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SYMPOSIUM

S1 - NEUROSCIENCE-BASED COGNITIVE ASSESSMENTS TO DETECT THE PRECLINICAL PHASE OF ALZHEIMER'S DISEASE. S. WOODRUFF-PAK[1], J. RABER[2], J. KAYE[2] *(1. Temple University, USA; 2. Oregon Health and Science University, USA)*

Decline in cognitive function is the key change heralding the onset of mild cognitive impairment and dementia in Alzheimer's disease (AD). The assessment of this change has traditionally relied on brief cognitive screening tests that are not sensitive to the earliest cognitive changes. Detecting these early changes before clinical AD symptoms develop is essential for the success of potential therapeutic interventions. Translational cognitive tests of eyeblink classical conditioning, object recognition, and spatial navigation show promise in detecting early changes associated with subclinical neuropathology. Extensive knowledge on the neurobiological substrates of eyeblink conditioning, object recognition, and spatial navigation has been developed in non-human mammalian species and extended to humans. The tests are also well characterized in normal aging, in animal models of AD, and some have been used successfully in AD in humans. In addition, traditional clinical testing typically relies on sporadic or intermittent testing or examinations that are brief and conducted in a clinic setting at times that are convenient for the examiner. The capabilities of ubiquitous unobtrusive computing platforms and sensor enriched home environments allows assessment of cognitive function freed from the constraints of time and space such that assessments can be conducted in the course of a person's typical day in their natural home environment at multiple times or even continuously for some data types. These methodologies go beyond simple implementation of standardized cognitive tests to a home PC to what may be called assessment of functional or everyday cognition, the ability to directly examine a person's process of thought in real time as activities of daily living are conducted. This symposium will review relevant background with regard to progress in assessing cognition using novel neuroscience-based cognitive tests, automated tests of functional cognition, and tests assessing cognition at home. Several completed and on-going studies will be discussed. Diana S. Woodruff-Pak, Ph.D., Professor of Psychology and Neurology and Founding Director of the Neuroscience Program at Temple University has spent several decades investigating the model system of eyeblink classical conditioning in mice and rabbits, including mouse and rabbit models of AD, and extending the neurobiological and behavioral findings to normal human aging and AD. Her group has demonstrated that eyeblink conditioning is useful in differential diagnosis in dementia and in the early detection of AD. There is a practical advantage to eyeblink conditioning because most neuropsychological tests require a fairly high level of cognitive functioning and fail to differentiate among types of dementia. The tests are beyond participants' capacity, any many perform at floor levels. Eyeblink conditioning is enjoyable for participants because they simply watch a video during the automated 30-minute procedure. Because eyeblink conditioning is simple, non-threatening, non-invasive, and well characterized neurobiologically, it is a useful addition to test batteries designed to detect preclinical AD. Jacob Raber, Ph.D., Professor of Behavioral Neuroscience and Neurology and Affiliate Scientist in the Division of Neuroscience, ONPRC, at Oregon Health and Science University developed humanized versions of the mouse object recognition and spatial navigation tests and demonstrated the sensitivity of these tests to detect effects of sex and apoE4 on cognition. The object recognition and spatial navigation (Morris water maze) tests have been well characterized in rodents. Dr. Raber created human versions of these tests that are among the most widely used to assess cognition in rodent models of AD. The human assessments of spatial navigation are automated and of object recognition automated or involving hard copies, relatively brief, and easy to administer and score. Dr. Raber's group has amassed normative data over the human life span on the human versions, called Memory Island and NINL (Novel Image, Novel Location), and they have demonstrated the tests' sensitivity in detecting cognitive performance. The NINL test is of demonstrated utility in identifying biomarkers of cognitive function and susceptibility to cognitive impairments over time. Jeffrey Kaye, M.D., Professor of Neurology and Biomedical Engineering and Director of the Layton Aging and Alzheimer's Disease Center at Oregon Health and Science University, as well as Director of the Oregon Center for Aging and Technology (ORCATECH) has developed a scalable unobtrusive home-based monitoring system to assess activities and behaviors known to change prior to the development of MCI. These activities such as patterns of movement about the home, walking speed, computer use, prospective memory for medication taking, and sleep or night-time behaviors provide the opportunity to capture thousands of instances of these activities in an individual and model trajectories of change predictive of MCI. Dr. Kaye will describe several studies using these novel automated measures of functional or everyday cognition that have been implemented in home settings. These metrics, captured in the familiar surroundings of participants' homes, detect changes in normal everyday capacity and provide a new approach to create ecologically valid clinical trials for the assessment of preclinical functional and cognitive change.

S2 - THE ALZHEIMER'S PREVENTION INITIATIVE. PIERRE. P.N. TARIOT, J.B. LANGBAUM, A.S. FLEISHER *(Banner Alzheimer's Institute, Phoenix, USA)*

We have proposed an "Alzheimer's Prevention Initiative (API)" to evaluate some of the most promising experimental anti-amyloid therapies in 24-month, multi-center, randomized, placebo-controlled trials (RCT) in people who, based on their age and genetic background, are at the highest imminent risk of developing symptoms using brain imaging, cerebrospinal fluid (CSF) biomarker, and cognitive endpoints. In the first of two programs, we propose an initial study that is a combined RCT and cohort study. We will enroll cognitively normal autosomal-dominant early-onset AD (EOAD) causing mutation carriers within 15 years of their estimated age at clinical onset, who will be randomized to experimental treatment or placebo, as well as a subset of noncarriers, who will be assigned to placebo treatment in order to prevent forced genetic disclosure. Study participants will be comprised of presenilin 1 (PS1) E280A mutation carriers and noncarriers from the world's largest EOAD kindred, located in Antioquia, Colombia, followed by Francisco Lopera and his team, as well as EOAD kindreds in the United States. In the carriers, we will compare rates of change on drug vs placebo in cognitive performance, cerebral fibrillar Aβ deposition, rCMRgl decline, and CSF t-tau and p-tau levels. Our hypothesis is that treatment will show a clinical-biomarker pattern indicative of slowed progression of illness. In the cohort study, we will compare baseline difference and patterns of change in the placebo-treated carriers and in the non-carriers in order to better understand the progression of changes in these outcomes in the two groups. We expect that as new agents become available they will be incorporated into the treatment trial in an adaptive manner. In the second program, we propose to enroll cognitively normal APOE ε4 carriers close to their estimated median age of clinical onset, and study the effects of drug vs placebo on clinical-biomarker endpoints. In addition to examining the possible effectiveness of experimental therapies for presymptomatic treatment of AD in these populations, these studies will help to 1) clarify the extent to which the treatment's effects on the best established AD biomarkers predict clinical benefit, evidence that is critically needed for regulatory agencies to qualify the relevant biomarkers for use as surrogate endpoints in the accelerated approval of presymptomatic AD treatments, 2) provide a better test of the amyloid hypothesis than clinical trials in symptomatic patients, when these treatments may be too little too late to exert their most profound effects, 3) to establish AD prevention registries needed to support these and other presymptomatic AD trials, and 5) to give those individuals at highest imminent risk of AD symptoms access to the most promising investigational treatments in clinical trials. In preparation for the first presymptomatic treatment trial, we have analyzed a series of datasets in order to indentify a new cognitive composite score that is sensitive to cognitive decline to be used as a primary cognitive outcome. In a parallel fashion, we examined longitudinal neuropsychological test battery data from the Antioquia PS1 cohort as well as longitudinal data from two cohort studies at the Rush Alzheimer's Disease Center in order to determine the optimal test combination for a presymptomatic treatment trial in EOAD and APOE ε4 carriers, respectively, by calculating the mean-to-standard-deviation ratio (MSDR) for each combination of one to six neuropsychological assessments. The optimal combination of tests was nearly identical for both genetic-risk groups. Similar efforts have been undertaken with Dr. Lopera in order to establish the RCT infrastructure in Colombia, including establishing a Colombia API Registry, which will have enrolled 1500 PS1 E280A carriers and noncarriers by 2012, and several small pilot studies designed to assess the feasibility of brain imaging and fluid biomarker studies in this population as well as to better understand the cross-sectional and longitudinal behavior of these measures in this EOAD group. These biomarker studies include sMRI, fMRI, CSF and amyloid PET, and FDG PET. We will present the latest findings from the API in preparation for planned presymptomatic treatment trials.

S3 - IMPROVING MEASUREMENT METHODOLOGY TO DETECT TREATMENT EFFECT IN CLINICAL TRIALS. W. RODMAN SHANKLE[1-4], A. ATRI[5-7], S. HENDRIX[8] *(1. Shankle Clinic, Newport Beach, CA USA; 2. Medical Care Corporation, Newport Beach, CA USA; 3. Memory and Cognitive Disorders Program at Hoag Neurosciences Institute, Newport Beach, CA USA; 4. Department of Cognitive Sciences, UC Irvine, Irvine, CA USA; 5. Memory Disorders Unit and Massachusetts Alzheimer's Disease Research Center, Department of Neurology, Massachusetts General Hospital, Boston, MA USA; 6. Geriatric Research, Education and Clinical Center (GRECC), ENRM VA Medical Center, Bedford, MA USA; 7. Harvard Medical School, Boston, MA USA; 8. Pentara Corporation, Salt Lake City, UT USA)*

Clinical trials of AD therapy have recently produced a number of negative results—sometimes unexpected. The reasons for these failures may be due to inefficacious

treatment, or could be due to inadequate measurement or inefficient data analysis in clinical trials. There are at least six such issues. 1. The samples selected are heterogeneous in their rates of progression, severity, and underlying pathophysiology. Recent advances in AD biomarkers will improve clinical trial sample homogeneity. Better measurement methods can naturally detect treatment responsive subgroups without using ad hoc approaches. 2. The tests used to represent key outcomes were developed for more severe impairment (dementia), and may be insensitive for measuring change in asymptomatic or mild cognitive impairment patients. 3. The test item responses and summary scores used to represent key outcomes are usually not optimally scaled using modern measurement theory. For example, it is common to assign scores of '0' and '1' to incorrect and correct test item responses, without determining if they are properly scaled with respect to each other. The distance between correct and incorrect responses may also differ for different items. Multi-dimensional optimal scaling methods can address this issue, plus define the number of independent dimensions measured by a given test. Tests such as the ADAS-Cog, the CDR, the MOCA, the NPI, the NTB, AVLT, MMSE, Mini-Cog, and others have not yet been optimally scaled. Item response theory is a step forward, but assumes the test measures a single underlying dimension of information, which may be incorrect. 4. Summary test scores as well as their item responses do not measure the underlying component processes involved in the affective, behavioral, cognitive or motor abilities being evaluated. These component processes are executed by specific neural circuits, which can be damaged by brain diseases such as AD. Measurement of the component processes of a given ability therefore provides more direct and sensitive assessment of the effects of a brain disease, and the effects of treatment on a brain disease. For example, wordlist memory tests are useful measures of change in mild cognitive impairment due to AD. However, associative encoding—a component process of memory performance—is activated by anterior hippocampal circuitry, which is involved earlier in AD than posterior hippocampus. Measuring the component process of associative encoding is therefore more likely to detect AD earlier and more sensitively measure treatment effect in early AD. 5. Identification of methods to improve outcomes for proof-of-concept studies while paving the way for future scale validation for regulatory approval. Such methods will likely need to be powerful for the small samples typically studied in proof-of-concept studies. 6. Measurement of longitudinal clinical trajectory in AD to enhance detection of treatment effects. By solely analyzing change scores, current data analysis methods ignore important information that constitute a rich history, or path, of how a patient gets from the baseline to the final visit. Additionally, these data analysis methods are often very traditional and elementary, and consist of ANOVA (or t-tests) or simple linear regression, and not advanced analytic modeling methods such as mixed fixed and random effects regression, generalized estimating equations or latent growth curve/structural equation models. Utilizing all available data and more advanced longitudinal analysis methods to characterize the complete clinical trial trajectory of a subject, including assessing different forms of progression (not just computing "rates" of change that presuppose only linear trajectories over time) and calculating the entire "area under the curve" (not just a change score) can enhance detection of treatment effects in AD. This symposium will introduce some recent advances in measurement and longitudinal data analysis methods that can improve detection and interpretation of treatment effect in AD clinical trials. Specific topics covered will include: 1. Shankle- Generative cognitive processing modeling methods to measure treatment effect. Data from the Myriad Phase III FDA trial of Flurizan vs. placebo will be analyzed to show the potential for analysis of small samples, the ability to compare performance of different memory tests, and the measurement of treatment effect on underlying cognitive processes involved in memory performance. 2. Hendrix—Use of a subset of the ADAS-cog and MMSE items substantially improves the sensitivity to decline in Mild AD and MCI patients. The items that provide the best sensitivity to decline in Mild AD and MCI are similar across different patient populations. 3. Atri—Explanation and demonstration of area under the curve analysis to compare treatment group trajectory differences using 1) actual clinical trial data; and 2) modeled data projected from the same clinical trial.

S4 - EVENT-RELATED POTENTIAL BIOMARKERS FOR EARLY DIAGNOSIS AND TREATMENT TRIALS OF ALZHEIMER'S DISEASE. L. SCHNEIDER[1], A. BUDSON[2] *(1. University of Southern California, USA; 2. Boston University, USA)*

A series of recent failures of Alzheimer's disease (AD) therapeutic clinical trial is leading to a paradigm shift in our understanding of the disease and the strategies to develop AD treatments. Lack of cognitive improvement in spite of evidence of reduction of plaque burden has forced researchers to reconsider the amyloid hypothesis and, in particular, the link between the biochemical dysfunction and cognitive symptoms observed in AD. The U.S. Food and Drug Administration has recently indicated that while ancillary data from structural, molecular, or metabolic biomarkers is preferable, a change in a cognitive test, by itself, may be sufficient clinical evidence for approval of a new drug. On the diagnostic front, recent revisions of NINCDS-ADRDA criteria under the aegis of the Alzheimer's Association and the National Institutes of Health reaffirm the central role of evidence of cognitive decline in the staging of Alzheimer's disease. These developments have renewed the focus on cognitive biomarkers. Large scale biomarker studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) have led to a remarkable improvement in our understanding of the changes in various biomarkers throughout the course of the disease. While the molecular, structural, and metabolic biomarkers are being actively validated, detecting subtle cognitive changes, especially in the preclinical or early clinical stages of AD, poses a significant challenge. Similarly, lack of standardization in administering and scoring of cognitive tests complicates efforts to evaluate cognitive treatment effects. Recent advances in event-related potential (ERP) technology have renewed the interest of AD clinical researchers in ERPs as useful cognitive biomarkers. This symposium reviews application of ERPs for early detection of the disease and evaluation of treatment efficacy in preclinical and clinical AD trials. John Olichney, MD, UC Davis, will review clinical data from cognitive ERP paradigms sensitive to subtle cognitive changes early in the AD disease process. In particular, ERP studies of memory and language processes which have demonstrated sensitivity to AD will be emphasized. The evidence that ERPs can be useful to predict prognosis in MCI and the earlier "preclinical" stages of disease will be discussed. The talk will shed light on how ERPs can play a valuable role in AD clinical trials, with utilities in cohort selection, monitoring disease progression and cognitive improvement. Steven Leiser, PhD, Lundbeck Research USA, will discuss ERP biomarkers in rat models for preclinical research in the pharmaceutical industry. P300 is an intensively studied ERP elicited by infrequent or "oddball" sensory stimuli and related to updating working memory. Consequent to the wide ranging correlates of P300 to cognitive function, P300 amplitude and latency worsen progressively in Alzheimer's disease. Thus, ERP is a useful cognitive biomarker in AD drug discovery. An ERP potential corresponding to the P300 has been validated in behaving rodents based on the high potential translational value. The behavioral dependence of this rodent ERP component closely mirrors the human P3 component. Additionally, pharmacological attributes of the rodent ERP recapitulate the properties shown for human P3. These observations provide face, construct, and predictive validity for existence of a P300 homolog in the behaving rodent. These findings justify evaluation of this ERP component in animal disease models, and for evaluation of novel CNS therapeutics. Marta Segerdahl, MD, PhD, AstraZeneca R&D, will present data from an industry-sponsored AD clinical trial in which ERP is being used as one of the primary endpoints. It is a Phase II, multi-center, randomized, double-blind, placebo-controlled, crossover study to evaluate the pharmacodynamic effect of single and multiple oral doses of AZD1446/placebo and a single dose of Donepezil on quantified electroencephalography (qEEG) and ERP in patients with AD. The purpose of the study is to evaluate whether treatment with single and multiple oral doses of AZD1446 for 1 week will have effect on qEEG and ERPs in patients with AD. The total treatment period is 9 weeks, divided into 5 equally long sub-periods of 7 days and 4 wash-out periods of 7 days each. Karim Bennys, MD, Montpellier University Hospital, FRANCE will discuss the relevance of ERP biomarkers in predicting the evolution of patients with MCI. Results from a study on 71 MCI patients compared to 31 healthy control subjects. They benefited from an initial assessment that included a neuropsychological evaluation, and ERP. They were followed for one year, and during their last visit they benefited again from ERP and neuropsychological tests. At the end of the study 2 subgroups of MCI patients were differentiated according to their clinical evolution from baseline to follow up: 41 MCI progressors (MCI-P) and 30 MCI non progressors (MCI-non P). MCI-P patients had a significant decline in their executive functions compared to MCI-non P group at baseline and follow up especially on TMT B and verbal fluency (p< 0.0001). At baseline MCI-P have increased P3b latencies and low P3b amplitudes compared to MCI-non P. MCI-P showed an inversion of the P3b rostrocaudal gradient with a significant decrease of the amplitude of P3b in parietal area compared to MCI-non P. At follow up 17 MCI-P patients had converted to Alzheimer's disease. The study reported a significant rate of decline of the amplitude of N2 and P3b in frontal area among groups. Furthermore, MCI-P had a higher decrease in rostrocaudal gradient of P3b and prolonged N2 and P3b latencies than MCI-non P. Sensitivity and specificity was around 80% and 70%, using P3b amplitude to discriminate MCI-P from MCI-non P.

S5 - ARE THE NEW AD DIAGNOSTIC CRITERIA HELPFUL IN CLINICAL TRIALS? A.D. KORCZYN *(Tel-Aviv University Medical School, Israel)*

Alzheimer's disease is an important target for clinical trials and interventions. Previous studies suffered from unclear criteria which may have been of limited value in clinical studies and leading to difficulties in implementation and interpretation of the results. In order to overcome these obstacles, new criteria have recently been proposed, with special emphasis on early and very early stages of the disease.
The symposium will briefly describe the criteria, and will address issues of practical constraints, relevance to power calculations, and generalizability of results to the real world

S6 - CONVERSION FROM MCI TO DEMENTIA. THE WEIGHT, QUALITY AND RELIABILITY OF THE EVIDENCE. N. SMAILAGIC, A. NOEL-STORR, T. QUINN *(1. Cochrane Dementia and Cognitive Improvement Group, University of Cambridge, UK; 2. Cochrane Dementia and Cognitive Improvement Group, University of Oxford, UK; 3. Cochrane Dementia and Cognitive Improvement Group, University of Glasgow, UK)*

Improvements in the quality of clinical trial reporting have driven improvements in their conduct.The same needs to be true of studies of diagnostic test accuracy in dementia. The Cochrane Collaboration has developed a methodology for systematic reviews and meta-analysis of studies of diagnostic test accuracy. • An example: This symposium will use a review of amyloid ligands to illustrate some of the principles of systematic reviews of diagnostic test accuracy in dementia. Data on cross-sectional and longitudinal studies will be compared, drawing attention to some of the tautologies in cross-sectional studies. The number of patients who have converted to dementia in such studies will be discussed. • Reporting Standards: The STARD statement has specified the reporting standards required for studies of diagnostic test accuracy. An assessment is provided, based on a systematic review of the biomarker literature, of the overall quality ofthe literature. In particular, we focus on the reporting of blinding as vital information which is commonly missing. Recommendations are made for the reporting standards which should be met in longitudinal dementia studies. • Reliability of 'dementia' outcome: The NIA-AA and proposed DSM5 diagnostic criteria do not address the central question which continues to bedevil all diagnostic studies in dementia: when can the functional impairment of a patient be regarded as sufficient to make a diagnosis of dementia? The inherent unreliability of this concept requires a process to optimise this key outcome measure. Similar problems

affected the assessment of disability in stroke, which is a major outcome in trials of stroke. The process by which this issue was addressed in stroke, and implications for dementia are described.

S7 - MEASURING THE EARLIEST SYMPTOMS OF MILD COGNITIVE IMPAIRMENT. D. MILLER[1], L. FRANK[1], R. DOODY[2], C. LEIBMAN[3], W. LENDERKING[1] *(1. United BioSource Corporation, USA; 2. Baylor College of Medicine, USA; 3. Janssen Alzheimer Immunotherapy, USA)*

Recent recommendations for clinical and research diagnostic criteria for MCI due to AD, coupled with renewed efforts to develop effective treatments for very early disease stages, underscore the need for improved measurement of mild cognitive impairment. Absent definitive biomarkers that can distinguish progressive, pathological processes from non-pathological ones, can reports from patients, clinicians and caregivers help quantify treatment effects and identify successful treatment? Communication 1: Using a specific trial as a case study, this session will address the potential to expand endpoints for MCI due to AD. The potential value of patient and informant reports will be highlighted as a means to improve signal detection in treatment trials of this condition (Doody et al2009); Although MCI due to AD probably represents early Alzheimer's disease (AD), MCI trials with approved AD treatments have all failed to prove efficacy. Although this may indicate that early treatment with these drugs is simply not beneficial, the negative studies could also reflect the challenge of accurately measuring relevant outcomes in this population. In this trial, treated MCI subjects showed a small but significant drug/placebo difference on a self-rated psychometric scale (consistent with prior studies) and on a cognitive measure, the ADAS-Cog (also consistent with prior trials), but not on the Clinician's Interview-based Impression of Change or CDR sum of the boxes. Placebo responses were seen on the standard AD outcome measures. Treated subjects rated themselves as improved relative to baseline, while placebo subjects showed no change on the Perceived Deficits Questionnaire (PDQ). Additionally, informants for placebo patients felt they worsened over time, while informants for treated patients felt they exhibited relatively little change. These results suggest that currently used measures in AD trials may be insensitive to treatment effects in MCI due to AD. Additionally, they raise the possibility that patients themselves might be the most accurate assessors of treatment response. The PDQ data encourage closer examination of specific item content to help identify features of MCI due to AD that could change with treatment and are not captured by standard outcome measures. Communication 2: This session will review the industry's perspective of both the risks and benefits of industry partnerships in pre-competitive instrument development. Critical Path Institute's (C-Path) efforts in cognition will be discussed. C-Path seeks to modernize the scientific process through which a potential drug, biological product or medical device is developed. Programs were developed with input from the Food and Drug Administration (FDA)/European Medicines Agency (EMA)/Pharmaceuticals and Medical Devices Agency (PMDA), industry and academia. Since operational/management funding comes from state and federal grants and not from the medical products industry, this non-profit acts as a neutral third party. The prodromal stage of AD presents significant challenges: defining and identifying this population; naming the specific syndrome addressed; designing trials to capture the subtle impairment in this slowly progressing phase, and the recognized dearth of valid and reliable measures. C-Path serves to coordinate major research efforts, including measure development in cognition, using a model where multiple stakeholders collaborate. Both the benefits and risks of industry partnerships in pre-competitive instrument development will be discussed, and why the benefit far exceeds the risk in this effort. Communication 3: This session will present the results of qualitative research conducted in over 150 patients with MCI due to AD, AD patients, normal controls, and the patients' informants. This research was conducted by the Cognition WG to serve as the basis for the development of a new Patient-reported outcome (PRO) instrument designed to measure treatment effects in MCI due to AD. Important concepts and symptoms identified by MCI patients will be highlighted. Additionally, evidence that these patients retain insight and are able to accurately report mild deficits in cognition and function will be presented. Summary: At present, there is an emphasis on the diagnosis and treatment of mild cognitive impairment at its earliest presentation. Multiple organizations appreciate the limitations of existing trial endpoints and the need to create robust new measures, some of which are based on patient self-report, to improve signal detection in clinical trials with this population. The potential for collaborative measure development is demonstrated by C-Path's PRO Consortium Cognition Working Group. Data generated by that Consortium suggest that patient self-report holds promise for the measurement of treatment effects in MCI due to AD

S8 - NOVEL CONCEPTUAL MODELS OF DEMENTIA [NCMD]'. Z.S. KHACHATURIAN *(PAD2020 Potomac, USA)*

This meeting, of the PAD2020 virtual Workgroup [WG] will review the progress of an ongoing multi-national collaborative effort to promote new thinking and formulation of alternative models of the pathobiology of Alzheimer's disease. The objective of the symposium, and the WG, is to address the limitations of current conceptual models of dementia; i.e., one of the crucial scientific obstacles to therapy development. The multi-national WG is conducting comprehensive assessment of all theories on the pathogenesis of Alzheimer's syndrome and formulating alternative conceptual model[s]. The outcome of this collaborative model-building exercise will: a) integrate all current ideas about the syndrome into new or alternative conceptual model[s] and, b) identify gaps in knowledge and potential barriers in to advancing the discovery-development of disease modifying/preventive therapies. After three decades of remarkable progress in understanding the neurobiology of Alzheimer, it is well-timed to takes stock of the advances and to chart new directions for exploration. The new model[s] should: a) generate crucial studies to determine the validity of all theories - alternative conceptual models, b) readily account for both biological and clinical phenotypes of the syndrome and, c) accommodate the full-spectrum of the clinical features of the disorder [ranging from pre-clinical stages to the end]. One of the forceful rationale for searching alternative models of pathogenesis stems from the need to address the issue of mixed pathologies in differential diagnosis, which increasingly appear to be the norm in the general population. A prospective new model of pathogenesis needs to take this into account such questions as: a) how do several pathologies interact with each other in pre and clinical phases and, b) how do they all contribute to symptom development.

S9 - AMYLOID-RELATED IMAGING ABNORMALITIES IN AMYLOID-MODIFYING THERAPY RESEARCH. J. TOUCHON[1], M. CARRILLO[2], S. SALLOWAY[3], G. KINNEY[4] *(1. Montpellier University Hospital, France; 2. Alzheimer's Association, Chicago, IL, USA; 3. Butler Hospital, RI, USA, 4. Janssen AI San Francisco, CA, USA)*

Amyloid imaging related abnormalities (ARIA) have now been reported in clinical trials with multiple therapeutic avenues to lower amyloid-β burden in Alzheimer's disease (AD). In response to concerns raised by the Food and Drug Administration, the Alzheimer's Association Research Roundtable convened a working group to review the publicly available trial data, attempts at developing animal models, and the literature on the natural history and pathology of related conditions. The spectrum of ARIA includes signal hyperintensities on fluid attenuation inversion recoverysequences thought to represent "vasogenic edema" and/or sulcal effusion (ARIA-E), as well as signal hypointensities on GRE/T2 thought to represent hemosiderin deposits (ARIA-H), including microhemorrhage and superficial siderosis. The etiology of ARIA remains unclear but the prevailing data support vascular amyloid as a common pathophysiological mechanism leading to increased vascular permeability. The workgroup proposes recommendations for the detection and monitoring of ARIA in ongoing AD clinical trials, as well as directions for future research.

FOCUS SESSION

CLINICAL TRIALS IN FRONTOTEMPORAL DEGENERATION AND RELATED DISORDERS. A. BOXER[1], J. CUMMINGS[2], M. GOLD[3], H. FELDMAN[4], D. KNOPMAN[5], I. MACKENZIE[6], T. HUEY[7], H. ROSEN[8], J. KRAMER[8], W. HU[9] *(1. University of California, San Francisco, USA; 2. Cleveland Clinic Lou Ruvo Brain Institute, USA; 3. Allon Therapeutics USA; 4. Bristol Myers Squibb, USA; 5. Mayo Clinic, Rochester, USA; 6. University of British Columbia USA; 7. Columbia University; 8. University of California, San Francisco, USA; 9. Emory University, USA)*

Frontotemporal degeneration (FTD) is a common cause of dementia that currently has no effective treatment. A handful of clinical trials in FTD and related disorders are currently underway, and more are planned for the near future. Although less common than AD, FTD offers a number of advantages for successful development of disease-modifying therapies that can potentially de-risk drug development for AD and other more common indications. Most FTD is strongly linked to a single molecular pathology involving one of two single proteins (either tau or TDP-43) which may allow more focused clinical investigations of drugs targeting these molecules than in AD. Second, because FTD is an orphan disease with no approved or effective therapies, there are regulatory and marketing advantages to developing treatments for FTD. Third, FTD patients tend to be younger, with fewer comorbidities and concomitant medications, but faster disease progression than AD, potentially facilitating the conduct and design of efficacy trials. The availability of validated research criteria for FTD and a range of validated clinical rating scales and biomarkers that can be used in FTD clinical trials, hold the potential to accelerate treatment development. This symposium will discuss the state of the art in FTD treatment and clinical trial methods. Topics will include: clinical features, biology and epidemiology of FTD; the current FTD treatment landscape; regulatory strategies; clinical rating scales; MRI, PET and fluid biomarkers, for differential diagnosis and monitoring disease progression; development strategies focused on lead molecular targets.

ORAL COMMUNICATIONS

O1 - OPTIMIZING THE ADAS-COG FOR MCI AND EARLY AD. N. RAGHAVAN, M.N. SAMTANI, M. FARNUM, E. YANG, V. LOBANOV, G. NOVAK, V. NARAYAN, A. DIBERNARDO *(Johnson and Johnson, USA)*

Current FDA guidelines for clinical trials of Alzheimer's Disease (AD) include demonstrating efficacy on both a cognitive and a global measure to ensure the clinical meaningfulness of drug effects. The Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) is the standard cognitive assessment tool in clinical trials. Although useful for symptomatic trials in moderate AD, it has well-known ceiling effects that limit its ability to measure cognitive changes early in the disease. This presents an important challenge to research efforts aimed at intervening early in the disease process with disease-modifying therapies. There is a growing consensus in the scientific community around the need to develop better outcome measures, particularly for clinical trials targeting earlier stages of the disease. Composite endpoints that could adequately capture both primary symptoms as well as clinical relevance have recently been advanced. We utilize the rich dataset from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study to present an empirical characterization of the ADAS-Cog component subscales, as well as other cognitive, functional and global measures at various stages of the disease. We further identify the most informative subscales, as well as additional cognitive and functional

measures, for Mild Cognitive Impairment (MCI) and early AD cohorts. We present two different types of modified endpoints designed to detect changes in early AD. The proposed endpoints are evaluated as outcome measures for two-year clinical trials on patients with (a) early AD, (b) MCI and (iii) MCI-A pathology (based on a threshold of CSF A1-42<192 mg/mL).This talk will present a novel, empirical approach for developing composite measures with clear advantages for clinical trial design. We will show how this approach can be adopted to derive new data-driven composite scales with improved performance characteristics for use in clinical trials, including minimizing floor and ceiling effects, improved coverage of relevant cognitive and global domains, improved dynamic range over a period relevant to early AD trials, as well as optimizing the variability of endpoints that can be used for patients with milder disease.

O2 - PLASMA AMYLOID B CONCENTRATIONS AND PROGNOSIS IN INCIDENT DEMENTIA CASES: THE PROSPECTIVE THREE-CITY STUDY. A. GABELLE, F. RICHARD, L.A. GUTIERREZ, S. SCHRAEN-MASCHKE, J.F. DARTIGUES, C. TZOURIO, A. ALPEROVITCH, K. RITCHIE, L. BUEE, P. AMOUYEL, J. TOUCHON, J.C. LAMBERT, C. BERR *(University Hospital of Montpellier Gui de Chauliac, Montpellier, France)*

Introduction: New recommendations from the National Institute on Aging Alzheimer's association workgroups describe the interest of biomarkers in diagnosis of Alzheimer Disease and especially, in prodromal stage of the disease. Among these biomarkers, low cerebrospinal fluid (CSF) levels of A β B1-42 are strongly associated with ongoing or future AD in patients with MCI. However, since CSF sampling is an invasive, time-consuming procedure, there has been increasing interest in establishing whether the quantification of plasma A β peptide levels is also relevant. Studies on plasma A β 1-40 and A β 1-42 peptide levels as potential biomarkers for incident Alzheimer's disease have yielded contradictory results. A low plasma A β 1-42/A β 1-40 ratio seems to be interesting to determine the risk of conversion from MCI to AD and to predict a short-term risk of dementia. No study examine whether these markers measured in the two years preceding disease onset could be associated with dementia prognosis, assessed through cognitive impairment or decline and mortality. Objectives: To explore the relationship between plasma A β 1-40 A β 1-42 and truncated A β (A β n-40 and A β n-42) concentrations and prognosis in population based incident dementia cases followed in the Three-City (3C) Study - a prospective French cohort study of men and women aged 65 and over. Materials and methods:The 3C study (Bordeaux, Montpellier, and Dijon) is a population-based study of the relationship between vascular factors and dementia. 9,294 non-institutionalized subjects aged > 65 (selected from electoral rolls) agreed to participate in the study. The baseline data collection included sociodemographic and lifestyle characteristics, symptoms and complaints, main chronic conditions, medication use, neuropsychological testing and these data have been updated at each follow up exam (nearly every two years). At inclusion, blood samples were obtained from 8,414 individuals. The diagnosis of dementia is established at each follow-up examination using a three-step procedure. First, the evaluation of neuropsychological tests (MMSE, the Isaacs Set Test (IST), and the Benton Visual Retention Test (BVRT)) is performed by trained psychologists, then the subject is examined by a neurologist and last an independent committee of neurologists reviewed all potential prevalent and incident cases of dementia in order to obtain a consensus. The cognitive decline was defined based on the difference between latest score observed during follow-up and baseline score, divided by length of follow-up. Subjects exhibiting a decline equal to or greater than the upper quartile (i.e. ≥2.13 points per year for MMSE; ≥1.48 for BVRT and ≥2.43 for IST) were defined as fast decliners. We focused our analysis on the 129 individuals diagnosed as 2-year incident dementia and followed during 7 years. On these subjects, baseline plasma levels of A β 1-40, A β 1-42, A β n-40 and A β n-42 have been measured using an xMAP-based assay technology. None of the participants were demented at the inception of the study when plasma sample were obtained. The association between plasma A β peptides levels and baseline cognitive score, cognitive decline and death were examined. A β variables (A β 1-40, A β 1-42, A β n-40, A β n-42, A β 1-42/ A β 1-40 and A β n-42/ A β n-40) were examined as a continuous characteristics (per standard deviation increase). First, the Spearman correlation coefficient was used to investigate possible bivariate linear associations between A β variables and cognitive score. Second, multiple regression analyses was performed including various potential confounders known to be associated with cognitive score or decline: age, sex, educational level, study center, ApoE, marital status, Body Mass Index, alcohol consumption, smoking status, vascular risk factors (hypertension, hypercholesterolemia, diabetes). Logistic regression models were used to determine the association between A β concentrations and the risk of fast cognitive decline controlling for potential confounders listed above. The associations of A β levels with the risk of mortality were determined by Cox proportional hazards regression. Results: These 129 dementia cases have been classified as follow: 88 cases of AD (42 possible, 46 probable), 25 cases of mixed/vascular dementia, 7 cases of dementia with Parkinsonism, 9 cases of other types of dementia, 4 undefined dementia. At baseline, mean age was 78.4 years (sd=5.7) and 71 patients were female (55.8%). Primary level of education was reported for 42.5% of subjects. The mean score of MMSE was 25.6 (sd=2.0) at baseline visit and, 2 year later at time of diagnosis, it was equal to 22.6 (sd=2.9). For IST, the mean baseline was 24.7 (sd=5.8), decreasing to 22.3 (sd=5.9) at time of diagnosis. At baseline, 74 per cent of subjects were classified as MCI. We showed that an increased level of plasma A β is associated with poorer cognitive status two years before dementia diagnosis in an incident dementia population based sample. In AD patients this is only evidenced for the truncated form A β n-42 and A β n-42/ A β n-40 ratio. Faster cognitive decline is related to plasma levels only in AD cases with a decreased risk when levels of A β n-42 increased. We also demonstrate a significant decreased risk with the two ratio of the two forms, truncated or not, A β n-42/ A β n-40 and A β 1-42/ A β 1-40. Similar results are obtained in crude or multivariate analysis controlling on potential confounding factors such as age, sex, educational level, APOE status and vascular risk factors. There was no association with mortality during the 7-year follow up (mean follow-up 6.1 years, 63 deaths) neither in all dementia cases nor in AD. Discussion: For the first time, this study highlights the interest to measure plasma A β peptides (A β 1-40, A β 1-42, A β n-40 and A β n-42) concentrations in patients in a critical period before diagnosis. This result is consistent with previous data, obtained with CSF sample, on the biomarkers' dynamic in the course of the disease proposed by Jack et al., 2011. The association between ratios of truncated or not truncated forms of AÎ² is specific of AD cases (88 of the total 129 incident cases followed). A specific interest will be addressed to the truncated forms of A β AÎ² in the early diagnosis of AD, and especially the A β n-42/ A β n-40 ratio. Conclusion: Plasma A β levels, if measured at a prodromal stage of the disease, may be potential useful markers to indicate demented individuals susceptible to develop more deleterious evolution. These results need to be replicate on larger samples and with repeated dosages before any future clinical application.

O3 - BAYESIAN DATA MINING WITH ENSEMBLE LEARNING PREDICTS THE CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE. R. CHEN[1], K. YOUNG[2], L.L. CHAO[2], B. MILLER[2], K. YAFFE[2], M.W. WEINER[2], E.H HERSKOVITS[1] *(1. Department of Radiology, University of Pennsylvania, Philadelphia, PA. USA; 2. Center for Imaging of Neurodegenerative Diseases, UCSF VA Medical Center, San Francisco, CA, USA)*

Introduction: Prediction of disease progress is of great importance to Alzheimer's disease (AD) researchers and clinicians, yet prediction has proven difficult. Objectives: We propose a novel Bayesian data-mining method called Bayesian Outcome Prediction with Ensemble Learning (BOPEL), and we demonstrate the use of this approach to determine whether or not a subject with MCI will convert to AD within a 5-year period, based on baseline structural magnetic-resonance (MR) and MR spectroscopy (MRS) data. Material and methods: We analyzed data acquired from 26 subjects with amnestic MCI. All subjects had MCI at baseline, based on Petersen's criteria. We divided these 26 subjects into two groups. The converter group (n = 8) included subjects who met MCI criteria at baseline, but within 5 years of follow-up met the NINCDS-ADRDA criteria for AD. The non-converter group (n = 18) consisted of subjects who met MCI criteria at baseline and at follow-up. Each subject underwent MR and MRS examination at baseline. Based on structural MR data, we computed 70 regional volumes. Based on MRS data, we generated 7 neurochemical features, such as regional NAA. We normalized All MR-derived predictors (70 regional volumes and 7 neurochemical features) to zero mean and unit variance. We used these MR-derived baseline measurements, along with age, sex, handedness, education, and mini-mental state examination (MMSE) at baseline, as potential predictive variables, the goal being to predict the group-membership variable representing whether a subject with MCI converts to AD within 5-year period. We call this group-membership variable C. Partly due to the high cost of acquiring these data, most attempts at using MR-derived features to predict AD conversion have been hindered by undersampling (i.e., the number of variables greatly exceeds the number of subjects). To address the oversampling problem, we propose a new method that uses a combination of regularization, feature selection, and ensemble learning. BOPEL is based on a class of probabilistic graphical models called Bayesian networks (BNs). BN-based predictive models demonstrate excellent classification performance in many empirical studies, even when data are noisy and undersampled. The first step of BOPEL is feature selection; by reducing the number of potential predictive variables, we can improve prediction. There are a variety of BN-based data-mining methods that can identify a subset of variables that are highly predictive of C; however, this process may not be stable to small perturbations of the data. To select a robust predictor set, we employed ensemble learning to stabilize the predictor-selection process. In ensemble learning, we repeatedly apply bootstrap resampling to the original data set, resulting in a series of slightly different re-sampled data sets. We then generate a predictor set for each re-sampled data set. This series of predictor sets is called a feature ensemble. From this ensemble, we calculate the frequency of each predictor, and then rank predictors based on these frequencies, choosing the top-ranked features as the aggregated predictor set. We use internal cross-validation determine the number of highly ranked features to be included in the predictive model. Once we have selected predictors, the next step is to construct a BN based on those features. However, a single predictive model may not achieve high prediction accuracy. Therefore, we used boosting, a form of ensemble learning, to generate an ensemble of predictive models, and we used this model ensemble for prediction. Results: During the 5-year follow-up period, 8 of the 26 subjects had progressed to probable AD. We found no significant difference in age, sex, handedness, education, or MMSE measured at baseline. We used BOPEL to construct a model for predicting whether or not a subject with MCI would convert to AD within this 5-year period, based on structural MR and MRS features at baseline, and the demographical variables age, sex, handedness, education, and MMSE. We used leave-one-out cross-validation (LOOCV) to evaluate BOPEL's prediction accuracy. As estimated by LOOCV, for BOPEL, accuracy was 0.81, sensitivity was 0.63, and specificity was 0.89. The 26 models that BOPEL generated in the course of LOOCV contained a total of 13 different features. Of these features, 5 had frequency greater than 0.5 (that is, they were included in the majority of models): the left hippocampus (frequency = 1.0), the banks (i.e., adjacent cortical areas) of the right superior temporal sulcus (frequency = 0.65), the right entorhinal cortex (frequency = 0.80), the left lingual gyrus (frequency = 0.88), and the left rostral middle frontal gyrus (frequency = 0.58). We consider these features to be stable. To validate the model generated by BOPEL, we used an independent data set consisting of 48 subjects (30 non-converters and 18 converters) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The ADNI MR-acquisition protocol does not include MRS data. However, since the final diagnostic model built based on the PCD data

set used only structural-MR features, the lack of MRS data in the ADNI data set did not affect validation. Applying the predictive model that we generated from the PCD data set (which did not incorporate any information from the ADNI validation data set), and classifying subjects in the ADNI validation data set (converter/non-converter), we found that BOPEL's prediction accuracy was 0.75, sensitivity = 0.56, and specificity = 0.87. Discussion: In our analysis of data from the PCD study to predict AD conversion, we found that five features were highly predictive of AD conversion. We found that volumes of the left hippocampus and of right entorhinal cortex are predictive of conversion from MCI to AD. Hippocampus and entorhinal cortex measurements are among the biomarkers most consistently found to predict AD conversion. The other structures frequently included in our model ensemble are also known biomarkers for AD conversion. We included MRS features from the PCD study because several studies had demonstrated that MRS features differentiate normal elderly subjects, patients with AD, and patients with MCI. We found that the final predictive model generated by BOPEL did not include any MRS features. This result suggests that, given structural MR features, the additional predictive value of MRS features for AD conversion is not significant. However, we should be cautious accepting this finding because of small sample size. We found that BOPEL uses baseline structural-MR data to predict MCI-AD conversion with high accuracy. Of note, this model's prediction accuracy was almost as high for independently acquired ADNI subjects. BOPEL, a Bayesian approach to outcome prediction, has the following advantages over other approaches. First, it is accurate: BOPEL uses a BN representation with boosting to increase model-representation capacity, and incorporates resampling-based predictor selection to prevent over-fitting. Second, the generated predictive model is stable even when data are undersampled. Third, it generalizes well, as shown by comparable performance on an independently acquired data set. Conclusion: BOPEL can accurately predict whether a subject with MCI will convert to AD based on baseline MR imaging features. This work is supported by NIH AG13743, EB-009310. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative.

O4 - THE PLACEBO GROUP SIMULATION APPROACH (PGSA): AN ALTERNATIVE STUDY DESIGN FOR CLINICAL TRIALS IN PATIENTS WITH PRODROMAL AD. R. SPIEGEL, M. BERRES, A.R. MISEREZ, A.U. MONSCHN *(Memory Clinic, University Hospital, Basel, Switzerland)*

Introduction: As an alternative to ethically problematic Phase 3 long-term randomized placebo-controlled double-blind clinical trials (RPCTs) we are proposing a novel clinical study design, termed Placebo Group Simulation Approach (PGSA; Spiegel et al, Alzheimers Res & Ther 2011, Mar 21; 3 (2): 9). The PGSA uses mathematical modelling to forecast outcomes of prodromal AD patients from their own baseline data established at the outset of a clinical trial. These forecasted outcomes are then compared with the actual outcomes observed on candidate treatments, thus replacing a concomitant placebo group. The PGSA has been received with much interest in the AD community; some questions remain, however, regarding the generalizability of the PGSA algorithms. Objectives: The present study dealt with the question as to whether the published PGSA algorithms, that were developed using data from the MCI population of the Alzheimer Disease Neuroimaging Initiative (ADNI), are supported by findings from other, independently selected subject samples. As before, we focus on cognitive outcomes that are considered to be clinically relevant and have higher reliability and better metric properties than, e.g., time to "conversion to dementia". Material and methods: Data from the Uniform Data Set (UDS) collected at 29 AD centers in the USA and generously provided by the National Alzheimer's Coordinating Center (NACC) were used. We included 3274 subjects aged 55 to 90 with a diagnosis at baseline of single or multiple domain amnestic mild cognitive impairment (aMCI) in the analysis. Subjects underwent repeated evaluation of their cognitive function, about one year apart, resulting in 7476 subject visits. The outcome chosen for this analysis was the trajectory of the composite score of a Neuropsychological Test Battery (NP-Batt7), computed from the z-scores of seven standard tests of mental performance. Ten demographic, clinical, biological and neuropsychological candidate predictors were included in the mixed model used for analysis. Results: Using the Akaike Information Criterion for variable selection, the by far most important determinant of the outcome, i.e., the trajectory of the composite score of the NP-Batt7, were the NP-Batt7 scores established at baseline. Other significant predictors were (in order of importance) the interactions of time with ApoE4, with FAQ (a scale of daily functioning) scores at baseline, with education and gender. Comparison of the model-based with real observed values resulted in an R-square of 0.71, corresponding to a correlation between predicted and observed NP-Batt7 values of r = 0.84. Discussion: The NACC UDS sample is numerically larger and less narrowly defined than the ADNI data set, while the NP-Batt7 contains fewer tests than the NP-Batt used in previous analyses (Spiegel et al., 2011). Despite these differences an algorithm comprising a small number of variables, notably cognitive performance measured at baseline, plus a few routinely collected criteria, forecasts the trajectory of cognitive decline of aMCI subjects in subsequent years with high accuracy. This would allow sample sizes of a few hundred subjects to provide adequate power in forthcoming clinical long-term trials with experimental compounds aimed at secondary prevention of AD. Conclusion: The PGSA aims at minimizing the ethically problematic use of placebo in long-term clinical trials with prodromal AD subjects. The PGSA algorithms are used to simulate a virtual concomitant placebo group from baseline data of the experimental group, allowing subsequent comparison of observed treatment outcomes with forecasted outcomes in the simulated placebo group. PGSA models originally derived from ADNI MCI data predict both, cognitive endpoints and trajectories that correspond well with real observed values. The present analysis using data from a large NACC dataset support the validity of the published PGSA algorithms. We propose to use the PGSA mainly in advanced stages of clinical development of new drugs, i.e., at a point when important safety/tolerability data and first evidence of efficacy are available from Phase 1 and 2 RPCTs of shorter duration. What is needed now is the proof of the PGSA concept in a prospective study, i.e., a trial with prospective use of the PGSA models and the possibility of comparing forecasted with subsequently observed data.

O5 - NILVAD: An investigator driven European multi-centre placebo-controlled phase III trial of NILVADIPINE, a calcium channel blocker, in mild to moderate Alzheimer's disease. B. LAWLOR, R.A. KENNY, S. GAYNOR, M. MULLAN, F. CRAWFORD, F. PASQUIER, M. RIEPE, A. BORJESSON, M. OLDE-RICKERT, R. HOWARD, D.W. MOLLOY, J. KALMAN, M. TSOLAKI, U. LUCCA S *(St. James's Hospital, Dublin, Ireland)*

Introduction: There is a clear unmet medical and public health need for the development of new treatments for Alzheimer's Disease (AD) that have both symptomatic and disease modifying effects. NILVAD comprises a new consortium of research partners, clinical sites and advocacy groups in Europe created around FP7-Health 2011 that is proposing to test the efficacy and safety of nilvadipine versus placebo in mild to moderate AD. There is a very strong scientific rationale for the study: Nilvadipine, a calcium channel blocker that is already licensed for the treatment of hypertension in Europe, enhances Aβ clearance from brain and restores cortical perfusion in transgenic mouse models of AD. We have previously demonstrated that nilvadipine is safe and well tolerated in AD patients. Furthermore, clinical studies of nilvadipine have shown stabilization of cognitive decline and reduced incidence of AD in hypertensive subjects with mild cognitive impairment, indicating that this medication may have both symptomatic and disease modifying benefit. Objectives: 1.To test the symptomatic and disease modifying effects of nilvadipine versus placebo in mild to moderate AD; 2.To examine the modifying effects of frailty, exercise and social connection on the effect of nilvadipine in this patient population. Material and methods: NILVAD is planning to enroll 500 male and female patients with mild to moderate AD aged between the ages of 50 and 85 with a range of medical morbidities and frailty in the study. Subjects will be randomized to 8 mg nilvadipine or placebo for a treatment period of 18 months. The modifying effects of leisure activities and social engagement on treatment outcome will also be explored to inform future multi-modal therapeutic interventions. Over 20 clinical sites in 10 different countries have already agreed to participate in this investigator driven clinical trial. Results: If effective, nilvadipine would represent a significant development in the treatment approaches that currently exist for AD patients and would have a major impact on the health and social care costs incurred in Europe by this neurodegenerative disorder. In addition, the creation of the NILVAD network will support future clinical trials and research innovation in AD across Europe. Discussion: The project is expected to start in January 2012, pending the successful completion of negotiations with the EC. Conclusion: This investigator initiated clinical trial can only be delivered successfully by cooperation between expert clinicians, and large and small industry partners in cooperation with AD patients, their caregivers and the support of advocacy groups working through a network of clinical sites across Europe.

O6 - META-ANALYSIS OF COMPOSITE ENDPOINTS IN CLINICAL TRIALS OF ALZHEIMER'S DISEASE. M.W. RIEPE, D. WILKINSON, H. FURSTL, A. BRIEDEN *(University of Ulm, Günzburg, Germany)*

Introduction: The duration of dementia from mild to severe stage is several years. Patients remain in each stage for about three to five years with a slow and steady decline of function in Alzheimer's disease. Currently most clinical studies are performed in mild to moderate stage of disease or in moderate to severe stage of disease. To measure efficacy, clinical studies employ a variety of instruments. For a multitude of reasons the numerical results of clinical studies comparing different treatments vary. Meta-analyses on standardised mean differences are performed in recent times to account for variance of the magnitude of effects in clinical studies. In dementia research, meta-analyses pertain to the assessment of ˜cognition" "behavior" and "activities of daily living'™. These, however, are composite measures. E.g. "cognition" comprises single cognitive functions such as memory, orientation, language, and so forth. Calculation of effect sizes for single cognitive functions on treatment as assessed by the Alzheimer's Disease Assessment Scale (ADAScog), the Mini-Mental-Status Examination (MMSE), and the Severe Impairment Battery (SIB). In these scales, subdomains of "cognition", e.g. memory and language are represented in different proportions. Objectives: To assess whether it is appropriate to interpret clinical results of composite scales with meta-analytic procedures. Material and methods: To exemplify analysis of "cognition" we perform a mathematical analysis of the preconditions of effect size calculation and use original data of clinical studies with memantine to demonstrate the results. Results: We demonstrate that the major problem, which cannot be overcome by numerical methods, is the complex nature and neurobiological foundation of clinical psychiatric endpoints. This is particularly relevant for endpoints used in dementia research. "Cognition" is composed of functions such as memory, attention, orientation and many more. These individual functions decline in varied and non-linear ways. We demonstrate that calculation of effect sizes and meta-analyses on composite measures are subject to distortion by the structure of the composite measure and by the non-linearity of decline towards the endpoints being analyzed. Discussion: Statistical analysis needs to be guided by biological boundary conditions. Beyond inter-study variance, effect sizes for treatment with antidementia drugs are subject to disease stage, instruments used, and interaction thereof. Conclusion: Therefore, clinical interpretation is necessary to appraise therapeutic efficacy in clinical studies and meta-analyses thereof when patients with different severity are included or different instruments are used. Alternatively, severity-adapted endpoints should be used for appraisal and meta-analysis of therapeutic efficacy.

O7 - A RANDOMIZED CONTROLLED ALZHEIMER'S DISEASE PREVENTION TRIALS EVOLUTION INTO AN EXPOSURE TRIAL. R.J. KRYSCIO[1,2], E.L. ABNER[1], M. MENDIONDO[1,2], A. CABAN-HOLT[3], B.C. DENNIS[4], C.R. RUNYONS, F.A. SCHMITT[3,5], J.J. CROWLEY[6] FOR THE SELECT INVESTIGATORS *(Sanders-Brown Center on Aging; 1. Departments of Biostatistics; 2. Statistics; 3. Behavioral Science; 4. Neurology; 5. Psychiatry & Psychology, University of Kentucky, Lexington KY, USA; 6. Cancer Research and Biostatistics, Seattle WA, USA)*

Introduction: The rationale for the Prevention of Alzheimer's Disease (AD) by Vitamin E and Selenium (PREADViSE) trial is based on numerous animal models, human autopsy studies, as well as several large observational studies and at least one human AD clinical trial of vitamin E that investigated the role of antioxidants in the disease process. The PREADViSE trial was leveraged as a cooperative study of a large multi-center prostate cancer prevention trial for healthy older men (SELECT) directed by the Southwest Oncology Group. This 2x2 factorial randomized clinical trial (RTC) was terminated after up to 7 years of exposure due to a futility analysis (prostate cancer outcome) and is now an exposure study of approximately half of its men who volunteered for centralized follow-up. Objectives: The purpose of this presentation is to discuss PREADViSE in the context of an AD prevention trial as an ancillary study to a cancer prevention trial and to present the blinded results of the first year of its exposure study. Material and methods: SELECT enrolled 35,533 men aged 55 or older (50 if African American) at 427 sites throughout the United States, Canada, and Puerto Rico. It is one of the fastest enrolling large prevention trials in history. PREADViSE enrolled 7,553 of SELECT's oldest men (age 62 or older; 60 if African American) at 135 of these sites. In the RCT, annually PREADViSE participants took the brief Memory Impairment Screen (MIS), and if they failed they underwent a longer screening (based on an expanded Consortium to Establish a Registry in AD [CERAD] battery). CERAD failure resulted in visits to their clinician for medical examination with records of these examinations forwarded to the PREADViSE center for further review. Men were asked to donate a blood sample at baseline and then after 5 years; these samples were processed and stored at the biospecimen bank for the National Cancer Institute in Frederick, Maryland. In addition, a subset of the participants (n = 563) who passed the MIS underwent the CERAD test to form a longitudinal validation study of normal aging and the MIS. In the exposure study men are telephoned from the PREADViSE site and complete the MIS-T screen; and if they fail, a Modified Telephone Interview of Cognitive Status (TICS-M) exam is given. A failed TICS-M exam also leads to a visit to their clinician for an in depth examination and forwarding of records for a centralized consensus diagnosis by expert clinicians. A subset of the men who pass the MIS-T also take the TICS-M exam for validation purposes. Results: While this ancillary trial was open to all SELECT sites, only 34% chose to participate in PREADViSE. This illustrates some resistance from the cancer community to become involved in an area of research remote to their main interests. Subject reimbursement issues, securing local IRB approval for the ancillary study, and competing ancillary studies presented barriers to PREADViSE participation. For cooperating sites, personnel unfamiliar with dementia research were trained to administer both the MIS as well as the CERAD battery at the semi-annual meetings of the SELECT group. Continual staff turnover at both the local P.I. level as well as the certified research nurse level presented challenges to quality assurance and required ongoing training sessions. In the RCT portion of the PREADVISE study few participants (1.6%) failed the initial MIS screen. We noted significant practice effects from year to year even if we alternated equivalent versions of the MIS; hence, after four years the cut off score for failure was raised with some success in capturing failures. Examination of the CERAD results for a subset of those participants who passed the MIS indicated the failure to identify some cases, especially those of borderline memory impaired subjects. During the RCT 909 participants either dropped out or died while on study. Once the RCT was closed, participants completed a final in person visit at their SELECT site, and at this time the MIS, the AD-8 dementia screen, and signed consent for centralized follow-up in the exposure study were obtained. This process took one year longer than anticipated. Participation in the exposure study was excellent; exposure study participants had a mean age of 67.3 ± 5.2 years at baseline and 15.3 Â± 2.4 years of education, with an average initial MIS score of 7.6 ± 0.7. Of note: 10.7% were African Americans. These characteristics matched the non-participants indicating little evidence of selection bias in those volunteering for telephone participation. In the exposure study 2,814 men have been phoned to date (in their birth month), 16.6% could not be reached after 5 calls, and of those contacted 4.3% refused the screen even after consenting to the procedures at their clinical site. Most notable is that of the 2,246 men who were successfully contacted and participated, the failure rate for the MIS-T increased substantially to 8.7%. This was partially due to older age for the men, more uniform training of the screeners, and a more homogenous educational background of the screeners related to neuropsychology. Of the 207 men who took the TICS-M, 84% failed and were asked to contact their physicians for a more detailed memory assessment and approximately half of these had some form of dementia. Of note, several of these dementia cases are not AD. Discussion: The implementation of the ancillary study on memory and dementia incidence in a cancer prevention setting shows that with appropriate infrastructure conducting a large dementia prevention trial is feasible. Recruitment, adherence, and retention in the RCT were matters that required cooperation between the parent and ancillary personnel. Success in a future trial will be maximized by coordinating the initiation of the parent and ancillary trial, especially with regard to committees associated with the parent trial. The exposure study based on those who volunteered for centralized follow-up went smoothly and yielded a subset of volunteers that mimicked the RCT cohort on key demographics and appears to have increased the yield of incident cases partly due to aging of the cohort and partly due to individuals with more expertise in cognition monitoring the mental status of the participants. Conclusion: PREADViSE is based on sound research on the role of oxidative stress in AD. Partnering with a large cancer prevention trial led to a successful RCT at a very reasonable cost by taking advantage of the experience and efficient clinical trial management found in a cancer cooperative group. Challenges arose but were addressed with proactive solutions. Once unblended, the RCT and exposure study data have the potential to yield new information on long term exposure to antioxidant supplements under controlled conditions.

O8 - EFFICACY OF A NUTRICEUTICAL FORMULATION ON COGNITIVE PERFORMANCE AND FUNCTION IN PERSONS WITH MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE. R. REMINGTON[1], C. BECHTEL[2], J.J. LORTIE[3], H. HOFFMANN[3], L. DOSANJH[4], P. FISHMAN[4], A. SAMAR[5], T.B. SHEA[1] *(1. University of Massachusetts Lowell, USA; 2. Framingham State Univ, USA; 3. Knox College, USA; 4. Univ of Maryland, USA; 5. Worchester State Univ, USA)*

Introduction: A nutriceutical formulation (NF), consisting of vitamins E, B12, folic acid, S-adenosylmethionine, N-acetylcysteine, acetyl-L-carnitine) has been demonstrated in prior studies to maintain or improve cognitive performance and mood in persons with Alzheimer's disease (AD) and boost cognitive performance in adults with no known or suspected dementia. Objectives: Herein, we report initial results from an ongoing multi-site, placebo-controlled study of NF for AD and mild cognitive impairment (MCI). Material and Methods: Individuals with AD (age 82.4±9 years, education 12±3 years, MMSE 22±6) or MCI (age 62±2 years, education 15±2 years), randomly assigned to receive either NF or placebo, completed cognitive tests at baseline, 3 and 6 months. Family or staff caregivers completed mood/behavior (NPI) and activities of daily living (ADCS-ADL) inventories. Results: Participants with AD, receiving NF but not placebo, improved in Clox1 within 3 months ($p<0.01$) and maintained improvement at 6 months. Participants from both groups displayed similar baseline AEMSS scores in the Dementia Rating Scale; those receiving NF improved vs placebo at 6 months. Placebo participants declined 30% in ADL at 6 months; NF participants declined only 12%. Participants with MCI who received placebo but not NF declined ($p<0.05$) in the WAIS Digit Span by 6 months. Participants receiving placebo but not NF demonstrated a statistically significant decline in Clox1 over 6 months, while those receiving NF did not decline Discussion: These findings indicate that NF can maintain or improve cognitive performance and function prior to and during MCI and AD. Conclusion: Multi-site studies are ongoing and additional sites are recruiting; forthcoming data will also be presented.

O9 - THE EFFICACY OF DONEPEZIL ON A STRUCTURAL OUTCOME (HIPPOCAMPAL ATROPHY) IN THE RECENTLY DEFINED PRODROMAL ALZHEIMER'S DISEASE (AD) POPULATION CHARACTERIZED BY A PROGRESSIVE AMNESTIC SYNDROME OF THE HIPPOCAMPAL TYPE. B. DUBOIS[1], M. CHUPIN[2], B. CROISILE[3], G.L. TISSERAND[3], J. TOUCHON[4], A. BONAFE[4], P.J. OUSSET[5], A. AMEUR[6], O. ROUAUD[7], F. RICOLFI[7], A. VIGHETTO[3], F. PASQUIER[8], C. DELMAIRE[9], M. CECCALDI[10], N. GIRARD[10], S. LEHERICY[11], I. TONELLI[12], F. DUVEAU[12], L. GARNERO[2], M. SARAZIN[1], D. DORMONT[2] AND THE DONEPEZIL HIPPOCAMPUS STUDY GROUP (*1. Institut de la mémoire et de la maladie d'Alzheimer (IMMA) Hôpital de la Salpêtrière, Paris, France; 2. Cognitive Neuroscience and Brain Imaging Laboratory, CNRS UPR640, Paris, France; 3. Hôpital Neurologique Pierre Wertheimer, Lyon, France; 4. CHU, Guy de Chauliac, Montpellier, France; 5. Hôpital Casselardit, Toulouse, France; 6. Clinique Pasteur, Toulouse, France; 7. Hôpital général, Dijon, France; 8. CHRU, clinique de Neurologie, Lille, France; 9. Hôpital Roger Salengro, Lille, France; 10. Hôpital de la Timone, Marseille, France; 11. Inserm U610 and CENIR, Neuroimaging Unit, Paris, France; 12. Eisai SAS, La Défense 2 cedex, France)*

Introduction: Several studies have demonstrated that the acetylcholinesterase inhibitor Donepezil has a beneficial symptomatic impact on patients affected by Alzheimer's disease (AD), not only on cognitive performance, behaviors, but also on global functioning and on daily living activities, particularly in patients with mild AD. Hippocampal volumes correlates well with the severity of disease and atrophy is observed prior to the onset of clinical dementia.(Jack et al, 2004). Objectives: The main objective of this clinical trial is to study the efficacy of donepezil on a structural outcome (hippocampal atrophy) in the recently defined prodromal Alzheimer's disease (AD) population characterized by a progressive amnestic syndrome of the hippocampal type. Material and methods: The study was double-blind, randomized, placebo-controlled, with two parallel groups assigned to donepezil (10mg/d) or placebo for 52 weeks. Inclusion criteria were: (1) amnestic syndrome measured by the Free and Cued Selective Reminding Test (free recall â‰¤ 17 or total recall < 40); (2) preserved activities of daily living; and (3) clinical dementia rating stage of 0.5. Patients had brain MRIs at baseline and final visit (12 months) or in case of withdrawal after six months). For the first time with the prodromal AD population, the primary criterion for efficacy was a structural neuroimaging outcome: the annualized percentage change in hippocampal volume (left+right) measured by MRI, using a newly validated automatic segmentation technique that decreases measure variability (centralised lecture). Secondary outcomes included other brain MRI markers and cognitive performance. Results: 337 patients were screened and 216 randomized at 28 French clinical sites (placebo=103 and donepezil=113 patients).174 patients were included in the fully evaluable population (placebo=92; donepezil=82).The donepezil group exhibited a slower rate of atrophy (-1.89% (SE: 0.31)) than the placebo group (-3.47% (SE: 0.35)) with significant difference ($p= 0.001$). A significant lower rate of atrophy was observed on total brain volume measures. There was no significant difference in neuropsychological performance between groups. Adverse events were consistent with the known safety profile of donepezil. Conclusion: In this trial, hippocampal atrophy was reduced in patients with prodromal AD by 45% in one year with treatment of donepezil compared to placebo.

O10 - PRECLINICAL BEHAVIORAL DETECTION OF ALZHEIMER'S DISEASE. S. KARANTZOULIS[1], H. LAU[1], C.E. MYERS[2], R.P. KESNER[3], S. DE SANTI[4], A. GURNANI[1], H. SCHARFMAN[1,5], S. H. FERRIS[1] *(1. New York University Langone Medical Center, NY, USA; 2. DVA New Jersey Health Care System, and Department of Psychology, Rutgers University, USA; 3. Department of Psychology, University of Utah; 4. Bayer Healthcare Pharmaceuticals, USA; 5. Nathan Kline Institute, USA)*

Introduction: One of the first signs of AD is atrophy of the medial temporal lobes (MTL) measured with magnetic resonance imaging (MRI), including the entorhinal cortex (EC) and hippocampus (Hip). In addition, findings from fluorodeoxyglucose (FDG)-positron emission tomography (PET) demonstrate anterior MTL hypometabolism in preclinical AD; certain cerebrospinal fluid (CSF) biomarkers, indicative of AD pathology, are also altered (hyperphosphorylated tau [P-tau231] and beta amyloid [Aβ42/40]). Most recently, PET-amyloid imaging can provide a direct measure of regional amyloid accumulation in the brain. These advances enable us to predict which cognitively normal aged individuals will enter the first clinical stages of AD, but the necessary tests are expensive and invasive. It is likely that pathology visible on neuroimaging might also result in subtle functional changes that could be detected by behavioral tasks dependent on the EC and Hip. For example, the main afferent input to the dentate gyrus (DG) of the hippocampus, the perforant pathway, arises from EC layer II neurons, and deteriorates early in AD. These changes might therefore impair both the function of the EC, which has been hypothesized to include stimulus generalization, and the function of the DG, which has been suggested to include pattern separation. Thus, we hypothesize that performance on pattern separation tasks might be particularly vulnerable to very early AD pathology, and patients in preclinical stages might demonstrate stimulus generalization and/or pattern separation deficits before other clinical and behavioral symptoms emerge. If so, poor performance on such tasks might provide an early, inexpensive and noninvasive marker of early AD pathology. Objectives: To evaluate whether asymptomatic individuals who are likely to be in the first stages of preclinical AD as indicated by biomarkers (including MRI volume loss, abnormal CSF P-tau231 and Aβ-42/40, PET hypometabolism, and PET-amyloid accumulation) exhibit robust functional deficits on tasks that depend on the EC and Hip. The initial pilot phase of this project examined task performance in cognitively normal elderly subjects showing a range of MRI atrophy and CSF abnormality. Material and methods: Eighteen cognitively normal Alzheimer's Disease Center/Center for Brain Health participants (mean age = 73; mean education = 16 years; 78% female) with prior MRI scans as part of their clinical evaluations and who also received LPs for CSF biomarker studies (not yet included in analyses) completed two behavioral tasks. Task 1 involves Concurrent Discrimination (Phase 1) and Generalization (Phase 2) and takes 20 minutes. For each phase 1 trial, subjects see two objects (colored shapes) on a computer screen and pick the one they think is correct; correct answers are followed by a cartoon of a smiling face. Subjects learn through trial and error to choose the correct object from each of 8 pairs. Phase 1 continues until subjects achieve a criterion of 16 consecutive correct responses or complete a maximum of 96 trials. A key feature of the object pairs is that objects either differ in color or shape but not both; thus in each pair, either color or shape is relevant and the other feature is irrelevant with respect to predicting the correct response. Phase 2 (generalization) follows without explicit warning to the subject; subjects continue to choose the correct object from each pair, but now the irrelevant features are changed. Subjects are scored on total number of errors in each phase. Task 2 involves Spatial Discrimination (i.e., pattern separation) and takes 15 minutes. Each trial begins with a study phase, in which participants view a dot on a computer screen for 3 sec; after a randomized delay of 5-30 sec, two identical dots appear: one in the prior location and one in a different location (0.75, 1.75, or 2.75 cm from the prior location); subjects are asked to verbally identify the dot which appears at the prior location. There are 24 trials: two at each delay for each spatial separation. Response times and percent correct are recorded on each trial. Results: Two independent hierarchical regression analyses were conducted to determine if performance on the experimental tasks predicted bilateral hippocampal atrophy after demographic variables (age, education) were entered into the model. Subject age and education were entered as the first step in both regression analyses. The second step consisted of examining task performance. Demographic variables did not significantly predict bilateral hippocampal atrophy in either analysis. Trials to completion during probing on Task 1 (stimulus generalization) showed a trend towards a significant contribution to the prediction equation in the first analysis ($F [1, 14] = 3.443$, $R2 = .26$), accounting for an additional 26% of the variance ($p=.09$). In the second analysis, the number of errors on Task 2 (pattern separation) was a significant predictor of bilateral hippocampal atrophy ($F [1, 14] = 4.548$, $R2 = .30$), accounting for an additional 30% of the variance ($p=.05$). Thus, our preliminary analysis of the cognitive scores and the hippocampal volume data suggest relationships between lower performance on both our stimulus generalization and pattern separation tasks and greater hippocampal atrophy. Discussion: These initial results provide preliminary support for our hypothesis that cognitive tasks dependent on brain regions impaired by very early AD pathology can help identify individuals with preclinical AD who are at high risk for clinical progression to MCI and dementia stages of AD. We anticipate more robust task prediction of brain pathology as we examine a larger sample and include additional markers of early AD pathology (CSF amyloid and tau, PET metabolism and PET-amyloid accumulation). Such results would support the use of sensitive behavioral tasks as an efficient, cost effective method to screen participants for clinical trials in preclinical AD, including trials of drugs that may have failed when administered to more advanced AD patients. These trials could employ the same behavioral measures as sensitive cognitive outcomes to help demonstrate clinical efficacy in preclinical individuals. Conclusion: Initial results for two experimental tasks sensitive to impairment of the EC and perforant pathway indicate sensitivity to hippocampal atrophy in clinically normal elderly. The ability to identify individuals with very early AD pathology using sensitive, anatomically specific behavioral tasks and to screen for preclinical AD will be an important advance for early diagnosis, and will serve a critical role in clinical trials. The ability to efficiently screen for preclinical AD will facilitate selection of subjects for proof-of-concept efficacy trials of potential disease modifying agents, as well as help reduce the large size and long duration of primary prevention trials. Sensitive behavioral assays will also provide sensitive, inexpensive, noninvasive functional outcomes for these trials. The results may also advance our understanding of the etiology of AD and lead to new therapeutic strategies focusing on the EC and Hip, perhaps specifically the dentate gyrus.

O11 - A PHARMACOGENETIC-ASSISTED CLINICAL TRIAL TO ASSESS THE DELAY OF COGNITIVE IMPAIRMENT OF THE ALZHEIMER'S DISEASE TYPE. A.D. ROSES, K.A. WELSH-BOHMER, A.M. SAUNDERS, O.A. MAKEEVA, D.K. BURNS, M.W. LUTZ, D.G. CRENSHAW, C.A. METZ, S. BRANNAN *(Duke University School of Medicine, Durham, NC, USA)*

Introduction: There are no marketed drugs that can change the course of Alzheimer's disease (AD). The scientific literature and popular press lament the burgeoning costs associated with AD and the lack of effective therapies. As clinical trial failures mount and disease knowledge expands beyond amyloid as a target, disease prevention rather than intervention is gaining attention. Disease prevention studies are challenging: the study population is "healthy" and therefore the therapeutic must have an excellent safety profile in humans and, without an effective enrichment strategy to identify those at high risk, large numbers of individuals must be followed over a relatively long time to capture sufficient "events" to draw a significant conclusion. The latter, in particular, can result in lengthy set up times. However, by reversing the typical order of operational activities, and identifying sites and investigators, and consulting with regulators, ahead of selection of a therapeutic candidate and full protocol development, significant time savings may be achieved. This hypothesis is being tested with the OPAL (Opportunity to Prevent Alzheimer's disease) clinical study. OPAL is a pharmacogenetic-assisted clinical trial that will simultaneously qualify a genetic marker as a prognostic test, and test the efficacy of a drug for delaying the onset of cognitive impairment of the Alzheimer's type in a genetically identified, high-risk group. In 2009, Roses et al. described the association between different lengths, "short", "long" and "very long", of a polyT locus (rs10524523, aka "523") in TOMM40 with distinct ages at onset of late onset AD. TOMM4O is adjacent to, and in linkage disequilibrium with, the well-known late onset AD risk gene, APOE. Because of the linkage disequilibrium, the strong association of TOMM40 with AD in genome wide association studies was usually attributed to APOE. However, a phylogenetic analysis of high-resolution sequences from the APOE region revealed the relationships between different 523 alleles of TOMM40 and APOE $\hat{I}\mu 3$ and APOE $\hat{I}\mu 4$ as follows: APOE $\hat{I}\mu 4$ was nearly always linked to long 523 alleles and was associated with greater disease risk, but APOE $\hat{I}\mu 3$ was linked to either short or very long 523 alleles. The cis linkage of APOE $\hat{I}\mu 3$ to short 523 was associated with later disease onset, whereas APOE $\hat{I}\mu 3$-very long 523 was associated with earlier disease onset, in AD patients with the APOE $\hat{I}\mu 3/\hat{I}\mu 4$ genotype (mean onset ages of 70 versus 77 years, respectively). The TOMM40 523 marker, therefore, provides a useful prognostic indicator of risk of developing AD within a 5 - 7 year window. Although the association between the 523 alleles and age of onset is now confirmed in multiple, independent cohorts, the clinical utility of the marker must be prospectively qualified in a controlled clinical study. Objectives: Simultaneous qualification of the genetic predictor and assessment of delay of cognitive impairment by a therapeutic agent will expedite completion of both objectives and deliver important medicines in a timelier and less expensive fashion. As a pharmacogenetic-assisted clinical study using a, currently, unqualified or unproven genetic marker, OPAL must both verify the utility of the genetic marker in guiding subject selection and test drug efficacy against the delay of cognitive impairment endpoint. To achieve time savings, Zinfandel Pharmaceuticals sought to initiate some of the most time-consuming activities prior to identifying funding, the study drug, or formal clinical trial kick-off. To this end: 1) multiple disciplines at the regulatory bodies at the US FDA were consulted, 2) key investigators at suitable sites around the world were identified, 3) registries of cognitively normal subjects were developed, and 4) suitably qualified personnel were engaged. Material and methods: In order to achieve significant timesavings for prospective validation of a prognostic genetic test and a clinical prevention study, work was conducted, at-risk, by Zinfandel Pharmaceuticals prior to formal initiation of the clinical program. As a first step, sites located around the world with access to either a sizable population, >60 years of age, receiving longitudinal care from a central medical provider or an ongoing, longitudinal, epidemiological studies of older adults were identified. The presence of researchers eager to participate in a pharmacogenetically assisted delay of cognitive impairment (and subsequent delay of AD) study, was necessary. Institutional support and appropriate infrastructure were important factors in determining suitability of a site. Results: To date, seven centers have been identified as candidates: Tomsk, Russia; Perth, Australia; Basel, Switzerland; Durham, North Carolina; Kannapolis, North Carolina; Israel; and London, United Kingdom. Other sites are being assessed. One of the sites, Tomsk, is in a more advanced stage of preparedness. A registry of 2000 subjects is established and the subjects are undergoing neuropsychological evaluation to determine their eligibility for the clinical trial. Recruitment and evaluation of study subjects is a potential bottleneck in OPAL, with 500 subjects to be recruited at each site and evaluated with a battery of neuropsychology tests at randomization and then at 6 month intervals. These tests are relatively labor intensive. To accommodate the required throughput, "mini-factories" of neuropsychologists and other professionals, trained to conduct standardized neuropsychological tests, are being established at each site. The mini-factories will ensure continuity of capabilities for subject monitoring, since significant staff turnover during the 3 - 5 year study is anticipated, and quality assurance. These specialized and focused

clinical research organizations, pivotal to each site's clinical development structure, will be autonomous with respect to staffing, patient recruitment and follow-up, and will centrally monitor standardization of testing procedures, subject management practices, and accreditation. OPAL has dual objectives: qualification of a prognostic genetic test and evaluating a clinical agent. Different divisions within the US FDA assess genetic tests and drugs. Considering this, Zinfandel Pharmaceuticals requested that the FDA convene a Voluntary Exploratory Data Submission (VXDS) meeting to present the science supporting use the TOMM40 polyT biomarker as a predictor of age of disease onset, and to gain input on a study design that would simultaneously achieve both objectives. After approximately 9 months of discussions and meetings, in October 2009 a VXDS meeting was attended by representatives from CDER (including the Neurology group) and CDRH, and the merits of potential study designs were discussed. Discussion: At the time of the VXDS, the drug for the delay of onset arms of the study was unnamed, and the preferred design was appropriate for multiple candidate drugs. Following this meeting, Zinfandel Pharmaceuticals sought a partner with rights to a thiazolidinedione drug, and, on 10 January 2011, Zinfandel Pharmaceuticals and Takeda Pharmaceuticals announced an alliance to test the efficacy of pioglitazone for delaying the onset of cognitive impairment of the AD type and to qualify a predictive pharmacogenetic algorithm. The trial will be enriched for subjects at increased risk of developing cognitive impairment of the AD type within the subsequent 5 - 7 years according to an algorithm that includes APOE genotype, TOMM40 genotype at rs10524523, and the subjects' age at study entry. An Investigational New Drug application is on-schedule for filing with the US FDA in 2012. Conclusion: Zinfandel Pharmaceuticals and Takeda Pharmaceuticals are now in the process of demonstrating that early engagement with regulators, identification of qualified sites, establishment of registries of potential study subjects and sufficient numbers of qualified on-site neuropsychology investigators can achieve significant timesavings. A generation of future AD patients is waiting.

O12 - A RANDOMIZED CLINICAL TRIAL OF AN INHIBITOR OF RAGE-A-BETA INTERACTIONS IN PATIENTS WITH MILD TO MODERATE AD. D.R GALASKO, C. VAN DYCK, M. SABBAGH, R.T. THOMAS, P.S. AISEN, J. KUPIEC, J. BELL FOR THE ALZHEIMER'S DISEASE COOPERATIVE STUDY *(La Jolla, CA, USA)*

Introduction: The Receptor for Advanced Glycation Endproducts (RAGE) is expressed in neurons and vascular endothelial cells. Binding of Aβ to RAGE may influence Aβ transport at the blood-brain barrier. Upregulation of RAGE expression in astrocytes and microglia may trigger oxidative and inflammatory pathways and contribute to damage. PF-04494700, a small molecule that inhibits Aβ-RAGE interactions, is orally bio-available, well-tolerated and resulted in decreased amyloid burden and inflammation in an APP transgenic mouse model. In Phase 1 human studies, including a 10 week study in patients with AD, PF-04404700 was well-tolerated. Objectives: To carry out a randomized, multi-center, placebo-controlled clinical trial of PF-04494700 in patients with mild to moderate AD. To evaluate safety and tolerability. To measure effects of two different doses of PF-04494700 on measures of cognition, global ratings, instrumental ADL and behavior over 18 months. To evaluate changes in biomarkers of brain structure (MRI), biochemistry (CSF and plasma) and amyloid burden (amyloid imaging) over time in a subset of subjects. To measure study drug pK. Material and methods: 3 arm, parallel, double-blind clinical trial in subjects with mild to moderate AD (MMSE 14-26). Subjects were recruited at 40 ADCS sites across the USA and randomized to 5 mg or 20 mg of PF-04494700 once/day, (following a 6 day loading dose) or placebo, for 18 months. Safety and tolerability were monitored. The primary efficacy outcome measure was the ADAS-cog; secondary measures included CDR-sb, ADCS-ADL and psychometric tests. A subset of subjects had MRI, CSF and amyloid imaging studies. Results: 399 subjects (172 men, 227 women) were enrolled at 40 study sites. The first planned interim analysis when 50% of participants had completed a 6 month visit showed an excess of adverse events and greater cognitive decline in the 20 mg/day arm. Active treatment in that arm was immediately discontinued; subjects were notified and continued to be followed. Another planned interim analysis, 12 months after all subjects were randomized, found evidence of futility for the 5 mg/day dose vs placebo, but no safety concerns. Subjects were notified to discontinue the study drug, and treatment discontinuation and 3 month follow-up visits were scheduled. ADAS-cog, clinical and biomarker data will be presented. Conclusion: PF-04494700 showed favorable preclinical anti-AD actions and was well-tolerated in phase 1 studies. This phase 2 clinical trial showed lack of clinical efficacy of 5 mg/day, and accelerated cognitive decline and increased clinical adverse events after 6 months of exposure to 20 mg/day. Initial findings of this phase 2 trial do not support PF-04494700 for the treatment of mild to moderate AD.

O13 - DATA MATTERS: WHAT PAST EXPERIENCE CAN TELL US ABOUT POWER CALCULATIONS AND ANALYSIS PLANS FOR FUTURE ALZHEIMER TREATMENT TRIALS. S.D. EDLAND, M.C. ARD *(University of California, San Diego, USA)*

Introduction: We have recently reviewed published reports of sample size requirements for clinical trials in Alzheimer's disease [Ard and Edland, Power Calculations for Clinical Trials in Alzheimer's Disease. Journal of Alzheimer's Disease (in press)]. These reports, which are all based on longitudinal data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), consistently found that neuroimaging measures outperformed clinical measures in terms of total number of subjects required to detect a fixed percentage slowing of progression relative to placebo. The reports were widely disparate, however, regarding total number of subjects required for a given design and outcome measure. One critical determinant of differences in reported sample size was the statistical analysis plan (and implicit assumptions about data distributions) for the planned future trial. However, no formal test of these implicit assumptions has been reported. Objectives: The objectives of this research are to formally test the accuracy of model assumptions implicit in sample size calculations and to characterize the influence of these model assumptions on sample size estimates for Alzheimer treatment trials. Materials and methods: We will use data from ADNI and from over 3,000 participants in clinical trials performed by the Alzheimer's Disease Cooperative Study (ADCS) to investigate the validity of model assumptions (i.e., data distribution assumptions) implicit in the various statistical analysis plans used in Alzheimer treatment trials. Models will be fit to these large databases and standard lack of fit diagnostics reported. Computer simulations informed by ADCS data will be used to characterize in non-technical terms the actual power and relative performance of different analysis plans once sample size is fixed. We will examine accepted clinical outcome measures (the cognitive component of the Alzheimer's Disease Assessment Scale (ADAS-cog), the ADCS Activities of Daily Living functional scale (ADCS-ADL), and the Clinical Dementia Rating scale sum of boxes score (CDR-SB)), and two likely neuroimaging biomarker outcomes (hippocampal volume and cortical thickness). Results: Analysis of ADAS-cog scores show that power calculations are highly dependent on model assumptions used, and that power calculations based on incorrectly specified models can result in dramatically underpowered trials. Results for the ADCS-ADL scale, the CDR-SB, and the hippocampal neuroimaging measures will also be reported. Conclusion: Accumulating data from cohort studies and clinical trials can inform the design of future trials. One critical use of these data is to test the model assumptions implicit in power calculations before powering trials.

O14 - IDENTIFYING MIDDLE-AGED ADULTS FOR PARTICIPATION IN AD PREVENTION TRIALS USING DEMENTIA RISK SCORES VS. CEREBROSPINAL FLUID BIOMARKER CUTOFFS. C.M. CARLSSON, C.E. GLEASON, S.C. JOHNSON, H.M. BLAZEL, J.H. BARNETT, N. MARTIZA DOWLING, B.P. HERMANN, A.J. MARSH, M.A. SAGER, H. ZETTERBERG, K. BLENNOW, L. PUGLIELLI, C.S. ATWOOD, S. ASTHANA *(University of Wisconsin, USA)*

Introduction: Designing effective Alzheimer's disease (AD) prevention trials depends on careful selection of "preclinical" participants who are at physiologic risk for AD, but who do not yet manifest clinical symptoms. Various models have been proposed to predict risk of dementia, including models based on clinical risk factor profiles and cerebrospinal fluid (CSF) biomarker cutoffs. Applying these dementia risk scores and CSF cutoffs to well-characterized middle-aged adults with parental history of AD may clarify how well these models perform across various at-risk populations. Objectives: To evaluate the ability of clinical dementia risk scores (Kivipelto et al., 2006) and proposed CSF biomarker cutoffs (Mattsson et al, 2009; DeMeyer et al, 2010) to predict baseline cognitive performance in middle-aged adults at risk for AD. Material and methods: Baseline data from the "Evaluating Simvastatin's Potential Role in Therapy (ESPRIT) Study" were used in this analysis. The ESPRIT study is a single-site, 9-month randomized, controlled trial assessing the effects of simvastatin therapy on CSF and cognitive biomarkers in 100 asymptomatic middle-aged adults with parental history of AD. At baseline, participants underwent baseline vascular risk factor assessment, APOE genotyping, and a cognitive test battery targeting memory, language, executive function, and visuospatial skills. In addition, participants had baseline CSF collected and measured for β-amyloid 42 (Aβ42), total tau (t-tau), and phosphorylated tau-181 with xMAP technology using the INNO-BIA AlzBio3 kit (Innogenetics). Dementia risk scores were calculated using demographic and vascular risk factors and APOE4 genotype status according to methods proposed by Kivipelto et al (2006). CSF cutoffs for Aβ42 (less than or equal to 482 ng/L), t-tau (less than or equal to320 ng/L), and p-tau-181 -/=52 ng/L) (Mattsson et al, 2009) were used to identify "high risk" and "low risk" groups. In addition, CSF ABeta42 was plotted against log-transformed p-tau-181 and "AD signature" and "healthy signature" CSF cutoffs were applied based on those defined by De Meyer et al. (2010). Mixed effects models were used to assess the ability of dementia risk scores to predict cognitive performance on six pre-defined cognitive endpoints. Baseline cognitive performance in the CSF "high risk/AD signature" groups were compared to those in the "low risk/healthy signature" groups. Results: Mean (SD) baseline participant (n=100) characteristics were: age 53.5 (8.0) years (range 36-69 years), 16.2 (2.9) years of education, 70% women, 38% APOE4 carriers, n=95 with CSF for analysis. Mean (SD) CSF values for the study population were: CSF ABeta42=338.7 (80.2) ng/L, CSF t-tau=70.0 (63.3) ng/L, p-tau-181= 37.3 (17.9) ng/L. After calculating dementia risk scores, the majority of participants (n=48) fell within the lowest risk quintile based on clinical characteristics (0.3% risk of late life dementia); none of the participants fell within the highest risk quintile (16.3% risk). Dementia risk scores did not predict performance on any of the six cognitive outcomes (all p=0.15). Using CSF p-tau-181 cutoffs defined by Mattsson et al, 22 participants were "high risk" for AD and 73 at "low risk" Participants at "high risk" based on CSF cutoffs demonstrated poorer performance on processing speed compared to those at "low risk" (p=0.028). CSF cutoffs defined by DeMeyer et al. identified only 4 participants within the "AD signature" range. Compared to the other 91 participants, the 4 individuals in the high risk "AD signature" range also demonstrated poorer performance on measures of processing speed (p=0.031) and mental control (p=0.048). Discussion: In this select population of middle-aged adults with parental history of AD, predefined CSF cutoffs for AD risk appeared to better predict cognitive performance compared to dementia risk scores incorporating demographic, vascular, and APOE4 genotype data. Longitudinal studies are underway to clarify whether these CSF cutoffs predict future cognitive decline in this cohort of middle-aged adults at risk for AD. Conclusion: CSF biomarker cutoffs may be a promising way to identify middle-aged adults at risk for AD who may benefit from participation in AD prevention

trials. Further research is needed to clarify if models integrating CSF, neuroimaging, and clinical risk factors better predict those at risk for AD who may benefit from preventive therapies.

O15 - AMYLOID DEPOSITION AND WHITE MATTER LESIONS IN COGNITIVELY HEALTHY ELDERLY. L. GLODZIK, H. RUSINEK, L. MOSCONI, Y. LI, E. PIRRAGLIA, M. CUMMINGS, J. MURRAY, S. WILLIAMS, C. RANDALL, S. VALLABHAJOLUSA, M. DE LEON *(NYU Langone Medical Center, New York, USA)*

Introduction: Amyloid deposition as measured with positron emission tomography with Pittsburgh compound B PET-PIB is thought to reflect an ongoing Alzheimer's disease process and indicate an increased risk for future cognitive decline. It has been postulated that it can be a marker of vulnerable populations which could benefit the most from an early treatment. On the other hand, also hypoperfusion can also activate amyloidogenic pathway of beta-secretase, increase gamma-secretase gene transcription and expression and consequently amyloid beta deposition. A recent report suggest that even mild and transient deficits in perfusion resulted in long lasting increases in brain amyloid beta in laboratory animals. Consequently, vascular disease can contribute to increased amyloid deposition. However, the relationship between amyloid deposition and vascular disease other than cerebral amyloid angiopathy received much less attention in humans. Objectives: We examined relationships between regional PIB binding and white matter lesions (WML), as reflective of vascular disease, in cognitively healthy elderly. We hypothesized that subjects with increased WML burden would manifest increased PIB deposition. If proven correct, this would indicate the need to account for vascular burden while assessing amyloid deposition in the brain. Material and methods: Fifty three subjects were included (mean age 61.8 +/- 9.2, 69% female). They underwent extensive medical, neuropsychological and radiological evaluations (PIB-PET and MRI). For PET analyses cerebellar cortex was used as the reference region. An automated region of interest (ROI) technique was used to sample PIB images. PIB uptake was assessed in: posterior cingulate cortex/ precuneus (PCC+PRE), lateral temporal cortex (LTC), prefrontal cortex (PFC), inferior parietal lobe (IPL) and occipital cortex (OCC). The volume of WML was determined using in house developed software (Firevoxel). Topographical distribution of WML was classified as frontal, occipital and parieto-temporal. Results: PIB uptake differed significantly between regions (Friedman test, p<.001). The highest PIB binding was observed in lateral and posterior regions. The order of regions from the highest to the lowest PIB binding was: LTC, OCC, PCC+PRE, IPL and PFC. Also WML burden differed significantly between regions (p<.001), but conversely to PIB binding, the highest WML burden was observed in the frontal areas, followed by occipital and parieto-temporal regions. After accounting for age and gender, occipital WML volume moderately but significantly correlated with PIB uptake in PCC+PRE (p&.01) and OCC (p=.07). No other correlations were observed. Discussion: Our results do not support the hypothesis that vascular pathology significantly drives amyloid deposition. Frontal regions showing the highest WML burden had the lowest PIB binding. Nonetheless, in the regions with higher PIB uptake, this uptake is related to WML burden, suggesting that vascular pathology can contribute to already ongoing process of amyloid accumulation. Since our group of normal controls showed generally low PIB uptake, our findings warrant replication in more "advanced" groups. Conclusion: Vascular disease may contribute to already present process of amyloid accumulation. This contribution seem to be only moderate but may warrant accounting for while assessing amyloid deposition.

O16 - APPLICATION OF ITEM-RESPONSE THEORY (IRT) TO THE DETECTION OF TREATMENT EFFECTS ON FUNCTIONAL OUTCOMES IN ALZHEIMER'S DISEASE (AD). M.C. ARD, S.D. EDLAND *(University of California, San Diego, USA)*

Introduction: The Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale assesses an individual's ability to perform a range of everyday tasks and is frequently used as an endpoint in clinical trials for AD. While the ADCS- ADL has excellent face validity as a measure of the functional impact of AD, the manner in which it is constructed presents several challenges for longitudinal data analysis, including the use of different rating scales across items, item-specific gender and/or lifestyle biases, differences in the complexity or difficulty of indicated activities, and missing data at the item level. Objectives: We use IRT to develop a more powerful and efficient scoring procedure for the ADCS-ADL. Material and methods: IRT-based item-parameter estimates for the questions comprising the ADCS-ADL, and estimates of patient functional ability based on these item-parameters, are calculated using data from a clinical trial of 409 mild-to-moderate AD patients.Results: Compared to the scoring algorithm for the ADCS-ADL currently in use, IRT-based analysis of ADCS-ADL data yields estimates of patient functional ability that display increased sensitivity to change and improved statistical power to detect a hypothetical effect of treatment on disease progression. Discussion: IRT constitutes a family of quantitative models that assume that responses on specific items are jointly probabilistically determined by item characteristics and underlying subject-level trait(s), and are well suited to handling item heterogeneity and missing data. Consistent with these theoretical advantages, the use of IRT methodology in analyzing data from the ADCS-ADL is observed to lead to more efficient estimation of changes in patient functional ability over time. Conclusion: Identification of effective clinical interventions for AD depends on the availability of tests that are sensitive to disease-related functional decline. The present research explores the potential for improvements in the sensitivity of the ADCS-ADL as a functional outcome measure in AD clinical trials through an application of IRT techniques. Future work will extend and validate these results using a pool of over 3000 subjects.

O17 - RESPONDERS TO ELND005 (SCYLLO-INOSITOL) IN AN ALZHEIMER'S DISEASE STUDY OF 78 WEEKS DURATION: ANALYSIS OF THEIR CLINICAL, V-MRI, AND CSF BIOMARKER CHARACTERISTICS. A. PORSTEINSSON[1], R. SPERLING[2], S. SALLOWAY[3], G. CRANS[4], C. HERNANDEZ[4], S. ABUSHAKRA[4] *(1. University of Rochester Medical Center, Rochester NY; 2. Brigham and Women's Hospital, Boston MA; 3. Butler Hospital/Brown University, Providence RI; 4. Elan Pharmaceuticals, S. San Francisco, USA)*

Introduction: Drug candidates with potential for disease modification in Alzheimer's disease (AD) are thought to provide benefit when treatment is initiated at early stages of the disease, before the development of marked neuronal loss. ELND005 is an amyloid anti-aggregation agent that has been shown to decrease Amyloid pathology and Aβ oligomer-induced synaptic toxicity. Objectives: To analyze the baseline clinical, imaging (v-MRI), and CSF biomarker characteristics of clinical responders to ELND005, and to evaluate the correlations of changes in these outcomes to clinical response rates over the 78 week study duration. Materials and Methods: This was a post-hoc analysis of data from a placebo-controlled Phase 2 study in 353 patients with Mild/Moderate AD (MMSE 16-26), which evaluated 3 doses of ELND005 (250, 1000 and 2000mg all given bid). The 2 highest doses were discontinued due to safety findings; the main safety, efficacy, and imaging/CSF biomarker results have been previously reported (Salloway et al., in press, Neurology). For this analysis response was defined as stable scores on the NTB primary cognitive outcome (endpoint–baseline score ≥0), and included data from the 3 pooled dose groups. Baseline parameters and percent changes from baseline were compared using t-tests. Response rate was defined as the number of times a patient's NTB remained ≥0 at 12, 24, 48, or 78 weeks divided by the time in study. Correlation analyses were performed on the response rates. Results: The week 78 responders compared to non-responders (n= 39 and 109), had significantly higher baseline MMSE scores (mean 23.3 versus 20.5, p value < 0.001), and lower baseline tau and p-tau levels (n= 8 and 30, p-values < 0.005). The responders also had significantly lower percent decrease in brain volume (BV, p < 0.001 at 24 and 48 weeks, and < 0.0001 at 78 weeks); and lower percent increase in ventricular volume (VV, p< 0.05 at 48 weeks, and < 0.002 at 24 and 78 weeks). The strongest correlations to response rates were with BV (0.35 at 78 wks, and 0.31 at 24/48 wks); followed by correlations with VV (-0.28, -0.27, and -0.23 at 24, 48, and 78 wks), all p-values < 0.001, except VV at 78 weeks (p= 0.01). The response rate ratio of Mild to Moderate patients was 1.72 (CI: 1.34-2.21). Discussion: Responders to ELND005 had milder disease at baseline expressed as significantly higher MMSE scores and lower CSF tau and p-tau levels. Changes in brain and ventricular volume showed significant correlations with clinical response, with responders showing less brain atrophy. The correlations to CSF biomarkers changes may have been limited by the smaller CSF sample size. Conclusions: These analyses support the notion that Mild AD patients are more likely to show cognitive benefit in response to a potentially disease modifying treatment.

O18 - A 78-WEEK PHASE 2 STUDY OF ELND005 (SCYLLO-INOSITOL) IN ALZHEIMER'S DISEASE: CLINICAL OUTCOMES BY VARIOUS MMSE DEFINITIONS OF MILD DISEASE. S. SALLOWAY[1], A. PORSTEINSSON[2], G. CRANS[3], C. HERNANDEZ[3], S. ABUSHAKRA[3] *(1. Butler Hospital/Brown University, Providence RI, USA; 2. University of Rochester Medical Center, Rochester NY, USA; 3. Elan Pharmaceuticals, S. San Francisco, USA)*

Introduction: ELND005 (Scyllo-inositol) is an amyloid anti-aggregation agent that is being studied as a potentially disease modifying agent in Alzheimer's disease (AD). In the Phase 2 study in Mild/Moderate AD, the protocol-specified Moderate subgroup (MMSE 16-22) showed no consistent treatment effects at 78 weeks. In contrast, the Mild subgroup (MMSE 23-26) showed encouraging trends on some clinical outcomes (Salloway et al, In Press, Neurology). Objectives: To investigate the effect of ELND005 across a range of Mild AD populations by comparing clinical outcomes using a traditional MMSE range of 20-26 to a narrower range of 22-26 inclusive. Materials and Methods: This was a post-hoc analysis of data from the placebo-controlled study in 353 Mild/Moderate patients (MMSE 16-26), which evaluated 3 doses of ELND005 (250, 1000 and 2000mg all given bid). The 2 highest doses were discontinued due to safety findings; the main clinical and imaging/CSF biomarker results were previously reported (Salloway et al., in press, Neurology). A repeated measure model was used to compare changes from baseline between placebo and 250mg bid groups (m-ITT, N=166). At the MMSE ranges of 20-26 and 22-26, sample sizes for drug/placebo were n= 56/60 and n= 43/45. Due to the exploratory design, no corrections were made for multiple comparisons. Results: In the Mild subgroup with MMSE 22-26 (m-ITT analysis), the treatment differences (positive values favor drug, negative values favor placebo) were: NTB (0.200, p=0.071), ADCS-ADL (3.146, p=0.219), ADAS-cog (-2.645, p=0.250), and CDR-SB (0.971, p=0.102). The corresponding per-protocol results were: NTB (0.405, p=0.002), ADCS-ADL (2.395, p=0.385), ADAS-cog (-2.763, p=0.290), and CDR-SB (0.959, p=0.140). In the Mild subgroup with MMSE 20-26 (m-ITT analysis), the results were: NTB (0.135, p=0.176), ADCS-ADL (-1.179, p=0.613), ADAS-cog (-1.850, p=0.391), and CDR-SB (0.186, p=0.727). The corresponding per-protocol results were: NTB (0.284, p=0.017), ADCS-ADL (-0.811, p=0.746), ADAS-cog (-1.353, p=0.577), and CDR-SB (0.307, p=0.603). Responder rates (no decline on either NTB or ADCS-ADL) were higher in the drug than placebo group by 28% (p= 0.028) in the MMSE 22-26 subgroup, and by 9% (p=0.458) in the MMSE 20-26 subgroup. Discussion: In this post-hoc exploratory analysis, the Mild subgroup defined by MMSE range of 22-26 showed potentially larger ELND005 effects than the 20-26 range. Despite the smaller sample in the 22-26 MMSE range, the cognitive NTB endpoint approached statistical significance. Conclusions: These analyses support the choice of a Mild AD group defined by MMSE of 22-26 inclusive as a population with potential for benefit from ELND005

O19 - AMYLOID-BETA BURDEN AND NEUROPSYCHOLOGICAL TEST PERFORMANCE IN COGNITIVELY NORMAL FIRST-DEGREE RELATIVES AT VARYING GENETIC RISK FOR ALZHEIMER'S DISEASE. C.H. VAN DYCK, A. BRUCK, N.M. BARCELOS, B. PLANETA-WILSON, A.L. BENINCASA, M.G. MACAVOY, Y.-S. DING, J. GELERNTER, R.E. CARSON *(Yale University School of Medicine, New Haven, USA)*

Introduction: In Alzheimer's disease (AD) there is strong evidence that brain amyloid deposition precedes the emergence of dementia by many years. In addition, a greater accumulation of amyloid in the postmortem brain has been demonstrated in people who carry the major genetic risk factor for AD, APOE-ε4. Objectives: This study investigated the relationship between APOE-ε4 genotype, amyloid deposition, and neuropsychological test performance in pre-symptomatic individuals at varying genetic risk for AD. Materail and methods: Cognitively normal subjects aged 50-69 with a first-degree family history for AD were genetically screened to select three groups: APOE genotype ε4ε4 (n=14), ε3ε4 (n=14), and ε3ε3 (n=14), matched for age and sex. Subjects were then studied with 11C-labeled Pittsburgh Compound B ([11C]PiB) PET, MRI, and neuropsychological testing. PET and MR images were co-registered for application of a ROI template (AAL for SPM2) to generate regional time-activity curves with cerebellum as reference region. Parametric BPND images were then generated using SRTM2 such that BPND=0 reflected no specific binding. BPND was computed for a mean cortical ROI consisting of frontal, posterior cingulate-precuneus, lateral parietal, and lateral temporal ROIs. Results: APOE-ε4 carriers demonstrated significantly greater BPND (.17±.19) in comparison to non-carriers (.04±.09; F=6.35, p=.016, ANCOVA controlling for age and sex), with no dosage effect between ε4ε4 (.19±.13) and ε3ε4 (.15±.23) groups. Significant cortical [11C]PiB uptake was observed in APOE-ε4 carriers throughout the age range studied (as young as age 51 in a ε4ε4 subject). There was no significant effect of APOE genotype on neuropsychological test performance. There were also no significant associations between mean cortical [11C]PiB BPND and neuropsychological test performance in the overall sample. Discussion: These results corroborate and extend observations by Reiman et al (2009) but with a somewhat reduced APOE-ε4 effect in a younger sample (mean age 59 vs. 65). They suggest that in high-risk individuals significant amyloid deposition begins earlier than has been recently reported in large series of cognitively normal subjects (Morris et al, 2010; Rowe et al, 2010). Neuropsychological test results confirm the full cognitive normality of many at risk subjects with considerable fibrillar amyloid burden. Conclusion: In cognitively normal individuals at high-risk for AD, significant amyloid deposition begins earlier than has been previously reported. Detection of AD pathogenesis at a fully presymptomatic stage of disease may be necessary to enable the earliest therapeutic intervention. Thus, identification of individuals at high genetic risk, coupled with validation of biomarkers that herald onset of symptoms, will be critical for primary prevention trials in the near future.

O20 - STRATEGIES OF ENRICHMENT AND STRATIFICATION FOR EFFICIENT ALZHEIMER DISEASE CLINICAL TRIALS USING LONGITUDINAL STRUCTURAL MRI OUTCOME MEASURES. D. HOLLAND, L.K. MCEVOY, A.M. DALE *(University of California San Diego, USA)*

Introduction: Standard clinical or cognitive outcome measures for Alzheimer disease (AD) clinical trials may be influenced by symptomatic changes as well as disease-modifying effects of therapy. Also, since these measures show substantial inter-subject variability, clinical trial enrolment needs to be large to ensure adequate power. Subregional structural change from MRI, however, can be used to reduce sample size estimates (Holland et al. (2009), PNAS 106 20954-20959; McEvoy et al. (2010), Alzheimer Dis Assoc Disord 24 269-77), while providing an evidentiary setting to support disease modifying claims for therapy. Additionally, AD risk factors can be employed to selectively enroll participants to further reduce sample size requirements, or to stratify enrollees to enhance power and more finely monitor response to therapy. Since some regions may be more sensitive than others for monitoring change during different diseases stages, it is important to consider rates of change in multiple subregions. To ensure adequate power from longitudinal structural measures, two critical factors must be taken into account (Holland et al. (2011), Human Brain Mapping, Aug 9. doi: 10.1002/hbm.21386): (1) measurements of change need be free of methodological bias, or corrected for any additive bias; and (2) since not all atrophy taking place in healthy controls (HCs) is due to latent AD, sample size estimates need to be calculated from disease-specific change measures, i.e., change in patient cohorts relative to change in HCs essentially free of amyloid pathology. Cerebrospinal fluid (CSF) Abeta and ptau levels are well known indicators of AD pathology, and are predictive of decline in MCI. Another quantity that predicts AD development is a subject's volumetry-based linear discriminant analysis score (V), that rates the subject's baseline atrophy pattern in terms of how characteristic it is of mild AD (McEvoy et al. (2010), Radiology 251 195-205). In particular, an MCI subject's V relative to a threshold value can be used to categorize the subject as AD-like or not. Intrinsic factors like a subject's age and genetics also play roles affecting risk and rates of decline. The APOE e4 allele is the most important genetic risk factor for sporadic AD. Between a half and two-thirds of AD subjects are e4 carriers. APOE e4 is known to reduce the age of onset (Khachaturian et al. (2004), Arch Gen Psychiatry 61 518-524) and to accelerate rate of decline (Cosentino et al. (2008), Neurology 70 1842-1849). For a given disease stage, there is evidence that the younger the subject the rate of decline will be faster in general (Jack et al. (2007), Neurology 70 1740-1752). Objectives: To determine the degree to which longitudinal measures of subregional atrophy rates, especially when combined with CSF biomarkers, baseline atrophy score, APOE e4 status, and age, can enable reductions in sample size requirements for clinical trials of putative AD-modifying therapies, and/or provide stratification mechanisms to more finely assess response to therapy. Material and methods: Data used in the preparation of this article were obtained from the ADNI database (www.loni.ucla.edu/ADNI). Analyses were performed on measures of subregional change derived from longitudinal structural MRI processed with Quarc (Holland et al. (2011), Medical Image Analysis 15 489-497), and the best clinical outcome measure, Clinical Dementia Rating-Sum of Boxes (CDR-SB). Change with respect to baseline was the measure used in both cases. Power calculations were performed using standard methods as described in (Holland et al. (2011), HBM). The sample size required to detect 25% slowing in mean rate of decline for a hypothetical disease-modifying treatment versus placebo was estimated for a 24 month, two-arm, equal allocation trial, with a 6-month assessment interval, for 80% power and a 2-sided significance level of 5%. Mean rate of decline was calculated relative to rate of change experienced by HCs who tested negative for Abeta pathology, based on the cut-off value of CSF Abeta42 level >192 pg/mL, as determined by (Shaw et al. (2009), Ann Neurol 65 403-413). Analyses were performed on 311 MCI subjects, 131 AD subjects, and 58 Abeta-negative HCs, followed for up to 36 months at 6 or 12 month intervals. Results: For the full MCI cohort, sample size estimate for CDR-SB was N=583, 95% confidence interval CI=[416 894]. For (Abeta, ptau, e4)-positive subjects, N=286 [180 577]. For MCI subjects having AD-type atrophy at baseline (V-positive), N=284 [201 453]. For (Abeta, ptau, e4, V)-positive subjects, N=235 [143 536]. For the hippocampus, the corresponding numbers were N=392 [275 608], N=175 [114 329], N=152 [110 230], and N=115 [74 227], respectively. For the entorhinal cortex, N=294 [204 456], N=111 [75 196], N=95 [70 141], and N=53 [36 96] respectively. For the full AD cohort, sample size estimate for CDR-SB was N=279 [189 478]. Restricting to subjects who were e4-positive and/or 75 years of age or younger did not reduce sample size estimates. For the hippocampus, for all ADs N=120 [86 186]; for e4-positive ADs N=99 [68 163]. For the entorhinal cortex, the corresponding estimates were N=73 [52 112] and N=53 [36 85], respectively. Dichotomization by age (older or younger than 75 years) did not have a significant effect for these ROIs. In contrast, dichotomization by age had a pronounced effect for several other ROIs, especially when combined with e4 status for the inferior parietal, the bank of the superior temporal sulcus, and the middle temporal gyrus. For the latter ROI, for all ADs N=129 [89 193]; restricting to e4-positive AD subjects 75 years of age or younger gave N=51 [33 96]. Discussion: MCI is a heterogeneous category of at-risk subjects, and it is not certain that all of them will progress to AD. Rates of decline for MCI subjects are highly variable, but can more finely be categorized with respect to combinations of levels of CSF biomarkers, APOE e4 status, and baseline volumetric score. In particular, risk can be differentiated based on these factors. The smallest sample size estimate, over an order of magnitude smaller than that for the best clinical-cognitive score in the undifferentiated MCI group, and with upper bound on the CI less than 100, was found for the entorhinal cortex in (V, Abeta, ptau, e4)-positive subjects. Positivity with respect to V was the most effective single selection criterion. Essentially all AD subjects are Abeta- and ptau-positive. But APOE e4 status and age, and especially when combined, are powerful predictors of change, particularly for the inferior parietal, the bank of the superior temporal sulcus, and the middle temporal gyrus. For these ROIs, e4-positive subjects 75-years of age or younger require significantly smaller sample sizes than the undifferentiated AD group as a whole, making them competitive with the entorhinal cortex. Since therapy might differentially affect subregional atrophy rates, e.g., depending on targeted mechanism of the drug, local relative concentrations of soluble and insoluble Abeta, tau, ptau, degree of neuropil and neuronal damage, and neuronal type, it may be beneficial to assess multiple subregions, beyond the medial temporal lobe. Conclusion: Dramatic reductions in sample size estimates for clinical trials on MCI and AD subjects can be achieved by using subregional measures of change as outcome measures, and stratifying subjects based on age, APOE e4 status, baseline atrophy, and levels of CSF AD-related proteins.

O21 - TARGETING VASCULAR ACTIVATION: A NOVEL THERAPEUTIC STRATEGY FOR ALZHEIMER'S DISEASE. P. GRAMMAS, L. YIN, A. SANCHEZ, M. EVOLA, A. YOUNG (*Garrison Institute on Aging, Texas Tech University Health Science Center, Lubbock, TX, USA)*

Introduction. Alzheimer's disease (AD) is a progressive, neurodegenerative disease that affects more than 5.3 million people in the United States. Every 70 seconds, someone develops AD; Alzheimer's is the sixth-leading cause of death. The number affected is projected to sharply increase to 8 million by 2030. It is expected that the USA alone will see some 16 million cases by 2050. New therapeutic approaches are desperately needed. Central to developing new therapies is exploring new therapeutic targets. There is increasing evidence that perturbations in cerebral vascular structure and function occur in AD. More specifically, factors and processes characteristic of vascular activation and angiogenesis have been documented in the AD brain. Expression of these factors may result from chronic hypoxia which is known to stimulate angiogenesis as well as contribute to the clinical and pathological manifestations of AD. In addition, epidemiological studies suggest that some drugs purported to have beneficial effects in AD inhibit angiogenesis. We have shown that in AD brain microvessels express and/or release inflammatory proteins, including thrombin, vascular endothelial growth factor, angiopoietin-2, tumor necrosis factor-α (TNFα), transforming growth factor-β, interleukin (IL) IL-1β, IL-6, IL-8, monocyte chemoattractant protein-1, hypoxia inducible factor-1α, matrix metalloproteinases, and integrins (αVβ3 αVβ5), all of which have been implicated in endothelial activation and angiogenesis. Objectives. The objectives of the study are to determine whether pharmacologic interventions aimed at reducing vascular activation/angiogenesis diminish expression/ release of inflammatory and neurotoxic proteins from cerebrovasculature and improve cognitive function in an animal model of AD. Material and Methods. Animals. The APPSWE (2576) transgenic mouse, a widely

utilized model of AD, is employed. Drug. The vascular activation inhibitor Sunitinib (Sutent; Pfizer), a novel small molecule receptor tyrosine kinase inhibitor that is capable of penetrating the central nervous system, and has been clinically tested for safety and biological activity, is used. Drug is prepared and administered in rodent chow. Procedures. Animals (3 months of age) are trained on a radial eight-arm maze (RAM) for 14 days. AD mice then receive either Sutent (40 mg/kg/day) or vehicle in their diet and the ability of the animals to remember the training, an indicator of cognitive performance (i.e memory) is assessed by retesting in the maze. At the conclusion of the behavioral experiments, animals are sacrificed and tissue brain tissue processed for immunofluorescence. Also, brain endothelial cell cultures (passages 6-11) are established from isolated brain vessels to determine the effect of Sutent in vitro on injured brain endothelial cells. Results. From the start of RAM acquisition training, Sutent treated mice performed consistently better than control mice. Sutent treated mice steadily improved over the first five weeks of training and performance stabilized thereafter. Throughout Sutent administration, mice consistently completed the maze in fewer arm entries and made more correct arm entries before making a reentry error ($p<0.001$). In addition, Sutent treated mice maintained their stable performance of RAM in the absence of drug treatment for an additional 10 blocks of training ($p<0.001$) when Sutent administration was suspended on week 26. At the conclusion of behavioral experiments, examination of brain tissue sections showed that the increased expression of IL-1, IL-6, TNFα, thrombin and amyloid β demonstrable in AD mice is significantly ($p<0.001$) decreased in animals that had been treated with Sutent. Based on the immunofluoresence data, we initiated experiments to examine the effects of Sutent in vitro on brain endothelial cells. Endothelial cell cultures were "injured" using the oxidant-releasing compound menadione. Treatment of endothelial cell cultures with Sutent had no effect on endothelial cell survival but significantly ($p<0.01$) decreased oxidant-induced TNFα release. Discussion. The data show that administration of Sutent improves cognitive performance and diminishes the expression of vascular activation/angiogenic factors in an animal model of AD. Furthermore, in vitro Sutent appears to reduce oxidant-injury mediated release of inflammatory proteins. These results suggest that Sutent has vasculoprotective effects and may stabilize/improve the cerebrovasculature in AD. It is has been our working hypothesis that in AD an abnormal pathologically altered brain endothelium produces factors that are toxic to neurons and that vascular-derived factors could be important mediators of neuronal injury and death in neurodegenerative diseases such as AD. Identification of "vascular activation" as a target in AD would shift the neurocentric model of AD pathogenesis and could stimulate translational investigations in this newly defined area, leading to novel therapeutic approaches for the treatment of this devastating disease. Conclusion. New therapeutic approaches in AD are urgently needed. Data demonstrating a causal link between the activated vascular phenotype and cognitive impairment could provide valuable new insights into the development of AD. Furthermore, because several vascular activation inhibitor drugs are currently FDA approved or in use in Phase III clinical trials for cancer treatment, new clinical trials with these drugs could be rapidly designed and implemented in AD patients. The process of discovering and developing new drugs is lengthy and expensive. Therefore, innovative, off-label use of FDA-approved drugs as novel treatments for AD is a timely and cost-effective strategy. Vascular activation/angiogenesis inhibitors developed for cancer treatment but "repurposed" for AD, could provide a novel therapeutic approach for the treatment of AD.

O22 - DISEASE-MODIFICATION IN MCI WITH HOMOCYSTEINE-LOWERING B VITAMINS SLOWS ATROPHY OF PARTICULAR BRAIN REGIONS: THE VITACOG TRIAL. G. DOUAUD[1], H. REFSUM[2], C.A. DE JAGER[2], K. BRADLEY[2], R. JACOBY[2], S.M. SMITH[1], A.D. SMITH[2] *(1. FMRIB Centre, University of Oxford, Oxford, UK; 2. OPTIMA, University of Oxford, Oxford, UK)*

Introduction: Moderately raised plasma total homocysteine is associated with an increased risk of dementia and cognitive decline. Raised homocysteine has also been associated with both localised and more global brain atrophy in healthy elderly, mild cognitive impairment (MCI) and Alzheimer's disease. The tissue and plasma concentrations of homocysteine are largely determined by the body's status of certain B vitamins (folate, B6 and B12), which are cofactors or substrates for enzymes involved in homocysteine metabolism. Objectives: The VITACOG trial was designed to investigate the effect of administration of high doses of supplementary B vitamins (folic acid, vitamins B6 and B12) over two years in elderly subjects with MCI. We previously reported results from this trial showing that lowering homocysteine by B vitamin treatment in MCI slows the mean rate of whole-brain atrophy by 30%, as measured using the SIENA protocol (Smith et al. PLoS ONE 2010, 5: e12244) and also slows cognitive decline (de Jager et al. Int J Geriatr. Psych in press). Here, we wanted to identify which brain regions benefited from the decreased rate of atrophy in response to B vitamin therapy. Material and Methods: 168 volunteers with MCI over 70 y old underwent the same imaging protocol. Inclusion/exclusion criteria and MRI procedures were described in the previous reports. T1-weighted images were acquired at baseline and after 2 years. To assess differences in the distribution of gray matter (GM) between patients and controls, an optimised VBM analysis using FSL was carried out (Douaud et al., Brain 2007, 130:2375; Smith et al., Neuroimage 2004, 23(S1):208). This voxel-by-voxel approach is unbiased, in that it requires no a priori information about the location of possible differences in the grey matter, and is not operator-dependant. Eleven sets of images were discarded due to insufficient quality and 2 sets were excluded for being beyond 3σ of the mean, leaving 155 MCI subjects (75 placebo and 80 B vitamins). Both groups were similar in age (placebo: 75.7±4.0; actively treated: 76.7±5.2) and gender (63% and 61% of women, respectively). Finally, to achieve accurate inference including full correction for multiple comparisons over space, we used permutation-based nonparametric inference within the framework of the general linear model (5000 permutations) (Nichols & Holmes, Hum Brain Mapp 2002, 15:1). We looked for GM differences between baseline and follow-up scan in placebo and vitamin groups and then for differences in the changes in GM between the two groups. Results were considered significant for $P<0.05$, after correction for multiple comparisons using an initial cluster-threshold at $P = 0.05$ uncorrected. Results: The decrease in whole-brain GM volume was bigger in patients who took the placebo compared with those who took the B vitamins, though this was not significant ($p=0.09$). There were some areas with significant widespread regional decreases of GM in both the placebo and vitamin group over the 2 year intervention period. However, the GM loss was remarkably larger for the placebo group than for the treatment group, especially in temporo-occipital and cerebellar regions. Changes over time were significantly different between the placebo group and the treatment group in the left fusiform, supramarginal, inferior temporal gyri and parahippocampal gyrus, left retrolimbic area (precuneous), left cerebellum VI, and bilateral vermis and lingual gyrus. The significant results were used to define a large region-of-interest (ROI) and ROI-averaged GM volume changes were then extracted for all participants. The placebo group lost GM in the ROI, while there was either a smaller GM loss or even an increase of GM volume in the vitamin group. Discussion: The fact that trend in change in whole-brain volume did not reach significance is not inconsistent with the published SIENA result, as the SIENA analysis is specifically tuned to be sensitive to global longitudinal change, whereas the VBM approach is aimed at finding 'localised' effects. Overall, the findings show that the slowing of whole-brain atrophy in the B vitamin treated group in VITACOG is not a generalised phenomenon, but reflects highly regional effects of the treatment. The cortical regions that were relatively protected by B vitamin treatment are similar to those described in several studies as characteristic of conversion from normal elderly to MCI and/or from MCI to AD. The finding that parts of the cerebellum showed a reduced rate of atrophy in the B vitamin treated group is of interest in relation to the concept of the cerebellar cognitive affective syndrome (Schmahmann & Sherman, Brain 1998, 121:561). Conclusion: Our findings are consistent with a specific disease-modifying effect of B vitamin treatment in MCI. Future work will examine these regional changes in subgroups defined by their base-line level of homocysteine and other covariates such as ApoE4 status. We will also look for correlations with cognitive effects of the B vitamin treatment.

LATE BREAKING ORAL COMMUNICATIONS

LB1 - MRI FEATURES OF ASYMPTOMATIC AMYLOID RELATED IMAGING ABNORMALITIES-EDEMA (ARIA-E) IDENTIFIED AT BASELINE IN AD STUDY COHORTS, AND MR ARTIFACTS WHICH MIMIC ARIA-E. J. BARAKOS[1,2], C. CARLSON[3], W. ESTERGARD[3], J. OH[1], J. SUHY[1], C. JACK[4], E. SIEMERS[3] *(1. Synarc, San Francisco, CA; 2. California Pacific Medical Center, San Francisco, CA; 3. Lilly Research Laboratories, Indianapolis, IN; 4. Mayo Clinic, Rochester, MN, USA)*

Objectives: To understand the imaging features of naturally occurring amyloid-related imaging abnormalities-edema (ARIA-E) and describe how they differ from vasogenic edema (VE) encountered in routine clinical practice. Additionally, to outline a variety of magnetic resonance imaging (MRI) artifacts that may mimic ARIA-E. Introduction: ARIA-E (Sperling et al., 2011) or VE has been described in association with b-amyloid lowering therapy (Salloway et al., 2009). As part of ongoing Alzheimer's disease (AD) clinical trials, we set out to describe the optimization of MRI safety scans (fluid-attenuated inversion recovery imaging, FLAIR) to monitor for ARIA-E. In addition, various technical factors are outlined which may cause artifactual ARIA-E. These described imaging factors relating to ARIA-E are important for the evaluation of patients enrolled in AD clinical trials to ensure adequate monitoring for potential adverse events. Methods: Baseline (pre-study treatment) MRI were obtained from patients entering 4 ongoing trials of b-amyloid lowering agents for the treatment of AD (Carlson et al., 2011). Study H6L-MC-LFAN (IDENTITY) is a multicenter, randomized, double-blind, placebo-controlled, Phase III study comparing daily doses of 100 mg or 140 mg semagacestat with placebo in 1536 patients with mild to moderate AD. Study H6L-MC-LFBC (IDENTITY-2) is a similar Phase III study comparing daily doses of 140 mg semagacestat with placebo in 1111 patients with mild to moderate AD. In these trials, the MRI scans were obtained from patients entered into an optional volumetric MRI addendum (N=625). Two additional trials (H8A-MC-LZAM, EXPEDITION and H8A-MC-LZAN, EXPEDITION-2) are multicenter, randomized, double-blind, placebo-controlled, Phase III studies in patients with mild to moderate AD (N=1012 and 1040, respectively) receiving monthly infusions of 400 mg of the anti-Ab monoclonal antibody solanezumab or placebo. MRI exams were obtained in 2134 of 2681 screened patients from baseline scans obtained as part of the protocol. Across all 4 studies, MRI was obtained at approximately 273 imaging centers around the world with standardized site MRI training. Imaging was conducted on a wide range of platforms including GE, Philips and Siemens (1.5 or 3.0 Tesla). Results: In the review of the 2,759 study enrollee pretreatment MR scans, we identified two cases with ARIA-E. The first case was associated with overall imaging features consistent with cerebral amyloid angiopathy-related inflammation (Figure 1a-b). The second case of ARIA-E presented as a sulcal focus of FLAIR hyper-intensity which was not associated with any imaging features that would suggest the presence of blood product or potential artifact. The patient returned for follow-up imaging 4 weeks later, at which time the previously reported abnormalities had resolved. We also found a series of cases which revealed artifactual ARIA-E (n=6). Categories of artifactual ARIA-E were magnetic susceptibility artifact (Figure 2a), propofol/supplemental oxygen (Figure 2b), incomplete/poor FLAIR water suppression, or phasing and ghosting FLAIR artifacts. We describe the imaging features which allow differentiation of false positives from true

positive cases of ARIA-E. Discussion: We present two very different imaging appearances of naturally occurring ARIA-E observed in subjects with AD who enrolled in AD drug trials. Based upon the MRI appearance combined with clinical presentation, one case of ARIA-E was presumably related to angiitis associated with cerebral amyloid angiopathy. The hyper-intensity on FLAIR in the second case may be explained by vascular exudate with protein content high enough to shorten T1-relaxation in comparison to adjacent cerebral spinal fluid. Conclusion: In conclusion, ARIA-E differs from VE encountered in the routine clinical setting and may be identified in clinical trial patients with AD, at baseline. As such, a specific understanding of the unique features of ARIA-E is required in order to ensure optimal imaging protocols allowing for accurate detection. Additionally, examples of artifactual ARIA-E are presented with a review of imaging features which allow characterization as artifact and differentiation from true ARIA-E. References: Sperling et al. Alzheimer's Dement, 2011;7(4):367-385. Salloway et al. Neurology, 2009;73:2061-2070. Carlson et al. Alzheimer's Dement, 2011;7(4):396-401.

LB2 - INFLUENCE OF CSF BIOMARKERS ON COGNITIVE DECLINE IN AN INTERRUPTED MCI-TRIAL. O. PETERS[1], L.K. JOACHIM[1], K. SCHMIDTKE[2], M. HULL[2], E. RUTHER[3], S. TEIPEL[4], H.J. MOLLER[4], F. JESSEN[5], W. MAIER[5], J. KORNHUBER[6], C. LUCKHAUS[7], L. FROLICH[8], I. HEUSER[1] *(1. Department of Psychiatry, Charité - CBF, Berlin; 2. Center for Geriatric Medicine and Gerontology, University Hospital Freiburg; 3. Department of Psychiatry, University Göttingen; 4. Department of Psychiatry, Ludwig Maximilian University Munich; 5. Department of Psychiatry, University Bonn; 6. Department of Psychiatry, University Erlangen; 7. Department of Psychiatry, University Düsseldorf; 8. Central Institute of Mental Health, Mannheim)*

Introduction: Most clinical trials studying AChE-inhibitors in MCI have failed to influence conversion to dementia (Salloway et al. 2004, Feldman et al. 2007, Winblad et al. 2008, Doody et al. 2009). In an aborted trial testing the combination of galantamine plus memantine we have recently shown that only MCI subjects with the clinical diagnosis of presumed Alzheimers disease (AD) had a cognitive benefit after short-term treatment (Peters et al. 2011). Objectives: In this sample of MCI pts, we studied the influence of CSF-biomarkers at baseline, and the duration of treatment on the clinical outcome after 24 months. Material and methods: In a double-blinded placebo-controlled study 237 MCI were randomized to receive a combination therapy of galantamine plus memantine, galantamine alone or placebo. Recruitment was prematurely stopped before the planned sample size had been reached (Peters et al. 2011). Due to the interruption of the trial only 83 patients could be reexamined after 24 months. Results: Two years after baseline 12 out of 83 patients (14%) fulfilled the diagnostic criteria for dementia, all of whom had belonged to the subgroup of presumed AD. Converters received treatment for 630 ± 174 days over a period of 24 months (Non-converters: 211 ± 233 days). Retrospective analysis revealed that converters were characterized by a higher ADAS-cog (15.3 ± 2 vs. non-converters: 11 ± 0.5) at baseline; ADAS-cog increased significantly within 24 month only in converters. Cognitive worsening in converters was not influenced by the duration of treatment but was correlated with higher total TAU (621 ± 311 pg/ml vs. 372 ± 196 pg/ml) and lower A-beta 1-42 (508 ± 171 pg/ml vs 827 ± 391 pg/ml) at baseline. Discussion: In an interrupted MCI-trial cognitive decline in converters was not influenced by the duration of antidementive treatment but correlated significantly with the CSF biomarker profile at baseline. Conclusion: We conclude that neurobiological heterogenity in MCI-trials should be strictly limited. Salloway et al., Neurology 2004; 63:651-657, Feldman et al., Lancet Neurol 2007; 6:501-12, Winblad et al., Neurology 2008; 70 : 2024-2035, Doody et al., Neurology 2009; 72: 1555-1561, Peters et al., JNHA 2011, in press

LB3 - SOUVENAID® IMPROVES MEMORY IN DRUG-NAIVE PATIENTS WITH MILD ALZHEIMER'S DISEASE: RESULTS FROM A RANDOMIZED, CONTROLLED, DOUBLE-BLIND STUDY (SOUVENIR II). P. SCHELTENS[1], J. TWISK[2], R. BLESA[3], E. SCARPINI[4], C. VON ARNIM[5], A. BONGERS[6], J. HARRISON[7], S. SWINKELS[6], P. DE DEYN[8], R. WIEGGERS[6], B. VELLAS[9], P. KAMPHUIS[6] *(1. Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands; 2. Department of Health Sciences, VU University Medical Center, Amsterdam, The Netherlands; 3. Hospital de la Sta Creu i St. Pau, Barcelona, Spain; 4. Ospedale Maggiore Policlinico, University of Milan, Italy; 5. Department of Neurology, Ulm University, Ulm, Germany; 6. Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands; 7. Metis Cognition Ltd, Kilmington, UK & Imperial College, London, UK; 8. ZNA Middelheim, University of Antwerp, Belgium; 9. Gerontopole, INSERM U 1027, Toulouse, France)*

Introduction: Souvenaid® (Medical Nutrition), containing the specific nutrient combination FortasynTM Connect, is designed to support synapse formation and function in patients with Alzheimer's disease (AD). The nutrients in Fortasyn Connect are precursors and cofactors for the formation of neuronal membranes, and increasing their dietary intake can promote the synthesis of new brain synapses (Cansev et al., Alzheimers Dement, 2008; Kamphuis and Scheltens, J Alzheimers Dis, 2010). A proof-of-concept study ('Souvenir I') in drug-naïve patients with mild AD (MMSE 20-26) showed that Souvenaid taken once per day was safe and improved memory (WMS-r, delayed verbal memory) after 12 weeks, the co-primary endpoint of the study (Scheltens et al., Alzheimers Dement, 6, 1-10, 2010). The 'Souvenir II' study was designed to confirm the effect of Souvenaid on memory in drug-naïve patients with mild AD, and also to extend the investigation through a longer intervention period of 24 weeks and through utilization of the whole memory domain z-score of a Neuropsychological Test Battery (NTB). The Souvenir II study was recently completed and first results will be presented. Objectives: The Souvenir II study was designed to investigate the effect of Souvenaid on memory performance during 24 weeks intervention in drug-naïve patients with mild AD. Secondary objectives were to investigate safety and tolerance of the intervention, and to assess the effects on global cognition, functional abilities, and electroencephalography (EEG). Material and methods: The Souvenir II study was a randomized, controlled, double-blind study, conducted at 27 study centers in six European countries (the Netherlands, Germany, France, Belgium, Italy and Spain). Drug-naïve patients with mild AD (MMSE scores ≥ 20) and diagnosis of probable AD according to the NINCDS-ADRDA criteria, were randomly assigned (1:1) to Souvenaid, a 125 mL once-a-day drink containing Fortasyn Connect, or an iso-caloric control product. The duration of intervention was 24 weeks. The memory domain score of a Neuropsychological Test Battery (NTB) was the primary outcome parameter. This memory composite score was derived from the Rey Auditory Verbal Learning Test (RAVLT: immediate recall, delayed recall and recognition performance) and the Wechsler Memory Scale (WMS) verbal paired associates test (immediate and delayed recall). Secondary outcomes resulting from the NTB were the executive function domain, total composite score and individual item scores. The other NTB items were WMS Digit Span, Trail Making Tests part A and B, Category Fluency, Controlled Word Association Test, the ADAS-cog orientation task and the Letter Digit Substitution Test. Other secondary outcome parameters were the Disability Assessment for Dementia (DAD) scale, EEG (basic frequency and functional connectivity analysis), product compliance, tolerance and safety. Main study parameters were assessed at baseline, week 12 and week 24. For the statistical analysis of the data, a repeated measures mixed model was used. The trial was registered with the ICMJE compliant www.trialregister.nl (NTR1975). Results: A total of 259 drug-naïve subjects were randomized (2.6% screen failures). In the overall study population no differences in baseline characteristics were noted between the study groups. The mean age was 73.8 (± 7.7) years, the mean screening MMSE was 25.0 (± 2.8) and 51% were male. A pre-specified blinded interim analysis was conducted to check whether the calculated sample size was adequate and that no safety concerns had arisen, and the independent Data Monitoring Committee recommended continuation of the trial without modification. From the 259 subjects randomized, 238 subjects (91.9%) completed the study. Five subjects did not complete the study because of a (serious) adverse event ((S)AE); 3 in the Souvenaid group and 2 in the control group, and no differences between study groups were noted in the occurrence of (S)AEs. No clinically relevant differences in blood safety parameters were noted. The average compliance during 24 weeks was very high at 97% and not different between the groups. High compliance was confirmed by marked and significant changes in (nutritional) biomarkers of compliance, e.g. docosahexaenoic acid in erythrocyte membranes and plasma homocysteine. During 24 weeks, Souvenaid significantly improved the primary endpoint memory performance (composite memory domain z-score resulting from the NTB) compared to control product (repeated measures mixed model, p=0.025). The significant effect on memory performance was confirmed by individual tasks of the NTB memory domain. No effect was found on the secondary parameters NTB executive function domain score and on the DAD. EEG analysis is ongoing. Discussion: Based on the co-primary endpoint, the Souvenir I study showed that Souvenaid improved memory after 12 weeks in drug-naïve mild AD (mean MMSE score 23.9). The current Souvenir II study is the second study showing that the use of Souvenaid improves memory performance in drug-naïve patients with mild AD (mean MMSE score 25.0). This study also shows that use of Souvenaid in patients with mild AD for 24 weeks is safe: safety, tolerability and compliance in this study were consistent with findings from the Souvenir I study. The currently ongoing 24 weeks open label extension of the Souvenir II study will provide additional insights. The ongoing EU-funded (1) 'LipiDiDiet' study in 300 subjects with prodromal AD (according to criteria in Dubois et al, Lancet Neurol, 2007) aims to assess the effect of Souvenaid on the memory domain of a NTB during 24 months. This will further extend insights regarding the effects on memory in a very early stage of AD. The EEG analysis in the Souvenir II study and the ongoing Magnetoencephalography (MEG) substudy of Souvenir II will provide further understanding of the effect of Souvenaid on functional connectivity, thus investigate the hypothesis that Souvenaid can support synapse formation and function in mild AD. Conclusion: In conclusion, this study showed that 24-weeks of supplementation with Souvenaid is well-tolerated and improves memory in drug-naïve patients with mild AD. Footnotes: 1. The research is funded by the EU FP7 project LipiDiDiet, Grant Agreement N° 211696 Souvenaid is a registered trademark of N.V. Nutricia. Fortasyn is a trademark of N.V. Nutricia. The Souvenir II study forms part of the Souvenaid Clinical Trials Program.

LB4 - AFFITOPE® ALZHEIMER VACCINES – RESULTS FROM CLINICAL PHASE I SUPPORT THE FURTHER CLINICAL DEVELOPMENT OF AFFITOPE® AD02. A. SCHNEEBERGER, M. MANDLER, F. MATTNER, W. SCHMIDT *(AFFiRiS AG, Karl-Farkas Gasse 22, 1030 Vienna, Austria)*

Based on the notion that cerebral accumulation of certain Aβ species (unprocessed as well as N-terminally truncated and modified versions) is central to the pathogenesis of Alzheimer's disease (AD) and endowed with the knowledge that emerged during clinical testing of the first Alzheimer vaccine, AN1792 (Elan/Wyeth), AFFiRiS designed a new type of AD vaccines. Rather than relying on full-length Aβ itself or fragments thereof, AFFITOPE® vaccines use short peptides mimicking parts of the native Aβ sequence as their antigenic component. The technology created to identify these peptides, termed AFFITOME®-technology, concomitantly provides the basis for the multi-component safety concept (short antigens preclude activation of encephalitogenic T cells; AFFITOME®-technology controls specificity of antibodies induced) realized in AFFITOPE® vaccines. The AFFiRiS AD immunotherapy program focuses on two targets: AFFITOPEs® AD01 and AD02 (which differ in their peptide sequence) target the native N-terminus of Aβ while AFFITOPE® AD03 addresses N-terminally-truncated and pyroglutamate-modified forms of Aβ. AD03 currently undergoes phase I clinical testing.

Phase I testing of AD01 and AD02 was done in a parallel manner at two different sites and carried out as monocenter studies. In each study, 24 patients were vaccinated; 12 received the vaccine with adjuvant and 12 without. Clinical phase I data to the safety of AFFITOPEs® AD01, AD02 (and AD03 – as available), spanning a time period of 20+ months, support the safety concept inherent to AFFITOPE® AD vaccines. The recently completed analysis of secondary clinical endpoints of AD02-based treatment – regarding parameters such as the cognitive/functional performance of the patients (as assessed among others by MMSE, ADAScog, ADL), body weight development and vaccine induced immune responses over a time period of 20+ months – provides evidence for a disease modifying activity of AFFITOPE AD02®. This was particularly evident in patients who entered the phase I study at an early stage of their disease. The above results led AFFiRiS to initiate a multicenter phase II study aimed at evaluating the clinical activity AFFITOPE AD02®. The study design already takes into account the indicatory results of the phase I study and will include a total of 420 patients with early AD.

LB5 - A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF VITAMIN E IN AGING PERSONS WITH DOWN SYNDROME. A. DALTON, P. AISEN, W.-Y. TSAI, H. ANDREWS *(Mount Sinai School of Medicine, Bronx, USA)*

Introduction: Enormous need for therapy to reduce the occurrence and progression of Alzheimer's Disease (AD) in individuals with DS. Oxidative stress may be a contributing mechanism in AD complicating DS. Vitamin E therapy may provide therapeutic CNS antioxidant effect. Objectives: To conduct a multi-centered randomized clinical trial of vitamin E in aging persons with down syndrome (DS). The primary aim is to determine if vitamin E can slow the deterioration of aging persons with DS as measured by the Brief Praxis Test. Secondary Aims include determining if the treatment could produce a benefit in measures of clinical global change, cognition function and behavior. The study also assessed the ability of vitamin E to delay the diagnosis of AD in non-demented subjects with DS. Material and methods: Subjects: The trial recruited subjects with DS, aged 50 years or older were recruited with or without dementia that were medically stable with stable medication for 3 months or more. All had an informant who was familiar with the subject's daily behavior and function. Exclusion criteria included the inability to adequately perform the BPT (defined as a minimum score of 20), evidence of vascular dementia, major depression within the past 3 months, a history of coagulopathy or use of anti-coagulants, and use of vitamin E at a dose greater than 50 IU/ day during the previous 6 months. Recruitment occurred at 21 English speaking sites in 5 countries. Informed consent was obtained prior to any procedures in accordance with local standards and requirements. The primary outcome measure was the Brief Praxis Test which has been shown to demonstrate change over time in an aging DS population. Secondary measures included Secondary outcome measures included tests of verbal and visual memory (modified Fuld Object Memory Test, New Dot Test), Orientation Test, Vocabulary Test, The Behavior & Function and Questionnaire, Clinical Global Impression of Change (CGI-C). For those who did not have a diagnosis of dementia, DSM criteria for dementia was assessed at each visit. Intervention: Subjects were randomized to receive Vitamin E 1,000 IU orally twice daily or identical placebo in a one to one ratio for 3 years. Assessments were conducted at six month intervals. Safety measures assessed at each visit included vital signs, physical and neurological examination, a symptom checklist and adverse event reporting. The primary analysis used the general estimating equation techniques to assess change in BPT scores and secondary outcomes. Secondary analysis of incident dementia used Chi square. Results: 347 subjects were screened and 337 were randomized. The majority were male, white, had mild to moderate level of retardation, were not demented and living a residential facility. There were no differences between drug and placebo groups on these demographic features. The BPT demonstrated deterioration overtime but there was no difference between the drug and placebo groups in the rate of change. Drug placebo differences in subgroups of demented and non-demented individuals were also not significant. There was also no significant difference between drug and placebo on any of the secondary outcome measures. There were 44 cases of incident dementia (37%) in the drug group and 36 in the placebo group (29%) and this difference was not significant. Adverse events (AE) were common with 96% of subjects in the treatment group vs. 93% in the placebo group having one or more AE. The difference between groups was not different. There was also no difference between groups in the number of cases who experienced serious adverse events (SAE) (drug 31.5% vs. placebo 32%; p=1.0). There were more deaths in the treatment than placebo group (17% vs. 10%) and this approached significance (p=0.086). Discussion: This study found no benefit of vitamin E on cognition or function in aging individuals with DS. While there was no difference in AE or SAE between groups there was a trend toward higher deaths in the vitamin E group. To our knowledge this is the largest international multicenter trial in DS. It was successful in selecting measures that captured the deterioration of aging individuals with DS, regardless of dementia status. The CGIC was adapted for this population and demonstrated expected sensitivity to worsening although it was not affected by vitamin E. The study demonstrates a well established trial network for conducting randomized clinical trials in Down syndrome. Conclusion: Vitamin E does not benefit cognition or function in aging individuals with DS.

LB6 - TESAMORELIN, A GROWTH HORMONE-RELEASING HORMONE ANALOGUE, IMPROVES COGNITIVE FUNCTION IN MCI AND HEALTHY AGING: RESULTS OF A RANDOMIZED CONTROLLED TRIAL. L.D. BAKER, S.M. BARSNESS, S. BORSON, G.R. MERRIAM, S.D. FRIEDMAN, S. CRAFT, M.V. VITIELLO *(VAPSHCS, GRECC-182A, University of Washington, Seattle, WA, USA)*

Introduction: Animal and clinical studies show that the somatotrophic axis, which modulates circulating levels of growth hormone, growth hormone-releasing hormone (GHRH), and insulin-like growth factor I (IGF-I), has potent effects on brain function. Age- and disease-related changes in this axis set the stage for targeted therapeutic interventions to improve cognitive function. In an earlier pilot study, we demonstrated that six months of GHRH treatment had positive effects on cognition for healthy older men and women. These results also provided preliminary evidence that similar benefits might be observed for adults with mild cognitive impairment (MCI). Objectives: To examine whether 5 months of GHRH administration improved cognitive function in healthy older adults and in adults with MCI. Material and methods: Using a double-blind, randomized, placebo-controlled study design, 152 subjects (55-87 yrs old) were randomized to receive subcutaneous injections of tesamorelin, a stabilized analogue of human GHRH (1 mg/d, provided by Theratechnologies Inc.) or placebo 30 min before bedtime for 20 weeks. Sixty-seven subjects (n=31 amnestic MCI) in the GHRH group and 70 subjects (n=30 amnestic MCI) in the placebo group completed the study. Prior to enrollment, study candidates received a neuropsychological assessment with diagnostic adjudication and medical screening. At baseline and week 20, cognitive function was assessed including tests of executive function and episodic memory, oral glucose tolerance tests and body fat assessments were performed, and blood was collected for assay of IGF-I, glucose, and insulin. Results: Tesamorelin significantly increased plasma levels of IGF-I over baseline ($p<0.0001$) but remained within physiological range and decreased body fat ($p<0.0001$). Both for healthy older adults and adults with MCI, tesamorelin improved performance on executive function tests of response inhibition ($p=0.009$, Stroop Color Word Interference test) and set-shifting ($p=0.01$, Task Switching), and a statistical trend also suggested tesamorelin-related improvements in working memory ($p=0.07$, Self-ordered Pointing Test). On tests of memory, tesamorelin significantly improved delayed verbal recall for adults with MCI but not for healthy older adults (MANOVA tx*dx interaction, $p=0.05$). General cognitive status (MMSE), visual memory, word fluency, and processing speed were not affected by treatment. Discussion: This study is the first to demonstrate that short-term tesamorelin administration improves executive function for healthy and memory-impaired older adults, and has a favorable effect on verbal memory for adults with MCI. The likely mechanism to account for these effects relates to treatment-induced elevations in circulating IGF-1 that climbed to levels typically observed in younger adults. Increased IGF-1 in models of aging and neurodegenerative disease has well-documented plieotrophic salutary effects on brain health and function, including cognition. Conclusion: Short-term administration of a GHRH analog, tesamorelin, had favorable cognitive effects in healthy adults and in adults at high risk of progression to Alzheimer's dementia. Our findings set the stage for future studies to examine the impact of longer-term GHRH administration on brain health in normal and pathological aging.

LB7 - PHASE II CLINICAL TRIAL OF METFORMIN IN AMNESTIC MCI: RATIONALE, METHODS, AND BARRIERS AND ENABLERS OF SUCCESSFUL RECRUITMENT. T. PEREZ, S. THAREJA, E. ARANA, H. CHANG, E. BAGIELA, J.A. LUCHSINGER *(Columbia University Medical Center, New York, NY, USA)*

Introduction: Obesity, insulin resistance, and diabetes are related to a higher risk of Alzheimer's Disease. This observation has prompted clinical trials of interventions that treat or prevent diabetes in persons with Alzheimer's disease or at risk for Alzheimer's disease. We planned a phase II trial of metformin, a biguanide shown to be effective in the treatment and prevention of diabetes, in persons with overweight and obese persons with amnestic mild cognitive impairment (MCI), with the hypothesis that metformin will decrease cognitive decline compared to placebo over a 12 month period. There is anecdotal data indicating that recruitment into clinical trial of amnestic MCI is difficult, but there is paucity of data examining the enablers and barriers to successful recruitment. Objectives: The objectives of this presentation are to 1) provide the rationale and methodology of this clinical trial, and 2) to examine the enablers and barriers of recruitment. Material and methods: The study design is a placebo-controlled double-blind randomized clinical trial of metformin vs matching placebo lasting 12 months. Metformin was started at a dose of 500 mg a day and titrated to 1000 mg twice a day or the maximum tolerated dose. Participants were overweight or obese, without treatment for diabetes, with a maximum screening HbA1c of 6.9%, of both sexes, and between the ages of 55 and 90 years, and meeting criteria for amnestic MCI. The target sample size was 80 participants, with 40 participants enrolled in an imaging substudy. All participants underwent a comprehensive interview including a comprehensive neuropsychological battery. The primary outcomes are changes in the ADAS-COG and in uptake of fluorodeoxyglucose (FDG) in the posterior cingulate ascertained with Positron Emission Tomography. Secondary outcomes include change in plasma amyloid beta. A total of 7 different recruitment methods were used: Ads, Newsletters, talks and health fairs, flyers and pamphlets, referrals, websites and local cable television. We examined which recruitment methods were the most effective through examination of our recruitment logs. Calls from prospective participants were received and kept in a recruitment call log. The coordinator contacted the potential participants to conduct a telephone screening that included questions on demographics, medical history, medications, and the Telephone Interview of Cognitive Status (TICS). Once telephone screening was passed, participants were scheduled for an in-person screening including clinical and cognitive assessments that included the ADAS-COG and recall tests to assess

MCI criteria. Those who met eligibility criteria in the in-person screening were enrolled into the study and scheduled for their baseline/randomization visit. Results: Recruitment of the 80 participants was finished in February of 2011, with an 8 month delay; 70% of Participants have finished the study as of September of 2011 and the last participant will have its final assessment in February of 2012. The 12 month retention rate in participants who have finished the study is over 90%. Recruitment of the 80 participants in a single site took approximately 30 months. Recruitment was community and hospital based in New York City. Over 1800 calls were received from potential participants, 1426 were screened, 331 met telephone eligibility criteria and were invited for in person screening; 87 participants met eligibility criteria after in-person screening; 80 participants accepted to participate. Of the 80 participants, 60% were between the ages of 55-64.9 years, 54% were women, 39% were Hispanic and 31% were Non-Hispanic Black; 74% had a high school level education or higher, 43% were retired, 41% worked part/full time, 51% were obese, and 37% were single. Eighty four % of potential participants contacted found out about the study from paid ads in high circulation free newspapers, 7% through in-person talks in community groups, and 6% through hospital referrals. The most common causes of exclusion in telephone screening were use of diabetes medications (26%), followed by high TICS score (16%), and young age (15%). The most common cause of exclusion in in-person screening was high scores in recall tests (80%),followed by undetected diabetes (7.5%). We had significant delays in recruitment of participants that could only be overcome through increases in newspaper advertisement of approximately $80,000 over the originally budgeted amounts during the recruitment period. Discussion: Studies of recruitment of elderly persons in clinical trials usually estimate that 10 persons need to be screened for each participant enrolled in the study. The ratio in our study was somewhat higher due to the difficulty in finding persons who met criteria for amnestic MCI in the community, and due to the high prevalence of treated diabetes and undetected diabetes. Surprisingly, few participants were recruited in clinics and most were recruited from the community. Our use of newspaper ads was much higher than expected. It is important to bear in mind that this study included only one recruitment site. Conclusion: We successfully recruited the 80 participants with amnestic MCI planned for this phase II trial of metformin in amnestic MCI, but with significant delays and spending more resources in recruitment than originally planned, particularly in newspaper ads. Participants recruited from clinics were significantly less than expected. It is important for clinical trials of amnestic MCI to consider using a significant proportion of resources towards newspaper ads in high circulation newspapers. Our clinical trial will finish in February in 2012 and we will be able to report our first preliminary results in April of 2012. If there is preliminary evidence of efficacy on clinical or imaging outcomes a Phase III trial will be planned.

LB8 - THE EFFECTS OF ELND005 (SCYLLO-INOSITOL) ON EMERGENCE OF NEW NEUROPSYCHIATRIC SYMPTOMS IN A 78-WEEK PHASE 2 STUDY IN MILD AND MODERATE ALZHEIMER'S DISEASE. C. LYKETSOS, S. ABUSHAKRA, P. TARIOT, G. CRANS, C. HERNANDEZ, J. CEDARBAUM *(The Johns Hopkins Bayview Medical Center, Baltimore, MD, USA)*

Introduction: Behavioral and psychiatric signs and symptoms in AD are increasingly recognized as common and therapeutically challenging aspects of AD. The prevalence of these neuropsychiatric symptoms (NPS) increases with disease progression from MCI to later stages of AD dementia (Lyketsos et al., 2002). Some types of NPS may reflect regional monoaminergic neuronal dysfunction related to cortical AD pathology. Unlike the progressive course of cognitive/functional decline, NPS may have a fluctuating course, especially at earlier stages of AD (Tschantz et al. 2011). Clinical trials that only assess NPS burden at study endpoint may not capture the occurrence of emergent, clinically relevant, NPS. An alternate analytical approach is to evaluate the emergence of new NPS at any time during a trial. This approach was applied to data from a Phase 2 study of ELND005 (Scyllo-inositol) in Mild/Moderate (M/M) AD. ELND005 has amyloid anti-aggregation and neuronal protective effects in vitro, and is being investigated as a potentially disease modifying oral treatment for AD. Objectives: To evaluate the effects of ELND005 on the emergence of at least 2 new NPS over a 78-week study period in M/M AD patients enrolled in a Phase 2 study. Material and methods: This was a post-hoc analysis of data from Study AD201, a dose-ranging, 78 week study in M/M AD (MMSE 16-26). A total of 353 patients were randomized to either placebo (n=83) or 1 of 3 ELND005 doses (250mg: n=88, 1000mg: n=89, 2000mg: n=91; all administered BID), and 351 received at least 1 dose of study drug. The main efficacy and safety results were recently reported (Salloway et al., in Press, Neurology). Due to safety findings leading to early discontinuation of the 2 high dose arms, the main efficacy analyses only compared the 250mg and placebo arms. In the entire study population, the co-primary cognitive and functional endpoints were not significantly better on treatment. However, the 250mg dose showed positive trends on cognition (NTB) in the pre-specified analysis of the Mild AD group. The reported pre-specified analysis of the NPI, a secondary outcome measure, was based on change from baseline to study end in total score (t-NPI: sum of 12 item sub-scores, each= frequency x severity). In this additional analysis, emergence of a new NPS was defined as a score of 0 at baseline that became >0 at any subsequent visit, for any of the 12 NPI items. P values were not adjusted for multiplicity testing in these post hoc analyses. Results: The t-NPI mean scores were low at baseline in the overall M/M (P/250mg: 8.1/10.4) and in both subgroups (Mild: P/250mg= 8.0/9.0; Moderate: P/250mg= 9.2/10.0), with maximal possible score being 144. When t-NPI scores at baseline were compared to endpoint, there were no significant treatment effects in the M/M or either subgroup. The rate of the 3 most common NPS at baseline were similar in the Mild and Moderate groups: apathy (in each 45%), depression (42%/43%), and anxiety (33%/35%). In the Mild group, the 3 most frequently emerging new NPS on placebo were: depression, appetite changes, and agitation; while in the Moderate group they were: apathy, aberrant motor behavior, and agitation. The proportion of M/M patients who developed ≥ 2 new NPS on placebo or 250mg was 72% and 55% (p=0.033, N=79/82, respectively). In the Moderate group (MMSE 16-21), the proportion of new NPS on placebo or 250mg was 71% and 59% (p=0.332, N=35/39, respectively); in the Mild group (MMSE 22-26) it was 73% and 51% (p=0.048, N=44/43, respectively). In the Mild group, the effect of ELND005 in reducing the emergence of new NPS, was mostly driven by decreased emergence of depression and anxiety, followed by decreases in appetite change and apathy. Discussion: The above analyses of NPS emergence using the NPI scale provide a consideration of behavioral pathology that is more in tune with the fluctuating nature of these symptoms than change in total NPI scores at study end. These results suggest that ELND005 may significantly reduce the emergence of new NPS, particularly in the Mild AD group that has a low level of baseline NPS. These effects were especially evident on depression and anxiety, the "affective cluster". This therapeutic effect appears distinct from that of commonly used psychoactive drugs, which are meant to alleviate already established symptoms. Conclusion: In Mild AD, ELND005 at 250mg bid decreased the emergence of new NPS, effects driven primarily by a decrease in the emergence of depression and anxiety, and to a lesser extent, of appetite changes and apathy. These effects are clinically relevant since NPS are frequently associated with increased morbidity and healthcare costs. These apparent effects of ELND005 on NPS are supportive of its potential as a disease modifying agent.

LB9 - RESPONDER ANALYSES FROM A PHASE 2 PLACEBO-CONTROLLED STUDY OF ELND005 (SCYLLO-INOSITOL) IN MILD AND MODERATE ALZHEIMER'S DISEASE. A. PORSTEINSSON[1], R. SPERLING[2], G. CRANS[3], C. HERNANDEZ[3], S. ABUSHAKRA[3] *(1. University of Rochester Medical Center, Rochester NY; 2. Brigham and Women's Hospital, Boston MA; 3. Elan Pharmaceuticals, S. San Francisco, USA)*

Introduction: ELND005 (Scyllo-inositol) is being investigated as a potentially disease modifying oral treatment for Alzheimer's Disease (AD). In non clinical studies ELND005 has shown in vitro Amyloid anti-aggregation and neuronal protective effects from oligomer-induced synaptic injury; and in transgenic CRND8 mice has shown reduction of cortical amyloid burden and improved learning deficits. The safety and efficacy results of ELND005 from a Phase 2, dose-ranging, 78 week study in Mild to Moderate AD (M/M AD) were recently reported (Salloway et al. Neurology 2011). In the overall study population, the co-primary cognitive (NTB) and functional (ADCS-ADL) endpoints were not significantly better on treatment. However, in a pre-specified analysis of Mild patients the 250mg twice daily (BID) dose showed positive trends on the NTB, and a significant trend on a pre-defined responder analysis. The detailed responder analyses have not been previously described. Objectives: The objective of these additional analyses is to describe the responder rates from the Phase 2 Study, using additional exploratory criteria for clinical response, to inform the choice of optimal responder definitions in future AD studies. Material and methods: This was a post-hoc analysis of data from Study AD201, a dose-ranging, 78 week study in M/M AD which enrolled 353 patients (MMSE 16-26). A total of 351 patients were randomized to either placebo (n=83) or 1 of 3 ELND005 doses (250mg: n=88, 1000mg: n=89, 2000mg: n=91; all administered BID), and received at least 1 dose of study drug. Due to safety findings leading to discontinuation of the 2 high dose arms, the efficacy analyses were based only on the 250mg and placebo arms. In addition to NTB responders, the CDR-SB responders were also explored, since the CDR-SB may be used as a primary global/comprehensive outcome measure in future studies. For all clinical outcome measures, changes from baseline (CBL) were calculated so that a positive change indicated clinical improvement. The additional responder definitions were: 1. NTB responders: those whose NTB score remained stable or improved over 78 weeks (NTB z-score CBL ≥ 0); 2. CDR-SB responders: those whose CDR-SB score remained stable or improved over 78 weeks (CDR-SB CBL ≥ 0); and 3. Responders based on either NTB or CDR-SB CBL being ≥ 0. The proportions of responders using these definitions were analyzed in both the overall study populations and in the Mild group (MMSE 22-26, inclusive). All analyses are shown for the m-ITT population; p-values were not adjusted for multiplicity testing in these additional analyses. Results: The proportions of NTB responders in the M/M group on placebo and 250mg were 15.7% and 32.7% (m-ITT analysis: p= 0.07, N=51 and 52, respectively). In the same group, the proportions of CDR-SB responders on placebo and 250mg were 13.7% and 15.4% (difference NS); and the proportions of responders on either NTB or CDR-SB were 23.5% and 38.5%, and also not significantly different. In the Mild group the proportions of NTB responders on placebo and 250mg were 15.6% and 50.0% (m-ITT analysis: p< 0.01, N=32 each). In this Mild group, the proportions of CDR-SB responders on placebo and 250mg were 18.8% and 21.9% (difference NS); and the proportions of responders on either NTB or CDR-SB were 25.0% and 56.3% (p = 0.02). Discussion: The NTB responder rates on ELND005 were greater than on placebo by ~17% in the M/M population, and by ~34% in the Mild group; but there were no differences in the CDR responder rates in the M/M and Mild groups. The rates of response to either NTB or CDR-SB on treatment were greater than placebo by ~15% in the M/M population, and by ~31% in the Mild group. The responder definition based on CDR-SB only may have been limited by the small sample size in this Phase 2 study. Using the definition of responders on "either NTB or CDR-SB" provides a way to describe clinical benefit based on both cognitive and global domains. In both the NTB responder analysis and in the "either NTB or CDR-SB" analysis, the responder rates in the Mild groups were significantly higher than in placebo. These data support the previously reported positive NTB trend at endpoint seen on ELND005 250mg dose in the pre-specified analysis of the Mild AD group. Conclusion: In the Mild AD group, approximately 50% of patients receiving ELND005 250mg bid remained stable or improved over 78 weeks, as assessed by the NTB; and approximately 56% remained stable

or improved over the same period on either the NTB or CDR-SB. These responder rates were significantly higher than placebo response rates, using either definition. Since responder rates are less likely to be influenced by outlier values than group means, inclusion of these responder analyses in AD studies will have additional value in assessment of potential treatment effects.

LB10 - TOWARDS RETINOID THERAPY FOR ALZHEIMER'S DISEASE. K. SHUDO, H. FUKASAWA, M. NAKAGOMI, N. YAMAGATA, Y. AMANO, T. MIKI *(Itsuu Laboratory, Tokyo, Japan)*

Introduction: Alzheimer's disease (AD) is associated with a variety of pathophysiological features, including amyloid plaques, inflammation, immunological changes, cell death and regeneration, altered neurotransmission, and age-related changes. Retinoic acid receptors (RARs) and their ligands, retinoids, are relevant to all of these. Here we propose retinoids, in particular RARa- and RARb-specific ligand, tamibarotene (Am80), as a candidate drug for treatment of AD. References: Goodman, PNAS 100, 598-63(2003): Fahrenholz, Neurodegener Dis 7, 190-192(2010): Shudo, Cur Alz Res 6, 303-311(2009): Lerner, Expert Rev Neurother 9, 1615-21 (2009): Ding, J Neurosci 28,11622-11634(2008). Objectives: The synthetic retinoid Am80 is RARa-and RAR-b specific (it does not activate RARg nor RXRs). Am80 is an approved drug in Japan and clinical studies are in progress in US as a non-cytotoxic chemotherapeutic agent. Am80 is a potent immunomodulator towards psoriasis, rheumatoid arthritis and experimental autoimmune encephalomyelitis. A lot of information on retinoids suggest that neurodegenerative diseases may be treated by retinoids. During past years, several pharmacological data have accumulated by the sake of co-workers, and we have prepared a clinical trial for AD by Am80 at Osaka City University. Materail and methods: The experimental requirements for AD may be: 1) Decrease of amyloid Abeta42 in the brain, 2) Anti-inflammatory effects of brain damage caused by such as LPS and IFNg, 3) Modulation of nerve transmission systems, 4) Improvement of behavior, recognition and memory, 5) Nerve regeneration. Here we show several evidences regards to Am80 on these issues. Results: Experimental results on Am80 in animals are: 1) Oral administration of Am80 decreased insoluble Abeta42 in APP23 transgenic mice. Retinoid induces ADAM10 (alpha-secretase which cleaves APP inside the Abeta42 sequence). 2) Ameliorate the inflammation damage and dopaminergic cell death in brain caused by LPS-IFNg. 3) Increase TTR(transthyretin), VAChT, and Ach in the brain which are down-regulated in the senescence-accelerated mice (SAMP8). In the same mice, the latencies significantly decreased in the light and dark box test. 4)Improve the scoplolamine-induced memory deficit. 5) Improve the recovery of physically damaged spinal code injury, which may involves the regeneration of nerve cells. 6) Improve the age-related decrease in REM sleep in SAMP8 mice. 7) Ameliorate autoimmune inflammation in MS model. Discussion: On these observations in animals suggest Am80 satisfies the preclinical pharmacology for AD as a candidate . Since Am80 is an approved drug in Japan, and clinical safety data are accumulaing. A clinical study is ongoing to evaluate the safety and efficacy of oral use of Am80 for mild to moderate AD. Conclusion: A synthetic retinoid tamibarotene(Am80) was suggested to be a candidate drug for treatment of Alzheimer's disease. A clinical study has started in Japan (ClinicalTrials gov NCT 01120002. JAPIC CTI 101115).

LB11 - COGNITIVE DECLINE IN THE ELDERLY POPULATION OF THE GUIDAGE STUDY – A 5-YEAR FOLLOW UP OF SUBJECTS WITH MEMORY COMPLAINTS. IS IT POSSIBLE TO IDENTIFY SUBJECTS AT RISK FOR DECLINE? : P.-J. OUSSET[1,2,3], S. ANDRIEU[1,2,3,5], H. MATHIEX-FORTUNET[4], P. GARNIER[4], J. TOUCHON[6], B. VELLAS[1,2,3] *(1. INSERM U 1027, Toulouse, France; 2. University of Toulouse III, Toulouse, France; 3. Gerontopole, Toulouse University Hospital, Toulouse, France; 4. Ipsen, Boulogne, France; 5. Department of Epidemiology and Public Health, Toulouse University Hospital, Toulouse, France; 6. Montpellier University Hospital, France)*

Background: The GuidAge study assessed the potential efficacy of standardized Gingko biloba extract (EGb761) for the prevention of Alzheimer's dementia (AD) in elderly subjects with memory complaints. The aim of this analysis was to describe the subjects who underwent clinically relevant cognitive decline during the 5-years of follow-up. Methods: 2854 subjects aged 70 years or older were assessed annually with a full cognitive battery. We identified 4 candidate indicators for cognitive decline: MMSE score, Free and Cued Selective-Reminding-Test (FCSRT) Free Recall, FCSRT Total Recall, and Clinical Dementia Rating sum of boxes (CDR-SB). The first step was to determine clinical relevant thresholds for these 4 measures by comparing their levels between two clinically specified populations: normal subjects (CDR=0), and MCI subjects (CDR=0.5) at baseline. The association of these indicators with further conversion to AD was assessed in terms of sensitivity and specificity. Finally, we compared baseline characteristics of the subjects with or without clinical decline during the follow-up, using the most efficient of these indicators. Results: A decrease of at least 1 point of MMSE total score, a decrease of at least 4 points of FCSRT Free recall score, a decrease of at least 2 points of FCSRT total recall score, an increase of CDR sum of boxes of at least 1 point have been identified as possible indicators of decline, with a significant difference between CDR-0 and CDR-0.5 subjects ($p<.0001$). Among these markers, CDR-SB showed the best predictive value for conversion with a sensitivity of 85.7 and a specificity of 84.4. Subjects having presented a cognitive decline (i.e.: increase of the CDR sum of boxes of at least 1 point) during the GuidAge study were at baseline older, most of them being aged more than 75 yrs, with a shorter mean duration of spontaneous memory complaint, a poorer educational level, and an increase rate of failure to 5 second leg stance test. More subjects failed to MMSE recall score. Mean FCSRT, verbal fluency, and TMT scores were also more impaired at baseline in the decliner group. Conclusions: The GuidAge study enabled 2854 elderly subjects with memory complaints to be followed-up for 5 years. Clinically relevant cognitive decline was observed in some subjects, and predictive factors will be described. These results could allow a better identification of target population for future prevention trials.

LB12 - REPRESENTATIONS AND PRACTICES OF PREVENTION IN ELDERLY POPULATIONS: INVESTIGATING ACCEPTANCE TO PARTICIPATE IN AND ADHESION TO AN INTERVENTION STUDY FOR THE PREVENTION OF ALZHEIMER'S DISEASE (ACCEPT STUDY). S. ANDRIEU[1,2,3,4], N. COLEY[1,2], V. GARDETTE[1,2,3], J. SUBRA[5], S. OUSTRIC[1,2,5], A. GRAND[1,2,3,4], B. VELLAS[1,2,3] *(1. INSERM U 1027, Toulouse, France; 2. University of Toulouse III, Toulouse, France; 3. Gerontopole, Toulouse University Hospital, Toulouse, France; 4. Department of Epidemiology and Public Health, Toulouse University Hospital, Toulouse, France; 5. Department of Primary Care, Toulouse University Hospital, Toulouse, France)*

Background : In the domain of Alzheimer's disease (AD) prevention, various potentially protective factors have been identified in epidemiological studies. Some of these factors are lifestyle-related, for example dietary habits, physical exercise and social activities. Although the results of these observational studies have been relatively consistent, the results of intervention studies remain disappointing. Methodological problems could explain these negative results, like the selection of the population, a plausible assumption is that the older people who agree to take part in these intervention studies differ from those who refuse, and are those that are least likely to benefit from such programs. The aim of this study was (i) to study the determinants of participation in and adhesion to a prevention trial in a population of older individuals via a quantitative approach using a questionnaire, (ii) to study the representations and practices of prevention in this population using a qualitative approach using semi-structured interviews and focus groups. Method : The study population for the ACCEPT study was recruited at the time of inclusion of subjects in a prevention trial. The population was made up of persons aged 70 years or older, living at home and demonstrating some form of frailty, defined as a spontaneous memory complaint to their general practitioner or difficulties in carrying out instrumental activities of daily living. We used a quantitative approach based on the administration of a self-completed questionnaire sent to 1680 subjects having accepted to take part in the prevention trial, and to the sample of subjects meeting the inclusion criteria but having refused to take part. The qualitative approach, carried out at the moment of inclusion, involved subjects that having accepted to take part and subjects that having refused. Semi-structured interviews was carried out in order to understand the logic leading to refusal or acceptance. Results : We will present the first results of this study with the determinants of acceptance (socio-demographic characteristics, psychosocial characteristics, the notion of memory problems and the related risk of Alzheimer's disease perceived by the subject, the subject's level of health- and prevention-related knowledge, and the duration of the relationship between the subject and the investigating doctor. Conclusion : The analysis of the results will combine the viewpoints of the different disciplines. It will allow us to better understand the logic at work, to characterise the populations at risk of refusal, and perhaps to remove some of the barriers to participation in prevention programs. The identification of such barriers will provide feedback in terms of the conception and management of prevention measures.

POSTERS

P1 - BRAIN METABOLITE CHANGES IN MILD AND MODERATE ALZHEIMER'S DISEASE: CORRELATION WITH V-MRI AND CLINICAL MEASURES OF DISEASE SEVERITY. S. ABUSHAKRA, G. CRANS, S. NARAYANAN, E. LIANG, C. HERNANDEZ, D. ARNOLD *(South San Francisco, USA)*

Introduction: Elevated Myo-inositol (mI) levels in parietal grey matter is a consistent finding in Proton-MR spectroscopy (MRS) studies of Alzheimer's disease (AD), and is one of the earliest metabolic changes in MCI (Kantarci et al., 2000). MCI and AD patients show mI elevations of 7-10% and 17-20%, respectively, compared to age-matched controls (Kantarci et al., 2002 and 2007; Zhu et al., 2006; Schott et al., 2010). Few studies have evaluated mI changes at the more advanced stages of AD dementia. Objectives: The objective of this analysis was to compare cortical mI and N-acetyl aspartate (NAA) levels in Mild and Moderate AD patients, and to explore their correlations with clinical and v-MRI measures. Material and methods: Post-hoc analyses were performed on baseline data from a completed Phase 2 clinical trial of Scyllo-inositol (ELND005 Study AD201, Salloway et al. 2011, Neurology, In press). The study enrolled 353 AD patients. Randomization was stratified by MMSE (Mild: 22-26, Moderate: 16-21), ApoE4 gene number, and AD medication use. Co-primary endpoints were NTB and ADCS-ADL, and lateral ventricular volume was a key imaging biomarker. A subset of 95 patients underwent both MRS and v-MRI (including assessment of white matter disease [WMD] volume) at study baseline. MRS imaging utilized 1.5T or 3T scanners, and a 1-cm3 voxel positioned centrally on the posterior cingulate gyrus, just behind the corpus callosum. Metabolites analyzed included mI (a biomarker of glial activation) and N-acetylaspartate (NAA, a biomarker of neuronal integrity), quantified as molar ratios to Creatine (Cr) using LCModel. Ratios of mI/Cr and NAA/Cr were compared using t-tests, and correlated to baseline clinical assessments (NTB, ADAS-cog, ADCS-ADL, CDR-SB, MMSE, and NPI), and v-MRI measures (ventricular, brain, hippocampus volumes, and WMD volume). Results: The MRS group (52 females, 43 males) had a mean age of 71.2 years, 66.3% were ApoE4 carriers (0 gene: 32; 1 gene: 42; 2 genes: 21), and 92.6% were on AD medications. Mean MMSE scores in Mild and Moderate subgroups were 23.2 (n=57) and 17.8 (n=38);

mean mI ratios were 0.85 and 0.91 (7.1% higher in Moderate, p=0.022), mean NAA ratios were 1.31 and 1.24 (5.3% lower in Moderate, p=0.026), and NAA/mI ratios were 1.58 and 1.39 (12.0% lower in Moderate, p=0.002). MI ratios correlated inversely to brain volume (r=-0.30, p=0.003), NTB (r=-0.23, p=0.027), and WMD (r=-0.22, p=0.034). NAA ratios were positively correlated with NTB (r=0.30, p=0.004), age (r=0.28, p=0.007), and MMSE (r=0.27, p=0.011). NAA/mI ratios were positively correlated with NTB (r=0.37, p=0.001), brain volume (r=0.36, p=0.001), WMD (r=0.26, p=0.014), and age (r=0.24, p=0.024). Discussion: The observed elevation of Myo-inositol levels in Moderate compared to Mild AD extend the prior findings in MCI and Early/Mild stages of AD. The strongest correlations were between NAA and cognition (NTB) and mI and brain volume; these distinct correlation profiles of NAA and mI suggest that they reflect distinct pathological cascades. Conclusion: The correlation of mI to both brain volume and cognition supports the relevance of Myo-inositol as a metabolic marker of AD progression.

P2 - THE SCOPOLAMINE MODEL, COGNITIVE P300 POTENTIALS AND QUANTITATIVE EEG: FROM REGION-SPECIFIC TARGETS TO BIOMARKER OF DRUG EFFICACY. P. BOEIJINGA, N. PROSS, P. DANJOU, L. SOUFFLET, E. VOLTZ, R. BARNOUIN *(FORENAP Consulting and R&D, Rouffach, France)*

Introduction: The P300 is obtained in an auditory "oddball" paradigm and forms a window to information processing related to cognition in distributed systems deep in the brain such as the dorsal hippocampal formation (Boeijinga, Dialogues Clin Neurosci 4 (n°4);388-394, 2002; see http://www.dialogues-cns.org/brochures/15/htm/15_70.asp). In patients suffering from Alzheimer's Disease amplitude and P3-latency deficits compared to normal controls have been described (v Deursen et al. Brain Cogn. 69(3);592-599, 2009) using midline scalp electrodes. We recently studied the effect of scopolamine, used to model cognitive impairment in healthy subjects and which is associated with similar changes in P300 similar as in patients. We were able to reverse the deteriorated P3-latency with cognitive enhancing drugs like donepezil (5 mg, Parks et al. European Neuropsychopharmacol. Vol. 20, Suppl 3, Page S320, 2010). Amplitude effects were not found, possibly due to the position of electrodes. Increasing the number of electrodes is a logical step for full characterisation of putatively overlapping sources (Elting et al. J Clin Neurophysiol. 20(1);26-34, 2003); in the present contribution P300 and background EEG were assessed in young volunteers using a multi-electrode array of 28 electrodes. Brain oscillations in the delta and alpha band have been shown suitable markers of the disease process and the scopolamine model using low resolution electromagnetic tomography or 3-D reconstructions (sLORETA, Soufflet et al. at the ICAD-meeting this year). Objectives: The aim of the present study was to evaluate the potential of donepezil given as pre-treatment to reverse scopolamine-induced deteriorations in EEG/ERP measures. Material and mehods: The study population comprised 27 healthy, non-smoking young male volunteers. They all participated in a larger crossover study and only 2 visits are highlighted here. At each of the 2 periods, scopolamine (0.5 mg, s.c.) was given 2 hours after the single dose of donepezil (Aricept™, 5 mg) or matching placebo. Pharmacodynamics were obtained at 3, 4, 5 hours after donepezil (for clarity 1,2 and 3 hours after scopolamine). P300 responses were obtained using a series of frequent tones (85% of all trial, frequency 500 Hz) and infrequent tones (15% of all trial, frequency 2000 Hz), the latter had to be counted silently. In addition, EEG was assessed in 2 blocks of 3 minutes of resting condition with the eyes closed, one block with controlled vigilance and the second in free-running, more-or-less alert wakefulness. P300 mean surface was extracted within the latency range 232 - 352 ms for topographic mapping. Non-parametric inferential tests were performed for each individual time-point. Tomographies in the frequency domain were calculated using the sLORETA software in the following EEG frequency bands : delta (0.5-3.5 Hz), theta 1 (4-5.5 Hz), theta 2 (6-7.5 Hz), alpha-1 (8-9.5 Hz), alpha-2 (10-12.5 Hz), beta-1 (13-17.5 Hz), beta-2 (18-20.5 Hz), beta-3 (21-32 Hz) and gamma (35-45 Hz). Differences between the two conditions were based on voxel by voxel t-tests on log-transformed data, and a "boot-strap-like" correction for multiple comparisons was performed. Results: P300 maps displayed centro-parietal maximum spreading more to left/right hemispheres than in the frontal direction. Scopolamine alone induced a significant reduction of P300 amplitude from 3h to 5h post-dosing, most dramatic at 4h over the whole scalp. Donepezil reversed the effect at 5h over bi-lateral post-temporal scalp regions but not in midline regions. Scopolamine significantly increased EEG power in the delta band already at 1h bilaterally in central regions, cingulate gyrus and not so much frontally, while it decreases alpha 1 power in all posterior brain areas. The latter showed large inter-subject variability and was most acceptable for the circumstances in which vigilance levels were kept constant. When subjects were pretreated with donepezil 2 h before the challenge the excess in delta was counteracted with near-significant changes in superior frontal gyrus, effects probably stemming from Brodmann area 6 and 24 (p<0.01, cingulate gyrus). Alpha-1 was significantly reversed with largest t-values in post-central gyrus of the parietal lobe (t-score: 2.6, Brodmann area 5). For a sub-group from our population with more homogeneous scopolamine responses, alpha-1 reversals were predominant in the parahippocampal gyrus (N=21; t-score 3.5, Brodmann area 37 and 30, at the posterior borders towards area 19), and these cortical regions were also associated with alpha-2 reversals. Discussion: The effects on the P300, a cognitive response which indexes attentional resources form a sound validation of the "proof-of-pharmacology" of the brain potential evaluations. Moreover, the results presented here have construct validity since neuronal activity related to information processing in deep structures is definitely involved. The study of topographies of amplitudes have strengthened and completed our pioneering work on P3-latency deteriorations (Parks et al. European Neuropsychopharmacol. Vol. 20, Suppl 3, Page S320, 2010). The effects put in evidence by way of electromagnetic tomography of the EEG are -to the best of our knowledge- new in the field of "proof-of-principle". The most robust effects concern the delta activity. It remains to be elucidated what is the role of sources of alpha activity in temporal lobe parahippocampal domains, but our original finding is worthwhile to follow up. It is tempting to attribute a role in temporal coding of for example multimodal sensory information, which makes sense in the anatomical substrate. A good understanding of changes in current sources underlying oscillatory phenomena is of great importance to interpret qEEG displays with less complexity of its metric in future trials. Conclusion: Evidence of the ability of donepezil to reverse, at least partially, the effects produced by scopolamine in healthy male volunteers using qEEG and ERP is now a fact. The excess in delta activity under scopolamine is considered as sign of hypovigilance or even sleep propensity and therefore EEG measures as biomarker could predict the clinical efficacy of cognitive enhancers on attention. Indeed, the proposed methodology of reversal by donepezil can be easily extended to novel non-cholinergic pharmacotherapies, and examples of succesfull substitutions of NCE's with GABA-ergic or glutamatergic mechanism of action will be discussed with the audience. Phase II studies in AD are time consuming and expensive. The risk for attrition can be lowered by performing a fairly quick assay using brain potentials in the scopolamine model without patients, namely in healthy volunteers as shown in this paper. A translation to qEEG mapping for research units with stand-alone PC's is within reach.

P3 - THE IMPORTANCE OF S1-POCKET OF GLUTAMATE CARBOXYPEPTIDASE II IN EXERTING AMYLOID BETA DEGRADATION ACTIVITY. H. KIM, S.K. LEE, M.-J. KIM, S.I. PARK *(Osong Health Technology Administration Complex, South Korea)*

Introduction: Glutamate carboxypeptidase II (GCPII) is a membrane-bound metallopeptidase that catalyses the hydrolysis of neurotransmitter N-acetyl-L-aspartyl-L-glutamate (NAAG). Recently, we identified a new novel function of GCPII, which degrades amyloid-beta (Aβ) peptides in the brains of Alzheimer's disease model mice. GCPII catalytic domains are composed of two active sites; S1- and S1'- pocket. The S1'-pocket contributes primarily to the high affinity binding of NAAG and GCPII inhibitors including 2-(Phosphonomethyl) pentanedioic acid (2-PMPA), whereas the S1-pocket seems to be involved in 'fine-tunning' for substrate specificity. Objectives: We characterize the Aβ degrade mechanism on GCPII using the site directed mutagenesis assay and the in silico molecular modeling between GCPII active site and Aβ peptide. Material and methods: Site-directed mutagenesis. The pcDNA-hGCPII plasmid was used as a template, and each mutation was introduced by two complementary oligonucleotide primers harboring the desired mutation. NAAG cleavage assay. The activity of endogenous Glutamate carboxypeptidase II protein (GCPII) was performed as described previously (Robinson et al. 1987). GCPII/Aβ Complex modeling The mode of binding of Aβ and S1' pockets were modeled using program O (http://xray.bmc.uu.se/alw yn/A-Z_frameset.html) (PDB file: 1z0q (Aβ), 2oot (GCPII)). Computational docking was performed using manual docking method ELISA. Vectors encoding the hGCPII and various mutant hGCPII genes were transfected into PC3 cells in a 12-well plate. The culture medium was changed into Aβ 1-40 of Aβ 1-42 peptide-treated medium about 30 hr later, and the cells were incubated for another 16 hr. The medium was collected and assayed for residual Aβ 1-40 of Aβ 1-42 using ELISA kits (Invitrogen). Results: When 2-PMPA was treated, it does not affect Aβ degradation activity of GCPII. Additionally, using site-directed mutagenesis against GCPII each pockets, we observed that mutations of S1'- pocket but not of S1-pocket led to loss of function on glutamate production, maintaining the Aβ cleavage activity of GCPII. Based on the experimental results together with the molecular modeling, we suggest that Aβ degradation mechanism is different from NAAG hydrolysis mechanism and that S1-pocket of GCPII is more important in degrading Aβ. DiscussionA glutamate is a common excitatory neurotransmitter in brain; however, if it is produced too much by GCPII, it could damage neurons. In fact, potent GCPII inhibitors are known to decrease brain glutamate levels and protect neurons in several neurodegenerative diseases. Therefore, the GCPII mutant proteins, which allow Aβ degradation but inhibit glutamate production, could be a new AD therapeutic strategy. Conclusion: Using the site-directed mutagenesis of S1- and S1'- pocket on GCPII, we substrate specificity is conserved on S1-pocket. Also, notice that the Aβ computational modeling of GCPII/ Aβ complex shows structural evidence the Aβ substrate specificity on GCPII S1-pocket. With this evidence, we identify that Aβ degrading action of GCPII which have some structural different mechanism compared to that of NAAG degrading action.

P4 - EVENT-RELATED POTENTIAL (ERP) & QUANTITATIVE ELECTROENCEPHALOGRAPHY (QEEG) BIOMARKERS FOR ALZHEIMER'S DISEASE: THE COGNISION(TM) SYSTEM. M. CECCHI[1], D.A. CASEY[2], G.A. JICHA[3], P.R. SOLOMON[4], P.M. DORAISWAMY[5], D.A. WOLK[6], S.E. ARNOLD[6], C.D. SMITH[3], M.V. KULKARNI[1] *(1. Neuronetrix; 2. University of Louisville, KY; 3. University of Kentucky, KY; 4. The Memory Clinic, VT; 5. Duke University; 6. University of Pennsylvania, USA)*

Introduction: Current diagnostic criteria for Alzheimer's disease (AD) consist primarily of clinical and ,neuropsychological tests. Such evaluations can achieve high diagnostic accuracy when employed in specialty memory clinics. However, this level of diagnostic accuracy remains beyond the economic and/or geographic reach of most of the patients, primarily because it is only available at major research hospitals, and is extremely expensive. A large majority of patients are diagnosed at local community healthcare centers, where the expertise and accuracy of AD diagnosis is lower. Over the past few decades, researchers have focused on several biological markers linked to AD pathology

such as amyloid burden in the brain or magnetic resonance imaging (MRI) volumetry features. While these biomarkers are promising, the required invasive and/or expensive procedures are often unavailable in community clinics. Moreover, proposed revisions to AD diagnostic criteria advocate that AD diagnosis should involve evidence of pathological biochemical process as well as cognitive impairment, with cognitive decline as the primary indication. With the help of event-related potentials (ERP) and quantitative electroencephalography (qEEG), the COGNISION™ System is designed to gather information early in the cognitive decline process associated with AD. The system is non-invasive, inexpensive, and potentially available in community-based health centers. Furthermore, it has the potential to address issues related to psychometric testing such as requirement of specialized test administrators and prolonged evaluation time. Objectives: The primary goal of the ongoing study is to validate the COGNISION™ System as a tool to aid physicians in diagnosing AD in clinical settings. In this multi-center study, the objective is to demonstrate its user-friendly design and ability to separate AD subjects from healthy, age-matched controls irrespective of variations in testing locations and personnel. Materials and methods: Cohorts: - 100 Early Stage ADs ; - 100 Aged-matched Healthy Controls. Sites: - University of Kentucky - Duke University - University of Pennsylvania - The Memory Clinic - Norton Neuroscience Center. Study Endpoints: - Validate Classifier Performance (Primary) - Differential Diagnosis (Secondary) - Drug Effects (Secondary). ERP Protocol: The ERP oddball paradigm selected for the study is designed to target attention and working memory; cognitive impairments that have been implicated in AD. At the end of the session, 3 minutes of EEG data is also being recorded while the subject is resting. Results: - We have completed 23 Subjects (20 Healthy Controls, 3 ADs) from 3 clinical trial sites - Preliminary analysis of notable differences in amplitude and latency of P300 are summarized below: (Group | Gender | T P300 Fz-L (ms) | D P300 Fz-A (μV) | T P300 Cz-A (μV)); (Ctrl, M, 272.04, 11.40, 8.19); (Ctrl, F, 400.04, 19.72, 7.57); (Ctrl, F, 272.04, 6.24, 6.92); (AD, F, 456.04, 4.34, 7.43); (AD, F, 320.30, 9.40, 1.75); (AD, M, 456.03, 8.22, 3.12); Ctrl Mean (±SEM) (T P300 Fz-L (ms): 314.71±42.67, D P300 Fz-A (μV): 12.45±3.93, T P300 Cz-A (μV): 7.56±0.37); AD Mean (±SEM) (T P300 Fz-L (ms): 410.79±45.24, D P300 Fz-A (μV): 7.32±1.53, T P300 Cz-A (μV): 4.10±1.71); (T - Target tone, D - Distractor tone, L - Latency, A - Amplitude) Discussion: The trends of mean amplitudes and latencies of ERP peaks for control and AD cohorts are encouraging. The preliminary analyses reinforce findings from numerous past ERP studies of AD. Recruitment of more subjects, particularly in the AD arm, will enable training of artificial neural network (ANN) based classifiers. Recent ERP studies based on ANN's have reported accuracy, sensitivity, and specificity in the range of 70-80% for accurately classifying AD subjects from age-matched healthy controls. If reported trends of amplitudes and latencies persist, ANN-based classifiers should meet or exceed previously reported classification parameters; thereby validating the utility of ERPs in AD diagnosis. Conclusion: According to the context updating theory of P300, updating the working memory underpins the response to the target stimulus whereas attention underpins the response to the unexpected distractor stimulus. The delayed latencies and diminished amplitudes of P300 peaks in response to target and distractor tones in an oddball paradigm are considered to reflect the underlying cognitive decline in these two domains in AD. Accumulation of more data is expected to help tease apart the differential impairment of these domains in AD and non-specific dementias. Expected statistically significant differences in amplitudes and latencies of various ERP peaks should lead to development of ANN-based classifiers with high classification accuracy.

P5 - DIFFERENCES AMONG PROTOCOLS FOR MANUAL HIPPOCAMPAL SEGMENTATION: PREPARATORY STEPS TO AN EADC-ADNI DELPHI PANEL FOR THE DEVELOPMENT OF A HARMONIZED PROTOCOL. M. BOCCARDI, M. BOCCHETTA, R. GANZOLA, N. ROBITAILLE, A. REDOLFI, G. BARTZOKIS, R. CAMICIOLI, J.G. CSERNANSKY, M.J. DE LEON, L. DETOLEDO-MORRELL, R.J. KILLIANY, S. LEHERICY, J. PANTEL, J.C. PRUESSNER, H. SOININEN, C. WATSON, S. DUCHESNE, C.R. JACK JR, G.B. FRISONI *(Brescia, Italy)*

Introduction: Harmonization of the many protocols for manual segmentation of the hippocampus is required, since hippocampal volumetry will be used for diagnosis and tracking of Alzheimer's disease (AD). A survey of segmentation protocols allowed the identification of anatomical sources of heterogeneity in volume estimates. Objectives: The aim of the study is to provide quantitative information about the extracted differences among protocols, to be fed to an international Delphi panel of experts that will generate a harmonized protocol. Material and methods: We operationalized landmark differences among protocols into segmentation units (SUs), through extraction of landmarks, semantic harmonization, and convergence of similar variants, in order to achieve a limited number of well defined portions of the hippocampus, that are differentially segmented in different existing protocols. We computed intra- and inter-rater reliability for each SU for both expert and naive tracers on 20 Alzheimer's Disease Neuroimaging Initiative (ADNI) scans (4 subjects per degree of visual medial temporal atrophy that we computed according to Scheltens et al. 1992), and estimated the contribution of SUs to the volume difference between AD, Mild Cognitive Impairment (MCI) and control subjects on a sample of 77 subjects. The 20 subjects for the computation of intraclass correlation coefficients were 8 healthy controls, 3 AD, and 9 MCI patients. The 77 subjects were 31 controls with normal Cerebrospinal Fluid (CSF) AÎ² levels, 23 (subsequently converted) MCI, and 23 AD patients. All MCI and AD had abnormal CSF AÎ² levels. Results: We defined four SUs: Minimum Hippocampus (MinH), Alveus/Fimbria, Tail, and Subiculum. Reliability figures for SUs were all above 0.963 for intra-, and all above 0.905 for inter-rater, except Alveus/Fimbria (intra-rater: 0.863; inter-rater: 0.885). Noticeably, the intra-rater reliability of MinH and Alveus/Fimbria traced together (intra-rater: 0.993, 95% confidence interval: 0.983-0.997) was significantly higher than that of both SUs (95% confidence interval: 0.687-0.944). The intra-rater reliability re-computed by the naive tracer provided analogous figures. The average volume difference between patients and controls was 538 mm3, with MinH contributing to over 66% of this difference, Tail 27%, Alveus/Fimbria 12%, Subiculum over 5%. The SU volume differences between patients and controls were significant for all SUs except the Subiculum. Discussion: The informative value for identifying AD-related atrophy differs across SUs. Precise definition and dedicated attention to heterogeneity among anatomical landmarks might have an intrinsic harmonization value as illustrated by the high reliability demonstrated in the current study. Conclusion: Reliability and informativeness of individual SUs will help an international panel of experts to define which SUs should be included in a harmonized protocol. Updated information on this ongoing project is available at www.hippocampal-protocol.net.

P6 - CUT-OFF OF THE CSF BIOMARKERS FOR AD DIAGNOSIS IN FRENCH MEMORY CENTERS. J. DUMURGIER, O. VERCRUYSSE, C. PAQUET, S. BOMBOIS, J. HUGON, C. CHAULET, F. PASQUIER, J. TOUCHON, J.-L. LAPLANCHE, S. SCHRAEN-MASCHKE, S. LEHMANN, A. GABELLE *(Montpellier University Hospital, CHU Gui de Chauliac, Montpellier, France)*

Introduction: One of the priorities for Alzheimer's disease (AD) researches is the development of diagnostic tools used in routine clinical practice to optimize positive and differential diagnostic of AD. Biomarkers such as biological and morphological imaging (MRI) or functional (TEP-FDG) take a prominent place. They are included in the new criteria of AD, especially in prodromal stage of the disease. These biomarkers can accessed in vivo to neuropathological characteristics of the disease: the senile plaques with deposits of Aβ-amyloid peptides (Aβ42 and Aβ40), and neurofibrillary tangles due to abnormal protein Tau. The place of each biomarker in the diagnostic' panel depends on what they measure: the pathophysiology or the disease progression, and also the availability of technical platforms in routine clinical practice. In French Memory center, only the CSF is available for clinical practice in a majority of centers. The CSF decreased Aβ42 associated with an increase in Tau protein and its phosphorylated form P-Tau, is a valuable clinical aid. The CSF biomarkers interpretation depends on the pre-analytical conditions and on the cut-off used by each laboratory. Actually, no study has determined the cut-off to be used in clinical daily practice in memory centers. Objectives: To evaluate the CSF biomarkers cut-off for positive and differential AD diagnosis in a population of patients with cognitive complaint in three French Memory Centers (Lille, Montpellier and Paris) and also to determine the inter-centers variations assays of CSF biomarkers. Materials and Methods: We investigated 1062 CSF samples (424 from Lille, 407 from Montpellier and 231 from Paris) that were referred to the three laboratories between 2008 and 2010. These patients have given their written consent to participate respectively to the three biobanks. CSF concentrations of Aβ42, Tau and P-Tau were measured by the same ELISA technic by each laboratory. The diagnoses of patients were based on clinical, neuropsychological and structural or functional brain imaging. The investigators (neurologists, geriatricians) were blinded to the neurochemical outcome measures. The AD patients were diagnosed based on DSM IV and NINCDS-ADRDA criteria. The MCI diagnosis is referred to the Peterson criteria. Patients with others dementia (Dementia of Lewy Bodies, Frontotemporal dementia, Parkinson disease with dementia, mixed dementia…) fulfilled specific diagnostic criteria. We have characterized patient groups by means and standard deviation (SD). The Mann-Whitney U-test was employed comparisons of diagnostic groups. The global diagnostic accuracies were assessed by the area under the curve (AUC) of receiver operating characteristic curve (ROC). Cut-off points were determined at the maximum Youden index providing a sensitivity of >80%. In a second part, we analyzed inter-centers variations assays of CSF biomarkers. 30 CSF samples from each laboratory were reanalyzed by the two others laboratories. The results of the CSF biomarkers were compared between the three laboratories. Results: The mean age of the 1062 patients is 69.0 [SD +/- 10.5] years old; 53.9% are women and the mean MMSE is 21.0 [+/-6.4]. 515 subjects are AD patients (48.5%), 129 MCI (12.1%) and 418 are non-AD dementia (39.4%). For the all subjects, the mean CSF biomarkers are respectively of 522.5 +/- 249 for Aβ42; 447 +/- 314 for Tau; 71.4+/- 40 for P-Tau; 0.87 for the IATI; 2+/-1.9 for the ratio Aβ/Tau and 10.3 +/- 8.3 for the ratio Aβ/P-Tau. For AD group, the mean CSF biomarkers are respectively of 426 +/- 200 for Aβ42; 600 +/- 319 for Tau; 92+/- 42 for P-Tau; 0.54 for the IATI; 1+/-1 for the ratio Aβ/Tau and 5.9+/-4.8 for the ratio Aβ/P-Tau. About the cut-off the best for our cognitive French population are Aβ42 < 500 ; TAU > 306 ; P-Tau > 59.2 ; IATI < 0.76 ; Aβ42 / Tau ratio < 1.5. The best combination for the CSF biomarkers is Aβ/Tau <1.5 and P-Tau>59.2 with a sensitivity at 74% and a specificity at 89%. The inter-centers variations assays of CSF biomarkers will be detailed. Conclusion: This is the first study to analyze the best CSF biomarkers cut-off for positive AD diagnosis in a large cohort of French patients consulting in memory centers. About inter-centers variability's, our results are particularly interesting in term of procedure harmonization about biomarkers in Europe.

P7 - DYNAMIC BAYESIAN NETWORK MODELING REVEALS ALTERED TRAJECTORY INTERACTION BETWEEN HIPPOCAMPUS AND THE ENTORHINAL CORTEX IN MILD COGNITIVE IMPAIRMENT. R. CHEN, E.H. HERSKOVITS AND THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE *(Department of Radiology, University of Pennsylvania, Philadelphia, PA. USA)*

Introduction: Brain networks are of fundamental interest in understanding the neuropathology of Alzheimer's disease (AD). Longitudinal morphometric studies of Alzheimer's disease are informative about evolving processes, however, most of these longitudinal studies are based on general linear mixed models, which cannot describe the dynamics of interactions among brain regions. In this study, we use dynamic Bayesian

networks (DBNs) to model interactions among trajectories of brain regional volumes; this approach has the advantage of being able to reveal the network structure among brain regions. Researchers have consistently reported that hippocampus and entorhinal cortex are affected by AD. Therefore, herein we focus on these two brain structures in subjects with mild cognitive impairment (MCI), who are at relatively high risk for conversion to AD. Objectives: Our goal is to model the interaction between the volume trajectories of the hippocampus (H) and the entorhinal (E) cortex, for normal elderly and adults with MCI. In particular, we wish to generate models that will indicate whether the interaction between the trajectory of hippocampal volume and that of the entorhinal cortex volume is changed in adults with MCI, relative to the interaction in normal elderly control subjects. Material and methods: A Bayesian network (BN) is a probabilistic graphical model that represent a joint distribution compactly. In a BN, each node represents a random variable, and a directed edge represents an association. The collection of edges is referred to as the structure of a BN. Although BNs can consist of discrete or continuous variables, BNs consisting of solely discrete variables can represent arbitrary probability distributions; since we wish to model nonlinear interactions among variables, we adopt the discrete BN form for this analysis. A DBN is a BN extension that provides a general framework to integrate multivariate time series. In DBN modeling of interactions among the trajectories of hippocampal volume and entorhinal cortex volume, our DBN contains two time points, with an instance of each variable (H and E) in each time slice (t and t + 1). Edges are added from nodes at time t to the nodes they influence at t+1. Each node at t + 1 has a transition probability table, which contains the probabilities of transitions among states. For example, P(H(t+1)=volume reduction | H(t)=stable) = 0.1 indicates that when the hippocampus is stable, it has 10% chance of undergoing volume reduction in the next time point. Notice that P(H(t+1)=stable | H(t)=stable) = 1.0 - P(H(t+1)=volume reduction | H(t)=stable). Often the structure of a DBN is unknown, and there may not be sufficient expertise to manually construct a DBN model. If we have adequate data, we can use standard BN data-mining techniques to infer this DBN structure from observed data. We can then compute transition probabilities using the maximum-likelihood method. All subjects were from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI, version 2010-11-20). The ADNI general eligibility criteria are described in the ADNI protocol summary page. MCI subjects in the ADNI database had Clinical Dementia Rating (CDR) of 0.5. Subjects in the ADNI study underwent up to 5 assessments (baseline, 6 months, 12 months, 18 months, and 24 months). Subjects with at least 3 assessments were included in our analysis. High-resolution MR images were acquired with a standardized protocol. Our study included 174 normal controls (NC), and 266 subjects with MCI. Structural-MR images were processed by ADNI investigators, yielding volumes for the hippocampus and entorhinal cortex. We normalized brain regional volumes by total intracranial volume calculated for the same MR sequence. We calculated the rate of change of a brain region as follows. We calculated the rate of change of a brain region. For a brain region A, the rate of volume change is defined as rate = (volume of A at time t â€“ volume of A at time t-1)/(time interval). Thus, a structure with volume reduction has rate <0 (negative slope). Since DBNs are based on discrete variables, we estimated the mean and variance of the rate for a structure, across all subjects, and labeled each region as having undergone volume reduction if the rate was less than one standard deviation below the mean; otherwise, we labeled that region as stable for that time interval. Results: For the normal elderly group, DBN modeling found that H(t+1) was associated with H(t), and that E(t+1) was associated with E(t). The transient probability tables were: P(H(t+1) = stable | H(t) = stable) = 0.964, P(H(t+1) = stable | H(t) = volume reduction) = 0.963, P(E(t+1) = stable | E(t) = stable) = 0.936, P(E(t+1) = stable | E(t) = volume reduction) = 0.952. In contrast, for the MCI group, DBN modeling found that H(t+1) was associated with H(t), and E(t+1) was also associated with H(t). The transient probability tables were: P(H(t+1) = stable | H(t) = stable) = 0.883, P(H(t+1) = stable | H(t) = volume reduction) = 0.910, P(E(t+1) = stable | H(t) = stable) = 0.860, P(E(t+1) = stable | H(t) = volume reduction) = 0.760. Discussion: We found that the interaction between the trajectory of hippocampal volume and that of entorhinal-cortex volume was altered in adults with MCI, relative to normal elderly. In normal elderly, there is no interaction between these two trajectories. That is, these two processes are independent of each other. However, in MCI subjects, these two trajectories are associated. Our finding is consistent with the existing evidence that AD pathology affects the hippocampus and the entorhinal cortex. The atrophy in AD begins in the entorhinal cortex; then spreads throughout the limbic system, including the hippocampal formation. Therefore, we would expect a temporal association between hippocampal volume and entorhinal-cortex volume in subjects with MCI. The transient probability tables for normal aging and MCI also suggest that more subjects with MCI than normal elderly subjects undergo regional volume loss. In particular, P(H(t+1) = volume reduction | H(t) = volume reduction) = 0.037 and 0.090, for normal elderly and MCI subjects, respectively. Conclusion: Comparing subjects with MCI to normal controls, DBN modeling reveals differing volume-trajectory interactions between hippocampal and entorhinal-cortex volumes. To our knowledge, this is the first study to investigate the interactions the trajectory of hippocampal volume and that of entorhinal cortex volume in subjects with MCI. This work is supported by NIH AG13743, EB-009310. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative.

P8 - NONINVASIVE ASSESSMENT OF DRUG BINDING SITE WITH POSITRON EMISSION TOMOGRAPHY IS USEFUL IN THE PREDICTION OF THE EFFICACY OF CHOLINESTERASE INHIBITOR. N. OKAMURA, M. KASUYA, H. ISHIKAWA, N. TANAKA, Y. FUNAKI, R. IWATA, K. MEGURO, K. YANAI *(Tohoku University School of Medicine, Sendai, Japan)*

Introduction: Cholinergic deficit is consistently found in the brain of patients with Alzheimer's disease (AD). Reduction in the activity of acetylcholinesterase (AChE) is evident in AD brains and correlated with cognitive decline. For this reason, cholinergic enhancement is a major approach to the treatment of AD. Currently, several AChE inhibitors are widely prescribed to improve cognitive function in AD patients. However, not all patients respond to these treatments. It is thus important to identify factors that determine individual responses to the treatment with AChE inhibitors. Functional imaging techniques using positron emission tomography (PET) have been applied to monitor drug action in living patients. Use of radiolabeled AChE inhibitor as PET tracer enables direct investigation of drug binding to AChE in the brain. Objectives: Donepezil hydrochloride is currently the AChE inhibitor most widely used for the treatment of AD and exhibits selective binding ability to AChE. To measure the amount of donepezil binding to AChE in the brain, we performed a clinical PET imaging study using 11C-labeled donepezil in AD patients. The purpose of this study is to determine the relationship between the amount of donepezil binding site and the treatment efficacy of donepezil in AD patients. Material and methods: Six aged normal subjects and 12 AD patients participated in this study. [11C]donepezil PET scans were performed using a SET-2400W PET scanner (Shimadzu Inc., Japan). Following a 68Ge/Ga transmission scan of 7 min duration, a dynamic emission scan was started soon after intravenous injection of 7.1-9.5 mCi of [11C]donepezil. Emission data were acquired for 60 min. Arterialized venous blood samples were obtained from a forearm vein during PET scan, and radioactivity was measured in a well-type scintillation counter. To measure donepezil-binding AChE density in the brain, the distribution volume (DV), the ratio of [11C]donepezil concentration in tissue to that in plasma at equilibrium, was calculated by Logan's graphical analysis. In AD patients, [11C]donepezil PET scans were performed both before and after orally administering donepezil (5 mg/day) for 6 months. After follow-up, AD patients were classified into responders (n=9) and non-responders (n=3) based on the clinical global impression scale. Results: The DV of [11C]donepezil was high in AChE-rich brain regions such as the striatum, thalamus, and cerebellum, and moderate in the neocortex. Compared with aged normal subjects, AD patients showed significantly lower [11C]donepezil DV throughout the brain. In AD patients, [11C]donepezil DV of the responders (19.1±5.7) was significant higher than that of the non-responders (14.6±4.4) at baseline. In addition, orally administered donepezil induced substantial reduction of DV in the brain. The magnitude of DV reduction at 6-month follow up was greater in the responders (-44.8%) than in the non-responders (-15.6%). Discussion: The distribution of donepezil in human brain was successfully visualized using [11C]donepezil PET. The DV of [11C]donepezil at baseline was higher in the responders than in the non-responders, suggesting that the patients who have a higher capacity of donepezil binding in the brain show a greater response to donepezil treatment. The reduction of [11C]donepezil DV at 6 month is mainly caused by the competitive binding inhibition by orally administered donepezil. A greater reduction of DV in the responders means the higher amount of donepezil binding to AChE than in the non-responders. Individual differences in oral bioavailability, pharmacokinetics and blood–brain barrier permeability might influence the amount of brain uptake and treatment response of donepezil. Conclusion: In vivo assessment of donepezil binding to AChE is useful for the prediction of treatment efficacy of donepezil in AD patients. PET imaging with radiolabeled drugs can contribute to a better understanding of the mechanisms of inter-individual differences in drug response.

P9 - ALZHEIMER'S DISEASE BIOLOGY OF A 96 GENE EXPRESSION ASSAY DEVELOPED TO AID IN THE DIAGNOSIS OF THE DISEASE. A. LONNEBORG, G. GRAVE, H.-M. ANDERSEN, L. KRISTIANSEN, T. LINDAHL, L. ROED, P. SHARMA *(DiaGenic AS, Oslo, Norway)*

Introduction: We have developed a blood-based gene expression test for the early detection of Alzheimer's disease (AD) (1, 2). The test is intended to aid in the diagnosis of mild to moderate AD by detecting systemic effects of the disease as a specific gene expression pattern in peripheral blood. The ADtect® is a 96 gene expression assay evaluated by an algorithm resulting in a test score indicating the presence or absence of AD. The 96 genes have been selected based on the predictive value of the algorithm and not on a presumed association with AD pathology. It has been shown that 32 genes encode proteins with a biological function associated with AD, brain or neuronal function (2). Objectives: The presentation aims to demonstrate the biological significance of the 96 gene expression signature of ADtect®. Material and methods: Analysis of the biological and pathological function as well as pathway analysis of genes included in ADtect® was made using Ingenuity IPS. Results: Of the 96 genes included in the expression signature, we now show that more than 50 genes encode proteins with a biological function associated with AD pathology. The biological functions include processing of APP, tau, and mitochondrial processing as well as inflammation, calcium regulation and ubiquitin-associated protein processing. Discussion: Although the primary site of AD is in the brain it is apparent that all characteristic features that has been associated with the disease can also be detected in blood. Conclusion: The results from this analysis suggests an association between the majority of the genes included in ADtect® and all characteristic aspects of biology and pathology that has been related to AD. The results further suggest that ADtect® is able to detect characteristic features of AD biology and pathology in blood, in distance to the primary site of the disease.

P10 - DEVELOPMENT OF A BLOOD-BASED GENE EXPRESSION TEST TO IDENTIFY PRODROMAL ALZHEIMER'S DISEASE. A. LONNEBORG, L. ROED, G. GRAVE, T. LINDAHL, E. RIAN, A. K. KNUTSEN, P. SHARMA *(DiaGenic AS, Oslo, Norway)*

Introduction: There is a clear need for convenient and reliable tests for the detection of Alzheimer's disease (AD) at a prodromal state of the disease. Such a test can be used not only to aid the diagnosis at this early stage but also aid pharma in their development of

novel drugs to help prevent this devastating disease. A blood-based test would fulfill the requirement of being convenient. We have previously developed a test based on the expression of a selected set of genes in blood able to detect Alzheimer's disease. The method should have potential also to detect AD at a prodromal stage of the disease. Objectives: To identify a set of informative genes in blood and generate a gene expression model able to predict AD at a prodromal stage of the disease. Material and Methods: Based on a whole genome expression study a set of informative genes are identified. The informative value of these genes is confirmed and a prediction model generated using RT-PCR on RNA isolated from whole blood of individuals with Mild Cognitive Impairment (MCI) and cognitively healthy individuals. These individuals have been followed for up to three years and a several of those initially identified with MCI has converted to AD. Results: A prediction model has been generated able to predict prodromal AD with good accuracy. Discussion: Although blood is not the primary site of the disease the results show that cells in the body fluid are affected by the disease in a characteristic manner. The results also show that expression of a selected set of genes in blood potentially can be used as a biomarker already at this early stage of the disease. Conclusion: The study shows that gene expression in blood can be used to classify AD at a prodromal stage of the disease before the individual have reached a demented stage of the disease.

P11 - CLINICAL LONGITUDINAL STUDY OF INFLAMMATORY FACTORS IN PLASMA AND PBMCS OF PATIENTS WITH ALZHEIMER'S DISEASE: PREDICTIVE VALUE OF CYTOKINES. A. JULIAN[1], G. PAGE[1], T. DANTOINE[5], P. KROLAK-SALMON[6], G. BERRUT[7], C. HOMMET[8], O. BEAUCHET[9], O. HANON[10], L. BLANCHARD[3], S. BRISHOUAL[3], S. RAGOT[3], M. PACCALIN[1,2,3,4] *(1. Research Group on Brain Aging, EA 3808, University of Poitiers, Department of Geriatrics; 2. University Hospital Poitiers; 5. Limoges, 7. Nantes , 10. Broca Paris; 3. Centre d'Investigation Clinique INSERM 802; Research and Resource Memory Centers: 4. Poitiers; 6. Lyon; 8. Tours; 9. Angers, France)*

Introduction: Alzheimer's disease (AD) is a complex and progressive neurodegenerative disorder that is the most common form of dementia in the elderly individuals. Besides the well-known histopathological lesions: senile plaques and neurofibrillar tangles, chronic inflammation is described at central and peripheral levels. Indeed, many studies described a massive production of proinflammatory cytokines by peripheral blood mononuclear cells (PBMCs) which may modulate the immune response in AD. Furthermore, blood derived cells seem to accumulate in the AD brain and induce phagocytosis of the β-amyloid peptide (Aβ) more efficiently than the resident microglia. The double-stranded RNA-dependent protein kinase (PKR) is associated with degenerative neurons in AD brains. Recently, we reported that the activation of PKR in PBMCs of patients with AD controls the production and release of cytokines. It was interesting to propose a longitudinal study to follow the levels of inflammatory factors in plasma and in PBMCs and the activation of PKR to see if these factors could predict the cognitive decline in AD. Objectives: - To look for a correlation between cytokines IL-1β, IL-6, TNFα and chemokine RANTES/CCL5 levels and cognitive scores at diagnosis - To evaluate the predictive value of IL-1β, IL-6, TNFα and RANTES/CCL5 levels on the cognitive decline after 6 and 12 months of follow up. - To seek a correlation between inflammatory mediators and activation of protein kinase PKR in PBMCs of patients with AD. Material and methods: Diagnosis of AD was made according to the NINCDS-ADRDA criteria. Inclusion criteria included MMSE score ($16 \leq$ MMSE <26), lack of symptomatic treatment of AD and C-reactive protein < 3 mg/L. The cognitive decline was also assessed by the test ADAS-cog. All patients gave their written informed consent before inclusion. Extraction of PBMCs was performed by centrifugation on a Ficoll-Histopaque gradient. PBMCs were cultured for 48h with or without the specific inhibitor of PKR, the C16 compound commercially available from Merck Chemicals. Then, cells were lysed and a protein assay was performed for further analysis. The expression of the active form of PKR was determined by western blot. The assessment of cytokines and chemokine levels was performed according to the technology of Xmap Luminex® 100 IS. Statistical analysis examined the predictive value of cytokines IL-1β, IL-6, TNFα, and chemokine CCL5 on the cognitive decline in patients with AD. Results: Sixty-three patients were included, mean age 80.65 ± 0.86 years [55-91, mean MMSE score 21.08 ± 0.35 [16-25] and mean ADAS-cog score 14.37 ± 0.66 [4.6-28]. Thirty-six were screened again at 6 months, mean MMSE score 19.78 ± 0.74 [13-28] and mean ADAS-cog score 16.56 ± 1.28 [6.25 – 40.30]. Levels of plasma TNFα at inclusion (day 0) were correlated with the ADAS-cog score at day 0 ($r = 0.333$; $p = 0.008$) and with the MMSE and ADAS-cog scores at six months ($r = -0.393$; $p = 0.035$) and ($r = 0.428$; $p = 0.009$), respectively. Levels of IL-1β and CCL5 produced by PBMCs were correlated with MMSE score at day 0 ($r = -0.628$; $p = 0.021$; $n=13$) and ($r = -0.618$; $p = 0.032$; $n=12$), respectively. The analysis in PBMCs showed a significant reduction of CCL5 after one year of follow-up. Discussion: Our study, including patients with mild to moderate stage, shows for the first time that the level of TNFα in plasma at diagnosis has a significant cognitive prognostic value after 6 months of follow-up. Some studies have shed light on a molecular signature of inflammatory factors including TNFα, IL-1, IL-6 and CCL5 in plasma and PBMCs. However, very few longitudinal studies of inflammatory factors are recorded in the literature. Chemokine CCL5 in PBMCs should also be pointed out as this chemokine is known to be neuroprotective. Our results showed that the levels decrease after one year of follow-up in correlation with the cognitive decline. Conclusion: This study highlights 2 data: (1) plasma TNFα as a predictive marker of decline at 6 months that could help identifying patients at risk of rapid cognitive decline, (2) CCL5 produced by PBMCs as the most relevant inflammatory marker to monitor the disease.

P12 - THE B-AMYLOID POOL IN BLOOD HELPS TO DISTINGUISH BETWEEN PRODROMAL AD (PROBABLE) MCI AND OTHER MCI. V. PEREZ-GRIJALBA, I. MONLEON, M. BOADA, L. TARRAGA, I. SAN-JOSE, P. PESINI, M. SARASA. *(Araclon, Zaragoza, Spain)*

Introduction: Current biomarkers of amyloid-beta (CSF and PET amyloid imaging) primarily reflect cortical amyloid fibrils deposition which could characterize stage I of preclinical Alzheimer's disease (AD, Sperling at al. Alzheimer's & Dementia (2011) 1-13). However, as circulating oligomeric forms of amyloid may be critical in the pathological cascade, it might be possible to found still earlier biomarkers that would allow detecting the true onset of the pathological process. We have reported that several blood Aβ markers, including the calculated total Aβ40 + Aβ42 (pool in blood), discriminated between healthy people and mild cognitive impairment (MCI) patients with high sensitivity and specificity. Objectives: The present work was aimed to validate those results in a new population sample with a special focus in the comparison between probable-MCI (equivalent to prodromal AD) and possible-MCI. Material and methods: We measured Aβ40 and Aβ 42 free in plasma (FP), total en plasma (TP) and cell bound (CB) in groups (n=16 each) of healthy controls (HC) 45-54, HC 55-64 and HC>65 years old, probable-MCI, possible-MCI and AD patients by ELISA sandwich (ABtest40 and ABtest42. Araclon Biotech Ltd. Zaragoza, Spain). Results: In agreement with our previous work, we found that all Aβ blood markers increased in probable-MCI with regard to HC >65 (except CB Aβ40). These differences reached statistical significance for TP Aβ40, CB Aβ42, total Aβ 42 and the total pool in blood. Discussion: Interestingly, we also found that total Aβ42 and the total pool in blood measurements were significantly higher in probable-MCI, considered the prodromal stage of AD, than in possible-MCI, considered to have less chance to convert to AD. Not significant increments were found in any marker neither between probable-MCI and mild-AD patients nor between possible-MCI and aged matched HC. Conclusion: These results reinforce the interest of blood Aβ markers for early diagnostic of Aβ pathology, screening of participants and assessment of efficacy in clinical trials of Aβ - targeted drugs.

P13 - 6-BIOMARKER ALGORITHMS IDENTIFY ALZHEIMER'S DISEASE AT HIGH ACCURACY. M. ZELLNER, A. GRAF, R. BABELUK, M. VEITINGER, E. UMLAUF *(Medical University of Vienna, Vienna, Austria)*

Introduction: Late-onset Alzheimer's disease (LOAD) is the most common form of dementia among the elderly. Hallmarks of this disease are the accumulation of neurofibrillary tangles, intracellular amyloid plaques, and neuronal loss primarily in the temporal lobe and neocortex of the brain. LOAD can only be confirmed with certainty by post mortem examination. Currently, diagnosis is done by reviewing the medical history, mental status tests (MMSE, ADAS-cog), neurological tests, and brain imaging (MRI, CT, PET). These tests are labour-and cost-intensive. Objectives: Identification of Alzheimer's disease biomarkers using platelets, which can be easily isolated at high purity from whole blood. Platelets serve as a peripheral model system for neurons, with which they share similarities such as altered amyloid precursor protein (APP) processing, increased membrane fluidity, mitochondrial dysfunction, and oxidative stress. Materail and methods: 42 Alzheimer's disease patients (mean age = 81.9 ± 7.89 yrs) and 43 age- and sex-matched control individuals (mean age = 80.1± 7.51 yrs) were analyzed by 2-dimen-sional differential gel electrophoresis. Furthermore, the Apolipo-protein E genotype and the poly-morphism rs4925 of GSTO-1 (Glutathione S transferase omega-1) at amino acid position 140 (alanine versus aspartate) of these individuals were determined. Algorithms of the most significant LOAD-biomarkers were generated using logistic regression and were assessed by Receiver operating characteristic (ROC) curves and Area under the curve (AUC). Results: Several algorithms that contain five or six of the LOAD biomarkers apolipoprotein E4 (ApoE4), mono-amine oxidase B, coagulation factor XIIIa, glutathione S-transferase omega wild type (wtGSTO-1) and mutant (mutGSTO-1), and tropomyosin showed AUC above 0.9 but differed in the weighting of these biomarkers. Best AUC were obtained when our finding that wtGSTO-1 is prominent in nonApoE4 LOAD patients was taken into consideration: Algorithm 1: AUC = 0.938 (95% confidence interval 0.8839-0.9923 and Algorithm 2: AUC = 0.952 (95% confidence interval 0.8799 - 1.0000). Discussion: Several algorithms that contain six platelet LOAD biomarkers showed AUC above 0.9 but differed in the weighting of these biomarkers. Two of the best algorithms: Algorithm 1: AUC = 0.938 (95% CI 0.8839-0.9923), Algorithm 2: AUC = 0.952 (95% CI 0.8799-1.0000). Conclusion: The combination of LOAD biomarkers presented here may serve as basis for the development of a fast, easy, accurate, and cost-effective diagnostic tool for Alzheimer's disease using platelets that are easily isolated from whole blood.

P14 - AGE-EXPANDED NORMATIVE DATA FOR THE RUFF 2&7 SELECTIVE ATTENTION TEST; EVALUATING SELECTIVE ATTENTION IN OLDER INDIVIDUALS FOR CLINICAL TRIALS. A. CABAN-HOLT, E. ABNER, R. KRYSCIO, B. DENNIS, F. SCHMITT *(Sanders-Brown Center on Aging, Lexington, KY, USA)*

Introduction: Selective attention is a cognitive function that is the ability to block out external distractions and focus on a required task. Such abilities, which utilize planning and reasoning, fall under the general term of "executive functioning". Such abilities are important in the assessment of cognitive decline, as difficulty with attention can exacerbate problems with memory and thinking, and can inhibit an individual's ability to complete a necessary task. Thus, selective attention is frequently assessed in older individuals suspected of having Mild Cognitive Impairment (MCI) and dementia, particularly of the Alzheimer type (DAT). Assessment measures exist that tap into selective attention (like the

Stroop Test; Stroop, 1935), often do not have sufficient normative data in older adult age ranges. This is of particular importance to clinical trials in MCI and DAT, since participants in such trials are older adults. Without sufficient normative data for older adults on various measures of cognitive skills that are suspected to change in dementia, it is difficult to determine whether test performance is abnormal and if true decline has occurred, particularly in high functioning adults. Clinical trials in DAT benefit from normative test data for measures of skills suspected to demonstrate change during the course of DAT. The current poster addresses this problem by providing age-expanded normative data for the Ruff 2&7 Selective Attention Test (RSAT; Ruff & Light, 1996). This measure may hold promise in the diagnosis of AD in clinical trials for a few reasons. The RSAT is a paper-and-pencil test that is easily administered in five minutes, and yields speed and accuracy scores for both controlled and automatic attention conditions. Further, selective attention has been shown to decline in DAT and MCI, as well as in normal older adults (Mapstone, Dickerson, & Duffy, 2008). Thus, test data to help distinguish the performance of normal older adults from those with MCI or DAT on this measure is a valuable addition to the clinical trials field. The current poster shows the baseline RSAT data for 471 cognitively normal men over the age of 60 enrolled in the Normal Aging (NAG) substudy of the PREADViSE clinical trial. Objectives: To provide age-expanded normative baseline data on the RSAT for men ages 60 to 90. To provide additional data to the existing normative dataset of Ruff and Light (1996); increasing it by approximately 50%). To expand the geographic sampling region of the normative data in the United States making the test results more generalizable. To determine whether RSAT data is affected by demographic factors such as: age, race, and education, or family history of dementia. Materials and methods: Data for the current study was collected for the Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADViSE), a National Institute on Aging sponsored clinical trial. The primary goal of PREADViSE is to determine whether Vitamin E and Selenium (alone or in combination) will reduce the incidence of DAT in a group of men age 62 and older (age 60 and older if African American or/and Hispanic). Participants in the PREADViSE study were recruited exclusively from the participant pool of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) clinical trial. The SELECT trial is sponsored by the National Cancer Institute to examine the potential of Selenium and Vitamin E to prevent prostate cancer. The SELECT study had a total of 35,553 male participants at 420 research sites in the United States, Canada, and Puerto Rico. 123 of the SELECT sites became trained on the administration of PREADViSE procedures. Total PREADViSE enrollment was 7,553 participants. The RSAT normative sample consists of 471 cognitively intact male volunteers (mean age = 69.5 ± 5.7 years, range 60 - 90) in the Normal Aging sub-study of the PREADViSE trial. Participants with a baseline Mini-Mental Status Exam (MMSE) score below 26 were excluded (n = 37). Results: Correlation analyses and analysis of variance (ANOVA) show effects of age, race, and education on some variables. Results indicate that age-expanded norms provide a more accurate reflection of the performance of older individuals on the RSAT. The relationship between the mean response for each of the four endpoints Controlled Search Speed, Automatic Detection Speed, Controlled Search Accuracy, Automatic Detection Accuracy, Accuracy Difference and two factors' age group (60-69, 70-74, and 75 plus) and education (high school or less, some college, and college plus) was assessed with an analysis of variance (ANOVA) using PROC GLM in SAS 9.2®. Because African Americans were over-sampled in the NAG sub-study, several additional analyses were performed to determine the effect of adding race (African American versus Caucasian) to the ANOVA model, including its interactions with age and education. The possible interaction between age and education, without race in the model, was also assessed. Statistical significance was determined at the 0.05 level. Results: Controlled Search Accuracy (CSA) scores were found to be independent of both age and education level, while Automatic Detection Accuracy (ADA) scores were dependent on only education level and Automatic Detection Speed (ADS) and Controlled Search Speed (CSS) scores were dependent on both age and education. A college education or higher was associated with significantly higher speed scores than high school or less, regardless of age, while increased age was associated with significantly lower speed scores regardless of education. Only one of the additional analyses produced a significant result: race had a modest but significant effect on ADA. The mean ADA score for African-Americans is 95.0 ± 4.7 compared to 96.9 ± 3.0 for non-African-Americans; both mean scores reflect average performance (based on suggested clinical interpretation due to Ruff & Allen, 1996). Discussion: Correlation analyses and analysis of variance (ANOVA) show effects of age, race, and education on some variables. Results indicate that age-expanded norms provide a more accurate reflection of the performance of older individuals on the RSAT. These analyses point out the critical importance of having age-expanded normative data when classifying older individuals' cognitive status. In the case of the RSAT, comparing scores of individuals over the age of 70 to those who are younger (55-69 years of age) places them at a disadvantage in terms of clinical interpretation of their scores and increases the likelihood that they will erroneously be viewed as having a cognitive impairment when in fact their performance is average compared to others in their age group. Conclusion: The age-expanded normative data presented in this poster show a higher accuracy for demonstrating true cognitive impairment in older adults as compared to the current normative data available in the procedures manual for the RSAT (Ruff & Light, 1996). With the age-expanded normative data provided in this poster the RSAT is shown to be an effective measure of selective attention in individuals over the age of 70. Use of this measure in clinical trials should be considered given the age-expanded normative data for older age groups that will allow for setting cut points for abnormal selective performance, a more generalizeable sample due to more geographic regions being sampled, and that performance by race has been addressed.

P15 - VARIABILITY IN MMSE SCORES BETWEEN SCREENING AND BASELINE VISITS IN 2 LARGE, MULTI-NATIONAL ALZHEIMER'S DISEASE STUDY PROGRAMS: A CONCERN AND POTENTIAL SOLUTIONS.

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Introduction: Regardless of the indication, it is paramount that only subjects who meet the defined inclusion/exclusion and the specified severity criteria be enrolled in a clinical trial. This is particularly the case with Alzheimer's disease (AD), where other potential causes of a subject's cognitive impairment must be ruled out. Once the diagnosis is clarified, the severity of the disease must be determined. By doing so, the investigator is able to distinguish between mild, moderate, and severe stages of the disease and further establish a given subject's appropriateness for a particular trial. Frequently, the Mini-Mental State Exam (MMSE) (1), a brief cognitive assessment with total score of 30 points, is used to determine the severity level, and may even be used to help further stratify subjects within a trial. The MMSE entry criteria are often established only at the screening visit. We report on an analysis of MMSE score changes from screening to baseline visits over the course of 2 separate but methodologically similar, multi-national AD clinical trial programs, "IDENTITY" and "EXPEDITION". Objectives: To assess differences in MMSE scores from screening to baseline visits when only the score at the screening visit is used as study entry criteria. Methods: A total of 3405 patients were enrolled in these 2 AD programs (2399 in one, and 1306 in the other). MMSE scores at both Screen (when inclusion criteria were established) and Baseline visits were assessed for the degree of change; time between visits; whether time between Screen and Baseline impacted on the degree of change; and the number of patients whose MMSE would no longer meet inclusion criteria if they were also required at the Baseline visit. Both of the programs employed the same MMSE cutoffs for study inclusion. Additionally, these programs employed a rater surveillance program to assess the quality of the ongoing ratings. One component of this program was to assess raters' adherence to MMSE administration and scoring conventions at the Screening visit. When errors in either administration or scoring were detected by calibrated Clinicians, the raters in question were remediated and the scoring of the MMSE was corrected. Such a program has been shown to significantly decrease the error rate on subsequent assessments (2). Results: Of the 3405 patients, 854 (25%) had MMSE scores that did not change from Screening to Baseline, 1071 (31.5%) changed + 1 point, 676 (19.9%) changed +2 points, and 814(23.6%) changed +3 points or more. The distribution and number of scores that increased (1320 (38.3%)) was quite similar to those that decreased (1231 (36.2%)). When the time between Screening and Baseline visits was assessed for impact on score change for the entire group of 3405 patients, the interval significantly differed for those scores that changed 3 or more points (mean interval = 23.6 days) when compared to those that did not change or only changed by 1 point (mean intervals of 20.7 and 21.2 days respectively). The data were further analyzed to determine how many patients would no longer have met the MMSE inclusion criteria had it been required at both Screen and Baseline visits. Of the 3405 patients, 244 (7%) would no longer have met the MMSE inclusion criteria at Baseline. For this subgroup, 44 (18%) changed + 1 point, 64 (26.2%) changed + 2 points and 136 (56.7%) changed + 3 points or more between their Screen and Baseline visits. A Chi-Square analysis found that the distribution of score changes between the group that continued to meet MMSE inclusion at the Baseline (n = 3161) and those that did not (n = 244) was statistically significantly different to $p < 0.001$. However, when the duration of time between the Screen and Baseline visits for each group (those continuing to meet inclusion criteria versus those who would not have) was compared, there was no statistically significant difference in the intervals for each degree of score change. Additionally, for the subgroup that would no longer have met the MMSE inclusion criteria at Baseline, there was a statistically significant difference in the interval between Screen and Baseline for subjects who changed only + 1 point (mean interval of 19.4 days) and those that changed + 3 or more points (mean interval of 25.1 days) ($p = 0.01$). 45.9% (n = 112) of subjects who no longer would have met MMSE criteria were out of range by 1 point in either direction, 33.2 % (n = 81) would have been 2 points out of range and 20.9% (n = 51) would have been out of range by 3 or more points. Discussion: This analysis raises the issue of requiring a subject to meet the MMSE or severity inclusion criteria at both the Screen and Baseline time points as roughly 7% of the initially qualified pool of subjects in this analysis would no longer have met that criterion by Baseline. Additionally, nearly a quarter of all eligible (those who met MMSE inclusion at the Screening visit) subjects had score swings of 3 or more points on the MMSE in less than the month between Screening and Baseline visits, a change that might be greater than expected during that time period. One possible explanation for that degree of change is the practice effect. However, this is unlikely, given that subjects were as likely to show improvement of 3 or more points as they were to show worsening on the MMSE. Other possible explanations include a change in the subject's medical status and/or medications. Both of these need to be addressed by the investigator when they see significant score swings in such a relatively short period of time. The possibility that investigators may unconsciously or consciously alter either their administration and/or scoring of the MMSE in order to enable a subject to be enrolled in the trial must also be considered. Conclusion: Getting subjects who meet both the correct diagnosis and are of the desired clinical severity in Alzheimer's disease clinical trials can be particularly challenging. Not doing so can potentially negatively impact study results. When a scale is used at screen and baseline visits, consideration should be given to requiring both scores meet inclusion criteria. Further, utilizing a surveillance program that can monitor the quality of the assessments throughout the study, and remediate raters when these occur is a step toward achieving that goal (2). Additionally, such a program might also be used to assist in diagnostic adjudication. References: 1. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state': a practical method for grading the mental state of

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P16 - USE OF INFORMANT-REPORTED WEB-BASED DATA COLLECTION TO ASSESS DEMENTIA SYMPTOMS: VALIDATION IN RELATION TO THE DEPENDENCE SCALE. K. ROCKWOOD[1], A. ZENG[1], C LIEBMAN[2], A. MITNITSKI[1]
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Introduction: The world wide web offers unprecedented access to the experience of people with dementia and their care partners. How best to make use of this access remains unclear. Given that the concept of progressive dependence offers a unifying understanding of disease progression, and can help bridge from clinical endpoints to estimates of treatment value for external decision makers, we undertook a construct validation study of web-based symptom profiles in relation to the 15 item Dependence Scale. Material and methods: Data come from an online survey on www.dementiaguide.com. Care partners build individualized patient profiles from 70 symptoms detailed on the site's SymptomGuide™ (SG). Care partners select symptoms to target for monitoring disease progression and treatment efficacy. Respondents were invited to also complete a questionnaire, which included the DS. For profilees diagnosed with Alzheimer's disease (AD) DS scores and SG scores were correlated. DS scores were also compared with SG reports of dependence in Instrumental and basic Activities of daily Living (I)ADLs, and behavioural symptoms and with a symptom-based staging algorithm. Results: Of 250 profilees, most care partners (81%) were women, in middle age (range 51-60 years) living in the same home (46%) or visiting daily (10%). At the lowest levels of dependence (DS<5) none of the profilees was in long term care; at the highest (DS>12) almost all were. An AD diagnosis was reported for 97 people (60% women; most aged between 81-85 years) most (65%) with DS scores between 5-10. The mean number of targeted IADL symptoms increased from 0 at DS<2 to 8 at DS>10. Psychiatric symptoms were present at DS>t5, and ADL symptoms at DS<8. The correlation between the DS and the SG staging algorithm was 0.63. Conclusion: In an online survey, the DS showed good construct validity in relation to the need for institutional care, (I)ADL disability, behavioural symptoms, and a symptom-derived staging algorithm. That individualized patient descriptions accords with staging suggests that the web can be used to better understand the lived experience of dementia. The facility with which the web allows individualized data to be collected can also assist in a better understanding of treatment value.

P17 - COMPARISON OF MOTOR PERFORMANCE IN UPPER AND LOWER EXTREMITIES UNDER DUAL-TASK PATIENTS WITH MILD ALZHEIMER'S DEMENTIA. A.M.K. WONG, S.-W. CHOU, C.-W. WU, C.C. HUANG, M.-C. CHIOU, H.-C. FUNG *(Chang Gung Memorial Hospital, Taiwan)*

Introduction: Alzheimer's dementia is a progressive disease that threaten elder people in self care and quality of life. Early diagnosis and early treatment are very important. Objectives: Besides of cognitive test, executive function, by gait analysis (Vicon MX system) and trial making test (TMT) by electronic board with dual task by digit counting (foreward and backward) for assessment. Material and methods: Ten elderly people who were diagnosed by neurological specialists as mild AD patient. Among them, 2 were men and 8 were women, with age in 74.0±8.6 year old, MMSE score in 17.7±4.1, and CDR, score in 0.8±0.3. Another 10 older people without dementia in age and sex matched were selected as control group. Results: We found that backward counting (BC) in 3 digits during gait performance in mild AD patients revealed remarkable change in velocity, cadence,CV of stride length and stride time them control group, while forward counting (FC) in 3 digits did not reach significant change. Discussion: For upper extremity performance, all TMT tasks were very sensitive to detect the difference of reaction time between mild AD group to control group, including single task, random sequential test, or dual task with BC 2 digits. Conclusion: In conclusion, dual tasks of gait or TMT performance might reveal obvious impairment of executive motor function in very mild AD patients. However, motor test of upper extremity was more simple in test, less expensive in cost of instruments, and easily movable device for patient check up than gait analysis system.

P18 - FRAMEWORK FOR PATIENT SYNCHRONIZATION VIA ADAS-COG 13 AND ITS CONSEQUENCES FOR DISEASE PROGRESSION VISUALIZATION AND CLINICAL TRIALS. E. YANG, M. FARNUM, V. LOBANOV, T. SCHULTZ, N. RAGHAVAN, M.N. SAMTANI, G. NOVAK, V. NARAYAN, A. DIBERNARDO *(Johnson and Johnson, USA)*

Introduction: Alzheimer's Disease (AD) is a progressive disease characterized by worsening cognitive decline over a long period of time. Studies into AD often require trials of long duration due to the time scales of the disease progression, as well as the lack of precision in the measurements. In current analysis plans for AD trials, subjects are synchronized to the start date of the trial. This has the consequence of introducing a great deal of inter-subject variability due to the fact that the patients may be at significantly different stages of disease progression at any given point in time. This is somewhat mitigated through the stratification of subjects by clinical diagnosis but again, there can be significant differences in disease duration within these categories. We hypothesize that this variability in the disease severity of patients in a given trial, is one of the most important factors in terms of explaining the inter-subject variability seen in these trials. In addition to reducing the inter-subject variability in a given trial, being able to properly predict the disease duration of a given subject also will allow the use of patients who span the different stages of AD. This is advantageous, because it allows one to obtain the natural history progression of Alzheimer's with respect to different markers of AD pathology in by following a heterogeneous cohort of subjects over a short period of time, rather than a homogenous cohort of subjects over a much longer period of time. Secondly, we propose that through proper synchronization, we can also derive greater power in our clinical trials by reducing the apparent noise within a given endpoint. Objectives: We will present work which shows that synchronizing patients based upon their ADAS-Cog 13 score will allow us to analyze the ADNI dataset and obtain empirical predictions as to the progression of the different pathological phases associated with AD. Secondly, we will show how synchronization can be applied to clinical trials to increase the power of a trail, as well as to more effectively visualize and analyze the results of alternative trial designs.Material and methods: The process of synchronization assumes that one of the factors leading to the variation within the measurements is due in part to the fact that the patients lie along different points on the disease timeline. Given an accurate model of disease progression, it should be possible to determine how far long upon the timeline of disease progression a patient is. The time from disease initiation, then becomes the foundation of synchronization. We calculated the time from disease initiation from the ADAS-Cog 13 score of patients in the ADNI trial. This time from disease initiation was then used as to synchronize all of the other measurements such as levels of CSF biomarkers and volumes of specific brain regions, allowing us to determine the evolution of these different markers of AD. Secondly, it allows for more accurate estimation of the future progression, and thus allows us to more accurately determine the effects of drugs upon disease progression. The more accurate estimation of the disease progression within a clinical trial thus enables us to determine with greater accuracy whether the drug itself has an effect vs. placebo. Using a simple mixed-effect model of disease progression that depends on time and whether a patient was administered a drug, we can show that when time is adjusted by our calculated time from disease initiation, we get a much stronger correlation between time and disease progression, as well as a stronger signal indication whether a subject was in the placebo arm of the trial, or whether a subject was administered a drug. Results: In terms of charting disease progression, the synchronization has allowed for the confirmation of the hypothetical disease timeline proposed by Jack et al. However, because the results are derived from data obtained from the ADNI trial, we are able to determine the period of time that elapses between the different stages of Alzheimer's. In our results, we have determine the changes in β-amyloid levels in the CSF take place more than 4 years prior to any changes in the levels of tau, or phospho-tau. Changes in hippocampal volume occur in two stages, with a slow progressive stage occurring proximally to changes in β-amyloid levels, and accelerating at the time that tau and phospho-tau levels change, with neuronal death correlating with the release of tau proteins into the CSF. While we predict that cognitive decline starts at around the same point as changes in the levels of tau, or accelerating hippocampal atrophy, levels of cognitive impairment as detectable by ADAS-Cog, take place almost 4 years after changes in levels of tau. In the evaluation of clinical trials, we utilized two trials for galantamine. From the analysis we were able to show that by changing the time axis, we were able to obtain a 3-5 order of magnitude improvement in the statistical significance of the drug vs. placebo population, thus allowing for a 10 fold decrease in the population size of a trial given the same number statistical power. Discussion: The synchronization of patients based upon the disease timeline, allows us to first reconstruct the disease timeline with respect to other biomarkers. This allows us to get a better idea as to the temporal characteristics of the different pathological events. From here, it is possible to determine, the relationship between the different pathological markers associated with AD, yielding important insight which may be used to guide interventions. Furthermore, synchronization allows us to obtain this data without running a study that takes as long as it takes the AD to progress through the different disease stages. In the case of trial design for pharmaceutical agents, the reduction of the apparent noise, allows for more accurate prediction of disease progression, thus allowing us to reduce the number of patients needed. Conclusion: To our knowledge, this is the first attempt to properly place patients upon a disease timeline, rather than a trial timeline. By doing so, we have increased the overall fidelity of the data, and are thus able to gain a better of the disease process, as well as better process the results of clinical trials.

P19 - MICROARRAY-BASED TRANSCIPTOMIC SIGNATURES TO HELP IMPROVING THE SUCCESS RATE OF AD CLINICAL TRIALS. P. BEURDELEY, L. DESIRE, V. KOTRAIAH, M. PANDO, I. BARBER *(Exonhit, Gaithersburg, USA)*

Introduction: CNS drug development remains challenging when compairing development times (clinical phase and approval phase) in various therapeutic areas. Kaitin demonstrated that drug development in the field of CNS is the longest, taking approximatively 10 years compared to any other disease with an average of 7.6 years in Oncology. In addition, the approval success rate reaches only 8.2% in CNS while in Oncology this rate is close to 19% (DiMasi, 2010). In 2009, Lon Schneider tried to explain these failures by analyzing 23 clinical trials of more than 18 months. He stated that "at least two things need to occur to improve chances for detecting efficacy with current outcomes. A greater proportion of the placebo sample needs to measurably worsen on the primary outcome scale, and the drug group needs to improve over baseline to overcome the broad variances in change" (Schneider, 2009). In 2008, R. Becker stated that "unfortunately, in spite of their using of larger numbers, higher levels of variance appear to account for the failure of two trials to reach statistical significance" (Becker, 2008 August). Therefore it is critical to expand the identification and use of clinically relevant biomarkers which can contribute to the renewal of AD drug development. Objectives: The objective is

to show how, a non invasive and reproducible diagnostic test, AclarusDx™ , could increase the success rate of clinical trials by reducing the variability in patient inclusion. Furthermore, the use of the human Genome-Wide SpliceArray™ (hGWSA) technology used for the development of AclarusDx™ test, can bring to pharmaceutical companies the capacity to identify at completion of clinical phase II studies, an additional signature to distinguish potential responders from non responders to the drug being developed. Material and methods: The blood-based transcriptomic signature (AclarusDx™) was developed by comparing 90 AD patients to 87 asymptomatic control subjects. The performance of the signature was then evaluated in a final independent blinded population of 164 individuals (91 AD and 73 controls). This biomarker will serve a valuable tool for patient recruitment in AD clinical trials. In parallel, Exonhit conducted a phase IIA clinical trial with its compound EHT 0202 as adjunctive therapy to one cholinesterase inhibitor in mild to moderate AD patients. During the study, blood samples were collected from each randomized patient at different time points, notably before treatment initiation and at study completion. Using sixty AD patients having either responded or declined during the study period with regards to ADAS-cog total score, we report on the identification of blood-based transcriptomic signatures associated with treatment response of EHT 0202 at study exit, and prediction of drug response at study entrance, using Exonhit's SpliceArray™. Results: To overcome the issues raised above, the pharmaceutical industry needs a tool which is objective to improve the homogeneity of patient's population at inclusion. A user friendly blood-based test could be used as a Quality Control tool for recruitment. The AclarusDx™ signature consists of 170 probesets which map to 136 genes. A significant number of them are associated with inflammatory pathways and are independent of pathways involved in amyloid or tau metabolism. The AclarusDx™ performance on this validation cohort had a sensitivity of 81.32% (95% CI : [73.31%; 89.33%] and a specificity of 67.12% (95%CI : [56.34%; 77.89 %]). Beyond the Quality Control of the recruitment phase, the use of this hGWSA technology brings to pharmaceutical companies a unique added value: the capability to identify, at completion of Phase II study, a signature monitoring the response to the treatment as well as a signature able to discriminate responders from non responders at baseline, prior to drug administration. In the EHT 0202 study, we identified specific expression profiles for decliners and improvers that allowed a clear discrimination of these subgroups at study exit after administration of EHT 0202. This discrimination was specific of EHT 0202 and not detected for the coadministered cholinesterase inhibitors. When the analysis was conducted at the gene level and not at the splice event level, no discrimination between responders and decliners could be made. Importantly, transcriptomic profiling of the patients prior to treatment allowed to prospectively identify blood expression biomarkers which could be potentially useful to prospectively predict patient response.Discussion: Several hypotheses explain why it is so difficult to demonstrate the efficacy of new compounds: variance in patient's recruitment, lack of sensibility of the scales, human dependant assessment tools and inter-rater variability, the lack of predictive biomarkers to identify drug responders from non responders. These issues being identified, the aim is to find a way to solve them in order to foster success of future drug developments in AD. Exonhit has developed a unique blood based test, AclarusDx™ , using its Genome-Wide SpliceArray™ technology which allows the identification of a disease specific transcriptomic signature. This test requires a simple blood drawing which makes it very easy to include in the recruitment process for quality control and to reduce the population variance. Beyond the quality control of the recruitment phase, the use of the technology offers a unique added value: the capability to identify, at completion of phase II study, an additional signature able to differentiate prior to treatment intake, potential responders from non responders to the drug assessed in the trial. The use of this additional signature in the upcoming clinical development phase allows to enrich the population with highly probable responding patients. Thus, the information brought by hGWSA may contribute to better stratify the patients and select the patients likely to respond to the drug, therefore improving the chance of success of its clinical development. Conclusion: A way to increase the success rate of clinical trials in the field of Alzheimer would be to combine a "Quality Controlled" recruitment phase with AclarusDx™ together with the power of the hGWSA technology to define a signature in order to prospectively identify responders.

P20 - THE BRIEF EPISODIC MEMORY ASSESSMENT: A NEW SCALE TO MEASURE THE EPISODIC MEMORY IN ALZHEIMER'S DISEASE TO COMPLEMENT NEW ONE-PLUS-ONE IN VIVO DIAGNOSIS STRATEGY.
C. YAVORSKY, A. KHAN, A. DEFRIES, M. OPLER

Background: Recent advances in biomarker technology have allowed for the development of highly predictive tests for Alzheimer's disease (AD) when combined with clinical verification through standard psychometric tests. Recent proposals by Bruno Dubois and others have outlined a one-plus-one strategy wherein in vivo diagnosis could be possible by combining one clinical measure with one or more biomarkers (e.g., ApoE4). While current research in the AD area utilizes the ADAS-Cog and/or the MMSE as standard clinical measures, these measures do not exclusively address the specific deficits expected in an amnesic syndrome of the hippocampal type as expressed with AD. Because it is episodic memory degradation that is most strongly predictive of conversion from mild cognitive impairment (MCI) to AD it is felt that a clinical measure targeting this deficit would be of great clinical utility. The aim of this study was to utilize current knowledge of neural correlates of different stages of episodic memory function and their modulation by Alzheimer's disease (AD) to develop a psychometrically sound instrument. Methods: Firstly, the authors developed a brief scale that captures the patient's registration, storage and retrieval of information along the four identified domains of episodic memory. This scale is aimed specifically at the assessment of this deficit in AD patients. The examination also included a psychiatric assessment, an evaluation of cognitive function using the MMSE, and assessment of any changes in behavior in those suffering from AD, using the NPI. A second stage was to confirm Brief Episodic Memory Assessment in institutionalized subjects. Reliability and validity were assessed, and the Brief Episodic Memory Assessment was cross-validated with the Autobiographical Memory Interview (AMI). Results: Preliminary results indicate good test-retest reliability and adequate sensitivity and specificity. The Brief Episodic Memory Assessment was positively and significantly correlated with other measures of episodic memory. The Brief Episodic Memory Assessment yields a total score, scores for 3 lifetime periods and the duration of episodic memory impairment. Conclusions: The current results suggest that a richer understanding of the memory deficits in AD can lead to the development of an instrument which taps different aspects of episodic memory function. Furthermore, this scale can aid in the screening, assessment and treatment of early AD and complement the newly developed one-plus-one strategy.

P21 - PRACTICE EFFECTS IN A LONGITUDINAL, MULTI-CENTER ALZHEIMER'S DISEASE PREVENTION CLINICAL TRIAL.
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Introduction: Practice effects (PE), the phenomenon of improving or maintaining one's test score over time, is a known threat to reliability and validity of study findings especially in clinical trials that focus on cognition as part of their primary or secondary outcomes. Incorporating PE may also be critical for Alzheimer's disease prevention trials. Few studies have investigated PE over the long-term; however, there is a suggestion that tracking PE can provide early clues to cognitive decline among normals and those with MCI. Objectives: The NIA-sponsored PREADViSE study, in conjunction with the NCI-sponsored prostate cancer prevention trial SELECT, seeks to examine the effectiveness of the antioxidants Vitamin E and Selenium in preventing Alzheimer's disease in older men in the United States, Canada, and Puerto Rico (N=7,553). Participants have completed Memory Impairment Screens (MIS) annually for up to 9 years. We hypothesized that despite efforts to mitigate PE with alternating test versions, MIS scores would improve over time. Materail and methods: PREADViSE participants who completed baseline and three consecutive follow-up MIS with alternating versions were included in the current analyses (N=3,094). A subset of men who received the same version of the MIS at baseline and first follow-up (N=713) was also analyzed to determine effect of alternate forms on PE. Linear mixed models (LMM) were used to estimate mean MIS performance over repeated visits while controlling for test version, baseline age, education level, race, and all two-way interactions between visit with age, race, and education. Results: Among men with four visits and alternating MIS versions, there is no evidence of a significant PE at the first follow-up (P = 0.133). Neither those with high education, whose scores start high and remain so over time (those with college education or better gain an average of 0.02±0.03 points from baseline to third follow-up, P = 0.54), nor the oldest participants, whose scores decline over time (for example, 85-year-olds lose an average of 0.14±0.06 points from baseline to third follow-up, P = 0.018), show evidence of PE over all visits. Non-minority men, men with lower education, and younger men do show PE at the second and/or third follow-up visits. Unlike those who received alternating versions, men given the same version at baseline and first follow-up do show a significant improvement over the baseline score (P = 0.0001). The mean increase of 0.13±0.03 points (from 7.55±0.03 at baseline to 7.68±0.03 at first follow-up) closes 29% of the gap between the baseline score and the ceiling score of 8. Discussion: These findings suggest heterogeneity of PE over time with respect to age, education, and race, which could affect dementia case ascertainment in longitudinal studies. Conclusion: Incorporating PE into clinical trial procedures and analyses of outcomes may prove to inform true effects as well as false positive and false negative case ascertainment rates. Use of alternate test forms in clinical trials is supported, as PE was both more pronounced and sooner evident when the same version was used consecutively.

P22 - COMPLIANCE WITH THE REQUIREMENTS OF ANTI-ALZHEIMER'S WITH THE MAIN RECOMMENDATIONS ISSUED IN MARCH 2008 HAS.
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Introduction: Studies concerning the evolution of French demography provide an aging population thus implies an increase in diseases like dementia. Alzheimer's disease has been declared as \"great national cause\" in 2007. To optimize supported patients, the recommendations of the reflection of an expert group of the High Authority for Health (HAS) were published in March 2008. A program entitled \"Prescribing in the Subject Better Aged\" was engaged in parallel. To evaluate the monitoring recommendations HAS, medical practices concerning the prescription of anti-Alzheimer's in older people should be regularly evaluated. To assess this data, a study was conducted in our hospital group. It divides into 3 sites and have 600 beds. Objectives: The objective of this study is to investigate the requirements of patients receiving drugs \"Anti-Alzheimer's" (Aricept ®, Exelon ®, Reminyl ® and Ebixa ®) and to oppose the recommendations HAS March 2008 on this therapeutic class. According to the results, areas for improvement will be drafted. Their effectiveness will be evaluated six months after their establishment, then 1 year later. Material and methods: With our prescriptions software Phedra, we identified all patients receiving anti-Alzheimer's. Medical records were then studied using the software of patient

global care Actipidos. For each patient age, area of hospitalization, the creatinine clearance average, the neurodegenerative disease, MMSE score, and the prescription were collected. The drug prescription has been opposed to medical diagnosis then pharmaceutically analysed. The study is observational, descriptive thanks to the patient records study and comparative between D0, M6 and M12. M6 and M12 are not yet carried out. Results: 34 cases of patients with neurodegenerative diseases have been studied in their entirety. The mean age observed is 88 years and 82% of patients are women (sex ratio: 0.21). 76% of patients hospitalized in Internal Medicine Geriatric (Long Term Care: 12% Aftercare and Rehabilitation: 12%). The creatinine clearance average is 46.3 ml / h (moderate renal insufficiency). 5 patients with severe renal insufficiency and 14 with moderate renal insufficiency. The distribution of diseases is as follows: 70% are suffering from Alzheimer's disease (AD), 6.9% for vascular dementia and 10.3% have dementia undiagnosed precisely or under diagnosis. Mini-Mental State Evaluation (MMSE) was performed in 79% of cases. The average MMSE is 12. Specialists set up 26 of the 34 treatments during a hospital stay in geriatric institutions. 100% of prescriptions of Aricept ® and Reminyl ® PC is the optimal dose (10 mg to Aricept ® and 16 mg to Reminyl ®). Ebixa ® 10mg cp is found as monotherapy in 76% of prescriptions or 26 patients. The dosage found in 74% of cases is the optimal dose of 20 mg per day. Ebixa ® cp 10mg is administered to a patient with dementia with Lewy bodies. This indication is not included in the Summary of Product Characteristics. Ebixa ® in the indication of Alzheimer's disease is found in combination, associated with Exelon ® only once on the 34 requirements. A patient receives Ebixa ® while he just suffers from a light stage of the disease. Treatment was instituted for a patient with a MMSE less than 2. 35% of patients have a dosage not suitable to their renal function. Finally, 82% of prescriptions contain at least one psychotropic drug. The most psychotropic drugs are found psychoanaleptics followed. In total, 25 out of 34 prescriptions include at least one non-compliance with the latest recommendations of the HAS of March 2008. Discussion: The national problem of homogenization of the prescriptions of anti-Alzheimer's led to the drafting of the HAS recommendations. The work carried out reflects the current difficulty to establish a protocol for the care of patients suffering for neurodegenerative diseases. Anti-alzheimer's are regularly prescribed without taking into account their clinical or pharmacokinetic data. Thus, adaptation according the renal clearance is often overlooked and sometimes the optimal dose is not reached because of adverse reactions. This remark reflects the current lack of medical knowledge about treatments and their adverse reactions. Non-conform practices found during this study reflect the data. The prescription of anti-Alzheimer's is not justified in pure vascular dementia or in other dementia undiagnosed precisely. The MMSE is a simple tool to establish a first cognitive assessment for a patient. This questionnaire rated from 1 to 30 points enables to graduate the disease (light, moderate, severe). Anticholinesterases are indicated for light to moderate Alzheimer's disease. Ebixa ® is indicated for moderate to severe forms of AD, however, it is unnecessary to initialize a treatment with anti-Alzheimer's when the MMSE is less than 2. The average stage is moderate, it is therefore surprising that Ebixa ® is found in 76% of prescriptions. The optimal dose of Ebixa ® is 20 mg when the patient has no renal failure but have to be reduced to 10 mg during a severe renal insufficiency. The institutional policy found in the program \"Better Prescribing for the Elderly \" says that psychotropic medication must be prescribed at minimal level to the elderly because of increasing risk of falls and have to be reassessed periodically (for instance: \"Get Up and Go Test"). Prolonged use of this drug class may also be the cause of cerebrovascular accidents of elderly. It is also not recommended to combine them with anti-Alzheimer's because of the increase in extrapyramidal disorders, liver disorders and their anticholinergic effects. However, behavioral problems are frequently encountered in patients suffering from neurodegenerative diseases. Thus, despite the instructions for proper use, the use of a psychotropic drug is often the most effective solution to overcome active disorders in particular. The introduction of treatment is mainly performed during a hospital stay. This data demonstrates the diagnosis difficulties in city due to the lack of specialists. The large number of prescriptions with at least one non-compliance with the recommendations of the HAS (25/34) explain the disparity of care for patients with cognitive disorders. Conclusion: The right prescription of anti-Alzheimer's remains still difficult to interpret. Indeed, treatments currently on the market are not curative but symptomatic and sometimes their use is empirical and not based on a scientific consensus. Nevertheless, to fullfil the aim of an improvement and to suit the recommendations, corrective actions and information of our consultant physicians will be established. The study will be repeated in 6 months and 1 year.

P23 - EXAMINING RECRUITMENT IN A PHASE II MULTISITE INDUSTRY-SPONSORED INTERVENTIONAL TRIAL IN MILD-TO-MODERATE ALZHEIMER'S DISEASE. J.D. GRILL[1], D. ELASHOFF[1], J. HAZEL[2], R. BERMAN[2], V. CORIC[2] *(1. Mary Easton Center for Alzheimer's disease Research at UCLA, Los Angeles, CA, USA; 2. Bristol-Myers Squibb Research & Development, Wallingford, CT, USA)*

Introduction: Clinical trials in Alzheimer's disease (AD) struggle to enroll, with most failing to meet their recruitment timelines. Research is needed to understand factors that impact site enrollment and retention. Identification of modifiable factors that impact enrollment may enhance AD trial recruitment through alternate study designs or improved trial conduct. Objectives: To examine the impact of site-related factors on clinical trial recruitment, retention, and other study outcomes from one multisite Phase II AD trial. Materail and methods: BMS-013 was a phase II, multicenter, double-blind, 5-arm placebo-controlled study of a gamma secretase inhibitor, BMS-708163, in patients with mild-to-moderate AD (ClinicalTrials.gov id#NCT00810147). The primary study objective was to assess the safety and tolerability of BMS-708163 in patients with mild-to-moderate AD. Four doses of BMS-708163 were tested against placebo. Among 41 study sites, 35 were in the US and 6 were international (Sweden, Finland, Denmark). Patients age 50-90 who met NINCDS-ADRDA criteria for AD and scored within the range 16-26 on the MMSE at screen were eligible. Patients were excluded for cognitive impairment due to some other cause, a history of stroke (MRI required within 12 months or one was performed in the screen window), or concomitant medications that might interact with BMS-708163. The risks discussed in the informed consent document included possible gastrointestinal complications associated with the therapy under study. At study initiation, the treatment period was 12 weeks, followed by a 12-week washout. In-study protocol amendments subsequently extended the treatment period to 24 weeks and discontinued the washout period. Study visits were conducted every-other week. Standard laboratory, clinical, and cognitive outcome measures (e.g. ADAS-cog, MMSE, CDR, Trails, Category and Letter Fluency tests, Digit Span Forward and Backward, ADCS-ADL) were performed. Optional substudies utilizing MRI and CSF biomarker outcomes were conducted. Quantitative analyses of trial enrollment data are ongoing. The total enrollment (number baselined) and enrollment rate (number baselined per month of open enrollment) of each site will be considered. Specific factors such as the type of site (academic vs commercial) and the type of IRB utilized (local vs. central) will be examined for effects on total enrollment and enrollment rate. The demographic characterization of enrolled subjects will be analyzed. Longitudinal analyses will assess study completion and placebo decline. Results: BMS-013 was conducted from February 2009 through June 2010. 338 mild-to-moderate AD subjects signed informed consent (or had consent provided by a legally acceptable representative) and 209 were successfully randomized. Enrollment was completed about 1 month ahead of an anticipated 8-month recruitment timeline. Among those enrolled, 141 subjects completed the trial. Further analyses are ongoing, results are pending and will be presented. Discussion: Late phase multicenter trials in AD enroll large patient populations, necessitating many sites to complete recruitment. Larger trials bring greater challenges, such as increased regulatory burden and potential for site variance in study conduct and results. This analysis is intended to guide the development of future AD clinical trials. Conclusion: BMS-013 is a unique AD clinical trial in that it completed enrollment ahead of schedule.

P24 - ESTIMATING SAMPLE SIZES FOR PREDEMENTIA ALZHEIMER'S DISEASE CLINICAL TRIALS BASED ON THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE. J.D. GRIL[1], L. DI[1,3], D. ELASHOFF[1,3], P.H. LU[1], O. KOHANNIM[2], L. APOSTOLOVA[1], J.M. RINGMAN[1], J.L. CUMMINGS[4], P. THOMPSON[2] AND THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE *(1. Mary Easton Center for Alzheimer's Disease Research; 2. Laboratory of NeuroImaging, Department of Neurology; 3. Department of Medicine Statistics Core, University of California, Los Angeles, David Geffen School of Medicine; 4. Lou Ruvo Institute for Brain Health, Cleveland Clinic, Las Vegas, NV, USA)*

Introduction: No treatment has been demonstrated to slow Alzheimer's disease (AD) progression. To date, most AD clinical trials have enrolled only persons meeting criteria for dementia. As AD pathology precedes dementia diagnosis by years, investigational drugs may have greater efficacy when tested in predementia populations, for whom pathological burden of disease is less. Objectives: To examine the sample sizes needed for predementia trials using various primary cognitive outcome measures and enrolling populations enriched at baseline through genetic and biomarker strategies, based on longitudinal data from the initial phase of the AD Neuroimaging Initiative (ADNI I) study. Material and methods: We modeled clinical trials in cognitively normal and mild cognitive impairment (MCI) populations, using longitudinal data from the ADNI I. Because, as yet, the US Food and Drug Administration will not approve medications based on surrogate markers for AD, we focused on cognitive outcome measures. Sample sizes were estimated using sample size/arm = $2(u + v)2 \times (2\sigma 2)/(\Delta\mu)2$ where u = 0.841 to provide 80% power; V = 1.96 to test at the 5% level; $\Delta\mu$ is the change in annualized percentage cognitive decline; and σ is the SD of rates of change in the groups (assuming SD is the same in treatment and placebo groups). Sample size needs for trials of 12, 24, and 36 months were assessed using the mean population change at each time point. We examined sample sizes needed for trials using the following cognitive outcome measures: the AD assessment scale-cognitive subscale (ADAS-cog); the Mini-Mental Status Examination (MMSE); the Clinical Dementia Rating Scale-sum of boxes (CDR-SB); the Rey Auditory Verbal Learning Task (RAVLT, total learning score and delayed recall score); the Trails A and B tests; category fluency (animals); the digit span backward test (maximum length and total correct scores); the Boston Naming Test; and the Wechsler Logical memory II (delayed paragraph recall). We examined how trial sample sizes were impacted by enrichment of the population at baseline. Enrichment strategies included carrier status for the apolipoprotein E (ApoE) genotype ε4 allele and various cerebrospinal fluid (CSF) protein analysis criteria, including: amyloid β1-42 (Aβ1-42) < 192 pg/mL; total Tau (tTau) > 93 pg/mL; Tau phosphorylated at threonine 181 (pTau) > 23pg/mL; ratio of tTau/Aβ1-42 > 0.3; and ratio of pTau/Aβ1-42 > 0.1. Results: The population enrolled as normal in ADNI I demonstrated progressive mean worsening at 12, 24, and 36 months only on the CDR-SB. Mean worsening at 36-months, relative to baseline, was observed for the CDR-SB (0.23 ± 0.82), MMSE (-0.10 ± 1.38), RAVLT total score (-3.77 ± 8.91) and RAVLT delayed recall score (-0.74 ± 3.49). The sample sizes of trials using these outcomes calculated based on populations enriched for the ApoE ε4 genotype or for CSF biomarkers indicative of AD at baseline were numerically lower than those observed using the entire ADNI I normal population. For example, a 36-month trial at 80% power using the MMSE based on the entire normal population required 50,790 participants/arm to demonstrate a 25% drug effect, whereas the same trial enriched for CSF Aβ required 8114 participants/arm. Trials based on all of the available MCI data that used the ADAS-cog and CDR-SB would

require 1046 and 458 participants/arm, respectively, to demonstrate a 25% drug effect at 24-months. Enriching for ApoE ε4 carriers reduced the needed sample sizes for 24- and 36-month trials using all assessed outcome measures, except for the Wechsler Logical Memory II (at 24-months). For example, a 24-month trial of ApoE ε4 carriers using CDR-SB as a primary outcome would require a sample size of 338 participants/arm. Enrichment through CSF criteria similarly reduced the necessary sample sizes for all trial outcome measures, with the exception of the Wechsler Logical Memory II at 24-months. A 24-month trial enriched for low CSF Aβ using CDR-SB as a primary outcome would require 372 participants/arm. Among the examined enrichment strategies, no single strategy consistently produced the lowest trial sample sizes across outcome measures for any length trial. For all trial lengths and enrichment strategies, the CDR-SB required the smallest samples sizes among the outcome measures examined. Discussion: Enrichment strategies for predementia AD clinical trials are likely to reduce the needed number of study participants, even if trials use cognitive measures as primary outcomes. Further research is needed to determine if preclinical trials, enrolling cognitively normal participants who are positive for a biomarker of AD, are feasible. A variety of strategies are likely to be effective for enriching MCI populations; those that produce the least burden on subject recruitment should be considered first. Conclusion: Predementia clinical trials can be improved by enriching the enrolled population.

P25 - WHAT PROMISING RECRUITMENT STRATEGIES PROMOTE CONTINUED PARTICIPATION IN ALZHEIMER'S DISEASE PREVENTION TRIALS? L.E. JACOBSON, H.M. BLAZEL, C.E. GLEASON, S.C. JOHNSON, M.A. SAGER, K.M. PATERSON, S. STHANA, C.M. CARLSSON *(University of Wisconsin, Madison, WI, USA)*

Introduction: Alzheimer's disease (AD) will affect an increasing number of older adults in the coming decades unless effective preventive strategies are developed. At the Wisconsin Alzheimer's Disease Research Center (ADRC), the SHARP Study is currently underway to identify potential AD prevention strategies in middle-aged adults at increased risk for AD. Subject participation and retention is essential for trial success. Objectives: To identify factors promoting enrolment and retention in AD prevention trials by evaluating recruitment barriers and promising outreach strategies. Material and methods: The SHARP study is an NIH-funded, 18-month, randomized, double-blind, controlled trial assessing the effects of simvastatin vs. placebo on AD biomarkers and cognition in middle-aged adults with a parental history of AD. SHARP study visits are conducted at a university-based hospital in Madison, Wisconsin. Enrolled participants complete nine visits which include blood draws, MRI scans, brachial artery ultrasounds, lumbar punctures and neuropsychological testing. We sorted all potential participants into two groups (enrolled vs. declined) and evaluated factors that may have influenced their decision to participate or not, including: ineligibility, aversion to lumbar puncture (LP) or to taking medication, distance travelled, time constraints, or unknown/lost contact. For all contacts, we determined how they heard of the study. Results: Of 204 persons approached (mean age 54 y, 75% female), 66 participants enrolled in the trial (mean age=54, 76% female) (goal n=90). Participants tended to travel greater distances than those who declined participation (median 57 miles travelled for participants vs. 14 miles for those who declined [P=0.090]). The primary reason participants declined the study was ineligibility 37% (P= 0.001). When compared to aversion to LP, medication usage or unknown/lost contact, a statistically significant number of participants did not participate due to eligibility criteria (P=0.001). There was no difference shown when comparing the number ineligible to those who declined due to time (P=0.250). The majority of SHARP participants heard of the study through a program sponsored event 27%. Of all participants that heard of SHARP through previous participation at the center, 65% enrolled in SHARP (P=0.001). Total, 23% of enrolled participants heard of us this way. Potential participants that heard of the study through clinic, referral, web or print advertisement were not more likely to enroll or decline. Discussion: Subject participation and retention is essential for trial success. By assessing the reasons that participants declined the study and determining the method they learned of the study, our group hopes to design futures studies in a manner that promotes continued participation in these trials. Conclusion: Distance from the center is not a significant recruitment barrier, while program familiarity increases likelihood of participation. These data promote effective recruitment by evaluating barriers and revealing underutilized advertising methods. We recommend further assessment of participant satisfaction and motivation in order to identify factors promoting continued participation in AD prevention trials. Possible techniques to overcome barriers may include fewer study visits and web based "remote" visits.

P26 - PROTOCOLS FROM HELL: A REVIEW OF DIFFICULTIES IN CONDUCTING CLINICAL TRIALS IN ALZHEIMERS DISEASE. S. KURRLE, R. HOGARTH *(Hornsby Ku-ring-gai Hospital, Hornsby, Australia)*

Introduction: Designing clinical research studies involving subjects with impaired cognition requires a specific skill and knowledge set. Over the past 10 years several disquieting trends have been observed within the field of sponsored global trials in Alzheimer's disease with respect to study design, and demands on subjects, study partners, and research staff. The globalisation of clinical trials has provided many opportunities for the standardisation of trial processes, the acceptance of ICH-GCP and international credentialing. The down side of globalisation is the "one size fits all" approach by sponsors. Experienced researchers know that this is not always the case; consent, privacy and injury insurance for example can differ considerably between countries and even within the states or provinces of the same country. Objectives: To present a snapshot of the difficulties of conducting clinical trials in dementia, from protocol design to study completion, focusing on the issues raised by subjects, study partners, investigators and study coordinators currently involved in multi-centre dementia drug trials in Australia. Material and methods: All dementia study coordinators in Australia were invited to contribute by submitting a list of issues which they had observed or experienced while conducting clinical trials with dementia subjects. Caregivers of subjects were also invited to comment on study procedures. Investigators contributed with feedback and submission of further issues following a presentation of this work at the annual meeting of the Australasian Consortium of Centres for Clinical Cognitive Research (AC4R). Results: Issues Identified by Investigators and Coordinators: 1. Length and complexity of language of consent forms; 2. Frustration from study staff with continual need for re-training; 3. Number of study procedures per visit; 4. Lack of suitability of psychometric tests for subjects; 5. Number of psychometric tests per visit; 6. Lengthy MRI sequences; 7. Collection of urine samples; 8. Wasted resources; 9. Surprise activities. Issues Identified by Caregivers and Subjects: 1. Number of study visits; 2. Length of each study visit; 3. Repetitive questionnaires; 4. Presentation and packaging of study drug; 5. Child proof containers. Discussion: A number of concerns have been raised in this project. Of particular concern is the length (up to 26 pages) of patient information and consent forms. Clearly a person with cognitive impairment sufficient to meet study inclusion criteria would be unable to understand the contents of many of the consent forms reviewed. The onerous nature and length of study visits was also of concern with subjects clearly fatiguing later in the day, and performing less well. Surprise activities requested by the sponsor included the need to photocopy and fax to the US all subjects' cognitive assessments to allow an assessment of inter-rater reliability to occur. Conclusion: This project presents an overview of current problems impacting on the conduct of research in the field of Alzheimer's disease. Problems reported were consistent between all the investigators and coordinators and across many different protocols. Wider consultation between sponsors, experienced investigators and study coordinators could lead to reduced costs, and higher subject retention rates with the design of protocols tailored to suit the target population.

P27 - STATISTICAL CONSIDERATIONS FOR DESIGNING A LONGITUDINAL CLINICAL TRIAL IN EARLY (PRODROMAL) ALZHEIMER'S DISEASE SUBJECTS. Y. PENG, M. RYAN *(PFIZER Inc, Collegeville, PA, USA)*

Introduction: Though the majority of Alzheimer's Disease (AD) clinical trials are conducted in subjects with mild to moderate dementia, it has been recognized that the optimal time to intervene with treatments may be at an earlier stage. This timing may be especially true for experimental therapies that have the potential to change the underlying disease progression, years before the onset of dementia. Emerging longitudinal data have suggested that imaging or CSF biomarkers may be valuable tools for helping to select the target patient population that is most likely to progress over the course of a clinical trial. Objectives: To quantify the impact of baseline CSF biomarker levels on disease progression of early AD subjects via clinical evaluations such as CDR-SB, ADAS-Cog, and Functional Activities Questionnaire (FAQ), and further to explore its impacts on clinical trial design if subjects are selected based on CSF biomarker enrichment criteria (LM Shaw et al, 2009). Material and methods: Based on recent data extracted from the ADNI data base, we explore the potential impact on the study design of a longitudinal clinical trial if subjects are selected based on CSF biomarker enrichment criteria. The effects of these CSF enrichment criteria are compared on clinical efficacy outcomes including the CDR-SB, ADAS-Cog 13-item version, and Functional Activities Questionnaire (FAQ). Results: For a clinical study with 24-month follow-up, the standardized CDR-SB mean change from baseline at Month 24 increases from 0.74 with all MCI subjects included to 0.97 if only those MCI subjects included when the baseline ratio of Total Tau to CSF Abeta is greater than 0.39, increases from 0.56 to 0.70 for ADAS-Cog 13 total score, and increases from 0.89 to 1.15 for the FAQ. Consequently, a 24-month study designed to detect an effect size of 30% reduction in disease progression could require 35%-40% fewer subjects if the biomarker enrichment criteria are applied to select subjects. Results will be presented based on various biomarker selection criteria, clinical endpoints and study durations. Results will be discussed in the context of the observed declines in historical large-scale clinical trials on similar patient population. Discussion: Results and conclusion presented are based on a single data set from the longitudinal observational ADNI study where study participants could be different comparing to those from a typical clinical trial setting with experimental treatment involved. Also for a multi-center large scale clinical trial, it could be a challenge to assure the assay sensitivity so that subjects will be selected consistently regardless which laboratory or assay is used to process the biomarker data. Operationally, selecting subjects into a clinical trial based on baseline biomarker information will likely increase the screen fail rate, therefore prolong the overall study duration. Data from real clinical trials will provide valuable information for direct assessments of the overall impacts of incorporating baseline biomarker information in clinical development for early AD subjects. Conclusion: Using CSF biomarker to select target subjects should help effectively 1) reduce study sample size and 2) shorten treatment duration required with an adequate power under a proof of concept type clinical study setting. It could ultimately help a faster readout of the study result, and accelerate decision making clinical developments.

P28 - WHICH ARE THE REASONS TO NOT INCLUDE AD PATIENTS IN CLINICAL TRIALS? A. ROLLIN-SILLAIRE[1,2], L. BREUILH[1,2], N. JOURDAN[1,2], F. PASQUIER[1,2] *(1. Université Lille Nord de France, UDSL, EA 1046, F-59000 Lille, France; 2. Memory Clinic, Lille University Hospital, F-59000 Lille, France)*

Introduction: Given its very high prevalence, dementia is a major public health problem. Current treatments for Alzheimer disease (AD) are not disease modifiers and have shown only modest effects with reduction of symptoms. New medication

developments for disease modification are an urgent need for society and clinical trials are indispensable. However few AD patients are included in clinical trials because of several factors (e.g. age, absence of study partner). Objectives: The objective of this study was to assess the different reasons why AD patients are not included in clinical trials.Material and methods: The Lille Memory Clinic database was reviewed in 2009 to select all patients suitable for inclusion in four AD clinical trials (named A, B, C and D). A first selection was made according to four criteria: (i) diagnosis of AD with or without white matter lesion, (ii) age, (iii) MMS score and (iv) symptomatic treatment of AD (cholinesterase inhibitor and/or memantine) authorized or not by clinical trial. Patients could be selected for several clinical trials. Then, data of patients fulfilling these criteria were reviewed with all inclusion/exclusion criteria of the four clinical trials performed in 2009 at the Memory Clinic. Every reason for exclusion was listed. Results: From the first selection, 205 patients were selected among 1833 patients: 202 for clinical trial A, 188 for clinical trial B, 26 for clinical trial C and 42 for clinical trial D. Then, from the second selection, the reasons not to include patients in clinical trials were: abnormalities on MRI scans (56.9%) mainly white matter lesions (93.3%) then lacunar infarct (11.3%), medication not authorized (37.3%), absence of study partner (37.1%), not authorized associated disease (24.4%), contraindication to perform MRI (9%), patient's institutionalization (8.3%), change of diagnosis with time (3.9%), visual/auditory impairments (2.9%), alcohol consumption (2%), low education level (1%) and biological abnormalities (0.49%). Concerning the willingness to participate to clinical trial, 58 patients (28.3%) wanted to participate and 10 (4.9%) have declined. From the first selection, 8 patients (4%) were finally included in the clinical trial A, 4 patients (2%) were finally included in clinical trial B, 4 patients (15.4%) were finally included in clinical trial C and 1 patient (2.4%) was finally included for the clinical trial D. Discussion: A high proportion of AD patients presented with vascular abnormalities on MRI scan (white matter lesion, lacunar infarcts, territorial infarction), which could be expected by: (i) selection of patient from the database â€"diagnosis of AD with or without white matter lesion- and (ii) frequent cerebrovascular pathology associated with AD given previous epidemiologic studies. The presence of study partner is an essential factor to patient's participation in trials because of primary and secondary outcomes. The prohibition of symptomatic treatment of AD reduces the number of patients eligible for clinical trials. Conclusion: To increase the number of AD patients who could participate in clinical trials, the main factors to be taken into account when designing large studies are: (i) the presence of white matter lesions and (ii) a symptomatic treatment with a cholinesterase inhibitor and or memantine.

P29 - ASSESSING RELIABILITY OF DISTRIBUTED DATA ENTRY OF THE ADAS-COG IN A MULTICENTERED CLINICAL TRIAL. S. WALTER, D. GESSERT, M. DONOHUE, P. AISEN AND ALZHEIMER'S DISEASE COOPERATIVE STUDY *(University of California at San Diego, San Diego, USA)*

Introduction: The Alzheimer's Disease Assessment Scale - Cognitive (ADAS-Cog) is the most frequently utilized primary outcome measure in clinical trials of Alzheimer's Disease and dementia. Variance within the ADAS-Cog is well documented. Because of this, the Alzheimer's Disease Cooperative Study (ADCS) is working to eliminate other sources of variance by minimizing test errors due to transcription and data entry. Objectives: To examine the impact of an audit of the ADAS-Cog on primary outcome reliability and variance in a multi-centered clinical trial utilizing distributed data entry. Material and methods: Distributed data entry by Electronic Data Capture (EDC) is growing to be the standard in multi-centered clinical trials. The Alzheimer's Disease Cooperative Study (ADCS) has utilized distributed data entry by web-accessible EDC systems since 2004 on nine completed multicenter clinical trials. In order to reduce data errors due to transcription and entry, ADCS data collection and data entry procedures include the following: • Data is collected on standard source documents designed and distributed by the ADCS. • Data is required to be entered by site personnel within 48 hours of collection. • Electronic copies of source documents are uploaded to the ADCS for double-scoring by clinical monitors. • Clinical monitors review every ADAS-Cog comparing source documents against the entries in the EDC. Queries are communicated to sites in real time. The RAGE Inhibitor study, a clinical trial in collaboration with Pfizer, was stopped in August 2010 following an futility analysis based on ADAS-Cog change scores. In December 2010, ADCS Leadership initiated a 100% audit on the primary outcome measure for the RAGE Inhibitor Trial. After the final monitor visit, sites provided copies of each page of the ADAS-Cog worksheets. These were data entered into a separate eCRF by the quality control team at the ADCS Coordinating Center. Timeline of Audit: 12/14/2010 Audit initiated; 1/14/2011 First audit queries generated ; 4/14/2011 Final query resolution; 4/15/2011 Data Lock. Results: The audit evaluated a total of 2200 ADAS-Cog records. There were a total of 2600 fields in 600 records with data entry errors corrected by sites. All discrepancies were corrected prior to data lock. Paper based transcription error rates were 8 per 1000. We are comparing the data prior to the audit to the cleaned final dataset in order to determine whether the audit impacted reliability of the data and test variance. Discussion: How reliable is distributed data entry? Where are the errors most frequently occurring? How can clinical monitoring or quality control processes be adjusted prevent data entry and transcription errors from clouding study outcomes?

P30 - NPT001: A NOVEL THERAPEUTIC APPROACH FOR REDUCING LEVELS OF BOTH B-AMYLOID PLAQUES AND NEUROFIBRILLARY TANGLES IN ALZHEIMER'S DISEASE. R. FISHER, K.S. GANNON, R. KRISHNAN, H. TSUBERY, M. LULU, M. GARTNER, M. PROSCHITSKY, M. BECKER, J. WRIGHT, E. ROCKENSTEIN, E. MASLIAH, D. KIRSCHNER, D. MYSZKA, B. SOLOMON *(NeuroPhage Pharmaceuticals, Cambridge, USA)*

Introduction: Misfolded protein aggregates diagnostic of AD include both extra-neuronal Î²-amyloid plaques and intracellular neurofibrillary tangles (NFTs). The significance of both of these aggregates for behavioral and cognitive deterioration has been established in animal models and implicated in human disease progression. Plaques contain aggregated fibrils of amyloid-Î² (fAÎ²), and NFTs contain aggregated fibrils of microtubule-associated protein tau. Using biophysical and biochemical methods, we show that filamentous bacteriophage M13 directly and potently dissociates a broad class of amyloids, including fAÎ², tau, yeast prions, and alpha-synuclein. Here, we establish a biochemical rationale for M13 binding and dissociation of amyloid fibers, and we show that following a single administration of purified and formulated M13 (NPT001) to several transgenic mouse models of AÎ² or tau pathology, NPT001 mediates both AÎ² plaque and tau aggregate clearance, respectively, producing behavior and cognitive benefits without observed adverse effects. These data indicate that NPT001 has broad amyloid clearance activity. To establish the feasibility of NPT001 administration for human clinical testing, we have been carrying out preclinical efficacy and brain distribution studies. Our data show that NPT001 is a potential candidate for treating a broad array of neurodegenerative diseases involving amyloid accumulation. Objectives: 1. Establish a biochemical rationale for NPT001-mediated amyloid fiber remodeling and dissociation; 2. Measure potency and efficacy of NPT001 in vitro. 3. Test NPT001 efficacy in transgenic neurodegenerative disease models of protein misfolding. 4. Based on preclinical data, determine the feasibility of clinical testing of NPT001 in Alzheimer's disease patients. Material and methods: Biochemical and biophysical assays for assessing interactions between M13 and amyloid fibers (fAÎ², tau, alpha synuclein) included: (1) surface plasmon resonance (SPR) binding, (2) thioflavin T (ThT) fluorescence emission, (3) X-ray fiber diffraction, (4) quantitative amyloid fiber filter retardation, and (5) differential detergent solubility. In addition, we have devised a novel M13-amyloid fiber binding assay, based on co-pelleting of fluorescently labeled M13 bound to amyloid fibers. Transgenic animal models for testing AÎ² plaque, tau aggregate, and alpha synuclein aggregate reductions after intracranial injection (IC; 2 Î¼L intrahippocampus) or continuous intracerebroventricular (ICV) infusion of NPT001, include hAPP models (PDAPP, APP751, Tg2576); tauP301L model (Tg4510); and human alpha synuclein overexpression (LineD) model, respectively. Hyperactivity and Y-maze tests assess behavior and spatial memory. Measures for fAÎ² and tau aggregate reductions, M13-AÎ² co-localization, cellular activation, and microhemorrhage detection used established immunohistochemistry and neuropathology techniques. Results: Direct, high affinity M13 binding to fAÎ² (KD=4nM) was shown by SPR. Consistent with its binding affinity, M13-mediated fAÎ² dissociation EC50 is low nanomolar, shown by loss of x-ray fAÎ² diffraction and by reduction of amyloid ThT fluorescence. Dose- and time-dependent amyloid fiber dissociation are shown by quantifying loss of filter retention and increased detergent solubility of M13-treated fibers. The temperature dependence of NPT001-amyloid interactions suggests that the mechanism of amyloid dissociation is through hydrophobic interactions. Consistent with these in vitro data, we demonstrate in vivo co-localization of administered M13 and brain plaque, and potent NPT001-mediated reduction of AÎ² plaque (40%-70%) and tau (50%) without adverse effects within 7 days after a single IC administration into various transgenic mouse models. Immunohistochemistry following NPT001 treatments shows modest transient microglia activation (Iba1), but no evidence for astrocyte activation (GFAP) or microhemorrhage (iron stain). Rodents show striking M13 brain distribution and excellent tolerability after NPT001 administration. Primate studies are ongoing. Discussion: A biochemical explanation of the observed protein aggregate reducing activities of NPT001 in transgenic models is based on the observed potent and avid binding between M13 and AÎ². SPR binding and a novel co-pelleting binding assay produce comparable KD values of 4 nM and 7 nM, respectively. Binding is concentration, time, and temperature dependent, and heat-treated M13 has 3-fold lower binding, based on competition binding assays. The observed binding KD is consistent with NPT001 efficacy in fiber dissociation activity assays (filter retardation, Xray fiber diffraction, and detergent solubility assays). Within 1 week following single NPT001 dose administration to brains of transgenic mouse models for tauopathy and Alzheimer's disease, significant (>50%) tau and AÎ² aggregate reductions. Following NPT001 treatments, no observed increase in astrocyte activation or microhemorrhage is found, although a transient increase in microglia activation (Iba1) occurs. We hypothesize that NPT001 mechanism of aggregate clearance is mediated both by the amyloid fiber binding and remodeling activities measurable in vitro, as well as an immune component, mediated by microglia uptake and subsequent degradation of NPT001-amyloid complexes. We are currently testing for microglia clearance in cell culture models. Brain distribution and safety margin data during NPT001-mediated amyloid reduction in animal models suggests that human testing will be feasible. Conclusion: NPT001 is a novel approach for reducing brain AÎ² & tau loads, a potential treatment strategy for Alzheimer's disease. We are planning a Phase 1 test of safety and activity in AD patients that will include PET imaging for AÎ² plaque load before and after administration of NPT001. NPT001 has broad activity for mediating dissociation of misfolded protein aggregates, which suggests that other neurodegenerative diseases with amyloid pathology are potential therapeutic targets.

P31 - IMPACT OF INITIATION OF TREATMENT WITH MEMANTINE OR CHOLINESTERASE INHIBITORS (CHEI) ON THE USE OF PSYCHOTROPIC DRUGS: ANALYSIS OF RAMQ DATABASE. J. LACHAINE[1], C. BEAUCHEMIN[1], A. CROCHARD[2], S. BINEAU[3] *(1. Faculty of Pharmacy, University of Montreal, Montreal, Quebec, Canada; 2. Market Access Department, Lundbeck SAS, Issy-Les-Moulineaux, France; 3. Global Outcomes Research Division, Lundbeck SAS, Issy-Les-Moulineaux, France)*

Introduction: Patients with Alzheimer's disease (AD) show a high incidence of behavioural and psychological symptoms (BPS) which have a great impact on the quality of life of both patients and caregivers and often lead to the prescription of psychotropic drugs and specially neuroleptics. Though neuroleptics use has been associated with cerebrovascular morbidity and mortality. These drugs are not recommended for treatment of elderly demented patients and they are contra-indicated in this patient population in the United States. Memantine and ChEIs (donepezil, galantamine, rivastigmine) are prescribed in Canada for the treatment of AD and reimbursed by the Quebec provincial health plan (RAMQ) as a monotherapy for patients with moderate to severe AD or mild to moderate AD respectively. A study based on a French Health Insurance database (CNAMTS) demonstrated that using memantine allows to stabilize the consumption of psychotropic drugs and anti-psychotics in particular. The purpose of this study was to address the same question but in another setting and adding other antidementia treatments, the ChEIs. Objectives: The objective of the present study was to assess in real life practice the impact of the initiation of treatment with memantine or ChEIs on the use of psychotropic drugs. Material and methods: A retrospective analysis of prescription claims from the RAMQ database was conducted. Data on medical services and pharmaceutical prescriptions were obtained for the period from 2003 to 2009 for a first random sample of patients who received at least one prescription of memantine (memantine cohort) and a second random sample of patients who received at least one prescription of a ChEI (ChEI cohort). Trends in the proportion of patients receiving at least one psychotropic drug, neuroleptics, antidepressants and anti-anxiety agents were estimated one year before and after the first prescription of memantine or a ChEI. Trends before and after initiation of treatment with memantine or a ChEI were tested for statistical differences using an ANCOVA analysis. Results: Data were obtained from the RAMQ database for a total of 2,007 patients (mean age 82.2 years) in the memantine cohort and of 2,026 patients (mean age 76.7 years) in the ChEI cohort. The proportion of females was 67.6% in the memantine cohort and 67.4% in the ChEI cohort. Memantine cohort: The proportion of patients using at least one psychotropic drug in the year preceding initiation of memantine increased by 58.5%, from a proportion of 0.45 to 0.71. This proportion only increased by 3.5% (0.71 to 0.74) in the year following initiation of memantine. Whatever the psychotropic drug considered (neuroleptic, antidepressant, anti-anxiety agent), the prescription of memantine slowed in a statistically significant manner the growth of its use. Focusing on the neuroleptics, the proportion of patients using the drug one year prior to initiation of memantine, on the month of initiation and one year after initiation, rose from 0.219 to 0.465 then to 0.474, meaning growth rates of 112.2% before memantine initiation vs. 1.9% after (p=0.01). For antidepressants, the proportion rose from 0.239 to 0.354 then to 0.364 (48.3% vs 2.8%, p=0.01). For anti-anxiety agents, the proportion rose from 0.175 to 0.247 then to 0.251 (41.3% vs. 1.5%, p=0.01). ChEI cohort: The proportion of patients receiving at least one psychotropic drug in the year preceding initiation of a ChEI increased by 17.7%, from a proportion of 0.40 to 0.47. This proportion increased by 20.2% (0.47 to 0.56) in the year following initiation of treatment with a ChEI. Contrary to what was observed with memantine, no statistically significant growth rate difference was found for the use of neuroleptics, antidepressants and anti-anxiety agents before vs. after initiation of a ChEI treatment. Thus the proportion of patients receiving a neuroleptic one year prior to ChEI initiation, on the month of initiation and one year after initiation, rose from 0.05 to 0.09 then to 0.17, corresponding to an increase rate of 87.6% before ChEI initiation vs 86.2% after. For antidepressants, the proportion rose from 0.22 to 0.26 then to 0.33 (19.9% vs. 28.0%). For anti-anxiety agents, the proportion rose from 0.257 to 0.261 then to 0.277 (1.9% vs. 6.0%). Discussion: MMSE scores are not included in the RAMQ database, but it is highly probable that the 2 populations studied did not have the same severity; the indication for ChEI being less severe (mild-moderate) than for memantine (moderate-severe). AD severity is associated with an increasing prevalence of BPS and even though not recommended, neuroleptic drugs are used to control the BPS. As expected, data showed a higher proportion of patients receiving neuroleptics 12 months prior to initiation of treatment with memantine than with a ChEI (0.22 vs 0.05 respectively) with an even greater growth over the 12 month period before memantine than before ChEI (112.1% vs. 87.6%). Drug use levels and evolution for the other psychotropics were fairly similar between the two groups during the pre-initiation period. Over the 12 months following initiation of a specific anti-dementia treatment, the prescription dynamics of psychotropic drugs differed substantially between the 2 cohorts and this was of particular interest for neuroleptics. After the initiation of the prescription of memantine, the growth rate of the proportion of patients receiving a psychotropic drug decreased significantly for all psychotropic drugs studied over the following 12 months with a pre-initiation growth rate of 58.5% vs. 3.5% after. The stabilization effect was the greatest for neuroleptic use shifting from 112.1% to 1.9%. On the contrary, in the ChEI group, the proportion of patients receiving at least one psychotropic drug continued to increase with a dynamic that was equivalent to prior ChEI initiation with 17.7% before vs 20.2% after. This was true for all psychotropic drugs including neuroleptics for which pre-initiation increase rate was 87.6% vs 86.2% post-initiation. Conclusion: The results of this analysis of the RAMQ database : - confirmed that the initiation of memantine has a notable stabilization effect on the prescription of psychotropic drugs and neuroleptics in particular, like it had already been shown in a study with French Health Insurance database, - showed that such an effect was not found with a ChEI. Funding for this study was provided by Lundbeck SAS

P32 - COMBINATION MEMANTINE WITH ACETYLCHOLINESTERASE INHIBITOR DELAYS THE ADMISSION OF ALZHEIMER'S DISEASE PATIENTS TO NURSING HOME: COST-EFFECTIVENESS ANALYSIS IN FRANCE. J. TOUCHON[1], J. LACHAINE[2], C. BEAUCHEMIN[2], A. CROCHARD[3], B. RIVE[4], S. BINEAU[4] *(1. Faculty of Medicine, University of Montpellier, France; 2. Faculty of Pharmacy, University of Montreal, Montreal, Quebec, Canada; 3. Market Access Department, Lundbeck SAS, Issy-Les-Moulineaux, France; 4. Global Outcomes Research Division, Lundbeck SAS, Issy-Les-Moulineaux, France)*

Introduction: Alzheimer's disease (AD) is a neurodegenerative disease that in 2003 was estimated to affect 7.8 million people across Europe. A long-term French cohort study (PAQUID) has estimated that the prevalence of dementia in France in people aged 75 or over is 17.8%, with AD being the cause in 79.6% of cases. AD is mainly characterized by memory loss, difficulty in performing daily activities as well as mood and behaviour changes. The available medications to treat AD are the Cholinesterase inhibitors (donepezil, rivastigmine and galantamine) and the NMDA receptor antagonist memantine (MEM). The combination MEM and Cholinesterase inhibitor (ChEI) is associated with significant clinical benefits in terms of cognitive function, ability to perform daily activities, mood and behaviour compared to a ChEI alone. A recent observational study by Lopez et al. showed that combining MEM with ChEI treatment significantly delayed the admission to nursing home in patients with AD. Objectives: To evaluate in the French setting the cost-effectiveness of the combination memantine with Cholinesterase inhibitors compared to ChEI monotherapy in Alzheimer's disease patients. Materail and methods: A cost-effectiveness analysis employed a 3-state Markov model ("non-institutionalized", "institutionalized" and "dead") and compared the treatment alternatives in terms of time to nursing home admission, Quality Adjusted Life Years (QALYs) and costs over a 7-year time horizon. Annual transition probabilities between states were derived from two observational cohort studies: Lopez et al 2010 (US) for institutionalisation probabilities and Helmer et al 2001 (FR) for death probabilities. Costs were valued from healthcare system and societal perspectives, and included cost of AD medications (French National Health Insurance database, 2009), costs of care in community and in institution (French National Assembly on AD management, report 2005). Results were reported in EUR 2010. Health-related utilities were obtained from a published economic evaluation in AD (Getsios et al 2001). Costs and QALYs were discounted at annual rates of 0% (base-case analysis), 3% and 5%. Deterministic and probabilistic sensitivity analyses were carried out to test the robustness of model assumptions. Results: Over the seven-year time horizon, patients treated with ChEI monotherapy spent on average 41.6 months before institutionalisation. Overall costs were â,¬74,576 (healthcare system perspective) or â,¬92,406 (societal perspective). QALYs were estimated at 2.36. The combination memantine with ChEI was associated with a longer time to nursing home of 8.9 months, QALYs gains of 0.19 and a cost saving of â,¬6,256 (healthcare system perspective) or â,¬2,471 (societal perspective), i.e. a dominant treatment scenario versus ChEI monotherapy. Discussion: This economic evaluation is the first to demonstrate that, in the French setting, time to nursing home admission has a significant impact upon the cost-effectiveness of different treatments for AD. These results are in line with those found in the first application of the economic model, which was conducted in a Canadian setting. Nevertheless the model does possess certain limitations due to the assumptions necessary for its design. We made the hypothesis that there was a lifetime duration of treatment. Risk of death was derived from the PAQUID study and was assumed to be constant over time. Then it was also assumed that utility values associated with institutionalization and non-institutionalization of French AD patients are comparable to those found in the study by Geistos et al, which was conducted in the United States. Furthermore, the death rates used were for dementia patients, which were assumed to be equivalent to Alzheimer's patients. Finally nursing home dynamics in France are assumed to be comparable to those found in the study by Lopez et al, which was conducted in the United States. However, despite the limitations of the model, the sensitivity analyses confirmed the robustness of the base-case results. Conclusion: This economic evaluation suggests that, from both a healthcare system and a societal perspective, the combination memantine with ChEI is a cost-effective strategy in the management of AD patients compared with ChEI monotherapy. Funding for this study was provided by Lundbeck SAS

P33 - THE TACRINE DERIVATIVE 7-MEOTA IN THE TREATMENT OF AD. O. SOUKUP[1,2], J. PATOCKA[4], J. ZDAROVA-KARASOVA[1,2], M. POHANKA[1,3], D. JUN[1,3], K. KUCA[1,3] *(1. University hospital of Hradec Kralove, Czech Republic; 2. Department of Toxicology; 3. Center of Advanced Studies, Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic; 4. Department of Radiology and Toxicology, Faculty of Health and Social Studies, University of South Bohemia Ceske Budejovice, Czech Republic)*

Introduction: Alzheimer disease (AD) is progressive neurodegenerative disease with unknown etiology. There are various hypotheses concerning pathophysiology of the disease. One of them is the cholinergic hypothesis, where the cholinergic transmission mediated by acetylcholine is supposed to be impaired during the illness. There are various approaches in the treatment of AD, however AChE inhibitors represent 4 of 5 approved drugs for the treatment. One of these compounds, tacrine, was restricted to use due to serious side effects. Objectives: 7-Methoxy-derivative of tacrine (7-MEOTA) is centrally active anticholinesterases agent pharmacologically executive in the same way as tacrine. This compound has been introduced to the Army of the Czech Republic as an antidote against incapacitating agent (Agent 15, BZ compound). However, its potent

anticholinesterases properties and similarity to tacrine have predetermined this compound for further investigation as a potential anti-AD drug. Some preclinical studies and first clinical studies with 7-MEOTA were realized in the 90´s, but the next development was finished due to a financial issues. Our aim is to put into the spotlight again this interesting molecule and obtain the pharmacological profile of this compound with relevance to the AD (AChE inhibition, muscarinic receptors affinity, antioxidant properties etc.) Material and methods: Modified Ellman´s method has been used to test the anticholinesterases potency on pure enzymes by using spectrophotometer. Moreover, the enzyme activity of the brain homogenates of various species (human, rat, mouse, pig, guinea pig) was determined by using of automatic titrator. Antioxidative characteristics were assayed for the Ferric reducing antioxidant power (FRAP) and Thiobarbituric acid reactive substances (TBARS). The interaction with muscarinic receptors was investigated by using radioligand (3H-QNB) binding studies, where the rat brain homogenate served as a source of the receptors. Cytotoxicity of tested drugs was determined on the liver HEP2G cell line by using CellTiter 96 and MultiTox-Fluor assay kits. Data concerning the liver damage and acute toxicity were reviewed from the literature. Results: The AChE inhibitory properties revealed higher affinity of tacrine (IC50=0.5±0.1μM) than of 7-MEOTA (IC50=15.0±2.4 μM). The inhibition of both cholinesterases in the brain homogenate of various species (AChE and BChE) exerted rather similar scheme. Affinity to the brain muscarinic receptors was higher in case of 7-MEOTA (IC50=3.6μM) than in the case of tacrine (IC50=12.6μM). Antioxidant examination based on FRAP test revealed that 7-MEOTA caused significant shifts of low molecular weight antioxidants levels from 195 μmol/l at the experiment beginning to 286 μmol/l in the end. On contrary to 7-MEOTA, tacrine exerted some increase as well, however, the shift was not significant. Cytotoxicity was found higher for 7-MEOTA (IC50=35μM) than for tacrine (IC50=90μM). The acute toxicity of tested compounds was found to be the other way around. Discussion: Hepatotoxicity, was one of the reasons of withdrawing of tacrine from the market, however 7-MEOTA did not exert any signs of hepatotoxicity even in the chronic experiment probably due to a different metabolization in the liver. In other words, this could also explain why 7-MEOTA exerts higher cytotoxic effect on hepatic cell line in vitro, but not in vivo, where probably a toxic metabolite of tacrine is the cause of the hepatotoxicity. Notably, acute toxicity of 7-MEOTA on the whole organism persisted lower than in case of tacrine. Furthermore, we found that 7-MEOTA exerted slightly better antioxidant properties in comparison with tacrine. Also the affinity to the brain muscarinic receptors has been found higher in case of 7-MEOTA, which could play a beneficial role in the treatment of AD. Conclusion: All these results in the aspects, which are usually related to the treatment of AD leads us to the belief that, 7-MEOTA itself or one of its derivatives should be put into the spotlight again for advanced research. This work has been supported by the Resarch Project MZO 00179906.

P34 - A NOVEL NEUROTROPHIC DRUG FOR COGNITIVE ENHANCEMENT AND ALZHEIMER'S DISEASE. M. PRIOR, Q. CHEN, P. MAHER, D. SCHUBERT *(Salk Institute For Biological Studies, La Jolla, USA)*

Introduction: At present, there are few drugs that improve the memory deficits associated with normal aging and none that prevent cognitive decline in chronic neurodegenerative conditions such as Alzheimer's disease (AD), which is the most common cause of dementia in the elderly, affecting more than 24 million people worldwide. Historically, the search for a treatment for AD has been focused on the amyloid beta peptide (ABeta) that mediates familial Alzheimer's disease pathology. Unfortunately, drugs for AD that were developed through this approach have not been successful to date in clinical trials, perhaps because one target is not sufficient or because the targets are also critical for normal brain function so that their inactivation results in toxicity. Therefore, a different approach to drug discovery for AD is needed. Objectives: Given that age is the greatest risk factor for AD, our laboratory explored an alternative drug discovery paradigm to select drug candidates for neurodegenerative disease that were based on efficacy in cell models of multiple age-associated pathologies rather than exclusively amyloid metabolism. This scheme identified a highly potent compound that was further investigated for its effects in AD in vivo. Materail and methods: Behavior Assays Normal Rodents: Rat Novel Object Recognition: Male Sprague-Dawley rats were used and the testing was done by Behavioral Pharma, Inc. (La Jolla, CA). Testing commenced at 8wks of age with drugs administered 60 min prior to testing at 10mg/kg body weight. Mouse Behavioral Testing. For the Barnes maze, Y maze and NOR tests, male C57BL/6J mice were provided J147 (200ppm) in standard rodent chow or were given control feed starting at 6 weeks of age. Barnes maze testing was initiated 2 weeks into J147 exposure. Y maze and NOL testing took place 7 and 8 wks into exposure, respectively. The APP/PS1 transgenic mice (line 85)were used for AD studies. Spatial memory was determined in 9 month old huAPPswe/PS1 transgenic mice fed J147 at 200 ppm in food for the previous 5 months using the Morris water maze (MWM). AD Reversal with aged APP/PS1 transgenic mice: Alzheimer's disease mice were allowed to age to 20 months old. The mice were then randomly assigned to two groups, 11 mice were put on the control food diet and 12 mice were put on J147 food diet at a concentration in the food of 200 ppm. Following three months of treatment, all mice were analyzed for cognitive performance by the 2 day water maze, the elevated plus maze and fear conditioning. Tissue Preparation and Immunoblotting. For all experiments mice were sacrificed at ages indicated in the text with one hemibrain fixed in 4% parformaldehyde for immunohistochemistry and the other hemibrain was dissected to extract the hippocampus. Protein was extracted from hippocampal tissue samples to yield soluble and insoluble protein for western blots. Protein concentrations were determined using the BCA protein assay (Pierce). Equal amounts of protein were solubilized in SDS-sample buffer, separated on 12% or 10-20% SDS-polyacrylamide gels, transferred to Immobulin P and immunoblotted with antibodies. ANOVA analysis with the Tukey post hoc test was used to determine differences between means for Western blot analysis. Immunohistochemistry: Brains were fixed and cryostat sectioned into coronal (30 um) sections. Sections were submerged in 0.3% H2O2 for 10 min to eliminate endogenous peroxidase activity and treated with 1% borate to eliminate free paraformaldehyde. Sections were incubated with primary antibody in 0.3% Triton X-100 in KPBS plus 2% filtered serum or BSA overnight at 4Â°C, and with primary antibodies (1:1000) in 0.3% Triton X-100 for 1 hr at room temperature. After incubation with secondary antibody and ABC reagent, sections were developed using metal-enhanced DAB solution. Sections were mounted to slides, dried, dehydrolyzed, treated with xylene, and covered using dibutyl phthalate xylene. Images were captured by a Zeiss digital camera connected to a Zeiss VivaTome microscope, and image analysis on sections was performed using Axiovision software. Neurogenesis in Young WT mice: Bromodexoyuridine (BrdU) is commonly used as a marker for dividing cells and is also considered a marker for neurogenesis. Male WT mice (9 months) that had been fed J147 (200ppm) or control diet were injected with 100mg/kg BrdU for seven days and sections from these mice spaced at 240um apart throughout the entire rostro-cadual extent of the hippocampus were immunostained with BrdU antibody. Images were captured by a Zeiss digital camera connected to a Zeiss VivaTome microscope, and image analysis on sections was performed using Axiovision software. Golgi Staining For Dendritic Spine Analysis: Dendritic spine analysis was analyzed in 30 month old wildtype mice on control and J147 diet (200ppm) for 6 months as well as 8 month old control wildtype mice using the golgi staining technique. Briefly, hemibrains were processed according to FD Rapid Golgi Stain kit instructions and then sectioned at 100um thickness and once again stained according to the manufacturer's guidelines for this kit. Images were captured by a Zeiss digital camera connected to a Zeiss VivaTome microscope, and image analysis on sections was performed using Axiovision software. Results: Our drug discovery scheme identified an exceptionally potent, orally active, neurotrophic compound (J147) that facilitates memory in normal rodents, prevents behavioral and synaptic protein loss in AD transgenic mice, and reverses cognitive loss in aged transgenic AD mice. J147 is also neurogenic in both very old and young mice and reduces the significant loss in dendritic spines that occurs with age. Strikingly, we have found that the neurotrophic and memory-enhancing activities of J147 are associated with the induction of brain derived neurotrophic factor (BDNF), a growth factor that is reduced with age and in AD brain, that is required for normal cognitive function, and is implicated in neurogenesis. Discussion: A large number of potential pharmaceutical, nutritional, and immunological therapies have been tested in clinical trials for AD, but to date they have not altered cognitive decline in humans. None of these compounds have shown the broad range activities of J147 in cell culture and in animals. J147 is unique in its ability to enhance LTP, potentiate learning and memory in both normal and AD transgenic animals, maintain synaptic proteins, reverse cognitive loss in aged AD transgenic mice, increase neurogenesis and prevent the loss in dendritic spines that occurs with age. Therefore, the range of biological activities of J147 relevant to human AD appears to be more extensive than any of the compounds previously tested in clinical trials. In addition J147 is very potent, has good medicinal chemical properties for a CNS drug, is apparently safe, and is orally active. We have identified its metabolites in rodent plasma and human and mouse microsomes and shown that they have similar biological activity as the parent compound. J147 appears to be an ideal candidate for human clinical trials. Conclusion: Thus J147 is an exciting new compound with the potential to be an AD therapeutic by slowing disease progression through neuroprotection as well as providing immediate cognition benefits. These dual attributes improve the chances for success as a disease-modifying drug as well as in short-term clinical trials that use currently accepted approvable measures of outcome.

P35 - CORRELATIONS OF PHARMACOKINETIC (PK) MEASURES TO PHARMACODYNAMIC (PD) EFFECTS OF ELND005 (SCYLLO-INOSITOL) FROM A PHASE 2 DOSE-RANGING STUDY IN MILD TO MODERATE ALZHEIMER'S DISEASE. E. LIANG, J. WAGG, F. JONSSON, J. CEDARBAUM, S. ABUSHAKRA *(Elan Pharmaceuticals, Inc.San Francisco, CA, USA)*

Introduction: ELND005 (Scyllo-inositol) is being investigated as a potentially disease modifying oral treatment for Alzheimer's Disease (AD). In non clinical studies ELND005 has shown in vitro Amyloid anti-aggregation and neuronal protective effects from oligomer-induced synaptic injury. In transgenic CRND8 mice, ELND005 reduced cortical amyloid deposition and improved learning deficits. The safety and efficacy results of ELND005 from a Phase 2,dose-ranging, 78 week study in Mild to Moderate AD (M/M AD) have been previously reported (Salloway et al. In Press, Neurology). Due to safety findings in the 2 high dose arms, the main efficacy analysis was based on the 250mg and placebo arms. In the M/M population, the co-primary endpoints NTB (Neuropsychological Test Battery) and ADCS-ADL (Activities of Daily Living) did not achieve significance. However, the 250mg twice daily (BID) dose demonstrated a significant CSF Abeta42 reduction at week 78, and beneficial trends on several clinical outcomes in the pre-specified Mild group. Objectives: To evaluate the correlations of drug exposure across the studied dose range to the observed clinical and CSF biomarker effects in M/M AD patients group to support dose selection for future studies. MAaterial and metods: A total of 351 patients with M/M AD (MMSE 16-26) received either placebo (n=82) or 1 of 3 ELND005 doses (250mg: N=87, 1000mg: N=89, and 2000mg: N=91; all administered BID). In addition to plasma levels in all patients, CSF and brain levels of ELND005 were assessed in a subset of patients who underwent lumbar punctures or Proton-MRS imaging (N = 351, 92, 101, respectively). A population PK model was developed and used to generate post-hoc ELND005 patient-level steady-state exposure metrics, i.e., daily area under the concentration-time curve (AUC0-24), maximum, minimum and average concentrations (Cmax, Cmin, and Cavg) in plasma, CSF, and brain compartments. Correlations of

estimated steady-state exposure metrics to change from baseline to Week 78 on NTB-z score, CDR-SB (Clinical Dementia Rating-Sum of Boxes), and CSF biomarker levels (Aβx-42, Aβx-40, Aβx-42/Aβx-40 ratio, total Tau, and P-tau) were evaluated. For each outcome, mean changes from baseline were calculated for each exposure quartile and plotted on the mid-point of each quartile exposure range. All plots were visually inspected to identify any systematic trends. All exploratory analyses were completed within the S-Plus® Version 8.1 environment. When appropriate, correlation coefficient (r) and significance (p value) of exposure-response was calculated in Mild AD patients. Results: Significant correlations between exposure metrics and a number of clinical/CSF biomarker endpoints were identified, primarily in the Mild AD group (MMSE 22-26) over the lower range of exposures (corresponding to pooled placebo and 250 mg BID dosing groups). For the NTB and CDR, the exposure-response relation in Mild patients (N=22-25/quartile) demonstrated a reverse V-shaped triphasic curve: NTB and CDR scores improved compared to placebo with increasing concentrations that corresponded to the 250mg exposure range and showed less improvement compared to the 250mg exposures at the concentration range corresponding to the 1000mg and 2000mg exposures. In Mild AD patients of the 250 mg and placebo groups, a significant exposure-response correlations were observed for the NTB z-score ($r=0.32$, $p=0.02$), and a near significant trend was observed for the CDR-SB ($r=0.23$, $p=0.09$). In the Mild AD patients across all doses, a significant correlation was also observed between CSF Aβx-42 reduction and steady-state ELND005 exposures ($r= -0.82$, $p <0.05$). Discussion: These PK/PD analyses suggest that exposures within the range provided by the 250mg BID dose, but not by higher doses (1000mg BID and 2000mg BID), are associated with clinically beneficial trends on the NTB and CDR-SB in Mild AD patients. The reverse V-shaped exposure-response relationship of exposure to ELND005 and the NTB and CDR responses suggests that doses ≥1000mg BID, which provided saturating CNS exposures, did not provide additional, if any, clinical benefit. In Mild AD patients, the PK/PD correlations for the cognitive and global clinical outcomes are also supported by significant correlations between exposure to ELND005 and Aβ42 reduction, which is consistent with results of preclinical studies in Tg CRND8 mice. Possible limitations of this analysis, however, include the relatively small sample size in the Mild AD group (N=95), and the limited CSF subset with week 78 data (N=20). Conclusion: The results of exposure-response analyses were consistent with the prior dose-response analysis for the clinical outcomes. The significant correlations of drug exposure to both clinical and CSF Aβ42 outcomes in the Mild AD group support the choice of the 250mg BID dose for future studies in this population.

P36 - EFFECT OF RATANASAMPIL (TIBET-MEDICINE) ON CHANGES OF SERUM B-AMYLOID PROTEIN AND INFLAMMATORY MARKERS IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE. A. ZHU, Y. CHU, X. ZHONG, G. LI, B. LIAO, J. ZHOU, S. GU, M. YU *(Qinghai Provincial Hospital, Xining, China)*

Introduction: Ratanasampil (RNSP) is a traditional Tibetan medicine often used for the treatment of stroke and cerebrovascular diseases. The vasodilatory effects of Ratanasampil and our previous discoveries that RNSP can reduce β-amyloid protein levels and increase learning and memory in Alzheimer's mouse models (Tg2576) led us to investigate whether RNSP can improve cognitive functions in Alzheimer's patients. Objectives: Investigate RNSP's specific effects on cognitive function in mild-to-moderate Alzheimer's patients living at high altitude. If we observed significant improvements in cognitive function in the patients, we would further examine the role of RNSP in Alzheimer's disease (AD)-related signaling. Material and methods: In this study, 146 AD patients living in Qinghai province (altitude about 2000-3200 meters) were divided into three balanced groups according to a series of criteria. The first group received high-dose Ratanasampil orally (1 gram every day); the second group received low-dose Ratanasampil orally (0.33 gram every day); and the third group received a placebo (Piracetam). 140 patients completed 16 weeks of treatment. Each patient was evaluated 3 times during the 16-week treatment (at the beginning of the treatment, and at 4 week and 16 weeks after treatment). The outcomes were assessed using 3 evaluation tools: "Mini Mental State Examination (MMSE)", "Alzheimer's disease Assessment Scale-cognitive Subscale (ADAS-cog)" and "Activity of Daily Living Scale (ADL)" by psychiatrists blinded to the treatment assignments. Serum Aβ40 and Aβ42 levels were measured in all patients at the beginning of the study (baseline levels) using a sandwich ELISA and were measured again after 4 weeks and 16 weeks of treatment. Safety assessments including electrocardiograph (ECG) and standard laboratory tests were carried out in all patients on the 0, 4th and 16th week of treatment. Results: Compared to the same group before treatment, MMSE scores, ADAS-cog scores and ADL scores were significantly improved ($p < 0.01$, $p < 0.01$ and $p < 0.05$, respectively) in the patients after 16-week treatment with high-dose RNSP, while no significant differences were observed in either the low-dose RNSP treatment or placebo groups ($p>0.05$, $p> 0.05$). After 16-week treatment, compared with before treatment, serum TNF-α, IL-1β, IL-6 and Aβ42 levels were significantly decreased ($p< 0.01$) in the high-dose RNSP group, whereas no significant differences were found in the low-dose treatment and placebo group. Serum Aβ42/Aβ40 ratio was significantly decreased after 4-week and 16-week treatment in the high-dose RNSP group ($p< 0.05$, $p <0.01$). Furthermore, serum Aβ42 concentration had a strong positive correlation with TNF-α, IL-1β and IL-6 levels. Safety assessments did not show any obvious adverse effects in either treatment or control groups. Discussion: We showed in this study that RNSP (1 gram/day) improved cognitive function of mild-to-moderate Alzheimer's patients living at high altitude. Therefore, RNSP could be a good drug candidate to undergo further testing in patients with Alzheimer's disease. We also found that RNSP (1 gram/day) significantly reduced serum Aβ42 concentration, decreased the Aβ42/Aβ40 ratio and the level of several Alzheimer's disease-related inflammatory biomarker such as TNF-α, IL-1β and IL-6.This suggested that RNSP could inhibit inflammatory responses and retard the progression of Alzheimer's disease and thus improve the cognitive function of Alzheimer's patients. Conclusion: High-dose RNSP treatment for 16 weeks significantly improved cognitive function in mild-to-moderate Alzheimer's disease patients living at high altitude. Further the investigations revealed that high-dose RNSP also decreased serum Aβ42 concentration and therefore the Aβ42/Aβ40 ratio and reduced several pro-inflammatory factor levels including those of TNF-α, IL-1β and IL-6.

P37 - ETAZOLATE TREATMENT IN A GENETIC MODEL OF ALZHEIMER DISEASE: RESCUE OF COGNITIVE IMPAIRMENTS AND PHYSIOLOGICAL BIOMARKERS. D. COLAS, K. YANAGISAWA, B. CHULUUN, G. HAGIWARA, C.H. CRAIG *(Stanford University, Stanford, CA, USA)*

Introduction: Alzheimer disease is characterized by abnormal processing of APP leading to the neurotoxic production of beta-amyloid through activation of the beta-secretase pathway. APP is alternatively processed for producing trophic soluble-App-alpha fragments (sApp-α), especially in physiological conditions, by alpha-secretase activity. Therefore an imbalance in the alpha/beta pathways regulation could account for the abnormal production of beta-amyloid in AD. Accordingly, pharmacological tools aiming at stimulating the production of alpha-secretase derivatives such as sApp-α have been envisioned as possible treatment strategy for AD in conjunction to beta-amyloid lowering agents. Etazolate (ETZ), a GABA-A receptor modulator and phosphodiesterase-4 (PDE4) inhibitor has been shown to increase sApp-α in vitro and in vivo, and to counteract beta-amyloid neurotoxicity in vitro. ETZ was also shown to improve cognition in normal aged rats. Nevertheless, the effects of ETZ in vivo in the context of a beta-amyloid burden and the cognitive deficits associated with AD have not been reported so far. Additionally, our work in different animal models suggest that APP modifications are associated with profound changes in integrated biological parameters such as the sleep-wake cycle and associated EEG synchrony, providing possible physiological biomarkers for translational research. Objectives: The present study aimed at characterizing the effect of a chronic treatment of ETZ on the behavior (locomotor activity and cognition), the sleep-wake cycle and associated EEG parameters in transgenic mice over expressing beta-amyloid. Material and methods: We used four months old Tg-APPSswe-PS1ΔE9 mice (or Tg-App/PS) over expressing human mutated App (Swedish) and Presenilin-1 and characterized by increased production of beta-amyloid. Mice were initially obtained from JaxLab and maintained on a 12h light-dark cycle at 24ºC with food/water ad libitum. We showed that 4mo old Tg-App/PS mice were also characterized by increased locomotor activity, impaired cognition, decreased sleep and decreased NREM sleep delta power (EEG synchrony in the 1-4Hz range). Groups (n=8) of Tg and Wild-Type (WT) mice were treated with either saline (SAL) or ETZ (from Sigma) 1mg-kg for 2 weeks (daily i.p.). We assessed locomotor activity (using the open field (OF) procedure), working memory, using the object preference test (OP) and long term memory (LTM) using the novel object recognition (NOR) paradigm with a 24h delay between training and recognition. Prior to the treatment the mice were equipped with EEG/EMG electrodes allowing the analysis of sleep-wake architecture and spectral analysis of the EEG (for methods see Colas D., et al, 2008). The EEG/EMG recordings and the OF procedure were achieved in the last day of the treatment. The cognitive testings (OP and NOR) were achieved four days after the end of the treatment. Results: Behavioral effects of ETZ treatment: TG mice treated with ETZ showed normal levels of locomotor activity compared to WT. TG mice treated with SAL remained hyperactive. The OP test showed that TG-SAL mice have a biased preference for identical objects. ETZ treated mice, similarly to WT-SAL and WT-ETZ mice, show a normalized object preference. Using the 24H NOR test, we show that ETZ treated TG mice had a normalized LTM, showing a typical increased exploration of the novel object. Those behavioral improvements were associated with increased REM sleep and increased NREM sleep delta power in TG-ETZ mice only. Discussion: ETZ treatment in Tg-App/PS mice rescued locomotor hyperactivity and impaired cognition. The effect of ETZ on the cortical content of beta-amyloid and other APP derivatives is currently investigated. ETZ could exert its therapeutic actions either via an increased production of sApp-α which has been shown to have neurotrophic effects, and/or decreased production of beta-amyloid. Alternatively, ETZ could produce its beneficial effects through direct activation of its pharmacological targets, i.e. GABA-A receptors and PDE4. Acute effects of ETZ on cognition will therefore be investigated. The changes observed in REM sleep and delta power are evocative of a consolidated sleep and provide possible biomarkers for current clinical trials. Moreover, changes in sleep physiology associated with the ETZ treatment maybe indicative of underlying mechanisms, since GABA-A and PDE4, known ETZ targets, are involved in sleep/EEG regulation. In turn sleep homeostasis has been shown to modulate the beta-amyloid production. Conclusion: Using an animal model of AD we showed that a chronic ETZ treatment was rescuing the cognitive deficits characterizing this model. The behavioral effects of the drug regimen were associated with changes in key biomarkers that could help design future clinical trials and provide insights into the normal function of App. Both working memory and long term memory were improved by ETZ. ETZ is currently a candidate drug studied in clinical trials for possibly stimulating the alpha-secretase pathway of APP processing.

P38 - SOUVENAID® AS AN ADD-ON INTERVENTION IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE USING ALZHEIMER'S DISEASE MEDICATION: RESULTS FROM A RANDOMIZED, CONTROLLED, DOUBLE-BLIND STUDY (S-CONNECT). R. SHAH[1], P. KAMPHUIS[2], S. LEURGANS[1], S. SWINKELS[2], C. SADOWSKY[3], A. BONGERS[2], S. RAPPAPORT[4], J. QUINN[5], R. WIEGGERS[2], D. BENNETT[1], P. SCHELTENS[6] *(1. Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois, United States; 2. Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands; 3. Department of Neurology, Nova Southeastern University, USA; 4. Agewell Health, Indianapolis, Indiana, United States; 5. Department of Neurology, Oregon Health and Science University and the Portland VA Medical Center, USA; 6. Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands)*

Introduction: Souvenaid® (Medical Nutrition), containing the specific nutrient combination FortasynTM Connect, is designed to support synapse formation and function in patients with Alzheimer's disease (AD). The nutrients in Fortasyn Connect are precursors and cofactors for the formation of neuronal membranes, and increasing their dietary intake can promote the synthesis of new brain synapses (Cansev et al., Alzheimers Dement, 2008; Kamphuis and Scheltens, J Alzheimers Dis, 2010). In a proof-of-concept clinical study (Souvenir I) with drug-naïve, mild AD patients, Souvenaid taken once daily for 12 weeks was safe, as compared to patients randomized to an iso-caloric control product. Participants taking Souvenaid showed better performance on delayed verbal recall using the Wechsler Memory Scale-revised but did not differ in performance on Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) (Scheltens et al., Alzheimers Dement, 2010). Post-hoc secondary analysis of the Souvenir I study indicated that participants with worse baseline performance on ADAS-cog were more likely to have better ADAS-Cog performance after Souvenaid use (Kamphuis et al., J Nutr Health Aging, 2011). As the ADAS-cog may be more sensitive to change in moderate AD (Black et al., Alzheimers Dement, 2009) and since Souvenaid had not been tested in moderate AD patients already taking AD medications, the findings of the Souvenir I study led to the design of the S-Connect study. Objectives: The primary objective of the S-Connect study was to investigate the 24 week effect of daily Souvenaid use on cognitive performance in patients with mild-to-moderate AD on stable doses of AD medication. Secondary objectives were to investigate safety and tolerance as well as to assess the effects of Souvenaid on functional abilities and global clinical impression. Material and methods: The S-Connect study was a 24-week randomized, controlled, double-blind study in participants with mild-to-moderate AD (as defined by NINDS-ADRDA criteria), a Mini-Mental State Examination (MMSE) score between 14-24 (inclusive), and stable intake of cholinesterase inhibitors and/or memantine. The study was registered (www.trialregister.nl, NTR1683). The Institutional Review Boards of the 48 United States clinical centers approved the study. Potentially eligible patients and/or their legally authorized representatives provided written consent to study participation. Randomization (1:1) to daily oral intake of Souvenaid, a 125 milliliter once-a-day drink containing Fortasyn Connect, or an iso-caloric control product was performed using a computer-generated, random length permuted block study treatment randomization code. The primary outcome parameter was the 11-item ADAS-cog subscale. Secondary outcome parameters were product use counts, change in nutritional biomarkers, adverse event rates, the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scale scores, and Clinical Dementia Rating Sum of Boxes (CDR-SOB) score. A pre-specified blinded interim analysis was conducted to check whether the calculated sample size was adequate and that no safety concerns had arisen, and the independent Data Monitoring Committee recommended continuation of the trial without modification. Main study parameters were assessed at baseline, week 12 and week 24. For the statistical analysis, a repeated measures mixed model was used. Results: A total of 527 participants were randomized (265 to Souvenaid and 262 to control). The mean age was 76.7 (± 8.2) years, mean MMSE score at screening was 19.4 (± 3.1) and 48% were male. There were no differences in baseline characteristics between the two study groups. Study completion was not different by group (86.0% in the Souvenaid study group vs. 85.1% in the control group). Both study groups showed a modest increase of ADAS-cog scores over time; however, no 24-week differences between the groups on the primary endpoint ADAS-cog were noted. Overall product compliance during the study was 94% and was not different between the groups. Souvenaid compliance was confirmed by significant changes in (nutritional) biomarkers including erythrocyte membrane docosahexaenoic acid and plasma homocysteine levels. No group differences in adverse event rates were found and no clinically relevant differences in blood safety parameters were noted. No difference between the groups was observed on the secondary parameters, ADCS-ADL and CDR-SOB. Discussion and Conclusion: Secondary analysis from the Souvenir I study suggested a beneficial effect on cognition in a subgroup of patients with worse cognitive function as measured by baseline ADAS-cog scores (mean MMSE score 22.9). The current study does not confirm the presence of an effect on cognition in patients with more moderate AD (mean MMSE score 19.4) using AD medication. Souvenaid in combination with acetylcholinesterase inhibitors, and/or memantine was safe and well-tolerated, extending the findings in the prior study with drug- naïve AD patients (Scheltens et al., Alzheimers Dement, 2010). Studies to confirm and extend the effects of Souvenaid in drug-naïve mild AD and drug-naïve prodromal AD are ongoing. Footnotes: Souvenaid is a registered trademark of N.V. Nutricia. Fortasyn is a trademark of N.V. Nutricia. The S-Connect study forms part of the Souvenaid Clinical Trials Program

P39 - ARE TRANSGENIC MICE VALID ANIMAL MODELS FOR THE SEARCH FOR NEW TREATMENTS FOR ALZHEIMER'S DISEASE (AD)? J.L. HOLTZMAN *(University of Minnesota, Minneapolis, USA)*

Introduction: AD is characterized by dementia associated with extracellular deposits of beta-amyloid (abeta) in the form of plaque and intracellular deposits of hyperphosphorylated tau in the form of tangles. Since tangles are seen after a variety of brain insults, such as stroke and trauma, their presence does not indicate the basic, underlying biochemical defect leading to the cognitive decline seen in AD. Furthermore, most investigators believe that the dementia is due to the toxicity of abeta either in the form of plaque or soluble aggregates. Yet, there is a poor correlation between plaque burden and cognitive decline. On the other hand, linkage studies have established that the familial forms of AD are due to mutations in three genes; Amyloid Precursor Protein (APP) and presenilins 1 and 2, all of which are involved in the production of abeta. Yet, genome-wide association studies have indicated that SNP's in only two genes, ApoE and clusterin/ApoJ, are consistently associated with sporadic AD. Neither has a direct role in abeta production. A further concern is that abeta is produced in everyone. Yet it is not clear why deposits only occur in the brains of the elderly? In studies from my laboratory we have found that all of the abeta in the CSF is N-glycosylated and bound to two chaperones from the endoplasmic reticulum (ER), ERp57 and calreticulin. On the other hand, other laboratories have reported that the abeta in plaque is present as the naked peptide. Hence, the modifications that we have observed normally keep the abeta in solution. Furthermore, these findings suggest that plaque forms when there is a decline in the capacity of the cell to catalyze the formation of this complex. Since many of the proteins necessary for a functioning memory undergo these same modifications, our findings suggest that the dementia associated with AD is due to a decrease in the capacity of the ER to N-glycosylate newly synthesized synaptic membranes proteins and form complexes with the ER chaperones. In spite of the marked differences in the genetics of the familial and sporadic forms of the disease and possible differences in their basic cell biology, a number of workers have developed transgenic mouse models transfected with the mutant forms of the human genes associated with familial AD. Since with age these animals show the two cardinal signs of AD, cognitive decline and plaque deposition, they have been widely employed to study the cell biology of AD and to identify potential therapeutic agents for the treatment of this condition. Objectives: Determine the outcomes of Phase 3 clinical trials of agents which were effective in transgenic mice to determine whether these animals are valid models for the search for therapies for sporadic AD. Material and methods: Phase 3 clinical trials were identified through PubMed and www.ClinicalTrials.gov with the search terms Alzheimer's Disease. For PubMed the search terms were limited to human and treatment. Recent trials were identified through www.fiercebiotech.com and Google alert. After a completed phase 3 trial was identified, transgenic mouse studies were identified by a search on PubMed with the drug name and transgenic mice as the search terms. Results: To date there have been seven completed phase 3 trials of agents which were initially demonstrated to be effective in transgenic mice but failed to show any clinical benefit. The most glaring example of these failures is the Elan vaccine trial in which patients received either abeta with an adjuvant or placebo. The vaccine induced antibodies to abeta which cleared the plaque. Yet, in a follow up study Holmes et al. reported that although the vaccine led to lower plaque burdens at autopsy, it had no effect on the cognitive decline. Instead the subjects' cognition proceeded unabated to severe end stage dementia. It is difficult to reconcile the validity of a paradigm which posits that the dementia is due to abeta toxicity when a treatment which clears plaque has no effect on cognition. In spite of these results, Elan/J&J/Pfizer and Lilly, as well as several other firms, are currently performing phase 2 and 3 clinical trials of both monoclonal and polyclonal antibodies to abeta. Yet, even if these agents should show some therapeutic benefit, in light of their cost, as exemplified by the application of antibodies to the treatment of malignant, inflammatory and autoimmune diseases, it is difficult to discern how they could have a major impact on the treatment of such a common disorder as AD without placing yet another massive, financial burden on our already stressed health care system. Failures of other agents which were active in transgenic mice include: two gamma secrease inhibitors, tarenflurbil from Myriad/Lundbeck and semagacestat from Lilly; MK-677 from Merck, an agent which increases the secretion of insulin-like growth factor 1 (IGF-1); the GEM trial of Ginkgo biloba; the Women's Health Initiative of estrogen in an elderly population either alone or in combination with a progestin; and docosahexaeonic acid, an omega-3 fatty acid. The last three trials were funded by the NIH. Discussion: The repeated failure of agents which were effective in transgenic mice to show efficacy in phase 3 clinical trials raises a major issue for the development of therapies for sporadic AD. These failures suggest that the dementia is not due to the toxicity of abeta, but rather to more fundamental biochemical changes which probably underlie the aging process in general. In particular, our findings suggest that plaque is only a biomarker for a fundamental defect in the posttranslational processing of plasma membrane proteins in general and synaptic proteins in particular. These findings would indicate that the dementia is due at least in part to this decline. A second issue which is rarely discussed in the context of abeta's role in AD, is the well known decrease in brain volume seen with age which has been shown to be a robust predictor of the future development of dementia. It is generally thought this decrease is equally divided between loss of synapses and white matter. To my knowledge the abeta paradigm does not address the basis for this decrease in myelin content. Yet our findings might suggest a possible cause for this loss. The myelin sheath is an onion-like structure surrounding the axon which is formed from the plasma membrane of the oligodendrocytes in the brain and Schwann cells in the periphery. Our studies on abeta suggest that this decrease in myelin could be due to a decline in the capacity of these cells to catalyze the posttranslational processing of their plasma membrane proteins. With a decrease in the thickness of the

myelin sheath, there is a decline in the speed of nerve transmission and a slowing of thought processes. Conclusion: Transgenic mice have not proven to be reliable models for the identification of potential therapies for AD. Furthermore, if the two, large scale, current phase 3 trials of monoclonal antibodies, bapineuzumab from Elan/J&J/Pfizer and solanezumab from Lilly, which have been demonstrated to clear plaque, fail to halt the cognitive decline, it would seem difficult to continue to search for therapies based on the paradigm that the accumulation of abeta is the cause of the dementia seen in AD.

P40 - EFFICACY STUDY OF LP-PLA2 INHIBITOR 859 IN THE HYPERCHOLESTEROLEMIC RABBIT MODEL OF ALZHEIMER'S DISEASE.
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Introduction: Human epidemiological data indicated that inhibition of Lp-PLA2 might lower Alzheimer's disease (AD) neuropathology. These results require preclinical exploration in an animal model of AD such as the hypercholesterolemic rabbit. Rabbits have a closer phylogenetic proximity to primates than do rodents, and this closer relation is expressed in the amino acid sequence of Aβ, which is identical to the human sequence. Rabbits have an extensively characterized profile on a measure of learning and memory that closely parallels human performance and that is impaired in human patients diagnosed with AD: Eyeblink classical conditioning (EBCC). In probable AD, there is very limited EBCC, and EBCC identifies AD early in disease onset. Drugs approved to treat memory impairment in AD ameliorate EBCC deficits in AD model rabbits. The fact that the same classical conditioning task can be tested in rabbits and humans makes EBCC a valuable preclinical test of drugs targeted to treat AD. Objectives: Our major goal was to evaluate the efficacy of inhibition of Lp-PLA2 with a novel Lp-PLA2 inhibitor called '859 in reducing AD neuropathology and ameliorating impaired EBCC in the hypercholesterolemic rabbit model. We examined a dose of 10 mg/kg of '859 administered at diet onset or 29 days after diet onset over a 10-week period to address the function of Lp-PLA2 inhibition in the scope of an amyloid study, including cerebral amyloid angiopathy (CAA), intracellular Aβ, and extracellular Aβ plaques as well as learning and memory and blood-brain barrier (BBB) permeability. Material and methods: Six groups of young male SPF New Zealand white rabbits (n = 8/group, 48 total) were tested: Groups 1-5 were AD model rabbits fed a regimen of 2% cholesterol and trace copper and treated with 10 mg/kg '859 or vehicle daily from Day 1-72 or from Day 29-72 or administered vehicle daily from day 29 to day 72 and 10 injections of galantamine (3.0 mg/kg) 30 min before each EBCC session. Group 6 was fed a normal diet and received no treatment. Drug and vehicle were administered daily s.c. Blood was collected at baseline the day the cholesterol/copper regimen was initiated and on Days 29, 32, and 72. EBCC (750 ms trace paradigm) was carried out beginning 56 days after diet onset. Three rabbits in each treatment group were injected with tracer for the assessment of BBB permeability (fluorescent tracer, sodium-fluorescein). In plasma collected on Days 1, 29, 32, and 72 and the posterior right hemisphere of the brains, Aβ 1-40 and 1-42 levels were quantified with a standardized colorimetric sandwich ELISA assay. Lp-PLA2 and cholesterol level analyses were also carried out on plasma. Immunohistochemistry was performed to examine CAA, intracellular Aβ, and extracellular Aβ plaques. Primary antibodies included mouse monoclonal anti-Aβ raised specifically against amino acid endings with 40 and 42 of Aβ (Clones 11A50-B10 and clone 12F4, respectively, 1:200 dilution, Covance SIGNET line). A PaxCam3 Digital Camera System (MIS, Villa Park, IL) interfaced with a Nikon LabPhot microscope and a PC was used to analyze images photographed using a Plan Apo 20x objective. Optical digital analysis software was used to identify specified saturation and pixel densities in temporal cortex that included hippocampus. Results: Plasma Lp-PLA2 levels were analyzed at Days 1, 29, 32, and 72 the 40 AD model rabbits. ANOVA results indicated that AD model rabbits injected daily with '859 from Day 1 had significantly lower levels of Lp-PLA2 throughout the course of the 72-day experiment. However, the group that received daily injections of '859 after 29 days on the cholesterol copper regimen did not have Lp-PLA2 levels that were significantly lower than vehicle-treated rabbits. Changes in cholesterol level did not account for the differences in Lp-LPA2 levels. Total cholesterol level rose significantly over the 72 days of the experiment in all rabbits treated with a high cholesterol diet. There was a low level of BBB permeability in the untreated control rabbits and high permeability in AD model rabbits. However, brain/plasma ratio of '859 indicated low brain permeability of the drug. On some measures of trace EBCC, galantamine-treated AD model rabbits showed significantly better performance -- a replication of previous work. However, rabbits treated with '859 did not acquire EBCC more rapidly than control rabbits. There was a statistically significant effect of treatment with 1-72 days with '859, with significantly fewer Aβ40 plaques in the brains of these rabbits. Analysis of tissue stained for Aβ40 indicated numerically lower levels of CAA and intracellular Aβ40 in '859-treated rabbits that were not statistically significant. Discussion: Although '859 administration significantly reduced the number of extracellular Aβ40 plaques, there was not a statistically significant decrease in intracellular Aβ40. Analysis of CAA indicated numerically lower levels of Aβ40 in coronal and leptomeningeal vessels, but only half the sample was analyzed thus reducing the statistical power. The result that trace EBCC was not affected by treatment with '859 occurred possibly due to floor effects of the difficult 750 ms trace paradigm. Our multiple studies of EBCC in human AD and in rabbit and rodent models indicated that the delay paradigm is most sensitive to human AD-related impairment drug efficacy in animal models of normal aging and AD. At the time we initiated the present study, most data with AD model rabbits were collected in the 750 ms trace EBCC paradigm. Subsequently, we have demonstrated that the 750 ms delay paradigm is more sensitive in AD model rabbits because the delay paradigm is less difficult and there is less of a floor effect in learning. Conclusion: Overall, the hypercholesterolemic rabbit has proved to be a useful model of AD for the study of Lp-PLA2 inhibiting drugs. Major positive results of the study are that 72 days of treatment of '859 dramatically lowered plasma Lp-PLA2 levels and significantly reduced the number of extracellular Aβ40 plaques in the temporal lobe/hippocampal region of the brain. The BBB was numerically less permeable in '859- than in vehicle-treated AD model rabbits. Impaired EBCC was not ameliorated. A challenge for studies of Lp-PLA2 inhibition will be to demonstrate efficacy when neuropathology is present. Administration of '859 to AD model rabbits already treated for 29 days on the cholesterol/copper regimen and showing AD pathology was much less effective in lowering Lp-PLA2 levels than was administering '859 on Day 1 when the rabbit brain is free from pathology. Human AD is diagnosed clinically only when neuropathology is advanced. These results suggest that treatment may be required with drugs such as '859 for individuals at risk to develop neuropathologies associated with elevated Lp-PLA2 levels before extensive pathology is present. Development of Lp-PLA2 inhibitors that have efficacy in patients who have existing neuropathology is also desirable.

P41 - THE EFFECTS OF A MULTI-NUTRIENT DRINK ON FUNCTIONAL CONNECTIVITY IN PATIENTS WITH ALZHEIMER'S DISEASE.
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Introduction: Loss of synaptic connections, causing disruption in neuronal communication, is one of the important causes of the cognitive problems in Alzheimer's disease (AD). Previous work has demonstrated that nutrients act as precursors or co-factors for the formation of synapses. The multi-nutrient drink Souvenaid®, containing a specific mix of nutrients (docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), uridine monophosphate (UMP), choline, vitamins B6, B12, folate, phospholipids, vitamins C, E, and selenium, registered as FortasynTM Connect), is developed to improve synapse formation and is intended for the dietary management of AD. The proof of concept study ('Souvenir I') in 225 drug-naive mild AD patients showed that Souvenaid improved memory performance, both in the overall intention to treat population (baseline MMSE 20-26) and in the prespecified subgroup of patients with very mild AD (baseline MMSE 24–26) (Scheltens et al. 2010, Alzheimers Dement 6, 1-10). Synaptic loss occurs early in the disease process and strongly correlates with the cognitive decline, including delayed recall, in mild cognitive impairment and early AD (Scheff et al. 2006, Neurobiol Aging 27, 1372-84). Hence, the observation that memory performance in very mild AD is improved by the intervention is in line with the hypothesis that the specific combination of nutrients in Souvenaid may improve synaptic formation and function. In addition, animal studies have shown that the administration of the specific combination of nutrients in Souvenaid has led to increased neurite outgrowth and dendritic spine density (Wurtman 2009, Annu Rev Nutr 29, 59-87). In humans, the electrical activity generated by neuronal communication at the synapse can be measured indirectly by 'functional connectivity' studies using electroencephalography (EEG) and/or magneto-encephalography (MEG). Objective: To explore the effect on neuronal communication after 24 weeks nutritional intervention with Souvenaid compared to control product in drug-naive mild AD patients. Material and Methods: The Souvenir II study (NTR1975) is the first trial to use EEG and MEG as biomarker to explore changes in functional connectivity after nutritional intervention with Souvenaid. The Souvenir II study is a 24-week double blind randomised controlled study in 259 drug-naive mild AD patients (MMSE ≥ 20). Patients receive either Souvenaid or control product. Primary outcome measure is the memory domain score resulting from a neuropsychological test battery (NTB) (based on the previously validated NTB of Harrison et al., 2007). Other study outcome measures include the NTB executive function domain score, total composite scores, the individual NTB item scores, safety and tolerance, the Disability Assessment for Dementia scale, blood biochemistry and EEG. For a subset of patients, MEG data were also collected. Resting state EEG and MEG data were recorded at baseline and after 12 and 24 weeks intervention. EEG and MEG data will be used to assess the effect on changes in functional connectivity as a measure of synaptic formation, and will be linked to the neuropsychological outcome measures. EEG and MEG outcome parameters are: 1) relative power in specific frequency bands, 2) Phase Lag Index as connectivity measure, and 3) clustering coefficient and pathlength in network analysis. Results: Enrolment for the Souvenir II study was completed in December 2010. A total number of 259 patients were randomised of which 238 patients completed the study. EEG was recorded in around 220 patients and MEG was recorded in a small subset of patients. First EEG and MEG results are expected to be available in 2012-2013. An example of EEG data will be presented at the poster. Discussion: To study the mode of action of Souvenaid in humans, electroencephalography (EEG) or magneto-encephalography (MEG) data were collected in the Souvenir II study. We expect an increase in neuronal communication in subjects who received Souvenaid for 24 weeks as compared to subjects who received the control product. Conclusion: The multi-nutrient drink Souvenaid contains a specific combination of nutrients, developed to improve synapse formation in AD patients. In the Souvenir II study, EEG and MEG measurements are used to provide information regarding the effects of Souvenaid on changes in functional connectivity as a measure of synaptic formation. Souvenaid and Fortasyn are registered trademarks of N.V. Nutricia.

P42 - THE LIPIDIDIET STUDY: RATIONALE AND STUDY DESIGN. Y. FREUND-LEVI[1], P.J. VISSER[2,3], M. KIVIPELTO[4], R.L. WIEGGERS[5], T. HARTMANN[6,7], H. SOININEN[8] *(1. Department of NVS, Section of Clinical Geriatrics, Karolinska Institutet, Karolinska University Hospital, Huddinge, Sweden; 2. Department of Psychiatry and Neuropsychology, Alzheimer Center Limburg, University of Maastricht, Netherlands; 3. Department of Neurology, Alzheimer Center, VU University Medical Center, Amsterdam, Netherlands; 4. Aging Research Center, Karolinska Institutet and Stockholm Gerontology Research Center, Stockholm, Sweden; 5. Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands; 6. Deutsches Institut für DemenzPrevention (DIDP), Neurodegeneration and Neurobiology; 7. Experimental Neurology, Homburg, Germany; 8. Department of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland)*

Introduction: Scientific evidence indicates a clear role of nutrition in the development and progression of Alzheimer's disease (AD). Freund-levi et al. (2006, Arch Neurol 63, 1402-8) showed an effect of n-3 fatty acid supplementation on delayed word recall and attention in a subgroup of very mild AD (MMSE >27). More recently, the multi-nutrient drink Souvenaid® (containing FortasynTM Connect, a specific combination of nutrients1) was tested in a proof-of-concept study in 212 drug naive mild AD subjects and demonstrated improved memory performance, both in the overall intention to treat population (baseline MMSE 20-26) and in the prespecified subgroup of patients with very mild AD (baseline MMSE 24 to 26) (Scheltens et al. 2010, Alzheimers Dement 6, 1-10). Objectives: To investigate the effects of Souvenaid in elderly who are at high risk of developing AD, the EU-funded "LipiDiDiet"™ study started in 2009. Material and methods: The LipiDiDiet study is a 24-month, randomised, controlled, double-blind, parallel-group, study in 300 prodromal AD subjects (according to criteria of Dubois et al. 2007, Lancet Neurol 6, 734-46). Subjects are randomly allocated to either active (Souvenaid) or an isocaloric control product. Primary outcome measure is cognitive performance as assessed by a modified version of the Neuropsychological Test Battery (NTB; Harrison et al. 2007, Arch Neurol 64, 1323-9). Secondary outcome measures include progression to AD, cognitive performance (ADAS-cog and MMSE), functional abilities (ADCS-ADL), depression (MADRS), MRI atrophy rate, plasma and CSF biomarkers, safety and tolerance and nutritional parameters. The major study parameters are assessed at baseline, and after 6, 12, and 24 months of intervention. Results: Enrolment for the LipiDiDiet study is ongoing. First results are expected to be available in 2014. Discussion: The positive effect of n-3 fatty acid supplementation on delayed word recall and attention in a subgroup of very mild AD and the benefits of Souvenaid on memory performance in mild AD have recently been demonstrated. To extend the evidence on the efficacy of Souvenaid, three phase III clinical studies were initiated, including the LipiDiDiet study. Conclusion: The multi-nutrient drink Souvenaid is formulated to stimulate synapse formation and is developed for the dietary management of AD. The LipiDiDiet study was designed to investigate the effects of Souvenaid in elderly who are at high risk of developing AD. 1. Souvenaid and Fortasyn are registered trademarks of N.V. Nutricia. 2. This research is funded by the EU FP7 project LipiDiDiet, Grant Agreement N° 211696.

P43 - RECOGNITION OF FACIAL EXPRESSIONS AND EMOTIONAL PROSODY IN ALZHEIMER DISEASE. H.A. COSTA, W.C. DE SOUZA *(Fortaleza - CE, Brazil)*

Introduction: It is already well known that the recognition of emotion, including facial expressions and emotional prosody, declines with age. Current researches suggest that natural aging isn't sufficient to explain the rate and type of deficits in individuals with Alzheimer's Disease (AD). It is important to investigate this abilities due to its role in the adaptative behaviour and social life. Objectives: This study investigated the existence of impairment in the recognition of emotional facial expressions and emotional prosody in patients with Alzheimer's, comparing them to healthy elderly with compatible age range. Also, we sought to determine the cognitive performance of AD patients and investigate the relationship of cognitive tasks with the subtests of the Florida Affect Battery, in search of possible predictors. Material and methods: Participants: the first group included 17 individuals with AD with mean age of 76 years (SD 6.37). The second group included 11 healthy individuals with mean age of 75.63 (SD 8.52). The participants should not present any psychiatric or neurological diseases. Also they should not have any visual or hearing impairment unless corrected appropriately. Materials: Subtests of WAIS-III, Clock Drawing Test, Animal Fluency Test, Mini Mental State Exam, for cognitive assessment were used. The Florida Affect Battery was used to access emotion. It consists in a battery of 11 subtests divided in visual (subtests 1 to 5) and auditory stimuli (subtests 6 to 10). Procedures: the set of subtests was applied individually, divided in at least 3 sessions during one hour each. Parametrical statistics was used (means, standard deviation, independent samples t-test and Pearson's correlation). Results: Comparing the results of the cognitive assessment, the difference between the means of the groups were significant (sig 0.00) to p=0.05, with better result of healthy individuals in all tests used. Comparing the results of the subtests of FAB, the difference between means was also significant (sig 0.00) to p=0.05 in all subtests, with worse performance of Alzheimer. The means and standard deviations for each subtests were (Alzheimer Disease and Healthy individuals respectively): Subtest 1 (m= 16,94, sd=3,43; m=18,91, sd=0,94), subtest 2 (m=15,71, sd=2,11; m=18, sd=1,41), subtest 3(m=13,06, sd=3,41; m= 17, 27, sd=0,78), subtest 4 (m=14,18, sd=2,5; m=18,09, sd=1,3), subtest 5(m=10,94, sd=2,51; m=17,45, sd=1,63), subtest 6(m=13,29, dp=2,59; m=15,64, dp=0,5), subtest 7 (m=16,47, dp=2,91; m=19,18, dp=0,75), subtest 8A (m=10,82, sd=3,00; m=15,82, sd=0,75, subtest 8B (m=20,76, sd=4,92; m=28,09, sd=1,44), subtest 9 (m=10,35, sd=2,62; m=16,55, sd=1,12) and subtest 10(m=11,59, sd=2,64; m=18, sd=1,84). The groups showed different percentage of correct response according to different emotions: Happiness and Anger got the highest rates of recognitions in both groups: Healthy individuals (94.3 and 93.2%, for happiness and anger respectively)and Alzheimer group (90,2 and 84,7%,for happiness and anger respectively). There were significant correlations between Mini Mental and subtest 3 of FAB (r=0.711; p=0.05) and subtest 5 was correlated to most of the subtests of WAIS-III. Discussion: The results show that individuals with AD were impaired in the cognitive tasks proposed. Also the recognition of facial expression and emotional prosody were affected in that group. Considering the results of the subtests of Florida Affect Battery it is possible to notice that the elderly in general have a better performance in purely perceptual tasks (subtests 1,2,6 and 7) than in those who require emotional recognition. Both groups tend to recognize better Happiness and Anger that probably have a better adaptive value. Those results probably affect the social interaction and the affective relationships of the individuals with AD since we use emotional signs as clues to social interaction. It was not possible to determine if the cognitive tasks could predict any impairment in the recognition of facial expressions or emotional prosody since the correlations were not related to the type of stimuli used (visual or auditory) but to isolated subtests. Conclusion: The results of T-test between both groups show an impairment in recognition of facial expressions and emotional prosody to the Alzheimer individuals. This impairment could not be associated do normal aging since the performance of Alzheimer individuals in cognitive tasks was significantly worse than the performance of healthy individuals.

P44 - RELATIONSHIP BETWEEN PATIENT DEPENDENCE ON OTHERS AND RESOURCE UTILIZATION IN ALZHEIMER'S DISEASE (AD): RESULTS FROM A LONGITUDINAL STUDY. L.A. LACEY, T. NIECKO, C. LEIBMAN, E. LIU, M. GRUNDMAN FOR THE ELN_AIP_901 INVESTIGATOR GROUP *(Janssen Alzheimer Immunotherapy, Dublin - Ireland)*

Introduction: Dependence on others for care needs has been recommended as a unifying construct in defining severity in AD and has been shown to correlate with measures of cognition, function and behavior. Published data also suggests that dependence could be a useful measure for studying the economic consequences of progression in patients with AD. Much of the support for the Dependence construct has been based on cross-sectional data showing relationships between dependence, measured using the Dependence Scale (DS), and clinical and socio-economic outcomes. Objectves: The objective of this study is to measure the latter relationship longitudinally. Material and methods: An analysis of data from participants with AD enrolled in a longitudinal observational study from 39 study sites across the United States and Europe, was conducted. The study was conducted between 2006 and 2009 and the entry criteria were similar to those used in the Alzheimer's Disease Neuroimaging Initiative (ADNI). The DS (range 0-15, higher score means more dependence), and measures of resource utilization (Rud lite 2.4) were administered at 6-monthly intervals. As the DS was introduced at week 26, all analysis refers to data collected at 3, six- monthly visits: week 26, week 52 and week 78. US unit costs (for 2010) were assigned to the collected resource utilization data and cost data was assigned to 6 cost categories: direct medical (inpatient and outpatient hospital care), direct non-medical (i.e. institutional care and community services), indirect (i.e. caregiver lost productivity), informal costs (i.e. caregiver time), total cost and total cost_2 (total cost less informal costs). Repeated measures models were used to examine the relationship between the DS and resource utilization over the 3 sequential time points. Repeated measures analyses were performed in SAS (v9.1.3) using the PROC MIXED procedure. This procedure uses restricted maximum likelihood (REML) for parameter estimation and allows for testing of within and between subject variance since measurements made on the same subject over time are often correlated. This modeling technique is suited to longitudinal study designs where repeated measurements on the same subject are performed. The repeated measures models tested were all of the form: Log (co 196 subjects with mild to moderate AD participated in the study. The mean age was 75.2 and 54.6% were female. The mean MMSE score at baseline was 21.7 (range, 14-30). The duration of AD was 3.3 years (range 0-15.8). Each participant contributed a maximum of 3 paired observations for resource use cost and DS to the analysis. For subjects with no missing DS score for all 3 time points, the mean (SD) DS scores were 5.26 (2.4), 5.49 (2.4) and 6.06 (2.9) for weeks 26, 52 and 78, respectively. In addition, for subjects with no missing cost data for all 3 time points, the mean (SD) 6 monthly-total costs were $9,304(14,482), $10,429(14,409) and $13,940(22,381) for weeks 26, 52 and 78, respectively. The repeated measures models confirmed a significant relationship between the DS and all cost categories, indicating an increase in cost with increasing dependence: direct medical costs (p=;0.05), direct non-medical costs (p=0.0001), indirect costs (p=0.05), informal care costs (p=0.0001), total costs (p=0.0001) and total costs_2 (no informal costs) (p=0.0001). For indirect and direct non-medical costs, patient gender was also a significant predictor (p=0.05, and p=0.005, respectively). Discussion: The analysis builds on previous cross-sectional data showing a relationship between dependence, measured using the DS and resource use costs and demonstrates that such relationships can be observed over time. The data suggests that as dependence increases, the management costs increase. This appears to be particularly strong for direct non-medical costs and informal care costs. Conclusion: The relationships observed in previously published cross-sectional analyses were confirmed longitudinally. These data further support the use of dependence as a predictor of resource utilization and associated cost when modeling the economic consequences of progression and interventions which may alter progression.

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