and further supports the potential utility of BIIB092 in the treatment of human tauopathies. An efficacy study in patients with PSP is ongoing (NCT03068468) and a phase II efficacy study in Alzheimer's disease is in development. Acknowledgments/ Disclosures: The study was funded by Bristol-Myers Squibb (BMS). IQ, GT, CB, MA, and GK are employees of BMS. MGru is a paid consultant to BMS. LIG has received research support from BMS, AbbVie, American Parkinson's Disease Association and has served as a consultant to BMS & AbbVie. LSH has received research support from BMS, AbbVie, AstraZeneca, Axovant, C2N, Eli Lilly, Forum, Genentech, Lundbeck, Pfizer, Roche, TauRx, and vTv, and has served as a consultant to BMS, Eli Lilly, and Lundbeck. NRM has received research support from the NIH and the Michael J. Fox Foundation. He has served on a scientific advisory board for Novartis. IL is supported by the National Institutes of Health grants: 5P50 AG005131-31, 5T35HL007491, 1U01NS086659 and 1U54NS092089-01; Parkinson Study Group, Michael J Fox Foundation, AVID Pharmaceuticals, C2N Diagnostics and Bristol-Myers Squibb. She receives her salary from the University of California San Diego. She has been a member of the Biogen and Bristol-Myers Squibb Advisory Boards and is a member of the Biotie/Parkinson Study Group Medical Advisory Board. DSG has received research support from AbbVie, Avanir, Biogen, BMS, Department of Defense, Eisai, GSK, Lilly, The McKnight Brain Research Foundation, and the NIH for the conduct of clinical trials. He has received personal compensation for consulting from Axovant and Grifols. TX has received research support from the Michael J. Fox Foundation, Parkinson's Foundation, the University of Chicago, BMS and Abbvie. YB has been on a speakers bureau for Teva. PT has received research support from BMS, Kyowa, the NIH, Northwestern University, the Michael J. Fox foundation, and the University of Minnesota. TZ has received research support from FARA (Friedreich's Ataxia Research Alliance).TZ has also been a consultant for Steniment Inc., Agilis., Glaxo Smith Kline, Shire, Sagene, SNC, Adamas, Osmotica, Edison, Retrotope, Reata, Baxalta. AB has received research support from the Bluefield Project to Cure FTD, Corticobasal Degeneration Solutions, the NIH, the Tau Consortium, the University of California, and the following companies: Avid, Biogen, BMS, C2N, Cortice, Eli Lilly, Forum, Genentech, Roche, and TauRx for conducting clinical trials. He has received personal compensation for consulting from AbbVie, Asceneuron, Ionis Pharmaceuticals, Janssen, Merck, and Novartis, and for serving on a DSMB for Neurogenetics. He has received stock/ options for serving on scientific advisory boards for Alector and Delos. MGro, POS and SI do not declare any relevant conflicts of interest.

LBP33: CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS CHARACTERIZATION OF ANAVEX™2-73 FOR DESIGNING A PHASE 2/3 STUDY IN MILD-TO-MODERATE ALZHEIMER'S DISEASE. Mohammad Afshar[1], Frédéric Parmentier[1], Ene I Ette[2], Emmanuel O Fadiran[3], Christopher U Missling[3] *((1) Ariana Pharma, Paris, France; (2) Anoixis Corp., Natick, MA; (3) Anavex Life Sciences Corp., New York, NY, USA)*

Background: ANAVEX2-73, a selective sigma-1 agonist with muscarinic receptor ligand properties was tested in a Phase 1 study in healthy volunteers and in a Phase 2a study in patients with mild-to-moderate Alzheimer's disease. ANAVEX2-73 demonstrated a favorable safety profile in both studies. The most common side effects across all AE categories tended to be of mild severity, and were resolved with dose reductions that were anticipated within the adaptive dose adjustment design of the Phase 2a study protocol. *Methods:* Clinical data from 54 subjects from the Phase 1 and the Phase 2a was analyzed with non-linear mixed effect (NLME) modeling and non-compartmental analysis approach. The QT/QTc data was analyzed according to ICH E14 guidelines. Relationship between dose and response was investigated using non-linear rule based Formal Concept Analysis (FCA, implemented in Ariana's KEM® software). *Results:* ANAVEX2-73 is metabolized into a pharmacologically active metabolite, ANAVEX19-144. Its pharmacokinetics is linear in the dose range studied and exhibits moderate pharmacokinetics variability. The apparent elimination half-life of the metabolite (21.45 hr) is approximately twice that of the parent drug (10.71 hr). No sex difference in the pharmacokinetics of ANAVEX2-73 was observed. The clearance of the drug is not a function of renal function, and younger subjects clear the drug twice as fast as elderly Alzheimer's disease subjects. ANAVEX2-73 administration does not prolong QTc interval, while ANAVEX19-144 was found to be anti-arrhythmic. A strong relation was observed between ANAVEX2-73 apparent dose and MMSE (Mini-Mental State Examination) response. Drug doses in the upper tertile increase the probability of improved MMSE score 2.1-fold (110%) during 57 weeks. Similarly, higher drug doses increase the probability of improved ADCS-ADL (Alzheimer's Disease Co-operative Study – Activities of Daily Living) score 1.6-fold (67%) during the same period. *Conclusions:* The clinical data from the completed studies enabled a detailed and robust dose-response analysis and the identification of optimal dosing for future studies. The data provides support to further clinical development of ANAVEX2-73 and further clinical studies in several indications are planned or underway. A more complete set of results will be available at the time of the conference.

LBP34: THE PLASMA FOR ALZHEIMER SYMPTOM AMELIORATION (PLASMA) STUDY. Sharon J. Sha[1], Gayle K. Deutsch[1], Lu Tian[2], Kara Richardson[3], Maria Coburn[3], Jennifer Guadioso[1], Tatiana Marcal[4], Ethan Solomon[5], Athanasia Boumis[1], Anthony Bet[3], Steven P. Braithwaite[6], Sam Jackson[6], Karoly Nikolich[6], Darby Stephens[1], Geoffrey A. Kerchner[1], Tony Wyss-Coray[1,6] *((1) Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA; (2) Department of Health Research and Policy, Stanford University, Stanford, CA, USA; (3) Department of Neurosurgery, Stanford University, Stanford, CA, USA; (4) Department of Pediatrics, Stanford University, Stanford, CA, USA Endocrinology (current address); (5) Alzheimer's Therapeutic Research Institute, University of Southern California, Los Angeles, CA, USA (current address); (6) Alkahest, San Carlos CA, USA)*

Background: Plasma obtained from young mice has been demonstrated in aged mice to restore memory and to stimulate synaptic plasticity in the hippocampus. Whether these findings translate to man is unknown as the effects of plasma on cognitive function have not yet been studied in aged humans or in patients with Alzheimer's disease (AD). The primary objective of this study was to assess the safety, tolerability and feasibility of infusions of plasma from 18-30-year-old donors in patients with mild to moderate AD. Secondary objectives were to determine the effect of plasma infusions on cognition, functional ability, and mood. To our knowledge, there are no publications describing the weekly administration of young plasma in this patient population. *Methods:* Patients with mild to moderate AD were recruited for a safety, tolerability and feasibility study of infusions of young plasma in humans. Nine subjects were enrolled and randomized to treatment under a double-blind crossover protocol with four once-weekly infusions of either ~250mL of plasma from 18 to 30-year-old male donors or saline, followed by a 6-week washout and then crossover to four once-weekly infusions of the alternate treatment. An additional 9 subjects were

enrolled and treated under an open label amendment with four once-weekly infusions of ~250mL of plasma from male donors aged 18-30. Patients and/or informants were administered the ADAS-Cog 13-item version, Trail Making Test Part A (TMTA) and Part B (TMTB), Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI-Q), Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), the Functional Activities Questionnaire (FAQ) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) prior to infusions, after the fourth infusion, and after the eighth infusion (when applicable). All analyses were carried out in the R programing language and environment. Safety measures were summarized by number of adverse events, proportion of patients experiencing adverse events and compliance rate. Measurements of laboratory tests were compared between baseline and 4-week post-treatment time-points using paired nonparametric rank tests. For each cognitive, mood and functional measure, we performed a linear mixed-effects regression analysis of both the crossover and open-label patients. The linear mixed-effect regression model takes into account performance at baseline, repeated measures, and missing data. *Results:* There was no difference in age, gender, or baseline Mini-Mental State Examination (MMSE) between the plasma crossover and plasma only groups. One patient discontinued treatment due to urticaria during plasma infusion. Another patient discontinued due to unrelated stroke. There were no related serious adverse events. Other adverse events included hypertension (3), dizziness (2), bradycardia (3), headache (3), tachycardia (3) and single reports of drowsiness, fatigue, lightheadedness, tachypnea, and vertigo. Overall, there was 96% compliance with visits. Analysis of secondary efficacy endpoints revealed that there was a statistically significant improvement on FAQ (the difference between treatment and control: -4.56, 95% CI: -6.11 to -3.01, p = 0.001) and ADCS-ADL (the difference between treatment and control: 3.17, 95% CI: 0.70 to 5.65, p = 0.031) after plasma treatment. There were no statistically significant changes on the ADAS-Cog 13, TMTA, NPI-Q, GDS or the CDR-SB when comparing the plasma or placebo treatment. Less than half the subjects validly performed the TMTB and an analysis of this endpoint was not conducted. No statistical adjustments were made for multiple testing. *Conclusion:* In this first study to assess the safety and feasibility of young plasma in people with mild to moderate AD, we found that young plasma was safe and well tolerated. After four weekly infusions of young plasma, patients with mild to moderate AD may have improved functional ability, though young plasma did not significantly alter mood or global cognition. There are several limitations to this study. The small sample size prohibits the generalizability to other individuals with mild to moderate AD without further study in a larger trial. Additionally, the significant improvements were observed on informant rating scales which are subjective. However, both the plasma crossover and open label plasma groups improved on these measures with more improvement observed in the plasma crossover group, suggesting that these findings were not due purely to a placebo-effect. Changes in a small study sample can be driven by a few individual responses rather than by overall group improvements. Despite these important limitations the results are promising and warrant further exploration of young plasma in future, larger, double-blinded clinical trials.

Theme: Clinical trials: Imaging

LBP35: CROSS-SECTIONAL ASSOCIATIONS BETWEEN TAU PATHOLOGY BURDEN MEASURED BY [18F]GTP1 PET IMAGING AND COGNITION IN AD. Michael Ward[1], Sandra Sanabria Bohorquez[2], Paul T. Manser[3], PhD, Edmond Teng[1], Gai Ayalon[4], Kristin R. Wildsmith[5], Geoffrey A. Kerchner[1], Robby M Weimer[6] *((1) Early Clinical Development; (2) Clinical Imaging Group; (3) Biostatistics; (4) Department of Neuroscience; (5) Biomarker Development; (6) Department of Biomedical Imaging; all Genentech, Inc., South San Francisco, CA, USA)*

Background: Disease severity and cognitive status in AD correlate better with histopathological burden of tau than of β-amyloid. [18F] GTP1 is a tau PET tracer recently developed to detect and measure tau pathology. The objective of the study was to characterize the relationship between tau, measured by [18F]GTP1 PET, and β-amyloid, measured by Amyvid PET, with cognitive measures at baseline in AD subjects, focusing both on global neurocognitive measures and on indices of specific cognitive domains. *Methods:* [18F]GTP1 images and neurocognitive measures (MMSE, ADAS-Cog13, RBANS, CDR-SB) were collected as part of an ongoing natural history study from Amyvid-positive AD subjects (aged 50-85), classified by clinical severity as prodromal (MMSE 24-30, CDR = 0.5), mild (MMSE 22-30, CDR 0.5 or 1) or moderate (MMSE 16-21, CDR 0.5 or 1 or 2). [18F]GTP1 SUVR images were acquired over a 30-minute window starting 60 minutes post-injection, using the cerebellar gray as reference. We evaluated cross-sectional associations among overall tau pathology burden (mean [18F]GTP1 SUVR across the cortical mantle: WCG – whole cortical gray), overall β-amyloid burden (composite Amyvid SUVR), and performance on the neurocognitive measures, for 44 AD subjects at the screening/baseline visits. Using Spearman partial correlations, relationships of cognitive performance with burden for one proteinopathy (tau/β-amyloid) were further explored after adjusting for associations with burden for the second proteinopathy (β-amyloid/tau). *Results:* Spearman correlations between WCG [18F]GTP1 SUVR and neurocognitive measures were small to moderate (MMSE: r = -0.28, ADAS-Cog13: r = 0.44, RBANS Total: r = -0.52, CDR-SB r = 0.33), and consistently greater in magnitude than correlations between composite Amyvid SUVR and the same neurocognitive measures (MMSE: r = -0.22, ADAS-Cog13: r = 0.23, RBANS Total: r = -0.37, CDR-SB: r = 0.21). Spearman correlations were also moderate between WCG [18F]GTP1 SUVR and four of the five RBANS domain-level indices (Attention: r = -0.56, Language: r = -0.56, Immediate Memory: r = -0.44, Visuospatial/Constructional: r=-0.42), again consistently greater in magnitude than the same correlations with composite Amyvid SUVR (Attention: r = -0.45, Language: r =-0.35, Immediate Memory: r = -0.22, Visuospatial/Constructional: r=-0.33). Notably, the RBANS Delayed Memory index was not as well correlated with WCG [18F]GTP1 SUVR (r = -0.19) or with composite Amyvid SUVR (r = -0.09). In all reported Spearman correlations, WCG [18F]GTP1 SUVR explained 1.6-4.5 times as much of the variance on neurocognitive measures as did composite Amyvid SUVR. Spearman partial correlations between WCG [18F]GTP1 SUVR and several neurocognitive measures, adjusted for associations with composite Amyvid SUVR, were nominally statistically significant ($p<0.05$; RBANS Language: rp= 0.34), or approached nominal significance ($p<0.10$; RBANS Immediate Memory: rp= 0.30, RBANS Total: rp= 0.29, ADAS-Cog13: rp= 0.29, RBANS Attention: rp= 0.28). No Spearman partial correlations were found at the same nominal significance levels between composite Amyvid SUVR and the neurocognitive measures, after adjustment for associations with WCG

[18F]GTP1 SUVR (all such rp's were < 0.10 in magnitude). P-values were not adjusted for multiple comparisons. Regional analyses of [18F]GTP1 SUVR signal and their relationship with various cognitive measures will also be presented. *Conclusion:* In this cross-sectional study, the observed pattern of Spearman correlations and partial correlations suggests a greater utility of [18F]GTP1 PET imaging relative to Amyvid PET imaging as a biomarker correlate of cognitive performance, using both broad cognitive measures and domain-specific measures. Results from this study will help characterize the utility of [18F]GTP1 tau PET imaging in predicting cognitive performance, and will also help to discern the relationships between β-amyloid, tau, and cognition in AD.

LBP36: RETINAL HYPERSPECTRAL IMAGING FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE. Swati S. More, James M. Beach, Robert Vince *(Center for Drug Design, Academic Health Center, University of Minnesota, Minneapolis, MN)*

Background: While it is universally accepted that therapeutic intervention has the greatest effect on Alzheimer's disease (AD) when placed early in the disease course, there exists no technique to detect such a stage! Consequently, it is impossible to develop effective therapies targeting these early stages. Such events begin years to decades before clinical symptoms are perceived. Current diagnostic tests are expensive (PET, MRI), invasive (CSF biomarker sampling) and insufficiently predictive (genetic markers or serum amyloid load). The retina is the only part of the central nervous system that can be accessed non-invasively. AD pathology presents in the retina far before clinical symptomology. Our hyperspectral retinal imaging (HSI) technique targets this phenomenon and thus holds the promise to detect amyloidopathy in the early AD stages. The technique relies on Rayleigh spectral signature which is expected from small Aβ aggregates present in early pathogenesis, and gives opportunity to detect early disease in a truly non-invasive manner, with no need for application of exogenous label before testing; thus suitable for mass population screening. We have successfully established the use of this technique in mice, and are currently in the last stages of evaluation in a small scale human clinical trial. *Methods:* Subjects were recruited from patients being seen at the University of Minnesota Eye Clinic and from referrals from the FIT-AD Alzheimer's study at the University School of Nursing. Following a dilated eye examination, volunteers with severe retinopathies and glaucoma were excluded from further study. Individuals with pathologies that do not alter fundus reflectance properties, and with minor-to-moderate cataract, were included as a disease subcategory. Subjects with skin pigmentation indices of 2 or 3 on the Fitzpatrick scale were included in the present study. Twelve normal subjects (N, mean age 67 years) and nineteen Alzheimer's disease subjects (AD, mean age 77 years) are included in this report. Spectral reflectance (400 - 1000 nm) was obtained from different retinal areas (optic disc, regions of thick nerve fiber superior and inferior to the disc, the perifoveum, and peripheral retina) with a spatial-spectral imaging system mated to a clinical fundus camera. A second conventional camera documented each area probed by spectroscopy. After conversion to relative absorption units, spectral means from the different retinal areas (normal group) established baselines for comparison with spectra from different categories of AD, including subgroups with different minimum MMSE score, younger versus older subjects, and the inclusion or exclusion of minor retinal pathologies. Higher levels of amyloid aggregation in AD groups was indicated if light extinction over the blue spectral range (420 - 520) exceeded the baseline value. *Results:* We have successfully translated the retinal HSI technique to human AD subjects. There are no side effects or complications reported to date in this study. Both study groups adhered to 2 - 3 on Fitzpatrick scale, thus limiting effect of pigmentation differences. This technique has provided a strong spectral signature in the early stages of the disease (MMSE > 20), offering a tool for diagnosis before any clinical symptoms. Optical marker for amyloid aggregation is the spectral signature of Rayleigh light scatter from the small Aβ aggregation cross-section, which gives progressively greater isotropic scattering efficiency at shorter wavelengths, and an apparent increase in relative light extinction in blue wavelengths. The amyloid signature observed is unaffected by eye pathology such as parapapillary atrophy, cataract, etc. Presence of macular degeneration did not affect light scattering from the rest of the retina. Spectral signatures were reduced 2x in subjects 75 years or older, where confounding factors of older age may influence the detection of amyloidopathy. In subjects aged 60 to 75 years minor retinal pathology did not significantly reduce the signature. *Conclusion:* While AD cannot yet be treated with the intent to cure, sufficiently early diagnosis with retinal HSI will facilitate intervention with available therapeutics, adding years of productive, quality time to the patient's lifespan. The retinal HSI technique we have developed has shown promise in our small scale human trial for early AD detection. Such a tool could be valuable for high-risk AD individuals by starting frequent monitoring at an early age, thus acting as their own controls. Longitudinal study with larger cohort is warranted for successful clinical translation of this technique. This will also provide an opportunity to examine the utility of this technique for monitoring treatment outcome.

LBP37: SIMPLIFIED NON-INVASIVE TRACER KINETIC ANALYSIS FOR 18F-FLORBETABEN PET USING A DUAL TIME-WINDOW ACQUISITION PROTOCOL. Andrew W. Stephens[1], Henryk Barthel[2], Santiago Bullich[1], Norman Koglin[1], Georg A. Becker[2], Aleksandar Jovalekic[1], Susan De Santi[3], Osama Sabri[2] *((1) Piramal Imaging GmbH, Berlin, Germany; (2) Department of Nuclear Medicine, University Hospital Leipzig, Leipzig, Germany; (3) Piramal Pharma Inc., Boston, MA, USA)*

Background: Accurate quantitation of amyloid-beta (Aß) plaque load using positron-emission-tomography (PET) is important for monitoring disease in longitudinal studies, especially in response to therapy in interventional trials of Aß-modifying treatments for Alzheimer's disease (AD). The amount of Aß load in the brain is commonly assessed with PET imaging by means of standardized uptake value ratios (SUVRs) because of their simplicity. While an SUVR-based approach is found to be suitable to estimate amyloid deposition in most clinical research settings, this method might be influenced by changes in radiotracer clearance or cerebral blood flow (CBF) and could introduce a bias. This can be especially relevant in interventional trials where the effects of Aß-modifying drugs on CBF and radiotracer clearance are currently unknown. Full tracer kinetic analysis is not biased but has the disadvantage of requiring arterial blood sampling and long dynamic image acquisition. The objectives of this work were: (1) to validate a non-invasive kinetic modeling method for 18F-florbetaben PET using a simplified acquisition protocol with the best compromise between quantification accuracy and simplicity and (2) to assess the influence of CBF changes and radiotracer clearance on SUVRs and non-invasive kinetic modeling data in 18F-florbetaben PET. *Methods:* Data from twenty subjects (10 patients with mild to moderate AD based on clinical diagnosis and 10 age-matched healthy volunteers) scanned dynamically for 140 min were used. Arterial samples were collected during scanning and corrected for metabolites. The binding potential (BPND) obtained from the full kinetic analysis was compared to the SUVR and to non-

invasive tracer kinetic methods (simplified reference tissue model (SRTM), and multilinear reference tissue model (MRTM2)). Different approaches using shortened or interrupted acquisitions were compared to the results of the invasive full acquisition (0-140 min) modeling approach. Simulations were carried out to assess the effect of CBF and radiotracer clearance changes on SUVRs and non-invasive kinetic modeling outputs. *Results:* A 0-30 and 120-140 min dual time-window acquisition protocol provided the best compromise between patient comfort and quantification accuracy. By that, excellent agreement was found between BPND obtained using full and two time-window (2TW) acquisition protocols (BPND,2TW= 0.01+ 1.00xBPND,FULL, R2=0.97 (MRTM2); BPND,2TW= 0.05+ 0.92xBPND,FULL, R2=0.93 (SRTM)). Simulations showed a limited impact of CBF and radiotracer clearance changes on MRTM parameters and SUVRs. *Conclusion:* This study demonstrates accurate non-invasive kinetic modeling of 18F-florbetaben PET data using a simplified dual time-window dynamic acquisition protocol, thus providing a good compromise between quantification accuracy, scan duration and patient burden. In many research applications Aß load can be appropriately classified using SUVR methods at pseudo-equilibrium. However, in some cases, where maximum quantification accuracy is needed, a dynamic scan protocol may be beneficial. The current study provides a useful, pragmatic protocol to test the importance of dynamic scanning.

LBP38: VOXEL-WISE DETERMINATION OF THRESHOLDS FOR AMYLOID AND TAU POSITIVITY USING PET MAY IMPROVE THE POPULATION ENRICHMENT OF CLINICAL TRIALS. Tharick A. Pascoal[1,2,3], Sulantha Mathotaarachchi[1], Min Su Kang[1,2,3], Joseph Ththerriault[1], Monica Shin[1], Andrea L. Benedet[1,2,3], Sara Mohades[1], Jean-Paul Soucy[3,4], Serge Gauthie[1], Pedro Rosa-Neto[1,2,3] for the Alzheimer's Disease Neuroimaging Initiative *((1) Translational Neuroimaging Laboratory, The McGill University Research Centre for Studies in Aging, Alzheimer's Disease Research Unit, Douglas Hospital, McGill University, Montreal, Canada; (2) Department of Neurology and Neurosurgery, McGill University, Montreal, Canada; (3) Montreal Neurological Institute, Montreal, Canada; (4) PERFORM Centre, Concordia University, Montreal, Canada)*

Objective: Although the hallmark proteins of Alzheimer's disease (AD), amyloid-β (Aβ) and tau, accumulate in a continuum, dichotomization of individuals into 'positive' or 'negative' group using a global value is necessary to the enrich of clinical trials. In this regard, studies have focused in optimize these thresholds to screening individuals with high probability of disease progression in a constant trade-off between sensitivity and specificity. However, regardless of the technique used to dichotomize, individuals with similar protein burden across the whole cortex will invariably have the same classification. Here, we aimed to test whether the assessment of proteins positivity at every brain voxel have the potential to provide complementary information, at individual level, to track individuals on an AD pathway. *Methods:* We imaged 15 cognitively normal elderlies (CN) and 20 AD individual with [18F]NAV4694 Aβ PET and [18F] MK6240 tau PET imaging. Also, we assessed 211 CN, 311 mild cognitive impairment (MCI), and 79 AD from Alzheimer's disease neuroimaging initiative (ADNI) who underwent [18F]florbetapir PET at baseline as well as clinical assessment at baseline and at 2 years. In order to obtain parametrical maps with thresholds for protein's positivity, we performed a voxel-wise receiver operating characteristic curves (ROC) analysis, contrasting controls with AD individuals. The thresholds at every voxel were assumed with the least distance from point to the curve, which provided the protein load values with the best trade-off between sensitivity and specificity for AD. Additionally, parametric maps of Aβ positivity at every voxel were generated with the thresholds obtained contrasting, using [18F]florbetapir, CN and AD for each MCI individual. *Results:* We found a wide range of Aβ thresholds to a diagnostic of AD across the brain cortex for both [18F] NAV4694 and [18F]florbetapir ligands (Figure 1A and 2B). For the aforementioned Aβ PET ligands, sensitivity and specificity for these thresholds reached 95% in voxels in the precuneus, posterior cingulate, medial prefrontal, lateral temporal, and putamen, whereas the lowest values were found in the medial temporal lobe (Figure 1C,D and 2C,D). [18F]MK6240 had the highest threshold values in the mediobasal temporal structures, with a high area under the curve across most of the brain cortex (Figure 3). In the Figure 4, two representative cases, a MCI progressor (Fig. 4.A) with a global mean [18F]florbetapir SUVR of 1.17 (male, 79 y.o, APOE ε4 negative, MMSE = 28), and a nonprogressor (Fig. 4.B) with a global mean [18F]florbetapir SUVR of 1.22 (male, 69 y.o, APOE ε4 positive, MMSE = 29). The progressor had Aβ positivity in the precuneus, posterior cingulate, inferior parietal and left temporal cortices, whereas the nonprogressor had Aβ positivity in superior frontal gyrus and anterior cingulate cortices. In addition, probabilistic maps showed that MCIs global amyloid positive nonprogressors (Figure 4D) (global SUVR (mean) = 1.33 (0.1)) had higher positivity in voxels manly in anterior cingulate, whereas MCI progressors (global SUVR (mean) = 1.36 (0.14)) reached 100% of positivity in clusters in the posterior cingulate, precuneus, frontal and temporal cortices (Fig. 4C). *Conclusion:* We found that MCIs Aβ positive progressors and nonprogressors had similar global Aβ load but different patterns of Aβ positivity across the brain cortex. These results highlight that the analysis of Aβ positivity at every voxel might provide important information, overlooked by averaged composites regions, regarding the regional patterns of Aβ abnormality associated with the highest probability of clinical progression to dementia. I addition, in a preliminary baseline analysis, we have shown that the analysis of tau positivity at every brain voxel has the potential to better select among the tau positive individuals the ones with a pattern of protein accumulation that are morel likely to progress.

Figure 1

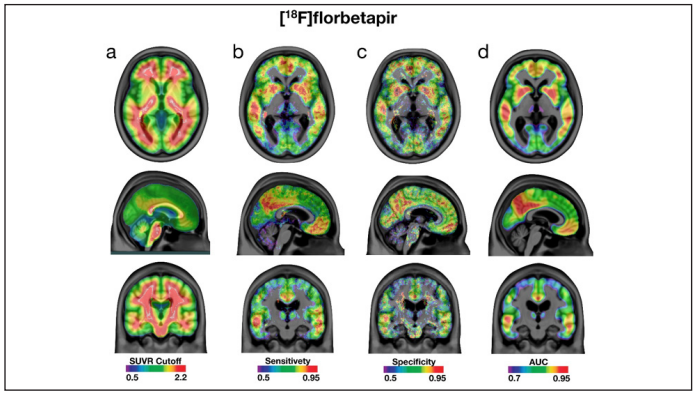


Figure 2

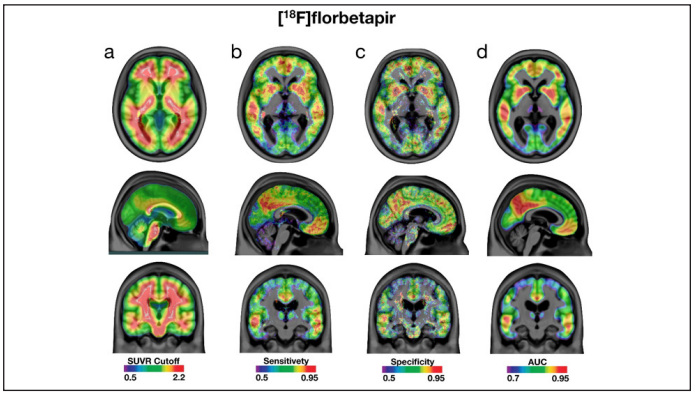


Figure 3

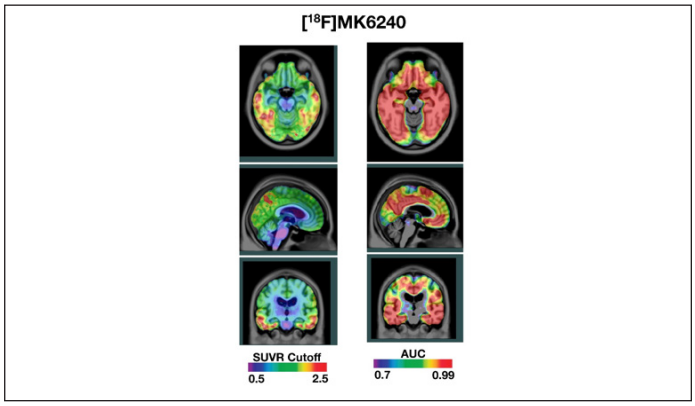
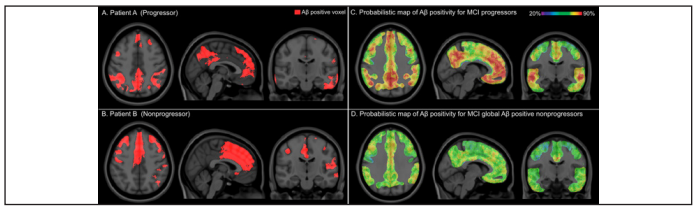


Figure 4



Theme: Clinical trials : biomarkers including plasma

LBP39: NEUROIMAGING MARKERS OF CEREBROVASCULAR DISEASE PREDICT COGNITIVE IMPAIRMENT, BRAIN ATROPHY AND DEMENTIA IN A COHORT OF COMMUNITY DWELLING ELDERS. Tammy M. Scott[1,2], Rafeeque A. Bhadelia[3], Irwin H. Rosenberg[1,2] *((1) Jean Mayer USDA Human Nutrition Research Center on Aging; (2) Friedman School of Nutrition Science and Policy; 3Harvard Medical School)*

Background: Individuals at high risk for vascular disease are also at greater risk for cognitive decline. Where memory loss is often the first clinical indication of Alzheimer's disease, loss of executive function may be a marker for vascular cognitive impairment or dementia. Since cerebral hypoperfusion and microvascular abnormalities precede cognitive and neurodegenerative changes, we have argued that non-hereditary Alzheimer's disease has significant cerebrovascular etiopathogenesis. Better understanding of potentially modifiable risk factors for vascular disease can aid in developing long-term intervention strategies for controlling or preventing the cognitive dysfunction attributable to cerebrovascular disease. The purpose of this study was to evaluate the relationship of cerebrovascular pathology on MRI and cognition, and to determine whether these associations differ according to sub-types of cerebrovascular disease. *Method:* Analyses included a subset of the Nutrition, Aging, and Memory in Elders (NAME) cohort who had undergone magnetic resonance imaging (MRI) and cognitive testing. The study cohort consisted of community-based elders age 60 years and older. Magnetic resonance images were obtained on a 1.5T Symphony Siemens' scanner. A board-certified neuroradiologist, blinded to other data, assessed the images for small and large vessel infarcts (SVI and LVI, respectively) and white matter hyperintensity (WMHI) severity and location (periventricular pvWMHI, and subcortical svWHMI). Sulcal, ventricular, and hippocampal atrophy was also rated. The neuropsychological test battery was designed to assess multiple cognitive domains. Principal components analysis of the cognitive tests was used to derive composite scores for use in subsequent data analyses. The resulting three components were interpreted as measuring memory, attention, and executive function. Consensus diagnosis of dementia was made by the study psychiatrist, neuropsychologist, neurologist and neuroradiologist. Prevalence of neuroimaging markers of cerebrovascular disease was established and the relationship between LVI, SVI and WMHI was tested using chi-square and logistic regression. Kruskal-Wallis H test was used to evaluate the relationship between cerebrovascular variables and brain atrophy, and Pearson Chi-Square for the relationship with dementia diagnosis. Analysis of covariance was used to assess the relationship between neuroimaging markers and cognition. Unless otherwise indicated, all parametric analyses were adjusted for age, sex, education level, race (black/not black), diabetes, hypertension, and serum creatinine level. *Results:* Relationship between neuroimaging markers of cerebrovascular disease: Individuals with SVI were more likely than those without to have concomitant pvWMHI (OR 3.22, 95% CI 1.69-6.13). There was no statistically significant association between pvWMHI and LVI (OR 1.46, 95% CI 0.66-3.24). There was no association between scWMHI and SVI or LVI. Within those individuals without evidence of either small or large vessel infarct, there was an equal distribution of pvWMHI and scWMHI, with 32.8% having primarily pvWMHI, 27.9% having primarily scWMHI, and 15.2% having a combination of both pvWMHI and scWMHI. Vascular pathology and cognition: The presence of LVI on MRI was associated with lower executive function (mean difference = 0.531 standard deviation, SE ±0.168; P=0.002) and better memory (mean difference = 0.350 standard deviation, SE ±0.169; P=0.040) scores. The presence of SVI was significantly associated with lower memory scores only (mean difference= 0.268 standard deviations, SE ±0.132; P=0.042), but with trends for lower executive function and attention (mean differences of 0.239 and 0.256 standard deviations respectively, P<0.10). Presence of pvWMHI was associated with lower executive function scores (mean difference=0.285 standard deviations, SE ±0.105; P=0.007); scWMHI was not associated with cognitive function in this study population. These relationships did not change after further adjustment for presence of large and small vessel infarcts. Brain atrophy grade was inversely related to executive function score (r=-0.182, P=0.002), and hippocampal atrophy grade was inversely associated with both memory (r=-0.274, P=0.001) and executive function scores (r= -0.166; P=0.004). Cerebrovascular disease, brain atrophy and dementia diagnosis: Those individuals with vascular MRI findings (SVI, LVI and/or pvWMHI) had significantly greater degrees of ventricular, sulcal, and hippocampal atrophy than did those without (X2(2)=43.4, 30.6, and 20.3, respectively; P=.0001 for all), and were more likely to have been diagnosed with dementia

(X2 10.4, P=.001). *Conclusion:* Our findings show a significant relationship between neuroimaging markers of cerebrovascular disease and cognitive impairment and dementia diagnosis. There was also a significant overlap between cerebrovascular disease and sulcal, ventricular, and hippocampal atrophy. While current research on Alzheimer's disease has focused on beta-amyloid deposition, tau-pathology, cell death of cholinergic neurons and microglial activation and inflammation, greater attention to the cerebrovascular contribution to this neurodegenerative disease may present an additional target for therapeutic intervention.

LBP40: MEASUREMENT OF THE KINETIC BEHAVIOR OF NEWLY GENERATED BACE1-CLEAVED APP IN THE HUMAN CENTRAL NERVOUS SYSTEM IN ALZHEIMER'S DISEASE: INITIAL PROOF-OF-CONCEPT. Robert J. Vassar[1], Randall J. Bateman[2], Bruce W. Patterson[3], Justyna A. Dobrowolska Zakaria[1] *((1) Department of Cell & Molecular Biology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; (2) Department of Neurology, Washington University in St. Louis, St. Louis, MO, USA; (3) Department of Medicine, Washington University in St. Louis, St. Louis, MO, USA)*

Background: The amyloid hypothesis proposes that increased production and/or decreased clearance of amyloid-beta (Aβ) leads to higher order amyloid structures that initiate a cascade of events, culminating in neuronal death that manifests as Alzheimer's disease (AD). Sequential cleavage of Amyloid Precursor Protein (APP) generates Aβ. APP may be processed in one of at least two pathways, initially being cleaved by either α- or β-secretase (BACE1). α-secretase cleavage of APP precludes Aβ formation and produces soluble APP-α (sAPPα). Alternatively, BACE1 cleavage of APP releases soluble APP-β (sAPPβ) and subsequent cleavage by γ-secretase produces Aβ. Therefore, while sAPPβ is a direct product of BACE1 cleavage of APP, Aβ is an indirect product of BACE1 processing that also requires γ-secretase activity. Nevertheless, BACE1 processing of APP is an obligate initial step in Aβ production, and sAPPβ is a surrogate marker of BACE1 activity. In some studies BACE1 and sAPPβ are increased in cerebrospinal fluid (CSF) and post-mortem AD brain. Our previous data demonstrate an increase in CSF sAPPβ: sAPPα ratio in AD subjects versus age-matched controls, indicating a pathophysiological shift toward BACE1 processing of APP. Further, sAPPβ and Aβ concentrations are highly positively correlated in human CSF, but sAPPα and Aβ correlate less well, which suggests BACE1 activity mediates both sAPPβ and Aβ differences among people. In brains of postmortem AD and amyloid mouse models, we have shown that BACE1 levels are dramatically increased in dystrophic neurites surrounding amyloid plaques, which exhibit increased BACE1 cleavage of APP and the generation of both sAPPβ and Aβ. Recently it was shown that CSF Aβ38 and Aβ40, as surrogate markers of Aβ production, were elevated in humans with amyloid deposition. Moreover, the correlation between Aβ38 and Aβ40 and amyloid load was most pronounced in subjects negative for ApoE4. Since ApoE4 reduces Aβ clearance, the correlation between Aβ38 and Aβ40 and amyloid load in ApoE4 negative subjects indicates a subgroup of individuals in which the mechanism of Aβ accumulation is not simply due to decreased clearance. Together these findings suggest increased BACE1 activity may cause increased Aβ in an AD subpopulation, but has not been directly assessed until now. *Methods:* Using highly sensitive stable isotope labeling kinetics (SILK)/immunoprecipitation (IP)/liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods, we quantified sAPPβ and sAPPα in CSF from human AD subjects and controls to determine β- and α-secretase activity in human CNS. In this proof-of-concept study, newly generated sAPPβ and sAPPα were measured in six elderly human subjects who had undergone [U-13C6]leucine labeling and hourly CSF collection over 36 hours. Two of the subjects had brain amyloidosis (Amyloid+), and the remaining four were free of amyloid (Amyloid-). Serially-sampled CSF underwent sequential IP to isolate sAPPβ (using a neo-epitope sAPPβ-specific antibody-bead complex) and then sAPPα (using a W02-antibody bead complex). Peptides resulting from tryptic digest of the purified sAPPβ or sAPPα were quantified by LC-MS/MS using the Dionex UltiMate 3000/TSQ Quantum Ultra system. To determine kinetic behavior of APP metabolites, the fraction of the metabolite derived from de novo synthesis was measured by calculating hourly sAPPβ and sAPPα mole fraction labeled (MFL), normalized to plasma leucine enrichment, over 36 hours. In order to determine each subject's newly generated APP metabolites by absolute quantitation, normalized sAPPβ or sAPPα MFL was multiplied by the absolute concentration of sAPPβ or sAPPα, respectively. Absolute concentrations were previously determined by sAPPβ and sAPPα specific ELISAs. *Results:* Both sAPPβ and sAPPα turnover rates were slower in Amyloid+ subjects. There was a slight upslope of the ratio of newly generated sAPPβ:sAPPα in the Amyloid+ subjects (slope, m=0.018) which was significantly higher than the Amyloid- group (m=0.012; p=0.02); both slopes were significantly non-zero ($p<0.0001$). This indicates that sAPPβ turnover rate is marginally slower than sAPPα, and this difference is accentuated in the setting of amyloid deposition. Newly generated sAPPβ, as well as the absolute ratio of newly generated sAPPβ:sAPPα, were significantly elevated in Amyloid+ subjects ($p<0.0001$). In contrast, newly generated sAPPα was not significantly different between groups. Importantly, these results strongly suggest increased processing of APP by BACE1 in the subjects with brain amyloid deposition. *Conclusion:* We will next expand this proof-of-concept study to include a larger sample size. We hypothesize that most AD patients overproduce Aβ due to increased BACE1 activity as measured by increased absolute production of sAPPβ. By directly measuring the kinetics and newly generated sAPPβ in vivo, we are determining if, and by how much, BACE1 activity is increased in AD subjects. These results would allow for characterization of AD subpopulations most likely to benefit from BACE1 inhibitors. Outcomes will elucidate human CNS APP physiology and AD pathophysiology and also prove useful for measuring pharmacodynamic effects of candidate therapeutics. BACE1 is currently a high priority target for AD, thus results of altered BACE1 activity in AD are critical for understanding AD pathophysiology and development of disease modifying therapeutics.

LBP41: HIGH SERUM LEVELS OF MALONDIALDEHYDE AND 8-OHDG ARE BOTH ASSOCIATED WITH EARLY COGNITIVE IMPAIRMENT IN PATIENTS WITH ACUTE ISCHEMIC STROKE. Jincai He, Zhihua Liu, Yuntao Liu, Xinjie Tu, Huiping Shen, Huihua Qiu, Huijun Chen *(Department of Neurology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China)*

Backgrounds: Post-stroke cognitive impairment (PSCI) is an increasing prevalent sequel after stroke that may associates with poor functional outcome and increased risk of recurrent stroke. However, traditional known risk factors of PSCI including older age, sex differences and previous history of stroke are not readily amenable to treatment. Increasing evidence has demonstrated the vital role of oxidative stress pathways in the regulation of cognitive impairment related process. We aimed to explore the relationship between oxidative stress biomarkers and the presence of PSCI. *Methods:* 193 first-ever acute ischemic stroke patients were consecutively

enrolled in the current study. Oxidative stress biomarkers such as malondialdehyde (MDA) and 8-hydroxydeoxyquanosine (8-OHdG) were measured within 24h after admission. Cognition function was evaluated by the Mini-Mental State Examination (MMSE) at 1 month after stroke. PSCI was defined by MMSE score ≤17 points (illiterate), ≤20 points (education level of primary school), or ≤24 points (education level of secondary school or above) respectively. Moreover, PSCI must be judged to be the consequence of stroke. *Results:* Serum levels of 8-OHdG and MDA were both significantly higher in the PSCI ($p < 0.001$) compared with the non-PSCI group. Both of serum 8-OHdG and MDA levels negatively correlated MMSE score. We found that both 8-OHdG and MDA had good diagnostic accuracy for PSCI .ROC curve analysis was used to evaluate the usefulness of 8-OHdG to discriminate the presence of cognitive impairment and showed an area under curve (AUC) value of 0.700 (95% CI, 0.626-0.773; $p<0.001$), and the optimal cut-off value for 8-OHdG as a diagnostic marker of stroke was 185.63 ng/L, which yielded a sensitivity of 68.3% and a specificity of 67.4%. The AUC value for MDA in discriminating the patients with cognitive impairment from the non-PSCI group was 0.793 (95% CI, 0.731-0.856; $p < 0.001$). The optimal cut-off for MDA was 2.59 nmol/ml, which showed a sensitivity of 83.2% and a specificity of 62.0%. Moreover, the combined model (8-OHdG and MDA) showed greater discriminatory ability (AUC, 0.826; 95% CI, 0.769-0.883; $p < 0.001$) than either factor alone. After adjusting for age, sex, BMI, hypertension, diabetes mellitus, CAD, hyperlipidemia, smoking, drinking, BI score, NIHSS score, PSQI score, HAMD score, drug use, higher 8-OHdG levels also independently predicted a cognitive impairment in the 4th week after IS (adjusted OR=1.014, 95%CI (1.007-1.020), $p<0.001$). Similarly, higher MDA level also were independently associated with PSCI after controlling the same confounding variables mentioned above (adjusted odds ratio [95% confidence interval], 2.985 (1.990-4.478), $p<0.001$). Moreover, in multivariate analysis, there was an increased risk of PSCI associated with serum 8-OHdG levels above the cut-off (185.63 ng/L) after adjustment for the above variables (adjusted OR6.261, 95%CI2.766-14.176, $p<0.001$). And serum MDA levels above the cut-off (2.59 nmol/ml) also increased the adjusted OR (OR [95% CI], 14.130 [5.250, 38.032], $p < 0.001$) after adjustment for the same variables. *Conclusion:* High serum levels of malondialdehyde and 8-OHdG are associated with the presence of PSCI at 1 month after stroke.

LBP42: ANALYTICAL PERFORMANCE OF THE LUMIPULSE® G B-AMYLOID1-42 ASSAY: MEASUREMENT OF WITHIN-LAB PRECISION AND CSF SAMPLE STABILITY. Robert A. Rissman[1], Louise Monte[1], Floyd Sarsoza[1], Amanze Orusakwe[2], Manu Vandijck[3], Ryan Gailey[4], John Lawson[2], CJ Traynham[2], Zivjena Vucetic[2] *((1) Department of Neurosciences, University of California, San Diego, School of Medicine; (2) Fujirebio Diagnostics, Malvern, PA, USA; (3) Fujirebio Europe NV, Ghent, Belgium; (4) Fujirebio US, Malvern, PA USA)*

Background: Alzheimer's disease (AD) is a debilitating disease that will only increase in incidence as the aging population continues to grow. At present, the only definitive method to diagnose AD is post-mortem autopsy. As a result, there is a clear unmet clinical need with respect to a reliable AD detection method in the at-risk patient population. Cerebrospinal-fluid (CSF) biomarkers such as Amyloid β 1-42 (Aβ1-42) have shown promise as potential biomarkers for early detection of AD in living individuals, but are known to have several assay-dependent limitations. To improve analytical performance of these assays, significant effort has been made to advance manual assay platforms towards automation. In the present study, analytical performance of one such automated platform, the Lumipulse G β-Amyloid 1-42, assay was evaluated. *Methods:* Patient pools were generated for 3 CSF levels: CSF Low Pool ≈ 350-450 pg/mL Aβ1-42, CSF Medium Pool ≈ 750-850 pg/mL Aβ1-42, and CSF High Pool ≈ 1100 pg/mL Aβ1-42. Studies were performed on the aforementioned pooled human CSF samples (CSF- Low, CSF-Medium, CSF-High), and 3 control samples provided within the Lumipulse β-Amyloid 1-42 Controls kit. In total, three studies were performed. Study A evaluated run-to-run variation over 3 days of testing (days 1, 3 and 6) in the 3 CSF pools with samples run in duplicate. Study B investigated the effect of freeze-thaw cycles on CSF sample stability. The 3 CSF pools were subjected to 1, 2 and 3 freeze-thaw cycles with samples run in triplicate over multiple days. Lastly, Study C evaluated run-to-run variation weekly for 4 weeks in the 3 controls provided in Lumipulse β-Amyloid 1-42 Controls kit. The controls were run on the same day each week in duplicate with a new vial of each control level reconstituted each week. Repeatability (within-run), between-day, and total (within laboratory) precision were calculated using the Analyse-IT program for Studies A and C. Study B evaluated the percent change in Aβ 1-42 concentration relative to baseline (i.e. unfrozen CSF) after these samples underwent freeze-thaw cycles. *Results:* In Study A, within-run, between-day, and total precision were as follows for the 3 CSF samples: (CSF Low: ≤ 2.2%, 0.8%, 2.3%; CSF Medium: ≤ 1.3%, 1.6%, 2.1%; and CSF High: ≤ 2.1%, 2.6%, 3.4%, respectively). Study B evaluated the percentage of Aβ 1-42 lost in each sample post- freeze-thaw relative to baseline CSF levels. This study revealed that Aβ1-42 levels were relatively stable up to 3 freeze-thaw cycles in the 3 CSF samples (CSF Low: ≥ -5.7%, CSF Medium: ≥ -8.0%, CSF High: ≥ -6.8%). Lastly, Precision was evaluated in the 3 controls provided in the Lumipulse β-amyloid 1-42 Controls kit with within-run, between-day, and total precision as follows: (Level 1: ≤ 2.0%, 1.7%, 2.6%; Level 2: ≤ 1.9%, 1.1%, 2.2%; and Level 3: ≤1.6%, 0.0%, 1.6%, respectively). *Conclusions:* The present work demonstrates the automated Lumipulse G β-Amyloid 1-42 assay reliably quantifies Aβ 1-42 CSF levels with a high degree of precision. Further, Aβ1-42 levels are stable through 3 freeze-thaw cycles on the Lumipulse G β-Amyloid 1-42 assay. These results suggest automated assays such as the Lumipulse G β–Amyloid 1-42 will prove vital in the continuing effort to improve methods of AD detection. Acknowledgements: This project was funded by a Fujirebio US, Inc, contract to RAR using UCSD ADRC Neuropathology and ADCS Biomarker Core infrastructure funded to RAR by NIH grants AG10483 and AG005131

LBP43: UTILITY OF EVENT RELATED POTENTIALS IN A MEMORY DISORDERS CLINIC. Katherine Turk[1,2], Cheongmin Suh[1], Prayerna Uppal[1], August Price[1,3], Ala'a El-Shaar[1], Andrew E. Budson[1,2] *((1) Center for Translational and Cognitive Neuroscience, VA Boston Heathcare System; (2) Department of Neurology, Boston University School of Medicine (3) William James College)*

Background: Early and accurate diagnosis of Alzheimer's disease (AD) remains central to studying the pathophysiology of AD and to clinical trials aimed at altering disease course. Event-related potentials (ERPs), a type of quantitative electroencephalogram (EEG), are a potential biomarker of AD. Altered ERP signals have been demonstrated in the progression and subsequent conversion to dementia in mild cognitive impairment (MCI) (Papaliagkas, 2011), and have also been detected in presymptomatic individuals (Quiroz et al., 2011). Although ERPs have the potential to be sensitive biomarkers with low cost and low invasiveness, the promise of this technique in clinical practice has not yet been fully realized. *Methods:* Thirty-eight subjects who presented with memory loss underwent standard clinical workup including history and physical,

neuroimaging, laboratory studies, and a neuropsychological battery, leading to a clinical diagnosis. All subjects consented to an ERP session using a three-tone auditory oddball paradigm with a seven-electrode device. ERP results were reviewed by two behavioral neurologists blinded to the clinical details of each subject. Amplitude and latency of ERP peaks were rated in the AD or healthy older adult range (Cecchi et al 2015). The total sum of the number of peaks in the diseased range was computed and a diagnostic rating was made for each ERP study as consistent with MCI due to AD, mild AD, moderate AD, or inconsistent with AD. *Results:* Spearman's correlation showed that the total number of ERP peaks that fell into the mild AD range correlated inversely with Montreal Cognitive Assessment (MOCA); correlation coefficient of -.535 and p-value of .001. *Conclusions:* These results validate the clinical utility of ERPs in general and the specific ERP review method used, showing that it correlates well with screening measures of cognitive decline. Future analyses can evaluate whether ERPs can reliably distinguish between AD and other neurodegenerative conditions, and also how ERPs compare to other AD biomarkers including amyloid PET scans and quantitative MRI cortical volume measurements. 1. M. Cecchi et al., A clinical trial to validate event-related potential markers of Alzheimer's disease in outpatient settings. Alzheimers Dement (Amst) 1, 387-394 (2015). 2. V. T. Papaliagkas, V. K. Kimiskidis, M. N. Tsolaki, G. Anogianakis, Cognitive event-related potentials: longitudinal changes in mild cognitive impairment. Clin Neurophysiol 122, 1322-1326 (2011). 3. Y. T. Quiroz et al., Event-related potential markers of brain changes in preclinical familial Alzheimer disease. Neurology 77, 469-475 (2011).

LBP44: ANALYSIS OF SEX/GENOTYPE INTERACTIONS IN BASELINE EXPEDITION3 DATA. Valerie Bruemmer, Helen M Hochstetler, Melissa Anna Maria Pugh, Sara Kollack-Walker *(Eli Lilly and Company, Indianapolis, IN, USA)*

Background: There is evidence that men and women experience the clinical continuum of Alzheimer's disease (AD) differently and may have varying levels and types of comorbidity that affect the course of the disease. Although clinical trials are carefully randomized to match numbers of men and women in placebo and treatment arms, additional information may be revealed by assessing by looking at study cohort baseline differences between these two groups. There is increasing interest in understanding sex-specific variation in clinical symptoms (cognitive, behavioral and functional), underlying brain pathophysiology, and the role of comorbidity and risk factors in AD. This study examines sex-specific characteristics of participants in the EXPEDITION3 clinical trial baseline cohort. *Methods:* EXPEDITION3 was a multicenter, global AD treatment study that included more than 2000 participants 55 to 99 years of age who met diagnostic criteria for probable AD from the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ARDA). Participants had mild AD dementia (baseline Mini-Mental State Examination [MMSE]: 20-26) with evidence of amyloid pathology by either florbetapir positron emission tomography (FPB-PET) scan or cerebrospinal fluid (CSF) amyloid beta 1-42 (Aβ1-42). Participants were excluded if structural imaging findings were inconsistent with a diagnosis of AD, their Geriatric Depression Scale (GDS) score was > 6 or they met the National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) vascular dementia criteria. Baseline data, including patient demographics and characteristics, comorbid conditions, concomitant medications, cognitive and functional tests, and volumetric magnetic resonance imaging (vMRI), were compared between male and female participants. MRI volumes were corrected for intracranial volume and age. FBP-PET or CSF data were available from participants based on the modality used to confirm amyloid pathology either by PET scan or lumbar puncture, respectively. Flortaucipir-PET data for tau were available in a small subset of the cohort. Two sample t-tests were conducted for continuous variables and the Fisher's Exact Test or Chi-Squared test for categorical variables. Bonferroni correction was used to adjust for multiple comparisons. *Results:* Male participants had more years of education (14.6 years vs 13.02, p<.001) than female participants. A higher percentage of male participants, compared to female participants, had cardiac disorders (27.1% vs 17%, p<.001) and coronary artery disease (11.4% vs 4.0%, p<.001), and male participants had a greater mean score for body mass index (26.2 vs 25.0, p<.001). In contrast, a higher percentage of female participants compared to male participants reported endocrine disorders (24.1% vs 11.0%, p<.001), psychiatric disorders (53.4% vs 41.0%, p<.001), and musculoskeletal and connective tissue disorders (51.6% vs 40.3%, p<.001). Compared to the female subgroup, male participants had somewhat better cognition with higher mean scores on MMSE (23.1 vs 22.5, p<.001), although the difference was small and mean scores on the Alzheimer's Disease Assessment Scale-Cognitive 14-item subscale (ADAS-Cog14) (28.7 vs 29.7, p=.224) did not differ between groups. None of the variables related to function were significantly different between men and women in this cohort. Male participants compared to female participants had smaller MRI volumes (mm3) of the left hippocampus (2903.4 vs 2978.6, p<.001) and left entorhinal cortex (1323.8 vs 1395.2, p<.001), and greater ventricular volume (52429.0 vs 47256.1, p=<.001). The contribution of APOE4 carrier status to these differences in the male and female participants is being investigated and results will be available at the time of presentation. *Conclusion:* Although there were no measurable differences in pathologic biomarkers of amyloid and tau, greater left-sided brain atrophy of the hippocampus and entorhinal cortex was observed in the male participants, and this was evident even though tests of cognition were the same. These findings are contrary to the belief that women are able to withstand more pathology at the same level of cognition. This may be true in the mild cognitive impairment stage, but eventually men experience greater brain volume loss in the dementia phase. Alternatively, our data reflect more cognitive reserve in male participants, who had significantly higher levels of education. Future studies to uncover the interactions between sex, comorbidity and biomarkers on the course of AD may identify those most vulnerable to progression of clinical symptoms and help to inform the development of treatments for specific populations.

LBP45: CENTRAL LABORATORY VALIDATION AND PERFORMANCE ASSESSMENT OF NEW AUTOMATED AB1-42 AND TOTAL TAU IMMUNOASSAYS. Didier Pitsi[1], Joachim Vandroemme[2], Walter Hofer[2], Els Decoster[3], Astrid Coppens[2] *(1) BARC Global Central Laboratory, Ghent, Belgium; (2) CRI Medical Laboratory, Ghent, Belgium; (3) CRI Medical Laboratory at the time of these experiments, Ghent, Belgium)*

Background: For many years, manual ELISAs have been the standard way of measuring CSF amyloid-beta (Ab) peptides and tau proteins. Recently, automated immunoassays have been developped that may improve the performance and the throughput of such assays, which can be useful for both routine and clinical trials testing of Alzheimer's disease (AD) patients samples. BARC is a Central Laboratory testing clinical trial samples for its biopharmaceutical partners which is active in the field of AD, where it mostly uses manual ELISAs for measuring Ab and tau. In this study, BARC's Belgian medical laboratory, CRI, validated the use of the Lumipulse

G600II benchtop system from Fujirebio for measurement of Ab1-42 and total tau in routine and in clinical trials. *Methods:* Biobanked CSF samples from 87 apparently healthy volunteers (aged 0-91 years) were pooled 4 by 4 to prepare 21 working aliquots. These were used to assess the precision, accuracy and total error of Ab1-42 and total tau measurement across 2 different product lots on the Lumipulse G600II. *Results:* Between-run precision on the two lots of Ab1-42 and tau was of 9.7% and 5.9%, and of 4.2% and 10.7%, respectively; interlot variability was of 4.7% in the hands of operator 1 and of 9.1% with operator 2 for Ab1-42, and of 9.9% and 12.2% for tau. Accuracy measured on IQC controls was of 0.7%, 0.4% and 1.5% and of 1.9%, 1.1% and 0.8% for Ab1-42 and tau low-, medium- and high-level controls, respectively. Total error was measured over 5 days on quadruplicate IQCs and was of 2.6%, 1.8% and 3.5% and of 6.0%, 4.7% and 3.2% for Ab1-42 and tau low-, medium- and high-level controls, respectively. *Conclusion:* Both Ab1-42 and total tau automated immunoassays on Lumipulse G600II are accurate tools for the analysis of these important biomarkers in human CSF. Few other methods are available for measuring both of these biomarkers in clinical routine. Typically, manual ELISAs are more work-intensive and give more variable results, with CVs around 15%. With an improved ease of use and a good correlation to the reference measurement procedure, the Lumipulse total tau and Ab1-42 assays are useful additions to our testing arsenal

LBP46: APPLICATION OF THE REVISED DIAGNOSTIC CRITERIA FOR THE EARLY STAGES OF ALZHEIMER'S DISEASE TO THE LIPIDIDIET STUDY POPULATION.

Tobias Hartmann[1,2], Kaj Blennow[3,4], Pieter Jelle Visser[5,6], Alina Solomon[7,8,9], Suzanne B Hendrix[10], Miia Kivipelto[7,8,9], Hilkka Soininen[7,11] on behalf of the LipiDiDiet clinical study group *((1) Deutsches Institut für Demenz Prävention (DIDP), Medical Faculty, Saarland University, Homburg, Germany; (2) Department of Experimental Neurology, Saarland University, Homburg, Germany; (3) Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden; (4) Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; (5) Department of Psychiatry and Neuropsychology, Alzheimer Center Limburg, University of Maastricht, Maastricht, the Netherlands; (6) Department of Neurology, Alzheimer Center, VU University Medical Center, Amsterdam, the Netherlands; (7) Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland; (8) Department of Clinical Geriatrics, NVS, Karolinska Institutet, Huddinge, Sweden; (9) Clinical Trials Unit, Department of Geriatric Medicine, Karolinska University Hospital, 14152 Huddinge, Sweden; (10) Pentara Corporation, Salt Lake City, UT, USA; (11) Neurocenter, Department of Neurology, Kuopio University Hospital, Kuopio, Finland)*

Background: LipiDiDiet is 24-month randomised, controlled, double-blind, parallel-group, multi-country trial (with optional yearly extensions) in prodromal Alzheimer's disease (AD) with the specific multi-nutrient Fortasyn Connect, showing no significant effects of intervention on the primary endpoint (neuropsychological test battery composite score), but significant group differences on secondary endpoints of disease progression measuring cognition and function and hippocampal atrophy were observed. New updates on trial results are presented including a focus on diagnostic criteria results. The International Working Group 1 (IWG-1) was the first to publish research criteria for the diagnosis of AD in subjects with mild cognitive impairment (MCI), so-called prodromal AD. The LipiDiDiet study was initiated shortly after this publication, and as such is one of the first randomised controlled studies in subjects with prodromal AD according to the IWG-1 research criteria. Diagnostic criteria for this early stage of AD have been revised and added, resulting in four different research criteria: IWG-1 (2007/2010), IWG-2 (2014), National Institute of Aging-Alzheimer Association (NIA-AA) (2011), and draft NIA-AA 2018 (July 2017). There are two main differences between the IWG-1 and IWG-2 criteria. Firstly, the definition of in-vivo evidence of AD pathology: medial temporal lobe atrophy on Magnetic Resonance Imaging (MRI) is included in IWG-1, but not in IWG-2 criteria. Secondly, the clinical AD phenotypes: IWG-1 focuses on a typical amnestic phenotype, while IWG-2 also includes atypical, non-amnestic phenotypes. The NIA-AA (2011) and draft NIA-AA (2018) criteria include both amnestic and non-amnestic phenotypes and focus on amyloid as the defining biomarker for AD pathophysiology. It has previously been shown that the IWG-1, IWG-2, and NIA-AA (2011) criteria predict cognitive decline with reasonable accuracy and that the IWG-1 criteria have relatively high specificity due to requirement of an amnestic phenotype (Brain 2015, 138, 1327–38). The main aim of the present analyses is to compare the IWG-1, IWG-2, NIA-AA (2011), and draft NIA-AA (2018) research criteria on the prevalence of prodromal AD (or MCI due to AD) in the LipiDiDiet study population, using centrally analysed cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) data collected at baseline. *Methods:* LipiDiDiet enrolled subjects with prodromal AD according to the IWG-1 criteria. Most subjects were included based on (locally analysed) MRI data as evidence for underlying AD pathology. At baseline, MRI data and (optionally) CSF samples were collected using study-specific protocols. The central MRI analyses were performed by VU University Medical Center, the Netherlands. Medial temporal lobe atrophy (MTA) was visually rated on coronal reconstructions of T1-weighted MRI scans using a five point scale. The central CSF analyses were performed in the Clinical Neurochemistry Laboratory at Sahlgrenska University hospital, Sweden. CSF Aβ40 and Aβ42 concentrations were measured using the MSD Abeta Triplex (Meso Scale Discovery, Rockville, Maryland) and the Aβ42/40 ratio was calculated as [Aβ42/Aβ40]x10. CSF total tau (T-tau) and tau phosphorylated at threonine181 (P-tau) were measured using INNOTEST sandwich ELISAs (Fujirebio, Ghent, Belgium). *Results:* In total, 311 subjects with prodromal AD were included in the LipiDiDiet study. For 287 subjects, centrally analysed MRI (n=279) and/or CSF data (n=107) were available to assess MTA and/or CSF T-tau, CSF P-tau, CSF Aβ42, and CSF Aβ42/40 ratio. The prevalence of prodromal AD (MCI due to AD) based on centrally assessed MRI and/or CSF data were similar across the different research criteria. According to the IWG-1 criteria, 91% (262/287) had prodromal AD. Using the IWG-2 criteria, 76% (81/107) had prodromal AD. Based on the NIA-AA 2011 criteria, 87% (93/107) had a high likelihood of AD, none (0/107) had low likelihood, 1% (1/107) had isolated amyloid pathology (IAP), and 12% (13/107) had suspected non-Alzheimer pathophysiology (SNAP). According to the draft NIA-AA (2018) criteria, 24% (26/107) had 'Alzheimer's pathophysiology contributing to MCI', 64% (68/107) had 'AD contributing to MCI', and 12% (13/107) had 'non-Alzheimer pathophysiology contributing to MCI'. In total, 88% (94/107) had abnormal amyloid in CSF, providing evidence for the presence of AD pathophysiologic processes in this LipiDiDiet study population, which was largely selected based on medial temporal lobe atrophy (IWG-1). *Conclusion:* The LipiDiDiet study population of subjects with prodromal AD according to the IWG-1 criteria, showed a CSF biomarker profile as expected for a prodromal AD (MCI due to AD) population according to the IWG-2, NIA-AA 2011, and upcoming NIA-AA 2018 research criteria and revealed a frequency of ApoE ε4 genotype in the expected range for

a sporadic AD population. These results confirm previous findings, suggesting that a prodromal AD population based on the IWG-1 criteria reveal a study population similar to prodromal AD based on the IWG-2, and both NIA-AA criteria. This is encouraging for study centers recruiting prodromal AD subjects for clinical research which may have access to different types of assessment tools.

Theme: Clinical trials : cognitive and functional endpoints

LBP47: EXPLORING THE UTILITY OF THE DIGITAL CLOCK DRAWING TEST IN CAPTURING SUBTLE COGNITIVE CHANGES AND BIOMARKER EVIDENCE AT THE PRECLINICAL STAGE OF ALZHEIMER'S DISEASE. Dorene M. Rentz[1,2], Kathryn V. Papp[1,2], Irina Orlovsky[2], William Souillard-Mandar[5], Dana Penney[3,4], Randall Davis[3], Keith A. Johnson[1,2,5] *((1) Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA USA; (2) Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA USA; (3) Digital Cognition Technologies, Waltham, MA USA; (4) Department of Neurology, Lahey Hospital and Medical Center, Burlington, MA, USA; (5) Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA USA)*

Background: Developing tools for efficiently measuring cognitive change in clinically normal older adults is both a major challenge and a necessity, particularly as Alzheimer's Disease (AD) prevention trials move into asymptomatic populations. A new approach for assessing cognitive function has been developed via novel software that processes information from a digital pen. This software is able to capture nuances in cognitive performance, i.e., mental speed/efficiency, time to decision-making and organizational details by providing a window to "see through" how an individual completes a cognitive task, even if the task is completed correctly. We used this novel approach to explore whether the Digital Clock Test (DCTclockTM, from Digital Cognition Technologies) was suitable for 1) distinguishing subtle cognitive impairment from normal performance in clinically normally older adults and 2) determining whether digital pen variables were associated with AD biomarker measures in this sample. *Methods:* We recruited 105 clinically normal subjects (63 from the Harvard Aging Brain Study (HABS), 42 from a community sample who underwent cognitive testing only). All subjects were administered the A4 Preclinical Alzheimer Cognitive Composite (PACC) and additional cognitive measures including Trail Making Tests A and B and controlled oral word fluency tests. Previously reported composite factor scores were derived for cognitive domains including Executive Functions, Processing Speed, and Memory. For the DCTclock, subjects completed first a Command and then a Copy version of the clock, which yielded both an overall score for the test and a set of individual composite scales for each clock including drawing efficiency, simple and complex motor, information processing, and spatial reasoning. Subjects from HABS also underwent PET imaging. Amyloid accumulation was assessed using PiB in 1) an aggregate of frontal, lateral and retrosplenial cortices and 2) frontal lobes. Tau accumulation was quantified using flortaucipir (a.k.a. AV-1451) in inferior temporal and entorhinal regions. Finally, glucose metabolism in association cortices was observed using FDG. Pearson R correlations were used to assess the relationship between DCTclock metrics and performance on traditional cognitive measures. In addition, PACC performance was used to identify groups with subtle cognitive impairment (SCI) (<0.5 standard deviations on the PACC compared to a normative sample) versus normal performance (NP). Linear regression models were used to explore the relationship between DCTclock and variables of interest including 1) group status as SCI vs. NP and 2) biomarkers. Post-hoc linear regression analyses were used to explore the combination of SCI vs. NP group membership and biomarkers in the same models. *Results:* The DCTclock overall score and composite scales were correlated with traditional neuropsychological tests and composites, particularly for Executive Function (r=0.40, p=0.001) and Processing Speed (r=0.56, p<0.001). Age and education were not associated with the DCTclock score, however, performance by sex exhibited a non-significant trend with males performing better than females (t=-2.13, p=0.056). The DCTclock score differentiated SCI from NP groups (B=0.04, p<0.001) and worse performance was associated with greater amyloid burden in whole brain (B=-0.004, p=0.001) and frontal regions (B=-0.005, p=0.001) as well as lower parietal FDG (B=0.002, p=0.012). Furthermore, the DCTclock score exhibited a non-significant trend with worse performance being associated with greater inferior temporal tau deposition (B=-0.002, p=0.054). DCTclock drawing efficiency (a measure combining metrics such as time spent, pen stroke count, size of the drawing) and spatial reasoning (a measuring combining geometric and spatial placement properties of the drawing) were significantly predictive of SCI vs. NP both for the copy (B=0.452, p=0.023; B=0.506, p=0.026, respectively) and command (B=0.529, p=0.031; B=0.783, p<0.001, respectively) clock drawing. This relationship was consistent for amyloid deposition in the global aggregate on the copy clock (B=-0.052, p=0.031; B=-0.110, p<0.001, respectively), while only spatial reasoning was significantly related to global amyloid on the command clock drawing (B=-0.069, p=0.005). Similarly, copy drawing efficiency (B=-0.024, p=0.024) and spatial reasoning (B=-0.045, p<0.001) were significantly related to inferior temporal tau, however, this relationship was only consistent for spatial reasoning (B=-0.025, p=0.013) on the command clock drawing. *Conclusion:* The DCTclock Test was highly correlated with standard neuropsychological tests for executive functioning and processing speed, suggesting good construct validity with these cognitive domains. Furthermore, the DCTclock Test was highly sensitive to distinguishing subtle cognitive impairment from normal performance and associated with numerous AD biomarkers suggesting that the DCTclock may prove useful in identifying individuals with preclinical AD. The use of DCTclock for measuring cognitive performance is a revolutionary approach to standard paper and pencil assessments. These outcomes suggest that the development and validation of such measures would allow for more automated assessments of cognition that might be sensitive to subtle changes related to preclinical AD. This technology also has the potential to impact AD clinical trials by increasing the reliability of cognitive endpoints, thus yielding more sensitive measurements of change over time.

LBP48: CLINICAL MEANINGFULNESS OF CLINICIAN'S INTERVIEW-BASED IMPRESSION OF CHANGE PLUS CAREGIVER INPUT (CIBIC-PLUS) SCALE IN RELATION TO GOAL ATTAINMENT IN PARTICIPANTS ON CHOLINESTERASE INHIBITORS. Susan E Howlett[1,2,3], Justin Stanley[1], Helen Wong[1], Arnold Mitnitski[1,2], Kenneth Rockwood[1,2] *((1) DGI Clinical Inc., Halifax, NS, Canada; (2) Division of Geriatric Medicine, Dalhousie University, Halifax, NS Canada; (3) Department of Pharmacology, Dalhousie University, Halifax, NS, Canada)*

Background: The Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) is a global assessment of change. It has been widely used in trials of drugs for dementia

symptoms. The CIBIC-Plus measures disease severity and degrees of changes in the clinical state with a 7-point, judgment-based rating scale. It evaluates cognition, behavior, and function, yielding written and numerical summaries from semi-structured interviews. Although its clinical meaningfulness is unclear, achieving personalized goals through Goal Attainment Scaling (GAS) has been shown to be clinically meaningful to both patients and caregivers [1, 2]. To evaluate the clinical meaningfulness of CIBIC-Plus change, we compared CIBIC-Plus with clinically meaningful changes in patient/carer-rated GAS in people with mild-moderate Alzheimer's disease (AD) treated with either of two cholinesterase inhibitors. We also compared CIBIC-Plus scores with change in the Alzheimer's Disease Assessment Scale-Cognition subscale (ADAS-Cog) and with measures of everyday function in the same individuals. *Methods:* In an exploratory analysis, we examined the performance of CIBIC-Plus in two multicenter Canadian cholinesterase inhibitor clinical trials in participants with mild-moderate AD. The Atlantic Canadian Alzheimer's Disease Investigation of Expectations (ACADIE) study was a 12-month prospective, uncontrolled, open-label trial of donepezil [1]. The Video-Imaging Synthesis of Treating Alzheimer's disease (VISTA) study was an 8-month double-blinded, placebo-controlled evaluation of galantamine [2]. Only the VISTA treatment group was considered in these analyses. Both trials collected data on CIBIC-Plus, GAS, ADAS-Cog and everyday function. Change scores were determined by taking the difference between baseline and follow-up at 8 months in VISTA and 9 months in ACADIE. The severity of dementia was measured with the Clinician Interview Based Impression of Severity (CIBIS) at baseline and the assessment of change with CIBIC-Plus at follow-up visits. For CIBIC-Plus, participants were classified as improved (< 4), no change (4), or worse (> 4). ADAS-Cog scores and everyday function were also used to characterise the degree of dementia in each individual. Clinical meaningfulness was defined as concomitant scores of CIBIC-Plus < 4 and GAS > 50. The relationships between initial treatment responses (at 2 months in VISTA and 3 months in ACADIE) and follow-up responses were assessed with odds ratios (OR) to evaluate the ability of initial response in CIBIC-Plus to predict endpoint results. *Results:* Participants in both the ACADIE and VISTA trials had similar characteristics at baseline. The total sample was largely composed of women (70%), with mean age of 76.1 (±7.7) years old, and ADAS-Cog (25.0 ± 9.0) and CIBIS (3.6 ± 0.8) scores consistent with mild dementia. Individuals who improved (CIBIC-Plus < 4) showed significant improvements in goal attainment (GAS mean change = 9.4; 95% CI = 6.9-11.9; P < 0.001) and in cognitive impairment (ADAS-Cog mean change = -2.2; CI = -3.4 to -1.1; P < 0.001) at follow-up. In contrast, standard tests of everyday function showed no change or deterioration (mean change = -0.2; CI = -2.5 to 2.1; P = 0.873) with improvements in CIBIC-Plus scores. Interestingly, those who did not change (CIBIC-Plus = 4) saw significant improvements in GAS (mean change = 5.0; CI = 1.7-8.3; P = 0.007), but not in ADAS-Cog or function. Participants who worsened on CIBIC-Plus showed significantly worse cognitive impairment (ADAS-cog mean change = 3.0; CI = 1.0–5.0; P = 0.005) and everyday function (mean change = -7.1; CI = -10.2 to -4.0; P < 0.001). Mean change in goal attainment declined slightly with CIBIC-Plus scores, but this was not statistically significant (GAS mean change = -1.1; CI = -3.9 to 1.7; P = 0.452). Compared with those who did not initially improve (2 months in VISTA, 3 months in ACADIE) (CIBIC-Plus ≥ 4), those who did (CIBIC-Plus < 4) were more likely (OR = 13.7; 95% CI = 5.6–33.9) to remain better (GAS > 50 and CIBIC-Plus < 4) at the follow-up. In contrast, those who initially worsened (CIBIC-Plus > 4) were significantly less likely (OR = 0.16; 95% CI = 0.04–0.74) to improve. Similar results were seen with worsening at follow-up. The greatest chance of an improved response at 8/9 months was when both the initial CIBIC-Plus and patient/carer-rated GAS scores had improved initially (OR = 141; 95% CI = 17.3–1143). Likewise improvement was uncommon by month 8/9 when the initial treatment response showed worsening (OR = 0.11; 95% CI = 0.03–0.41). *Conclusions:* These results show that improvement in CIBIC-Plus scores was accompanied by improvement in patient/carer-rated GAS. Initial CIBIC-Plus worsening was unlikely to result in improved GAS, ADAS-Cog and everyday function scores at follow-up. Even when no change was detected with CIBIC-Plus, improvement was detected with GAS. Thus, even minimal changes in severity as measured by CIBIC-Plus scores are associated with clinically meaningful change as assessed by GAS. References: 1. Rockwood K, Graham JE, Fay S, ACADIE Investigators. Goal setting and attainment in Alzheimer's disease patients treated with donepezil. J Neurol Neurosurg Psychiatry 2002;73:500-507. 2. Rockwood K, Fay S, Song X, MacKnight C, Gorman M, VISTA Investigators. Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. CMAJ 2006;174:1099-1105.

LBP49: ASSESSMENT OF IADL FUNCTIONING IN INDIVIDUALS WITH SUBJECTIVE COGNITIVE DECLINE USING THE VIRTUAL REALITY FUNCTIONAL CAPACITY ASSESSMENT TOOL (VRFCAT). Alexandra S. Atkins[1], Anzalee Khan[1,2], Ioan Stroescu[1], Kathleen A. Welsh-Bohmer[3], Brenda L. Plassman[3], Adam W. Vaughan[1], Dañela Balentin[1], & Richard S.E. Keefe[1,4] *((1) NeuroCog Trials, Durham, NC, USA; (2) Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA; (3) Duke University Bryan ADRC, Durham, NC, USA; (4) Duke University Medical Center, Durham, NC, USA)*

Background: Reliable evaluation of cognition and functioning is critical to the effective assessment of mental health in aging individuals. Although the assessment of cognition is largely standardized with the use of performance-based neuropsychological instruments, assessment of functioning relies heavily on informant-reported measures that require identification of a reliable informant and often lack sensitivity to subtle functional declines in preclinical and prodromal MCI/AD). Increasing interest in clinical trials for prevention and early intervention highlights the need for tools that are performance-based and sensitive to subtle deficits in instrumental activities in daily living (iADL) in healthier, non-demented individuals. The Virtual Reality Functional Capacity Assessment Tool (VRFCAT) was developed as a performance-based assessment of iADL functioning. Using a realistic virtual reality environment, the VRFCAT assesses a subject's ability to complete instrumental activities (called objectives) associated with a shopping trip, including searching the pantry at home, making a shopping list, selecting and paying for the correct bus to the store, shopping, paying for the purchases, and returning home. The VRFCAT provides automatic scoring and data management in compliance with 21 CFR Part 11 compliance requirements. In previous studies, the VRFCAT has demonstrated high test-retest reliability and has shown strong relationships to cognition, sensitivity to declines in healthy aging, and sensitivity to pronounced functional deficits in schizophrenia (Atkins et al., 2015; Keefe et al., 2016). We present findings from an ongoing study to collect census-matched normative data in 650 healthy individuals and 60 individuals with subjective cognitive decline. We describe preliminary findings comparing performance of healthy older adults (≥55 years) and older adults with subjective cognitive decline. *Methods:* Data collection is ongoing and currently includes 378 participants, including 175 healthy young adults (YA, <55 years), 185 healthy older adults (OA, ≥55 years), and 18 individuals with

subjective cognitive decline. Participants with subjective cognitive decline were classified as such based on total scores of ≥ 4 on the self-reported Mail-In Cognitive Function Screening Instrument (MCFSI). In addition to the VRFCAT, all participants were evaluated with standard cognitive assessments including the Montreal Cognitive Assessment (MoCA), Trail Making Part B, and Logical Memory subtest of the Wechsler Memory Scale. Participants aged ≥55 years completed the MCSFI. Those with subjective cognitive complaints were asked to provide an informant to complete the ADCS Activities of Daily Living-Prevention Instrument (ADCS-ADL-PI). Key outcome measures for the VRFCAT included total time to complete all 12 objectives as well as individual objective times and error rates. *Results:* Participants with subjective cognitive decline performed significantly lower than OAs without subjective decline on all standard neurocognitive measures, suggesting subjective decline was associated with objective deficits in this sample. Mean MoCA scores were 26.95 (SD=1.8) for healthy OAs and 24.28 (SD=2.90) for participants with subjective decline. VRFCAT total completion time and error rate both demonstrated strong sensitivity to differences between groups ($p \leq .001$), as did individual task completion times for each of the VRFCAT objectives. Tasks most sensitive to differences between healthy OAs and those with subjective cognitive decline included (1) creating a shopping list based on items present in the kitchen (objective 3), (2) adding up the exact bus fare required (objectives 7 and 12), and (3) shopping for grocery items (objective 9). In the subjective cognitive decline group, VRFAC errors were correlated with ADCS-ADL-PI scores ($p=.49$, $p<.05$), indicating that increased VRFCAT errors were associated with greater informant-reported iADL decline. VRFCAT error and total time endpoints were both correlated with performance on the MoCA in OAs ($r=-.36$, $p<.001$ for VRFCAT time, $r=-.22$, $p<.001$ for VRFCAT errors). ADCS-ADL-PI scores were also correlated with the MoCA ($r=-.29$, $p<.001$). VRFCAT time was strongly correlated with TMT-B performance in both OAs ($r=.58$, $p<.001$) and individuals with subjective decline ($r=.81$, $p<.001$). *Conclusion:* Preliminary findings suggest the VRFCAT is sensitive to differences between healthy OAs and those with subjective cognitive decline, and demonstrate convergence between VRFCAT findings, objective cognitive testing, and informant reports of declining function. Findings offer encouragement for further development and customization of the VRFCAT as performance-based measure of functioning for prevention and early MCI/AD trials.

Theme: Cognitive assessment and clinical trials

LBP50: BREADTH AND DEPTH OF WORKING MEMORY AND EXECUTIVE FUNCTION IMPAIRMENT IN MILD COGNITIVE IMPAIRMENT. Terry E. Goldberg[1], Jesus Gomar[2]
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Background: Although working memory (WM) and executive function (EF) impairment may be evident in MCI, its characterization has remained incomplete. This study aimed to investigate the breadth and depth of WM/EF in individuals with Mild Cognitive Impairment (MCI) as compared to normal elderly control (NEC) participants, and Alzheimer's disease (AD) patients and the relationship of WM/EF to brain morphometrics and everyday functional competence. *Methods:* We assessed 48 MCI individuals, 58 probable AD individuals, and a sample of 124 NECs, with a wide range of WM/EF tests that covered functions such as attention, information manipulation, set-shifting, psychomotor speed, problem solving, and cognitive control and included the N Back, Tower of London, Stroop Test, Trailmaking tests, digit span, and Letter Number Span. We assessed regional brain morphometrics using Freesurfer image analyses after structural MRI and functional performance using the UPSA to analyze their relationship with WM/EF. *Results:* MCI subjects demonstrated significantly worse performance on nearly all tests of WM/EF. Effect sizes (Cohen's d) were in the .70 to 1.05 range. The modal MCI subject demonstrated impairment on five of 12 measures. As expected AD subjects performed worse than the MCI group. Factor analysis revealed an interpretable four-factor solution that included, cognitive speed, working memory involving short term information maintenance, and executive function involving simultaneous maintenance and manipulation of information, and episodic memory as a "control." These factors, in turn, were related in stepwise regression models to both specific and global cortical thickness reductions. WM/EF factors were also correlated with performance based measures of functional competence. *Conclusion:* To the best of our knowledge this is the most comprehensive study of WM/EF to date in MCI. It is also the largest non-ADNI study on WM/EF in MCI and it offers complementary findings that usefully extend and refine the heavily mined ADNI database. Tasks included 1. Assays of simple WM storage that engages the phonological loop; 2. More complex measures involving simultaneous storage and manipulation of information involving such processes as multiple re-sequencing of items, fully mentalized planning, and updating of information; and 3. Set switching in the context of speed demands and organized visual search. Impairment severity in the latter two types of task were in the medium to large ES range in MCI and differences were highly significant. Moreover, the modal MCI subject demonstrated impairment on four to six measures. For comparison, the modal EHC demonstrated no impairments and the modal AD subject demonstrated seven or nine impairments. Impairments were significantly associated reductions in dorso- and ventrolateral cortical thickness for EF. Speed determined in part by set switching and dynamic eye movement control was associated with superior frontal gyrus thickness reductions. Global cortical thickness reductions were also associated with all WM/EF subdomains. Memory performance was related to hippocampal volume. These findings suggest that several critical neural circuits that underlie "frontal" tasks are already compromised before AD is diagnosed. Last, several WM/EF subdomains were associated with functional competence. In summary, the results that we report suggest that WM/EF impairments in amnestic MCI are present, substantial, may be related to both dedicated circuitry and more global morphometric measures, and even at this potentially prodromal stage of AD, have clinically deleterious consequences.

LBP51: THE EARLY AD/ MCI ALZHEIMER'S COGNITIVE COMPOSITE (EMACC): DEVELOPMENT AND PRELIMINARY VALIDATION ACROSS FOUR LONGITUDINAL COHORTS OF A COGNITIVE ENDPOINT FOR CLINICAL TRIALS IN THE MCI AND EARLY AD STAGE OF DISEASE. Judith Jaeger[1], Clint Hagen[2], Henrik Loft[3], Yen Ying Lim[4], Andrew Aschenbrenner[5], Marta Segerdahl[3], Gary Tong[3], Michelle Mielke[2], Jason Hassenstab[5], Nikki Stricker[2]
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Background: Conventional psychometric theory would suggest that a battery of neuropsychological tests that are normally distributed and sensitive to change (improvement or decline), might be more sensitive to a drug effect in a disease modification trial

than a clinical rating tool designed to detect worsening of clinical symptoms (e.g. the Clinical Dementia Rating (CDR)). Data driven methods for establishing a composite cognitive endpoint adhering to these psychometric principals have been applied in the field of preclinical AD (e.g. Donohue et al1, Langbaume et al2, Hassenstab et al 3). Relative to preclinical AD, emergence of floor effects for several cognitive variables at the EAD stage suggests the need for a different cognitive composite at each disease stage hence justifying the present effort to develop a cognitive composite endpoint suitable for global clinical trials in the Early AD or MCI stages of disease. *Methods:* We conducted parallel independent but identical analyses in 4 longitudinal cohorts of elders in which a total of 1,167 clinically normal (CN) β-amyloid negative (Aβ-; confirmed with amyloid PET imaging) and 516 individuals with confirmed Aβ+ PET scans meeting criteria for MCI or EAD (i.e. including also mild AD with CDR=0.5 or 1) were compared with respect to slope decline on a battery of individual neuropsychological tests. Cohorts included the Australian Imaging, Biomarkers and Lifestyle (AIBL) study, the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Mayo Clinic Study of Aging (MCSA) and the Knight Alzheimer's Disease Research Center at Washington University in St Louis (WUSTL). Neuropsychological test variables were restricted to those that could be reliably used in a global trial (i.e., can be administered by a trained rater who is not a neuropsychologist, and readily subject to linguistic and cultural adaptation). In each cohort, standardized slopes were computed within the EAD/MCI Aβ+ subgroup on all possible combinations of composites containing between 4 and 8 neuropsychological test variables. Results were rank ordered in accordance with magnitude of slope decline from baseline. This step was conducted at years 2, 3 and 4. Based upon the patterns of individual tests falling in the top ranked composites in each cohort at all time points, two candidate composite measures were constructed. These composites were then compared to each other with respect to effect size separation from CN Aβ- controls at each time point using Linear Mixed Model (LMM) analysis. Based on these results, the final EAD/MCI Alzheimer's Cognitive Composite (EMACC) was chosen. Effect sizes were then compared to conventional endpoints (i.e. CDR Sum of Boxes (SB), Mini Mental Status Examination (MMSE)). *Results:* Commonalities were observed across the highest ranking (top 10) slope composites across time and across the 4 cohorts (i.e. a word list learning test was represented in almost all solutions). Importantly, each composite was comprised of cognitive tests that were common or represented similar cognitive domains across each cohort. The EMACC (see table 1) consists of validated measures of episodic memory, executive functioning, and processing speed. At year 2, the Cohen's d effect size (ES) reflecting the magnitude of separation between the two subject groups was similar for the EMACC relative to that of the CDR-SB in 3 cohorts. In AIBL, the ES for the CDR-SB was larger at 2 years than for the EMACC. Effect sizes on EMACC were similar to those of the ADAS-Cog in the ADNI Cohort. The ES on the EMACC was similar to that of the MMSE in three cohorts (the exception was WUSTL). In all cases, ES for the EMACC were numerically greater in years 3 and 4 than year 2. In all but one cohort (MCSA) the ES for EMACC was numerically greater in year 4 than in year 3. Additional details of the methods employed, sample characteristics, and preliminary validation of the EMACC will be presented. *Conclusion:* The EMACC is a new and sensitive composite of well-known and validated neuropsychological tests that performs comparably to the CDR-SB and MMSE, and is suitable for examining the effect of disease modifying compounds on cognitive decline in the EAD or MCI stage of Alzheimer's disease. 1. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. JAMA Neurol. 2014;71(8):961-970. 2. Langbaum JB, Hendrix SB, Ayutyanont N, et al. An empirically derived composite cognitive test score with improved power to track and evaluate treatments for preclinical Alzheimer's disease. Alzheimers Dement. 2014;10(6):666-674. 3. Hassenstab J, Hagen CE, Han B, et al. Reliability and reproducibility of Cognitive Composites for Alzheimer's Disease Secondary Prevention Trials: The Power-PACC. 13th International Conference on Alzheimer's and Parkinson's Diseases; March 31, 2017, 2017; Vienna Austria.

		FINAL EMACC MEASURES IN EACH COHORT							
		ADNI		AIBL		WUSTL		MCSA	
Domain	Paradigm	Test	Measure	Test	Measure	Test	Measure	Test	Measure
Memory	Word list learning	RAVLT	Trials 1-5	CVLT	Trials 1-5	FCSRT	Free Recall	RAVLT	Trials 1-5
	Digit Span			WAIS-R DS	Forw+Back	WAIS-R DS	Forward		
Executive + Psychomotor	Fluency	Category fluency	Animals	Category fluency	Animals	Category fluency	Animals+ Vegetables	Category fluency	Animals +fruits+ vegetables
				Letter Fluency	FAS	Letter Fluency	FAS		
	Trailmaking	Trailmaking Test	Trails A (secs)			Trailmaking Test	Trails A (secs)	Trailmaking Test	Trails A (secs)
	Conflict Inhibition		Trails B (secs)	Stroop	Color naming speed (secs)		Trails B (secs)		Trails B (secs)
	Coding	ADAS Number Canc	Total score	DSST	Total score	DSST	Total score	DSST	Total score

LBP52: A COMPARISON OF IN-PERSON AND WEB-BASED COMPUTERISED COGNITIVE TESTING USING CANTAB.

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Background: Testing individuals in their own homes and on their own devices has the potential to improve the efficiency of screening into clinical trials by obtaining patient reported or objective cognitive data before participants reach the clinic. Furthermore, such testing provides the opportunity for high-frequency at home monitoring in between site visits. In order to be useful, testing in the home environment needs to be robust and provide equivalent data to that obtained in a supervised setting. There are a number of issues which could compromise this comparability. Firstly, there may be differences in the performance of different computer systems, which could compromise the performance of the assessments. Secondly, in unsupervised settings participants may not behave as required, due to distraction or lack of motivation. Here we present the results of two studies aimed at validating at home web-based testing against in-person assessment. The first is a between-subjects comparison, which used a large-scale crowdsourced sample to also explore the impact of computer hardware on performance, and to derive markers of task performance and behaviour which could indicate lack of attention. In the second experiment, we directly address the comparability of web-based and in-person testing in a counterbalanced within-subjects study of community dwelling adults. *Methods:* Experiment one is a between-subjects study assessing the comparability of web-based and in-person testing. Six hundred participants between 18 and 70 were recruited for web-based testing through a crowd-sourcing platform, and these were compared to a matched sample of 94 participants assessed in a supervised setting. Participants completed tests of episodic memory (Paired Associates Learning - PAL) and working memory (Spatial Working Memory) from the CANTAB. Demographic data (e.g. age, education) were also recorded. From participants in the web-based condition, we collected data on reaction times, hardware and software platform, and browser behaviour. The latter was used to quantify participant engagement. The second experiment is a within-subjects counterbalanced cross-

over study. In this study, 47 participants recruited via social media and local advertising in and around Cambridge (UK), completed the CANTAB PAL and SWM tests on average one week apart. Tests were administered either on the iPad in a clinical unit, or via web-based testing in the home environment on a laptop/desktop computer. Participants were randomly allocated to two groups: in-person or web-based first, and all were tested twice, so all participants underwent testing in both settings. The study sample consisted of 47 participants (30 female and 17 male), 16 in the in-person first condition 21 in the web-based first condition. A multivariate analysis of variance (MANOVA) analysis was carried out to investigate whether there were statistically significant differences between the testing platforms (in-person vs web-based). The key outcome measures for each test were used as dependent variables and the platform as a fixed factor. Covariates in this model were Age, Gender and Level of Education. *Results:* In experiment one, there was no difference in distribution of scores between supervised and web-based testing. Within the web-based testing, there was no difference between hardware platforms or browser. A number of participants in the web-based condition showed trial-by-trial response time data which was more variable and slower than typically seen on supervised testing. This was significantly correlated with task performance, and age. Browser monitoring revealed whether participants tabbed to a different browser window during the task. This behaviour was associated with poorer performance, more variable reaction time, and younger age. These results point to response time and browser behaviour as useful metrics of task engagement in unsupervised settings. In our second experiment, we again found no significant effect of testing location (in-clinic or web-based: $F(21,66) = 0.67$, $p > .05$) overall, or any significant difference for the individual key outcome measures of the different tests, supporting the comparability of testing on the two platforms. *Conclusions:* The two experiments presented here aimed to assess the equivalence of CANTAB testing conducted in-person or remotely in a home setting. Our first, large-scale between subjects study showed an equivalent distribution of scores in the two conditions using a crowd-sourced sample, and revealed metrics of inattention which could be extracted from reaction time data to assess participant attention and compliance. However, there was the possibility that the participants in the crowd-source sample were atypical, and therefore would not reflect what would be seen in a community sample. Our second experiment addressed this limitation and provided a direct test of the equivalence of in-person and web-based testing methodologies, by employing a within subjects cross-over design. These findings support the validity of home-based computerised assessment.

LBP53: AUTOMATED VOICE-BASED TESTING: APPLICATIONS IN RECRUITMENT OF PATIENTS IN CLINICAL TRIALS. Nick Taptiklis[1], Francesca Cormack[1,2], Jennifer H Barnett[1,2] *((1) Cambridge Cognition, Cambridge, UK; (2) Department of Psychiatry, University of Cambridge, UK)*

Background: In clinical studies, accuracy and consistency in scoring and delivering cognitive tests are often problematic, with human error introducing unwanted between- and within- subject variance. Computerised cognitive assessment batteries such as CANTAB have demonstrated the benefits of automating the administration and scoring of visual tasks, but to date verbal tasks still require human scoring. The automation of voice-based cognitive assessments would open up new recruitment channels into clinical trials. Voice-based cognitive assessment delivered via telephone would enable recruitment and screening of additional populations not yet accessible via the web. Recent advances in automatic speech recognition from deep-learning-based systems provided by Amazon, Microsoft and others have led us to consider whether it may now be possible to automate voice-based cognitive assessment. However, these systems have been designed to support consumer interactions with devices, for example, setting reminders or selecting music, raising the question as to whether they can successfully recognize speech acts produced during the course of a structured clinical assessment. Here we describe the development and testing of two iterations of a voice-based cognitive testing battery, first using Amazon's Alexa speech recognition platform via their Echo consumer hardware device, and a second approach using Microsoft's speech service for web-based delivery. *Methods:* We developed a battery of three tasks modelled on traditional neuropsychological assessments, optimised for user experience and speech recognition performance. These tasks were digit span, list learning and verbal paired associates. Participants were also assessed using a standard CANTAB battery measuring similar cognitive domains (Paired Associates Learning, Spatial Working Memory and Rapid Visual Processing), and completed a modified System Usability Scale. In the first iteration, we assessed twenty participants using the automated voice battery on the Amazon Echo, with simultaneous independent audio recording of the testing session. Data from three participants was discarded due to audio recording failure, leaving an analysis sample size of seventeen. In the second iteration, the same battery was delivered to 20 participants via a web-based platform that recorded the full audio session, removing the need for independent audio recording. In both iterations, the speech recognition engines were weighted to expect words from the task. For the list-learning task, the engines were biased towards the target word list, and for the paired associates task the prompt words were included as well as the target words, and the digit span tasks were biased to expect digits. Audio recordings from both tasks were reviewed and manually scored. Where errors in recognition or scoring were observed the cause of the failure (e.g. hesitation, pronunciation) was recorded. Analysis focussed on four aspects of the performance of the automated voice battery: 1) the accuracy of the speech recognition engines; 2) the accuracy of the automatic scoring of cognitive performance; 3) the construct validity of the voice battery compared to other cognitive tests; 4) the acceptability to participants of the commercial speech recognition platforms as means of delivering cognitive tests. *Results:* In the first iteration of the battery, the list learning and paired associates both achieved 99% scoring accuracy. This was better than the raw speech recognition accuracy for these tasks (97% and 96% respectively). This was because in 88% of cases recognition errors were associated with participant recall errors. Participant performance on the list learning and verbal paired associates tasks was also significantly correlated with their performance on CANTAB PAL. The correlation between PAL and the automated list learning task is consistent with that found elsewhere in the literature for conventionally administered list learning tasks. In the first iteration, the digit span task performed less well, achieving 76% speech recognition accuracy. This was caused by the inability of the Amazon Alexa end-of-utterance detection algorithm to cope with participant speech patterns during digit span recall. Participants found the Alexa-based system easy to use, with an aggregate System Usability Score of 78%. The second iteration of the battery was constructed using Microsoft's speech recognition system. Here we customised the end-of-utterance detection which had caused the poorer performance of the digit span task. By weighting end-of-utterance detection by expected digit span, this second iteration of the system was able to achieve an improved measure of working memory. *Discussion:* Our initial research has shown meaningful assessment of cognitive performance is possible using state of the art voice recognition. While raw speech recognition accuracy is not yet at human level, by carefully controlling the task design it is possible to

achieve 99% scoring accuracy for some tasks. This has implications for automating quality control checks in clinical trials and for trial recruitment where telephone-based screening platforms may provide new means of accessing patients.

LBP54: USE OF THE INTERNATIONAL SHOPPING LIST TEST AS THE OBJECTIVE ASSESSMENT OF COGNITIVE IMPAIRMENT TO IDENTIFY SUBJECTS WITH EARLY ALZHEIMER'S DISEASE IN THE EISAI ELENBECESTAT MISSIONAD PHASE 3 CLINICAL TRIALS. Bruce Albala[1], Michelle Gee[2], Adrian Schembri[3], Paul Maruff[3] *((1) Eisai Inc., Woodcliff Lake, New Jersey, USA; (2) Eisai Ltd, Hatfield, UK; (3) Cogstate Ltd., Melbourne, Australia)*

Introduction: Impairment in episodic memory is central to the clinical presentation of dementia due to Alzheimer's disease (AD) as well as the earlier prodromal stage of AD (e.g., mild cognitive impairment due to AD [MCI]). Objectively establishing episodic memory impairment is a key inclusion criterion for identifying individuals appropriate for enrollment in clinical trials of putative AD disease-modifying therapies. In the MissionAD protocols, individuals with impaired performance on the memory test are further evaluated for AD via the determination of amyloid pathology from CSF sampling or PET imaging. Given the global footprint of the MissionAD phase 3 trials, the objective memory assessment needed to be robust to variations in language, culture, and socio-economic background. The International Shopping List Test (ISLT) is a three-trial verbal list learning test in which individuals must learn a shopping list of 12 common food items. The test yields two performance measures: a total recall score for ISLT learning and a delayed recall score. The ISLT has been validated for 90 languages/countries. Clinical studies have demonstrated that the ISLT is sensitive to the memory impairment seen in dementia and MCI. The ISLT is administered and scored using a computer program; therefore assessment data are unbiased and available in real time. The Eisai elenbecestat MissionAD phase 3 studies are designed to assess the effect of the BACE inhibitor elenbecestat (E2609) on clinical and biomarker outcomes in subjects with early AD. Entry into these studies requires individuals to demonstrate episodic memory impairment based on their performance on either the immediate recall or the delayed recall components of the ISLT. This report summarizes the effectiveness to date of the ISLT for identifying memory impairment associated with early AD in the ongoing elenbecestat MissionAD phase 3 program. *Methods:* Clinical sites identified individuals who may have Early AD (MMSE ≥24; CDR-GS=0.5; CDR Memory Box ≥0.5) for entry into the elenbecestat clinical trials. Following consent, the ISLT learning and delayed recall trials were administered as the objective cognitive assessment according to the study inclusion criteria. Consistent with the NIA-AA 2011 criteria for establishing a research diagnosis of MCI due to AD, the ISLT scores for eligibility were set at 1 SD below age-matched norms. Individuals also completed the Cogstate Brief Battery (CBB) between the ISLT learning and delayed recall trials. At the time of analyses (August 2017), 514 study subjects had initiated the ISLT (mean age=70.15, SD=8.19, range 50–85, 55.1% female). Analyses of ISLT data proceeded in three stages: 1. Acceptability of the ISLT was determined by computing the number of individuals who began, but did not complete, assessment; 2. The number of individuals with memory impairment (i.e., ISLT total or delayed recall performance ≤1 SD below age-matched controls) was expressed according to age and gender; 3. CBB performance was compared between groups with and without memory impairment sufficient for study entry. Estimates of agreement between classification of impairment on the ISLT and classification of impairment on the CBB were computed with the CBB used as the reference. *Results:* Of the 514 individuals evaluated, one (0.2%) did not complete the ISLT. The overall rate of classification of memory impairment in the sample was 63.0%, where impairment was classified for 271 (52.7%) subjects on the ISLT learning score, 281 (54.7%) subjects on the ISLT delayed recall score and 228 (44.4%) subjects on both ISLT scores. Memory impairment increased with increasing age (50–59=50.0%, 60–69=58.9%, 70–79=68.7%, 80–85=68.1%) and was more common in males (70.6% impaired) compared to females (56.9%). Comparison of CBB performance between normal and impaired groups indicated that the impaired group showed a large deficit on the Cogstate One Back Test (d=0.64), One Card Learning Test (d=0.70), and consequently on the learning/working memory composite (d=0.75). There was no impairment on the detection test (d=0.22), identification test (d=0.14), or psychomotor/attention composite (d=0.17). *Conclusions:* The results suggest that in the elenbecestat MissionAD phase 3 trials the ISLT is operating with high acceptability and identifies impairment in episodic memory. Performance on the ISLT is also associated strongly with poor performance on independent tests of learning and working memory (CBB). Although preliminary, these data provide a sound foundation for continued use of the ISLT in the elenbecestat MissionAD phase 3 program.

LBP55: ASSESSING RISK FACTORS FOR COGNITIVE IMPAIRMENT IN PATIENTS WITH DIABETES. Martin Rakusa[1], Matej Rakusa[2], Miro Cokolic[2] *((1) Department of Endocrinology and Diabetes University Medical Centre Maribor, Maribor, Slovenia; (2) Department of Neurology University Medical Centre Maribor, Maribor, Slovenia)*

Backgrounds: Patients with diabetes mellitus (DM) have higher risk not only for cognitive impairment but also for Alzheimer's disease in comparison to healthy population. Aim of our study was to evaluate cognitive status and risk factors in patients with diabetes. *Methods:* Tree hundred-ninety-seven patients with DM type 2 were included. Cognitive status was evaluated using Clock Drawing Test. Patients who scored 3 out of 4 points or less were considered cognitive impaired. Patients were divided into two groups. Data was nonnormally distributed. Age, duration of DM, years of education, serum HbA1c and serum glucose levels were compared between groups with Mann–Whitney U test. *Results:* Cognitive impairment was found in 58.3% of patients. Median age was 65.17 years (59.3 to 72.1 years), median duration of DM was 12 years (6 to 18 years), median blood glucose level was 8.1 mmol/L (6.5 to 10.1 mmol/L), median HbA1c was 7.3 % (6.6 to 8.3 %), median years of education were 12 (8 to 12 years). Significant differences between both groups were found for age, duration of diabetes and years of education. *Conclusion:* Cognitive impairment is common among DM patients in our group, despite relatively well managed DM. It is surprising that, HbA1c and glucose levels did not differ among groups. We should pay special attention to older patients, with long-term diabetes and lower education.

LBP56: PRELIMINARY FINDINGS OF APTEST: A PRESCREENING TOOL DEMONSTRATING INTIAL PREDICTIVE AND DIAGNOSTIC IMPLICATIONS. Pamela Voccia, Katherine Kruczek, Joy Kettren, Jennifer Cody, Nichole Skirvin *(Bioclinica Research, The Villages, Florida, USA)*

Background: A prescreening tool (Aptest) was developed and administered by members of a psychometric team at Bioclinica Research (formerly Compass Research) to facilitate the identification

of subjects who can meet study-specific inclusion/exclusion criteria. The goal of this project was to reduce screen fails and increase enrollment of viable subjects into studies that will further the advancement of Alzheimer's Disease (AD) research. *Methods:* During the initial phases of the study, internal screen fail data was reviewed. Screen fail rates for AD studies were calculated from October 2016 through March 2017. Screen fails were found to be primarily attributed to subjects not meeting inclusion/exclusion criteria on the following measures: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS – Delayed Recall), Free and Cued Selective Reminding Test (FCSRT), Mini-Mental State Exam (MMSE), Wechsler Memory Scale (WMS -Logical Memory II), and Clinical Dementia Rating scale (CDR). The 15-question Aptest was developed to screen for the processes measured by these scales. Beginning in April 2017, Aptest was used as the prescreening test for AD studies at The Villages research site. The test was administered to 300 subjects, 103 of whom were later screened for AD studies. Various composite cluster scores from the Aptest were compared to subject performances on subsequent administrations of RBANS, FCSRT, MMSE, WMS-LMII and CDR during screening. *Results:* Screen fail rates were recalculated from April 2017 through August 2017. This analysis revealed that the use of Aptest as a prescreening tool reduced screen fail rates by 25% for AD studies. Initial trends in data indicate that composite clusters within Aptest correlate with performance on the RBANS, FCSRT, WMS-LMII, and CDR. Initial comparative analysis revealed direct correlation between an Aptest composite cluster and subsequent CDR ratings on blinded administrations. *Conclusion:* Aptest is a screening test that can be administered in 5 to 10 minutes. Aptest results are not only yielding early indications of predictive validity, but also of diagnostic validity. Due to initial trends in data, a full independent investigation of this test will be conducted over several months which will include at least 200 subjects, half of which will fall within a healthy memory category, and half of which will have existing diagnoses of MCI or dementia. Each subject will initially be given the Aptest, the results of which will be compared to subsequent blinded administrations of selected subtests of the RBANS, MMSE, CDR, WMS and FCSRT. Cluster scores will be investigated to determine correlations between Aptest composites and performance on more involved cognitive measures. Further investigation and analysis is expected to result in a screening tool with both predictive and diagnostic validity. As such, the Aptest may prove to be a valid tool for both research and private clinical use.

LBP57: PSYCHOMETRIC PROPERTIES OF THE IMPRINT EYE TRACKING MEMORY ASSESSMENT: INTERNAL, TEST-RETEST AND ALTERNATE FORMS RELIABILITY. Nicholas T. Bott[1,2], Alex Lange[2], Robert Cosgriff[2], Paul Clopton[3], Beth Buffalo[2,4], Stuart Zola[2,5], Claudia Y. Santos[6], Peter Snyder[7,8] *((1) Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA; (2) Neurotrack Technologies, Inc., Redwood City, California, USA; (3) University of California San Diego School of Medicine, San Diego, California, USA (4) University of Washington, Seattle, Washington, USA; (5) Emory University Office of the Provost, Atlanta, Georgia, USA; (6) Interdisciplinary Neurosciences Program, University of Rhode Island, Kingston, RI, U.S.A; (7) Lifespan Clinical Research Center, Rhode Island Hospital, Providence, RI, USA; (8) Department of Neurology, Alpert Medical School of Brown University, Providence, RI, USA)*

Backgrounds: The recording of eye movements to assess cognition is a burgeoning area of research. Now that web cameras are increasingly part of the standard hardware of smart phones, tablets and laptop computers, we have the opportunity to develop eye movement tasks to efficiently and quickly assess cognitive function using these devices. Visual paired comparison (VPC) task paradigms assess recognition memory through comparison of the proportion of time an individual spends viewing a new picture (i.e., novelty preference) compared to a picture they have previously seen. A novelty preference is expected in individuals with normal memory function. By contrast, individuals with memory difficulties are characterized by more equally distributed viewing times between the novel and familiar pictures. The lack of novelty preference suggests impaired declarative memory for what has already been viewed. VPC tasks have been shown to reliably detect memory dysfunction in both primates and humans, and represent a paradigm deployable via devices with web cameras for the rapid assessment of declarative memory dysfunction. This study examined the internal and test-retest reliability on a VPC decisional task. *Methods:* This was an observational study of 44 healthy older adults with two risk factors for AD, including subjective memory complaints and a positive family history for the disease. Subjects completed two in-clinic visits with recording of eye movements on one of three image sets on a 5-minute VPC decision task by a standard eye tracker camera. Novelty preference was calculated as the ratio of time fixated on the novel image to time spent fixated on either image during each of the 20 test trials. Data from the standard eye tracker camera was scored using the product software. Internal reliability was analyzed using Cronbach's alpha procedure on a subsample of participants with complete trial data. Test-retest reliability was analyzed using Pearson correlations and Lin's concordance correlation coefficient procedure. Alternate forms were compared using one-way ANOVA. *Results:* Internal reliability estimate was good. Cronbach's alpha (n=24) was .82 overall with Cronbach's alpha ranging from .79 to .86 across image sets. Pearson correlation displayed good test-retest reliability (r=.79) with a mean follow-up of 300 days (n=44). Lin's concordance correlation coefficient demonstrated good concordance between time points (ϱc=0.77) with a mean follow-up of 300 days. One way ANOVA comparing novelty preference scores at each of the two time points across each of the three image sets demonstrated no significant differences in test scores (ps >.05). *Conclusions:* Analyses of internal reliability, test-retest reliability and equivalence of alternate image sets showed stable internal task properties with good test-retest reliability over long time intervals and equivalent performance across three alternate test forms. Built-in web cameras are a standard feature of most smart devices and can be effectively employed to track eye movements on VPC task paradigms. Brief assessment of declarative memory using such paradigms can be conducted with high accuracy and minimal cost, making them an ideal candidate for use in clinical trials.

LBP58: UTILITY OF THE INTERNATIONAL SHOPPING LIST TEST FOR DETECTION OF MEMORY IMPAIRMENT ASSOCIATED WITH PRODROMAL AND EARLY ALZHEIMER'S DISEASE IN CLINICAL TRIALS. Paul Maruff[1], Adrian Schembri[1], Shau Yu Lynch[2], Bruce Albala[2] *((1) Cogstate Ltd., Melbourne, Australia; (2) Eisai Inc., Woodcliff Lake, New Jersey, USA)*

Introduction: Memory impairment is a consistent manifestation of early Alzheimer's disease (AD). Therefore, screening for memory impairment is important for identifying individuals for inclusion in clinical trials of drugs designed to ameliorate the biological or clinical sequelae of AD. The International Shopping List Test (ISLT) is a 12-word/three-trial word learning test with established construct and criterion validity and high reliability for the detection of memory impairment in AD. The ISLT design enables its use in individuals from different language backgrounds, cultures and geographic regions

without the necessity for complex translations or cultural adaptions that must be applied to other verbal memory tests, such as the Free and Cued Selective Reminding Test (FCSRT) or Wechsler Memory Scale Logical Memory test (LM). While the ISLT has been used extensively to measure memory impairment in clinical studies, less is known about its utility as an objective memory inclusion instrument for clinical trials of AD. The aim of this study was to determine the sensitivity and specificity of the ISLT for classification of memory impairment associated with prodromal and early AD, to compare the magnitude of memory impairment associated with prodromal AD between the ISLT and the FCSRT and LM tests, and to determine the utility of the ISLT for classification of memory impairment as the objective cognitive inclusion criterion in a clinical trial setting (Eisai elenbecestat [E2609] phase 2 study). *Method:* Data for the ISLT immediate and delayed recall were drawn from three samples for the current analyses: (1) Cognitively normal amyloid negative (CNAβ–) adults from the Australian Imaging Biomarkers and Lifestyle (AIBL) cohort (n=100); (2) Aβ+ adults who met clinical criteria for MCI from the AIBL cohort (MCIAβ+; n=96); and (3) 84 of the 444 subjects who consented for the Eisai elenbecestat phase 2 BACE inhibitor study (E2609-G000-202), where subjects with MCI and mild-to-moderate dementia due to AD had an initial qualifying ISLT of ≥1.0 SD below age-matched controls and were Aβ+. This cohort of 84 subjects served as the Clinical Trial Validity sample. These subjects completed a second confirmatory ISLT (mean=66, SD=29.6 days) at the baseline visit prior to randomization. The ISLT normative data provided group means with SDs for individuals aged 60–90 years in quintiles. Clinically important episodic memory impairment was defined for each subject as occurring when performance on the ISLT total recall, delayed recall or both was ≤1 SD below the mean of the age-matched normative group. First, the number of individuals in each group with clinically important memory impairment was computed. For the AIBL CNAβ– and MCIAβ+ groups, the reliability of classification was determined by the extent to which the same classification was made on two assessments 6 months apart. Second, the difference in performance on the ISLT measures between the CNAβ– and MCIAβ+ group was expressed as a measure of effect size and compared to that observed on the LM and FCSRT tests. Rates of classification of clinically important memory impairment in each group were used to determine sensitivity (MCIAβ+ adults classified) and specificity (CNAβ– adults classified). Third, to determine the stability of the ISLT, the number of subjects in the Clinical Trial Validity sample classified as showing memory impairment on the ISLT at their baseline assessment was computed. *Results:* The ISLT identified memory impairment at baseline in 11% of the CNAβ– group from the AIBL and 9% of subjects after 6 months. For the MCIAβ+ group, memory impairment on the ISLT was classified in 83% of subjects on the first assessment and 87% on the second assessment. Examination of the stability of classification indicated that 1 (1%) subject in the CNAβ– group was classified on both ISLT assessments, while 80% of MCIAβ+ subjects were classified on both assessments. Compared with the CNAβ– group, the MCIAβ+ group showed statistically significant impairment on the total and delayed recall trials of the ISLT, LM and FCSRT with the magnitude of impairment (Hedges' g) equivalent for measures of immediate recall (ISLT=1.67, LM=1.21, FCSRT=1.41) and for delayed recall (ISLT=1.69, LM=1.27, FCSRT=1.41). Of the 84 subjects who initially qualified on the ISLT and were confirmed Aβ+, 80 (95%) met the objective cognitive criterion as impaired based upon their ISLT performance when retested at the later baseline visit just prior to randomization. *Conclusion:* The ISLT demonstrated high sensitivity and specificity for classifying memory impairment seen in prodromal AD. The magnitude of impairment on this test in MCIAβ+ was equivalent to other assessments of verbal episodic memory commonly used in clinical trials. Finally, the ISLT showed sensitivity and stability in classification of memory impairment in a clinical trial of a disease-modifying treatment in MCI/AD. The ISLT can serve as the objective inclusion criteria confirming cognitive impairment in clinical trials of prodromal/MCI or early AD.

LBP59: DCTCLOCK METRICS CORRELATE WITH NEUROIMAGING BIOMARKERS AMONG THOSE WITH AD GENETIC RISK. Braydon Schaible[1], William Souillard-Mandar[1], Randall Davis[1,2], Rhoda Au[3], Dana Penney[1,4] *((1) Digital Cognition Technologies, Inc., Waltham, MA, USA; (2) MIT Computer Science and Artificial Intelligence Laboratory, Cambridge, MA, USA; (3) Boston University Schools of Medicine and Public Health, Boston, MA, USA; (4) Lahey Hospital and Medical Center, Burlington, MA, USA)*

Background: By using novel software and machine learning algorithms, the DCTclock test transforms the traditional Clock Drawing Test into a sensitive cognitive screening tool able to detect and quantify subtle cognitive decline. Our prior work has demonstrated that DCTclock cognitive screening classification outperforms widely used cognitive screening tests including manual CDT scoring systems and the Mini Mental Status Examination (MMSE). Neuroimaging and genetic biomarkers are accepted gold standard markers of AD risk, but are expensive, invasive and provide no indication of cognitive status. Pilot work demonstrated that the DCTscore was associated with ApoE high and low genetic risk groups in a dementia-free population. In this study we examine the correlates of DCTclock metrics with brain MRI indices in a community-based sample stratified by low and high AD genetic risk. *Methods:* Subjects: 1220 dementia and stroke-free Framingham Heart Study (FHS) participants genotyped for ApoE were classified into High (ApoE4+, n=261) and Low AD (ApoE4-, n=931) risk groups. All participants were administered the DCTclock test for both the Command and Copy conditions, between 2011-2016. Participants with ApoE 2/4 (n=28) were excluded because of potential E2 protective effects. Of the remaining 1192 participants, we selected the subset with brain MRI imaging performed within one month of administration of the DCTclock (n=454; mean 0.13 days, sd=1.9 days). High and Low risk groups did not differ in age (mean=71.4, sd=17.3), gender (56.2% female), education (77.1% had some college education), or MMSE score (28.8, sd=1.5), 84.8% were right handed. DCT Metrics: Standard DCTclock metrics included DCTclock Score (0–100, representing overall cognitive function as assessed by DCTclock, 100 indicates maximum score), and three Composite Scale scores for each drawing condition: (1) Drawing Efficiency (DE), a combination of stroke count, total time, drawing size, and total ink length; (2) Information Processing (IP), a combination of the length of and distribution of latencies between pen strokes; (3) Spatial Reasoning (SR), a combination of geometric and spatial placement properties of the drawing. MRI metrics included well-accepted AD-associated total brain indices (grey matter, CSF volumetric measurements), and indices for specific regions (frontal, occipital, parietal, and temporal lobes). All MRI measurements were divided by total cranial volume. Linear regression, adjusting for age, gender, and education was then used to correlate DCTclock scores to MRI volumetric measurements. We created individual models for each pairing of a DCTclock metric and an MRI measurement. P-values were adjusted for multiple comparisons using the Bonferroni-Holm method, and statistical significance assessed on the adjusted p-values at the 0.05 level. *Results:* High and Low AD risk groups differed on the DCTclock Score (p=0.004) and on Composite scales, including command clock Drawing Efficiency (p=0.032), copy clock Information Processing

(p=0.017), and both command and copy clock Spatial Reasoning (p=0.022 and p=0.033, respectively). As Figure I indicates, poorer performances (lower DCTclock scores), were more frequently associated with the high-risk group compared to the low-risk group.

Figure 1
Density plots of DCTclock overall scores stratified by APoE4 risk group

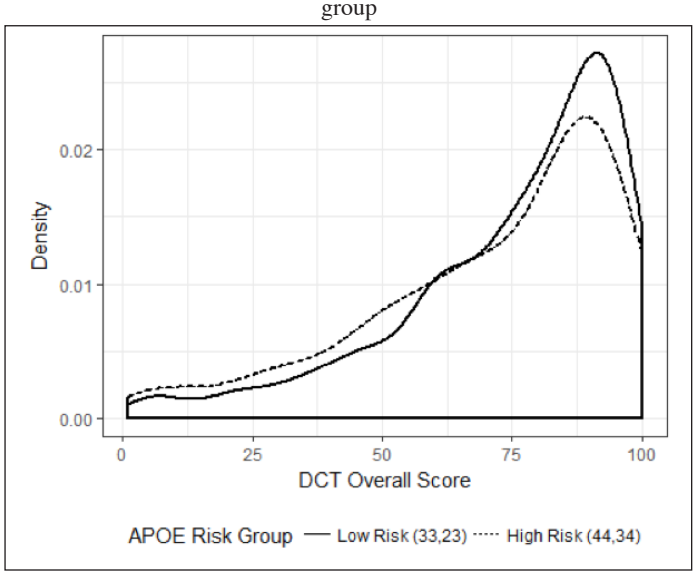
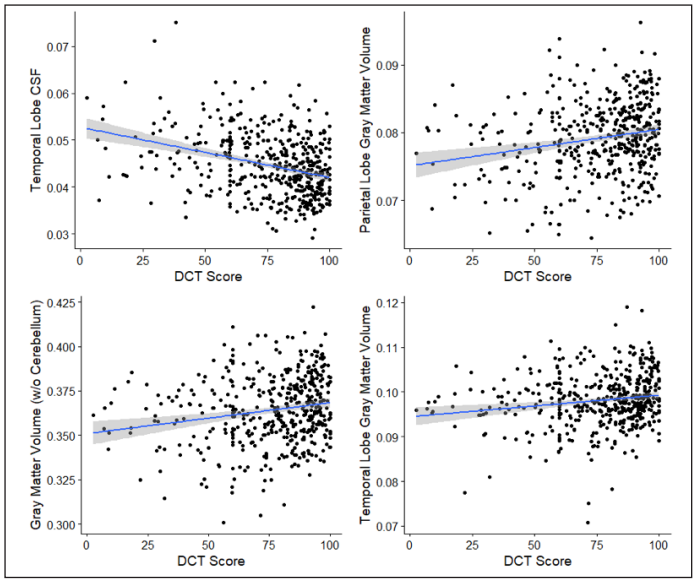


Figure 2
Scatter plots of DCT overall scores by MRI volumetric measurements



DCTclock Score showed a significant positive linear association with overall gray matter volume (total gray matter (p=0.004)) and with specific regions including parietal lobe gray matter (p<0.001) and temporal lobe gray matter (p=0.025). Temporal lobe CSF volume showed a negative linear relationship with DCT scores (p<0.001): lower CSF volume associated with higher DCTclock Score and Composite scales. Table II summarizes the linear regression results for DCTclock variables and MRI volumetric measures.

Table 1
Linear regression results for DCT variables on MRI volumetric measurements

DCT Variable	MRI Variable	Parameter Est.	Raw P-Value	Adjusted P-Value
DCT Overall Score	Total Gray w/o CRBL	0.00017	<0.001	0.004
DCT Overall Score	Parietal Gray	0.00005	<0.001	<0.001
DCT Overall Score	Temporal Gray	0.00005	<0.001	0.025
DCT Overall Score	Temporal CSF	-0.00011	<0.001	<0.001
IP COP	Temporal CSF	-0.00018	<0.001	<0.001
SR COM	Temporal CSF	-0.00012	<0.001	<0.001
IP COM	Temporal CSF	-0.00160	<0.001	<0.001
DE COM	Temporal CSF	-0.00013	<0.001	0.001
DE COP	Temporal CSF	-0.00015	<0.001	0.002
IP COP	Total Gray w/o CRBL	0.00034	<0.001	0.003
SR COM	Total Gray w/o CRBL	0.00019	<0.001	0.015
IP COP	Total Gray	0.00037	<0.001	0.030

Note: IP=Information Processing, SR=Spatial Reasoning, DE=Drawing Efficiency. COM=Command Clock, COP=Copy Clock, CSF=Cerebrospinal Fluid, CRBL=Cerebellum

Conclusion: Findings indicate that novel cognitive process variables captured by DCTclock are associated with AD-related neuroimaging biomarkers, and are differentiated among those who are high versus low AD genetic risk. Results suggest that DCTclock is sensitive to pre-clinical cognitive change with potential utility as an inexpensive and non-invasive cognitive screening tool.

Theme: Behavioral disorders and clinical trials

LBP60: DONEPEZIL TREATMENT IN PATIENTS WITH DEPRESSION AND COGNITIVE IMPAIRMENT ON STABLE ANTIDEPRESSANT TREATMENT: A RANDOMIZED CONTROLLED TRIAL. Davangere P. Devanand[1], Gregory H. Pelton[2], Kristina D'Antonio[3], Adam Ciarleglio[4], Jennifer Scodes[5], Howard Andrews[6], Julia Lunsford[7], John L. Beyer[8], Jeffrey R. Petrella[9], Joel Sneed[10], P. Murali Doraiswamy[11] *((1) Geriatric Psychiatry & Department of Psychiatry, Columbia University, New York, NY, USA; (2) Geriatric Psychiatry & Department of Psychiatry, Columbia University, New York, NY, USA; (3) Geriatric Psychiatry & Department of Psychiatry, Columbia University, New York, NY, USA; (4) Biostatics, Department of Psychiatry, Columbia University, New York, NY, USA; (5) Biostatics, Department of Psychiatry, Columbia University, New York, NY, USA; (6) Biostatics, Department of Psychiatry, Columbia University, New York, NY, USA; (7) Department of Psychiatry, Duke University, Durham, NC, USA; (8) Department of Psychiatry, Duke University, Durham, NC, USA; (9) Department of Radiology, Duke University, Durham, NC, USA; (10) Department of Psychology, Queens College, City University of New York, New York, NY, USA; (11) Department of Psychiatry, Duke University, Durham, NC, USA)*

Background: Depression and cognitive impairment are often comorbid in older adults but optimal treatment strategies for these patients remain unclear. To compare the efficacy and safety of add-on donepezil versus placebo treatment in depressed patients with cognitive impairment already receiving stable antidepressant treatment. *Method:* A randomized, double-blind, placebo-controlled trial was conducted in two University clinics. Older adults with both depression and cognitive impairment received open label

antidepressant treatment for 16 weeks followed by add-on donepezil or placebo for another 62 weeks. Open label antidepressant treatment with citalopram and then with venlafaxine if needed, followed by random assignment to add-on donepezil 5 to 10 mg daily or placebo. Neuropsychological test performance (ADAS-Cog and SRT total immediate recall) and instrumental activities of daily living (FAQ). A test of odor identification, MRI hippocampal and entorhinal cortex volumes and hyperintensities, and apolipoprotein E e4 genotype were assessed as possible moderators of treatment effects. *Results:* Of 81 consented patients, 79 patients completed baseline evaluation. Open antidepressant treatment was associated with improvement in depression with 63.93% responders by week 16. In the randomized trial, there were no treatment group differences between donepezil and placebo on ADAS-Cog ($t = 1.54$, $p = 0.13$), SRT Total Immediate Recall ($t = 0.42$, $p = 0.68$), or FAQ ($t=0.73$, $p=0.47$). There was no difference in dementia conversion rates between the two groups. Baseline cognitive impairment severity or apolipoprotein E e4 genotype did not influence donepezil efficacy. Donepezil treatment was associated with more adverse effects and drop outs than placebo. *Conclusion:* In the first long-term randomized trial of adjunctive donepezil for comorbid depression and cognitive impairment, there was no evidence to support the current common practice of adjunctive off-label cholinesterase inhibitor use in patients with comorbid depression and cognitive impairment. Given the high prevalence of comorbid depression with cognitive impairment and the increased risk of dementia posed by both conditions, the findings highlight the need to prioritize discovery of novel treatments for this clinically challenging population.

LBP61: MEMANTINE ER WITH AN ACHEI IMPROVES INDIVIDUAL SIB SCORES COMPARED WITH ACHEI ALONE: POST HOC ANALYSES FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY. George Grossberg[1], Ken Kramer[2], Suzanne Hendrix[3], Noel Ellison[3], Majid Kerolous[2] *((1) Saint Louis University, Saint Louis, MO, USA; (2) Allergan, Jersey City, NJ, USA; (3) Pentara Corporation, Salt Lake City, UT, USA)*

Background: Based on rigorous phase 3 studies demonstrating the efficacy of memantine on cognition, function, and global outcomes in patients with Alzheimer's disease (AD), both immediate- and extended-release (ER) formulations are approved in the US and EU for the treatment of moderate to severe AD. Memantine is an uncompetitive antagonist of N-methyl-D-aspartate (NMDA) glutamate receptors. In a previously reported double-blind study in which patients taking a stable dosage of an acetylcholinesterase inhibitor (AChEI) were randomized to memantine ER 28 mg/day (MemER) or placebo (PBO) for 24 weeks, memantine-treated patients significantly outperformed placebo-treated patients on the coprimary efficacy parameters, endpoint score on the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) and baseline-to-endpoint score change on the Severe Impairment Battery (SIB). At 24 weeks, the PBO-adjusted mean difference from baseline on the SIB was 2.6 points. To further characterize MemER effects, this post hoc analysis examines individual SIB score changes (improvement or worsening) of at least 5 points for the overall population receiving any AChEI and for a subgroup of patients receiving donepezil (DON 10 mg/day). *Methods:* Post hoc analyses were conducted on the SIB data set from the 24-week, double-blind, multinational MD-50 study (NCT00322153). In this study, patients with moderate to severe AD receiving a stable dosage of an AChEI (≥3 months) were randomized to once-daily MemER 28 mg or PBO. SIB changes from baseline to week 24 were compared for all patients (MemER/AChEI vs PBO/AChEI) and for the subgroup of patients receiving DON (MemER/DON vs PBO/DON). The distribution of SIB scores as change from baseline to week 24 were examined in 5-point increments (eg, absolute changes of 1 to 5, 6 to 10, 11 to 15). «Improvement/decline» was noted at 5-point changes; «notable improvement/decline» at 10-point changes; and «remarkable improvement/decline» at 15-point changes. *Results:* Of 676 patients in the safety population, 541 had SIB scores at baseline and week 24 and were included in this analysis (n=270 MemER/AChEI; n=271 PBO/AChEI); nearly 70% were treated with concomitant DON (n=187 MemER/DON, n=183 PBO/DON). At week 24, more patients receiving MemER/AChEI (40%) experienced a 5-point or greater improvement in SIB score compared with those receiving PBO/AChEI (31%). Almost twice as many MemER/AChEI patients had a notable improvement of ≥ 10 points on the SIB vs PBO/AChEI patients (23% vs 13%); twice as many had remarkable improvements (≥ 15 points) with MemER/AChEI vs PBO/AChEI (14% vs 7%). Fewer patients treated with MemER/ChEI declined by 5 or more points on the SIB vs those treated with PBO/AChEI (19% vs 24%), with similar results noted at declines of 10 or more (10% vs 13%) and 15 or more (6% vs 7%). Among patients taking DON, 44% of MemER/DON patients experienced a 5-point or greater improvement in SIB score at week 24 from baseline compared with 37% of those receiving PBO/DON. Almost twice as many MemER/DON patients vs PBO/DON patients demonstrated notable improvements of ≥ 10 points (27% vs 15%), and twice as many had remarkable improvements of ≥ 15 points (17% vs 8%) from baseline. Fewer patients treated with MemER/DON declined by 5 or more points vs PBO/DON (14% vs 20%) and 10 or more points (7% vs 9%). Results were similar between treatment groups for remarkable declines of 15 points or more (4% vs 4%). *Conclusion:* In this study of patients with moderate to severe AD, the mean improvement from baseline to endpoint (week 24) on the SIB was 2.6 points. Here, more patients treated with a combination of memantine ER and an AChEI experienced improvements (5, 10, and 15 points) greater than the placebo-adjusted mean difference on the SIB compared with those treated with an AChEI alone. Fewer patients treated with a combination of memantine ER and an AChEI experienced a decline in cognition when compared with an AChEI alone. Similar results were observed in a subgroup of patients treated with memantine ER and 10 mg donepezil vs those treated with donepezil alone. As no disease-modifying treatments for AD are available, these data further support that memantine ER combined with an AChEI impacts cognition, representing an important treatment option for patients with moderate to severe AD. Funding: Allergan plc

LBP62: USING RADIO SIGNAL-BASED SENSING AND MACHINE LEARNING FOR CONTINUOUS LONGITUDINAL MONITORING OF BEHAVIORAL SYMPTOMS IN DEMENTIA: A PILOT CASE STUDY. Ipsit Vahia[1], Zachary Kabelac[2], Chen-Yu Hsu,[2], Rumen Hristov[2], Patrick Monette[1], David Harper[1], William McGrory[3], Brent Forester[1], Dina Katabi[2] *((1) Division of Geriatric Psychiatry, McLean Hospital/Harvard Medical School, Belmont, MA, USA; (2) Computer Science and Artificial Intelligence Lab (CSAIL), Massachusetts Institute of Technology (MIT), Cambridge, MA, USA; (3) Robbie's Place Assisted Living, Marlborough, MA)*

Background: Assessments of behavioral symptoms (e.g. depression, anxiety, insomnia, agitation) in Alzheimer's Disease trials have relied exclusively on self- or observer report scales whose limitations are well documented. Mobile and wireless sensors have been used to offset some of these limitations and can provide continuous, passive behavioral data. However, in dementia, these

devices may not be ideally suited because of the need to carry/wear and regularly recharge the devices. Such devices are also unable to provide spatial information such as location, or vital signs. A wireless sensor developed at MIT may provide a solution to some of these issues. This device uses radio signals to map sleep, motion, spatial location and respiratory rate without touching the patient in any way. It collects data passively (i.e. requiring no active engagement by the person being monitored). In this study, we describe (a) the process of developing behavioral biomarkers using data from this device, (b) how such data can be used for clinical decision making, and (c) how combining information on socio-environmental factors can identify triggers of behavioral symptoms (thereby facilitating preventative intervention). While the device's validity has been established in prior publications, this work describes its first use in a clinical setting to monitor dementia symptoms. *Methods:* Device: Emerald is a device developed at MIT for in-home, non-intrusive patient monitoring. The device transmits low-power radio signals (100x lower power than WiFi) and monitors the reflection of these signals from people/ their environment to map behavioral information. Signal data are uploaded to the cloud where customized machine learning algorithms process the data to extract gait speed, sleep patterns, falls, spatial location, respiration (by measuring chest wall movements). Subject: We installed the device in the room of a 77-year old female with Alzheimer's disease in an Assisted Living facility. Data were collected from 05/17 through 08/17. We measured the patient's behavior continuously for this period along the metrics described in the next section. Metrics/Procedure: We conducted this study in three phases: In Phase 1 (2 weeks), we identified 4 behavioral markers of clinical relevance to this patient: gait speed, spatial location, respiratory rate and sleep patterns. We further developed a measure of pacing severity, which was the daily aggregation of number of episodes where the patient moved 6 feet or greater in the same direction without stopping. In Phase 2 (3 months), the lead author (IV), who was the patient's clinician utilized these markers to decide medication changes. Prior to implementing changes, the behavioral findings identified by the sensor were confirmed by Assisted Living staff who observed the patient daily. In Phase 3, we incorporated collateral information about the patient's social activity (e.g. number of visitors, trips outside the facility, group participation) and mapped these onto sensor data to assess temporal associations. *Results:* Over the course of the study, we documented 7403 episodes of movement. Phase 1: The device was feasible to use safely over an extended period continuously in an Assisted Living facility in the living environment of a dementia patient with behavioral symptoms. We qualitatively compared sensor data with staff-report information. We noted that staff reported the patient's behavior dichotomously as either 'calm' or 'restless'. By contrast, the sensor was able to detect variations in behavior by time of day, variations over a week, escalation in pacing, and episodes of awakening late at night. Phase 2: We identified the following clinical events/patterns, based on which clinical intervention was initiated: (1) the patient tended to go to bed around 6PM and awaken around 2AM, leading to night-time wandering, usually in her room (2) On 3 different occasions, we identified escalated pacing (defined as over 250 episodes of movement> 6ft). On each of these occasions, her dose of divalproex was increased by 250mg. In the last week of August, her quetiapine was discontinued and this appeared to increase her daily pacing episodes. We did not obtain any clinically actionable information based on respiratory rate. Phase 3: We identified that in the 24 hours following visits by her husband or son, her pacing severity increased by 40%. Hence, visits by family members were a trigger for agitation. *Conclusion:* This study establishes the safety and feasibility of using a radio-signal based non-wearable, non-mobile sensor in a residential care setting for dementia. Data collected by the device provided much more detailed information about behavior than staff report. Since most behavioral studies rely on staff report, a device such as this holds potential to exponentially improve the quality of clinical trial data. We demonstrated that device data could be used for early detection of behavioral changes and subsequent medication adjustment and to identify triggers for behavior symptoms, such as (in this case) visits from family members. Our preliminary findings point to a large potential for contactless radio-signal based devices in clinical trials as well as patient care.

Theme: Animal models and clinical trials

LBP13: SUVN-502 POTENTIATES THE PRECLINICAL PHARMACOLOGICAL ACTIVITIES OF CURRENT STANDARDS-OF-CARE FOR ALZHEIMER'S DISEASE. Ramakrishna Nirogi, Vijay Benade, Renny Abraham, Gopinadh Bhyrapuneni, Jyothsna Ravula, Koteshwara Mudigonda, Devender Reddy Ajjala, Ramasastry Kambhampati, Anil Shinde, Venkat Jasti *(Discovery Research, Suven Life Sciences Ltd, Hyderabad, India)*

Background: SUVN-502 is a pure and potent 5-HT6 receptor antagonist with excellent oral bioavailability and brain penetration in preclinical species. SUVN-502 demonstrated pro-cognitive activity and enhanced brain acetylcholine levels as a standalone treatment. SUVN-502 also demonstrated excellent margin of safety in the toxicological studies. It was also safe and well tolerated in healthy human subjects. *Methods:* The effect of SUVN-502 in combination with donepezil, memantine or donepezil + memantine was evaluated for pro-cognitive property (object recognition task), acetylcholine modulation (brain neurochemistry) and theta modulation (electrophysiology) in male Wistar rats. *Results:* SUVN-502 in combination with donepezil produced significant improvement in cognition, hippocampal acetylcholine release and elicited theta levels compared to donepezil treatment alone. Similarly, SUVN-502 potentiated the pharmacological effects of memantine in animal models of cognition, brain neurochemistry and electrophysiology. Co-treatment of SUVN-502 with donepezil and memantine significantly potentiated the procognitive effects of memantine and donepezil treatment in the object recognition task. SUVN-502 potentiated the effects of donepezil and memantine and produced significantly higher increase in brain acetylcholine levels and elicited theta levels in hippocampus. There were no significant changes in the plasma exposures of SUVN-502, donepezil or memantine when given alone or in combination. *Conclusions:* Results from the current investigation demonstrate that SUVN-502 potentiates the activities of all current standards-of-care and has potential to be combined with donepezil alone or memantine alone or both donepezil + memantine for the symptomatic treatment of Alzheimer's disease.

LBP14: THE PDE4-INHIBITOR ROFLUMILAST IMPROVES MEMORY: FINDINGS FROM A TRANSLATIONAL PERSPECTIVE. Arjan Blokland[1], Wim Riedel[1], Marlies Van Duinen[2], Anke Sambeth[1], Pim Heckman[1], Max Tsai[3], Gezim Lahu[4], Tolga Uz[3], Jos Prickaerts[2] *((1) Department of Neuropsychology and Psychopharmacology, Maastricht University, Maastricht, The Netherlands; (2) Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands; (3) Takeda Development Center, Takeda, Deerfield, USA; (4) Takeda Pharmaceuticals International, Takeda, Zürich, Switzerland)*

Backgrounds: The cognition enhancing effects of PDE-4 inhibitors (PDE4-Is) in animal studies have long been recognized [1]. Considering the increasing need for cognition enhancers for treatment

of several disorders, the translation to a human population seemed logical, but application of PDE-4Is was impeded due to emetic side effects. The development and approval of the PDE- 4I roflumilast, which shows low emetic properties, allowed testing PDE-4I cognition enhancing properties in humans for the first time. In fact, we assessed the cognition enhancing potential of roflumilast in a translational setting, including both rodents and human volunteers. In healthy 7-month-old mice, roflumilast dose-dependently improved memory consolidation in the object location task at 0.03 mg/kg and short-term memory in the spatial Y-maze at 0.1/kg. In a xylazine-ketamine model for emesis roflumilast was 100-times less potent suggesting a low emetic potential at cognition-enhancing doses [2]. *Methods:* Two human studies were conducted in which roflumilast was administered according to a double-blind, placebo-controlled cross-over design using three dosages in the 100-1000 μg range. *Results:* In a first study with young healthy subjects (18-30 years) treatment with 100 μg roflumilast improved the memory performance at the third trial of a verbal word learning task (effect size 0.68). This was associated with an enhanced event-related potential (higher P600 peak; effect size 0.62). Two higher doses (300 and 1000 μg) showed no effects. Roflumilast did not improve spatial working memory performance. Some side effects (i.e., nausea) were reported at the two higher doses but not at the 100 dose. In an experiment with old subjects (60–80 years), subjects were first screened for their performance on a verbal word learning task. Based on normative data [3], they were assigned to a normal (n = 20) or a memory impaired group (1–2 STDEV below normative data; n = 15). The effects of roflumilast (100, 250 and 1000 μg) were assessed in a verbal word learning task and a spatial working memory task. The 100 μg dose improved the verbal word memory performance in the normal memory performance group (effect size 0.96) and in the memory impaired group (effect size 0.76). No effects were found on the spatial working memory task. The dose of 100 μg was not associated with severe side effects (only one subject reported mild nausea). At the higher doses several subjects reported side effects, such as nausea and diarrhea.

Theme: New therapies and clinical trials

LBP15: SUVN-502 + DONEPEZIL + MEMANTINE (TRIPLE COMBINATION) REPRESENTS A PROMISING NEW APPROACH FOR SYMPTOMATIC TREATMENT OF ALZHEIMER'S DISEASE. Ramakrishna Nirogi, Renny Abraham, Vijay Benade, Pradeep Jayarajan, KoteshwaraMudigonda, JyothsnaRavula, Devender Reddy Ajjala, Ramasastry Kambhampati, Trinath Reddy Bandyala, Venkat Jasti *(Discovery Research, Suven Life Sciences Ltd, Hyderabad, India)*

Background: SUVN-502 is a pure 5-HT6 receptor antagonist being developed for the treatment of Alzheimer's disease (AD). It has good ADME properties and demonstrated robust efficacy and safety in animal models. In healthy human subjects, SUVN-502 was well tolerated following single or multiple oral administrations. *Methods:* SUVN-502 is currently being evaluated in a phase 2a, multicenter, randomized, double-blind, parallel group, 26-week, placebo controlled proof of concept study. This study is regulated by US FDA. A total of 537 subjects with moderate AD receiving stable doses of donepezil and memantine are planned to be recruited. Subjects will receive placebo or SUVN-502 (50 or 100 mg) on top of donepezil and memantine for 26 weeks. Rationale for phase 2 study: The effect of SUVN-502 + Donepezil + Memantine combination was evaluated for procognitive property (object recognition task), acetylcholine modulation (microdialysis) and theta modulation (electrophysiology) in animal models. *Results:* Co-treatment of SUVN-502 with donepezil and memantine significantly potentiated the procognitive effects of memantine and donepezil in the object recognition task. These effects were persistent after repeated administration. SUVN-502 also potentiated the effects of donepezil and memantine combination, in increasing the hippocampal acetylcholine modulation and brain oscillatory activity. There were no significant changes in the exposures of SUVN-502 or donepezil or memantine when administered alone or in combination. Thus, SUVN-502 is being evaluated in combination with donepezil and memantine in moderate AD patients. *Conclusions:* SUVN-502 + Donepezil + Memantine (Triple combination) represents a promising new approach for symptomatic treatment of Alzheimer's disease.

LBP16: NEUROPROTECTIVE AND TROPHIC EFFECTS OF BACOPA MONNIERA EXTRACT PROTECTS AGAINST AMYLOID ®-PEPTIDE AND HYDROGEN PEROXIDE-INDUCED TOXICITY AND OXIDATIVE STRESS; Manjeet Singh, Charles Ramassamy (*INRS- Institut Armand Frappier, Laval, Quebec, Canada)*

Backgrounds: Alzheimer's disease (AD) is the most common age-related neurodegenerative disease affecting millions of people worldwide. The aggregation of soluble amyloid-β peptide (Aβ) into fibrillar deposits is a pathological hallmark of AD. Strong evidence supports the role of the Aβ peptide induced oxidative stress (OS) and synaptic loss in the pathophysiology of AD. In brains of AD patients, different markers of oxidative stress are significantly higher and there is significant loss of synaptic proteins. Bacopa monniera (BM) have a long history of use for memory-enhancing therapy in Ayurveda, a 5000-year-old system of traditional Indian medicine. Although a number of both animal and clinical studies supported its role as a memory enhancer, but there is dearth of studies on the molecular and cellular mechanisms underlying the neuroprotective effects of BM. *Methods:* The objective of this study was to further investigate whether BM extract can protect against Aβ peptide and H2O2- induced toxicity. To screen the neuroprotective and trophic effects of BM we used human SK-N-SH neuroblastoma and rat PC12 cells. They were treated with amyloid beta (Aβ) peptide and hydrogen peroxide hydrogen peroxide (H2O2). Cytotoxicity and cell survival was measured by using LDH and XTT assays by using commercial kits. The antioxidant activity of BM was confirmed by measuring its ability to scavenge reactive oxygen species (ROS) and superoxide levels in SK-N-SH cells by using various fluorescent dyes. Effect of BM treatment on the expression of synaptic proteins was measured by western blot analysis. *Results:* We demonstrate that a treatment with BM extracts significantly protected the human SK-N-SH neuroblastoma cell line against Aβ peptide and H2O2 induced toxicity from 0.05 μg/ml and from 1.0 μg/ml respectively in various cell survival assays. Furthermore, a treatment with BM extract significantly reduced the levels of intracellular ROS and superoxide. Additionally BM treatment from 5.0 μg/ml significantly induced synaptic proteins such as synaptophysin and neurofilament-light in PC12 cells. *Conclusions:* Although the exact mechanisms underlying the toxicity of Aβ peptide are unclear, oxidative stress and synaptic dysfunctions play an important role in the pathogenesis of AD. Aβ peptide has been shown to generate hydrogen peroxide (H2O2) and depleted cellular reduced glutathione (GSH). Furthermore, deposition of amyloid (senile) plaques is also associated with loss of synaptic morphology and functions and dystrophic neurites, which could lead to cognitive decline. New approaches that target synaptic integrity and modulate oxidative stress might be useful in preventing Aβ peptide-induced neurotoxicity and could provide disease modifying therapeutic benefits in AD. Thus, our findings indicate that BM extract may act

as a neuroprotective and trophic antioxidant and may have beneficial effects in the AD therapy.

LBP17: PHASE 1 STUDY OF THE MUSCARINIC M1 POSITIVE ALLOSTERIC MODULATOR VU319 FOR ALZHEIMER'S DISEASE: EXPLORATION OF NOVEL MARKERS OF TARGET ENGAGEMENT. Paul A Newhouse[1], Alexandra Key[1,2], Alexander Conley[1], Robert Gould[3], Carrie Jones[3] *((1) Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center; (2) Vanderbilt Kennedy Center, Vanderbilt University; (3) Vanderbilt Center for Neuroscience Drug Discovery, Department of Pharmacology, Vanderbilt University)*

Background: Loss of cholinergic signaling is principally related to cognitive decline in Alzheimer's Disease (AD) and stimulation of these receptors improves cognitive performance. While acetylcholinesterase inhibitors (AChEI) are modestly helpful in the early stages of AD, neurodegeneration limits their effectiveness, and warrants the development of alternative cholinergic treatments. Treatments that target the M1 muscarinic cholinergic receptor may augment the effects and lengthen the effectiveness of AChEI's. Efforts to develop M1-selective agonists all showed cross-reactivity with M2 and M3 receptors and failed due to side effects. *Methods:* We have a mature development program for muscarinic cholinergic M1-positive allosteric modulators (PAM) with a lead compound VU0467319 (VU319), a highly selective M1PAM that has advanced to Phase 1. M1 PAMs potentiate the response of the M1 receptor to acetylcholine, enhancing activity-dependent signaling. VU319 and related compounds (e.g VU595) show M1-mediated effects on hippocampal synaptic plasticity, excitatory drive to prefrontal cortex, and basal ganglia function and have robust effects on domains of both hippocampal and prefrontal cortical-dependent cognitive function in animal models that reflect cognitive domains impaired in AD. These results support the hypothesis that M1-selective PAMs may have efficacy in improving cognitive function in AD. Phase 1 studies consist not only of standard measures to establish maximum tolerated doses and safety, but also to establish a functional biomarker of central M1 target engagement. *Results:* We report evidence from early phase drug trials using event-related potentials (ERP) and cholinergically-responsive psychomotor cognitive tasks developed in our laboratory as markers of CNS engagement. We explore whether M1 PAM treatment may potentiate M1 in the CNS in humans by evaluating changes in electroencephalography (EEG) functions (e.g. altered ERPs) at doses that do not produce typical muscarinic side effects. Additionally, we are utilizing specific cholinergically-responsive attention, memory, and psychomotor cognitive tasks developed in our laboratory. *Conclusion:* Together with safety measures, these novel cognitive biomarkers will establish the dose range to be used in future clinical studies utilizing measures that are relevant for improving cognitive function in AD and may also be useful as functional biomarkers for Phase 2/3 clinical trials.

LBP18: EFFICACY AND SAFETY OF THE CHINESE MEDICINE SAILUOTONG IN VASCULAR DEMENTIA: A RANDOMISED, CONTROLLED, DOUBLE-BLIND, PARALLEL-ARM TRIAL. Jianping Jia[1,2,3,4,5], Cuibai Wei[1], Shuoqi Chen[1], Fangyu Li[1], Yi Tang[1], Wei Qin[1], Lu Shi[1], Min Gong[1], Hui Xu[1], Fang Li[6], Jia He[7], Haiqing Song[1], Shanshan Yang[8], Aihong Zhou[1], Fen Wang[1], Xiumei Zuo[1], Changbiao Chu[1], Junhua Liang[1], Longfei Jia[9], Serge Gauthier[10] *(1) Department of Neurology, Xuan Wu Hospital, Capital Medical University, Beijing, China; (2) Beijing Key Laboratory of Geriatric Cognitive Disorders; Beijing, China; (3) Center of Alzheimer's Disease, Beijing Institute for Brain Disorders, Beijing, China; (4) Key Laboratory of Neurodegenerative Diseases, Ministry of Education; Beijing, China; (5) National Clinical Research Center for Geriatric Disorders; Beijing, China; (6) Department of Gerontology, Fuxing Hospital, Capital Medical University, Beijing, China; (7) Department of Health Statistics, Second Military Medical University, Shanghai, China; (8) Department of Neurology, Daqing Oilfield General Hospital, China; (9) Department of Neurology, Henry Ford Hospital, Detroit, USA; (10) Centre for Studies in Aging, McGill University, Montreal, Canada)*

Backgrounds: No licensed medications are available to treat vascular dementia (VaD); thus, this study evaluated whether SaiLuoTong (SLT) is effective for the treatment of this disease. *Methods:* This was a randomised, controlled, double-blind, parallel-arm trial performed at 16 centres. Patients with mild to moderate VaD were randomly assigned to one of four groups (4:4:2:2): SLT 360 mg (Group A; 180 mg orally twice daily), SLT 240 mg (Group B; 120 mg orally twice daily) for 52 weeks; and placebo control (Groups C1 and C2) for the first 26 weeks, and then SLT 360 mg and 240 mg (180 mg for C1 and 120 mg for C2 orally twice daily) for the next 26 weeks. Randomisation was conducted using an interactive web response system followed by stratification according to VaD severity and academic centre. All of the patients, caregivers, and study personnel were blinded to treatment allocation. The co-primary outcomes were progression on the vascular dementia assessment scale cognitive subscale (VaDAS-cog) and the Alzheimer's disease cooperative study-clinical global impression of change (ADCS-CGIC) from baseline assessed at weeks 26 and 52 in the modified intention-to-treat population. This trial was registered at clinicaltrials.gov (NCT01978730). *Results:* In total, 388 patients were screened from March 28, 2012 to February 25, 2013, and 325 were included in the final analysis. At week 26, the changes in VaDAS-cog scores from baseline were −3·25 (SE 0·45) for Group A ($p < 0·0001$), −3·05 (0·45) for Group B ($p < 0·0001$), and −0·57 (0·45) for Group C ($p = 0·15$), with a significant difference among groups ($p < 0·0001$). Scores in Group C changed significantly from baseline to week 52 ($p = 0·00070$ for Group C1; $p < 0·0001$ for Groups C2). For ADCS-CGIC at week 26, the scores were 3·57 (SE 0·10) for Group A, 3·57 (0·10) for Group B, and 3·88 (0·10) for Group C, showing a significant difference among groups ($p = 0·027$). At weeks 52, continuous cognitive improvement was observed in all of the groups. No significant difference in adverse events was seen among groups ($p = 0·066$ at week 26, $p = 0·78$ at week 52). *Conclusion:* SLT was found to be safe and potentially effective for mild to moderate VaD at week 26 against placebo. Similar benefits were reproduced at week 52 in the control group, supporting the results of the first 26 weeks.

LBP19: INCREASED IMMUNE SIGNALING PREDICTS MITIGATION IN AD CLINICAL OUTCOMES – AN ALTERNATE ROUTE TO PREVENTION. John Breitner[1], Pierre-Francois Meyer[2], Judes Poirier[1,2] *((1) Douglas Hospital Research Centre, Montreal, QC, Canada; (2) McGill University Faculty of Medicine PREVENT-AD Research Group1, for the Alzheimer's Disease Neuroimaging Initiative)*

Background: One might prevent Alzheimer's disease (AD) dementia by delaying or avoiding the development of disease pathology, but an alternate route to prevention is suppression of symptom expression associated with such pathology. Cognitive symptoms of AD are commonly thought to be caused in part by an inflammatory reaction surrounding the disease's characteristic lesions. [1]. *Methods:* To explore immune marker modulation as a route to prevention of symptoms, we therefore studied immune / inflammatory markers in the CSF of two groups of research participants. In the PREVENT-AD cohort of aging asymptomatic persons at elevated risk of AD [2] – all with either a parental history of AD dementia or two or more affected siblings – we assayed CSF from 101 participants for the "classic" AD biomarkers Aβ42, total (t-)tau, and 181-P-tau using strict JPND BIOMARK-APD procedures. We also assayed apoE protein concentration along with 45 immune/inflammatory markers from the same CSF measured using the Milliplex HCYTMAG60PMX29BK xMap kit (EMD Millipore) and the MesoScale Discovery (MSD) V-plex neuro-inflammation panel-1. ApoE and eight of the 27 CSF immune markers increased with t-tau/Aβ1-42 ratio (all PFDR ≤ 0.05), with most of this relationship attributable to tau. However, four markers (apoE, IL-15, IL-8 and IL-12p70) also increased with higher Aβ concentration, suggesting increased clearance of Aβ [3]. To explore the implications of these immune marker elevations, we turned to 306 CSF donors from the ADNI-1 cohort (90 Healthy Controls (HC); 147 with MCI; 69 with AD dementia). *Results:* The 83 ADNI CSF protein analytes did not include immune markers specifically, but we detected 23 such markers significantly related (PFDR ≤ 0.05) to "stage" of AD pathogenesis (0 = normal; 1 = Aβ+, tau-; 2 = Aβ+, tau+; and 3 = Aβ-, tau+, or 'SNAP'), defined using ADNI recommended cut-offs. We then used 1000-fold k-means cluster analysis to identify a set of 13 such markers with known immune activity ("Immune Class" markers). Using z-scores for individual markers, we created a composite summary score as the mean of individual marker scores. These Immune Class summary scores showed little relationship to clinical diagnostic group among persons with Stage 0., but powerful and consistent relationships to clinical outcomes for participants at Stages 1 and 2. The latter were exemplified at Stage 1 by an odds ratio (derived from multinomial logistic regression) of 0.08 (95% CI 0.02 – 0.48) for a contrast between AD dementia and HC outcomes for each 1.0 s.d. increase in Immune Class summary score. That is, in persons with Aβ pathology only, each 1.0 s.d. increase in Immune Class summary score implied a >10-fold increase in the probability of an HC diagnosis vs. dementia. Indeed, at either Stage 1 or 2, all of the 3 possible diagnostic contrasts (HC vs. MCI, MCI vs.AD, etc.) showed similar results, with all but one contrast (HC vs. MCI at Stage 2) having a p-value <0.05. Furthermore, at both Stages 1 and 2, a 1.0 s.d. increase in Immune Class summary score predicted significant attenuation in the 4-yr rate of subsequent cognitive decline, as measured by the ADAS-cog-11 (or ADAS-cog-13 or MMSE). *Conclusions:* These findings suggest that "immune" marker activity is a powerful predictor of improved clinical outcomes in persons having CSF evidence of amyloid (+ tau) pathology. We suggest, therefore, that increased immune signaling may be an adaptive response to development of AD pathology. At any rate, these findings cast doubt on the advisability of anti-inflammatory treatments in persons with established AD pathology. Instead, treatments that foster immune marker signaling should be considered as a possible strategy for prevention of AD symptoms. 1. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. (2015) Neuroinflammation in Alzheimer's disease. Lancet Neurol 14, 388-405. 2. Breitner JCS, Poirier J, Etienne PE, Leoutsakos JM, PREVENT-AD Research Group (2016) Rationale and Structure for a New Center for Studies on Prevention of Alzheimer's Disease (StoP-AD). J Prev Alz Dis 3, 236-242. 3. Mawuenyega KG, Sigurdson V, Ovod L, et al. (2010) Decreased clearance of CNS Amyloid-β in Alzheimer's disease. Science 330:6012.

LBP20: CHARACTERISTICS OF SLEEP AND WAKEFULNESS MEASURED WITH ACTIGRAPHY IN PATIENTS WITH IRREGULAR SLEEP-WAKE RHYTHM DISORDER AND ALZHEIMER'S DISEASE. Margaret Moline[1], Patricia Murphy[1], Gleb Filippov[1], Naoki Kubota[2], Mohammad Bsharat[1], Manuel Kemethofer[3], Andrew Satlin[1] *((1) Eisai, Inc., Woodcliff Lake, NJ, USA; (2) Eisai Co., Ltd. Tokyo, Japan (3) The Siesta Group, Vienna, Austria)*

Background: Sleep disturbances appear early in the course of Alzheimer's disease dementia (AD) and have an effect on the quality of life of both patients and their caregivers. The type of sleep problems experienced in these patients has been associated with a loss of circadian rhythmicity1-2. Patients with AD can spend much of the night awake, resulting in lower sleep efficiency and unrefreshing sleep3. Disrupted sleep at night is also associated with behaviors such as confusional arousals and wandering4. AD patients also have difficulty maintaining wakefulness throughout the daytime hours, and report excessive daytime sleepiness. When sleep is not consolidated at night but rather distributed in irregular sleep bouts across the 24-hour period, this condition is referred to as Irregular Sleep-Wake Rhythm Disorder (ISWRD). This circadian rhythm sleep-wake disorder is associated with decreased amplitudes of the sleep-wake and alertness rhythms, and with less predictability of the sleep-wake pattern from day to day5-6. Actigraphy is a way to characterize sleep-wake patterns in patients with ISWRD across the 24-hour day, for several days or more. Here we describe preliminary results of actigraphy patterns obtained during screening of patients with mild to moderate AD and ISWRD for a Phase 2 proof-of-concept study for the dual orexin receptor antagonist lemborexant. *Methods:* Patients were between the ages of 60 and 90 years and had a diagnosis of AD, based on National Institute on Aging/Alzheimer's Association Diagnostic Guidelines, and met criteria for ISWRD, based on DSM-5 criteria for Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type. In addition, subjects were required to complain of difficulties with both staying asleep during the night and staying awake during the day at least 3 times per week for at least 3 months. Subjects were instructed to wear an actigraphy device (MotionWatch 8, CamNtech; MW8) continuously on the non-dominant wrist for approximately 14 days. [Note: For ease of communication, 24-hr intervals are hereafter referred to as 'days']. To be included in the analysis, subjects were required to have scorable data from a minimum of 5 days of each 7 days, with 'scorable' defined as missing no more than 10% of data (i.e., 144 minutes) during a given day. Activity data were collected in 30-second epochs. A validated algorithm7 was applied to score each epoch as sleep or wake. Caregivers recorded the subjects' bedtime each night and out-of-bed time each morning on a sleep log and also noted intervals when the actigraphy device was removed from the subject's wrist. The in-bed and out-of-bed intervals were used to calculate Sleep Efficiency (SE; epochs of sleep/time in bed) and Wake Efficiency (WE; epochs of wake/time out of bed). *Results:*

Among 47 subjects screened, actigraphy records from 38 subjects met criteria for inclusion in the analysis. Of those excluded, 2 were given actigraphy devices but no data were recorded; 2 wore the actigraph for fewer than 14 days; 4 wore the actigraph for at least 14 days but did not meet the criterion requiring 90% non-missing data for at least 5/7 days; 1 had no accompanying sleep log. The subjects' mean age was 76 years (63 to 87 years); there were 19 men. The mean Mini-Mental State Exam score was 21 (11 to 28). The actigraphy-derived group mean SE was 77.9% (55.0% to 92.2%), and mean WE was 69.1% (40.1% to 92.1%). Actigraphy-derived sleep-wake measurements show that these patients spent an average of a quarter of the time in bed awake, reflecting substantially disrupted nighttime sleep. In addition, these subjects slept for almost a third of the out-of-bed hours during the daytime. *Conclusions:* In this patient sample, actigraphy corroborated the patient and caregiver reports of fragmented and irregular sleep-wake patterns of AD patients with ISWRD. These findings suggest that questions related to the ability to maintain wakefulness in addition to the typical questions about nighttime sleep should be included when conducting a diagnostic evaluation of patients with AD. The results also suggest that the actigraph device was generally well-tolerated, supporting the use of this methodology to study the effect of therapeutic interventions in patients with AD and ISWRD.References: 1. Guarnieri B, Sorbi S. Sleep and cognitive decline: A strong bidirectional relationship. It is time for specific recommendations on routine assessment and the management of sleep disorders in patients with mild cognitive impairment and dementia. Eur Neurol. 2015;74:43 8. 2. Musiek ES, Xiong DD, Holtzman DM. Sleep, circadian rhythms, and the pathogenesis of Alzheimer Disease. Exp Mol Med. 2015;47(3): e148. 3. Liguori C, Romigi A, Nuccetelli M, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer Disease. JAMA Neurol. 2014;71:1498-1505. 4. Gehrman PR, Marler M, Martin JL, et al. The relationship between dementia severity and rest/activity circadian rhythms. Neuropsychiatr Dis Treat 2005;1: 155–163. 5. Peter-Derex L, Yammine P, Bastuji H, Croisile B. Sleep and Alzheimer's disease. Sleep Med Rev. 2015;19:29-38. 6. Satlin A, Volicer L, Stopa EG, Harper D. Circadian locomotor activity and core-body temperature rhythms in Alzheimer's disease. Neurobiol Aging. 1995;16(5):765-71. 7. Oakley NR. Validation with polysomnography of the Sleepwatch sleep/wake scoring algorithm used by the Actiwatch activity monitoring system. Technical Report, Minimitter, Inc. Bend, OR, 1997.

LBP21: MULTIPLE ASCENDING DOSE STUDY WITH A PRODRUG OF GALANTAMINE: A PHARMACO-EEG ANALYSIS WITH EVIDENCE OF POSITIVE EFFECTS ON COGNITION. D.G. Kay[1], E t'Hart[2], C. Bakker[2], A. Maelicke[1,3], Sonja Simpraga[4], Klaus Linkenkaer-Hansen[4,5], Simon-Shlomo Poil[5], G.J. Groeneveld[2] *((1) Neurodyn Cognition Inc., Charlottetown, PE, Canada; (2) Centre for Human Drug Research (CHDR), Leiden, the Netherlands; (3) Galantos Pharma, Nieder-Olm, Germany; (4) Vrije Universiteit Amsterdam, the Netherlands; (5) NBT Analytics BV, Amsterdam, the Netherlands)*

Background: Cholinesterase inhibitors (ChEIs) enhance cognitive functioning in patients with Alzheimer's disease (AD). The use of ChEIs and their maximum dose is limited by side effects, largely gastrointestinal, such as nausea, vomiting and diarrhea. These side effects are caused by stimulation of peripheral acetylcholine receptors. Memogain® is a pharmacologically inactive prodrug of galantamine, a ChEI and allosteric potentiating ligand (APL) of nicotinic acetylcholine receptors (nAChR). Due to the enhanced lipophilicity of Memogain compared to galantamine, it has one order of magnitude higher bioavailability in the brain than oral galantamine. Administration of Memogain is by way of an intranasal spray. After entering the brain, Memogain is enzymatically cleaved to active galantamine, accordingly enhancing the bioavailability of the active drug in the target organ, brain. Evidence from an extensive pre-clinical development program and a single ascending dose (SAD) human clinical trial [Baakman et al. (2016) Alzheimer's & Dementia: Translational Research & Clinical Interventions 2: 13-22] has demonstrated Memogain to have reduced peripheral side effects and a higher safety margin than galantamine, with evidence of improved cognitive enhancement. Additionally, in pre-clinical animal models of AD, Memogain has been demonstrated to both diminish plaque burden (via enhanced microglial removal of plaques), and to promote increased neurogenesis leading to restored cognitive function. Thus Memogain has the potential of being disease modifying. The work presented here is in addition an initial report of a multiple ascending dose (MAD) study in healthy subjects designed to assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of increasing doses of Memogain repetitively administered over a seven day period, in comparison to oral galantamine (Kay et al. [2016] JPAD 3: s1, P2-26, Pg370). We previously reported that Memogain was determined to be safe following seven days of repeat dosing. Most prevalent adverse events (AEs) were nasal complaints. The gastrointestinal AEs reported of Memogain were less intense compared to a single oral dose of 16 mg galantamine. After 22 mg Memogain, the reaction time on the n-back test improved with 98.2 msec (n=12, 95% CI [-156.8 - -39.5], p=0.0014) and the adaptive tracking performance improved consistently (n=12, 95% CI [0.540 - 3.146], p=0.0067) compared with placebo. Here the results of a pharmaco-EEG evaluation of subjects, are presented as an exploratory adjunct to the PD outcomes indicating improved cognition following Memogain administration. *Methods:* The present study was conducted at the Center for Human Drug Research (CHDR), Leiden (The Netherlands) and was a randomized, double blind, placebo controlled, sequential cohort, multiple ascending dose study in 48 healthy elderly subjects (>65 yrs.). Each cohort consisted of 12 subjects who were administered two doses of Memogain daily for 7 consecutive days. Cohort 1 received 2 x 5.5 mg [11 mg] of Memogain per day, cohort 2 received 2 x 11 mg [22 mg] of Memogain per day, plus a cross-over administration of a single dose of 16 mg oral galantamine (for CSF PK determination of drug concentrations), and cohort 3 received 2 x 22 mg [44 mg] of Memogain per day. Pharmaco-EEG measurements were performed for 4 min eyes closed / 4 min eyes open, on day 1 and day 7 at the following time points: Day 1: 2x pre-dose measurement (-1.5 and -1hr), Day 7 only one pre-dose measurement. Post dosing measurements were made at 30 min, 1.5 hr, 3 hr, 4.5 hr, 7 hr using a standard 10-20 electrode montage with 21 channels. *Results:* Following Memogain administration an increase of the central alpha frequency and decrease in central theta frequency were observed, which may be linked to a normalization (increase) of the dominant frequency. Memogain increased long-range temporal correlations (LRTC), which have been observed to be attenuated in Alzheimer disease patients. Interestingly, promising effects in terms of reducing the 'Alzheimer's disease index' score, were observed following Memogain administration. The 'Alzheimer disease index' was derived from an independent EEG dataset with 40 mild-to-moderate Alzheimer's disease patients (MMSE; 18-26, age; 65-85, CDR, 0.5-2), and 35 healthy control subjects (age-matched, MMSE > 27), by optimizing the separation between these two groups using elastic-net logistic regression. The identified index was a weighted sum of 12 EEG biomarkers (Simpraga et al. [2017], Sci Rep7(1): 5775). *Conclusion:* Memogain was safe in elderly in the dose range investigated. Memogain influenced pharmaco-EEG outcomes in elderly subjects that were consistent with the positive effects on

cognition documented in improved tests related to sustained attention and working memory.

LBP23: MATRIX THERAPY, A NOVEL APPROACH FOR ALZHEIMER'S DISEASE AND RELATED TAUOPATHIES. Dulce Papy-Garcia[1], Mohand-Ouidir Ouidja[1], Fernando Sineriz[2], Denis Barritault[2] *((1) CRRET-CNRS 9215, Université Paris Est Créteil, Creteil, France; (2) OTR3, Paris, France)*

Backgrounds: Other than the accumulation of amyloid plaques and neurofibrillary tangles, Alzheimer's disease (AD) is characterized by an altered neural microenvironment represented by an extracellular matrix (ECM), which in normal conditions is centrally involved in major trophic events regulating cell behavior in the AD brain. Heparan sulfates proteoglycans (HSPG) are key components of the neural ECM and their heparan sulfate (HS) chains are recognized to be central players on the molecular scaffold that hosts and protects trophic factors signals, essential for the welfare and growth of neurons. In AD, an altered ECM impairs tissue homeostasis and in addition is now recognized to furnish the place in where proteopathic particles spreads from one cellule to another (spreading). Matrix Therapy is a new concept with products currently in the clinical market based in the efficient replacement of the proteoglycanic component of the extracellular matrix (ECM) and cell surface, which are altered in disease and/or after injury. Our technology uses heparan sulfate mimetics (HM) that have shown clinical benefits in pathologies in where ECM is dismantled such in inflammatory and healing processes. In a healthy tissue, proteoglycans, and particularly heparan sulfates proteoglycans (HSPG), regulate the activity of heparin binding proteins, including a number of neurotrophic factors as BDNF, GDNF, and FGFs. Moreover, in case of tauopathie, HSPG have demonstrated to be the main cellular receptors of tau proteopathic seed. Thus, in tauopathy, while HSPG loss their capacities to regulate tissue homeostasis, they deleteriously participate to the spreading of proteopathic seed. Based on these knowledge, we designed and produced the F6 molecule, a HSPG mimetic able to replace the altered proteoglycanic matrix in the brain, promoting HSPG neurogenic and neuritogenic activities, while inhibiting the uptake of tau proteopathic seeds by healthy cells. Here we show results demonstrating that F6 treatment in animal models of tauopathy results in tauopathy reduction and cognitive improvement. *Methods:* We used a mice model of accelerated senescence with tauopathie. F6 molecule was administrated orally and/ or IP at different doses. Animal brains were analyzed for hyper phosphorylated tau and by cell death markers. A battery of behavior test was used to assess cognitive improvement. ELISA methods were used to evaluate the capacity of F6 to bind to tau, to tau oligomers, and to growth factors involved in neurogenesis, neuritogenesis and cell survival. In cells, we evaluated the capacity of F6 to potentiate these growth factors activities and to impede tau oligomers cellular uptake. *Results:* Evaluation of the F6 molecule in an accelerated senescent model of tauopathy showed that the HM treatment strongly decreases tauopathy in the brain and efficiently promotes cognitive recovery. While potentiating trophic factors activities involved in cell survival, neurogenesis and neurogenesis, F6 binds tau protein proteopathic seeds resulting in inhibition of their cellular uptake, and consequently in inhibition of tauopathie spreading. *Conclusion:* HM-F6 based matrix-therapy is a novel approach for AD. While avoiding cellular uptake of proteopathic seeds and inhibiting tauopathy spreading, HM-F6 protects and potentiate trophic factors functions, promoting neurogenesis, neuritogenesis and cell survival. Matrix therapy offers the possibility of treating disease with single compounds carrying multi-target activity, paving the way for the development of new therapies for AD and related tauopathies.

LBP24: ALLOPREGNANOLONE AS A REGENERATIVE THERAPEUTIC FOR ALZHEIMER'S DISEASE: PHASE 1B/2A OUTCOMES. Roberta Diaz Brinton[1], Gerson Hernandez[2], Christine Solinsky[3], Meng Law[4], Yonggang Shi[5], Dogu Aydogan[6] Jin Gahm[7], Wendy Mack[8], Naoko Kono[9], Kathleen Rodgers[10], Claudia Lopez[11], Ronald Irwin[12], Michael Rogawaski[13], Chun-Yi Wu[14], Lon Schneider[15] *((1) Center for Innovation in Brain Science, University of Arizona Health Sciences, Tucson, AZ, USA; (2) Center for Innovation in Brain Science, University of Arizona Health Sciences, Tucson, AZ, USA; (3) Department of Clinical & Experimental Therapeutics, University of Southern California, Los Angeles, CA, USA; (4) Department of Neuroradiology, University of Southern California, Los Angeles, CA, USA; (5) Laboratory of Neuro Imaging, USC Stevens Neuroimaging and Informatics Institute, University of Southern California, Los Angeles, CA, USA; (6) Laboratory of Neuro Imaging, USC Stevens Neuroimaging and Informatics Institute, University of Southern California, Los Angeles, CA, USA; (7) Laboratory of Neuro Imaging, USC Stevens Neuroimaging and Informatics Institute, University of Southern California, Los Angeles, CA, USA; (8), Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA; (9) Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA; (10) Center for Innovation in Brain Science, University of Arizona Health Sciences, Tucson, AZ, USA (11) Center for Innovation in Brain Science, University of Arizona Health Sciences, Tucson, AZ, USA; (12) Department of Pharmacology, University of Southern California, Los Angeles, CA, USA; (13) Department of Neurology, University of California at Davis, Davis, CA, USA; (14) Department of Neurology, University of California at Davis, Davis, CA, USA; (15) Department of Psychiatry, University of Southern California, Los Angeles, CA, USA)*

Background: Phase 1b/2a double blind placebo controlled multiple ascending dose clinical trial of allopregnanolone (ALLO) administered IV using a regenerative regimen for twelve weeks to establish safety, maximally tolerated dose and MRI based indicators of regeneration. ClinicalTrials.gov Identifier: NCT02221622. *Methods:* Phase 1b / 2a Double blind, placebo controlled multiple ascending dose clinical trial design. Primary objectives: determine safety and maximally tolerated dose. Secondary exploratory objectives: feasibility and impact of ALLO on MRI indicators of regeneration and cognition, lPBMC derived iPSCs differentiated to neural stem cells were used to develop biomarker strategy to identify potential regenerative responders. *Results:* Allopregnanolone in 3 dose cohorts was intravenously infused once per week for 12 weeks to 24 participants (18 allopregnanolone + 6 placebo). Within 15 minutes of infusion initiation, peak plasma level was reached Cmax = 46.34 +/- 23 nanomolar at the lowest dose. Maximally tolerated dose was established by onset of sedation. The Cmax closely correlated (R=0.77) with Allo delivered in mg/kg dose. Twelve-week exposure of up to 10 mg of ALLO once per week resulted in no detectable adverse effects or ARIA. Structural analysis of MRI-based indicators of gray matter volume were consistent with regeneration in select brain regions. Cognitive function measured by ADAS-cog 14 was not improved. However, Cogstate indicators were consistent with improvement. Biomarker of ALLO response correlated with change in MRI structural volume. *Conclusion:* Allopregnanolone is a first in class regenerative therapeutic for MCI and 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; DOD. W81XWH-09-1-0746 to MAR; P50AG05142 to HChui & LS; Alzheimer Drug Discovery Foundation to RDB.

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