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- Epidemiology
- Biomarkers
- Intervention
- Clinical Trials

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Editorial

The Journal of Prevention of Alzheimer's Disease - JPAD
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A Turning Point in Alzheimer's Research: Harmonized Research Strategies and Novel Investments in Public Health Infrastructure Are Reenergizing the Field, and Rekindling Hope for Those Affected by Alzheimer's and Related Dementias

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Alzheimer's disease (AD) and related dementias (ADRD) are complex global health issues that require resources and commitments from around the world. The international research community continues to build upon knowledge and generate fresh ideas and strategies to move toward an effective therapy to treat, delay, or prevent ADRD. With accelerated momentum and more funding, the field is poised to hasten the discovery of interventions to stop, slow, or prevent disease progression, and improve care and quality of life for those affected.

The urgent need for interventions

An estimated 50 million people worldwide are currently living with dementia—a number that is expected to grow to 82 million by 2030, and more than triple to approximately 152 million by 2050 (1). The worldwide estimated cost of dementia is approximately US$1 trillion, a figure that will double to approximately US$ 2 trillion by 2030 (1). A crisis of this magnitude requires significant commitment and investments. In the US, the National Institutes of Health (NIH) is leading the way with $2.3 billion in funding for ADRD research (2).

The growing awareness of the complexity of AD and the importance of pursuing strategies that combine multiple treatment approaches are the most impactful developments in dementia science in recent years. Combination treatment approaches include pharmacological therapies and lifestyle modifications, in order to achieve the goal of effectively treating or preventing ADRD by 2025. This knowledge is supported by accumulating evidence that the underpinnings of AD occur over an extended period of time (3). Advances in cancer and heart disease, including early detection and interventions, also recognize and support a multi-pronged approach to addressing underlying disease complexity.

While furthering our understanding of the biological underpinnings of ADRD at all stages along the disease continuum, one guiding principle will be to advance strategies similar to those used for cancer and heart disease. These strategies focus on early detection and prevention, as well as a combination of lifestyle and pharmacologic interventions. Another aim will be to place an unprecedented emphasis on coordinating and harmonizing all research efforts so that all avenues of exploration and research build upon and reinforce one another. These objectives already are reflected in current avenues of research, funding strategies and initiatives, and forthright new directions in public health infrastructure.

Focus on prevention and lifestyle

In keeping with efforts to address AD at all stages along the disease continuum, the field has evolved toward placing a more intense focus on prevention. This focus has led to the design and launch of several revolutionary secondary prevention trials during the past seven years, which are targeting underlying pathophysiology in individuals at risk for AD with the goal of preventing AD symptoms. Among the largest secondary AD prevention trials currently underway are the Alzheimer's Prevention Initiative (API) Autosomal-Dominant AD, API APOE4 trial, Dominantly Inherited Alzheimer Network Trials Unit, and Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease/Longitudinal Evaluation of Amyloid Risk and Neurodegeneration trials (4). With an emphasis on coordinating and harmonizing research efforts, FBRI and the Alzheimer's Association lead the Collaboration for Alzheimer's Prevention, which functions to encourage regular dialogue among the prevention studies regarding all aspects of study design and outcomes. As the field reaches the midpoint of 2019, these trials are maturing,

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and lessons from their launch and progress are informing the next generation of clinical studies and paving the way for improved clinical and diagnostic decision making.

The AD field remains firmly committed to examining and better understanding the role of multiple lifestyle factors in the development and prevention of AD, based on growing evidence that exercise, education, complexity of occupation, and other lifestyle factors may have protective effects for those at risk for dementia. Among the most intriguing findings in this area to date have been those from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) Study. This large-scale two-year study, which demonstrated that combination therapy comprising physical exercise, nutritional modification, cognitive stimulation, and self-monitoring of heart health risk factors had a protective effect on cognitive function, has ignited hope and inspired the launch of similar trials around the world to determine whether such factors might also be preventive for dementia.

In 2019, recruitment is now underway for the largest of these trials, the U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER). U.S. POINTER, led and funded by the Alzheimer's Association, is a two-year clinical trial to evaluate whether lifestyle interventions that simultaneously target multiple behavioral modifications protect cognitive function in older adults at increased risk for cognitive decline. U.S. POINTER will enroll approximately 2,000 older volunteers (ages 60-79) from five large health care networks across the United States. Community partners, including the national network of Alzheimer's Association Chapters, will assist with intervention delivery and in turn set the stage for an accessible and sustainable community-based model for strategies to reduce risk. Two lifestyle interventions will be compared to determine whether cognitive benefits from a structured program differ from those of a self-guided program.

U.S. POINTER and FINGER are part of a global network, bringing together initiatives designed to evaluate multimodal lifestyle interventions. This network Worldwide FINGERS (WW-FINGERS), convenes annually virtually and in person with aims of sharing experiences, harmonizing data, and planning joint international initiatives for the prevention of cognitive impairment or dementia.

A BOLD initiative

While the research community is devoted to advancing potential interventions to stop, slow, or prevent disease progression, there are millions affected worldwide, including more than 5.8 million Americans, living with Alzheimer's today. There continues to be a significant unmet need for improved quality of life for those already living with AD and their caregivers. To help reduce some of the burdensome costs associated with AD, the field has recognized that it is essential to invest not only in basic and clinical research but also in an international public health response to AD, with a focus on comprehensive disease assessment, monitoring and care.

A milestone in meeting these needs in the US, the Building Our Largest Dementia (BOLD) Infrastructure for Alzheimer's Act—legislation designed to create a vital public health infrastructure to address AD—was signed into law on December 31, 2018. The passage of this historic act, which attracted enormous bipartisan support and demonstrated that Congress remains fully committed to the fight against Alzheimer's disease, represents a critical step toward addressing the AD public health crisis. The new law will lead to the establishment of Alzheimer's public health centers of excellence across the US, provide funding to public health departments to implement effective Alzheimer's interventions, and increase analysis and timely reporting of data on cognitive decline and caregiving to inform future public health initiatives and improve measures of progress.

The BOLD Infrastructure for Alzheimer's Act was originally developed and shepherded into law by the Alzheimer's Impact Movement (AIM), the advocacy arm of the Alzheimer's Association. AIM will also help to further existing policies designed to strengthen the US response to AD. In 2005, for example, the Alzheimer's Association partnered with the Centers for Disease Control and Prevention to create and launch the Healthy Brain Initiative (HBI) and Public Health Road Maps. The HBI Road Maps feature strategic actions that state and local public health departments can take to address cognitive impairment, promote improved cognitive functioning, and help meet the needs of caregivers. The passage of the BOLD Infrastructure for Alzheimer's Act will enhance implementation of the HBI Road Maps by promoting early detection and diagnosis, reducing lifestyle-related risks, and preventing avoidable hospitalizations.

Looking ahead

As the world's largest nonprofit funder of Alzheimer's research, and as the nonprofit with the highest impact worldwide in Alzheimer's and dementia science, the Alzheimer's Association is currently investing over $165 million in more than 450 best-of-field active projects in 25 countries. Through policy and research initiatives, the Alzheimer's Association continues its mission of serving as both a leader and a catalyst in funding, as well as orchestrating a broad range of research initiatives. In our role as a global convener, we are actively pursuing opportunities to expand public and private investments in AD research, advance the proliferation of potential therapeutic targets, launch new clinical trials to test these interventions, and design novel studies to help us better understand risks for dementia as well as the best

approaches to clinical and long-term care.

Research investments in the biological underpinnings of the disease (often referred to as basic research) continue to be a top priority. AIM has been instrumental in securing increased federal funding at unprecedented levels to support critical basic and translational science research by the NIH, which leads the nation in biomedical research on ADRD. Recent efforts by AIM have more than quadrupled Alzheimer's research funding at the NIH since the passage of the National Alzheimer's Project Act, and have led to an historic $425 million increase for Alzheimer's research at the NIH for fiscal year 2019.

Increased federal funding for the NIH has come at a critical moment. Many of the late-stage clinical trials today were designed during a time when funding for research into the biological underpinnings of the disease was inadequate. Recent phase 3 studies have not yielded the results that are desperately needed: more effective treatments for Alzheimer's dementia. Today, many companies are changing the way that they invest in and develop future drugs including moving toward venture capital approaches to partnerships and licensing and outsourcing research in lieu of their own in-house research. Increased dollars in the field for discovery of innovative and diverse mechanisms and targets is more critical than ever to enable the development of future treatments from the bottom up, from novel ideas through biotech early development and beyond. With these vital boosts in NIH funding, scientists are able to work at a more rapid pace to advance basic disease knowledge, explore ways to reduce risk of dementia, discover new biomarkers for early diagnosis and drug targeting, and develop potential treatments.

As we move forward at a rapid pace, the coordination and harmonization of all initiatives will remain the key to success for finding prevention and treatment options. In all of our endeavors—whether we are working toward a common language or nomenclature for generating and testing hypotheses, or establishing common measures of neurodegeneration and neuronal injury—the AD community will continue to thrive as long as we remain committed to unifying our efforts (5). With continued persistence and dedication, careful orchestration of initiatives will sustain our focus on developing multipronged treatment strategies over the AD continuum and will greatly improve our likelihood of achieving effective treatment and prevention of ADRD.

Disclosures: MC Carrillo, HM Snyder, R Conant and R Egge are employees of the Alzheimer's Association.

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Editorial

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Can Digital Technology Advance the Development of Treatments for Alzheimer's Disease?

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Abstract

The report explores the potential digital technology has to generate novel endpoints and digital biomarkers for Alzheimer's disease drug development studies. Drawing from literature and novel pilots, we explore the value of innovative digital technology to digitize physiological behaviours such as sleep disturbance and gait changes. Technology now exists to monitor and quantify our use and interaction with electronics in the home, the use of social platforms and smart-phones, geolocation, sleep and activity patterns. These multimodal digital data are a feasible alternative to capturing the more complex activities of daily living that require higher cognitive processes and are a sensitive predictor of disease. The combination of biosensors and the internet of things (IoT), offers the potential to collect highly relevant, objective data in a continuous, passive and low burden manner. Digital endpoints and biomarkers could have value in the diagnosis, monitoring and development of therapies for patients living with Alzheimer's disease.

Key words: Digital biomarkers, clinical trials, ecological momentary assessment, gait, ADL, Alzheimer's disease, smartphone.

What is the Problem?

There have been no new Alzheimer's disease drug therapies on the market in over a decade. Alzheimer's disease is a complex multifactorial disease and there are many reasons proposed for this stasis, including limited validated drug targets, lack of reliable surrogate biomarkers, slow and variable disease progression, and the dependency on soft endpoints (1). The limited sensitivity of existing tools to detect and monitor Alzheimer's disease is compounded by the narrow set of outcomes (2). These limitations become even more impactful in trials of disease-modifying therapies; current measures of cognition are not sensitive in individuals with very early stages of the disease (3) and profoundly affect the value of these assessments in studies where subjects with no or minimal symptomatology are followed for several years before they may reach a pre-defined outcomes.

The Solution?

In its most recent, draft Guidance the Food and Drug Administration (FDA) (4) accepts that cognition, in its entirety, encompassing all its constituent processes and domains, is meaningful in terms of daily function. However, it caveats this with the following statement that reinforces the dilemma facing the industry: "when measured using conventional approaches with sensitive tools directed at particular cognitive domains, the meaningfulness of measured changes may not be apparent." This still leads to a certain need for co-primary endpoints where cognitive change needs to be accompanied by a benefit reflected by an independent endpoint assessing daily function, operationalized as "Activities of Daily Living" (ADL). The more complex activities linked to independent living are assessed by Instrumental Activities of Daily Living (IADLs) and include items such as housework, communication using computer and telephone, food preparation etc. There is a growing body of evidence that subtle deficits in IADL, particularly those that are performance based, are more sensitive to early cognitive decline and may be present in mild cognitive impairment (MCI) (5, 6).

Smart Home Technology

Smart home technology is readily available, combining sensors and connected devices that monitor and control the use of appliances in the home (7). These systems are a network of connected technologies that can monitor a number of activities in the home including; the opening and closing of doors, movement in specific locations, heat and light and the presence or absence of an individual. In a short pilot, we combined smart home data (Table 1) with actigraphy data to explore the potential to generate insights more usually collected by questionnaires (8). Connected home systems are already utilized by health agencies to support older adults living in the community (9) as part of healthy aging programs for safety and health monitoring (10). There are significant possibilities for their use in drug development studies by providing continuous data to generate novel endpoints

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Table 1. Objective Sensor data and related ADL question (7)

Device/Sensor	End Point	Example of ADL questions
Smart Plug	Switching on and off electrical device	Did subject use a household appliance to do chores?
Motion Sensor	Movement in the house. (Out of Bed- Specific rooms)	Did the subject move in or outside the house?
Presence Sensor	Proximity to house	Did subject get around (or travel) outside of his/her home?
Multipurpose Sensor	Entering and leaving house	Did subject get around (or travel) outside of his/her home?
Actigraphy Device	Number of Steps	Activity (inside/outside of Home)

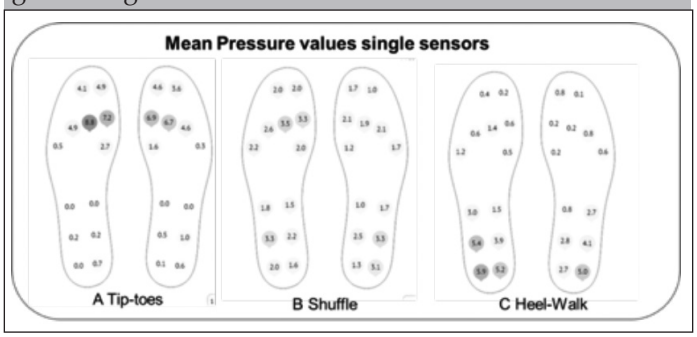
that have the potential to be more sensitive to change than existing methodologies. Digital technologies could benefit Alzheimer's disease research by generating a more patient centric assessment by removing domains from questionnaires better captured by passive digital technologies (Table 1). These new multi-modal assessments could facilitate the capture of complex digital IADL's, such as the ability to use a smartphone, conduct online banking, social media interaction etc. New composite digital endpoints could emerge by mapping the discordance between subjective data of the individual's perceived behaviour and their objective data as gathered by sensors. Finally the high number of data points reduces the bias from rare samples during the pre-scheduled on site study visits, what should increase the robustness and reliability of the data, ultimately leading to less data variability (11).

Gait

There is growing interest in gait change as a marker for cognitive decline. Reports of gait disturbances have been found to precede dementia by more than 5 years (12, 13). While the use of wrist or ankle worn physical activity monitors (PAM) to collect steps and gait cadence is well established, assessing spatiotemporal gait is not a simple process and is limited to specialist clinics equipped with electronic walkways. This significantly affects the utility of this approach in clinical trials due to the limited number of sites available for gait assessments.

New technology such as smart-insoles is emerging. In a recent pilot, we used smart insoles to quantify gait speed and stride variability (14) in a non-clinical setting. The potential value of smart-insoles is in the portability of the technology, enabling their use outside of specialist gait clinics and thereby monitoring gait change in the individual's home or residential care setting. This has the potential to capture more nuanced assessment of gait change, including balance, inter-gait variability and even stance. These devices generate vast quantities of data leading to the possibility of using machine learning to identify new clinical sensitive signals within the data set. However it was outside the scope of our pilot study to determine the minimal clinically important differences (MCID) for cognitive decline. In addition, it should be noted that factors such as footwear and data transfer could impact the operationalization of these devices in a clinical trial.

Figure 1. The smart insoles generate data from 13 embedded tri-axial accelerometers each capable of generating 100hertz data



The static report shows pressure distribution, single pressure values and total forces for the single sensors embedded in the insoles when a healthy volunteer engaged in different patterns of walking.

Smart Phones and Smart watch

The smartphone and smartwatch are emerging as significant digital tool for the collection of disease specific biomarkers and endpoints for Alzheimer's disease. Smartphone are widely available and have an array of inbuilt technology including accelerometers, gyroscopes, magnetometers, global positioning system (GPS), proximity sensors, ambient light sensors, microphones, cameras, touch-screen sensors. These sensors facilitate the capture a multitude of data including; activity, cadence, speech, tremor and location. Smartphones can facilitate the ready deployment of a growing array of applications (apps) and can be to deploy cognitive assessments and gamification. Used outside of the clinic as screening tools, frequent burst cognitive assessments have the potential to make results more reliable and can potentially offer a means of continuous longitudinal monitoring. Changes in language and voice are being evaluated as predicators of disease progression (15, 16) with the goal to develop smartphone apps that could be used to for this purpose.

Smartwatches are evolving from simple actigraphy devices that measure sleep and activity to biosensors that that contain an array of sensors including photoplethysmography (PPG) and electrodermal activity (EDA) sensors. These biosensors can generate

a myriad of endpoints including sleep disturbance, activity, heart rate, respiration rate, oxygen saturation and galvanic skin response. These biosensors could have particular utility in the ongoing research into the influence of cardiovascular factors on the development and progression of AD (17). It is entirely feasible that biosensors capable of continuously monitoring cardiovascular and respiratory signals could play an increasingly significant role as low burden tools to generate new targets for treatment and prevention of AD.

What does the future look like

Clinical development programs for Alzheimer's disease are becoming larger and longer; the sustainability of existing methodologies and study designs is questionable. There is growing interest in the use of digital technology and exploring the transformative potential of these technologies as a means of providing additional insights (18).

The value of actigraphy devices in the study of this population has been previously discussed (19) and this report focuses on primarily on two areas gait assessment and IADL where digital technology could have a significant impact on patient centric trial design and the generation of new digital endpoints. There is significant potential for the use of connected devices and IoT, particularly for disease-outcome driven prevention studies. These sensors are gaining acceptance by health care systems as a means of keeping older adults in the community. They are relatively easy to install and can passively capture individuals' behaviour as they go about their normal activities of daily living. These use cases are ensuring that the systems are becoming more robust in terms of connectivity and compliant in terms of data privacy and security and more robust for the generation of data for use in clinical trials.

There is potential value in combining data from multimodal digital devices and developing composite end-points that are more responsive to change then viewing each dataset as a singularity. Advanced analytic platforms that use artificial intelligence and machine learning are available that can ingest data from multiple sources including; sensors, smartphone, smart-home, environmental, geolocation, voice and questionnaires, generating insights into behavioural changes and cognitive decline. The correlation of these data with clinical observations and laboratory biomarkers could help characterise the populations, monitor progression over time and assess the efficacy of interventions.

What more needs to be done

As with any new outcome assessment, digital endpoints need to be clinically validated. The technology is required to measure endpoints that are both meaningful to the patient and clinically relevant. The data generated by the digital assessment needs to capture the concept of interest that reflects the meaningful health aspect for individuals living with Alzheimer's disease. In addition, the data generated needs to measure meaningful change that is consistent across specific populations. The same scientific rigor and data quality criteria are required whether considering digital or traditional methodologies. The digital technology need verification and validation to ensure there is sufficient scientific evidence to support its use in a specific study (20). Data privacy, security and storage need to align with local regulations. The potential of Digital Biomarkers and endpoints is immense, however, if a digital strategy is to be successful, the inclusion of a conscious patient centric approach including strategies to quantify and reduce patient burden and ensure patient engagement is essential.

Conflict of Interest: There are no conflicts of interest.

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Commentary

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Is a Large-Scale Screening for Alzheimer's Disease Possible? Yes, in a Few Years

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Recent evidence on blood-based biomarkers is pointing the way towards a new era of large-scale, feasible, cost-effective and non-invasive screening for Alzheimer's disease (AD). This was one of the main focuses of the recent meeting of the European Union-North American Clinical Trials in AD (EU/US CTAD) Task Force, which took place in Barcelona in October 24-27, 2018, and convened drug and diagnostics developers from industry and academia in order to define a roadmap for the development and marketing of blood-based biomarkers (1).

According to the recent National Institute on Aging - Alzheimer's Association (NIA-AA) and International Working Group (IWG-2) diagnostic criteria (2–4), AD biomarkers can be assessed using neuroimaging techniques (i.e. magnetic resonance, MR; and positron emission tomography, PET) and/or cerebrospinal fluid (CSF) collection, and include amyloid (PET or CSF), tau (PET or CSF) and neurodegeneration (MR, PET, or CSF). Among them, only MR is usually performed in the general memory clinics, allowing the routine assessment of neurodegeneration in patients with suspected AD. On the contrary, the assessment of AD pathophysiological biomarkers (amyloid and tau) is often limited to academic memory clinics due to high costs and limited accessibility of the technology. These reasons also limit a large-scale use of biomarkers in lower- and middle- income countries.

The EU/US CTAD task force has taken stock of the situation in this field. Research on amyloid peptide assays in plasma has been developing quickly, and consistent evidence indicates high sensitivity (0.76-1.00) and specificity (0.75-0.84) for amyloid status (5,6). Such values make plasma amyloid a reliable screening tool. On the contrary, the results on blood-based tau biomarkers are less exciting. Indeed, the correlation between plasma and CSF tau is weak, likely due to rapid clearance of tau in the bloodstream. Neurofilament light chain (NfL) has been proposed as a reliable marker of neuronal injury. Indeed, a recent paper showed that NfL levels are higher in mild cognitive impairment (MCI) and AD dementia patients than healthy controls. The authors also assessed the longitudinal association between NfL level and AD features including CSF biomarkers, imaging measures and cognitive test results. They found that NfL level increased over time in all groups, especially in MCI and AD dementia patients. Moreover, longitudinal changes of NfL correlated with baseline CSF biomarkers (Aβ42: β=-3.11; phosphorylated-tau: β=2.70; total-tau: β=2.99, $p<0.001$), MR measures (hippocampus: β=-4.56; ventricle: β=3.55; entorhinal: β=-3.79; temporal: β=-4.35, $p<0.001$), fluorodeoxyglucose-PET (composite uptake: β=-3.79, $p<0.001$), and cognitive performance (Mini-Mental State Examination: β=-4.35; Alzheimer's Disease Assessment Scale–Cognitive subscale: β=4.59; Clinical Dementia Rating Scale-Sum of Boxes: β=4.46, $p<0.001$) (7). Finally, the EU/US CTAD Task Force also focused on "-omics" analyses, i.e. approaches that allow to provide insight into the molecular mechanisms underlying AD and other diseases. Within this framework, the ongoing European Medical Information Framework – Multimodal Biomarker Discovery (EMIF-MBD) project will provide further evidence on non-invasive AD biomarkers in pre-dementia stages (1, 8).

The development and marketing of blood-based biomarkers will limit the number of people requiring more expensive testing, enable screening, support clinical diagnosis, and allow repeated sampling as possible pharmacodynamic markers in clinical trials. Noteworthy, blood-based biomarkers will be used to estimate the individual's risk to develop MCI or dementia, and this would be particularly valuable for people with subjective cognitive decline, for whom amyloid- and tau- PET are currently not recommended due to lack of evidence on their cost-effectiveness. Moreover, preliminary evidence suggests that prevention is more effective in patients with higher risk for dementia (i.e. in amyloid-positive vs amyloid-negative patients) (9). Thus, blood-based biomarkers will play a key role in the definition and implementation of personalized treatment or prevention interventions. Furthermore, their use might make available a larger pool of subjects eligible for clinical trials testing disease-modifying drugs, facilitating their development.

Efforts, time and resources are still needed to understand whether blood-based biomarkers are actually

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clinically useful, and to create standardized diagnostic procedures, but the initial results are highly promising and justify impartial optimism regarding a near future when a large-scale screening for AD is possible.

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The 2018 Revised FDA Guidance for Early Alzheimer's Disease: Establishing the Meaningfulness of Treatment Effects

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Abstract

The present report reviews the revised 2018 FDA guidance for early AD, with an emphasis on meaningfulness of clinical outcome assessments (COAs). A radical shift is evident in the importance given to establishing the meaningfulness of COAs in the 2018 draft versus the 2013 draft. The implications of this shift include the assertion that cognition is clinically meaningful, but that a persuasive effect on cognition, depending upon disease stage of the participants in the trial, is one that is of enough magnitude, established across multiple relevant domains, and can be supported by biomarkers reflecting underlying AD pathological changes. Meaningfulness is established through an understanding of the conceptual relevance of what is being measured and magnitude of any treatment effect. Precedent exists within other FDA guidance and independent good practices publications as to how meaningfulness may be assessed e.g. via evaluation of content validity and concepts such as minimally important difference. Additionally, FDA is developing a series of methodological Patient Focused Drug Development (PFDD) documents to provide further guidance on this topic, which are aimed at addressing gaps in methodology and recommended best practice. Importantly, application of PFDD approaches to AD is behind that in other areas and there is limited published content validity for COAs and a lack of supportive qualitative research. Initiatives to build robust conceptual models of AD and develop novel direct measures of meaningful health outcomes will have a significant impact on measurement of efficacy in clinical trials and on payer determinations of beneficiary value. Greater recognition of what is meaningful from the perspective of the patient and caregiver will inform regulatory reviews and determinations for payment and coverage of treatments.

Key words: Cognition, function, clinical relevance, patient focused drug development, regulatory guidance.

Introduction

FDA first published draft guidance on "Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease" in 2013. This guidance made mention of the co-primary approach at the AD dementia stage, where a functional or global assessment would "ensure the clinical meaningfulness of a cognitive benefit that may be observed." Challenges for early disease were related to mild or absent functional impairment, for which solutions might include integrated cognition-function assessment (e.g. CDR-Sum of Boxes), cognition assessment alone, or time-to-dementia. The terms 'meaningful' or 'meaningfulness' were used twice, once in relation to the co-primary approach and once in relation to a biomarker effect. In 2018, a revision was published "Early Alzheimer's Disease: Developing Drugs for Treatment" (1). Notably, with respect to clinical outcomes assessments (COAs) the revised draft guidance does not mention any example assessments, but now uses the terms 'meaningful' or 'meaningfulness' 27 times, suggesting an important shift in focus. The use of these terms in the revised draft guidance can be broken down into two different contexts: that of conceptual relevance ('is what is being measured meaningful?') and that of magnitude of effect ('is the size of a treatment effect sufficient to confer a benefit?') [Figure 1]. Importantly, the guidance also introduces a clinical staging framework and clarifies the focus as Stages 1-3. Stage 1 includes patients with characteristic pathophysiologic changes of AD but no evidence of clinical impact; Stage 2 includes patients with characteristic pathophysiologic changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures, but no functional impairment; Stage 3 includes patients with characteristic pathophysiologic changes of AD, subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment; and Stage 4 includes patients with overt dementia. This guidance does not discuss definitions of or methods for establishing conceptual relevance and meaningful magnitude of effect. However, precedent exits within other FDA guidance and publications as to how this may be addressed.

FDA is currently developing a series of four methodological PFDD guidance documents to address collection and submission of patient experience data and other relevant information from patients and caregivers for medical product development and regulatory decision making. This includes a new patient experience data table to be reviewed as a part of new drug applications. This table includes multiple types of suitable data including

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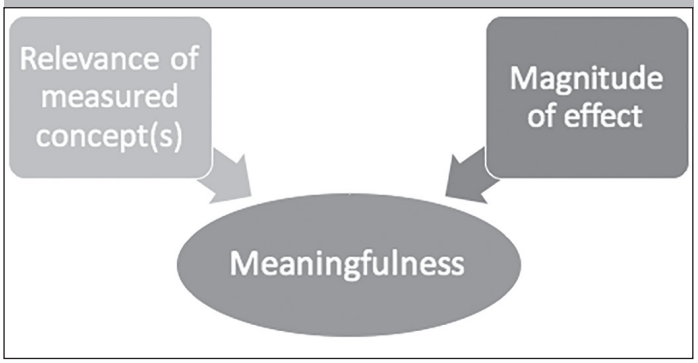
that from COAs, qualitative studies in patients and caregivers, PFDD stakeholder meetings, and survey, natural history and patient preference studies. A key component of this work is the development and validation of COAs as measures of treatment benefit. In the 2009 FDA PRO guidance, two important issues are discussed which are the need to establish content validity i.e. "the extent to which the instrument measures the concept of interest" and the need to define a clinically meaningful magnitude of change. These two issues are considered important to all COA types by FDA i.e. patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO) and performance-based outcome (PerfO) assessments. Each of these will be discussed here in relation to the revised draft early Alzheimer's disease (AD) guidance.

The present report will review the revised 2018 FDA draft guidance for early AD, with an emphasis on the meaningfulness of COAs and the implications for COA development and validation.

Figure 1. Establishing the meaningfulness of a treatment effect



Relevance of measured concept(s)

FDA revised draft guidance for early AD mentions meaningfulness in the context of conceptual relevance in several places e.g. "cognition is meaningful, but when measured using conventional approaches with sensitive tools directed at particular domains, the meaningfulness of measured changes may not be apparent." suggesting that both the domains measured (concept) as well as the ability of sensitive tools to measure small effects (magnitude), should be considered. Also, the need to ensure coverage of important cognitive concepts is expressed e.g. "cognitive changes of particular character, perhaps defined by magnitude or breadth of effect(s), may represent clinically meaningful benefit." suggesting again that both breadth of measurement across multiple domains (concept) as well as magnitude, are important to clinical meaningfulness This suggests the importance of conceptual relevance or content validity i.e. ensuring important measurement concepts are captured ('breadth' of assessment); distinguishing between direct, interpretable measures of important health outcomes and indirect ('conventional') measures.

Content validity (ensuring the breadth of relevant concepts for measurement)

Establishing concepts of interest (COIs) for measurement is foundational for COA development (2). COIs can be identified via literature review and qualitative research in patients, caregivers and clinicians. This work may be used to build a conceptual model of a disease or condition, or a conceptual framework for a given COA to ensure content validity i.e. that important measurement concepts are captured. To date, relatively little qualitative research has been conducted in people with early (predementia) AD, and their families and caregivers, with no explicit published conceptual model(s). However, published research has suggested there are potential gaps in existing measurements including concepts such as "situational lapses," "burdensome coping strategies," "slowness," and modern instrumental activities of daily living (iADLs) such as cell phone, or email use (3–5). As one would predict given the limited amount of qualitative research conducted in AD, there are relatively few COAs based on qualitative insights, or with well described conceptual frameworks, exceptions being e.g. the C-PATH Cognition Working Group PRO (6), and Amsterdam iADL questionnaire (7). Recently, a first conceptual model for the dementia stage of the disease has been published (8), which has been used to evaluate the conceptual relevance of four COAs in mild-moderate AD (ADAS-Cog, ADCS-ADL, NPI, and Dependence Scale). Importantly, this work concluded that these "assessment measures do not appear to capture the concepts most relevant to/important to patients with mild/mild-moderate AD."

To address this gap and the lack of established conceptual models across the spectrum of AD, a patient and caregiver-led collaboration of industry, academics, government agencies and advocates, the Alzheimer's Disease Patient and Caregiver Engagement (AD PACE), has been formed. The aim is to understand what matters most to individuals across the spectrum of the AD lived-experience (including individuals with underlying AD pathology who are asymptomatic or have mild cognitive impairment), matching FDA PFDD initiatives and policies, and eventually informing clinical development programs, regulatory submissions, payer value models, coverage and payment determinations, and research on care and services (https://www.usagainstalzheimers.org/networks/ad-pace).

Direct versus indirect measures of important health outcomes

Although good practice discussions have suggested PerfO development should utilize qualitative insights from patients and caregivers (9), published evidence indicates cognitive tests (cognitive PerfO assessments)

have not employed robust qualitative data in their development. Often such tests are not intended as direct measures of meaningful health aspects and the test activities are not a part of a person's usual normal life. Thus, the meaning of a score is not intrinsically known and must be established during validation (2). For example, the widely used Digit Symbol Substitution Test is not an activity of daily life and the meaning of a score or score change in number of symbols substituted is not directly interpretable. However, data show that performance is strongly correlated with real world functional outcome and functional capacity and such data may then be used to support meaningfulness and score interpretation. Many cognitive tests and test batteries are based on empirical models arising from disciplines within the cognitive neurosciences (neuropsychology, cognitive and experimental psychology, psychopharmacology etc.). Within this conceptual model, cognitive function is viewed as: common to all people not a sign or symptom unique to a given disease or condition; composed of concepts not readily isolated, quantified, reported, or observed (i.e. not best known to the patient); and most reliably measured by objective tests. Cognitive assessments may be developed based on face validity, and theoretical and quantitative models using empirical evidence of impairment in different domains.

Application to novel composite outcomes

Several novel composite outcomes have been proposed for early AD and these have broadly been developed and/or validated as either integrated assessments of cognition and function for MCI due to AD/prodromal AD (Stage 3), or as cognition only assessments for preclinical AD (Stages 1 and 2). Examples of these include ADCOMS (10) for Stage 3 and the ADCS-PACC (11) for Stages 1 and 2. Such assessments may be further subdivided in respect of their conceptual basis as empirically driven, theory driven, or a combination (12). ADCOMS and ADCS-PACC have been differentiated as being empirically driven and theory driven respectively. For ADCOMS, statistical modeling within target datasets was used to select and weight items for "sensitivity to clinical decline." The theory-driven approach for the PACC initially selected "4 measures that are well established as showing sensitivity to decline in prodromal and mild dementia, and with sufficient range to detect early decline in the preclinical stages of the disease" based on a literature review. Thus, they could be considered close in conceptual basis, though making use of different methodologies. Importantly, none of these composites has been based on a predefined conceptual model or framework or used qualitative patient-caregiver insights in the development and selection of items, with all incorporating 'conventional' cognitive test items that are indirect measures of meaningful health outcomes. Though there has been some attempt to retrospectively confirm the content validity of the ADCOMS using qualitative data (15), the use of statistical modelling to select and weight items and the incorporation of cognitive tasks, which are not part of usual normal life, suggests an indirect measure for which the meaning of scores must be established (13). Indeed, the EU/US/CTAD Task Force in discussing current prevention trials argues that cognitive changes are "possibly the best "biomarker" for AD trials." Thus like imaging or fluid biomarkers, cognitive measures also have the potential to be developed and validated as intermediate or surrogate clinical trial outcomes (12). As reported in this journal, a study is now underway named iMAP to assess the meaningfulness of two cognitive composites (RBANS and APCC) in preclinical disease, and will evaluate this via ability to predict clinically meaningful differences as determined by diagnosis of MCI or dementia due to AD and changes in Clinical Dementia Rating Global Scores [CDR Global] and Clinical Dementia Rating Sum of Boxes [CDR-SOB]) (14).

Magnitude of effect

Several techniques exist for the estimation of meaningful effect, including response thresholds for individual patients and change or difference thresholds for groups of patients. Multiple terms have been employed to describe these approaches including minimally important difference (MID) or minimally clinically important difference (MCID), and different individual patient (e.g. minimum detectable change (MDC), clinically important responder (CIR) and group estimates (e.g. minimum detectable difference (MDD), clinically important difference (CID) estimates. The most well-established of these techniques are anchor-based and distribution-based estimates, though other techniques such as exit interviews and vignettes might be employed. Additionally, data regarding patient and caregiver preferences and priorities in respect of magnitude of effect may be derived from quantitative stated preference methods, or other approaches suited to the population under study (15).

Anchor- and distribution-based approaches

Anchor-based approaches to determining meaningful within-patient change involve the use of an external reference with already established relevance. The most commonly used of these are 'global transition questions,' examples of which are patient or clinician global impression (PGI and CGI) ratings. Mean change in the target scale for the group, which was e.g. "minimally improved" or "minimally worse" on a CGI of change, would be used as one estimate of the minimally important difference (MID). Another approach is the 'clinical anchor,' also described as 'known groups' where

there is an accepted difference in clinical status that may be used as an anchor (16) or biological parameters with established clinical interpretation such as hemoglobin levels (17). In AD, the most well-established are the various forms of clinical staging of the disease. Dividing the disease into clinically defined stages based on severity of cognitive and functional impairment, or related concepts such as functional dependence has been widely employed in diagnosis, management and treatment. Staging criteria and instruments have also been used as clinical trial outcomes, including in time-to-event designs. Whilst there is clear face validity to the relevance of delay, or prevention of e.g. MCI or dementia, the low frequency/long time to progression has made this a challenging endpoint. Closely related to this, it is also apparent that in applying stage progression as an anchor, estimates may be relatively large, representing several standard deviations of change (18). Given this and the paucity of other anchors in available data sets, clinician judged change has more often been used (19).

Distribution-based, or internal estimates utilize statistical properties of the measures themselves and of these the most common are effect size metrics e.g. the standard deviation (SD) and the standard error of measurement (SEM) that incorporates some measure of scale reliability e.g. test re-test or Cronbach's α as a measure of internal consistency reliability.

Other approaches

More recently, approaches have been proposed that may serve as alternatives to or supplement anchor and distribution-based methods. Examples of these include bookmarking/standard-setting and scale-judgment. In bookmarking/standard-setting, patients and experts are presented with clinical vignettes of a disease in order to reach a consensus on thresholds supportive of meaningful change (20). This may also involve the use of modern psychometric approaches such as Rasch in order to support the generation of the vignettes based on empirical evidence for a relationship between item level changes and the total score. Another approach is the scale-judgment method, in which panels of judges evaluate pairs of completed tests to determine whether the difference indicated by responses before and after an intervention constitute a meaningful change (21). Though beyond the scope of this article, it is notable that Goal Attainment scaling presents a potentially useful methodology in AD in respect of relevance and magnitude, since the achievement of self-selected goals has inherent face validity with respect to both relevance of the concept and magnitude of effect e.g. (22, 23).

Key messages

- Both cognition and function represent potentially meaningful health outcomes
  - o Indeed, there may be considerable conceptual overlap between the two
- No clinical outcome assessment tool should be viewed as inherently meaningful in all contexts, irrespective of whether it is intended to measure cognition or function
- Many traditional cognitive tests (cognitive PerfO) may be indirect measures of meaningful health outcomes i.e. the test itself is not an activity that is a part of daily life
  - o Indirect measures may still be meaningful, but the steps to establish relevance and interpretation may differ from direct measures
  - o Indirect measures might also be developed and validated as intermediate or surrogate outcomes
- Meaningfulness has two key elements
  - o Relevance of the concepts being measured
  - o Magnitude of any treatment effect
- Methodologies exist to establish the meaningfulness of COAs via qualitative methods such as assessment of content validity; and quantitative methods such as assessment of meaningful change and difference via anchor- and distribution-based approaches
- Traditional or 'gold-standard' COAs developed for the dementia stage of AD and prior to emerging good practice recommendations and PFDD guidance may lack established clinical meaningfulness in early AD

Conclusions

A key component of PFDD is the meaningfulness of COAs. This has two components: the concept being measured and whether this is relevant to patients, caregivers, and clinicians; and the size of any treatment effect. In order to conclude that a treatment benefit has been observed, it is critical to establish that both a meaningful concept has been measured and a meaningful magnitude of treatment effect has been achieved. Initiatives to build robust conceptual models via qualitative research, the development of novel direct measures of meaningful health outcomes, and the validation of indirect measures as intermediate or surrogate outcomes, will have a significant impact on measurement in clinical trials for AD over the coming months and years. Greater recognition of what is meaningful from the view of the patient and caregiver will inform not only regulatory reviews but will also be used to inform other aspects of drug development, as well as determinations for payment and coverage.

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Randomized, Placebo Controlled Trial of NPT088, A Phage-Derived, Amyloid-Targeted Treatment for Alzheimer's Disease

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Abstract

The engineered fusion protein NPT088 targets amyloid in vitro and in animal models of Alzheimer's disease. Previous studies showed that NPT088 treatment reduced β-amyloid plaque and tau aggregate loads in mouse disease models. Here, we present the results from an initial clinical study of NPT088 in patients with mild to moderate Alzheimer's disease. Patients were treated with 4 dose levels of NPT088 for 6 months to evaluate its safety and tolerability. Exploratory measurements included measurement of change in β-amyloid plaque and tau burden utilizing Positron Emission Tomography imaging as well as measures of Alzheimer's disease symptoms. At endpoint NPT088 was generally safe and well-tolerated with the most prominent finding being infusion reactions in a minority of patients. No effect of NPT088 on brain plaques, tau aggregates or Alzheimer's disease symptoms was observed.

Key words: Amyloid, Alzheimer's disease, β-amyloid plaques, tau tangles.

Introduction

Current state of research in early detection of Alzheimer's disease

The characteristic pathological findings in Alzheimer's disease (AD) are extracellular β-amyloid plaques and intracellular tau tangles. These deposits have been hypothesized to play an important role in the pathophysiology of AD, and removing plaques and/or tangles has been proposed as a potential treatment for AD. Multiple efforts have focused on β-amyloid, aiming to block production within the amyloid processing pathway or to remove β-amyloid plaques from the brain. Tau pathology has also been targeted, but fewer candidate treatments have been brought forward compared with those directed at β-amyloid.

Most efforts targeting amyloid have employed either antibodies or small molecules aimed specifically at either the β-amyloid or tau pathway, but not both. However, a defining feature of amyloid, including β-amyloid in plaque and tau tangles, irrespective of the specific underlying misfolded protein, is the characteristic structure based on β-pleated sheets (1). By targeting and binding this common structure, it may be possible with a single molecule to reduce multiple different forms of brain amyloid. The serendipitous discovery of amyloid binding by the bacteriophage M13 and the isolation of this activity to a specific domain of a capsid protein led to development of novel therapeutic proteins as investigational treatments for AD and other disorders associated with pathological amyloid deposition (2).

NPT088 is a fusion protein that in vitro and in animals binds multiple species of amyloid via its binding to the canonical amyloid fold (2,3). Briefly, NPT088 is composed of a binding domain derived from a minor capsid protein of the bacteriophage M13 fused to a human IgG1 Fc that is intended to mobilize clearance mechanisms following amyloid binding. In transgenic mouse models of neurodegenerative diseases, NPT088 reduces brain deposits of β-amyloid plaque and tau aggregate burden (4). Thus, unlike most antibodies, which target β-amyloid or tau but not both, NPT088 could potentially reduce both β-amyloid and tau burden in patients by virtue of its ability to bind broadly across amyloid species.

Single doses of NPT088 up to 30 mg/kg administered to healthy volunteers were well-tolerated with a plasma half-life of ~12 days (Proclara, unpublished data). We report here results of a multiple dose study in patients with AD assessing the safety and tolerability of NPT088, and exploring whether the reductions in β-amyloid plaque and tau observed in animal models could be translated into humans with AD.

Methods

The study was conducted at 19 sites in the United States. Participants were men and women 50-85 of years of age with a Mini-Mental State Exam (MMSE) score between 16 and 27 inclusive and a clinical diagnosis of probable AD (5) confirmed by florbetapir PET scan

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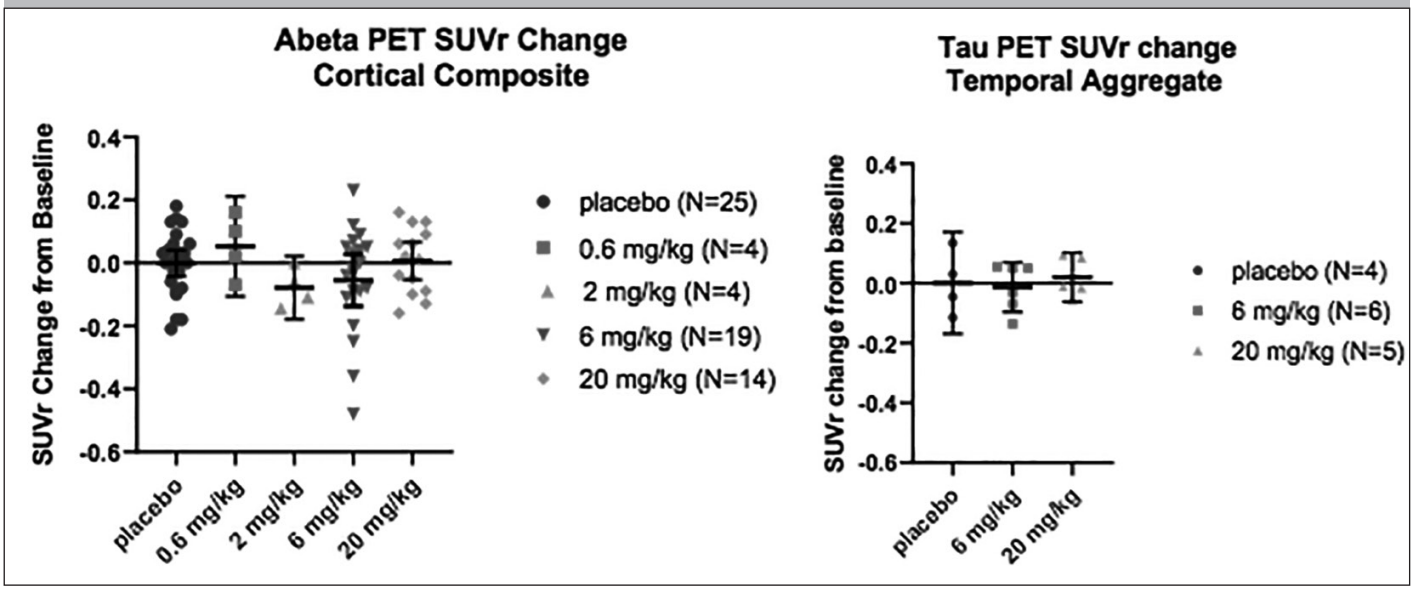
Table 1. Patient Characteristics and Key Outcomes

Patient Characteristics	Placebo (N=26)	0.6 mg/kg (N=6)	2.0 mg/kg (N=6)	6.0 mg/kg (N=25)	20 mg/kg (N=20)
Age Mean (SD)	73.5 (8.17)	73.7 (4.08)	76.7 (5.09)	70.4 (8.41)	74.3 (7.77)
M/F	7/19	2/4	2/4	7/18	9/11
MMSE Mean (SD)	21.2 (3.05)	21.2 (2.86)	20.2 (2.64)	21.1 (3.05)	20.4 (3.20)
Cognitive/Functional Outcomes	Placebo (N=26)	0.6 mg/kg (N=6)	2.0 mg/kg (N=6)	6.0 mg/kg (N=25)	20 mg/kg (N=20)
ADAS Cog13 (higher scores = worsening)					
Baseline (mean (SD))	32 (7.6)	34.5 (10.3)	34.8 (3.0)	31.5 (2.0)	31.0 (1.8)
LS Mean Change to Endpoint (95% CI)	-0.8 (-4.1, 2.4)	2.4 (-6.5, 11.3)	7.6 (-1.1, 16.3)	0.6 (-4.1, 5.3)	0.8 (-4.2, 5.8)
Mean Difference from placebo (95% CI)		-3.2(-13.4, 7.1)	-8.4 (-18.3, 1.5)	-1.4 (-5.7, 2.9)	-1.6 (-6.3, 3 .2)
CDR-SB (higher scores = worsening)					
Baseline (Mean (SD))	4.4 (1.3)	4.9 (1.5)	5.5 (1.8)	4.6 (1.2)	5.2 (1.9)
LS Mean Change to Endpoint (95% CI)	.5 (-0.2, 1.3)	1.6 (-0.4, 3.6)	1.3(-0.7, 3.2)	1.0(-0.1, 2.0)	0.4 (-0.7, 1.5)
Mean Difference from placebo (95% CI)		-1.1 (-3.3, 1.2)	-0.7 (-3.0, 1.5)	-0.5(-1.5, 0.6)	-0.1(-1.0, 1.3)
ADCS-ADL(lower scores = worsening)					
Baseline (mean (SD))	65.0 (8.8)	65.2 (4.8)	60.2 (8.9)	64.8 (7.7)	63.2 (8.2)
LS Mean Change to Endpoint (95% CI)	1.6 (-2.4, 5.7)	-3.6 (-14.2, 7.0)	-4.1 (-14.6, 6.4)	-3.5(-9.2, 2.1)	-4.5 (-10.5, 1.6)
Mean Difference from placebo (95% CI)		-3.2 (13.4., 7.1)	-8.4(-18.3, 1.5)	-1.4(-5.7, 2.9)	-1.6(-6.3, 3.2)

with either a composite SUVr > 1.2 or a positive central visual read (6). Symptomatic medications for AD were permitted provided the dose had been stable for at least 60 days. All patients also underwent a screening MRI to rule out conditions that could confound the diagnosis of AD as the primary cause of dementia. This was a double-blind, placebo-controlled study consisting of a 6-month treatment period and a 2-month safety follow-up. Four doses of NPT088 or placebo, intravenously administered monthly with a randomization ratio of NPT088:placebo of 2:1, were examined in sequential cohorts. The initial 2 cohorts (0.6 mg/kg and 2.0 mg/kg, respectively) were smaller and intended to provide initial safety and tolerability prior to dosing the 3rd and 4th cohorts (6 mg/kg and 20 mg/kg respectively). In addition to adverse event assessment, safety measures included MRI at baseline, 3 months and endpoint, and routine laboratory examinations. PET imaging with florbetapir-F18 PET imaging was repeated at Week 24 to evaluate potential changes in β-amyloid plaques, administered as a single intravenous bolus of 10 mCi (370 MBq) (± 10%) followed by acquisition of dynamic PET florbetapir PET scans at 50 to 65 minutes post-administration. Florbetapir binding was measured using PMOD software (PMOD Technologies, Zurich, Switzerland) to determine the composite cortical standard uptake value (SUV) ratio compared to a cerebellar reference region. Tau PET imaging was conducted at screening and then again at week 24 in a subset of patients to evaluate potential changes in brain tau aggregate loads. The investigational radiopharmaceutical MNI-960 (PI2620 under development by Life Molecular Imaging and Invicro) (7) was administered as a bolus of no more than 10 mCi followed by serial dynamic 3-D brain PET acquired for up to 180 minutes. MNI-960 binding was measured using PMOD software (PMOD Technologies, Zurich, Switzerland) to determine the both the regional standard uptake value (SUV) ratio compared to a cerebellar reference region. Other exploratory measures included measures of cognitive and functional change, including ADAS-Cog 13, ADCS-ADL, and CDR-SB at weeks 12 and 24. Plasma pharmacokinetics and anti-drug antibodies were also assessed. The study was reviewed and approved by each site's institutional review board, and each patient provided written informed consent to participate. The study was monitored by an independent data monitoring committee that that reviewed each cohort's data prior to approving initiation of the next dose.

The protocol-specified primary objective was to evaluate the safety and tolerability of multiple doses of NPT088. β-amyloid and tau PET and cognitive and functional measures were exploratory endpoints. The protocol had 80% power to detect adverse events that occurred in 9.6% or more patients in either of the two lower dose cohorts or in 3.6% or more of patients in the combined higher dose cohorts. Based on the results of Sevigny et al (8), at the planned sample size of 16 active and 8 placebo patients for each of the higher dose cohorts, the study was expected to have a power of 88% to detect a mean difference of 0.15 SUVr units in β-amyloid plaque between the active and placebo groups, assuming a dropout rate of up to 15% in the florbetapir PET analysis. For safety analyses, all randomized patients who received at least one dose of study drug were included. For PET and symptom measures all randomized patients who had at least one post-baseline measurement were included and were analyzed by ANCOVA that included MMSE

Figure 1. PET change from baseline



Legend: Change from baseline SUVr in β-amyloid (L) and tau burden (R) with mean (95% CI) after 24 weeks

strata as a covariate. A mixed model repeated measure approach was used for outcomes measured at more than one timepoint.

Results

A total of 85 patients were randomized to treatment. Of these, 83 (27M/56F) received study drug and were included in the safety analysis population, and 66 (78%) completed the study. Patient characteristics are summarized in Table 1.

Safety and tolerability

Adverse events were generally consistent with those expected in a population of AD patients and did not suggest differences between placebo and NPT088 with the exception of systemic hypersensitivity reactions related to infusion reactions, of which 17 were reported in 12 unique patients, all of whom received NPT088 (0.6 mg/kg: 2/6 patients (33%); 2.0 mg/kg: 2/6 patients (33%); 6.0 mg/kg: 6/37 patients (16%); 20 mg/kg: 2/30 patients (7%)). Using the National Cancer Institute's common terminology criteria for adverse events, version 4.03, 11 events were graded as mild, 3 as moderate and 1 as severe, and resulted in 5 of these 12 patients discontinuing the study early. Routine safety laboratories, including chemistry, hematology and ECG, did not suggest meaningful differences between groups. NPT088 was not associated with an increase in treatment emergent ARIA-E or ARIA-H compared with placebo.

Pharmacokinetic Results and Anti-drug Antibodies

NPT088 C_{max} and AUC increased with increasing dose in a dose proportional manner. At the 20 mg/kg dose, mean (SD) C_{max} was 538 (139) μg/ml after the final dose, mean plasma half-life was approximately 10 days, and drug did not accumulate with repeated dosing. Anti-drug antibodies were undetectable or low in most patients, and no difference in plasma NPT088 concentrations was observed between those patients in whom antibodies were detected and those without detectable antibodies.

PET Scans

At endpoint, the results of the florbetapir and MNI-960 PET scans did not demonstrate an effect of NPT088 on either β-amyloid plaque or tau aggregates (Figure 1).

Cognitive and Functional measures: Results for cognitive and functional measures did not demonstrate an effect of NPT088 (Table 1).

Discussion

This study was designed to assess the safety and tolerability of multiple doses of NPT088, and to explore whether preclinical data demonstrating effects on β-amyloid plaque and tau aggregates could be demonstrated in humans with AD. The results of the study showed that NPT088 was generally safe and well-tolerated. The only apparently drug-specific adverse effects were systemic infusion reactions, a predicted risk of administration of a drug derived from a non-human

phage protein. Reactions occurred in approximately 20% of patients assigned to active drug, and the majority were mild and did not preclude further treatment. One severe reaction was observed in a patient who experienced a drop in blood pressure, loss of consciousness and seizure-like activity during an episode that resolved within minutes without treatment and without sequelae.

The study did not demonstrate an effect of NPT088 to reduce either β-amyloid plaque or tau aggregate burden. With respect to β-amyloid, the failure to translate the animal findings into humans could be due to several factors. One possibility is that small effects were present but undetected due to sample size or other unknown issues. It may also be that the ability of NPT088 to bind β-amyloid plaque in humans differs from that in animal models, and that NPT088 was ineffective as a result, or that exposure to drug was suboptimal. In a single dose study in healthy humans, cerebrospinal fluid (CSF) exposures of NPT088 were 0.1%-0.25% of those in plasma (Proclara, unpublished data). The peak mean concentration of 538 μg/ml after the final dose in the 20 mg/kg group would correspond to ~5 nM in CSF, a concentration at which efficacy was observed in animals. However, trough concentrations of NPT088 were negligible at all doses, and if exposures continuously at or near Cmax are required for efficacy, this could account for the absence of a positive finding.

With respect to tau, the study encountered execution challenges related to limited MNI-960 production facilities, and the number of patients who received tau scans was much smaller than originally anticipated, making detection of any but the largest effects unlikely. Although uninformative about treatment effects, the results do provide data about the performance characteristics of MNI-960 in a patient population. A detailed discussion of these results will be the topic of a separate report.

In the absence of effects on either β-amyloid plaques or tau, the absence of changes in cognition or function is unsurprising. Given the relatively small number of patients in each group and the 6-month treatment duration, changes relative to placebo in cognitive and functional effects were not expected unless the drug led to dramatic improvements over baseline or, alternatively, a marked worsening. As evidenced by the results, neither of these occurred, although we cannot definitively rule out the possibility that smaller, undetected changes were present.

In summary, the results of this study indicate that apart from hypersensitivity reactions NPT088 is well tolerated in an AD population. Exploratory analyses did not yield evidence that NPT088 reduces β-amyloid or tau burden in humans with AD.

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Alzheimer's Disease Composite Score: A Post-Hoc Analysis Using Data from the LipiDiDiet Trial in Prodromal Alzheimer's Disease

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Abstract

As research evolves in prodromal AD, the need to validate sufficiently sensitive outcome measures, e.g. the Alzheimer's Disease Composite Score (ADCOMS) is clear. In the LipiDiDiet randomized trial in prodromal AD, cognitive decline in the study population was much less than expected in the timeframe studied. While the primary composite endpoint was insufficiently sensitive to detect a difference in the modified intention to treat population, the per-protocol population showed less decline in the active than the control group, indicating better treatment effects with regular product intake. These results were further strengthened by significant benefits on secondary endpoints of cognition and function, and brain atrophy. The present post-hoc analysis investigated whether ADCOMS could detect a difference between groups in the LipiDiDiet population (138 active, 140 control). The estimated mean change in ADCOMS from baseline (standard error) was 0.085 (0.018) in the active and 0.133 (0.018) in the control group; estimated mean treatment difference -0.048 (95% confidence intervals -0.090, -0.007; p=0.023), or 36% less decline in the active group. This suggests ADCOMS identified the cognitive and functional benefits observed previously, confirming the sensitivity of this composite measure.

Key words: Alzheimer's disease, prodromal, cognitive function, nutrients, Souvenaid, Fortasyn.

Introduction

Prodromal Alzheimer's disease (AD) is characterized by mild cognitive and functional impairment with defined changes in specific biomarkers (1-3). The LipiDiDiet trial was one of the first randomized clinical trials conducted in subjects with prodromal AD who were selected using the clinical and biomarker-based criteria originally described by Dubois et al. (1). The trial investigated the effects of the specific nutrient combination Fortasyn Connect (Souvenaid) on cognitive, functional, and other disease related parameters in this population (4). We previously reported that the intervention had no significant effect in the primary analysis on the 2-year primary endpoint, a 5-item neuropsychological test battery (NTB), yet significant differences for this endpoint were found in the pre-defined secondary analysis of the per-protocol population and the pre-defined subgroup analysis (4). Of note, in this trial population, the rate of cognitive decline as measured by the NTB score was several times less than expected, which means that the primary endpoint was insufficiently sensitive to detect a difference between the interventional and control groups (4). While such an observation adds important information about the early clinical course of prodromal AD (5, 6), it clearly highlights the ongoing need for more sensitive tools to detect changes in cognitive performance in this population.

Evaluating the effects of interventions for mildly affected populations with only limited cognitive and functional decline and subtle impairment such as subjects with prodromal AD, requires the use of sufficiently sensitive and informative composite outcome measures. The Clinical Dementia Rating - Sum of Boxes (CDR-SB) has been proposed as such a measure (7). More recently, the Alzheimer's Disease Composite Score (ADCOMS) was developed as a broader composite clinical outcome measure for trials in prodromal and mild AD dementia (8). ADCOMS consists of cognitive and functional items from three commonly used scales in AD dementia trials: the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE), and CDR-SB. In subjects with early AD, the combination of selected items from these scales was shown to have the highest sensitivity for measuring changes and intervention effects over time compared with the individual scales (8). Preliminary results from the first randomized controlled trial using ADCOMS

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as the primary outcome measure were interpreted as supporting the applicability of this composite score in subjects with early AD (9). However, more studies are needed to establish general applicability across different trial settings and the contribution of the different subdomains to the composite.

ADCOMS has been proposed as a new standard outcome measure for trials in prodromal AD; therefore, we did a post-hoc analysis of data from the LipiDiDiet trial primarily to compare Fortasyn Connect and control groups using ADCOMS and its subdomains as a potentially more sensitive measure of intervention effects than the NTB used in the primary analysis. An additional aim of the analysis was to use data from subjects with prodromal AD to provide broader knowledge of ADCOMS as a single clinical outcome measure in early AD trials.

Subjects and methods

Detailed methods for the LipiDiDiet trial (Netherlands Trial Registry NTR1705) were published previously (4). In summary, LipiDiDiet was a 24-month, double-blind, parallel-group, multi-center randomized controlled trial (11 sites in Finland, Germany, the Netherlands, and Sweden), with optional 12-month double-blind extensions. Eligible participants with prodromal AD, defined according to the International Working Group (IWG)-1 criteria (1), were randomly assigned (1:1) to active intervention (once-daily 125 mL drink containing the multinutrient combination Fortasyn Connect provided by Nutricia [Zoetermeer, the Netherlands]) or a same-taste iso-caloric control product. The primary outcome was the change in a cognitive function composite z-score based on five items of an NTB. CDR-SB was a secondary outcome while ADAS-cog-13 and MMSE were exploratory parameters. Participants provided written consent and the trial was approved by ethics committees of all sites and done in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines.

We used the LipiDiDiet trial data to do a post-hoc analysis of outcomes included in the ADCOMS tool, which consists of four ADAS-Cog subscale items (delayed word recall, orientation, word recognition, and word finding difficulty), two MMSE items (orientation time and drawing), and all six CDR-SB items (personal care, community affairs, home and hobbies, judgement and problem solving, memory, and orientation), as described previously by Wang and colleagues (8).

In this analysis, ADCOMS scores were calculated using the selected 12 items and corresponding partial least squares coefficients. Composite scores range from 0.0 to a maximum of 1.97, where higher values indicate worse performance. The contribution of the separate subdomains (ADAS-cog, MMSE, and CDR-SB) to the total score was explored by calculating the separate domains based on the same items and coefficients. Total ADCOMS scores and subdomain scores were calculated only if subject data were available for all 12 items. Statistical analyses were performed as planned using linear mixed models for repeated measures with real measurement time as continuous variable (primary model) or planned visit time as categorical variable (planned sensitivity model) in a modified intention-to-treat (mITT) population of all participants randomly assigned, excluding data after the start of rescue medication (defined as use of active product or Alzheimer's disease medication after dementia diagnosis). Further details about these statistical models were described previously (4). Additional sensitivity analyses using the primary and sensitivity models with baseline in the outcome vector, a 2-sided, independent t-test, and a non-parametric Mann-Whitney U test were performed to test the robustness of results. Effect sizes were reported using Cohen's d standardized effect size calculated based on the mean treatment difference over 24 months, estimated in the mixed model and pooled SD based on the sample size at the 24-month visit. Similar analyses were also done on a per-protocol dataset excluding participants with major protocol deviations.

Results

This analysis includes data obtained from 311 participants with prodromal AD (153 active group and 158 control group) enrolled between April 20, 2009, and July 3, 2013. In the mITT population, data were available for the post-hoc ADCOMS analysis from 278 participants (138 active and 140 control) at baseline, 225 (109 active and 116 control) at month 12, and 164 (73 active and 91 control) at month 24, which is comparable to the data available for the mITT analysis of the NTB primary outcome in the original paper (4).

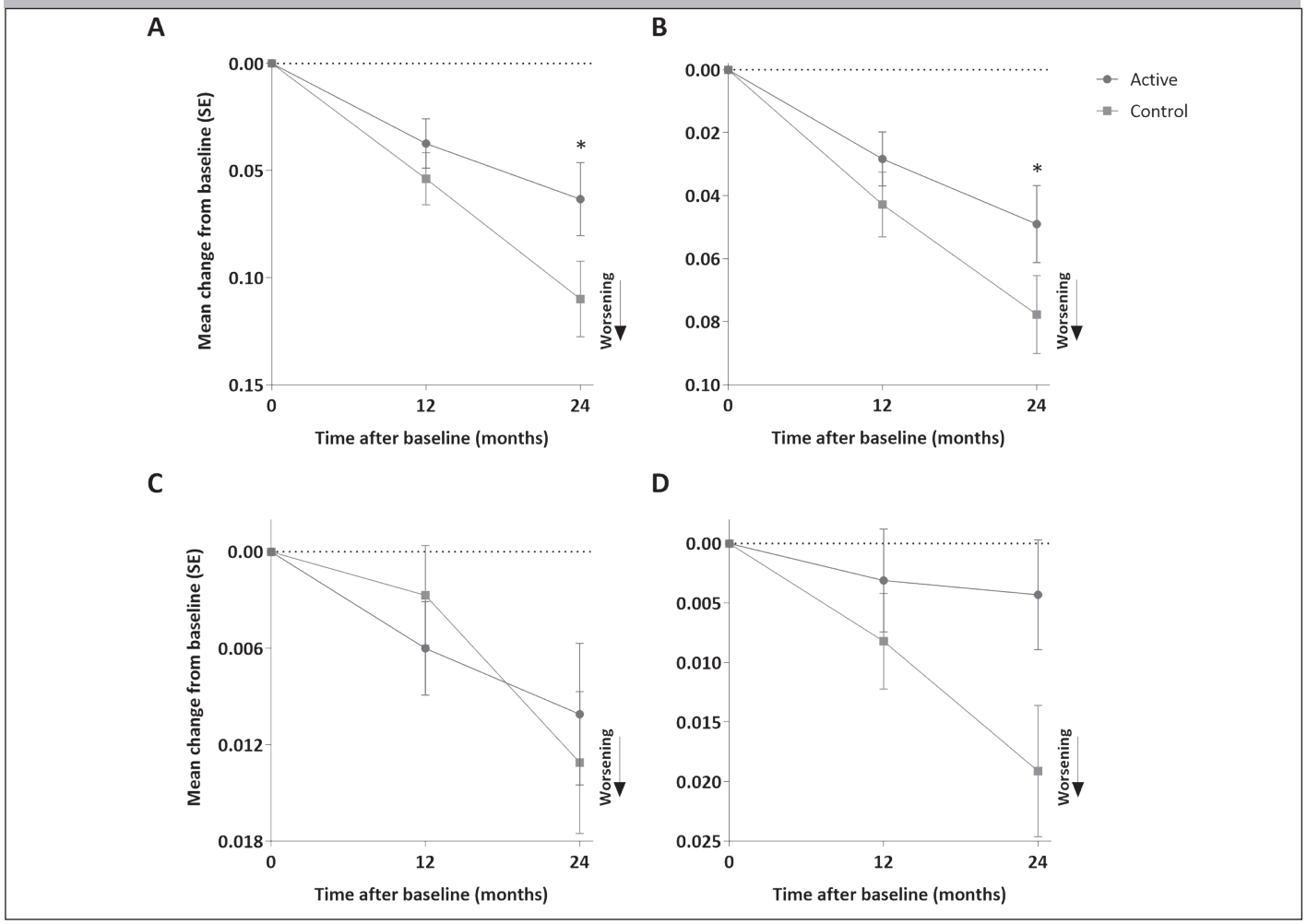
ADCOMS scores at baseline were 0.258 (standard deviation [SD] 0.143, n=138) in the active group and 0.247 (SD 0.140, n=140) in the control group (Table 1a). Figure 1 shows changes in ADCOMS scores and subdomain scores during the 24-month intervention period. While both groups showed higher ADCOMS scores over time, worsening was 36% less in the active group than in the control group (Figure 1A). The estimated mean change from baseline (standard error) was 0.085 (0.018) in the active group and 0.133 (0.018) in the control group; the corresponding estimated mean treatment difference was -0.048 (95% confidence intervals -0.090 to -0.007; p=0.023). Analysis of the ADCOMS subdomains (Figures 1B-D) showed that the difference between active and control groups was greatest for the six-item CDR-SB subdomain (34% less worsening) and the 2-item MMSE subdomain (63% less worsening). The estimated mean change from baseline (standard error) was 0.065 (0.016) in the active group and 0.099 (0.016) in the control group for the six-item CDR-SB subdomain (p=0.033), and 0.007 (0.005) in the active group and 0.019 (0.005) in the control group for the 2-item MMSE subdomain (p=0.065). No differences

Table 1. Post-hoc analysis of ADCOMS and its subdomains using LipiDiDiet trial data. (a) mITT population; (b) per-protocol population

Analysis[1]	Control (n=158) Mean (SD)[2] n		Active (n=153) Mean (SD)[2] n		Difference Estimate (95% CI)[3]	Percent effect[4]	MM[5] p value	MMs[6] p value	Effect size[7] Cohen's d
(a) mITT analysis									
*ADCOMS**									
Baseline	0.247 (0.140)	140	0.258 (0.143)	138					
Change baseline - month 12	0.054 (0.125)	107	0.037 (0.118)	104					
Change baseline - month 24	0.110 (0.156)	80	0.063 (0.143)	71	−0.048 (−0.090, −0.007)	−36%	0.023	0.023	0.31
Subdomains									
*ADAS-cog (4 items)**									
Baseline	0.094 (0.046)	140	0.091 (0.044)	138					
Change baseline - month 12	0.003 (0.032)	107	0.006 (0.030)	104					
Change baseline - month 24	0.013 (0.039)	80	0.010 (0.037)	71	−0.003 (−0.013, 0.007)	−16%	0.514	0.499	0.07
*MMSE (2 items)**									
Baseline	0.023 (0.033)	140	0.030 (0.039)	138					
Change baseline - month 12	0.008 (0.041)	107	0.003 (0.043)	104					
Change baseline - month 24	0.019 (0.049)	80	0.004 (0.039)	71	−0.012 (−0.025, 0.001)	−63%	0.065	0.068	0.27
*CDR-SB (all 6 items)**									
Baseline	0.130 (0.091)	140	0.137 (0.095)	138					
Change baseline - month 12	0.043 (0.105)	107	0.028 (0.086)	104					
Change baseline - month 24	0.078 (0.110)	80	0.049 (0.103)	71	−0.034 (−0.065, −0.003)	−34%	0.033	0.032	0.25
(b) Per-protocol analysis									
*ADCOMS**									
Baseline	0.247 (0.142)	128	0.249 (0.131)	129					
Change baseline - month 12	0.043 (0.116)	87	0.040 (0.122)	89					
Change baseline - month 24	0.098 (0.154)	63	0.042 (0.128)	59	−0.054 (−0.099, −0.010)	−45%	0.018	0.018	0.39
Subdomains									
*ADAS-cog (4 items)**									
Baseline	0.096 (0.047)	128	0.089 (0.042)	129					
Change baseline - month 12	−0.001 (0.030)	87	0.007 (0.029)	89					
Change baseline - month 24	0.010 (0.038)	63	0.006 (0.033)	59	−0.003 (−0.013, 0.008)	−20%	0.613	0.608	0.06
*MMSE (2 items)**									
Baseline	0.024 (0.034)	128	0.029 (0.038)	129					
Change baseline - month 12	0.007 (0.043)	87	0.005 (0.044)	89					
Change baseline - month 24	0.014 (0.046)	63	0.002 (0.039)	59	−0.011 (−0.025, 0.003)	−73%	0.128	0.132	0.25
*CDR-SB (all 6 items)**									
Baseline	0.128 (0.092)	128	0.132 (0.088)	129					
Change baseline - month 12	0.037 (0.095)	87	0.028 (0.089)	89					
Change baseline - month 24	0.074 (0.114)	63	0.035 (0.092)	59	−0.045 (−0.078, −0.012)	−44%	0.008	0.008	0.33

1. Higher scores indicate worse performance; 2. Data for active and control groups are presented as observed means and SD; 3. Difference is calculated as (active − control) based on least squares means for change from baseline over 24 months as estimated in the mixed model; 4. Percent less worsening active vs control based on least squares means for change from baseline over 24 months as estimated in the mixed model; 5. MM (mixed model): linear mixed model for longitudinal data with change from baseline as outcome, baseline score and baseline MMSE as covariates, and real measurement time as a continuous variable. P value for effect of intervention over 24 months; 6. MMs (planned sensitivity model): mixed model for repeated measures with change from baseline as outcome, baseline score and baseline MMSE as covariates, and planned visit time as a categorical variable. P value for effect of intervention over 24 months; 7. Cohen's d standardized effect size calculated based on the mean treatment difference over 24 months as estimated in the mixed model and the pooled SD. Results are presented so that a positive effect size indicates improved performance in the active vs. control group and vice versa; mITT=modified intention-to-treat: all randomly assigned participants, excluding visit data after the start of rescue medication; PP=per-protocol: all participants from the modified intention-to-treat population, excluding the respective visits of participants with major protocol deviations defined during a data review of masked data; ADCOMS= Alzheimer's disease composite score. ADAS-cog=Alzheimer's disease assessment scale–cognitive subscale. MMSE=mini-mental state examination. CDR-SB=clinical dementia rating - sum of boxes. CI=confidence interval. SD=standard deviation.

Figure 1. Changes in ADCOMS and its subdomains during the 24-month intervention



(A) Alzheimer's Disease Composite Score. (B) Clinical Dementia Rating - Sum of Boxes 6-item subdomain. (C) Alzheimer's Disease Assessment Scale–cognitive subscale 4-item subdomain. (D) Mini-Mental State Examination 2-item subdomain. Data are observed mean change from baseline; error bars are standard error. * $p<0.05$ (mixed model, modified intention-to-treat).

between groups were observed for the 4-item ADAS-cog subdomain. The planned sensitivity analysis showed significant differences between groups over 24 months in worsening of ADCOMS scores (p=0.023) and worsening of six-item CDR-SB (p=0.032), while there was a trend on the 2-item MMSE (p=0.068) and no difference on the 4-item ADAS-cog (p=0.499). The additional sensitivity analyses on ADCOMS and subdomains confirmed the results (ADCOMS: primary model with baseline in the outcome vector, p=0.038; t-test, p=0.059; Mann-Whithney U test, p=0.036).

Per-protocol analysis including baseline data from 257 participants (129 active and 128 control) confirmed the findings in the mITT analysis (Table 1b).

Effect size analyses of changes from baseline over 24 months on ADCOMS score showed Cohen's d values of 0.31 in the mITT population and 0.39 in the per-protocol population, indicating a small to medium effect in the active group (10). Effect sizes >0.2 were also observed for the MMSE and CDR-SB subdomains in the mITT (0.27 and 0.25, respectively) and per-protocol (0.25 and 0.33, respectively) analyses.

Discussion

Research practice in subjects with prodromal AD is still evolving, and since the 24-month LipiDiDiet trial database was locked, there has been a growing recognition that combined cognitive-functional measurement tools may provide a more sensitive way to assess the efficacy of novel interventions than those currently available (7, 11). To reflect contemporary research practice, we used ADCOMS in a post-hoc analysis of the LipiDiDiet trial data and found a significant intervention effect for Fortasyn Connect over 24 months in subjects with prodromal AD. The active group showed significantly less clinical decline over 24 months as measured by ADCOMS, and this effect was driven largely by differences in the CDR-SB and MMSE subdomains. We previously reported a significant benefit for Fortasyn Connect using CDR-SB and showed that stabilization of CDR-SB scores was more pronounced with increasing baseline MMSE (4), which supports the notion that early rather than late treatment within

the prodromal phase of dementia may lead to better outcomes when using CDR-SB as a cognitive-functional measure. ADCOMS data in this post-hoc analysis (data not shown) also suggest that earlier intervention is associated with better outcomes for Fortasyn Connect.

The ADCOMS score is weighted toward the CDR-SB which functions as the framework of the score, but only takes on values from 0.5 to 7 (in increments of 0.5) for the majority of participants. The MMSE and ADAS-cog items provide further discriminatory ability between these seven points, enhancing the performance of the scale, but not performing as reliably when isolated. The inclusion of multiple measures of important cognitive domains stabilizes estimates and protects against spurious results. The CDR-SB has historically been more sensitive to progression, but less sensitive to treatment effects due to low variability, contrasted with cognitive scales which have been more sensitive to treatment effects but also highly variable. The weighted combination was designed to combine changes between points on the CDR-SB with detailed changes in cognitive items, with the sensitive items potentially differing from one study to another. In this case, the CDR-SB items and the MMSE items were sensitive to changes, and the ADAS-cog items were less sensitive, allowing the ADCOMS scale to detect treatment related changes due to both functional and cognitive contributions.

The effect size analysis reported here indicates that the magnitude of the intervention effect measured using ADCOMS was large enough to be clinically detectable. The effect size for ADCOMS (Cohen's d 0.31) was similar to the value previously reported for CDR-SB (0.33) (4). The magnitude of the intervention effects seen with ADCOMS and CDR-SB, both in this analysis and the original trial report (4), were more pronounced in the per-protocol analysis, possibly reflecting the importance of long-term protocol adherence.

These results should be interpreted with caution because of the post-hoc nature of the analysis with a relatively new cognitive-functional measurement tool. Nevertheless, ADCOMS was developed using robust methodology (8), and these analyses further contribute to the validation of ADCOMS in clinical trials in subjects with early AD and suggest applicability and sensitivity across different intervention strategies in the earliest stages of dementia. Our post-hoc ADCOMS analyses are consistent with the overall findings from the LipiDiDiet trial (4) and in combination with data from other authors (8), provide further evidence that ADCOMS, a broad measure of cognitive function, may be useful over a range of interventions and trial designs in early AD.

In conclusion, this analysis suggests that the cognitive and functional benefits observed in the LipiDiDiet trial were also identified using ADCOMS, adding to the accumulating evidence validating this sensitive and broad composite outcome measure in prodromal AD trials.

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Ethical standards: The study was approved by ethics committees of all sites and done in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines.

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Comparing the Standard and Electronic Versions of the Alzheimer's Disease Assessment Scale – Cognitive Subscale: A Validation Study

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Abstract

The Alzheimer's Disease Assessment Scale (ADAS-Cog) has become the de facto gold-standard for assessing the efficacy of putative anti-dementia treatments. There has been an increasing interest in providing greater standardization, automation, and administration consistency to the scale. Recently, electronic versions of the ADAS-Cog (eADAS-Cog) have been utilized in clinical trials and demonstrated significant reductions in frequency of rater error as compared to paper. In order to establish validity of the electronic version (eADAS-Cog), 20 subjects who had received a diagnosis of probable Alzheimer's disease (AD) at a private US Memory Clinic completed a single-center, randomized, counterbalanced, prospective trial comparing a version of the eADAS-Cog to the standard paper scale. Interclass Correlation Coefficient on total scores and Kappa analysis on domain scores yielded high agreement (0.88 - 0.99). Effects of order and mode of administration on ADAS-Cog total scores did not demonstrate a significant main effect. Overall, this study establishes adequate concurrent validity between the ADAS-Cog and eADAS-Cog among an adult population with diagnosed AD.

Key words: ADAS-cog, Alzheimer's disease, eCOA, cognition, neuropsychology.

The Alzheimer's Disease Assessment Scale (ADAS) was developed to provide a measure of change in the cognitive and behavioral functions known to be impaired by Alzheimer's disease. Conceptualized in the early 1980's in response to the then perceived lack of appropriate instruments available to test the efficacy of AD drug treatments (1, 2), the cognitive subscale (ADAS-cog), has since become the gold-standard for assessing the efficacy of putative anti-dementia treatments, serving as the primary or co-primary outcome for nearly all phase 2 and phase 3 drug development trials in patients with mild to moderate Alzheimer's disease (3-5).

The ADAS-cog is a well validated instrument which has been demonstrated to have adequate construct validity as compared to other neuropsychological and cognitive measures and to be sensitive to identifying cognitive impairment (3, 6). Despite its widespread use in clinical trials and acceptance by both the Alzheimer's Disease Cooperative Study Group (ADCS) and pharmaceutical industry (7), the ADAS has received criticism for its inconsistencies in scoring and administration (7, 8).

Given its importance to therapeutic development and in light of its history of variability in scoring and administration, there has also been an increasing interest in providing greater standardization, automation, and administration consistency to the scoring of the scale (9, 10). As technology has advanced, the use of electronic outcomes assessments (eCOA) has become more ubiquitous in both clinical practice and clinical trials. These advances have the potential to help improve the reliability of cognitive testing as well as provide a more efficient manner by which to collect and analyze data (9, 11).

As such, computerized versions of the ADAS-cog (eADAS-cog) have begun to be utilized in clinical trials and have been demonstrated to significantly reduce rater error rates compared to the paper scale (13, 14). While the eADAS-cog has been purported to be equivalent to paper in terms of validity, to date, there has not been a prospective trial comparing a tablet based version of the eADAS-cog with the paper scale in a clinical population. The aim of the present study was to determine the validity of the eADAS-cog by comparing it to the standard paper-and-pencil ADAS-cog (pADAS-cog) in an outpatient memory disorders clinic. As the content of the scales is identical, it was hypothesized that (1) there would be no significant differences between the total score and/or individual domain scores between the electronic and paper versions and (2) there would be a high rate of agreement between tasks demonstrating concurrent validity.

Methods

Participants

This study was conducted in accordance with guidelines on human subject's research and approved

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by the Williams College Institutional Review Board. Participants included 22 adult subjects (Age M = 81; SD = 5.1; Range 70-88) who had previously undergone evaluation and received a diagnosis of probable Alzheimer's disease at a private US Memory Clinic.

Inclusion criteria included: (1) a clinical diagnosis of probable Alzheimer's disease as established in accordance with the updated National Institute on Aging and Alzheimer's Association workgroup (NIA-AA) guidelines (15); (2) an age range of 50-90 inclusive; (3) community dwelling, fluent in English and able to understand and sign informed consent; (4) Mini Mental State Examination (MMSE) score 12-26 inclusive; and (5) adequate visual, auditory, & cognitive abilities to perform all aspects of cognitive and functional assessments. Eligible participants could not be currently participating in other clinical research protocols and could not have had an ADAS-cog administered to them in the month prior to enrolling.

Patients who agreed to participate were consented and randomly assigned to one of two study conditions related to the order in which the study measures were administered. Participants undertook an MMSE and were either administered the pADAS-cog or the eADAS-cog at their initial visit. Participants then returned to clinic for two subsequent visits at one month intervals (+/- 3 days) at which time study assessments were repeated. Study conditions were counterbalanced so that participants were randomized to one of two testing conditions in which they were tested with one version of the ADAS-cog (paper or electronic), returned one month later and received the other version and then again returned after one month and received the version they took initially a second time (7). Participants were tested on average 27 days (SD = 3.2) between Visit 1 and Visit 2 and on average 29 days (SD = 4.3) between Visit 2 and Visit 3. All testing was completed between March and September of 2017.

Measures

The ADAS-cog 13, (2) item assessment was utilized for this study. The 13 items assessed included: (1) Word Recall, (2) Commands, (3) Constructional Praxis, (4) Delayed Word Recall, (5) Naming Objects & Fingers, (6) Ideational Praxis, (7) Orientation, (8) Word Recognition, (9) Number Cancelation, (10) Remembering Test Instructions, (11) Comprehension, (12) Word Finding Difficulty, (13) Spoken Language Ability. Scores are generated for the individual items and summed generating a total score out of a possible maximum score of 85. As there are several versions of the scoring manual which can accompany the ADAS-cog, for this study the 1998 version, with its corresponding manual, was utilized (16).

The electronic version of the ADAS-cog was used with permission from the Alzheimer's Disease Cooperative Study (ADCS) and adapted as an electronic clinician-reported outcome (eClinRO) (17) by Bracket Global, LLC. The electronic version of the ADAS-cog is downloaded as an application and installed by a trained technician on a tablet computer. Administration instructions are identical to that of the paper version of the ADAS-cog and appear directly on the tablet. The tablet touch screen and keyboard were used for administration and scoring directly on the tablet by the examiner. All examiners performing study assessments were doctoral level neuropsychologists who had completed prior training and certification on both the paper and electronic version of the ADAS-cog.

The Constructional Praxis and Number Cancellation stimuli were completed on paper with the examiner entering scores into the tablet. Other stimuli included in the standard ADAS-cog kit were used for both electronic and paper assessments. Scores for all individual domains as well as total score are automatically calculated and provided to the examiner for confirmation.

Statistical Analysis

Analyses were performed in R 3.4.4 environment (18). Kappa analyses were computed on the item level between two visit pairs (i.e., Baseline-Visit 2 and Visit 2-Visit 3) using quadratic weighting to measure the agreement between the eADAS-cog and pADAS-cog.

Total scores were compared through an intra-class correlation (ICC) analysis with the type of scale serving as substitute for the classic examiner set-up. The intra-class correlation coefficient provides a statistic for how strongly the ratings from the types of scales relate to each other across each subject.

A three-way split-plot-factorial analysis of variance was conducted to examine the effects of one between variable (i.e. order of administration) and two within variables (i.e., scale type/mode of administration and visit).

As an additional means of assessing agreement between methods of clinical measurement, a Bland and Altman (20) analysis was performed as another measure of scale agreement as well as to examine systemic bias in scale type by plotting the differences by the means of the total scores from each type and comparison between BL-V2 and V2-V3. This method of comparison has come to be known as a Bland-Altman "limits of agreement" plot and is commonly regarded as a standard for determining whether two methods may be used interchangeably when 95% of the paired mean differences lie within ± 1.96 standard deviations from the mean difference line (20).

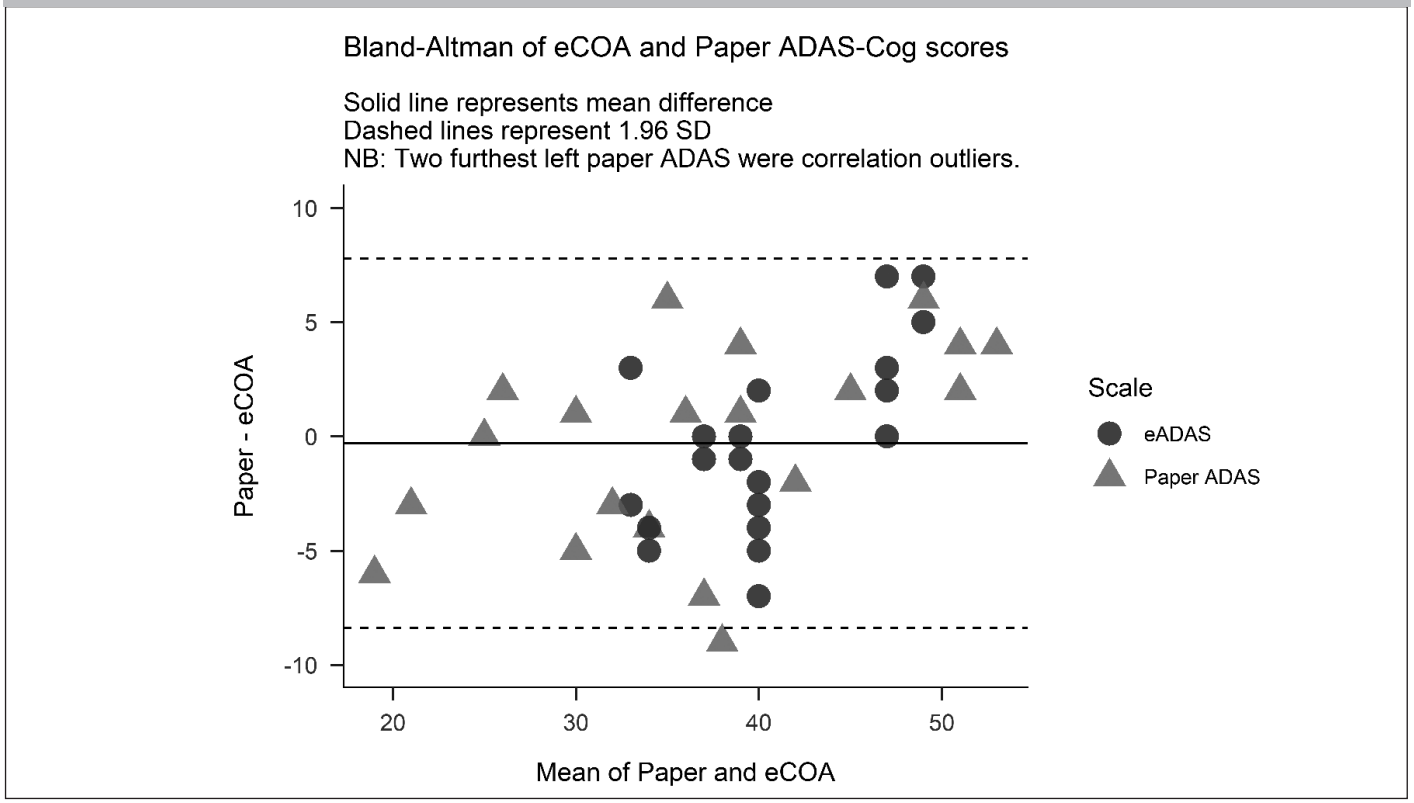
Results

The study sample consisted of 20 subjects with diagnosed probable Alzheimer's disease who completed

Table 1. Test-Retest Reliability of eADAS-Cog and pADAS-Cog in Patients with AD

Comparison	Item	N	eADAS M	eADAS SD	pADAS M	pADAS SD	Agreement	Agreement Score
BL and V2	Word Recall	20	7.2	1.44	7	1.12	Weighted Kappa	0.99
BL and V2	Commands	20	0.65	0.67	0.65	0.75	Weighted Kappa	0.95
BL and V2	Constructional Praxis	20	1.6	0.99	1.45	0.6	Weighted Kappa	0.95
BL and V2	Delayed Word Recall	20	9.65	0.88	9.45	1.32	Weighted Kappa	0.94
BL and V2	Naming	20	0.6	0.75	0.6	0.75	Weighted Kappa	0.98
BL and V2	Ideational Praxis	20	0.8	0.77	0.75	0.64	Weighted Kappa	0.96
BL and V2	Orientation	20	3.9	1.68	4.1	1.89	Weighted Kappa	0.95
BL and V2	Word Recognition	20	8.95	2.56	8.25	3.14	Weighted Kappa	0.95
BL and V2	Number Cancellation	20	3.85	1.04	3.6	0.88	Weighted Kappa	0.95
BL and V2	Total Score	20	38.95	6.97	37.9	7.72	ICC	0.88
V2 and V3	Word Recall	20	7	1.3	7.05	1.15	Weighted Kappa	1
V2 and V3	Commands	20	0.75	0.79	0.6	0.75	Weighted Kappa	0.93
V2 and V3	Constructional Praxis	20	1.6	0.88	1.45	0.69	Weighted Kappa	0.94
V2 and V3	Delayed Word Recall	20	9.55	0.89	9.2	1.4	Weighted Kappa	0.92
V2 and V3	Naming	20	0.65	0.59	0.6	0.75	Weighted Kappa	0.97
V2 and V3	Ideational Praxis	20	0.9	1.02	1	0.97	Weighted Kappa	0.90
V2 and V3	Orientation	20	4.25	1.8	4.45	2.09	Weighted Kappa	0.94
V2 and V3	Word Recognition	20	8.9	2.92	9.05	2.78	Weighted Kappa	0.95
V2 and V3	Number Cancellation	20	3.8	1.11	3.75	0.79	Weighted Kappa	0.96
V2 and V3	Total Score	20	38.85	7.26	39.3	8.64	ICC	0.84

Figure 1. Bland-Altman "limits of agreement" plot displaying the differences between the eADAS and pADAS total scores plotted against the average of the two scores for each of the 20 participants. This indicates that the two methods of administration show excellent agreement across the range of severity without notable bias or skewing in either direction



all study visits at a specialized U.S. memory clinic. Participants had a mean of 13.8 years of education (SD = 2.8; Range 11-20). The overall sample was predominantly Caucasian (90%) and female (55%). Bivariate analyses were performed to investigate relations between demographic variables and group. Results indicated no significant differences between groups with regard to demographic variables.

Results of the kappa analyses of domain scores demonstrated near perfect agreement on all items (κ range 0.90 to 1.00) and ICC range for total scores were between .84 to .88 (Table 1).

The analysis found a significant main effect of order of administration, $F(1, 48) = 6.09$. MSE = 343.1, $p = .017$. However, the main effects of scale type and visit were not significant $F(1, 48) = 0.74$, MSE = 16.4, $p = .396$ and $F(2, 48) = 0.29$, MSE = 16.4, $p = .750$, respectively) and neither was the interaction, $F(1, 48) = 0.06$, MSE = 3.3, $p = .809$.

A second analysis was performed after removing two subjects with outlying scores as determined after fitting a regression model and examining points with the highest leverage and influence. The second analysis did not find a significant main effect of scale type ($F(1, 42) = 0.01$, MSE = 0.54, $p = .91$) study group ($F(1, 42) = 0.60$, MSE = 124.09, $p = .443$), nor visit ($F(2, 42) = 0.29$, MSE = 11.52, $p = .752$). The interaction was also not significant, $F(1, 42) = 0.02$, MSE = 0.90, $p = .882$.

Finally, inspection of the Bland-Altman Plot (Figure 1) did not indicate the presence of any proportional bias with all values within +/- 1.96 SD of the mean difference.

Discussion

This study compared a novel electronic version of the ADAS-cog to the standard paper and pencil version in a clinical population with diagnosed Alzheimer's disease. Results of the analysis indicate a high level of psychometric concurrence between the traditional paper administration of the ADAS-cog and the eCOA based administration with individuals performing comparably between the two mediums as demonstrated by kappa ranges between 0.90 – 1.00 on individual domains and an ICC of 0.86 for total scores.

Factorial analysis indicated that there was no significant differences between groups. Further, the scores collected via the eADAS-cog exhibited a similar grouping around the mean difference line on a Bland-Altman plot for test-retest reliability as compared to the paper-based administration and demonstrated in prior analysis (Figure 1) (7).

This increase in reliability is potentially due to the greater uniformity built directly into the electronic version of the scale including all standardized instructions, scoring conventions from the scale and automated scoring including item and total scores being calculated by the tablet. As the ADAS-cog is often used as a primary or key secondary endpoint in large scale clinical trials that include hundreds of sites across numerous countries, variability in administration and scoring can introduce undesirable variance in data.

Electronic versions, such as the eADAS-cog, that help increase standardization of administration and improve scoring algorithmically have the potential to make a major impact on the reliability and validity of clinical trial study data (13, 19). Namely, electronic data capture at the point of contact with study subject eliminates transcription and tabulation errors as well as decreases the need for onsite source verification. Further, utilizing an electronic medium allows for improved data management, security, enforcement of study specific conventions and risk based monitoring.

This is the first studies to compare a novel electronic version of the ADAS-Cog utilized in clinical trials to the standard paper and pencil version and as such there are limitations to note. While all examiners underwent both paper and electronic ADAS-cog training, no information specific to familiarity with or prior use of electronic outcomes was collected. Further, no qualitative information regarding the acceptability of the electronic version ADAS-Cog was collected from participants, nor were variables such as time to complete quantified between mediums. Future research comparing differences between electronic and paper versions of similar measures could benefit from comparing prior experience using electronic mediums, acceptability of the electronic format and other variables such as time to complete or ease of use. Further, as this was a pilot study, the sample size is relatively small and was comprised mostly of a homogenous population with regard to age, years of education and race/ethnicity; it is unclear to what extent these findings would generalize to a more diverse population. However, this sample does represent a typical patient population encountered at memory disorders clinic. In addition, the subjects enrolled were previously characterized with regard to diagnosis, stage of disease and biomarkers, when available, which enhances generalizability of these findings to use in trials with similar criteria (12).

Overall, this study demonstrated adequate concurrent validity between the well-established paper-and-pencil version of the ADAS-cog and a newer electronic version (eADAS-cog) among an adult population with diagnosed probable Alzheimer's disease. Utilization of the eADAS-cog will help to increase the accuracy of the ADAS-cog and has the potential to help provide more reliable and valid data in clinical research trials.

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of Williams College IRB approved this study, and all volunteers gave written informed consent before participating.

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Short Communication

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Neuropsychological, Psychiatric, and Functional Correlates of Clinical Trial Enrollment

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Abstract

Screen failure rates in Alzheimer's disease (AD) clinical trial research are unsustainable, with participant recruitment being a top barrier to AD research progress. The purpose of this project was to understand the neuropsychological, psychiatric, and functional features of individuals who failed screening measures for AD trials. Previously collected clinical data from 38 patients (aged 50-83) screened for a specific industry-sponsored clinical trial of MCI/early AD (Biogen 221AD302, [EMERGE]) were analyzed to identify predictors of AD trial screen pass/fail status. Worse performance on non-memory cognitive domains like crystalized knowledge, executive functioning, and attention, and higher self-reported anxiety, was associated with failing the screening visit for the EMERGE AD clinical trial, whereas we were not able to detect a relationship between screening status and memory performance, self-reported depression, or self-reported daily functioning. By identifying predictors of AD trial screen passing/failure, this research may influence decision-making about which patients are most likely to successfully enroll in a trial, thereby potentially lowering participant burden, maximizing study resources, and reducing costs.

Key words: Cognition, Alzheimer's disease, mild cognitive impairment, clinical trial.

Difficulty with participant recruitment is considered one of the top barriers to Alzheimer's disease (AD) clinical research progress (1). Many barriers exist to successful recruitment, including patient comorbidity, limited availability of studies and logistical issues, and eligibility criteria (2, 3). While most clinical drug trials targeting AD currently require recruitment of patients with mild dementia severity or Mild Cognitive Impairment (MCI), only 20 to 25% of patients diagnosed with AD are eligible for AD clinical trials (2), due to factors like medical comorbidities and medications (3), or the lack of an adequate study partner (4). More specifically, screen failure rates are strikingly high, as roughly ten patients may need to be screened to enroll one participant (5). These screen failure issues appear to be widespread across the industry (2), and are problematic for drug study sponsors, clinical trial sites, and participants themselves. Failed screening visits represent wasted time and lost revenues for both sponsors and sites, add to existing logistical and scheduling challenges, and extend the timelines to reach recruitment quotas (6). Additionally, high screen failure rates amplify participants' perception of AD drug trial inaccessibility and dampen participant interest (7). Consequently, the current trial recruitment strategy is not optimally prepared to take on the National Plan to Address Alzheimer's Disease's ambitious goal of preventing and treating AD by 2025.

To begin to address potential solutions to the ever-present recruitment shortage, AD-related programs and task forces have focused on patient registries, raising participant awareness, site performance and funding, and reducing barriers to participation (5). Unfortunately, there is little to no emphasis on reducing screen failure rates based on study inclusion criteria for the current sources of participants already being recruited. Disease severity is a common cause of participant screen failure (8), which is typically measured by cognitive test performance and/or informant/participant rating scales of functioning. However, there tends to be minimal overlap between measures of disease severity used in clinical trials and those used in typical clinic settings, and judgment about severity in a clinical trial is often based upon multiple metrics that may be discrepant. As a result, for patients recruited through referral from clinic, physicians and study teams have limited capacity to predict who will meet inclusion criteria for disease severity prior to the AD trial screening visit, which contributes to higher screen failure rates.

To help address the current limitations of recruitment strategies in AD clinical trials, the current study seeks to better understand the neuropsychological, psychiatric, and functional features of individuals who pass/fail screening measures for AD trials, using previously collected data from patients enrolled both in a cognitive specialty clinic and an AD clinical trial. We hypothesized that worse performance on memory, other cognitive

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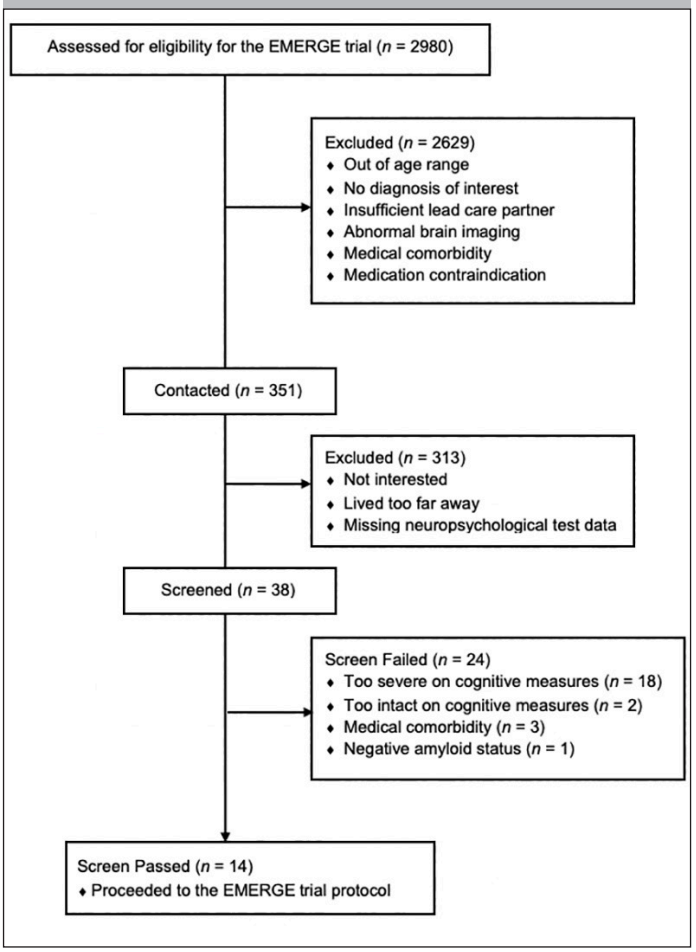
functioning domains, and psychiatric measures during the clinical evaluation would be associated with lower participant screen failure into an AD clinical trial, and that younger participants would be more likely to fail AD clinical trial screening measures. Similarly, we expected worse self-reported daily functioning would be associated with lower screen failure rates.

Methods

Sample and Study Design

The current study is a retrospective, cross-sectional analysis of the neuropsychological, psychiatric, and functional predictors of AD clinical trial enrollment. A database in the Division of Cognitive Neurology at a university in the western United States was searched for participants having (1) previously received a clinical diagnostic workup (including dementia-expert cognitive evaluation and diagnostic neuropsychological assessment) at the university's transdisciplinary cognitive specialty clinic and subsequently diagnosed with either MCI or early AD and (2) previously screened for a specific industry-sponsored clinical trial of MCI/early AD (Biogen 221AD302 (9), Phase 3 Study of Aducanumab in Early Alzheimer's Disease [EMERGE], which will be referred to as "the EMERGE trial" for the remainder of this manuscript). Thirty-eight participants met the inclusion criteria for this retrospective study, and no other inclusion/exclusion criteria were applied to the current study. Please see Figure 1 for a flow diagram of participants recruited for the EMERGE trial, with the 38 participants who "Screened" for the trial representing our current study's sample population. As a result of the inclusion age for the EMERGE trial being between 50 and 85, only those aged participants were included in the current study. Fourteen participants screen passed the EMERGE trial, and 24 screen failed. Causes for screen failure included medical comorbidity (n = 3), negative amyloid status (n = 1), and inappropriate disease severity (n = 20) based on the participant-based Mini-Mental Status Examination (10) (MMSE) and Repeatable Battery for the Assessment of Neuropsychological Status (11) (RBANS), and the informant/participant-based Clinical Dementia Rating Scale (CDR) (12). Specifically, for the EMERGE trial the participant needed to score between 24-30 on the MMSE, at or below a demographically-normed standard score of 85 on the Delayed Memory Index from the RBANS, and at the level of 0.5 on CDR. Of the 18 participants with too severe of impairment on cognitive/informant examination at EMERGE screening, 17 participants performed below the cutoff for the MMSE, and one participant performed worse than permissible on the CDR. Both participants who were too intact on the cognitive/informant examination performed above the cutoff on the RBANS Delayed Memory Index. All procedures for the current study received approval by the university's Institutional Review Board.

Figure 1. CONSORT-like flow diagram of participants evaluated for the EMERGE trial, with those "Screened" representing the current study's sample population



All participants underwent a standard clinical neuropsychological evaluation during the diagnostic neuropsychological assessment prior to their screening for the EMERGE trial, which included the following commonly administered neuropsychological, psychiatric, and functional tests. Readers are referred to Lezak and colleagues (13) and respective test manuals for test descriptions and psychometric properties.

- Neuropsychological measures: Digit Span, Arithmetic, Information, and Matrix Reasoning subtests from the Wechsler Adult Intelligence Scale-IV, which measure attention, crystalized intelligence, and executive functioning, respectively; Brief Visual Memory Test-Revised (BVMT-R), which measures visual learning and memory; Hopkins Verbal Learning Test-Revised (HVLT-R), which measures verbal list-learning and memory; Trail Making Test Part B (TMT-B), which measures executive functioning; Montreal Cognitive Assessment (MOCA), which measures mental status; and Controlled Oral Word Association Test (COWA), which measures language. All individual subtests

Table 1. Demographics and neuropsychological, psychiatric, and functional performance based on screening status

Measure	Screen Passed	Screen Failed	p value	95% CI (Lower)	95% CI (Upper)
Sample size (n)	14	24			
Age (years)	71.5 (8.2)	73.0 (6.5)	.53	-6.40	3.32
Education (years)	17.3 (2.5)	15.9 (2.7)	.13	-0.44	3.18
Gender (female [n = 18]; male [n = 20])	17%; 55%	83%; 45%	0.02	--	--
MOCA	22.9 (3.7)	20.7 (4.2)	.12	-0.60	4.92
BVMT-R Delayed Recall	2.5 (2.7)	3.0 (3.6)	.71	-2.69	1.85
HVLT-R Delayed Recall	2.6 (2.5)	3.2 (3.9)	.64	-3.12	1.96
Digit Span	26.5 (5.1)	22.7 (5.2)	.04	0.21	7.32
Arithmetic	14.0 (2.5)	11.1 (3.2)	.006	0.91	4.93
Information	20.2 (1.3)	11.4 (2.7)	.001	5.71	11.89
COWA	39.4 (12.1)	31.9 (12.0)	.09	-1.12	16.12
TMT-B	104.2 (46.4)	181.5 (103.2)	.004	-128.37	-26.37
Matrix Reasoning	15.5 (4.2)	11.8 (5.2)	.03	0.36	7.08
Zung Anxiety Inventory	27.8 (1.3)	38.8 (1.9)	<.001	-13.55	-7.95
GDS	4.3 (3.7)	4.5 (5.1)	.89	-3.73	3.24
FAQ	3.4 (3.5)	5.0 (5.6)	.37	-5.21	1.98

Note: 95% CI = 95% Confidence Interval of the Difference, MOCA = Montreal Cognitive Assessment, BVMT-R = Brief Visual Memory Test-Revised, HVLT-R = Hopkins Verbal Learning Test-Revised, COWA = Controlled Oral Word Association Test, TMT-B = Trail Making Test, Part B, Zung = Zung Anxiety Inventory, GDS = Geriatric Depression Scale, FAQ = Functional Assessment Questionnaire. Values listed as Mean (Standard Deviation).

utilized raw scores, with higher scores indicating better performance for all tasks except TMT-B.

- Psychiatric measures: Self-reported depression was assessed using the 30-item Geriatric Depression Scale (GDS), and self-reported anxiety was examined via the Zung Anxiety Self-Assessment Scale. Higher scores reflect greater symptoms of depression or anxiety.
- Functional measures: Self-reported instrumental activities of daily living were assessed using the 10-item Functional Activities Questionnaire (FAQ). Higher scores indicate lower functioning.

Statistical Analysis

Group status of screen pass/fail was based on the EMERGE trial criteria described above. Evaluation of normality was undertaken for all continuous variables (14, 15), and all measures were determined to have a normal distribution except the FAQ. Independent samples t-tests were used to compare normal continuous data from neuropsychological, psychiatric, and functional performances with screen pass/fail group status, and independent samples Mann-Whitney U tests were used to compared non-normal continuous data (i.e., FAQ). For the categorical analysis of gender, Fisher's exact test analysis was calculated based on screen pass/fail group categorization as the independent variable. Measures of effect size were expressed as Cohen's d values for continuous data and Phi coefficients for categorical data. Two-tailed alpha levels were set using Holm's Sequentially Rejective Bonferroni Test in order to control for multiple comparisons.

Results

Of the 38 participants in the current study, 14 participants screen passed this AD clinical trial, and 24 screen failed. The mean age was 72.5 years old (+/- 7.1 years) and the mean level of education was 16.4 years (+/- 2.7 years). All participants were non-Hispanic/Caucasian. No significant differences in age nor education were observed between screen pass/fail groups, $t(36) = -0.64$, $p = .53$, $d = -0.21$, for age and, $t(36) = 1.54$, $p = .13$, $d = 0.51$, for education (see Table 1). Conversely, higher screen failure rates were significantly related to female gender ($p = .02$, Fisher's exact test, Phi = -0.40), with 83% of female participants screen failing this AD trial versus 45% of male participants.

There was no difference in performance on visual memory, $t(35) = -0.38$, $p = .71$, $d = -0.13$, or verbal memory tasks, $t(34) = -0.47$, $p = .64$, $d = -0.16$, between screen pass/fail groups, nor on a composite screen of mental status (MOCA), $t(35) = 1.59$, $p = .12$, $d = 0.54$. In contrast, performance differences were observed between screen pass/fail groups on several non-memory cognitive domains. Specifically, the screen fail group for this AD clinical trial tended to perform worse on Information, $t(8) = 6.56$, $p = .001$, $d = 4.63$, TMT-B, $t(32.84) = -3.09$, $p = .004$, $d = -1.08$, and Arithmetic, $t(36) = 2.95$, $p = .006$, $d = 0.98$. While trends were observed, no group differences were evident for Matrix Reasoning, $t(35) = 2.25$, $p = .03$, $d = 0.76$, Digit Span, $t(35) = 2.14$, $p = .04$, $d = 0.72$, or COWA,

$t(34) = 1.77$, $p = .09$, $d = 0.61$ after controlling for multiple comparisons. Additionally, the screen fail group reported greater levels of anxiety, $t(6) = -9.38$, $p < .001$, $d = 7.66$, but not depression, $t(32) = -0.16$, $p = .89$, $d = -0.06$. An independent samples Mann-Whitney U test indicated that there was no difference in endorsements on the FAQ between the screen pass (Median = 14.69) and the screen fail (Median = 16.94) groups, U = 134.00, p = .49.

Discussion

The current study analyzes neuropsychological, psychiatric, and functional data from clinical neuropsychological and neurological evaluations that were collected prior to the EMERGE trial screening visits in order to predict trial appropriateness and subsequently reduce AD trial screen fail rates. All results should be considered within the context of the small sample size of this exploratory study. Our results revealed that worse performance on non-memory neuropsychological domains was related to screen failure status for the EMERGE AD clinical trial. Specifically, participants performing worse on domains related to crystallized intelligence ($d = 4.63$), executive functioning ($d = 1.08$), and attention ($d = 0.98$) tended to screen fail this trial, and while not remaining significant after controlling for multiple comparisons, additional measures of executive functioning and attention possessed moderate to large effect sizes ($d = 0.72 – 0.76$) . The directionality of our findings—that worse performance on non-memory domains is associated with screen failing an AD trial—is somewhat unexpected. Upon further consideration, this result may be explained by the typical recruitment pathway from clinic to trials, which requires a diagnosis of interest (e.g., MCI or AD), but is otherwise up to the discretion of the physician to predict if the patient will "fit" into a trial. Physicians may erroneously view more globally-impaired patients as being better fits into clinical trials, resulting in greater recruitment of those patients and subsequently higher screen failure rates for those patients whose disease severity is too advanced for a particular trial. Alternatively, it is possible that participants who screen fail AD trials may have deficits that are atypical for MCI/early AD, and that their non-memory impairments may be at least partly due to non-AD pathology. These results suggest that recruiting patients into clinical trials earlier in their disease course, when their disease severity is less, may result in reduced screen failure rates in AD trials.

Conversely, we were not able to detect a relationship between memory-related tasks and screen fail/pass status. This finding was opposite of our hypothesis and in contrast with several large-scale studies suggesting that conversion to AD is associated with memory impairment (Alzheimer's Disease Neuroimaging Initiative [ADNI] (16)). One explanation may be that the measures used in the EMERGE trial to gauge memory severity are not as sensitive to subtle changes in memory as neuropsychological memory measures that approximate a normal distribution of test performances. Specifically, only 3 points out of a total of 30 on the MMSE pertain to memory 10, and the CDR incorporates an ordinal scale of memory performance (0 – No Impairment, 0.5 – Questionable Impairment, 1 – Mild Impairment, 2 – Moderate Impairment, and 3 – Severe Impairment) with few participants in outpatient settings scoring at the highest levels (e.g., CDR levels 2 and 3 require "severe memory loss" with "new material either rapidly lost" or "only fragments remain" (12)). An alternative explanation may be that memory dysfunction is so common in AD and for patients considered for an AD trial that it is not necessarily surprising that memory performance does not distinguish who will be successfully screened into an AD clinical trial. As such, these results suggest that such memory dysfunction may be necessary but not sufficient to screen pass into an AD clinical trial, and that performances on other non-memory cognitive domains possess higher discriminative value.

In addition, our results showed that greater endorsements of anxiety are associated with higher screen failure rates ($d = 7.66$). This finding is congruous with research consistently observing higher levels of self-reported anxiety in more severe presentations of AD (17), and is similar to our other results suggesting that participants who screen failed the EMERGE trial displayed worse disease severity. Together, these results further support the notion that recruitment of patients earlier in the disease course may reduce screen failure rates in AD clinical trials. In contrast, a subjective measure of functional skills was not significantly associated with screen failure status in our study, which was unexpected given other findings in the literature that greater endorsements on functional scales were associated with greater conversion to AD (18). It is possible that the non-normal distribution of the sample of FAQ scores (skewness value of 1.62 [Standard Error (SE) = .42] and skew/SE ratio of 3.84, kurtosis value of 2.55 [SE = .82] and kurtosis/SE ratio of 3.10) may have limited our ability to find significance, though like memory dysfunction, functional loss may be necessary but not sufficient to discriminate screen pass/fail status.

Further, the current study examined demographic variables that were hypothesized to influence screen failure rates in this AD clinical trial. Our study observed that women displayed greater screen failure rates than men. This finding seems counter to research suggesting that women tend to worry more about health-related factors and men tend to minimize health-related risks (19), though this result potentially sheds light on the importance of spousal and care partner involvement (4) in patients with MCI or AD. Specifically, in this preliminary study, 78% of female participants were accompanied by their male spouse as care partner (14 of 18), and 90% of male participants were accompanied

by their female spouse as care partner (18 of 20). As the majority of participants who screen failed the EMERGE trial did so due to below-cutoff performance on the MMSE (71% of overall screen failures, and 94% of participants failing due to performing too severely on screening measures), these differential results based on gender may suggest that male care partners may not identify the need for their partner to be involved in an AD trial until later in the disease, at which point the partner may have advanced to more severe disease states that would exclude them from successful trial enrollment. Finally, the lack of a significant difference between screen pass/fail groups for factors like education and age was contrary to our hypotheses, and to research showing that reduced education level and advanced age are both associated with worse cognitive performance (13).

Study Limitations

The proposed study is not without limitations. As alluded to above, our sample size likely hindered our ability to find statistical significance for some analyses. Additionally, our study is only attempting to examine clinical predictors of screen failure for patients that have already been diagnosed with the condition of interest (MCI or AD) and pre-screened for easily identifiable exclusionary medical comorbidities. Also, our sample is not representative of all patients seeking care from a cognitive specialty clinic or identified through advertisement without a prior clinical evaluation, and our predictor and outcome variables are also specific to those measures administered in our particular clinical evaluations and for this particular trial, respectively. Finally, this study is the first step in developing a rigorous model to investigate further ways to reduce AD trial screen failure rates, and does not address all barriers to AD trial recruitment or initiatives being undertaken elsewhere to improve recruitment (such as creating registries of trial-ready participants). Although this study only addresses pharmacological AD trials, one would assume that results would relate to non-pharmacological AD trials as well. This would be a future direction to examine, along with consideration of issues with enrolling a wider demographic of participants into AD trials associated with homogeneity of trial samples related to education (mostly highly educated), ethnicity (Caucasian), language (English-speaking), care-partner status (mostly opposite-gender spouse), and health status (without sensory impairments that would exclude from cognitive testing). Of importance, these preliminary findings do not suggest that other innovations described briefly above should not be undertaken, but propose a method to optimize successful recruitment of participants from current recruitment sources.

Future Directions

This current study is an exploratory examination of potential cognitive and psychiatric factors that may influence screen failure rates in AD clinical trials. By identifying predictors of AD trial screen failure that are already available to AD clinical trial teams, we hope to influence decision-making about which participants are most likely to be successfully enrolled in a trial with minimal additional effort required by the AD trial team. For example, if faced with limited screening resources, a clinical trials team member might review existing neuropsychological test results to identify a male patient with AD and memory dysfunction but otherwise largely preserved cognition rather than a female patient with AD and global cognitive dysfunction and anxiety, as the latter individual is more likely to screen fail the trial. Consequently, by building upon these initial findings, this research has potential to reduce screen fail rates in AD clinical trials, which will lower participant burden, maximize study resources, and cut costs. Future examination of 1) a collection of industry-sponsored trials and 2) large-scale databases from multi-site studies such as ADNI may further refine the process and potentially examine predictors not evaluated in the current study. Future studies could also apply this methodology to patients attending Annual Wellness Visits to streamline the pathway of participation from the Primary Care Clinic to AD intervention trials. Overall, these findings have the potential to advance the field by helping to enhance trial-recruitment infrastructure and to encourage greater engagement of older adults in AD research.

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Ethical standards: This study was conducted according to the University of Utah's standards for Ethical Research. All procedures for the current study received approval by the University's Institutional Review Board.

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Original Research

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Application of the NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease Using Cerebrospinal Fluid Biomarkers in the AIBL Study

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Abstract

BACKGROUND: The National Institute on Aging and Alzheimer's Association (NIA-AA) have proposed a new Research Framework: Towards a biological definition of Alzheimer's disease, which uses a three-biomarker construct: Aß-amyloid, tau and neurodegeneration AT(N), to generate a biomarker based definition of Alzheimer's disease.

OBJECTIVES: To stratify AIBL participants using the new NIA-AA Research Framework using cerebrospinal fluid (CSF) biomarkers. To evaluate the clinical and cognitive profiles of the different groups resultant from the AT(N) stratification. To compare the findings to those that result from stratification using two-biomarker construct criteria (AT and/or A(N)).

DESIGN: Individuals were classified as being positive or negative for each of the A, T, and (N) categories and then assigned to the appropriate AT(N) combinatorial group: A-T-(N)-; A+T-(N)-; A+T+(N)-; A+T-(N)+; A+T+(N)+; A-T+(N)-; A-T-(N)+; A-T+(N)+. In line with the NIA-AA research framework, these eight AT(N) groups were then collapsed into four main groups of interest (normal AD biomarkers, AD pathologic change, AD and non-AD pathologic change) and the respective clinical and cognitive trajectories over 4.5 years for each group were assessed. In two sensitivity analyses the methods were replicated after assigning individuals to four groups based on being positive or negative for AT biomarkers as well as A(N) biomarkers.

SETTING: Two study centers in Melbourne (Victoria) and Perth (Western Australia), Australia recruited MCI individuals and individuals with AD from primary care physicians or tertiary memory disorder clinics. Cognitively healthy, elderly NCs were recruited through advertisement or via spouses of participants in the study.

PARTICIPANTS: One-hundred and forty NC, 33 MCI participants, and 27 participants with AD from the AIBL study who had undergone CSF evaluation using Elecsys® assays.

INTERVENTION (if any): Not applicable.

MEASUREMENTS: Three CSF biomarkers, namely amyloid β1-42, phosphorylated tau181, and total tau, were measured to provide the AT(N) classifications. Clinical and cognitive trajectories were evaluated using the AIBL Preclinical Alzheimer Cognitive Composite (AIBL-PACC), a verbal episodic memory composite, an executive function composite, California Verbal Learning Test – Second Edition; Long-Delay Free Recall, Mini-Mental State Examination, and Clinical Dementia Rating Sum of Boxes scores.

RESULTS: Thirty-eight percent of the elderly NCs had no evidence of abnormal AD biomarkers, whereas 33% had biomarker levels consistent with AD or AD pathologic change, and 29% had evidence of non-AD biomarker change. Among NC participants, those with biomarker evidence of AD pathology tended to perform worse on cognitive outcome assessments than other biomarker groups. Approximately three in four participants with MCI or AD had biomarker levels consistent with the research framework's definition of AD or AD pathologic change. For MCI participants, a decrease in AIBL-PACC scores was observed with increasing abnormal biomarkers; and increased abnormal biomarkers were also associated with increased rates of decline across some cognitive measures.

CONCLUSIONS: Increasing biomarker abnormality appears to be associated with worse cognitive trajectories. The implementation of biomarker classifications could help better characterize prognosis in clinical practice and identify those at-risk individuals more likely to clinically progress, for their inclusion in future therapeutic trials.

Key words: Alzheimer's disease, biomarkers, progression, longitudinal.

Alzheimer's disease (AD) is a progressive, neurodegenerative disease characterized by neurodegeneration, synaptic loss, and the accumulation of extracellular-amyloid plaques and tau intracellular neurofibrillary tangles (1, 2). Several key imaging and cerebrospinal fluid (CSF) biomarkers have been identified in AD (3, 4). Deposition of beta-amyloid (Aβ-amyloid) plaques is one of the most important pathologic hallmarks of AD and is widely thought to be the initiating and primary driver of disease (amyloid hypothesis) (5, 6). Measures of Aβ-amyloid include

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amyloid imaging with positron emission tomography (PET) as well as CSF Aβ1-42, and studies have shown that these markers may be detectable over a decade before symptom onset (6, 7). Neurodegeneration and synaptic loss are also apparent prior to symptom onset, and may be visible on brain magnetic resonance imaging (MRI) as structural atrophy in regions consistent with AD (3). Other methods of assessing neurodegeneration include fluorodeoxyglucose [FDG]-PET, which measures brain metabolism as an indicator of synaptic activity (8, 9) and CSF total tau (t-tau), which is also indicative of synaptic loss and neurodegeneration (4, 10). Finally, tau pathology may be assessed using tau PET or CSF phosphorylated tau (p-tau), which has shown utility for predicting progression from mild cognitive impairment (MCI) to AD dementia as well as differentiating AD from other forms of dementia (3, 4, 11, 12).

Based on these biomarkers of Aβ-amyloid (CSF Aβ1–42), neurodegeneration (t-tau) and tau pathology (p-tau), various constructs have been developed to accurately identify individuals in the earliest (pre-symptomatic) stages of disease who are likely to progress to MCI and AD. Initial diagnostic research criteria developed by the National Institute on Aging and Alzheimer's Association (NIA-AA) classified individuals with evidence of Aβ-amyloid pathology (i.e., abnormal Aβ-amyloid PET and CSF Aβ-amyloid) into three stages of preclinical AD based on the presence or absence of markers of neuronal injury (i.e., FDG-PET, structural MRI, or measures of tau) and evidence of subtle cognitive change (13). The criteria were further expanded to include two additional categories for cognitively normal individuals, including those with no biomarkers of AD (i.e., normal Aβ-amyloid, neurodegeneration, and tau) and those without evidence of Aβ-amyloid pathology but who are positive for other markers of neuronal injury, also referred to as suspected non-AD pathophysiology (SNAP) (14). These classifications were able to characterize 97% of cognitively normal individuals from a population-based sample (14) and have been shown to correlate with the cognitive trajectories and disease progression of individuals over time (15, 16).

While previous iterations of the NIA-AA criteria were based on a two-marker construct using evidence of Aβ-amyloid pathology and neurodegeneration as a single category, it is thought that segregating measures of pathologic tau (i.e., tau PET, CSF p-tau) from other markers of neuronal injury may help to better distinguish AD-related pathology from other neurodegenerative conditions (3). The recent NIA-AA Research Framework: Towards a biological definition of Alzheimer's disease (4) is therefore based on a three-marker construct. The recent framework uses normal (-) or abnormal (+) levels of Aβ-amyloid deposition ("A"), pathologic tau ("T"), and neurodegeneration ("(N)") as constructs to create the AT(N) classification system. In this contribution, we interrogated the AT(N) classification system to improve understanding for its implementation and applicability in characterizing and understanding the pathogenesis of AD. Firstly, we apply the AT(N) classification system to CSF biomarkers from well-characterized participants in the longitudinal Australian Imaging, Biomarker & Lifestyle (AIBL) Flagship Study of Ageing. Secondly, we describe the long-term clinical and cognitive trajectories of AIBL elderly cognitively normal controls (NCs) as well as AIBL MCI individuals, using the three-marker construct.

Methods

The AIBL cohort

The AIBL cohort study of aging combines data from neuroimaging, biomarkers, lifestyle, clinical, and neuropsychological assessments. Two study centers in Melbourne (Victoria) and Perth (Western Australia), Australia recruited individuals with MCI and with AD from primary care physicians or tertiary memory disorders clinics. Cognitively healthy NC participants were recruited through advertisement or via spouses of participants in the study. Exclusion criteria included a history of non-AD dementia, Parkinson's disease, schizophrenia, bipolar disorder, current depression, cancer in the past 2 years (with the exception of basal-cell skin carcinoma), symptomatic stroke, uncontrolled diabetes, or current regular alcohol use. Between November 3, 2006, and October 30, 2008, AIBL recruited 1112 eligible volunteers who were at least 60 years old and fluent in English. Full details on the study design and inclusion criteria have been reported elsewhere (17). An enrichment cohort of 86 participants with AD, 124 MCI participants, and 389 NC participants were recruited by AIBL between March 30, 2011, and June 29, 2015. At baseline, the AIBL study participants had an average age of 72 years, 58% were female, and 36% were Apolipoprotein E (APOE) ε4 carriers. APOE ε4 carriage was determined as previously described (18). Two hundred AIBL participants (140 NC, 33 MCI and 27 AD) with a mean age of 73 (50% Males) who had undergone lumbar puncture were included in the current study.

Assessment of CSF biomarkers

Lumbar puncture was used to collect CSF from 200 AIBL participants in the morning after overnight fasting, with a protocol aligned to the Alzheimer's Biomarkers Standardization Initiative (ABSI). Lumbar puncture was performed in the sitting position using a strictly aseptic technique and gravity drip collection. CSF was collected into a polypropylene tube and placed on ice prior to centrifugation (2000 ×g at 4°C for 10 minutes), and the supernatant was transferred to a second polypropylene tube and gently inverted. Samples were aliquoted

(500 μL) into Nunc cryobank polypropylene tubes (NUN374088) and stored in liquid nitrogen vapor tanks within 1 hour (kept on dry ice prior to storage) and only thawed once, immediately before analysis. CSF levels of Aβ1-42, t-tau, and p-tau were measured by electrochemiluminescence Elecsys® immunoassay (Roche Diagnostics, Penzberg, Germany) that uses a quantitative sandwich principle. Levels were measured using the Roche cobas® e601 analyzer (Roche Diagnostics) with a total assay duration of 18 minutes.

Application of the NIA-AA Research Framework

The NIA-AA Research Framework (4), details grouping of individuals based on AT(N) criteria, where: 'A' represents Aβ-amyloid or associated pathologic state—here 'A' is defined using CSF Aβ1-42; 'T' represents aggregated tau (neurofibrillary tangles) or associated pathologic state—in this current study 'T' is defined using CSF p-tau; '(N)' represents neurodegeneration or neuronal injury—here '(N)' is defined using CSF t-tau. Individuals were classified as being positive or negative for each of the A, T, and (N) criteria. A+ was defined as having a CSF Aβ1-42 level ≤1054.00pg/mL and A- as having a CSF Aβ1-42 level >1054.00 pg/mL. T+ was defined as having a CSF p-tau level ≥21.34 pg/mL and T- as having a CSF p-tau level <21.34 pg/mL. (N)+ was defined as having a CSF t-tau level ≥212.60 pg/mL and T- as having a CSF p-tau level <212.60 pg/mL. Individuals were then classified as belonging to one of the eight AT(N) combinatorial groups: A-T-(N)-; A+T-(N)-; A+T+(N)-; A+T-(N)+; A+T+(N)+; A-T+(N)-; A-T-(N)+; A-T+(N)+. In line with the NIA-AA Research Framework (4), the eight AT(N) groups were collapsed into four main groups of interest: those with normal AD biomarkers (A-T-(N)-), those with non-AD pathologic change (A-T+(N)-; A-T+(N)+; A-T+(N)-), those with AD pathologic change (A+T-(N)-; A+T-(N)+), and those with AD (A+T+(N)-; A+T+(N)+).

Cognitive markers

All participants underwent extensive neuropsychological testing, as previously described (17). Briefly, the tests comprising the AIBL clinical and neuropsychological battery were selected to cover the main domains of cognition affected by AD and other dementias, and are all internationally recognized as having good reliability and validity. The full battery comprised: the Clinical Dementia Rating (CDR) Scale, Mini-Mental State Examination (MMSE) (19), Clock-Drawing Test, California Verbal Learning Test – Second Edition (CVLT-II) (20), Logical Memory (LM) I and II (Wechsler Memory Scale [WMS]-III; Story A only) (21-23), Delis–Kaplan Executive Function System (D-KEFS) verbal fluency (24), 30-item Boston Naming Test (BNT) (25), the Stroop Test (Victoria version) (22), the Rey Complex Figure Test (RCFT) (26), Digit Span and Digit Symbol-Coding subtests of the Wechsler Adult Intelligence Scale – Third Edition (WAIS–III) (27), the Wechsler Test of Adult Reading (WTAR) (28), the Hospital Anxiety and Depression Scale (HADS), and the Geriatric Depression Scale (GDS).

Clinical and cognitive trajectories were evaluated using the AIBL-Preclinical Alzheimer Cognitive Composite (AIBL-PACC) (29), a verbal episodic memory composite, an executive function composite (30), CVLT-II Long-Delay Free Recall (CVLT-II LDFR), MMSE, and CDR Sum of Boxes (CDR SoB) measures. The AIBL-PACC was constructed by summing Z-score measures of CVLT-II LDFR, LM-II, MMSE, and Digit Symbol-Coding. The verbal episodic memory composite was created from Z-scores of CVLT-II LDFR, CVLT-II recognition false positives, and LM-II, and the executive function composite was generated from Z-scores of D-KEFS letter fluency and category switching totals as well as the colors/dots interference measure from the Stroop Test (Victoria version).

Analysis

Demographic information was assessed across clinical classifications for 200 AIBL participants who had undergone CSF evaluation. Participants were classified into one of eight categories based on the three-construct model of AT(N) in the NIA-AA Research Framework. The prevalence of the AT(N) groups was assessed across the clinical classification groups. The eight AT(N) groups were then collapsed into four main groups of interest: those with normal AD biomarkers, those with non-AD pathologic change, those with AD pathologic change, and those with AD. Baseline cognitive performance was assessed across these four groups within the NC and MCI clinical classification groups using boxplots and one-way t-tests. Longitudinal change in cognitive performance over time, separately for the NC and MCI, was assessed using boxplots and one-way t-tests of the random slopes obtained from linear mixed-effect models. In the linear mixed-effect models, the cognitive measure represented the dependent variable; age, sex, and APOE ε4 status were included as interacting independent factors and time since CSF evaluation was included as a random factor. The dependent variable was evaluated every 18 months for a mean follow-up of 4.5 years. The number of participants progressing towards more advanced disease (i.e., NC to MCI/AD and MCI to AD) within each of these four groups was also evaluated using descriptive statistics, due to the small number of conversions more sophisticated analyses such as Cox proportional hazards analyses could not be undertaken.

Table 1. Demographics

Metric	AD	MCI	NC	Total
Number of participants	27	33	140	200
Males, n (%)	15 (55.6)	23 (69.7)	61 (43.6)	99 (49.5)
Mean age, years (SD)	73.77 (8.2)	73.1 (6.5)	72.15 (6.0)	72.54 (6.3)
Years of education, n (%)				
<9	4 (16.7)	5 (15.2)	6 (4.3)	15 (7.6)
9-12	10 (41.7)	15 (45.5)	53 (37.9)	78 (39.6)
13-15	5 (20.8)	5 (15.2)	25 (17.9)	35 (17.8)
>15	5 (20.8)	8 (24.2)	56 (40.0)	69 (35.0)
APOE ε4 carriers, n (%)	12 (44.4)	11 (33.3)	31 (22.1)	54 (27)
Mean duration of follow-up, years (SD)	2.78 (2.0)	3.56 (2.3)	5.14 (2.7)	4.54 (2.7)

AD, Alzheimer's disease; APOE, Apolipoprotein E; MCI, mild cognitive impairment; NC, normal control; SD, standard deviation.

Sensitivity Analysis I

Participants were assigned to one of four groups (A-T-; A+T-; A-T+; A+T+) based on their CSF Aβ1-42 and p-tau levels as described above. Baseline cognitive performance was assessed across these four AT groups within each clinical classification group using boxplots and one-way t-tests. Longitudinal change in cognitive performance over time was assessed using boxplots and one-way t-tests of the random slopes obtained from linear mixed-effect models. In the linear mixed-effect models, the cognitive measure represented the dependent variable; age, sex, and APOE ε4 status were included as interacting independent factors and time since CSF evaluation was included as a random factor.

Sensitivity Analysis II

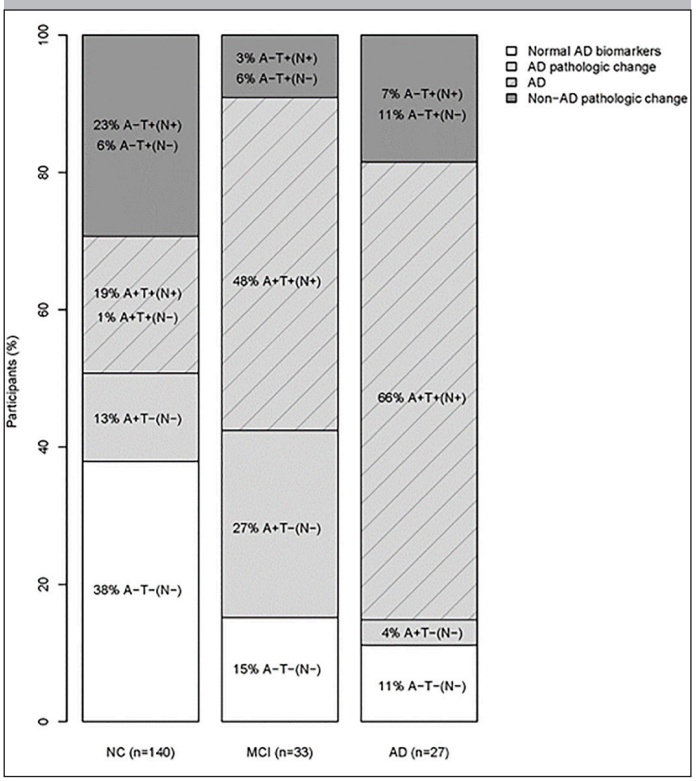
Participants were assigned to one of four groups (A-N-; A+N-; A-N+; A+N+) based on their CSF Aβ1-42 and t-tau levels as described above. Baseline cognitive performance was assessed across these four A(N) groups within each clinical classification group using boxplots and one-way t-tests. Longitudinal change in cognitive performance over time was assessed using boxplots and one-way t-tests of the random slopes obtained from linear mixed-effect models. In the linear mixed-effect models, the cognitive measure represented the dependent variable; age, sex, and APOE ε4 status were included as interacting independent factors and time since CSF evaluation was included as a random factor.

Results

Demographics

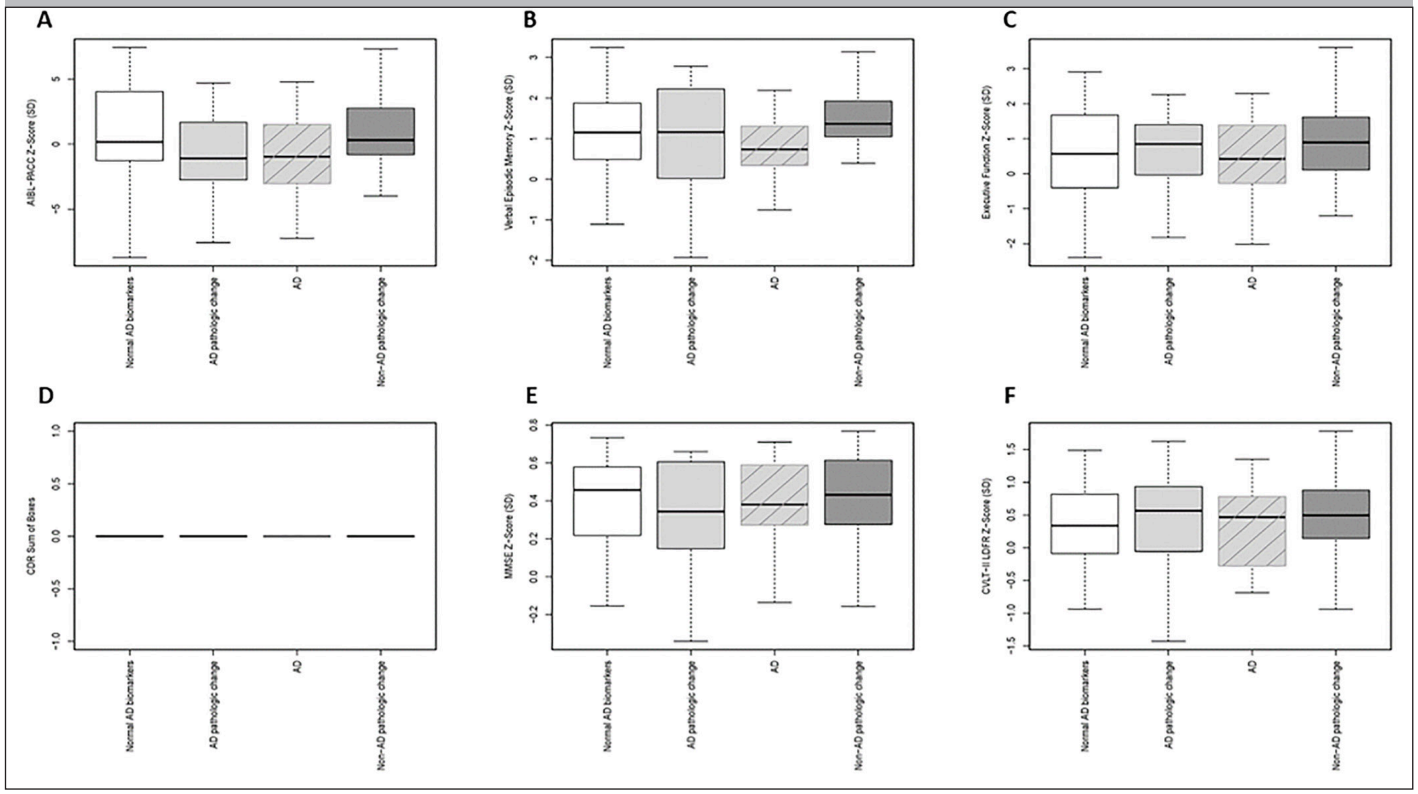
The majority of participants (140/200) were cognitively healthy (NC) and the remaining comprised MCI or AD (n=33 and n=27, respectively) (Table 1). There was a higher prevalence of males in the MCI and AD samples compared to the NC sample. Reported ages at baseline did not differ across the three samples (averaging around 73 years). The NC participants had a higher level of education and had fewer APOE ε4 carriers. The mean duration of follow-up for all participants was 4.54 years.

Figure 1. Prevalence of the AT(N) groups across clinical classifications



AD, Alzheimer's disease; MCI, mild cognitive impairment

Figure 2. Cross-sectional performance on the six cognitive measures (A: AIBL-PACC; B: Verbal Episodic Memory; C: Executive Function; D: CDR Sum of Boxes; E: MMSE; F: CVLT-II LDFR) for the four contracted AT(N) groups in NC



AD, Alzheimer's disease; AIBL-PACC, Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing – Preclinical Alzheimer Cognitive Composite; CDR, Clinical Dementia Rating; CVLT-II LDFR, California Verbal Learning Test – Second Edition; Long-Delay Free Recall; MMSE, Mini-Mental State Examination; NC, normal control; SD, standard deviation.

Prevalence of AT(N) groups

The prevalence of each of the eight AT(N) classifications within the AIBL NC, MCI, and AD samples are given in Figure 1. The highest proportion of NC participants (38%) had normal AD biomarkers; 13% had AD pathologic change, 20% have AD, and 29% had non-AD pathologic change. In the MCI and AD samples, 75% and 70% of participants had AD pathologic change, respectively.

Cross-sectional cognitive performance in NC

In general, NC participants with biomarkers consistent with AD performed the worst on the cognitive composite markers and MMSE (Figure 2A–C and E). Differences were not observed for CDR SoB with all NCs scoring 0 on this test (Figure 2D). The NC participants with normal AD biomarkers had the lowest scores on the CVLT-II LDFR (Figure 2F). In general, within the NC sample those classified as having non-AD pathologic change had similar scores to those with normal AD biomarkers. Regarding the sensitivity analyses, The A+T+ group had significantly (p=0.03) lower baseline scores for AIBL-PACC in comparison to the A-T- group and the A+T+ group had significantly lower baseline scores for the Verbal Episodic Memory composite than the A-T+ group. Also, the A+N+ group had significantly lower baseline scores for the Verbal Episodic Memory composite than the A-N+ group. No other differences were observed in the sensitivity analyses of differences in the NC at baseline.

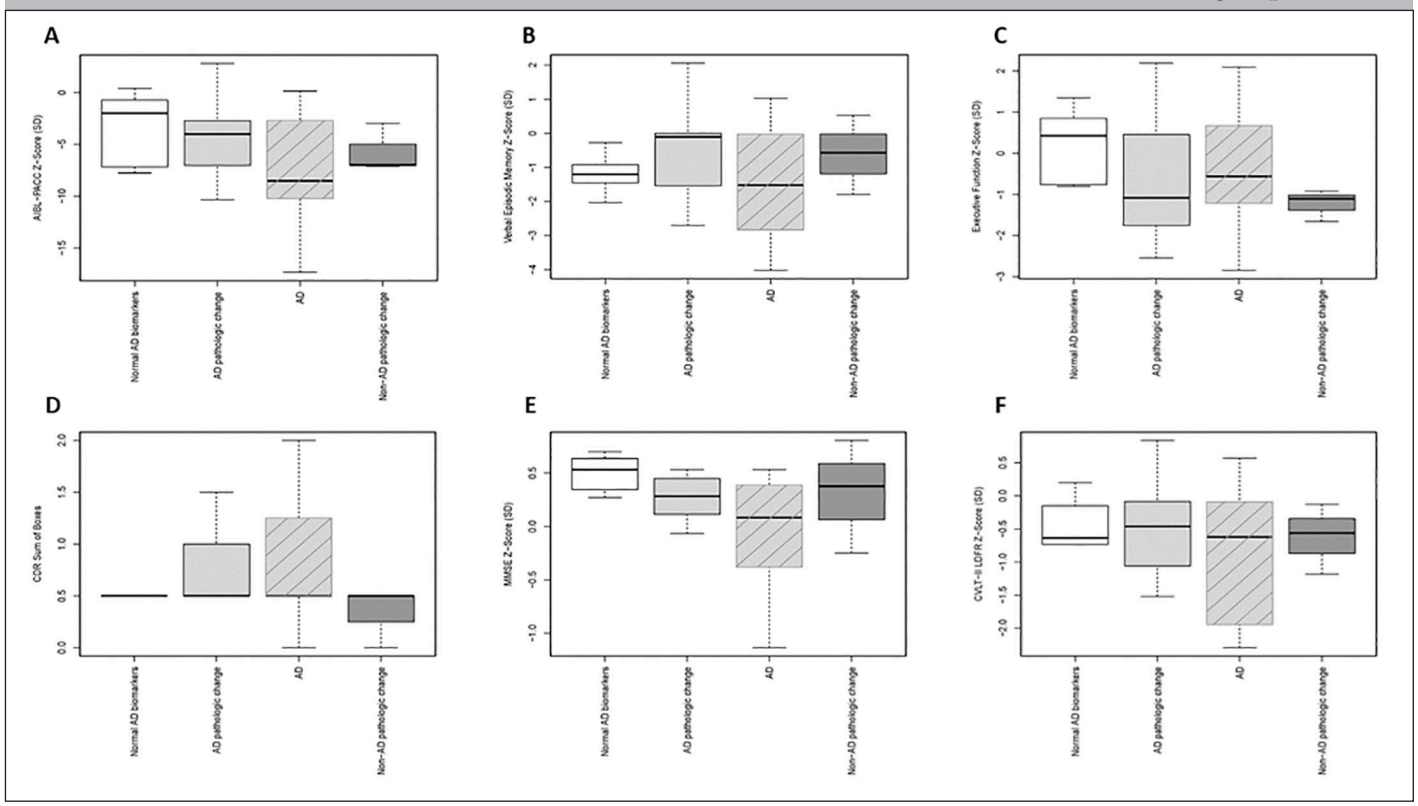
Cross-sectional cognitive performance in MCI

For MCI participants there was a decrease in performance from those with normal AD biomarkers, to those with AD pathologic change and then AD for the AIBL-PACC (Figure 3A). This trend was not observed in the other five clinical and cognitive markers considered (Figure 3B–F). No baseline differences were obsevered for the MCI in the sensitivity analyses.

Longitudinal change in cognitive performance

For both the NC and MCI participants, systematic differences were not observed in the rates of decline for the four groups considered (Supplementary Figures 1 and 2). No differences were observed in the sensitivity analyses.

Figure 3. Cross-sectional performance on the six cognitive measures (A: AIBL-PACC; B: Verbal Episodic Memory; C: Executive Function; D: CDR Sum of Boxes; E: MMSE; F: CVLT-II LDFR) for the four contracted AT(N) groups in MCI



AD, Alzheimer's disease; AIBL-PACC, Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing – Preclinical Alzheimer Cognitive Composite; CDR, Clinical Dementia Rating; CVLT-II LDFR, California Verbal Learning Test – Second Edition; Long-Delay Free Recall; MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment; SD, standard deviation.

Progression to disease

Over the period of follow-up (mean=4.54 years), of the 53 NC individuals with normal AD biomarkers, one progressed to MCI due to AD and one progressed to MCI not due to AD. Of the 18 NC individuals with AD pathologic change, two progressed to MCI due to AD. Of the 28 NC individuals with AD biomarkers, one participant died and there were no other transitions. Of the 41 individuals with non-AD pathologic change, one participant died, one progressed to MCI, and one progressed to vascular dementia. Of the nine MCI individuals with AD pathologic change, one progressed to AD. Of the 13 MCI individuals with AD biomarkers, two participants died and two progressed to AD. There were not enough events of progression to ascertain any statistically significant differences in progression between the groups.

Discussion

This analysis evaluated the AT(N) classification system in a well-characterized population from the AIBL cohort, including cognitively healthy NC participants as well as those with MCI and AD. Approximately two in five of the elderly NC had no evidence of abnormal AD biomarkers, whereas one in three had biomarker levels consistent with AD or AD pathological change and almost one in three had evidence of non-AD pathological change. Twenty-three percent of the NC participants had biomarker levels aligned with the SNAP category (A-(N+)), which aligns with other reports in the literature (3, 16).

Among NC participants, those with biomarker evidence of AD pathology tended to perform worse on composite cognitive outcome assessments and the MMSE compared with other biomarker groups. Participants with abnormal non-AD-specific biomarkers performed similarly to those with or without normal AD biomarkers across endpoints. No differences were observed across the four biomarker groups with respect to rate of decline on any outcome assessment.

Approximately three in four participants with MCI or AD had biomarker levels consistent with AD or AD pathologic change. For MCI participants, a decrease in AIBL-PACC scores was observed with increasing abnormal biomarkers; increased abnormal biomarkers were also associated with increased rates of decline across some cognitive measures. There were not enough events of disease progression (i.e., NC to MCI/AD or MCI to AD) to draw any conclusions about the risk of disease progression based on the biomarker constructs.

Despite the lack of statistically significant trends,

which is likely to be related to the small numbers of participants included, observations from the current study are qualitatively consistent with previous work showing that biomarkers of AD evident before clinical symptoms appear to predict cognitive deficit. In a natural history study classifying NC participants (N=166) with a two-marker construct, using Aβ-amyloid (assessed using amyloid PET imaging) and markers of neurodegeneration (hippocampus volume seen on MRI, FDG-PET), those with normal AD biomarkers showed improvement over time on a composite cognitive measure derived from eight neuropsychological tests, likely due to practice effects (15). Conversely, participants who either had evidence of Aβ-amyloid pathology or were considered SNAP participants had reduced practice effects, and those positive for both Aβ-amyloid pathology and markers of neurodegeneration showed cognitive decline (15). An analysis of a larger group of NC individuals from the AIBL cohort (N=573) also applied the two-marker construct, using amyloid PET as a marker of Aβ-amyloid pathology and hippocampal volume on MRI to assess neurodegeneration, and showed that amyloid-PET positivity conferred significant risk for cognitive decline, with structural evidence of neurodegeneration further compounding this risk (16). Applying this two-marker construct here in a sensitivity analysis, highlighted some baseline differences: individuals with abnormal CSF levels for Aβ-amyloid and one of the tau markers performed worse than participants with less biomarker abnormality on two of the cognition measures. No longitudinal differences were observed in the sensitivity analysis.

The composite AT(N) system for classifying AD used in the present analysis separates markers of tau pathology from other neurodegenerative markers which is thought to improve specificity in terms of differentiating patients with AD vs. non-AD pathology. However, our inconclusive findings suggest that further study of the AT(N) classification system and its comparison to the two-biomarker constructs in larger groups of participants across the disease spectrum is needed.

Our construct employed CSF-based immunoassay measures for determining A, T, and (N) status, in comparison to the imaging metrics employed in the previous studies discussed (15, 16). The availability of immunoassay methodology for evaluating AD and neurodegeneration biomarkers could have important implications for clinical practice as this type of testing may be more widely accessible and cheaper than imaging-based methodologies. In turn, this potential for great accessibility vs. imaging methodologies may facilitate wider application of AT(N) classification in clinical trial methodology to screen more potential participants and further enrich study populations with AD biomarker-positive individuals who are most likely to show AD-related disease progression within the duration of the study. A much wider application would be achievable once blood biomarkers become available.

There are a number of limitations to this study, including the small sample size, which may preclude any statistically significant differences being observed. Further, only a small number of disease progression events occurred precluding any evaluations to be made regarding the power of the AT(N) criteria to predict progression to disease. The participants were volunteers who were not randomly selected from the community, and were generally well educated; thus, these findings might only be valid in similar cohorts and this limitation precludes the generalization of the findings. In view of the stringent selection criteria in AIBL, which excluded individuals with cerebrovascular disease or other dementias, the effect of other comorbidities on the trajectories might be underestimated. Longitudinal cognitive performance was based on three composite measures as well as two clinical scores and one standard measure, which were corrected using within-study norms; however, other cognitive tests, or combinations thereof, might yield different results. Further, biomarker levels were obtained from a CSF immunoassay and different techniques may yield different results. The cut-offs used for dichotomous stratification were somewhat arbitrary and continuous variables might provide better predictors of progression. Another potential limitation is the non-specificity of t-tau for the (N) classification and other markers, such as neurofilament light, either in CSF of plasma, may provide a more robust assessment of (N).

In conclusion, increasing CSF biomarker abnormality appears to be associated with worse cognitive trajectories. The implementation of the AT(N) classification could help better characterize prognosis in clinical practice and identify those at-risk individuals more likely to progress, for inclusion in future therapeutic trials. However, our inconclusive findings suggest that further study of the AT(N) classification system in larger groups of participants is warranted.

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Conflict of interest: Samantha C. Burnham: reports speaker honoraria from Novartis outside the scope of the submitted work and research funding paid to her employers from F. Hoffmann-La Roche Ltd. Preciosa M. Coloma: is a full-time employee of, and own shares in, F. Hoffmann-La Roche Ltd. Simon Laws: received personal fees from Alzhyme outside the scope of the submitted

work. James Doecke: reports research funding paid to his employers from F. Hoffmann-La Roche Ltd. David Ames: reports receipt of financial assistance to his employer to assist with an international drug trial of an anti-Alzheimer's agent, owned by Eli Lilly. Christopher C. Rowe: reports speaker honoraria from GE Healthcare and Avid Radiopharmaceuticals, consulting fees from Avid Radiopharmaceuticals, AstraZeneca, and Piramal Imaging, and research grants from Avid Radiopharmaceuticals, GE Healthcare, and Piramal Imaging all outside the scope of the submitted work. Colin L. Masters: reports personal fees from Prana Biotechnology, Eli Lilly, and Actinogen outside the scope of the submitted work. Victor L. Villemagne: reports speaker honoraria from GE Healthcare, Piramal Imaging, and Avid Radiopharmaceuticals, and consulting fees from Lundbeck, AbbVie, Shanghai Green Valley Pharmaceutical Co. outside the scope of the submitted work and consulting fees from F. Hoffmann-La Roche Ltd. All other authors declare no conflicts of interest

Ethical standards: This work was conducted in accordance with the principles set forth by the Declaration of Helsinki. The institutional ethics committees of Austin Health, St Vincent's Health, Hollywood Private Hospital, and Edith Cowan University in Australia approved the AIBL study, and all volunteers gave written informed consent before participating.

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Original Research

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Prospective Evaluation of Cognitive Health and Related Factors in Elderly at Risk for Developing Alzheimer's Dementia: A Longitudinal Cohort Study

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Abstract

BACKGROUND: The CHARIOT PRO Main study is a prospective, non-interventional study evaluating cognitive trajectories in participants at the preclinical stage of Alzheimer's disease (AD) classified by risk levels for developing mild cognitive impairment due to AD (MCI-AD).

OBJECTIVES: The study aimed to characterize factors and markers influencing cognitive and functional progression among individuals at-risk for developing MCI-AD, and examine data for more precise predictors of cognitive change, particularly in relation to APOE ε4 subgroup.

DESIGN: This single-site study was conducted at the Imperial College London (ICL) in the United Kingdom. Participants 60 to 85 years of age were classified as high, medium (amnestic or non-amnestic) or low risk for developing MCI-AD based on RBANS z-scores. A series of clinical outcome assessments (COAs) on factors influencing baseline cognitive changes were collected in each of the instrument categories of cognition, lifestyle exposure, mood, and sleep. Data collection was planned to occur every 6 months for 48 months, however the median follow-up time was 18.1 months due to early termination of study by the sponsor.

RESULTS: 987 participants were screened, among them 690 participants were actively followed-up post baseline, of whom 165 (23.9%) were APOE ε4 carriers; with at least one copy of the allele. The mean age was 68.73 years, 94.6% were white, 57.4% were female, and 34.8% had a Family History of Dementia with a somewhat larger percentage in the APOE ε4 carrier group (42.4%) compared to the non-carrier group (32.4%). Over half of the participants were married and 53% had a Bachelor's or higher degree. Most frequently, safety events typical for this population consisted of upper respiratory tract infection (10.4%), falls (5.2%), hypertension (3.5%) and back pain (3.0%).

CONCLUSION (clinical relevance): AD-related measures collected during the CHARIOT PRO Main study will allow identification and evaluation of AD risk factors and markers associated with cognitive performance from the pre-clinical stage. Evaluating the psycho-biological characteristics of these pre-symptomatic individuals in relation to their natural neurocognitive trajectories will enhance current understanding on determinants of the initial signs of cognitive changes linked to AD.

Key words: CHARIOT, aging registry, cognitive health, pre-clinical, Alzheimer Disease.

Introduction

An increasing body of scientific evidence suggests that, in the field of Alzheimer's disease (AD), the optimal time to intervene with disease-modifying therapies is prior to the emergence of clinical symptoms of mild cognitive impairment (MCI) or AD dementia (1). The term "asymptomatic at-risk state for AD" (ARAD) (2) has been proposed as a descriptor for asymptomatic individuals with evidence of cerebral amyloid-β (Aβ) burden. Such individuals are at increased risk of progression to clinically symptomatic AD (3) and hence, potentially, good candidates for trials of preventative interventions.

Amongst cognitively normal (CN) individuals, subtle deficits or decreases in cognitive performance over time (even within the range of "normal" values) have been found to be associated with higher Aβ burden and/or carriage of the apolipoprotein (APOE) epsilon 4 allele with subsequent cognitive decline (3) and progression to MCI or dementia due to AD (4, reviewed in 5). This suggests that evolution of certain cognitive profiles may be sufficient in themselves (even in the absence of supporting biomarker information) to constitute an ARAD.

However, a putative ARAD cognitive profile has not yet been clearly identified or specified. Whereas many publications have focused on what may be termed 'late'

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MCI defined as individuals most likely to transition to dementia within a year or two, information is limited on cognitive characterization of memory and other cognitive domains and how these manifest and change, in cognitively healthy individuals in the "pre-clinical" stages. Such information may indeed improve our understanding of the natural evolution of AD over time both cognitively and functionally, and help to identify opportunities for intervention.

The goals of this non-interventional cohort study were (a) to prospectively collect information on cognitively healthy individuals to determine the value of biomedical, lifestyle and neuropsychological markers in predicting clinical progression or cognitive decline consistent with AD; and (b) to develop a well-characterized longitudinally followed, prospective readiness cohort, asymptomatic yet at risk for AD for future clinical trials. Here, we report on the methods employed for the extensive phenotyping of the study participants, as well as the population characteristics of the sample at baseline.

Methods

Study design

The CHARIOT (Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in dementia Research) PRO (Prospective Readiness cOhort) Main Study was a prospective, single center, non-interventional study conducted at the Imperial College London (ICL) in the United Kingdom. The Main Study recruited participants between the ages of 60-85 years from the CHARIOT Register at ICL, or self-referred. The CHARIOT Register is a community-based research register of older individuals without a diagnosis of dementia in the United Kingdom, who have provided informed consent to be invited to interventional and non-interventional studies for the prevention of AD and other age-related neurodegenerative diseases. The Register is managed by physicians, investigators, and staff of the School of Public Health (SPH) at ICL. Established in 2011, the Register is based on a collaboration between SPH and General Practitioner surgeries in central and west London, and now consists of ~ 30,000 consented volunteers (6).

The planned sample size of enrolled participants for the CHARIOT PRO Main study was 700. In order to yield sufficient likelihood of detecting a rare event (e.g., progression to MCI-AD), 630 participants should be enrolled with consideration of 10% overall dropout rate.

Table 1S of Supplementary Material presents the precision estimates with a sample size of 630 for varying rates (proportions) of rare event of interest. For example, with a sample size of 630 participants, the probability of detecting at least one event with a true event rate of 0.001 is 46.8%, and for all others it is greater than this. In total, 987 participants were screened, and 712 were eligible for follow-up, with 690 actively followed-up post baseline.

The Main Study was conducted in accordance with Good Clinical Practice (GCP) Guidelines, Guidelines for Good Pharmacovigilance Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), applicable national guidelines, and to the Declaration of Helsinki. An independent ethics committee approved participant written informed consent forms before enrollment collected during the baseline clinic visit.

Objectives

The investigations were aimed at better understanding the natural history of cognitive changes in asymptomatic participants that may precede the occurrence of clinically overt MCI or dementia due to AD. In addition, the study aimed to evaluate the sensitivity of baseline neuropsychological, biological and lifestyle measures for predicting longitudinal AD-related cognitive decline, in order to improve screening of individuals at risk for developing AD for future clinical trials.

Study population and selection criteria

Individuals aged 60 to 85 years without dementia were recruited and screened from the CHARIOT Register or self-referred. Concomitant therapies for treatment of stable medical conditions known in older population were permitted.

Participants were not eligible for enrollment if they met any of the following exclusion criteria: a previous diagnosis of dementia, MCI or other neurological disease or condition (such as Parkinson's disease); met criteria for AD dementia (per National Institute on Aging-Alzheimer's Association) at baseline; a history of traumatic brain injury, stroke or evidence of transient ischemic attack (TIA); epileptic seizures – excluding febrile seizures in childhood; significant psychiatric illness; hydrocephalus at any time; uncontrolled hypothyroidism or hyperthyroidism; any clinically significant unstable illness, metabolic problems or nutritional deficiencies; a clinically significant infection within 30 days of study entry; HIV positivity; history of alcohol or drug dependence or abuse; used memantine or cholinesterase inhibitors; chronically used medications known to impair cognition such as sedatives, anticonvulsants, or pain medications; had significant sensory or motor dysfunction; any physical disability that would prevent completion of study procedures or assessments; concurrent participation in an interventional or non-interventional trial (with exceptions, also based on PI judgement). Following baseline assessment, participants were excluded from follow-up if their age- and education-adjusted cognitive performance (z-score) on any Index of the Repeatable

Battery for the Assessment of Neuropsychological Status (RBANS) fell more than 1.5 standard deviations below normal (unless adjudicated for inclusion by the sponsor's medical monitor).

Sample size, schedule of events

The study aimed to enroll 700 participants. Over a two-year period, 987 participants were screened and 712 were enrolled. All enrolled participants were genotyped for apolipoprotein ε4 (APOE ε4) allele carrier or non-carrier status, and both participants and study investigators were blinded to APOE genotype status. Screening and baseline assessments were performed by study investigators, including trained psychometricians across one or two visits within 30 days. Enrolled participants were evaluated across the large number of study instruments every six months from baseline, for four years. The trial, however, was terminated early by the sponsor such that median follow-up time reached 18.1 months.

Outreach to participants who failed to attend their regularly scheduled bi-annual visit followed a 2-step approach. First, three attempts were made to contact the participant (via email or telephone within 1 week), and if needed a second step involved contact by a regular mail letter with delivery confirmation sent to participant's home. If the participant failed to respond to all outreach attempts, they were considered lost to follow-up.

Evaluations and Outcome Measures

Data collected at each time point per schedule of assessments is shown in Table 2S of Supplementary Materials. These included evaluations of medical status, vital signs, anthropometrics, cognitive function, mood, sleep, diet, physical and leisure activity, functional activity and biological sample collection (urine, saliva and blood). Use of medications known to impair cognition was prohibited within 48 hours or 4 times the half-life (whichever longer) before baseline cognitive assessments. All outcome measures were administered by or under the supervision of a qualified health professional or psychologist as appropriate.

At the time of initial enrollment, participants were classified as hypothetically at high (67, 9.4%), medium (91, 12.8%) or low (554, 77.8%) risk for developing MCI-AD, based on the participant's age and education-adjusted baseline cognitive performance on the RBANS Indices, as shown in Table 1.

Table 1. Participant Risk Group Classification

Risk Group Classification	RBANS Immediate and or Delayed Memory Index Score	Other RBANS Non-memory Domain(s)
High Risk	-0.6 to ≥-1.5 SD below normal	One or more -0.6 to ≥-1.5 SD below normal
*Medium Risk (amnestic)	-0.6 to ≥-1.5 SD below normal	All > -0.6 SD below normal
*Medium Risk (nonamnestic)	> -0.6 SD below normal	One or more -0.6 to ≥-1.5 SD below normal
Low Risk	> -0.6 SD below normal	All > -0.6 SD below normal

RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, SD = standard deviation

Cognition

All participants completed the RBANS, Mini Mental State Examination (MMSE), the Memory and Executive Function modules of the Neuropsychological Assessment Battery (NAB), and the National Adult Reading Test (NART). In addition, three supplemental cognitive assessments were administered: the CogState Brief Battery (CBB), the Cognitive Drug Research Assessment System (CDR-AS), or the Trail-Making and Verbal Fluency subtests of the Delis Kaplan Executive Function System (DKEFS). To minimise participant burden and fatigue, each participant was randomly allocated to undertake only one of these three assessments. Randomization was stratified by RBANS risk classification. Once randomized at baseline, the participant retained the same allocation at all follow-up visits.

Mini-Mental State Examination (MMSE)

The MMSE is a brief 11-item face-to-face examination used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. The examination includes stimuli for comprehension, reading, writing, and drawing tasks. It is widely translated and has shown validity and reliability in psychiatric, neurologic, geriatric and other medical populations (7).

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS (8) includes 12 subtests yielding five indices: the Attention Index is comprised of Digit Span and Coding, the Language Index consists of Picture Naming and Semantic Fluency subtests, the Visuospatial/Construction Index is made up of Figure Copy and Line Orientation subtests, the Immediate Memory Index is comprised of List Learning and Story

Memory subtests, and the Delayed Memory Index consists of List Recall, List Recognition, Story Recall and Figure Recall subtests. This face-to-face assessment takes approximately 25 minutes to complete.

Neuropsychological Assessment Battery (NAB)

NAB is a comprehensive, modular neuropsychological test battery designed to assess a range of cognitive skills and functions of adults from 18 to 97 years old. The specific cognitive domains of attention/concentration, language, memory, visuospatial and executive functioning are measured by specific co-developed and normed modules within the NAB. For the purposes of this investigation, the Memory and Executive Function modules were administered as these functions are considered to be most impacted early in the AD disease course (9). The NAB is administered face-to-face, and assessment time depends upon disease severity, with more impaired participants completing it faster. Specifically, the NAB Memory module takes approximately 45 minutes, whereas the Executive Function module is approximately 30 minutes in duration.

National Adult Reading Test (NART)

NART is a widely used measure of word reading that assesses pronunciation of 50 English words with irregular grapheme-phoneme and stress rules. Reading tests, such as the NART, have been shown to provide a good estimate of premorbid intellectual functioning, including in patients with neurodegenerative disorders (10). The NART is administered face-to-face and takes approximately 10 minutes to complete.

CogState Brief Battery (CBB)

The CogState Brief Battery is an approximately 15 minute computerized battery with demonstrated reliability, validity, and short term stability (11), developed expressly for maximal sensitivity to detect change. Employing playing cards as stimuli to assure cross-cultural acceptability, CogState consists of four tasks that respectively measure the functions of attention, processing speed, visual learning, and working memory. CogState employs standard psychometric paradigms (i.e., simple and choice reaction time, n-back and pattern separation learning), and has been validated for detection of dementia in both clinical and community based screening samples. Change over time (6-18 months) on the pattern separation learning task has been seen in healthy older adults testing positive for amyloid compared with those negative for amyloid (12). CogState can be administered via the internet or on a stand-alone computer and is available in over 50 languages.

Cognitive Drug Research Assessment System (CDR-AS)

The Cognitive Drug Research Assessment System (13) is an approximately 20 minute computerized battery designed to reliably measure changes in cognitive function in clinical trial situations. The fully automated system includes tests of episodic memory, working memory, attention and reaction time.

Delis Kaplan Executive Function System (DKEFS)

The DKEFS is a paper and pencil measure of verbal and nonverbal executive functions and has been normed and validated for children and adults from 8 to 89 years of age. The measure consists of nine subtests. For the purposes of this study, the Trail Making Test (TMT) and Verbal Fluency subtests were used. These two paradigms have a long history of frequent use in AD research (14). Total time to complete these two subtests of the DKEFS is approximately 20 minutes.

Mood

Geriatric Depression Scale (GDS)

GDS is a basic self-reported screening test used to identify depression in older adults (15). The 15-question version asks participants how they felt over the past week, and uses a Yes/No response format to enable the questionnaire to be used with moderately cognitively impaired individuals.

State-Trait Anxiety Scale

The Spielberger State-Trait Anxiety Inventory (STAI, forms Y-1 and Y-2) is a 40-item self-report instrument to assess current state anxiety and general anxiety levels (16). The STAI includes twenty items to assess the presence or absence of current (state) anxiety and twenty to assess general (trait) predisposition to anxiety, with each item scored from 1 to 4 according to intensity or frequency.

Patient Reported Outcome Measures

Revised Perceived Deficits Questionnaire (PDQ)

The PDQ was originally designed to capture decline in cognitive function most often caused by multiple sclerosis. In recent years, the PDQ has been used in at least one study of MCI (17). The PDQ is a 20-item questionnaire that covers four domains of cognitive function from the participant's perspective: attention/

concentration, retrospective memory, prospective memory, and planning/organization. The response options are answered on a five-point Likert scale, with 0 = never, 1 = rarely, 2 = sometimes, 3 = often, and 4 = almost always. Subscales can be calculated by summing raw scores for the relevant five items (subscale range is 0 to 20), and the total score is calculated by summing raw scores for all of the PDQ items (scale range is 0 to 80). A higher score indicates greater perceived cognitive impairment.

Work Productivity and Activity Impairment (WPAI)

The WPAI Questionnaire is an instrument to measure impairments in both paid work and unpaid work, yet un-validated within an older population, some of whom remain in employment including volunteer work. The scale consists of 6 questions regarding work and activity impairment due to health problems. The WPAI elicits data on hours worked, hours missed due to the target condition, hours missed due to other health problems and hours missed for any other reasons. Hours missed for «other reasons» is not used in the scoring, but only as a prompt to the respondent to exclude those hours from the count of actual hours worked. The WPAI yields four types of scores: (1) absenteeism (work time missed), (2) presenteeism (impairment at work / reduced on-the-job effectiveness), (3) work productivity loss (overall work impairment/absenteeism plus presenteeism), and (4) activity impairment. The sum of specific health problem impairment and impairment due to other health reasons is equal to impairment due to all health reasons. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, that is, worse outcomes (18).

Health Utilities Index Mark 3 (HUI3)

The HUI3 is a generic, preference-weighted, health status assessment completed by the participant that measures health status and health-related quality of life and allows the computation of utility scores. The 15-item questionnaire (15Q) is designed for self-completion, includes 15 multiple-choice HUI3 questions plus one global health question (Q16) common in many health surveys (19).

Lifestyle Measures

Imperial Lifestyle Questionnaire (ILQ)

Participants were asked to complete a self-reported questionnaire to address a wide range of health and lifestyle characteristics: demographics (age, marital status, ethnicity); socioeconomic status (education, income, employment status, type of occupation); activities of daily living (assessed by the Lawton scale (20)); occupational and leisure time physical activity (the Physical Activity for the Elderly Scale, PASE(21)) and the short form of the International Physical Activity Questionnaire, IPAQ(22)); leisure activities (frequency of social visits, reading, musical and artistic pastimes, speaking a second language, solo recreational mental activities e.g. puzzles); midlife experiences (occupation, physical and leisure activities, travel, training); smoking (type, quantity, duration; details of smoking at age 40, time since cessation; second-hand smoke exposure); health history (diagnosed conditions, related treatments, Rose angina questionnaire, surgical procedures, multivitamin use, weight and dietary change over time, use of medical services, family history); and female reproductive history (menstruation, childbearing, breastfeeding, hormone replacement therapy use).

A follow-up version of the above-listed content was administered every six months after baseline. The follow-up questionnaire was as above, except for factors that would not have changed since baseline: subsets of the questions on demographics (ethnicity, early education), the series on mid-life experiences, history of surgical procedures, previously diagnosed medical conditions, history of weight and dietary changes, history of use of medical services, family health history, childbearing and HRT use).

Scottish Collaborative Group Food Frequency Questionnaire

The semi-quantitative Scottish Collaborative Group food frequency questionnaire (SCG-FFQ) is a 150-item instrument designed to assess the habitual diet of United Kingdom residents over the previous 3 months. The SCG-FFQ is derived from the dietary questionnaires used in the Scottish Heart Health/ MONICA Study. The SCG-FFQ provides quantitative estimates of the intake of food and nutrients and is appropriate for ranking individuals into broad categories of intake (e.g., high, medium, and low) as opposed to absolute levels of intake. The SCG-FFQ has been validated among older adults in the United Kingdom (23).

Accelerometry

Willing participants were requested to wear actigraph wristwatch-like device that monitored rest and activity cycles for a prescribed time period to assess job-related, transportation-related, and recreation, sport and leisure-time physical activities. The measure also captures and quantifies periods of inactivity (e.g., sitting).

Sleep

Berlin Questionnaire

The Berlin Questionnaire is a simple sleep apnea screening questionnaire (10 items) used to quickly identify the risk (low to high) of sleep disordered breathing. The questionnaire consists of 3 categories and risk is based on the responses to individual items and overall scores in the symptom categories (24).

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-rated questionnaire which assesses sleep quality and disturbance over a 1 month time period. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The sum of scores for the 7 components gives 1 global score ranging from 0 (better) to 21 (worse). A total score of >5 is associated with poor sleep quality (25).

Safety Evaluation

Study events, whether serious or non-serious, were recorded throughout the study period from the time of informed consent until completion of the participant's last study-related procedure. A serious study event meets one or more of the following parameters: fatal; immediately life-threatening; requires hospitalization or prolongs existing hospitalization; permanently (or significantly) disabling; a congenital anomaly or birth defect (in an offspring); or medically significant. All serious study events were reported to the sponsor by study-site personnel within 30 days of their knowledge of the event. Each suspected adverse event included reporting of description (e.g. signs and symptoms or diagnosis), seriousness criteria, severity rating, duration (onset and resolution date), actions taken and outcome.

Results

Sample disposition and baseline characteristics

The study started in February 2014 and truncated in December of 2016 with a median follow-up time of 18.1 months. The early discontinuation was due to introduction of a follow-on ongoing substudy that enrolled participants from the Main study and the Register and was designed to enhance the scientific strength of the main study objectives, through the addition of more detailed AD-related assessments, including biomarker evaluation of participants' Aβ status (positron emission tomography and/or cerebrospinal fluid protein analysis), alongside brain structural and functional explorations via Magnetic Resonance Imaging (MRI).

For the main study, a total of 690 participants who met the primary analysis set criteria at baseline were analyzed.

Participant disposition is shown in Figure 1S of Supplementary Materials. The overall study attrition rates were 28% screen failure (275 out of 987), and 13% post baseline (91 out of 712).

No participant completed the study as it was terminated early. Discontinuations post baseline were primarily due to early study termination by sponsor (486, 83.1%), secondly due to withdrawal by the participant and lost to follow-up (80, 13.7%), and thirdly due to other reasons such as physician decision and protocol deviation (19, 3.2%). The participant overall estimated median time in study was 18.1 months, with 21.6 months for APOE ε4 carriers, and 17.8 months for non-carriers. The annual attrition due to participant dropout was within the expected range of approximately 10% per year. 72.5% of enrolled participants completed their 12 month visit, 51.4% completed their 18 month visit, 29.7% and 9.9 % completed their 24 month and 30 month visits respectively. Study participation rate by APOE ε4 status is shown in Figure 1S. The attrition rate was lower amongst APOE ε4 carriers than amongst non-carriers at all follow-up time-points, but due to incomplete follow-up and small sample sizes, the difference was not tested for statistical significance.

Demographic and baseline disease characteristics by participant APOE ε4 status are shown in Table 2. The mean (SD) age was 68.73 (3.757) years and was similar between APOE ε4 carriers and non-carriers. This age range is younger than might be expected in AD interventional trials as the initial inclusion criteria for age range was 60-75 years, but was increased to 85 years in a much later amendment to more closely reflect expected age of participants in interventional trials. The majority of study participants were white (94.6%) and 57.4% were female with very similar percentages in the two sub-groups. Of the 690 participants followed up post baseline, 165 (23.9%) were APOE ε4 carriers (the vast majority with 1 copy of the allele (97.0%)), and 525 (76.1%) were non-carriers. The percent of participants with family history of dementia of any type was 34.8%, with a somewhat larger percentage in the carrier group (42.4%) compared to the non-carrier group (32.4%). Over half of the participants (58.6%) were married, and 53% had a Bachelor's degree or higher- level education reflecting a high socioeconomic status. Summary statistics of baseline cognitive measures for participant by APOE ε4 status is shown in Table 3. The baseline values for the primary cognition outcome measures were numerically comparable between APOE ε4 carriers and noncarriers. There were no meaningful patterns of difference in performance for any of the assessment scale baseline values across the two subgroups.

Table 2. Participant demographic characteristic by APOE ε4 status

Characteristics	APOE ε4 Status		Total
	Non-carrier	Carrier	
Analysis set: all enrolled	525	165	690
Age (years)			
N	525	165	690
Mean (SD)	68.95 (3.867)	68.02 (3.294)	68.73 (3.757)
Median	68.00	68.00	68.00
<65	36 (6.9%)	20 (12.1%)	56 (8.1%)
>=65	489 (93.1%)	145 (87.9%)	634 (91.9%)
Sex			
N	525	165	690
Female	301 (57.3%)	95 (57.6%)	396 (57.4%)
Male	224 (42.7%)	70 (42.4%)	294 (42.6%)
Race			
N	525	165	690
White	502 (95.6%)	151 (91.5%)	653 (94.6%)
Black Or African American	2 (0.4%)	2 (1.2%)	4 (0.6%)
Asian	12 (2.3%)	5 (3.0%)	17 (2.5%)
Multiple	4 (0.8%)	6 (3.6%)	10 (1.4%)
Other	5 (1.0%)	1 (0.6%)	6 (0.9%)
Ethnicity			
N	525	165	690
Hispanic Or Latino	10 (1.9%)	3 (1.8%)	13 (1.9%)
Not Hispanic Or Latino	484 (92.2%)	142 (86.1%)	626 (90.7%)
Unknown	8 (1.5%)	3 (1.8%)	11 (1.6%)
Not Reported	23 (4.4%)	17 (10.3%)	40 (5.8%)
ApoE4 Status			
N	525	165	690
Non-carrier	525 (100.0%)	0	525 (76.1%)
Carrier	0	165 (100.0%)	165 (23.9%)
1 allele	0	160 (97.0%)	160 (23.2%)
2 alleles	0	5 (3.0%)	5 (0.7%)
Family history of AD or dementiaa			
N	525	165	690
No	355 (67.6%)	95 (57.6%)	450 (65.2%)
Yes	170 (32.4%)	70 (42.4%)	240 (34.8%)
Highest Level of Formal Education			
N	525	165	690
Did Not Complete Upper Secondary Education Or High School	85 (16.2%)	28 (17.0%)	113 (16.4%)
Completed Upper Secondary Education Or High School	93 (17.7%)	29 (17.6%)	122 (17.7%)
Some Post-Upper Secondary Education	64 (12.2%)	25 (15.2%)	89 (12.9%)
Completed Bachelor's Degree Or Equivalent	182 (34.7%)	48 (29.1%)	230 (33.3%)
Completed Master's Degree, Equivalent Or Higher	101 (19.2%)	35 (21.2%)	136 (19.7%)
Marital Status			
N	521	165	686
Single	82 (15.6%)	29 (17.6%)	111 (16.1%)
Separated	4 (0.8%)	5 (3.0%)	9 (1.3%)
Married	306 (58.3%)	98 (59.4%)	404 (58.6%)
Divorced	69 (13.1%)	23 (13.9%)	92 (13.3%)
Widowed	60 (11.4%)	10 (6.1%)	70 (10.1%)

Notes: ApoE4 = apolipoprotein E (E4 allele), a Family history of AD or dementia includes first-degree relative, parents, or siblings, percentages are calculated with the number of all enrolled subjects with a given demographic or disease characteristic in each column as the denominators.

Table 3. Summary of Baseline Cognition Outcome Measures by ApoE4 Status

	ApoE4 Status		
	Non-carrier	**Carrier**	**Total**
Analysis set: all enrolled	525	165	690
MMSE			
Total score (raw)a			
N	476	147	623
Mean (SD)	28.8 (1.3)	29.0 (1.3)	28.8 (1.3)
Median	29	29	29
CogState Brief Battery			
Composite Score 1 (DET-IDN) Speed of Performance (log 10 ms)b			
N	156	38	194
Mean (SD)	0.07 (0.883)	0.14 (0.835)	0.09 (0.872)
Median	0.13	0.30	0.20
Composite Score 2 (OCL-ONB) Accuracy of Performance (arcsine proportion correct)a			
N	155	38	193
Mean (SD)	0.02 (0.783)	0.05 (0.685)	0.03 (0.763)
Median	0.03	0.00	0.00
DKEFS - Trail-Making Test (scaled score)a			
Number-letter switching			
N	175	60	235
Mean (SD)	12.3 (2.2)	11.6 (2.8)	12.1 (2.3)
Median	13	12	13
DKEFS - Verbal Fluency (scaled score)a			
Letter fluency			
N	175	60	235
Mean (SD)	13.3 (3.4)	12.9 (3.5)	13.2 (3.4)
Median	13	13	13
Category fluency			
N	175	60	235
Mean (SD)	13.9 (3.3)	13.1 (3.3)	13.7 (3.3)
Median	14	12.5	14
Category switching			
N	175	60	235
Mean (SD)	13.2 (3.2)	12.9 (3.6)	13.2 (3.3)
Median	13	13	13
NAB (standard score)a			
Memory index score			
N	475	149	624
Mean (SD)	105.4 (14.3	103.5 (14.3)	104.9 (14.3)
Median	105	102	104
Executive functions index score			
N	475	149	624
Mean (SD)	114.2 (15.3)	114.8 (15.6)	114.4 (15.4)
Median	114	117	115
CDR-AS Composite Scores			
Power of attention (ms)b			
N	132	44	176
Mean (SD)	1271.4 (159.0)	1247.4 (133.9)	1265.4 (153.1)
Median	1249	1215	1245.5
Continuity of Attention (#)a			
N	132	44	176
Mean (SD)	90.5 (4.9)	90.4 (3.6)	90.5 (4.6)
Median	92.0	91.4	91.7

Table 3. Summary of Baseline Cognition Outcome Measures by ApoE4 Status (continued)

	ApoE4 Status		
	Non-carrier	**Carrier**	**Total**
Mean (SD)	196.2 (68.3)	189.0 (64.9)	194.4 (67.3)
Median	188	200	188.5
Response Variability (#)b			
N	132	44	176
Mean (SD)	51.9 (9.9)	55.0 (10.8)	52.7 (10.2)
Median	50.5	53.4	51.3
Quality of Working Memory (#)a			
N	132	44	176
Mean (SD)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)
Median	1.94	1.89	1.94
Quality of Episodic Secondary Memory (#)a			
N	132	44	176
Mean (SD)	183.4 (48.5)	177.3 (41.5)	181.9 (46.8)
Median	185.8	175.0	183.3
Speed of Memory (ms)b			
N	132	44	176
Mean (SD)	4367.5 (883.1)	4476.8 (1226.7)	4394.8 (977.6)
Median	4225	4243	4225
RBANS			
Total scale score			
N	522	165	687
Mean (SD)	106.7 (12.1)	106.3 (12.4)	106.6 (12.2)
Median	106	106	106
Delayed memory index score			
N	522	165	687
Mean (SD)	103.4 (9.3)	103.3 (10.1)	103.3 (9.5)
Median	102	102	102
Immediate memory index score			
N	522	165	687
Mean (SD)	106.8 (12.6)	105.8 (12.5)	106.6 (12.6)
Median	109	106	106
Attention index score			
N	522	165	687
Mean (SD)	107.6 (15.3)	106.1 (14.9)	107.3 (15.2)
Median	106	103	106
Visuospatial/constructional index score			
N	522	165	687
Mean (SD)	100.4 (13.8)	101.4 (16.4)	100.6 (14.5)
Median	100	100	100
Language index score			
N	522	165	687
Mean (SD)	106.5 (11.7)	106.5 (12.2	106.5 (11.8)
Median	105	104	105

Key: ApoE4 = apolipoprotein E (E4 allele), CDR = Cognitive Drug Research, Assessment System, DKEFS = Delis Kaplan Executive Function System; MMSE = Mini-Mental State Examination, NAB = Neuropsychological Assessment Battery; a. Higher scores indicate better performance; b. Lower scores indicate better performance; Score ranges: MMSE (raw): 0 to 30, DKEFS scaled scores: 0 to 19, NAB standard scores: mean=100, SD = 15; Percentages are calculated with the number of all enrolled subjects with a given cognition outcome measurement in each column as the denominators; The RBANS Index scores and Total Scale were calculated using Age based norms

Safety

As this was a non-interventional study, safety analyses focused on safety events that referred to occurrence of any untoward medical event such as any unfavorable and unintended sign, symptom, syndrome, or disease. The incidence of any safety event was 64.8% for APOE ε4 non-carriers and 71.5% for carriers. The most frequently occurring safety events with incidence of 3% or more were upper respiratory tract infection (10.4% overall) and fall (5.2%). The incidence of serious safety events

was 4.1% overall, which was numerically slightly higher among non-carriers (4.6%) than carriers (3.4%). The most frequently occurring serious safety events were prostate cancer, renal cell carcinoma, and Parkinson's disease, occurring in two participants each (0.3%), and all others occurred in 1 participant each.

Discussion

We report on baseline characteristics of 690 cognitively healthy participants, who were prospectively evaluated every 6 months for a period of 30 months (or early termination) for changes in performance on neuropsychological test measures from baseline. Data from this study, though short in duration, will allow for examination of biological, genetic, health, and lifestyle factors and markers that influence cognitive progression among individuals at-risk for developing MCI-AD.

This study assessed APOE genotype status for all enrolled participants. Though prevalence of APOE ε4 carriers in our cohort was as expected within a cognitively normal population (~25% of enrolled participants), we noted a paucity of APOE ε4 homozygotes (~1% of enrolled participants). Observed prevalence of APOE ε4 homozygosity markedly differs from frequency reported by other cohorts that include cognitively healthy older adults. For instance, prevalence of dual ε4 alleles in the cognitively normal participant group ranged from 3.6% in the Uniform Data Set of the Alzheimer's Disease Centres (UDS) program, to 6.1% in the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL) project up to 9.2% in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study (26). Notably these studies used total MMSE scores (24-30) to define normal cognition, as opposed to a more stringent cognitive assessment tool for designation of 'cognitive normal' status .

Thus, a probable explanation for the reduced homozygosity (ε4+/+) observed in the CPRO main study cohort could be the more sensitive test of cognition (RBANS) used for defining cognitive normal status during study screening and subsequent enrolment. There was no marked APOE ε4 genotype-related difference in cognitive test performance at baseline. This was to be expected since all participants were to be cognitively healthy at baseline and performed within age-matched population norms. Modelling of the longitudinal data will inform on which of these assessments could potentially detect the very earliest cognitive changes.

Our study has important caveats and limitations that should be discussed. The study lacked a biomarker assessment of the participants' amyloid pathology, an important predictor of clinical progression. In addition, no participant progressed to MCI during the study. Despite these lacks, the study included proxy measures of Aβ pathology and information on established risk factors for AD-related cognitive deterioration such as the major genetic risk determinant - APOE genotype status, as well as ample collection of relevant demographic information including age, sex, family history of dementia and subjective cognitive complaints (3, 27, 28).

Due to the relatively young age-range of the participants and the early termination of the study, the cohort may have included a significant proportion of cognitively high-functioning individuals who were unlikely to demonstrate clinical progression over the relatively short duration of follow-up. Furthermore, the early termination of the study reduced availability of data points due to low participation rates at later time points. Nevertheless, we do not expect this attribute to limit the ability to perform longitudinal modeling and analysis, in view of related studies that have reported cognitive changes even within such limited time frames (29, 30).

The CHARIOT PRO Main Study data will be useful for assessing impact of available AD-related measures, including lifestyle exposures and biological factors, on cognitive trajectories from the pre-symptomatic stage. Such analyses may contribute towards better understanding of risk-resilience, and maintenance of cognitive function that may be evident at the preclinical AD stage, in high risk individuals.

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Contributions of Authors: Dr. Udeh-Momoh served as the lead author, Drs. Udeh-Momoh, Car, Perneczky, Price, Andrews and Ward were co-investigators at School of Public Health, Imperial College London, and all contributed to the study design, coordination, data acquisition, and participated in data interpretation, development and critical review of the manuscript. Drs. Bassil, Su, Cohn, Giannakopoulou and Ms Robb, Perera and Curry were study investigators at School of Public Health, Imperial College London, and contributed to data acquisition and review of the manuscript. Dr. Ropacki contributed to the study conception, protocol design, and development of the manuscript. Drs. Novak, Arrighi, Ketter, and Brashear, contributed to study design and were responsible for data review, interpretation, and development of the manuscript. In addition, Dr. Arrighi was project pharmaco-epidemiologist and Dr. Raghavan served as project biostatistician, responsible for aspects of study design, statistical data analysis, statistical input and interpretation of data. Dr. Middleton served as the study site principal investigator, contributed to study conception and design, data review and interpretation and critical review of the manuscript. All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, provided direction and comments on the manuscript, made the final decision about where to publish these data and approved the final draft and submission to this journal.

Conflict of interest/disclosures: Janssen Research & Development, LLC, funded the study. Michael T. Ropacki was formerly an employee of Janssen and is an industry consultant. Gerald. Novak, H. Michael Arrighi, and Nandini Raghavan are employees of Janssen Research & Development, LLC and own stock/stock options in the company. Nzeera Ketter is a former employee, and H. Robert Brashear is an employee of Janssen AI Research & Development, LLC and both own stock/stock options in the company. Jianing Di is an employee of Janssen China Research and Development Center and owns stock/stock options in the company. Lefkos Middleton served as principal study investigator at Imperial College of London (ICL), has a consultancy agreement with Eli Lilly, Astra Zeneca and Takeda and is National Coordinator for the TOMMORROW, Amaranth and Generation Clinical Studies; and does not hold any agreement with any of the funders in relation to patents, products in development relevant to this study or marketed products. Chinedu Udeh-Momoh, Josip Car, Robert Perneczky, Geraint Price, Tresa Andrews and Heather Ward served as co-principal study investigators at ICL for Janssen Research & Development, LLC and all declare no conflict of interest. Catherine Robb, Darina Bassil, Martin Cohn,

Parthenia Giannakopoulou, Dinithi Perera, Lisa Curry and Bowen Su were study investigators at ICL and declare no conflict of interest.

Ethical standards: To ensure the quality and integrity of the research, this study was conducted in accordance with Good Clinical Practice (GCP) Guidelines, Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for pharmaceutical Engineering (ISPE), applicable national guidelines, and to the Declaration of Helsinki 2013, as modified by the 52nd World Medical Assembly, Edinburgh, Scotland, 2000, and clarified by the World Medical Assembly (WMA) General Assembly, Washington 2002 and Tokyo 2004. The Chariot-Pro Main study has received National Research Ethics Services approval (15/L0/0711) and internal Imperial College London (ICL) Research Ethics, Joint Research Compliance Office approval (JRCO:15/1C/2791). Prior to consenting onto the Chariot-Pro Main study, participants were provided with a detailed study information sheet outlining study procedures, as well as risks and benefits associated with participation. Participants were provided with a minimum of 48-hours to consider the information provided, and fully understand the study requirements prior to discussing further with study staff, where necessary; after which signed informed consent was obtained prior to undertaking any study procedures at the screening visit.

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Original Research

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Mediterranean-Dash Intervention for Neurodegenerative Delay (MIND) Diet Slows Cognitive Decline After Stroke

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Abstract

OBJECTIVE: This study sought to determine if the MIND diet (a hybrid of the Mediterranean and Dash diets, with modifications based on the science of nutrition and the brain), is effective in preventing cognitive decline after stroke.

DESIGN: We analyzed 106 participants of a community cohort study who had completed a diet assessment and two or more annual cognitive assessments and who also had a clinical history of stroke. Cognition in five cognitive domains was assessed using structured clinical evaluations that included a battery of 19 cognitive tests. MIND diet scores were computed using a valid food frequency questionnaire (FFQ). Dietary components of the MIND diet included whole grains, leafy greens and other vegetables, berries, beans, nuts, lean meats, fish, poultry, and olive oil and reduced consumption of cheese, butter, fried foods, and sweets. MIND diet scores were modeled in tertiles. The influence of baseline MIND score on change in a global cognitive function measure and in the five cognitive domains was assessed using linear mixed models adjusted for age and other potential confounders.

RESULTS: With adjustment for age, sex, education, APOE-ε4, caloric intake, smoking, and participation in cognitive and physical activities, the top vs lowest tertiles of MIND diet scores had a slower rate of global cognitive decline (β = .08; CI = 0.0074, 0.156) over an average of 5.9 years of follow-up.

CONCLUSIONS: High adherence to the MIND diet was associated with a slower rate of cognitive decline after stroke.

Key words: Stroke, cognitive decline, diet, nutrition, prevention.

Cognitive decline is a common and devastating clinical sequela of stroke (1). Compared to the normal rate of neuron loss with aging, ischemic stroke causes 3.6 years' worth of aging for every hour of untreated symptoms (2). With the average duration of a non-lacunar stroke lasting 10 hours, a brain may experience a magnitude of aging equivalent to several decades in just one day. Perhaps not surprisingly, stroke survivors have nearly double the risk of developing dementia compared to those who have not suffered a stroke (3). This results in a significant burden on our healthcare system, both in terms of the direct and indirect costs of stroke and dementia, as well as the emotional toll on patients and their caregivers. Therefore, lifestyle factors that may protect against these cognitive changes in stroke survivors are of great public health importance.

One lifestyle approach that may be effective for preventing post-stroke cognitive decline is diet. A number of studies have found protective associations between cognitive decline and greater adherence to the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets (4-7). There is limited data, however, on whether these dietary patterns might be effective in slowing the cognitive decline that can occur after stroke. In this study, we examined the associations among these healthy diet patterns and cognitive change in a community study of older adults with a clinical history of stroke.

Methods

Study Population

This study was conducted using data from the Rush Memory and Aging Project (MAP), a study of volunteers living in retirement communities and senior public housing units in the Chicago area. The ongoing open cohort study began in 1997 and includes annual clinical neurological examinations, as previously described (8). Beginning in 2004, MAP study participants began to complete comprehensive food frequency questionnaires (FFQ). Of the 1911 older persons enrolled in the MAP study, 1068 had at least one valid FFQ that served as the baseline for these analyses, of which 970 also had two or more annual cognitive assessments for the measurement of cognitive change. Among these, 106 participants had a clinical history of stroke. Average study follow-up time was 5.9 years (Figure 1). The Institutional Review Board of Rush University Medical Center approved the study, and all participants gave written informed consent.

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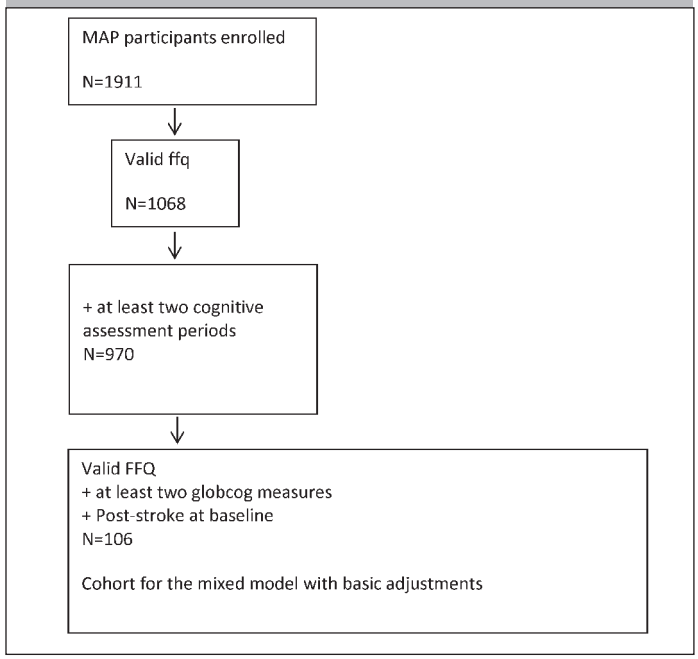
Figure 1. Analysis cohort



Cognitive Evaluations

Cognition was assessed in 5 domains (episodic memory, semantic memory, working memory, perceptual orientation, and perceptual speed), using annual structured clinical evaluations that included a battery of cognitive tests, administered by technicians trained and certified in standardized neuropsychological testing methods (9). Episodic memory was assessed with the following tests: word list, word list recall, word list recognition, East Boston immediate recall, East Boston delayed recall, logical memory 1 (immediate), and logical memory II (delayed). Semantic memory was assessed with the following tests: Boston naming (15 items), category fluency, and reading test (10 items). Working memory was assessed with the following tests: digits forward, digits backward, digit ordering. Perceptual orientation was assessed with the following tests: line orientation, progressive matrices (16 items). Finally, perceptual speed was assessed with the following tests: symbol digits modality-oral, number comparison, stroop color naming, and stroop word reading. Standardized scores were computed for each test, using the mean and standard deviation from the baseline tests, and the standardized scores were averaged over each cognitive domain and over all tests to create a global cognitive score. Out of all MAP participants, 93.4% complete annual cognitive evaluations. Of the participants in this study, 52.0% had 5 or more annual cognitive assessments, with a range of 2 to 10 years.

Diet Pattern Scoring

Diet pattern scores were based on responses to a modified Harvard semi-quantitative FFQ, that was validated for use in older Chicago community residents. (10). Typical frequency of intake of 144 food items was reported by participants over the prior 12 months. The caloric content and nutrient levels for each food item were based on age- and sex-specific portion sizes from national dietary surveys, or by a logical portion size (e.g. a slice of bread). Details of the dietary components and maximum scores for the MIND, DASH, and Mediterranean diets have been previously reported (4, 11, 12). Briefly, the MIND diet score is based on a combination of 10 healthy food groups (leafy green vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine) and 5 unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, fried food, and fast food). If olive oil was reported as the primary oil used at home, it was scored 1. Otherwise, olive oil consumption was scored 0. For the remaining components, the frequency of consumption of each food item for a given score component was summed and then given a concordance score of 0, 0.5, or 1, where 1 represented the highest concordance (4). The final MIND diet score was the sum of the 15 component scores.

Scoring for the DASH diet was determined based on consumption of 3 dietary components (total fat, saturated fat, and sodium) and 7 food groups (grains, fruits, vegetables, nuts, seeds and legumes, dairy, and meat) (12). Scores of 0, 0.5, and 1 were assigned to each food group based on the frequency of consumption. Total possible scores ranged from 0 (lowest) to 10 (highest) diet concordance.

The Mediterranean diet pattern was based on the MedDiet score as described by Panagiotakos and colleagues (11) that uses serving quantities of the traditional Greek Mediterranean diet as the comparison metric. Eleven dietary components (non-refined cereals, potatoes, fruits, vegetables, legumes, fish, red meat and products, poultry, full fat dairy products, the use of olive oil in cooking, and alcohol) are each scored from 0 to 5 and then summed for a total score ranging from 0 to 55 (highest concordance).

Covariates

Non-dietary variables in the analysis were obtained at the participant's baseline clinical evaluation through a combination of clinical evaluation, self-report, medication inspection, and measurements. The process is identical to that performed in the Religious Orders Study, and was designed to reduce costs and enhance uniformity of diagnostic decisions over time and space (13). Participants self-reported their birth date and years of education. A 5 point scale was used

Table 1. Baseline Characteristics of Memory and Aging Project Subjects with History of Stroke

Baseline Characteristic	Total	Tertile 1	Tertile 2	Tertile 3
n	106	37	40	29
MIND diet score (median, q1 q3)	7.5 (6.5, 9.0)	6.0 (5.5, 6.5)	7.5 (7.0, 8.0)	9.5 (9.0, 10.5)
Age yr, mean (SD)	82.8	82.9	83.3	82.0
Males N (%)	29 (27.4)	12 (32.4)	13 (32.5)	4 (13.8)
Education (yr, mean) (SD)	14.4	14.2	14.4	14.6
APOE-ε4 (%)	16.0	16.2	15.0	17.2
Total Energy Intake I (mean)	1783.9	1606.8	1914.7	1829.3
Cognitive Activity Frequency (mean)	3.0	2.9	3.0	3.2
Physical Activity Weekly (hr, mean)	2.8	2.9	2.2	3.5
Former or current smoker (%)	44.3	51.4	45.0	34.5

to assess the frequency of cognitively stimulating activities (such as writing letters, visiting the library, reading, and playing games) (14). Physical activity was determined by participants self-reported minutes spent over the previous 2 weeks on 5 activities (walking for exercise, yard work, calisthenics, biking, and water exercise) (15). A modified 10-item version of the Center for Epidemiological Studies-Depression (CESD) scale was used to evaluate depressive symptoms (16). High throughput sequencing was used to determine APOE-genotyping as previously described (17). Height and weight were measured to determine body mass index (BMI=weight in kg/height in m2) and modeled as two indicator variables, BMI ≤20 and BMI ≥30. Hypertension was defined by an average of 2 blood pressure measurements ≥ 160 mmHg systolic or ≥ 90 mmHg diastolic, or if the patient reported a clinical history of hypertension or was currently taking antihypertensive medications. Myocardial infarction history was based on the current use of cardiac glycosides (e.g. lanoxin or digoxin) or by self-reported history. Clinical history of diabetes was obtained by self-reported medical diagnosis or by current use of diabetic medications. Diagnosis of stroke was obtained through a combination of clinical evaluation and self-report to the question "has a doctor, nurse, or therapist ever told you that you have had a stroke?" (18). Medication use was based on interviewer inspection.

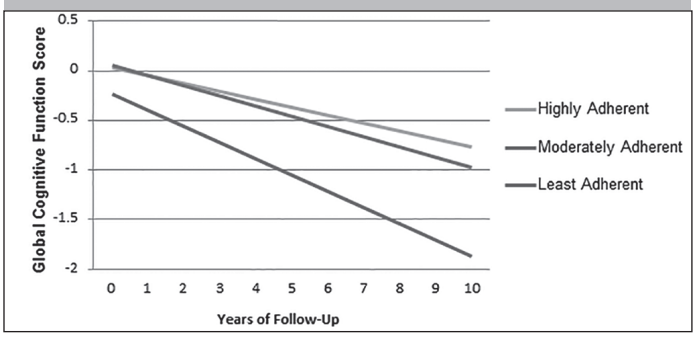
Statistical Analysis

The data were summarized using median and quartiles, mean and SD or number (relative frequency) as appropriate. Baseline characteristics were compared across MIND diet tertiles using Kruskal-Wallis, ANOVA, chi-squared tests or Fisher's exact tests, as appropriate. Linear mixed models were used to model the longitudinal global cognitive scores and the 5 cognitive domains on diet scores for the MIND, DASH, and Mediterranean diets to describe the relationships among dietary patterns and cognitive decline over time in stroke survivors. The 3 dietary patterns were examined in separate models: an age-adjusted model and a basic-adjusted model that included potential confounders previously associated with Alzheimer disease: age, sex, education, participation in cognitively stimulating activities, physical activity, smoking, and APOE-ε4. Total energy intake, which is closely related to diet, was also included as a potential confounder. The dietary scores were modeled as both continuous variables and as indicators of the top two tertiles in each of these models.

Results

Of the 106 MAP participants with a clinical history of stroke, the mean age was 82.8 years (SD=7.1) and 29 (27%) were male. The mean years of education was 14.4 (SD=2.7) Overall, 16% had APOE-ε4 alleles. Participants who had high MIND diet scores were less likely to be male, more likely to have never been smokers, and more likely to participate frequently in cognitive and physical activities (Table 1).

Figure 2. Cognitive Decline Over Time by Adherence to the MIND Diet



A graphical representation of the decrease in cognitive decline over time based on adherence to the MIND diet for 106 participants found to have had a stroke at baseline. The highest adherence (represented by the green line) versus lowest adherence (represented by the red line) to the MIND diet showed a significant decrease in cognitive decline (ß=0.08 CI= 0.00, 0.16). The decrease in cognitive decline for moderate adherence (represented by the blue line) versus lowest adherence approached significance (ß=0.06 CI= -0.01, 0.13).

Table 2. Cognitive Function by Dietary Pattern

Cognitive domains	Global Cognition	Episodic Memory	Semantic Memory	Visuospatial Memory	Perceptual Speed	Working Memory
Dietary Patterns n	**106**	**105**	**103**	**101**	**101**	**106**
MINDdiet						
T1	ref	ref	ref	ref	ref	ref
T2,β (Confidence interval)	0.058 (-0.011, 0.128)	0.025 (-0.048, 0.098)	0.030 (-0.033, 0.093)	0.062 (-0.001, 0.126)	0.047 (-0.019, 0.113)	0.023 (-0.041, 0.087)
T3,β (Confidence interval)	0.083 (0.007, 0.158)	0.041 (-0.038, 0.121)	0.070 (0.001, 0.138)	0.061 (-0.008, 0.130)	0.071 (0.000, 0.142)	0.033 (-0.037, 0.102)
linear-trend, P-value	0.034	0.300	0.043	0.129	0.059	0.368
Mediscore						
T1	ref	ref	ref	ref	ref	ref
T2,β (Confidence interval)	0.039 (-0.032, 0.110)	-0.004 (-0.078, 0.070)	0.032 (-0.032, 0.096)	0.015 (-0.046, 0.076)	-0.034 (-0.099, 0.030)	0.013 (-0.050, 0.076)
T3,β (Confidence interval)	0.062 (-0.017, 0.141)	0.028 (-0.053, 0.110)	0.065 (-0.006, 0.136)	0.062 (-0.003, 0.127)	0.041 (-0.030, 0.113)	0.034 (-0.036, 0.104)
linear-trend, P-value	0.113	0.551	0.070	0.072	0.392	0.341
Dashscore						
T1	ref	ref	ref	ref	ref	ref
T2,β (Confidence interval)	0.017 (-0.052, 0.087)	0.022 (-0.049, 0.094)	0.055 (-0.007, 0.117)	0.028 (-0.032, 0.088)	-0.00057 (-0.065, 0.064)	0.0048 (-0.056, 0.066)
T3,β (Confidence interval)	0.043 (-0.032, 0.118)	0.036 (-0.042, 0.113)	0.052 (-0.016, 0.120)	0.031 (-0.038, 0.099)	0.027 (-0.044, 0.099)	0.030 (-0.037, 0.097)
linear-trend, P-value	0.263	0.367	0.123	0.359	0.462	0.377

Adjustments – age, sex, education, APO-E4, late life cog act, caloric intake, physical activity, & smoking; Italicized and bold – statistically significant: Italicized – approaching significance

In separate models adjusted for age, sex, education, APOE-ε4, late-life cognitive activity, caloric intake, physical activity, and smoking, with diet scores modeled in tertiles, the top versus the lowest tertile of MIND diet scores were associated with a slower rate of global cognitive decline (β=0.08, 95% confidence interval (CI): 0.01, 0.16), as well as with a slower decline in semantic memory (β=0.07, 95% CI: 0.00, 0.14) and perceptual speed (β=0.07, 95% CI: 0.00, 0.14), (Figure 2). Those with moderate adherence (tertile 2) to the MIND diet showed a non-significant trend toward slower rates of cognitive decline. In continuous models, the MIND diet was associated with slower rates of decline in cognitive function over time for both global cognition (p=0.034) and semantic memory (p=0.04). The DASH and Mediterranean diets were not associated with slower rates of global cognitive decline over time (p =0.26 and p= 0.11, respectively) or slower decline in any of the 5 cognitive domains (Table 2).

Discussion

Although an extensive body of literature exists on the role of diet in stroke prevention, relatively few studies have examined the role of diet on cognitive decline post-stroke, even though stroke nearly doubles the risk of dementia (3). In the present study, we observed a community cohort of older persons with a clinical history of stroke but no diagnosis of dementia at their baseline enrollment to determine the role that diet may play in preventing post-stroke cognitive decline. In this observational study, we found that the MIND diet significantly slowed the rate of decline in global cognition, as well as in the individual cognitive domains of semantic memory and perceptual speed. The Mediterranean and DASH diets were not associated with slowing global cognitive decline or slowing decline in any of the 5 cognitive domains. This suggests that while the Mediterranean and DASH diets may be useful in preventing stroke and other cardiovascular conditions, the MIND diet, which is specifically tailored for brain health, may be more effective in preventing post-stroke cognitive decline.

Large, prospective cohort studies that established the role of diet in the prevention of cardiovascular disease include the Nurses Health Study, the Reasons for Geographic and Racial Differences in Stroke study, The Northern Manhattan Study, and The Framingham Heart Study (19-21). A smaller number of randomized controlled trials, such as PREDIMED[22], have also found diet to be effective in the prevention of cardiovascular outcomes including stroke. Fewer data exist on the role of diet in secondary stroke prevention, although several studies such as ONTARGET, TRANSCEND (23) and the Lyon Heart Study (24) have shown that diet may be a valuable target in secondary stroke prevention as well,

with some studies suggesting that diet may provide an effect size similar to that of statins (25).

Despite separate studies advocating the role of diet both in stroke prevention and the prevention of cognitive decline, most of these studies did not examine the role of diet in preventing cognitive decline in subjects with a history of stroke specifically, a population that is at higher risk for dementia than the general population. In fact, many of the existing large observational cohort studies have excluded subjects with a clinical history of stroke at baseline (20).

The MIND diet, which is a hybrid of the Mediterranean and DASH diets, was designed to emphasize nutrients that have been associated with dementia prevention and to discourage elements, such as saturated/hydrogenated fats, that have been associated with dementia (4). The MIND diet recommends greater than or equal to 3 servings of whole grain per day (26), greater than or equal to 6 servings of leafy green vegetables per week (in addition to one or more daily servings of other vegetables) (27), greater than or equal to 2 servings of berries per week (28), greater than or equal to one serving of fish per week (29), greater than or equal to 2 servings of poultry per week, greater than 3 servings of beans per week, and greater than or equal to 5 servings of nuts per week (30). The MIND diet recommends that olive oil be used as the primary source of fat (31, 32) and allows one serving of alcohol/wine per day (33). The following food items are discouraged by the MIND diet: red meat and products, less than 4 servings per week; fast food and fried food, less than one serving per week; butter/margarine, less than 1tsp per day; cheese, less than once per week; and pastries/sweets, less than 5 servings per week.

The MIND diet is a rich source of many different dietary components that have been linked to brain health, including vitamin E, folate, n-3 fatty acids, carotenoids, and flavonoids. Multiple prospective cohort studies have shown that avoiding saturated and trans-unsaturated (hydrogenated) fats and increasing the consumption of antioxidant nutrients and B-vitamins are associated with slower rates of cognitive decline (34-36). The emphasis on the consumption of berries vs. fruit in general was based on findings from multiple epidemiological studies of cognition, showing that, whereas overall fruit consumption does not appear to impart a protective effect (27, 37-39), the subtype of fruit, berries, does appear to slow cognitive decline (28). Vegetables, and leafy green vegetables in particular, have also been shown in several large prospective studies to reduce cognitive decline (27, 37).

The Mediterranean diet has been widely studied (40, 41) and recommends greater than or equal to 4 tablespoons of olive oil per day, 3 or more servings of tree nuts and peanuts per week, 3 or more servings of fruit per day, 2 or more servings of vegetables per day, 3 or more servings of fish (particularly fatty fish) per week, 3 or more servings of legumes per week, using white meat as a substitute for red meat, and drinking 1 or more glasses of wine with meals, 7 or more times per week. The Mediterranean diet limits soda to less than one per day, consumption of commercial baked goods, sweets, and pastries to less than 3 per week; spreadable fats to less than 1 per day; and red and processed meats to less than once per day.

The Mediterranean diet was associated with higher cognitive scores in a sub-study of PREDIMED[31], a randomized trial designed to test diet effects on cardiovascular outcomes among Spaniards at high cardiovascular risk. In our study, although the Mediterranean diet was associated with slower rates of global cognitive decline in the age-adjusted model, this association became nonsignificant when basic adjustments for sex, education, APOE-ε4, late-life cognitive activity, caloric intake, physical activity, and smoking were applied.

The DASH diet was not associated with slower rates of cognitive decline in our study, although prior studies have shown this diet to be effective for prevention of both cognitive decline (26, 42, 43) and stroke prevention (44).

This study has several limitations, the most important of which is that it is observational in nature; as such, it cannot claim a cause and effect relationship. While replication in other observational cohort studies would be useful to confirm the associations seen in this study, a diet intervention trial in stroke survivors is needed to establish a causal role between diet and post-stroke cognition. Another limitation of this study is its small sample size resulting in low power to observe associations. It may be possible to observe protective associations of the DASH and Mediterranean diets on cognitive decline in larger stroke populations. Nonetheless, many larger observational cohort studies examining the role of nutrition on cognitive decline have excluded subjects with a clinical history of stroke. Therefore, we believe that this is an important and under-studied population that may be disproportionately prone to developing dementia, and preliminary data are important to guide future studies.

Clinical history of stroke was determined by self-report or by diagnosis during an annual clinical neurologic examination, but the lack of MRI or CT to confirm this diagnosis or to differentiate between stroke sub-type is a limitation. Subjects with a clinical history of mild stroke or a radiographic infarct may have been excluded from our sample, but the Framingham Offspring Study found that individuals with silent cerebral infarcts have similar risk profiles to those with a clinical history of stroke (45). We suspect that the inclusion of these individuals in our analysis would have been more likely to strengthen our findings than to invalidate them. Other large prospective observational cohort studies, such as the Nurses Health Study (46) have employed questionnaires and clinical evaluations to identify cardiovascular outcomes, and

suggested that self-reported stroke is a valid approach to assessing the prevalence of stroke in a population (47-49). In the Tromso Study, researchers followed up with 213 individuals who had self-reported histories of stroke at a community health fair and found that upon more intensive evaluation (physician examination and review of medical records, including neuroimaging) 79.2% of self-reported strokes were confirmed (47). Self-reported stroke was found to have a similar prognostic value for predicting recurrent stroke in the Health in Men Study, and the authors concluded that self-reported stroke may be useful in further epidemiological studies (49).

The MAP cohort is an older, predominantly non-Hispanic white population, so findings should not be generalized to other ethnic groups or younger cohorts. The dietary questionnaires had limited questions regarding some of the dietary components and information on frequency of consumption. For example, a single item each provided information on the consumption of nuts, berries, beans, and olive oil. This study's strengths include the use of a validated food questionnaire for comprehensive dietary assessment, the measurement of cognitive change with a large battery of standardized tests annually for up to 10 years, and statistical control of the important confounding factors.

The MIND diet is a hybrid of the Mediterranean and DASH diets, with additional emphasis on the nutritional components that have been shown to optimize brain health. The MIND diet has previously been shown to slow cognitive decline in the general population in an observational cohort study (4), but it was unclear whether this association would remain strong for subjects with a clinical history of stroke. This observational study suggests that not only is the MIND diet strongly associated with slowing cognitive decline post-stroke, its estimated effect was twice the size of that observed in the overall MAP cohort (41). Additionally, the MIND diet appeared superior to the Mediterranean and DASH diets in slowing cognitive decline in stroke survivors. Given the projected burden of stroke and dementia in an aging population, further studies are warranted to explore the role of the MIND diet in preventing cognitive decline in stroke survivors. High adherence to the MIND diet was associated with slower rates of cognitive decline in an observational study of older adults with a clinical history of stroke.

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Ethical standards: The authors attest that they have provided an accurate account of the work performed as well as an objective discussion of its significance. Relevant raw data has been accurately provided. The authors attest that the work is original and has not been published elsewhere. Pertinent work from other sources has been appropriately cited. The Institutional Review Board of Rush University Medical Center approved the study, and all participants gave written informed consent.

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Original Research

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Financial Management Skills in Aging, MCI and Dementia: Cross Sectional Relationship to 18F-Florbetapir PET Cortical β-amyloid Deposition

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Abstract

BACKGROUND: There is a need to more fully characterize financial capacity losses in the preclinical and prodromal stages of Alzheimer's disease (AD) and their pathological substrates.

OBJECTIVES: To test the association between financial skills and cortical β-amyloid deposition in aging and subjects at risk for AD.

DESIGN: Cross-sectional analyses of data from the Alzheimer's Disease Neuroimaging Initiative (ADNI-3) study conducted across 50 plus sites in the US and Canada.

SETTING: Multicenter biomarker study.

PARTICIPANTS: 243 subjects (144 cognitively normal, 79 mild cognitive impairment [MCI], 20 mild AD).

MEASUREMENTS: 18F-Florbetapir brain PET scans to measure global cortical β-amyloid deposition (SUVr) and the Financial Capacity Instrument Short Form (FCI-SF) to evaluate an individual's financial skills in monetary calculation, financial concepts, checkbook/register usage, and bank statement usage. There are five sub scores and a total score (range of 0–74) with higher scores indicating better financial skill.

RESULTS: FCI-SF total score was significantly worse in MCI [Cohen's d= 0.9 (95%CI: 0.6-1.2)] and AD subjects [Cohen's d=3.1(CI: 2.5-3.7)] compared to normals. Domain scores and completion times also showed significant difference. Across all subjects, higher cortical β-amyloid SUVr was significantly associated with worse FCI-SF total score after co-varying for age, education, and cognitive score [Cohen's f2=0.751(CI: 0.5-1.1)]. In cognitively normal subjects, after covarying for age, gender, and education, higher β -amyloid PET SUVr was associated with longer task completion time [Cohen's f2=0.198(CI: 0.06-0.37)].

CONCLUSION: Using a multicenter study sample, we document that financial capacity is impaired in the prodromal and mild stages of AD and that such impairments are, in part, associated with the extent of cortical β-amyloid deposition. In normal aging, β-amyloid deposition is associated with slowing of financial tasks. These data confirm and extend prior research highlighting the utility of financial capacity assessments in at risk samples.

Key words: Preclinical Alzheimer's, financial capacity, amyloid PET.

The rapid growth of both aging populations and Alzheimer's disease (AD) cases across the world has spurred renewed interest into studies of financial capacity in the early stages of dementia (1-6). Financial capacity generally refers to one's ability to handle his or her own money and make appropriate decisions relating to financial affairs. Older adults hold a disproportionate share of wealth in most countries – a phenomenon referred to as graying of wealth - and in the US alone it is estimated that older adults hold some $18 trillion dollars in assets (1, 7, 8). Elderly subjects, especially those that live alone or are trusting, are also frequent targets (and victims) of financial fraud scams (9).

The estimated 45 million cases of AD dementia worldwide are expected to triple in coming decades barring an effective disease modifying therapy. There is now increasing interest in detecting AD at earlier stages such as mild cognitive impairment (MCI) or preclinical AD (defined by pathological biomarkers and/or genetic risk) (5). While loss of financial skills has long been recognized as a feature of advancing AD (10), the lack of sensitive instruments, with both performance based and timed measures, may have limited the full characterization of subtle financial capacity losses in the preclinical and prodromal stages of AD (11). Most instruments assessing instrumental activities of daily living in AD do not assess financial capacity in a comprehensive or performance based manner (3, 11).

The Financial Capacity Instrument (FCI), was designed to more thoroughly assess dementia populations on their financial ability (12). Initial studies of the FCI, by Marson and colleagues who pioneered the instrument, demonstrated that impairments in most financial activities were evident even in mild AD (4), that specific financial skill deficits could discriminate stable MCI from those that progressed to AD (5), that the instrument is capable of longitudinal use in MCI patients (13), and that MRI measures of hippocampal or angular gyri volumes were associated with FCI scores after co-varying for age, gender and education (14, 15).

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The Financial Capacity Instrument Short Form (FCI-SF), a modified version of the original FCI, was designed as a shorter test with items sensitive to the early stages of AD and includes both performance based and timed measures of complex financial abilities (16, 17). Recent studies of the FCI-SF have reported the FCI-SF Total Score may discriminate normal older adults from MCI or AD as well as some cognitive screening measures (17). Based on these promising findings, the FCI-SF is being tested in several studies for its utility as a screening or prognostic measure.

18F-florbetapir brain PET scan is a validated and US FDA approved test to measure the accumulation of fibrillary cortical β-amyloid deposition, one of the pathological hallmarks of AD (18). Prior reviews of 18F-florbetapir brain PET have also documented its initial utility for predicting future cognitive decline in aging and MCI (19). It is now being used to select subjects for disease treatment trials. Studies also report that between 20-30% of asymptomatic elderly subjects in research studies may have a positive scan suggesting the presence of preclinical AD pathology and a potential adverse long-term prognosis (20). These data raise the urgency to study the association between cortical β-amyloid deposition and financial capacity.

The Alzheimer's Disease Neuroimaging Initiative (ADNI), conducted across 50 plus sites in the US and Canada, has provided new insights into the timeline of biomarker changes in aging, MCI and AD (21-23).

The aims of this study were to use ADNI-3 data to analyze the relationship between cortical β-amyloid deposition and financial capacity (both global and across specific domains) in the cohort as well as in patient group and asymptomatic subjects. We also examined if FCI-SF scores would differentiate normal controls, MCI and AD (to confirm prior findings).

Methods

Study Design and Consent

Data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative-3 (ADNI-3) (adni.loni.ucla.edu). ADNI was launched in 2003 with the third installment (ADNI-3) starting in 2016. The primary goal is to determine the relationships among genetic, biomarker, imaging, cognitive, and clinical testing across the entire spectrum of Alzheimer's disease as it progresses from a preclinical stage to dementia. ADNI-3 (ClinicalTrials.gov identifier: NCT02854033) involves 59 North American sites and study participants across three cohorts: normal controls (NC), mild cognitive impairment (MCI) and AD. Details of protocols and methods can be found online using the study manual [www.adni-info.org, http://adni.loni.usc.edu/adni-3/] (24).

The institutional review board at Duke University Health System and at each ADNI site reviewed and approved the ADNI protocol. All subjects and their legal representatives, where appropriate, gave written informed consent prior to data collection.

Participants

The data used for these analyses were summarized from the ADNI-3 database as of October 17, 2018. Participants were grouped at their baseline as either cognitively normal (NC), mild cognitive impairment (MCI) or to have mild probable AD dementia (AD). All participants were between the ages of 55-90 and assigned a diagnosis based on subject and informant histories, neurocognitive testing scores, laboratory tests, physical exams, brain MRI, the Clinical Dementia Rating (CDR) and physician judgment. Normal subjects could have a subjective memory complaint, but must score within normal parameters on the Wechsler Memory Scale Logical Memory II (WMS-II) and have a 0.0 on the CDR Global Rating. MCI subjects are required to have a subjective memory complaint, an objective memory deficit documented by the WMS-II, a CDR Global Rating of equal to or less than 0.5, and to not meet the criteria for AD. AD subjects have a subjective memory complaint, a larger deficit documented by the WMS-II, an MMSE score between 20-24, a CDR global score of 0.5 or 1.0, and a probability of AD. Additionally, participants with scores higher than 6 on the Geriatric Depression Scale (GDS) were excluded from the study. Details of diagnosis criteria are available through the ADNI-3 protocol [http://adni.loni.usc.edu/methods/documents/] (24). Both new and rollover ADNI-3 subjects with demographic information, a recorded MMSE, FCI-SF, and 18-F florbetapir β-amyloid PET global SUVr were considered for inclusion. Cognitively normal subjects had to have a Mini Mental State Exam (MMSE) of 25 or greater. Details of these tests and standardization across sites are available elsewhere (www.adni-info.org).

PET imaging

Global cortical β-amyloid deposition was measured in ADNI-3 using 18F-florbetapir amyloid PET imaging which was required for new enrollees and highly encouraged for rollover subjects. Details of scan techniques, standardization, quality control and calculation of SUVrs are reported elsewhere (http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/). The global SUVr averages signals across cortical regions typically affected in AD with higher SUVr indicating greater cortical β-amyloid deposition. Freesurfer processing is used to extract florbetapir means from grey matter within 4 regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal)

Table 1. Baseline Demographic and Clinical Assessments by Diagnostic Group (mean ± SD)

	Control	MCI	AD
N	144	79	20
Age, y	71.61 ± 6.22	71.41 ± 6.74	74.84 ± 6.52 †‡
Gender, % female	52%	43%	45%
Education, y	16.83 ± 2.40	16.32 ± 2.78	15.45 ± 2.70 ‡
MMSE	29.14 ± 1.02	27.82 ± 2.35*	24.25 ± 3.57 †‡
18F-Florbetapir PET Global SUVr	1.13 ± 0.18	1.17 ± 0.25	1.43 ± 0.26 †‡

*MCI mean differs significantly from normal control means using 2-sample t-tests ($p < .05$) ; †AD mean differs significantly from MCI mean using 2-sample t-tests ($p < .05$); ‡AD mean differs significantly from normal control mean using 2-sample t-tests ($p < .05$)

and a reference region value is used to normalize the summary mean (25).

Financial Capacity Instrument –Short Form

The FCI-SF consists of 37 items that can evaluate an individual's financial skills in the domains of monetary calculation, financial concepts, register usage, and bank statement usage. There are five domain scores (i.e., Mental Calculation, Financial Conceptual Knowledge, Single Checkbook/Register Task, Complex Checkbook/Register Task, Using Bank Statement), and also a Total Score (range of 0–74), with higher scores indicating better financial capacity (16). The total score is a summary of the individual domains; Mental Calculation (0-4), Financial Conceptual Knowledge (0-8), Single Checkbook/Register Task (0-20), Complex Checkbook/Register Task (28), Bank Statement Management (0-14). Additionally, the FCI-SF considers Composite time during the grading of four specific tasks (i.e., medical deductible problem, simple income tax problem, single checkbook/register task, complex checkbook/register task) and includes two composite time scores for the two checkbook tasks and all timed tasks. Details of these tests and standardization across sites are available elsewhere (www.adni-info.org).

Statistical Methods

Demographic and cognitive variables were tested using analysis of variance (ANOVA) and t-tests. ANOVA and t-tests were also used to compare FCI-SF total score and subgroup scores between diagnostic groups. A multiple linear regression model was used to simultaneously estimate the effects of key baseline variables (gender, age, education, MMSE, β-amyloid SUVr) on FCI-SF Total Score as well as each FCI-SF domain. The significance threshold was set at .05 for our a-priori hypothesis. We also ran separate models in control and patient groups to examine the effect of β-amyloid in aging and memory impaired samples. A multivariate linear model was ran to analyze the direct relationship between the FCI-SF Total Score and β-amyloid SUVr. Lastly, we tested the effect of β-amyloid on specific FCI-SF domains. Our primary aim was to test whether greater β-amyloid deposition would be associated with lower financial capacity. To confirm prior findings we tested if FCI-SF scores would discriminate AD and MCI subjects from controls. Cohen's d and Cohen's f2 were used for estimating effect sizes. A Cohen's d effect of 0.5 is considered to be medium and >0.8 is considered a large effect. Cohen's f2 was used to estimate effect size between two continuous variables and a large effect is considered to be 0.4. All statistics were computed using R studio Version 1.1.463.

Results

Demographics

Table 1 displays demographic variables for the cognitively normal (n=144), MCI (n=79) and AD (n=20) subjects included in this study. AD subjects were significantly older than both the NC group and MCI group. AD subjects were also significantly less well educated than the NC groups. No significant gender difference was present between groups. As expected, t-tests showed that each group differed significantly in MMSE scores.

Effect of Diagnosis on Financial Capacity

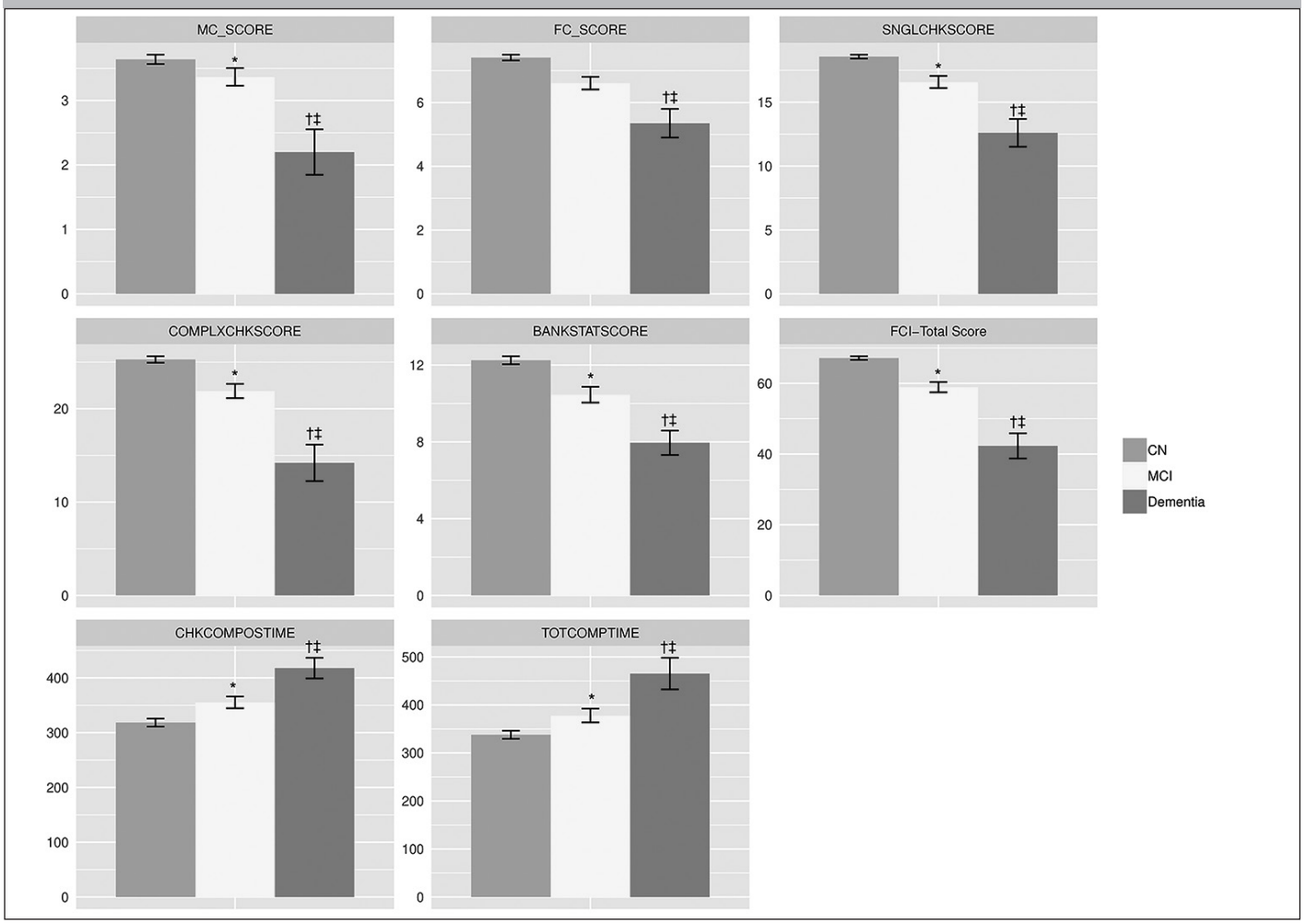
FCI-SF Total Score (mean ± SD) differed between NC (67.2 ± 6.18), MCI patients (58.9 ± 12.87) and AD patients (42.3 ± 15.96). ANOVAs showed the FCI-SF Total Score significantly differentiated all 3 diagnostic groups from one another ($p<.001$). ANOVAs showed that diagnostic groups differed significantly ($p<.0001$) on each domain; Mental Calculation , Financial Conceptual Knowledge, Single Checkbook/Register Task, Complex Checkbook/Register Task, Bank Statement Management, Check Composite Time, and Total Composite Time. Table 2 displays results of between group t-tests, which showed AD and MCI groups performed significantly worse than NC on FCI-SF Total Score and all domain scores (except the Mental Calculation domain score where the difference between the MCI and CN group did not reach significance). The effect size for AD versus NC

Table 2. FCI-SF Scores by Diagnostic Group (mean ± SD)

	Control	MCI	AD
N	144	79	20
FCI-SF Total Score (0-74)	67.15 ± 6.18	58.91 ± 12.87*	42.30 ± 15.96 †‡
Performance Domains			
Mental Calculation (0-4)	3.64 ± 0.87	3.37 ± 1.22	2.20 ± 1.58 †‡
Financial Conceptual Knowledge (0-8)	7.41 ± 1.09	6.61 ± 1.76*	5.35 ± 2.01 †‡
Single Checkbook/register (0-20)	18.57 ± 1.83	16.58 ± 4.20*	12.60 ± 4.86 †‡
Complex Checkbook/register (0-28)	25.28 ± 4.15	21.90 ± 6.79*	14.20 ± 8.73 †‡
Bank Statement Management (0-14)	12.25 ± 2.51	10.46 v 3.66*	7.95 ± 2.84 †‡
Time Components			
Checkbook/register Composite Time, s	318.37 ± 87.55	355.34 ± 95.38*	417.75 ± 84.08 †‡
Total Composite Time, s	337.89 ± 100.61	377.97 ± 128.11*	465.25 ± 146.89 †‡

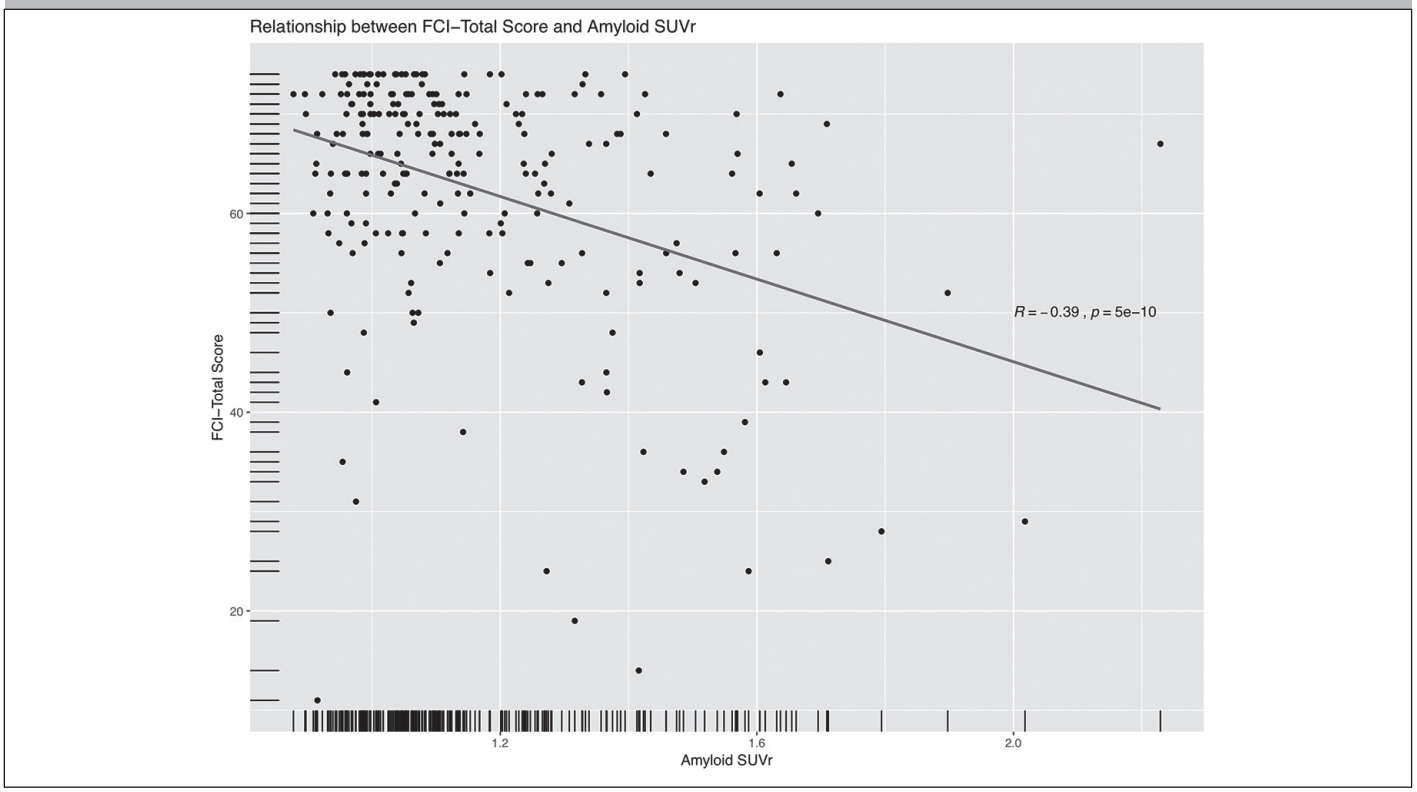
*MCI mean differs significantly from normal control means using 2-sample t-tests ($p < .05$); †AD mean differs significantly from MCI mean using 2-sample t-tests ($p < .05$); ‡AD mean differs significantly from normal control mean using 2-sample t-tests ($p < .05$)

Figure 1. FCI-SF Total and Items Score in Aging, MCI and AD



*MCI mean differs significantly from normal control means using 2-sample t-tests ($p < .05$); †AD mean differs significantly from MCI mean using 2-sample t-tests ($p < .05$); ‡AD mean differs significantly from normal control mean using 2-sample t-tests ($p < .05$)

Figure 2. Financial Capacity and Cortical ß-amyloid deposition in aging, MCI and AD



Higher FCI-SF Total Scores are inversely associated with greater cortical amyloid.

differences was large for the FCI Total Score [(d=3.1(CI: 2.5-3.7)] and all domain scores (d>1.1). The effect size for MCI versus NC was largest for the FCI-Total score [d=0.9(CI: 0.6-1.2)] followed by the two checkbook items (d=0.64) and medium for the completion time (d=0.36). Figure 1 shows FCI-SF scores by diagnosis.

Figure 3. Amyloid PET Images of Two Cases

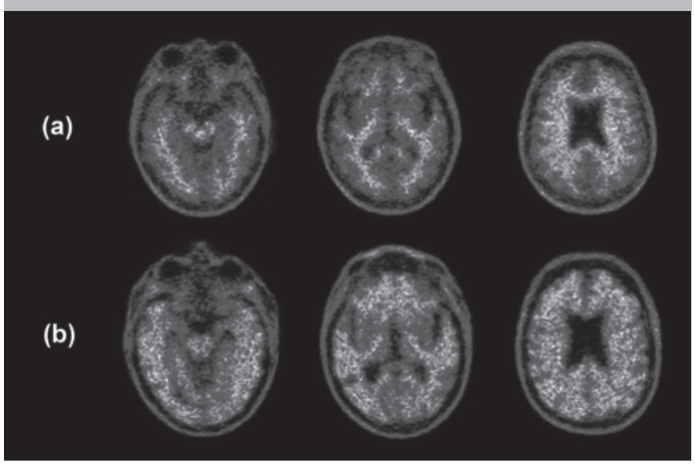


Figure 3a. 18F-Florbetapir PET image of a 74 year old normal control subject. PET scan is negative for β-amyloid. The subject had a normal financial capacity (FCI-SF Total Score=72); Figure 3b. 18F-florbetapir image of an 86 year old subject with mild Alzheimer's (MMSE=24). The PET scan is positive for β-amyloid. The subject had a significantly reduced financial capacity (FCI-SF Total Score=36).

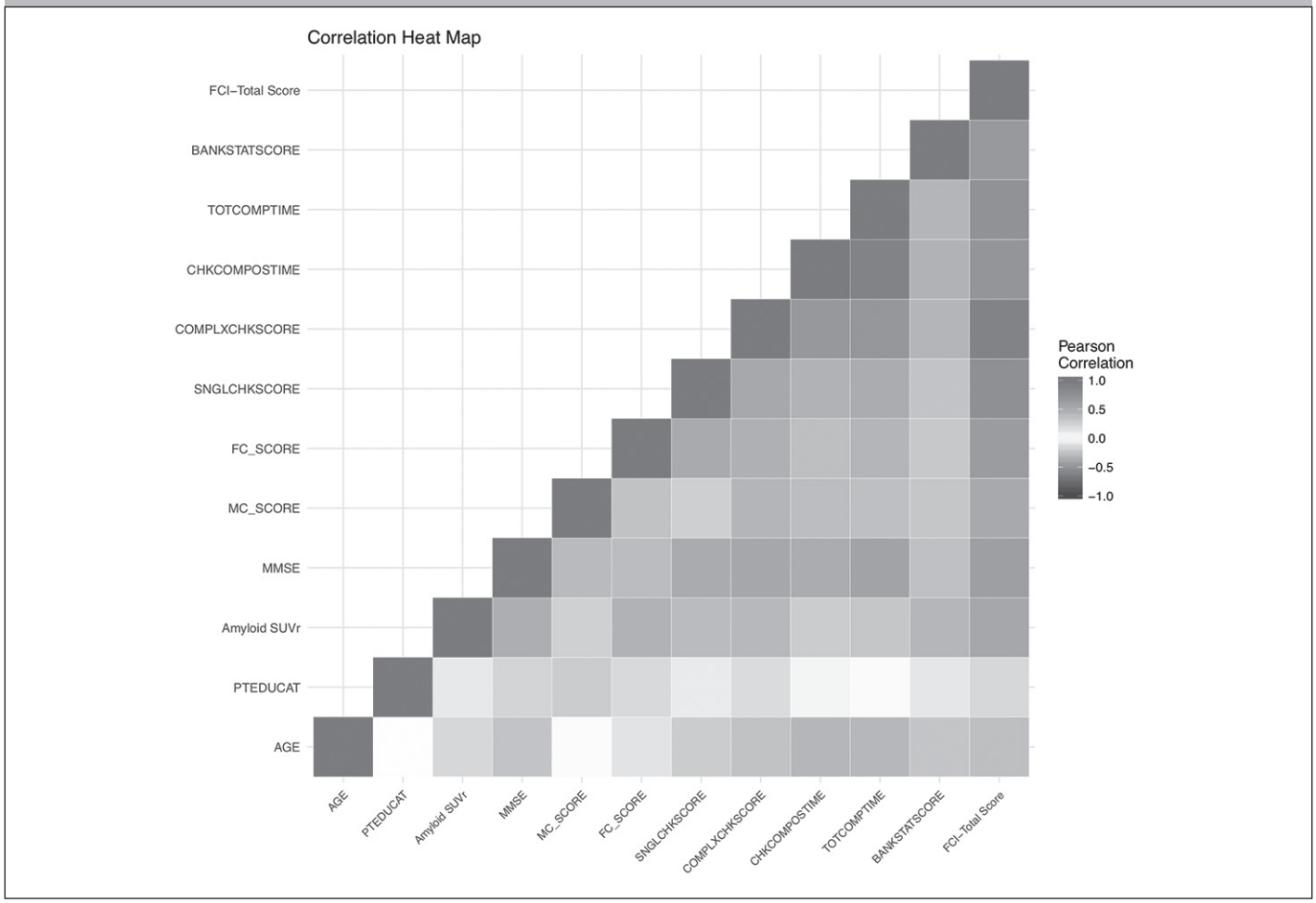
Effect of β-amyloid PET SUVr on FCI-SF Total Score

Figure 2 depicts the inverse relationship between lower FCI-SF Total Score and higher β-amyloid SUVr. Using an SUVr cut-off of 1.1, the effect size of β-amyloid positivity on lower FCI-SF total score was medium (d=0.55). Figure 3 illustrates color-rendered amyloid positive and negative PET scans from two subjects in ADNI-3 along with their financial capacity scores. After co-varying for age, education and gender, higher β-amyloid SUVr was associated with worse FCI-SF total score (p<.001) in the pooled sample. In this model, older age (p=.001) and lower education (p<.001) were also associated with worse FCI score but gender was not (p=.36). After co-varying for cognition as well (using the MMSE score), higher β-amyloid SUVr was still found to be associated with worse FCI-SF Total Score (p<.001) [Cohen's f2=0.75 (CI:0.51, 1.09)]. Older age (p=.04) and lower MMSE (p<.001) were also associated with worse FCI score in the pooled sample.

Relationship between β-amyloid SUVr and FCI-SF Subtest Domains

Multivariate linear regressions also show that higher β-amyloid SUVr was significantly associated with worse performance on all domains of the FCI-SF in the pooled sample; Mental Calculation (p=0.007), Financial

Figure 4. Heat Map of Correlations Among Variables



Conceptual Knowledge (p<.001), Single Check/Register (<.001), Bank Statement Management (p<.001), Complex Check/Register (p<.001), Check Composite Time (p<.001), and Total Composite Time (p<.001). Figure 4 is a heat map depicting the Pearson correlations between FCI-SF domains and β-amyloid SUVr with the significance and direction of correlation color coded.

Effect of β -amyloid PET SUVr on FCI-SF Scores in Cognitively Normal Older Adults

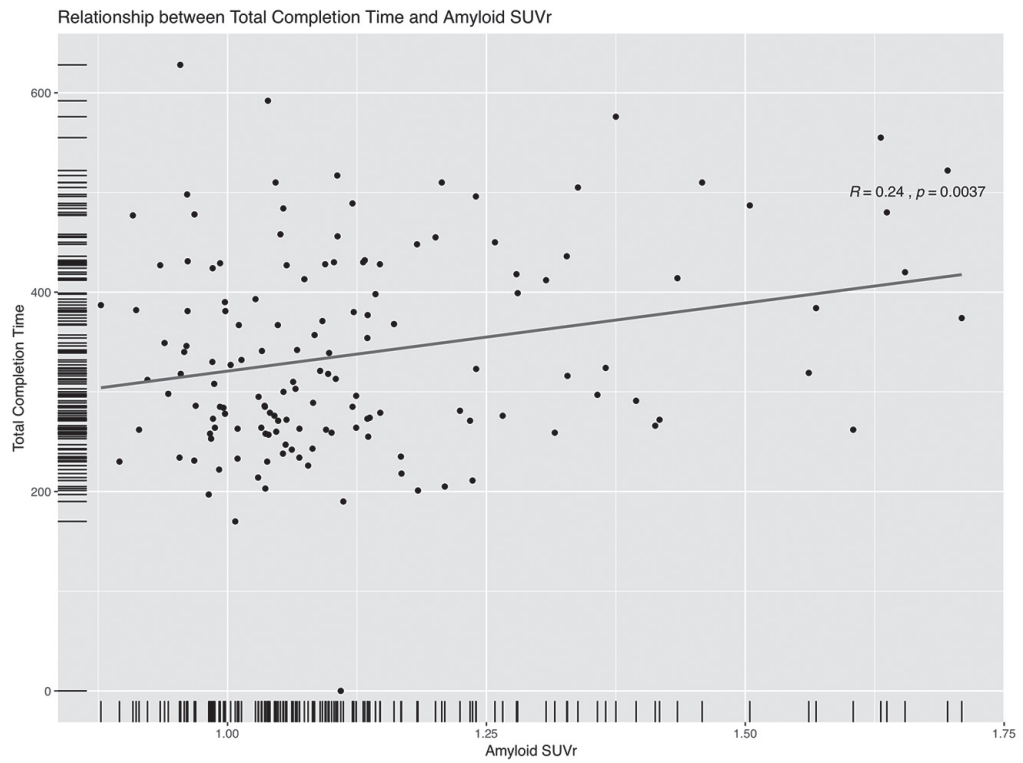
Simple linear regressions showed higher β-amyloid SUVr status was associated with slower Total Composite Time (p=.003) and Check Composite Time (p=.02), and worse Single Check/Register performance (p=.04) but other terms did not reach significance. Using an SUVr cut-off of 1.1, the effect size of β-amyloid positivity on slowing Total Completion Time was medium (f2=0.35). After co-varying for age, gender and education, higher β-amyloid SUVr was associated with slower Total Composite Time [Cohen's f2=0.198 (CI: 0.062-0.374)] (Figure 5) in normal older adults. After co-varying for age, gender and education, the effect of β-amyloid SUVr on FCI-SF Total Score failed to reach significance (p=.08). When cognition was added to this model, the effect of age on FCI-SF Total Score remained significant (p=.037) but the effects of β-amyloid SUVr, cognition, gender and education were not significant (p>0.05).

Discussion

We found the FCI-SF total score and all 5 domains as well as the completion time score were sensitive to detecting financial capacity impairments in both MCI and mild AD with large effect sizes. This confirms and extends prior findings (2, 4, 5, 6) to a sample from a multicenter ADNI setting. Overall, our study illustrates the feasibility and utility of administering the FCI-SF instrument across multiple raters and sites in the US and Canada and supports its utility and further development as a potential tool for assessing complex activities of daily living in MCI or AD in clinical trials.

Our study also found that cortical β-amyloid deposition had a significant effect on financial capacity. Furthermore β-amyloid load was linked with loss of skills on multiple financial domains such as mental calculation, conceptual knowledge, as well as handling checks and bank statements. This provides support that financial capacity may be more robustly associated with biomarker defined MCI due to AD and β-amyloid positive AD

Figure 5. FCI-SF Total Completion Time and PET Amyloid SUVr in Normal Controls



Total completion time was slower in normal control subjects with higher cortical amyloid.

dementia. It would be of interest to test whether disease modifying therapies impact financial capacity outcomes using the FCI-SF as a possible measure.

We also examined the links between cortical β-amyloid deposition and financial capacity declines in cognitively normal aging subjects. We found that a measure of financial quickness (total composite time) was adversely associated with increasing β-amyloid SUVr load and aging in normal subjects. The effect size for separating β-amyloid positive preclinical AD from amyloid negative controls on completion time was medium even with a relatively liberal SUVr cutoff for defining amyloid positivity. Our findings are consistent with a previous study (presented in abstract form) of FCI-SF scores in normal subjects from the Mayo Study of Aging which also found a significant effect of PIB-PET amyloid status on FCI completion time] (17). However, in our control sample, the effect of amyloid deposition on FCI-SF domains lost significance after co-varying for cognition.

The mechanisms underlying an association between amyloid deposition and financial capacity in aging and early dementia remain speculative since the neural circuits underlying financial capacity are not well understood. Prior studies have found associations between impaired financial skills and MRI measured angular gyrus volumes, hippocampal atrophy and white matter tract diffusivity (14, 26). Likewise, amyloid deposition has been associated with both functional and structural connectivity changes in preclinical and clinical AD (27, 28). Given the critical importance of white tract integrity to timed tasks, it is possible that alterations in white matter connectivity may underlie the links between amyloid and financial skills that we observed in our study. Further studies examining the relationship between FCI-SF and a variety of neuronal and pathological biomarkers may reveal additional insights.

Lastly, we found that there were no significant gender effects on FCI-SF score in normal aging or MCI subjects. This suggests the FCI-SF does not appear to have a significant gender bias in its raw scoring after adjusting for education effects. This supports the use of age and education adjusted norms for the FCI-SF (29).

There are some strengths and limitations to our study. ADNI-3 is a multisite study with participants in over 50 sites across the US and Canada. The careful and standardized protocol, entry criteria and rater training, and collection of amyloid PET data are the major strengths. As stated previously, the FCI-SF is a relatively well-studied and characterized tool. One weakness of our study is that our findings are cross-sectional and the sample studied from academic research centers may not be representative of the general population; hence the associations found should be viewed as preliminary warranting confirmation in longitudinal studies. The effect sizes reported for the AD subjects must also be viewed with caution given the relatively small sample of AD subjects and their larger standard deviations.

Further, while the FCI-SF is a promising tool, it has some potential disadvantages in that its relatively long, requires training of administration, and tools like "checks" may not be relevant to future generations. Lastly, our study cannot shed light on mechanisms underlying the association between amyloid and financial capacity and also cannot fully determine all such mediators that may underlie this effect. As data accumulates from ADNI-3 and other studies, such as the Brain Health registry and Mayo Study of Aging, some of these questions may be answered. Our findings thus should be viewed in that regard.

In summary, our study offers new insights into the links between pathological changes in the brain and financial capacity, a key functional activity essential for independent living. Our data also offers further guidance to researchers and clinicians on financial capacity changes in the early stages of preclinical and clinical AD dementia. We hope our findings serve to stimulate further research in this field which in turn may ultimately help clinicians to better monitor financial skills in at risk subjects and those with early dementia, and offer families timely advice to prevent financial adversity.

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Competing Financial Interests: MWW is the principal investigator for ADNI and all other authors are ADNI investigators at Duke. PMD is supported by NIH, DOD and Cure Alzheimer's Fund, has served as an advisor to and/or received grants from several companies and non-profits in this field, and owns stock in or serves on boards of companies whose products are not discussed here. Other co-authors may also have received grants or advisory fees from companies for other projects.

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Ethical standards: The institutional review board at Duke University Health System and at each ADNI site reviewed and approved the ADNI protocol. All subjects and their legal representatives, where appropriate, gave written informed consent prior to data collection.

Conflict of interest: We reported this under the existing para titled Competing Financial Interests.

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Supplement

ABSTRACTS

Symposia

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

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

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

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

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

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

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

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

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

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

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personalized medicine approaches.

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

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

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

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

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

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

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

The current world-wide prevalence of dementia is estimated at 35 million, and this number is projected to rise to over 100 million by 2050 if means of preventing, delaying, slowing or improving cognitive symptoms are not found. Most dementia is attributable to mixed age-related pathologies with Alzheimer's disease (AD) and vascular pathology being the two most common contributing elements. Vascular risk factors such as age, lack of exercise, cigarette smoking, hypertension, and obesity are associated with the risk of cognitive decline, dementia, vascular cognitive impairment (VCI), and AD. There is a need to detect and differentiate disease early and to treat its' root cause. Serum biomarkers that relate to different aspects of AD and VCI pathology include markers of neurodegeneration: neurofilament light chain and visinin-like protein (VILIP-1); markers of amyloidogenesis and

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

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

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

Plasma exchange (PE) with therapeutic albumin replacement (PE-A) as a potential therapeutic approach for Alzheimer's disease (AD) initiated by Grifols, started with promising results in patients' biochemical, cognitive, and neuroimaging assessments reported in a pilot study and a Phase 2 clinical trial. To further evaluate these findings, the AMBAR study was

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

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

The discovery that individuals with Trisomy 21, or Down syndrome (DS) have neuropathological features identical to those with sporadic Alzheimer's disease (AD) played a critical role in the identification of the amyloid precursor protein gene on chromosome 21 supporting the amyloid cascade hypothesis. People with DS have a lifetime risk for dementia in excess of 75% and comprise the world's largest population of genetically-determined AD. Just as studying DS helped identify the role of amyloid precursor protein mutations in AD pathogenesis, it is also likely to inform us of the potential benefit of manipulating the amyloid pathway on treatment outcomes in AD. It is critically important to the DS population and to the AD therapeutics field to conduct clinical trials, particularly those targeting amyloid accumulation, in individuals with DS. In this symposium, we will provide an update on recent developments in understanding the natural history of AD in DS as we prepare for clinical trials in this population. The predictable development of AD pathology and high incidence of dementia in individuals DS suggests that this is an important group in which trials in the preclinical or prodromal stage of AD to prevent or delay dementia should be considered. Recent work has demonstrated that AD biomarkers in DS behave similarly to those observed in both the sporadic and autosomal dominant AD populations. Dr. Michael Rafii, the symposium chair, will present a brief overview of the current state of the field. Dr. Andre Strydom will present 'Cognitive markers of preclinical and prodromal Alzheimer's disease in Down syndrome' based on results from the LonDowns consortium. We conducted the largest cognitive study to date with 312 adults with DS to assess age-related and Alzheimer's disease–related cognitive changes during progression from preclinical to prodromal dementia, and prodromal to clinical dementia. We have investigated cross-sectional changes in cognitive abilities associated with AD development in over 300 adults with DS. Memory and attention measures were most sensitive to aging, with significantly poorer performance starting in the early 40s. Similarly, performance for memory and attention outcomes was most sensitive to progression from preclinical to prodromal dementia, whereas performance for memory outcomes was most sensitive to progression from prodromal to clinical dementia. Using outcomes identified as sensitive to AD progression, we estimated possessing an

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

ROUNDTABLE

ROUNDTABLE 2: BACE INHIBITION: WHAT DO WE KNOW AND WHAT DO NEED TO KNOW?

Maria CARRILLO (1), Reisa SPERLING (2) *((1) Alzheimer's Association, United States, (2) Brigham & Women's Hospital, United States)*

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

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

Background: The Alzheimer Prevention Initiative (API) Generation Program assessed the effectiveness of the BACE1 inhibitor umibecestat or an active immunotherapy (CAD106) in delaying the onset of AD symptoms in APOE4 carriers. The Generation Program included two studies-Generation Study 1 (GS1, NCT0256551) and Generation Study 2 (GS2, NCT03131453) (Lopez Lopez et al., 2019) and was conducted in cognitively unimpaired people at risk for onset of clinical symptoms due to AD based on their age, APOE4 genotype and, for GS2, brain amyloid load. Recruitment and treatment with umibecestat was terminated in July 2019 after an early signal of mild worsening in some measures of cognitive function with umibecestat, similar to what had been seen previously with several other BACE inhibitors. **Method:** Both Generation studies planned treatment over 5-8 years in a double-blind, placebo-controlled, parallel design (Lopez Lopez et al., 2019). Participants were 60 to 75 years of age, had a study partner and were cognitively unimpaired at screening based on the RBANS delayed memory index score ≥ 85 and CDR global score of 0 (with investigator judgment allowed if either score was slightly out of range). Significant medical conditions were exclusionary. GS1 recruited only APOE4 homozygotes (HMs) while GS2 enrolled both HMs and APOE4 heterozygotes (HTs) who also showed elevated brain amyloid (PET or CSF). All participants underwent either CSF sampling for p-Tau/Abeta42 concentration or Amyloid PET scan. If the visual read of PET scan was negative, the SUVr was calculated and converted to centiloids for the three F18 tracers in order to rescue borderline cases using corresponding thresholds for amyloid positivity. Participants received disclosure of their risk estimates for developing clinical symptoms of AD based on their APOE genotype and, if HT, evidence of elevated brain amyloid. **Results:** Preliminary baseline data from all randomized participants from both Generation studies are summarized below. Generation Study 1: 478 HM participants

were randomized across both cohorts. In Cohort I with CAD106 or placebo, the 65 participants had mean age (SD) of 65.0 (4.2) years, 16.7 (3.5) years of education, 67.7% were women and 84.6% had a family history of AD. In Cohort II with CNP520 50mg or placebo, the 413 participants had a mean age (SD) of 66.2 (4.15) years, 16.3 (3.3) years of education, 56% were women and 83.8% had a family history of AD. In Cohort I / Cohort II respectively, the mean (SD) baseline cognitive scales were: MMSE 29.2 (0.98) / 29.0 (1.23), RBANS total 106.0 (12.5) / 102.9 (12.2), CDR-SB 0.1 (0.25) / 0.2 (0.4), ECog (subject) 46.3 (6.8) / 47.5 (7.8). A total of 314 participants underwent amyloid PET scan with Florbetapir: the mean SUVR was 1.23 (0.2) in cohort I (N=54) and 1.22 (0.19) in cohort II (N=260). Close to 64% of the subjects had elevated brain amyloid in both cohorts. Generation Study 2: 1143 participants were randomized (CNP520 15mg or 50mg or placebo), 226 were APOE4 HMs and 917 were HTs. The mean (SD) age was 68.4 (4.0) years , 15.8 (3.5) years of education, 62.8% were women and 69% had a family history of AD. Mean (SD) baseline cognitive scales were: MMSE 29 (1.2), RBANS total 100.9 (12.2), CDR-SB 0.2 (0.4), ECog (subject) 49.4 (9.35). The only marked differences observed in Baseline characteristics between HMs and HTs, included HMs being 2.4 years younger than HTs, and less female HMs (53%) than HTs (65%). 575 participants had an amyloid PET scan with Florbetapir (222 HMs and 890 HTs. Mean (SD) SUVR was 1.22 (0.21) in HMs randomized with any level of brain amyloid (66.2% were elevated), and 1.31 (0.17) in HTs randomized with elevated brain amyloid. Underlying AD pathology was assessed with a broad panel of biomarkers. In Study 1, 223 FDG PET scans were performed. Across both studies at Screening, 1111 LPs, 2934 amyloid PET scans with either florbetapir, flutemetamol or florbetaben, and 145 tau PET scans with flortaucipir, were performed. All 1617 participants randomized contributed blood samples (plasma and serum) and performed MRI scans to measure brain volumes as well as microhemmorhages (a subset also did resting-state functional MRI). These biomarkers will be analyzed later. **Conclusion:** This is the largest cohort of APOE4 HMs (including about 35% below amyloid elevation threshold) and amyloid-positive APOE4 HTs recruited in a global clinical trial program. Baseline characteristics of participants enrolled in the Generation Program were consistent with the target early AD population without objective cognitive impairment. Striking similarities in most Baseline characteristics reflect the main eligibility criteria shared across both trials. The anonymized study data, biomarker samples as well as images collected will be shared with the scientific community after study completion and reporting. **References:** Lopez Lopez et al. The Alzheimer's Prevention Initiative Generation Program: Study design of two randomized controlled trials for individuals at risk for clinical onset of Alzheimer's disease. A&D TRCI (2019) 5, 216-227.

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

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

Background: Volumetric MRI (vMRI) has excellent biomarker characteristics in natural history studies, including monotonic dependence on disease severity and strong correlations with clinical and cognitive outcomes. It is routinely used as an outcome biomarker in AD clinical trials, but there has been some concern in the field about treatment effects on brain atrophy being sometimes inconsistent with those on clinical outcomes. **Objectives:** To review the relationship between magnitudes of change in vMRI and primary clinical outcomes in published late-phase AD treatment trials, and to evaluate a simple framework to help distinguish disease-related from non-specific treatment effects on atrophy. **Methods:** We reviewed the relative magnitudes of treatment vs. control arm differences (irrespective of statistical significance) in published clinical and MRI results for clinical trials with AN1792, semagacestat (IDENTITY), avagacestat, bapineuzumab (301 and 302), solanezumab (EXPEDITION 3) and leucomethylthioninium bis(hydromethanesulphonate) (LMTM). ADAS-Cog was the primary clinical endpoint for all trials. AN1792, semagacestat, bapineuzumab, solanezumab and LMTM trials were conducted in subjects with AD dementia; avagacestat in subjects with prodromal AD. Placebo + treatment arm sample sizes for analysis ranged from 85 to 1462. All trials reported vMRI changes for whole brain (WBV) and hippocampus (HV) volumes; all except semagacestat reported vMRI changes for the lateral ventricular volume (VV); only solanezumab reported changes for additional brain regions (12 in total). Adjusted group-mean changes in ADAS-Cog and vMRI outcomes were converted to % change relative to control arms with respect to reported baseline measurements, for control and treatment arms, and directionality of change was harmonized to reflect worsening or improvement consistently across studies. To further interpret the vMRI changes, we considered how a set of brain regions affected to different degrees by the disease process, and that exhibit volume loss at different rates, would be affected by a treatment that modifies these rates of volume loss. A plausible disease-modification effect might be expected to alter the rate of atrophy in each region by a similar relative amount (e.g., 25% slowing). In contrast, a non-specific effect (e.g., inflammation or fluid shift) might be expected alter the rate of atrophy in each region by a similar absolute amount. Examining the pattern of relative and absolute differences in volume change between treatment and control arms, plotted against the change in the control arm, across different brain regions may thus indicate whether the observed effects are more consistent with a disease-related or with a non-specific effect. We examined published brain atrophy data from the above treatment trials in this framework. **Results:** The magnitudes of both ADAS-Cog and vMRI treatment vs. control arm differences ranged from small (a few percent) to large (40-50% for ADAS-Cog, WBV and HV; up to 130% for VV); some changes favored control and others favored treatment. When percent difference in each vMRI measure was plotted against percent difference in ADAS-Cog, with the exception of AN1792 these differences were overall directionally concordant and consistent in magnitude. Linear regression lines passed close to the origin and described the data well (WBV R2=0.84, VV R2=0.97, HV R2=0.82). Nominally discordant results (relative increase in ADAS-Cog and decrease in vMRI, or vice versa) were associated with small magnitudes of effect and/or lower doses (semagacestat, bapineuzimab) and/or shorter follow-up time (avagacestat); for these treatments the differences tended toward the overall regression lines as dose or follow-up time increased. In contrast to the pattern exhibited by the other trial results, AN1792 showed a relative difference in ADAS-Cog of approximately 26% that favored treatment, but relative differences in vMRI measures of 32-129% that favored placebo, and was a clear outlier. Considering the cross-region patterns of relative and absolute vMRI differences from control, most of the above trials exhibited relative percent

changes that were approximately proportional to the rate of change in the control arm and absolute percent changes that were approximately constant, although the directionality of effect (favoring treatment or placebo) was trial-dependent. AN1792 was the only data set to exhibit a pattern more closely resembling what would be expected for a non-specific effect, but we note that the VV changes were reported in a slightly different way to other trials which may affect this finding. This analysis is however limited by the fact that most trials reported only WBV, VV and HV. The 12 regions reported for solanezumab revealed a proportional slowing pattern that could be interpreted more confidently. **Conclusion:** With the exception of AN1792, the data from the treatment trials reviewed here (12 comparisons across 7 trials) revealed an overall pattern of directionally concordant changes between ADAS-Cog and WBV, VV and HV. Discordant findings were small in magnitude and more likely associated with lower doses or shorter follow-up times. Interrogating atrophy in a larger set of brain regions, and examining the patterns of relative and absolute treatment-placebo differences across brain regions, may help further interpret volumetric changes in intervention trials.

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

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

Discussion:

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

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

Oral Communications

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

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

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

Pathological tau protein is recognized as a target for development of disease-modifying treatments in Alzheimer's disease (AD). AADvac1 is an active vaccine targeting an epitope in the microtubule-binding repeat region of tau, the domain responsible for aggregation and common for all forms of tau pathology. The induced serum antibodies are strongly selective for pathological forms of tau and inhibit the progress of tau pathology in animals (Kontsekova et al., Alzheimers Res Ther, 2014). In the phase 1 study, AADvac1 has shown to be safe and highly immunogenic (Novak P, et al., Lancet Neurol., 2017). In addition, signals of efficacy have been observed (Novak P, et al., Alzheimers Res Ther, 2018). AXON Neuroscience is in the process of completing the randomized, placebo-controlled, phase 2 study in patients with mild AD to assess safety and efficacy of AADvac1. **Objectives:** The primary objective of the study is safety, the secondary objectives are efficacy and immunogenicity after two years of treatment with AADvac1 or placebo. Clinical efficacy has been assessed by CDR-SB, ADCS-ADL-MCI, MMSE and a custom battery of validated cognitive tests evaluating all important cognitive domains. A panel of biomarkers has been evaluated, including brain volumetry, brain metabolism, and biomarkers in plasma and CSF. **Methods:** The study population consists of very mild to mild AD patients (MMSE from 20 to 26 inclusive), defined by the NIA-AA criteria (McKhan 2011), and supported by evidence of hippocampal atrophy (Scheltens score ≥2) or positive CSF biomarkers. Study participants have been randomized to either AADvac1 or placebo in a 3:2 ratio. Treatment was administered 11 times during the study. The study has been conducted in 8 European countries; the last patient last visit is expected in June 2019. **Results:** 208 patients have been randomized, while close to the end of the study the dropout rate is 17.3%. No safety signal has been detected in blinded data, nor by the unblinded DSMB. As per the blinded preliminary analysis, the vaccine displays superior immunogenicity among all other active vaccines in AD, 98% of all tested vaccinated patients developed antibody response. At the conference, we will present the study results of efficacy, immunogenicity and safety assessments. **Conclusion:** The AADvac1 phase 2 study is on track to confirm the favorable safety profile and high immunogenicity, and is powered to confirm the compelling efficacy signals observed in the phase 1 study.

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

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

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

Background: Verbal neuropsychological tests are often used in the context of neurodegeneration in older adults. However, the potential for verbal assessments as large-scale, sensitive screening tools has yet to be reached because of their dependence on skilled raters. We conducted a large, at home feasibility study into whether a device-agnostic web-based technology (Cambridge Cognition's NeurovocalixTM platform) offers a reliable method of administering and scoring verbal neuropsychological tests across devices, platforms and demographics. **Objectives:** To determine the acceptability and feasibility of using Cambridge Cognition's NeurovocalixTM platform to remotely administer and score verbal neuropsychological tests, at scale and on participants own devices. **Methods:** 3,264 participants aged 17-86 years (M=34.5, SD=12.32) completed a battery of three automated tasks: digit span, serial subtraction and verbal paired associates. Repeated assessment was carried out at a delay of 3 months in 1,151 participants. Participant demographics, native language and information regarding the operating system, browser and platform on which the tasks were completed, were all collated. Voice data was recorded and stored for analysis and quality control. **Results:** Nearly half (47%) of participants completed the testing on a Microsoft Windows platform, and a further third (36%) completed the assessment on a mobile phone. There was no significant difference in performance depending on platform, suggesting that testing is feasible across a range of different devices. We observed expected differences in performance depending on task difficulty (e.g. easy vs hard word pairs, digits forward and back), and predicted relationships between demographic variables (e.g. age) and task performance. Qualitatively, participants reported that the automated instructions were clear and easy to understand, and that the tasks were enjoyable. We also present data on the repeatability of the assessments on these different platforms, and by participant age brackets. **Conclusion:** Together, these results demonstrate that remote, automated, voice-based, cognitive assessments are feasible and acceptable for younger and older adults. Furthermore, automatic speech recognition was shown to be scalable as participants' completed the verbal tasks in their own homes, and on their own devices (laptop, smartphone). These findings suggest potential for automatic speech recognition as a home-based monitoring or assessment methodology in the context of remote clinical trials.

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

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

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

Background: REVERSE-SD is a double-blind, placebo-controlled, phase 2b clinical study of the oral investigational drug neflamapimod in early-stage Alzheimer's disease (AD) with the primary objective of demonstrating the ability of the drug to reverse synaptic dysfunction ("SD") in the hippocampus, as evaluated by a test of episodic learning and memory – the Hopkins Verbal Learning Test. Neflamapimod is a highly selective brainpenetrant small molecule inhibitor of the alpha isoform of p38 MAP kinase (p38α). In 6- and 12-week duration phase 2a clinical studies in patients with early AD, neflamapimod demonstrated within-subject improvement in episodic memory function (Scheltens et al, ACTN, 2018; CTAD, 2016 & 2017) consistent with the potential for reversing hippocampal synaptic dysfunction derived from preclinical studies. P38α, which is expressed in neurons under conditions of stress and disease, plays a major role in inflammation induced synaptic toxicity, including the impairment of synaptic function (i.e. synaptic plasticity) in the hippocampus (Watterson, 2013; Prieto, 2015). Accordingly, small molecule p38α kinase inhibitors fully reversed spatial learning deficits in three distinct animal models (APP/PS1, aged rats, and aged hTau mice; Roy, 2015; Maphis, 2016; Alam, 2016), and genetic reduction of neuronal p38α in APP/PS1 mice improved synaptic transmission, reduced memory loss, and reduced amyloid pathology (Colié, 2017). Genetic reduction of neuronal p38α also protected mice from developing age-related hippocampal dysfunction (Cortez, 2017). Furthermore, a recent human GWAS study implicated the p38α pathway in the development of age-related decline in episodic memory (Huentelmann, 2018). **Methods:** Inclusion: Aged 55 to 85, with CDR-Global score of 0.5 or 1.0; CDR memory sub-score of at least 0.5; MMSE score of 20 to 28, inclusive; positive biomarker for AD, as defined by CSF Aβ1-42 <1000 pg/mL and phospho-tau/Aβ1-42 >0.24 in the Roche Eclesys® immunoassay; receiving either no AD-specific therapy or on

stable dose monotherapy (either cholinesterase inhibitor or memantine; dual therapy excluded). **Treatment:** randomized 1:1 to receive neflamapimod 40 mg capsules or matching placebo capsules twice daily with food for 24 weeks, stratified by baseline CDR-global score (0.5/1.0) and whether the subject is receiving background AD-specific therapy (yes/no). Primary endpoint: Episodic memory, as assessed by change from baseline to week 24 in combined z-score of total recall and delayed recall in Hopkins Verbal Learning Test – Revised (HVLT-R) in neflamapimod-treated subjects compared to placebo-recipients. Secondary endpoints: Change in Wechsler Memory Scale immediate or delayed recall composites, CDR-SB, MMSE, CSF biomarkers (total tau, p-tau181, Aβ1-40, Aβ1-42, neurofilament light chain, neurogranin, BDNF) in neflamapimod-treated subjects compared to placebo-recipients. Sample size: Approximately 76 patients per treatment arm (152 patients total). Provides 90% statistical power to detect effect size (ES) of 0.53 and 80% to detect ES of 0.46. Assuming a z-score decline of between 0.15 to 0.25 in the placebo-recipient group, neflamapimod treatment would need to show an increase in z-score of at least 0.21 to 0.38 to demonstrate a statistically significant positive treatment effect on the primary endpoint. **Results:** 477 subjects screened, and 161 patients were enrolled at 38 sites in the Czech Republic (5 sites), Denmark (3 sites), Netherlands (3 sites), United Kingdom (11 sites) and USA (16 sites). The last patient enrolled commenced dosing in early January 2019. The most frequent reasons for screen failure were out of range MMSE score and not meeting CSF criteria. At baseline, among patients randomized, mean age was 72 and 50% were female. 77% had a CDR-global score of 0.5 (CDR-memory sub-score was 0.5 in 48%, 1.0 in 51%, 2.0 in 1%); mean MMSE score was 23.8 (s.d.=2.5; median=24); mean HVLT total recall score was 15.9 (s.d.=5.7; 87% < 22) and mean HVLT delayed recall score was 3.0 (s.d=3.1: 42% had score of 0.0). As of June 1, 2019, 154 patients have completed week 12 assessments and 118 have completed treatment. There have been 10 early terminations, of which 4 were related to adverse events (nausea, fatigue, 2 unrelated intercurrent medical events); no new safety risks have been identified. Last patient, last visit will occur in July 2019 and database lock is anticipated by end of August 2019. All prospectively planned efficacy and safety analyses will be available for the meeting. **Conclusion:** The study has enrolled a well-defined early AD patient population with significant episodic memory defects at baseline. It is designed to provide clinical proof-of-concept for neflamapimod, and p38α kinase inhibition generally, as an approach to improve episodic memory function in patients with early AD. Further, the secondary clinical endpoints combined with CSF biomarkers will provide an initial assessment of the potential of neflamapimod to impact AD disease progression globally. Finally, as the first study to evaluate an approach that targets intra-neuronal molecular mechanisms underlying synaptic dysfunction, the findings will provide insights (e.g. responsiveness of the clinical and biomarker endpoints to such approaches) for the field to designing clinical trials evaluating therapies directed at synaptic dysfunction. Note: Authors presenting on behalf of REVERSE-SD investigators and study team.

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

Tobias BITTNER (1), Christina RABE (2), David CLAYTON (2), Angelica QUARTINO (2), Sandra SANABRIA BOHORQUEZ (2), Nan HU (2), Michael RABBIA (2), Harumi SHIMIZU (2), Udo EICHENLAUB (3), Jillian SMITH (4), Lee HONIGBERG (2), Dennis J. SELKOE (5), Susanne OSTROWITZKI (2) ((*1) F. Hoffmann-La Roche Ltd, Switzerland, (2) Genentech, Inc., United States, (3) Roche Diagnostics GmbH, Germany, (4) Roche Products Limited, United Kingdom, (5) Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital and Harvard Medical School, United States)*

Background: Crenezumab is a humanized anti-beta-amyloid (Aβ) monoclonal immunoglobulin G4 antibody that has been evaluated in clinical trials in patients with sporadic Alzheimer's disease (AD) [1,2], with a study in autosomal-dominant AD currently ongoing [3]. Crenezumab binds to monomeric and aggregated forms of Aβ, with a high affinity for Aβ oligomers [4,5], which may protect neurons from oligomer-induced toxicity [5]. The Phase III CREAD (NCT02670083 [6]) and CREAD2 (NCT03114657) studies that investigated the safety and efficacy of crenezumab at 60 mg/kg administrated intravenously (IV) every 4 weeks (q4w) in early (prodromal-to-mild; Mini-Mental State Examination (MMSE)) ≥22) AD were recently stopped based on an interim analysis of CREAD that indicated that the study was unlikely to meet its primary endpoint of change from baseline to Week 105 in Clinical Dementia Rating–Sum of Boxes (CDR-SB); no safety signals were observed in this analysis and the overall safety profile was similar to that seen in previous studies [7]. Post hoc analyses of preceding Phase II studies suggested an efficacy signal at the higher of two doses of crenezumab tested (15 mg/kg IV q4w). Biomarker results from Phase II studies suggested an increase in Aβ(1-42) and Aβ(1-40) in cerebrospinal fluid (CSF) and plasma, a decrease in soluble Aβ oligomer levels in CSF, and reduced accumulation of fibrillar amyloid as measured by florbetapir-PET SUVR after 69 weeks of treatment with crenezumab, compared with placebo [2,8]. The CREAD and CREAD2 studies also included assessments of imaging and fluid biomarkers to better understand the effects of crenezumab on the underlying pathology of AD, including amyloid plaques, neurofibrillary tangles, and neuronal degeneration and inflammation. **Objectives:** To assess the effect of crenezumab compared with placebo on changes in imaging and fluid biomarkers in patients with early (prodromal-to-mild) AD enrolled in CREAD and CREAD2. **Methods:** CREAD and CREAD2 were multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase III studies enrolling patients aged 50–85 years with early AD and confirmed evidence of cerebral amyloid pathology (by CSF and/or amyloid PET). At screening, patients were required to have an MMSE score of ≥22, a Clinical Dementia Rating Global Score (CDR-GS) of 0.5 or 1, and Free and Cued Selective Reminding Test (FCSRT) immediate free recall and cueing index scores of ≤27 and ≤0.67, respectively. Enrolled patients were randomized 1:1 to receive placebo or crenezumab (60 mg/kg q4w IV). Randomization was stratified by dementia status (prodromal vs. mild AD), APOE ε4 allele status (presence or absence), baseline anti-dementia medications (presence or absence), and geographic region. The primary endpoint for both studies was the change from baseline to Week 105 on the CDR-SB score. Biomarker data were collected in the main study or in one of four substudies to measure target engagement and evaluate treatment response and disease progression.

Assessments as per protocol included: amyloid PET, tau PET, volumetric MRI, CSF biomarkers (Aβ(1-42), Aβ(1-40), total tau, phosphorylated tau), and plasma biomarkers (Aβ(1-42), Aβ(1-40)). Additional exploratory measurements included CSF biomarkers of Aβ oligomers, neurofilament light chain (NfL), neurogranin, YKL-40, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), glial fibrillary acidic protein (GFAP), s100b, alpha-synuclein, and interleukin-6 (IL-6)), as well as plasma NfL. **Results:** Data from the CREAD and CREAD2 biomarker analyses will be presented. **Conclusions:** CREAD and CREAD2 were discontinued based on a pre-planned interim analysis of CREAD, which indicated that the study was unlikely to meet its primary endpoint. However, biomarker data from patients enrolled in these trials will help to advance our understanding of the potential change in these biomarkers under treatment with crenezumab, and of their role in the pathology and progression of AD. **References:** 1. Cummings JL, et al. Neurology 2018;90:e1889–e1897; 2. Salloway S, et al. Alzheimers Res Ther 2018;10:96 3. Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease; ClinicalTrials.gov Identifier: NCT01998841; 4. Adolfsson O, et al. J Neurosci 2012;32:9677–9689; 5. Ultsch M, et al. Sci Rep 2016;6:39374; 6. Lin H, et al. AAIC 2018; 7. F. Hoffmann-La Roche Ltd. Media release. January 30, 2019; 8. Yang T, et al. Ann Neurol 2019 in press.

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

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

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

Introduction: The Clinical Dementia Rating Scale – sum of boxes (CDR-SB) is often the primary endpoint of choice for clinical trials in early Alzheimer's Disease (AD). However, consensus among stakeholders (including health care professionals, payers, regulators, patients and caregivers) regarding what constitutes a clinically meaningful change on the CDR-SB is lacking. Establishing a threshold or range of score changes that reflect a meaningful change on the CDR-SB is of critical importance to aid the interpretation of clinical trial data and to demonstrate the value of novel therapies in AD. **Objective:** To establish a range of score changes that constitute a meaningful within-person (individual level) change on the CDR-SB in patients with prodromal AD. **Methods:** This was a secondary analysis of data from the Alzheimer's Disease Cooperative Study ADC-008 phase III clinical trial of Donepezil and Vitamin E, in patients with amnestic Mild Cognitive Impairment (MCI) (Inclusion criteria: Age = 55-90, MMSE = 24-30, Logical Memory delayed-recall score = 1.5-2 standard deviations below an education-adjusted norm and CDR-global score = 0.5, consistent with prodromal AD [non-biomarker confirmed]). Following standard methodology (Patient Focused Drug Development FDA draft guidance 2018; Coon & Cook, 2017), anchor- and distribution-based approaches were used to establish a range of score changes associated with a clinically meaningful change/decline at the individual level on the CDR-SB (collected every 6 months throughout the 36- month study). Anchors included the Global Deterioration Scale (GDS), a 7-point measure of cognitive impairment severity rated by the clinician, completed at baseline and every 6 months thereafter, and the Mild Cognitive Impairment-Clinician Global Impression of Change (MCI-CGIC), completed at months 6 and 12. Mean- and median- score changes on the CDR-SB in those experiencing a 1- or 2-category decline on the GDS and minimal- or moderate-worsening on the MCI-CGIC were calculated. Distribution-based analyses included 0.5 standard deviation (SD) and standard error of measurement (SEM), denoting the minimum score change that is considered to be greater than measurement error. Cumulative distribution function and probability density function plots were generated

to explore appropriate thresholds further. The proposed meaningful change thresholds focus on the 12 month time point, taking into consideration the sample sizes in each anchor category and the anchor-CDR-SB correlation. Additional time points will be presented. **Results:** A total of 769 prodromal patients with a CDR global score of 0.5 were included in the analyses (mean [SD] = age 72.9 [7.3] years, 46% female, 55% APOE ε4 carrier, mean [SD] CDR-SB = 1.8 [0.8], MMSE = 27.3 [1.9]). The CDR-SB demonstrated good psychometric performance overall (good test-retest reliability ICC ≈ 0.7, no floor/ceiling effects) and showed adequate correlation (r) with the GDS (r=0.50) and MCI-CGIC (r=0.53) changes at 12 months. For the GDS anchor, those experiencing a 1-category change (interpreted as a minimum decline) at 12 months had a mean [SD]/median score change of 1.08 [1.18]/1.00 (n=132) on the CDR-SB, while those experiencing a 2-category change (interpreted as a moderate decline) had a mean [SD]/median score change of 3.39 [1.92]/2.75 (n=14). For the MCI-CGIC anchor, those experiencing a minimal-deterioration had a mean[SD]/median CDR-SB score change of 0.64 [1.02]/0.50 (n=192), while those experiencing a moderate-deterioration had a mean[SD]/median change of 2.35 [1.66]/2.00 (n=43). Distribution-based thresholds for within-person changes were 0.39 (½ SD) and 0.45 (SEM), indicating that changes of 0.5 or greater are larger than measurement error. Taken together, these data suggest that a 1- point change is a reasonable threshold for a minimal deterioration, whilst a 2.5- point change might be a more appropriate reflection of a moderate deterioration. **Conclusion:** These values may be considered when defining a "progressor threshold" for the CDR-SB. Choice of the specific threshold will depend on the study design characteristics, in particular the target patient population and the length of trial. Such thresholds can be used to determine the proportion of patients who experience a meaningful decline and can contribute to the assessment of treatment benefit in the context of a clinical trial.

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

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

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

Background: The Alzheimer's Prevention Initiative (API) Generation Study 1 (GS1) has been evaluating the BACE1 inhibitor umibecestat (CNP520) and the active amyloid-b (Ab) immunotherapy CAD106 in cognitively unimpaired 60-75 year-old APOE4 homozygotes, including those with and without elevated amyloid levels. API Generation Study 2 (GS2) has been evaluating umibecestat in APOE4 heterozygotes with elevated amyloid levels and additional homozygotes, independent of the amyloid status (Lopez Lopez et al., 2019). Two doses of umibecestat were used in GS2: 50mg and 15 mg, with expected median CSF Aβ lowering of 86% and 68%, respectively. In GS1: Cohort I, CAD106 at 400ug/l with Alum and Cohort II umibecestat at 50mg were used. Umibecestat was discontinued in July 2019 due to mild worsening in several measures of cognitive function, and the participants continue to be followed to clarify the reversibility of these and any other observed effects. In this presentation, we will briefly describe the studies' original and revised design and aims and current status. **Design/Methods:** Randomization was initiated in March 2016 for Cohort I of GS1, in February 2017 for Cohort II and in December 2017 for GS2. Studies were implemented across 23 countries worldwide at 207 sites, with over half of the sites participating in both trials. Recruitment was supported by the Alzheimer's Prevention Registry and GeneMatch Program in the US, other local engagement and recruitment activities, and specially developed genetic counseling and disclosure programs. Enrollment to Cohort I with CAD106 was halted in November 2017 after 65 participants had been randomized to mitigate the risk that a large number of participants are exposed prior to the futility analysis of CNS activity. Following the disclosure of mild cognitive detrimental effects with verubecestat and atabecestat at CTAD in October 2018, Novartis and its partners, Banner Alzheimer's Institute and Amgen, implemented a series of measures to

enhance oversight of the safety of study participants receiving umibecestat or placebo. Study protocols were amended to include earlier cognitive, neuropsychiatric assessments, MRI scans as well as fluid biomarkers collection. Frequency of Data Monitoring Committee (DMC) meetings was increased, focusing on cognitive measures. An option to lower doses of umibecestat was added to the protocols, as this was considered to be an effective mitigation strategy. All trial participants and their study partners were informed of the findings with other BACE inhibitors. At that time recruitment across both studies continued unaltered and reached steady rate over 100 participants randomized per month. **Results:** In July 2019, recruitment and treatment with umibecestat was halted following a planned DMC review of the unblinded data. At that time, >1'200 cognitively unimpaired APOE4 homozygotes and > 10'000 APOE4 heterozygotes were identified by genetic screening; 704 homozygotes (35% of whom were amyloid negative) were enrolled in GS1 or GS2; and 913 amyloid-positive heterozygotes were enrolled in GS2. Umibecestat was associated with mild worsening in some measures of cognitive function with both doses tested (15 and 50 mg daily). The data available at the time of DMC review included 1260 participants randomized to umibecestat or placebo (369 in GS1 and 891 in GS2), with cognitive data available for 578 participants at month 3 and 483 at month 6. This early effect was similar to external data reported with several other BACE inhibitors. The mechanism leading to this worsening remains unknown. All participants were informed to stop treatment within 10 working days. They were all scheduled to attend a final evaluation and a follow-up visit after treatment discontinuation. GS1 Cohort 1 with CAD106 was not affected at the time of the CNP520 termination. **Conclusions:** The Generation Program has introduced programs and procedures to support enrollment in multi-study prevention trials, and it has demonstrated the ability to conduct them in an exceptionally large number of cognitively unimpaired participants willing to learn their AD risk estimate. Results from the Generation Program will be analyzed including follow-up visits off-treatment to evaluate the potential reversal of the observed early worsening of cognitive measures. Trial findings, data, biological samples, and motivated amyloid-positive and -negative participants will provide important resources for the advancement of AD prevention research. Upon study completion, findings will be reported and data and samples will be shared following CAP principles. API is exploring ways in which to continue to follow interested participants, provide a trial-ready cohort, and prepare for new prevention trials. **Reference:** Lopez Lopez et al. The Alzheimer's Prevention Initiative Generation Program: Study design of two randomized controlled trials for individuals at risk for clinical onset of Alzheimer's disease. A&D TRCI (2019) 5, 216-227.

OC12: RECRUITMENT STRATEGIES FOR THE GENERATION PROGRAM AD PREVENTION CLINICAL TRIALS: LESSONS FROM THE BUTLER HOSPITAL MEMORY & AGING PROGRAM. Jessica ALBER (1), Louisa THOMPSON (2), Stephen SALLOWAY (2), Ginamarie TONINI (3), Athene LEE (2) *((1) University of Rhode Island, United States, (2) Brown University, United States, (3) Butler Hospital, United States)*

Background: Alzheimer's disease risk assessment is critical in screening cognitively normal individuals for AD prevention trials, such as the Amgen/Novartis Generation Program, which recruits preclinical AD participants with at least one copy of the APOE ε4 allele. The Generation 1 trial recruits cognitively normal APOE ε4 homozygotes, regardless of amyloid PET status. The companion Generation 2 trial recruits APOE ε4 homozygotes, as well as APOE ε4 heterozygotes who are also amyloid positive (PET scan or CSF). Therefore, APOE genotyping is a critical first step in the recruitment process. The Butler Hospital Memory & Aging Program (MAP) has created several efficient and effective recruitment pathways, establishing active pipelines for APOE genotyping and disclosure, as well as a high randomization rate in the Generation 1 & 2 trials. **Methods:** There are three primary recruitment pipelines used by the Butler Memory & Aging Program for the Generation 1 & 2 trials. All pipelines begin with public engagement. We have 3-full time outreach coordinators, a social media specialist and several part-time staff dedicated to community events. The first recruitment pipeline is through the Banner Health Genematch Program, which refers participants who have completed a cheek swab test at home to local study sites. Butler is a Genematch site, meaning that we can also distribute these APOE genotyping kits to the public and mail them to Genematch for analysis, and we tend to use this method to genotype at large community events, where participants are not known to our program. If referred to our site, these participants are disclosed through the Generation Program consent mechanism. The second pipeline is through the Butler Alzheimer's Prevention Registry (BAPR), our trial-eligible cohort database of approximately 1500 adults aged 50-85. Interested volunteers can sign up online or at our community events. BAPR has several sub-studies, one of which is a local APOE genotyping and disclosure program. At visit 1, participants undergo brief cognitive screen, mood and functional assessments, and a clinical interview to determine psychological readiness for APOE genotype disclosure. At a second visit, participants receive counseling and APOE genotype is disclosed, and participants complete follow-up assessments at 3 days, 6 weeks, and 6 months. The third pipeline is a brief cheek swab consent through the Generation 1 study that can be used to genotype qualified participants. We use this consenting process to obtain swabs at local "swab parties" for interested registrants, which are conducted on Butler campus. Importantly, these individuals have already signed up for BAPR and meet general inclusion/exclusion criteria for clinical trials. Participants are disclosed through our local registry disclosure protocol, and if they meet entry criteria for Generation 1 or 2, are given the option to move forward in the screening process. In addition, we have started using the Spartan Cube, a research-only device for rapid APOE genotyping, at local events or "swab parties". **Results:** Since the inception of the Generation Program at Butler MAP in 2016, we have conducted 337 public events, speaking to approximately 34,000 individuals. We have conducted 360 Genematch swabs at 22 community events, and received 58 Genematch referrals to our site. 246 individuals have been recruited through our local registry. Of these, 129 have been APOE genotyped through our registry APOE substudy, and 117 have been genotyped through the Generation 1 mechanism at local "swab parties". Our current enrollment numbers for Generation 1 (APOE ε4 homozygotes) and Generation 2 (APOE ε4 heterozygotes) are as follows: Generation 1 – 40 screened (33 Genematch referrals, 6 local registry referrals, 1 self-referral (23 & Me)), 8 enrolled (20% randomization rate). Generation 2 – 59 screened (19 Genematch referrals, 40 local registry referrals), 21 enrolled (36% randomization rate). **Conclusion:** A multi-faceted recruitment approach, community outreach targeting at-risk individuals, and the development of a local APOE genotyping

program have been essential for successful recruitment in the Novartis/Amgen Generation Program.

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

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

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

Background: AL002 is a human anti-TREM2 monoclonal antibody in development for the treatment of Alzheimer's Disease (AD) patients. AL002 specifically binds to and activates TREM2, a receptor that is expressed on microglia cells; heterozygous mutations in TREM2 that reduce its function were found to increase the risk of sporadic AD. Non-clinical studies have demonstrated that activating TREM2 can induce microglia proliferation and effectively suppress AD pathology in vivo to prevent cognitive decline in a mouse model of AD. No adverse effects of AL002 were observed in non-clinical safety studies to date, enabling the first-in-human study. **Objectives:** This is a Phase 1 study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of AL002 in healthy volunteers and patients with mild to moderate AD. **Methods:** The single ascending dose (SAD) part of this study is a randomized, placebo-controlled, double-blind investigation in healthy volunteers (HV). This is followed by a randomized, placebo-controlled, double-blind, multiple-dose (MD) part in patients with a diagnosis of probable AD, aged 50-85 years, with a MMSE score of 16-28, a CDR global score of 0.5, 1, or 2, and a positive amyloid-PET scan based on visual read. The primary objective of this study is to evaluate the safety of single and multiple doses of AL002. **Results:** All single-dose healthy volunteer cohorts in this Phase 1 study have been dosed and preliminary safety and PK data are available. The multiple-dose AD cohort has also been initiated. **Conclusions:** To date AL002 has been seen to be generally safe and tolerable and is being considered for investigation in a proof-of-concept Phase 2 study.

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

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

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

Background: Current outcome measures available for use in clinical trials in early stage 1-3 (FDA 2018 Guidelines) Alzheimer's disease rely on combinations of self-report and episodic cognitive testing with test batteries that are relatively inefficient, not engaging or ecologically valid. Measures of everyday function and cognition assessed unobtrusively at home using embedded sensing and computing methods generates "digital biomarkers" (DBs) that decline during the pre-dementia period. This approach generates continuous everyday measures that are ecologically valid and can improve the efficiency of trials (reducing sample size or decreasing the time of observations, Dodge et al. 2015). Although, face-valid, DBs have not been assessed for their relationship to AD neuropathology. **Objective:** To determine the association of digital biomarkers to AD neuropathology in an initially cognitively intact community-based population. **Methods:** Individuals were enrolled in longitudinal cohort studies of DBs approved by the Oregon Health & Science University's Institutional Review Board (Life Laboratory IRB #2765; ISAAC IRB #2353). Details of the sensor systems and study protocols have been published elsewhere (Kaye et al., 2018; Lyons et al., 2015). Participants included in this study were 65 years and older, living independently, of average health for age, not demented at study entry, followed until death, and had brain autopsy data available. Participants were assessed both conventionally with standardized clinical function and cognitive tests including the Uniform Data Set protocol of the National Alzheimer's Coordinating Center. From the array of DB's, four measures representing four domains of function known to change with the progression of AD were selected based on their prior demonstration of differentiating those cognitively normal verses those with mild cognitive impairment: cognitive function (number of days with computer use measured by CPU activity), mobility (daily mean walking speed (cm/sec derived from in-series passive infra-red ceiling sensors), socialization (time out of home, hrs) derived from passive infra-red room occupancy and

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

OC17: THE ALZHEIMER'S CLINICAL TRIALS CONSORTIUM SEEKS PARTNERS FOR THERAPEUTIC TRIALS.

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Background: The Alzheimer's Clinical Trials Consortium (ACTC) was funded by the National Institute on Aging (NIA), National Institutes of Health (NIH) in 2018 with the mission to provide an optimal infrastructure, utilizing centralized resources and shared expertise, to accelerate the development of effective interventions for Alzheimer's disease (AD) and related disorders. Specifically, the ACTC is tasked with developing and conducting 5-7 studies over the next 5 years, targeting therapies for use across the spectrum of AD: from prevention to late stages of disease. The ACTC Leadership team is comprised of three Principal Investigators (PIs); Drs. Aisen, Sperling and Petersen, as well as the Project Scientist from NIA, Dr. Ryan. Leadership is guided by the consortium through the Steering Committee, Executive Committee and External Advisory Board. In addition, each PI has oversight responsibility over specific Units, which conduct the day to day work of the Consortium, and the Committees, which are brought in to advise within their specialized area of clinical trial and disease expertise. **Methods:** Member Sites were selected from the top academic research institutes across the United States. Each member site agreed to utilize the single IRB (Advarra) and Master Clinical Trial Agreement, towards the goal of expediting study start-up for ACTC Projects. Member Sites receive an infrastructure award to ensure trial readiness, sufficient to cover cost for one full time research coordinator and 5% of the Member Site PI's time. In addition, each site is encouraged to identify an Associate Site PI, ensuring longevity and stability of the consortium. A majority of the ACTC Units which serve as the ACTC Coordinating Center are located at the Alzheimer's Therapeutic Research Institute (ATRI) at USC. These include Administration, Biomarker, Biostatistics, Clinical Operations, Informatics, and Medical Safety. PET and Neuropathology Units are based at Harvard University. The Clinical Outcome Instrument Unit, MRI and Recruitment Units are all led by investigators across multiple institutions (Brigham and Women's Hospital, UC Irvine, Mayo Clinic, and UC San Francisco). Committees contribute to specialized areas of expertise in study design, conduct, or disease. These include the Project Evaluation Committee (PEC), Internal Ethics, Biospecimen Allocation Resources Committee, Non-AD Dementia, Non-Pharmacological Interventions, Neuropsychiatric Symptoms, Publications, Site Metrics and Study Budget, and the Committee for Inclusion, Diversity, Education in Alzheimer's disease clinical trials (IDEA-CT). The ACTC encourages both academic and industry groups to submit proposals for consideration. Public-private partnerships are also encouraged. Applicants must agree to NIH-stipulated data-sharing requirements. Proposal review occurs 3 times per year, coordinated with the deadlines for grant submission to the NIA. Each Proposal is reviewed and scored for feasibility, appropriateness for ACTC and scientific merit, and must be approved by the ACTC Project Evaluation Committee and the Steering Committee. Once approved, a small collaborative

team is formed to develop a competitive grant application. Development and endorsement of a proposal by ACTC does not guarantee NIA funding. **Results:** Within a few weeks of funding announcement, ACTC operationalized the proposal review process and the Steering Committee approved one study for grant development, which was funded. Three projects have been approved as affiliated with ACTC, leveraging components of the infrastructure. Two other projects focused on different mechanisms across the clinical continuum of Alzheimer's disease have been approved, and one has been submitted as a grant pending review by the NIA. The infrastructure of the consortium was successfully launched within the first year, including governance, committees, processes for policy and standard operations, communication platforms, and the Biomarker Repository as well as executed Site Master Clinical Trial Agreements and Central IRB agreements at Member Sites. **Conclusion:** The ACTC offers state-of-the-art clinical trials infrastructure, extensive expertise on trial design and execution, and a strong network of expert clinical trial sites. ACTC is continuing to request Phase Ib-Phase III proposals from the field for collaboration and is particularly interested in evaluating novel mechanisms for Alzheimer's disease and related disorders. Interested investigators may find more information at www.actcinfo.org. The performance of the ACTC will be assessed by metrics on project launch timelines, recruitment and diversity goals, development and validation of new trial methodologies, monitoring our sharing of data and methods, and training of new investigators.

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

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Background: There are no effective therapeutic options to delay the progression of Alzheimer's disease. The benefits of exercise on brain health in older adults at risk for dementia have become an important potential therapeutic intervention. There is an urgent need to evaluate the effectiveness of exercise in a large diverse population using accessible, cost-effective, and sustainable programs that can be readily implemented in community settings. The EXERT trial (NCT02814526) is a Phase 3, multicenter, randomized single-blind study to examine the effects of aerobic exercise on cognition and other measures of brain function in 300 adults with amnestic mild cognitive impairment (MCI). Here we describe the infrastructure and support system that was developed for delivery of the EXERT intervention programs in partnership with the YMCA. **Objective:** To test a model for exercise intervention delivery that could provide regular support for adults with MCI and a sustainable community-based program if the trial results are positive. **Methods:** The Alzheimer's Disease Cooperative Study (ADCS) and Wake Forest School of Medicine (WFSM) partnered with the YMCA of the USA (Y-USA) to assist with intervention delivery for EXERT at 14 sites nationwide. A total of 300 sedentary older adults (65-89 years old) will be randomized to one of two interventions: 4 days/week of either moderate-high intensity aerobic exercise (AX) or low intensity stretching, balance and range of motion (SBR) activities, which serves as the control. Each participating ADCS site has partnered with a YMCA regional association that includes several local branches. The ADCS sites are responsible for recruitment, outcomes assessments, medical safety and regulatory compliance, and the YMCAs for intervention implementation. Participants in both groups complete their exercise routines at participating YMCAs under the supervision of a study-certified trainer for the first 12 months, and independently in the final 6 months. Protocols were developed to provide education to trainers about MCI and personalized exercise prescriptions that can be readily implemented. Ongoing support is provided to trainers through regular phone conferences that offer opportunities for sharing experiences with participants to address challenges as they arise. During trainer-supervised sessions, objective measures of exercise duration and intensity are collected. Intervention implementation is overseen by an Intervention Oversight Committee (IOC) consisting of representatives from the ADCS, WFSM, and the Y-USA. Intervention fidelity is monitored through (a) web-based reports of participant adherence generated by the study data management system, (b) YMCA trainer reports during monthly conference calls, and (c) intervention fidelity site visits conducted by the IOC. EXERT is projected to complete enrollment in late Fall 2019. **Results:** To date, over 8300 supervised sessions have been completed at the YMCA, which reflects attendance rates of 79% across both intervention groups. The collaboration between the ADCs and the YMCA regional associations has generated effective procedures and systems to facilitate participant flow from recruitment to outcomes assessments and intervention delivery. YMCA trainer testimonials during monthly conference calls reflect their unwavering commitment to the trial and its participants, increased knowledge about and appreciation of cognitive impairment and its impact on daily function, as well as recognition of their role in patient care and quality of life. The results of intervention fidelity site visits confirm that YMCA trainers rigorously adhere to the protocol and are successful in creating an environment that study participants value. The partnership with the YMCA national office (Y-USA) has been instrumental in engaging appropriate YMCAs at participating sites, facilitating training and certification of YMCA staff, and problem-solving issues as they arise. Promoting high adherence to the EXERT interventions relies on a strong infrastructure with multiple resources to support participants and YMCA staff who provide a safe and motivating environment. **Conclusion:** Our success to date in achieving high rates of attendance at supervised exercise sessions at the YMCA and compliance to the EXERT interventions by once-sedentary participants with MCI provides growing support for a sustainable and cost-effective community-based model of intervention delivery. Such a model has the potential to be readily developed as a nationwide prevention strategy if the trial results are positive. **Funding:** NIA U19 AG010483

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

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

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

Background: It has been recognized that a combination of abnormal neurodegeneration biomarkers with a positive amyloid status provide a more powerful prediction of future cognitive decline than an amyloid marker measurement alone (Jack CR et al, Alzheimer's and Dementia, 2018). In particular, more rapid conversion to Alzheimer's disease (AD) dementia for an amyloid-positive prodromal population with glucose hypometabolism measured by 18F-fluorodeoxyglucose (FDG) PET has been reported (Iaccarino L et al, Journal of Alzheimer's Disease, 2017). However, the implementation of FDG-PET in clinical trials in AD has been operationally challenging as AD-specific PET scans to monitor Aβ plaques and pathologic fibrillar tau may be required, which increases patient burden and radiation exposure. In this respect, regional perfusion estimates derived from "early frames" imaging sessions supplementing conventional amyloid scans can serve

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

OC21: FCSRT INCLUSION CRITERIA SUPPORT RECRUITMENT OF A POPULATION WITH EARLY ALZHEIMER'S DISEASE LIKELY TO PROGRESS OVER 24 MONTHS: RESULTS FROM THE CREAD TRIAL.

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Background: When testing a potential disease-modifying drug for Alzheimer's disease (AD) that is expected to slow progression, the ability to show a treatment difference depends in part on predictable decline in the placebo group. Despite requiring an episodic memory deficit and amyloid positivity, approximately 30% of patients in the SCarlet RoAD trial (NCT01224106)—one of the first trials in prodromal AD (pAD)—did not show a decline in the Clinical Dementia Rating–Sum of Boxes (CDR-SB) score over 24 months, with a reported overall rate of decline in the placebo arm of 1.6 points [1]. The Free and Cued Selective Reminding Test (FCSRT) identifies the type of memory loss characteristic of AD (i.e., poor free recall not benefited by cuing). Based on learnings from SCarlet RoAD (stopped early following a futility analysis), we implemented FCSRT inclusion criteria for the Phase III Crenezumab in Alzheimer's Disease (CREAD/NCT02670083) trials to enrich for participants with early AD likely to progress in the 24-month trial. **Objective:** To describe the screening performance using FCSRT inclusion criteria and CDR-SB progression rates for trial participants in CREAD. **Methods:** Of 3,575 participants screened, 813 with early AD (n = 346 pAD and n = 467 mild AD [mAD]; National Institute on Aging and Alzheimer's Association criteria) were randomized in the CREAD trial from March 2016 to November 2017. Key inclusion criteria included a Clinical Dementia Rating global score of 0.5 or 1, a Mini-Mental State Exam score of 22–30, a FCSRT immediate free recall score of ≤ 27 (sum of 3 immediate recall trials), a Cuing Index (CI) of ≤ 0.67, and amyloid positivity by cerebrospinal fluid analysis or amyloid positron emission tomography scan. Cutoff values for FCSRT CI were derived from modeling the SCarlet RoAD data; a CI cutoff value of 0.67 provided adequate balance between sensitivity (84.2%) and specificity (34.8%) for distinguishing participants who progressed in CDR-SB from those who did not [2]. CREAD was powered to detect a 30% difference in rate of decline in CDR-SB between the overall

placebo and treatment arms based on an estimated decline of 2.6 points over 24 months in the placebo arm. Mixed model for repeated measures analyses were used to assess the change in CDR-SB over time in the trial population as a whole and in the pAD and mAD subgroups separately. Nonprogression in CDR-SB was defined as a change in CDR-SB (last assessment – baseline) of ≤ 0. **Results:** The CREAD trial was stopped early based on a preplanned interim analysis that indicated that the study was unlikely to meet its primary endpoint of change in CDR-SB from baseline to Week 105; no safety signals were observed, and the overall safety profile was similar to that observed in previous studies [3]. Baseline characteristics have been previously presented [4]. Approximately 47% of FCSRT administrations resulted in a screen failure. Among participants who met FCSRT eligibility and were ultimately randomized, the mean (SD) baseline CDR-SB in the placebo arm was 3.8 (1.6) for the whole early AD population, 3.1 (1.3) for pAD, and 4.3 (1.6) for mAD. The mean (SE) decline in CDR-SB in the placebo arm at 24 months was 3.6 (0.3) points for the entire early AD study population and 2.8 (0.4) points in the pAD and 4.2 (0.4) points in the mAD subsets (preliminary data; database not yet locked). Among placebo participants with at least one postbaseline CDR assessment (n = 393), 28% of patients with pAD and 20% of patients with mAD had no progression in CDR-SB over a median time of 17.5 months. Results were similar when both treatment arms were combined. This non-progression rate is compared with 30% of patients with pAD in SCarlet RoAD treated for 24 months. **Conclusion:** The CREAD trial was stopped early for low likelihood of meeting the primary endpoint. Adequate progression in CDR-SB, not only in the overall population, but also in both the pAD and mAD subpopulations, allowed for clear interpretation of the interim analysis results. While approximately half of the participants screened for CREAD failed early in the screening process due to not meeting FCSRT inclusion criteria, these FSCRT inclusion criteria may have helped to identify a population of patients with early AD with higher rates of progression. Further analyses on the impact of the chosen FCSRT inclusion criteria are ongoing and will be presented. **Références:** 1. Ostrowitzki S, et al. Alzheimers Res Ther 2017;9:95; 2. Smith J, et al. Presented at AAIC 2016, Toronto, Canada; 3. F. Hoffmann-La Roche Ltd. Roche to discontinue Phase III CREAD 1 and 2 clinical studies of crenezumab in early Alzheimer's disease (AD)—other company programmes in AD continue. Accessed online at: http://bit.ly/2TiSUX0 on March 18, 2019; 4. Lin H, et al. Presented at AAIC 2017, London, UK.

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

Background: Prodromal Alzheimer's disease (AD) clinical trials enroll patients with Mild Cognitive Impairment (MCI) who demonstrate biomarker changes associated with AD. Cerebrospinal fluid (CSF) levels of amyloid beta (AB), phosphorylated tau (p-tau), and total tau (t-tau) can be used as such biomarkers, as well as outcome measures for these trials. Relatively few data are available, however, to describe longitudinal within-subject changes in these proteins over time. This makes it difficult for investigators to design proof-of-concept clinical trials of putative disease-slowing therapies, including especially trials for which the primary outcome is t-tau or p-tau. **Objectives:** This study aimed to model proof-of-concept clinical trials with either t-tau or p-tau as the primary outcome. Specifically, we sought to estimate the sample sizes required to obtain 80% power for plausible treatment effects using empirical estimates of outcome variability and within-subject correlation. Noting that homogeneity of responses within eligible subpopulations reduces variability and increases power, we also quantified longitudinal changes in t-tau and p-tau and the variability in within-subject changes for participants satisfying different potential trial eligibility criteria. **Methods:** We examined data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) using subjects who had a baseline diagnosis of MCI and at least two measures of CSF tau, one of which must have been collected during the baseline visit. We modeled two-year, two-arm phase II trials and investigated the sample sizes required to estimate various treatment effects (50%, 75%, and 100% slowing of progression) with 80% power for different CSF biomarker eligibility criteria. Biomarker eligibility criteria were based on the cutoffs for CSF AB, t-tau, p-tau, the ratio of t-tau/AB and the ratio of p-tau/AB as defined in (1). We used empirical estimates of the within-subject correlation and the variance of t-tau and p-tau at two years. Sample sizes were calculated using an analysis of covariance (ANCOVA) model. To quantify longitudinal changes, we estimated the subject- specific slopes of t-tau and p-tau using a linear mixed effects model with a random intercept and random slope. We also compared the variability in the random slopes and intercepts associated in each of these subpopulations to investigate how these differed when different eligibility criteria were applied. **Results:** We observed increases in t-tau over time for every subpopulation (range: 4.87-6.07 pg/mL change for two years). The smallest sample size required to obtain 80% power to detect a 50% treatment effect was in a trial using low AB as an enrollment criterion. Such a trial required 4,734 subjects. The according sample sizes required to detect 75% and 100% decreases were n = 2,104 and n = 1,184, respectively. For subjects in this subpopulation, we estimated that, on average, t-tau increased by approximately 5.58 pg/mL in two years (95% confidence interval (CI): 2.51, 8.65) with a within-subject correlation of 0.84 (95% confidence bound (CB): 0.79, 0.88). The standard errors associated with the random effects were 54.31 and 0.54 for the random intercept and random slope, respectively. We also observed increases in p-tau for every subpopulation (range: 6.97 – 9.96 pg/mL change per year).The smallest sample size required to obtain 80% power to detect a 50% treatment effect was in a trial using high t-tau as an enrollment criterion. Such a trial required 1,284 subjects. The according sample sizes required to detect 75% and 100% decreases were n = 572 and n = 322, respectively. For subjects in this subpopulation, we estimated that on average, p-tau increased by approximately 9.96 pg/mL (95% CI: 6.54, 13.39) in two years, with a within-subject correlation of 0.43 (95% CB: 0.30, 0.57). The standard errors associated with the random effects were 19.03 and 0.52 for the random intercept and random slope, respectively. **Conclusion:** These results indicate that proof of concept trials with CSF tau as an outcome may be challenging, requiring large sample sizes to demonstrate even dramatic treatment effects. Nevertheless, in these models p-tau outperformed t-tau as an outcome, requiring fewer participants

due to greater change over time and reduced variance. The empirical estimates provided in this study may aid the design of future trials. **Reference:** 1. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Annals of neurology. 2009;65(4):403-13.

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

Background: MLC901 has its origins from Traditional Chinese Medication (TCM) and has been shown to promote cell proliferation, neurite outgrowth and the development of dense axonal and dendritic networks (1). MLC601 (the precursor of MLC901 with similar properties) is a possible modulator of amyloid precursor protein (APP). In human neuroblastoma cell line SH-SY5Y culture, it was shown to increase the level of sAPPα, which is a non-pathogenic soluble fragment of APP produced by physiological cleavage of APP by α and γ secretase (2). An in-vitro study (3) showed that MLC901 significantly reduced tau phosphorylation at various epitopes recognized by AT8, AT270 and PHF-13 antibodies. It also showed increased phosphorylation of glycogen synthase kinase 3β along with concurrent decrease in activation of cyclin dependent kinase (5). These pharmacological properties make MLC901 a possible disease modifying treatment for Alzheimer's Disease (AD). **Objectives:** The primary objective was to evaluate the safety of MLC901 as an add-on treatment for 6 months in patients with mild-to-moderate probable AD on standard treatment with acetylcholinesterase inhibitors (AChEIs) or memantine. The secondary objectives were to investigate 1) effect of MLC901 as add on therapy to standard treatments for 6 months on cognitive function in patients with mild to moderate AD. (2) long term safety of MLC901 as add-on treatment to standard treatments for up to 1 year in an open extension study. (3) long term effect of MLC901 on disease progression as an add-on treatment to standard treatments for up to 1 year in an open extension study. **Methods:** This is a one-year trial in mild to moderate probable AD where the first 6-months will be a randomized, double-blind, placebo-controlled trial during which MLC901 will be given as an add-on therapy to standard AD treatment (AChEIs or memantine). This is followed by 6-month extension study, where all subjects will be treated with open-label MLC901 in addition to standard treatment. Safety is measured by adverse events, vital signs, electrocardiogram (ECG), laboratory tests, physical and neurological examinations. For efficacy outcomes, cognitive function, behavior and activities of daily living are assessed by tests including the Alzheimer's Disease Assessment Scale- cognitive subscale (ADAS-Cog), Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL23), Neuropsychiatric Inventory (NPI), and Mini Mental State Examination (MMSE). The trial is registered at Clinicaltrials.gov- NCT03038035 and the methods published recently (4). **Results:** ATHENE recruited a total of 125 patients who are currently scheduled to complete follow up by end November 2019. The mean age of the study population was 78.6 ±6.7 years with 87 (70%) women and 111(88%) of Chinese ethnicity. The majority of patients (93%) were on AChEI as standard treatment (79% donepezil, 22% rivastigmine capsules and 12% rivastigmine patches) whilst 7% were on memantine. Baseline characteristics in the treatment arms were well balanced except in overall education and diastolic blood pressure, with more obtaining tertiary level education in arm B than arm A (22% compared to 5%; p=0.03); additionally, arm A had more illiterate patients than arm B (34% compared to 24%). The diastolic blood pressure was 71mmHg in arm B vs 67mmHg in arm A (P=0.01) but this was considered clinically non-significant. The most common comorbidity was hypertension (75%) followed by hyperlipidemia (71%) diabetes mellitus (37%) and stroke/TIA (14.9%). There were no significant differences between treatment groups in mean baseline ADAS-Cog (31±12 and 29±10), ADCS-ADL23 (47±17 and 50±16), NPI (11.1±14 and 11.0±12) and MMSE (15±4 and 16±4) in arms A and B respectively. **Conclusions:** ATHENE is investigating the safety and efficacy of MLC901 in mild to moderate Alzheimer's disease patients who are stable on standard available treatment. The trial is being performed in compliance with international guidelines and using Western clinical trial standards and the results will be available by early 2020. **References:** 1. Heurteaux C et al. NeuroAiD: properties for neuroprotection and neurorepair. Cerebrovasc Dis 2013;35 Suppl 1:1-7; 2. Lim YA, Murray LA, Lai MK, Chen C. NeuroAiD® (MLC601) and amyloid precursor protein processing. Cerebrovasc Dis. 2013;35 Suppl 1:30-7; 3. Lee WT, Hsian CCL, Lim YA, The effects of MLC901 on tau phosphorylation. Neuroreport. 2017; 28:1043-8; 4. Chen CLH, Sharma PR, Tan BY, Low C, Venketasubramanian N. The Alzheimer's disease THErapy with NEuroaid (ATHENE) study protocol: Assessing the safety and efficacy of Neuroaid II (MLC901) in patients with mild-to-moderate Alzheimer's disease stable on cholinesterase inhibitors or memantine-A randomized, double-blind, placebo-controlled trial. Alzheimers Dement (N Y). 2019 Jan 23; 5:38-45.

OC24: PHASE 1 STUDY OF NDX-1017: SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS IN HEALTHY VOLUNTEERS AND DEMENTIA PATIENTS. Hans MOEBIUS (1), Xue HUA (1), Kevin CHURCH (1), William WALKER (1), Philippe L'HOSTIS (2), Philippe DANJOU (3), Geoffrey VIARDOT (2), Leen KAWAS (1) *((1) Athira Pharma, Inc., United States, (2) Core Lab, Drug Evaluation and Pharmacology Research, Biotrial, France, (3) Phase 1 Unit, Drug Evaluation and Pharmacology Research, Biotrial, United States)*

Background: Alzheimer's disease (AD), the most common form of dementia, is a complex systemic failure involving multiple self-reinforcing pathologies, leading to neurodegeneration and cellular dysfunction, intensified by misregulated immune responses (1,2). Amyloid plaque build-up occurs long before the onset of cognitive deficits, while synaptic loss, neuro-fibrillary tau tangles, and neuron loss accompany the cognitive decline (3). Synaptic loss is the most reliable correlate of cognitive decline in AD (4). Neurotrophic factors represent a new therapeutic target to treat AD by inducing regenerative mechanisms and restoring brain homeostasis. Drugs that stimulate neurotrophic systems, like hepatocyte

growth factor (HGF) and its MET receptor, have the potential to treat all stages of AD, by directly targeting neurodegeneration, improving cognition, and addressing multiple aspects of the AD pathology including inflammation, cerebral blood flow, and glucose metabolism (5). AD patients exhibit reduced neuronal MET expression, particularly in the cortex and hippocampus, which may contribute to synaptic loss, neurodegeneration, and functional decline (6). Athira Pharma's lead compound, NDX-1017, is a small-molecule drug that penetrates the blood-brain barrier and aims to augment HGF/MET, a critical neurotrophic system underpowered in AD. NDX-1017 has the potential to relieve dementia symptoms and permanently alter the course of disease progression. In nonclinical studies, NDX-1017 has been shown to activate the HGF/MET system, induce pro-survival and regenerative mechanisms, stimulate spinogenesis and synaptogenesis, and reverse cognitive deficits in rat models of dementia. Treatment has also been shown to shift patterns of quantitative electroencephalogram (qEEG) activity in the APP/PS1 AD mouse model, with an immediate and sustained increase in gamma power. Doses that stimulate qEEG changes overlapped with the efficacious range in animal models of dementia, suggesting the utility of EEG as translatable biomarkers to guide dose optimization in clinical trials. **Objectives:** Phase 1 (NCT03298672) was a randomized, placebo-controlled, double-blind trial of NDX-1017. It involved single- and multiple-ascending doses in healthy volunteers, and multiple doses in AD patients. The study was designed to facilitate the translation of the safety, tolerability, and pharmacokinetics (PK) of NDX-1017 from healthy volunteers to the intended treatment population. qEEG and event-related potential (ERP) techniques were used to indicate brain penetration and explore pharmacodynamics, serving as translatable biomarkers to guide dose optimization. **Methods:** A total of 80 subjects received once-daily (o.d.) subcutaneous (s.c.) administration of NDX-1017 or matching placebo (n=8/cohort; 3:1 randomization). Subjects included 48 healthy young males (33.4 ± 6.3 years; 2, 6, 20, 40, 60, or 90 mg, s.c., o.d.), 24 healthy elderly (63.8 ± 3.9 years; 12 males [M]/12 females [F]; 20, 40, or 60 mg, s.c., o.d., 9 days), and eight AD patients (68.8 ± 7.8 years; 5M/3F; baseline mini-mental state examination [MMSE] 18 ± 7.5; 40 mg, s.c., o.d., 9 days). Safety and PK were assessed throughout the study. In single-dose studies, qEEG was conducted at pre-dose baseline and 1-hour post-dose. In multiple-dose studies, qEEG and ERP were conducted at pre-dose, 1 hour and 3 hours post-dose, on Days 1, 4, and 8. **Results:** NDX-1017 and placebo were safe and well-tolerated in healthy young, healthy elderly, and AD patients, at all doses evaluated. The PK were dose proportional, with no accumulation. In the single-dose studies, the main effect of qEEG was a dose-related increase in gamma induction, observed at doses between 20 and 90 mg; placebo and low doses (2 and 6 mg) had no effect on EEG. In the multiple-dose studies in healthy elderly, an immediate effect in gamma power induction was observed, confirming the findings in the single-dose studies. Additionally, a sustained effect on gamma power was observed, lasting beyond five times the half-life (half-life = 1.5 hours). In AD patients, gamma power and P300 demonstrated a positive shift after multiple doses of NDX-1017, supportive of target-related pharmacodynamics relevant for the treatment of AD. **Conclusion:** This study established preliminary safety, tolerability, and PK of NDX-1017. The positive qEEG response in humans replicated the EEG signature identified in nonclinical studies, suggesting brain penetration and target engagement, and informs dosing for future clinical trials. The normalization of qEEG components and P300 in AD patients suggests a treatment-dependent promotion of synaptic activities, and further demonstrates the therapeutic potential of NDX-1017. **References:** 1. Golde, T.E., et al. (2018). Alzheimer's disease: The right drug, the right time. Science 362(6420), 1250-1251; 2. Zhang, B., et al. (2013). Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. Cell. 153(3): 707-2; 3. Serrano-Pozo, A., et al. (2011). Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med. 1(1): a006189; 4. Koffie, R.M., et al. (2011). Alzheimer's disease: synapses gone cold. Molecular Neurodegeneration 6: 63; 5. Funakoshi, H., and Nakamura, T. (2011). Hepatocyte Growth Factor (HGF): Neurotrophic functions and therapeutic implications for neuronal injury/diseases. Current Signal Transduction Therapy 6, 156–167.; 6. Hamasaki, H., et al. (2014). Down-regulation of MET in hippocampal neurons of Alzheimer's disease brains. Neuropathology 34, 284–290.

OC25: REGULATION OF GLIAL CELL ACTIVATION AND NEURODEGENERATION BY ANTI-SEMAPHORIN 4D ANTIBODY PEPINEMAB (VX15/2503), A POTENTIAL TREATMENT FOR ALZHEIMER'S AND HUNTINGTON'S DISEASE.

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Background: Chronic inflammation is believed to play an important role in neuronal degeneration. Semaphorin 4D (SEMA4D) and its Plexin receptors (PLXNB1, PLXNB2) are expressed on brain neural, endothelial, and inflammatory cells. SEMA4D signaling through its cognate receptors triggers activation of inflammatory glial cells, inhibits migration and differentiation of glial progenitor cells that can replenish glia and repair damage to myelin, and disrupts endothelial tight junctions that are required for the integrity of the BBB. Antibody neutralization of SEMA4D ameliorates neurodegenerative processes in several preclinical models, including transgenic mouse models of Huntington's Disease (HD) and Alzheimer's Disease (AD). These data provided the rationale for initiating SIGNAL, a randomized (1:1), double-blind, placebo-controlled phase 2 study of treatment with anti-SEMA4D antibody, pepinemab (VX15/2503), in subjects with HD. **Objectives:** To evaluate safety and feasibility of treatment with pepinemab, a semaphorin 4D blocking antibody, and to incorporate FDG-PET as an early biomarker of brain metabolic activity and restoration of normal astrocytic activity. **Methods:** Mechanistic studies include histopathological investigation of SEMA4D expression and localization in brain cell types, as well as effects of SEMA4D on astrocyte function. Preclinical studies suggest that SEMA4D plays an important role in inflammatory activation of astrocytes, in which state they downregulate glucose transporter and glutamate receptor, reducing their normal function in brain energy metabolism and synaptic activity. We hypothesize that blocking SEMA4D-induced F-actin depolymerization may reduce inflammatory transformation, increase glucose uptake, and indirectly restore effects on synaptic activity and neural networks. The SIGNAL clinical trial has an adaptive design in which the results of 36 subjects randomized in Cohort A informed group size and treatment duration in Cohort B. Because of the important role astrocytes play in glucose transport and metabolism together with supporting data from several prior studies demonstrating

that loss of FDG-PET signal correlates with cognitive decline in AD, FDG-PET imaging was included as a key endpoint related to the potential mechanism of action. Additional study endpoints include volumetric MRI, cognition (HD-CAB), quantitative motor assessments, UHDRS and patient-reported outcomes. **Results:** Preliminary histopathological observations demonstrate marked changes in expression, distribution, and colocalization of SEMA4D with neuronal and glial cells in brains of diseased mice. Rat astrocyte cultures express high levels of PlexinB1 receptor, and binding of SEMA4D triggers significant depolymerization of F-actin, reducing astrocyte function. These effects on astroctyes are reversed with addition of blocking antibody. Antibody blockade of SEMA4D in preclinical studies in the murine CVN AD model also show beneficial effects on synaptic activity and improvements in behavioral deficits. Cohort A (n=36) of the SIGNAL clinical trial is complete and Cohort B (n=265) is fully enrolled. No concerning safety signals were identified following up to 12 monthly IV administrations in Cohort A or following 12 to 35 months of treatment in Cohort B subjects. Pepinemab treatment of Cohort A subjects trended toward stabilization of disease-related reduction in MRI volume and was favored over placebo in 24/31 ROI. FDG-PET also favored pepinemab in all ROI. The mean FDG-PET Index +/-standard error for pepinemab treatment (n=11) across all brain ROI examined was 0.46 +/- 0.25 (95% CI, -0.10 to 1.02); for placebo (n=8) it was -0.32 +/- 0.16 (95% CI, -0.69 to 0.05). The estimated difference between the means was 0.78 +/- 0.31 (95% CI, 0.11 to 1.40; p=0.025). Analysis of cohort A guided the design of Cohort B, which has enrolled 265 HD subjects for 17 to 35 months of treatment. Enrollment in cohort B was completed Dec 31, 2018 and clinical evaluation will continue through June 2020. **Conclusions:** Initial results have shown pepinemab to be well tolerated in subjects with neurodegenerative disease. In addition, the demonstrated increase in FDG-PET signal in Cohort A together with preclinical data demonstrating beneficial effects on synaptic activity and improvement in behavioral deficits in a murine AD model suggest that pepinemab warrants clinical investigation in AD as well. A randomized, placebo-controlled study of monthly infusions of pepinemab enrolling AD subjects is planned.

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

Background: A major challenge in treating brain diseases is presented by the blood-brain barrier (BBB) that constitutes an efficient barrier not only for toxins but also a wide range of therapeutic agents (1,2). In overcoming this impediment, ultrasound in combination with intravenously injected microbubbles (used as contrast agents in a clinical setting) has emerged as a powerful technology that allows for the selective brain uptake of therapeutic agents and blood-borne factors by transiently opening the blood-brain barrier (1). We have shown previously, that ultrasound in combination with microbubbles, but in the absence of a therapeutic agent, can clear protein aggregates that constitute the hallmark lesions of Alzheimer's disease, amyloid-beta (Abeta) in APP23 mice and Tau in pR5 mice (3,4,5). We have also shown that therapeutic ultrasound can be used as a general drug delivery tool, as demonstrated by a 10-fold increased uptake of a single chain antibody variable fragment (scFv) targeting the 2N isoform of Tau (4). We have further obtained safety and efficacy data in both mice and sheep (6) allowing us to move towards a phase 1 clinical trial using a custom-made therapeutic ultrasound probe. Of note, a recent trial proved safety of ultrasound-mediated BBB opening in five patients with early to moderate AD (7), and another trial in patients with glioblastomas revealed that even implanted transducers were well tolerated by the patients, without inducing neurotoxicity (8). **Objectives:** (i) To prepare a phase 1 clinical trial using ultrasound in combination with microbubbles in a small cohort of early-stage AD patients (MMSE >25). (ii) To evaluate the potential of ultrasound to achieve improved outcomes of the anti-Abeta antibody Aducanumab in APP23 mice. **Methods:** (i) To resolve which ultrasound parameters result in safe and efficacious opening of the BBB, we tested a matrix of ultrasound parameters (frequency, acoustic pressure, pulse length, pulse repetition frequency and sonication duration) in mice, using a single element probe. We further conducted sonications in sheep using a subset of these parameters, factoring in the attenuation of the sheep skull. We optimized the sonication work-flow in sheep. (ii) We have previously shown that ultrasound on its own, after 5-8 weekly treatment sessions, clears Abeta effectively and restores memory functions (3). To determine whether ultrasound would also facilitate the uptake and efficacy of the anti-Abeta antibody Aducanumab, we treated APP23 mice between 13 and 22 months of age monthly and compared the effects of Aducanumab with ultrasound and with combined treatments. **Results:** (i) We established a safe range of ultrasound parameters in mice and sheep. We successfully validated our custom-made probe demonstrating safe and efficacious BBB opening in sheep and establishing a treatment workflow in sheep, assisted by pre-treatment planning. (ii) Ultrasound-mediated BBB opening significantly increases Aducanumab uptake by the brain (using fluorescently labeled Aducanumab). We further found significant reductions in amyloid pathology in the combination treatment compared to either delivering Aducanumab on its own or using ultrasound on its own. **Conclusion:** Our preclinical data demonstrate the potential of microbubble-assisted ultrasound treatments as a new treatment modality for AD and other brain diseases. Ultrasound presents a cost-effective strategy in the context of using therapeutic antibodies to treat diseases of the brain. **References:** (1) Leinenga G et al. (2016) Ultrasound treatments of neurological diseases - current status and emerging applications, Nature Reviews Neurol 12:161-174; (2) Götz J et al. (2018) Animal models for Alzheimer's disease, Nature Reviews Neurosci, 19: 583-598; (3) Leinenga G, Götz J (2015) Scanning ultrasound efficiently removes amyloid-beta and restores memory in an Alzheimer's disease mouse model, Science Transl Med 11: 276ra33; (4) Nisbet R et al. (2017) Combined effects of scanning ultrasound and a tau-specific single chain antibody in a tau transgenic mouse model, Brain 140(5): 161-74; (5) Pandit R, Leinenga G & Götz J (2019) Repeated ultrasound treatment improves motor function and clears neuronal tau by autophagy, Theranostics, 9(13): 3754-3767; (6) Pelekanos M, Leinenga G et al. (2018) Establishing sheep as an experimental species to validate ultrasound-mediated blood-brain barrier opening for potential therapeutic interventions, Theranostics 8: 2583-2602; (7) Lipsman N et al. (2018). Blood-brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. Nat Commun 9, 2336; (8) Idbaih A et al. (2019). Safety and Feasibility of Repeated and Transient Blood-Brain Barrier Disruption by Pulsed Ultrasound in Patients with Recurrent Glioblastoma. Clin Cancer Res., in press

OC27: BASELINE CLINICAL AND BIOMARKER CHARACTERISTICS FROM A PHASE 2 TRIAL OF RO7105705 IN PRODROMAL-TO-MILD ALZHEIMER'S DISEASE (TAURIEL). Edmond TENG, Karen PICKTHORN, Paul MANSER, Kristin WILDSMITH, Sandra SANABRIA-BOHORQUEZ, Michael KEELEY *(Genentech, United States)*

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

OC28: COR388, A NOVEL GINGIPAIN INHIBITOR, DECREASES FRAGMENTATION OF APOE IN ALZHEIMER'S DISEASE CENTRAL NERVOUS SYSTEM. Michael DETKE (1), Debashish RAHA (1), Florian ERMINI (1), Casey LYNCH (1), Leslie HOLSINGER (1), Shirin ARASTU-KAPUR (1), Dave HENNINGS (1), Ursula HADITSCH (1), Sean BROCE (1), Theresa ROTH (1), Mai NGUYEN (1), Mark RYDER (2), Ira GOODMAN (3), Stephen THEIN (4), Stephen DOMINY *(1) ((1) Cortexyme, United States, (2) UCSF, United States, (3) Bioclinica, United States, (4) Pacific Research Network, United States)*

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

induced APOE loss of function and generation of pathological fragments.

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

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

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

Background: We previously demonstrated that P8, a water-soluble peptide from PS-1 NH2-terminal domain can substantially and specifically inhibit total Aß production in the brains of APP transgenic mice. These peptide-induced reductions of total Aß (and of Aß40 and 42) do not target the secretases and so do not modify or inhibit either ß- or g-secretase activities. The mechanism by which P8 reduces Aß includes its specific binding to the APP ectodomain resulting in an inhibition of APP processing to Aß. Subsequent studies have shown that P8 can be delivered to the rat brain by subcutaneous (SC) administration. **Objectives:** The primary objectives of this study were to evaluate the toxicity and toxicokinetic (TK) profiles of P8 in cynomolgus monkeys and in Sprague-Dawley rats when administered by SC administration once daily for 14 consecutive days. 2-Week Repeat-Dose Study of P8 in Cynomolgus Monkey. **Methods:** Animals received 14 daily doses at 0, 30, 100, or 300 mg/kg. Doses were chosen to provide exposures that were significant multiples of active levels seen in APP transgenic (Tg) mice. In-life parameters included clinical observations, body weights, blood pressure, electrocardiography, and clinical pathology (urinalysis, hematology, coagulation, and serum chemistry). Blood samples and CSF were collected at specified timepoints for TK. At terminal necropsy, gross observations, and organ weights were recorded. Tissues were collected, sectioned, stained with hematoxylin and eosin, and examined microscopically. **Results and Conclusions:** P8 was well tolerated by Cynomolgus monkeys at all doses, including 300 mg/kg/day. No P8-related mortalities occurred. Histologically, P8-treated animals had minimal subcutaneous fibroplasia, muscle cell degeneration/regeneration and mononuclear infiltrates at the injection site. Reductions in red cell parameters (RBC, hemoglobin and hematocrit) were noted across all treatment groups on Day 15, which could be secondary to the scheduled blood collections. Evidence of plasma systemic exposure was observed in all treated monkeys. The mean plasma Tmax values were at 0.5 hours post dose administration for all doses. The Tmax values appeared to independent of dose and day. The mean plasma exposure (Cmax and AUClast values) increased in a dose dependent manner. The mean plasma Cmax values increased in a dose proportional manner on Day 1 and Day 14. The mean plasma AUClast values increased in a dose proportional manner on Day 1 and in a greater than dose proportional manner on Day 14. The mean half-life values ranged from 0.55 to 2.1 hours and appeared to increase with dose. Day 1 to Day 14 values were comparable, suggesting no accumulation of P8 upon multiple dosing. None of the findings were considered adverse. 2-Week Repeat-Dose Non-GLP Study of P8 in Sprague-Dawley (SD) Rats. **Methods:** To evaluate the toxicity and TK profile of P8, SD rats were dosed once daily for 14 consecutive days via SC injection at 0, 30, 100, or 300 mg/kg. Doses were chosen to provide exposures that were significant multiples of active levels seen in APP Tg mice. In-life parameters included clinical observations, body weights, food consumption, and clinical pathology (hematology, coagulation, and serum chemistry). Blood samples and CSF were collected at specified time-points for TK. At terminal necropsy, gross observations and organ weights were recorded. Tissues were collected, sectioned, stained with hematoxylin and eosin, and examined microscopically. **Results and Conclusions:** P8 was well tolerated by rats, including at 300 mg/kg/day. No P8-related mortalities occurred and no changes attributed to administration of test article were apparent upon assessment of clinical observations, body weights, food consumption, hematology, coagulation, serum chemistry, gross pathology, or organ weights data. Microscopically, slightly increased incidences of minimal subcutaneous fibroplasia in the injection site were observed at ^{3}100 mg/kg. Evidence of plasma

systemic exposure was observed in all treated rats. The mean plasma Tmax values were generally at 0.5 hours post dose administration. The Tmax values appeared to be independent of dose and day. The mean plasma exposure (Cmax and AUClast) increased in a dose dependent manner. On Day 1, the mean plasma Cmax values increased in a less than dose proportional manner for female rats and in a dose proportional manner for male rats. On Day 14, the mean plasma Cmax values increased in a dose proportional manner for female rats and in a greater than dose proportional manner for male rats. On Day 1, the mean plasma AUClast values increased in a dose proportional manner for female rats and in a greater than dose proportional manner for male rats. On Day 14, the mean plasma AUClast values increased in a greater than dose proportional manner for both female rats and male rats. The mean half-life ranged from 0.28 to 0.56 hours and increased with dose. The mean plasma exposure (Cmax and AUClast) was higher in females than males (less than 2-fold). Day 1 to Day 14 values were comparable, suggesting no accumulation of P8 upon multiple dosing. None of the findings were considered adverse.

OC31: AN EXPLORATORY EXAMINATION OF NEUROTOOLKIT BIOMARKERS ACROSS AD STAGES.

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

Background: Alzheimer's disease (AD) has an extended preclinical phase when proteinopathies develop involving aggregation of β-amyloid (Aβ) into plaques and tau protein into neurofibrillary tangles and neurodegeneration starts. These processes are measureable in CSF using validated in-vitro diagnostic (IVD) immunoassays for Aβ42, Phospho-Tau (181P) and Total-Tau protein concentrations in CSF. An expanded biomarker panel also covering other pathophysiologies, including glial activation and inflammation (GFAP, sTREM2, s100b, IL6), synaptic degeneration (neurogranin, α-synuclein) and damage to long axons (neurofilament light-chain; NFL), based on high-precision techniques, is warranted. To accomplish this, the NeuroToolKit (NTK) is a panel of automated Elecsys® CSF immunoassays, developed to complement established IVD methods for Aβ42, pTau and tTau, with the aim of providing new insights for assessing disease progression and to serve as tools for diagnostics and monitoring of treatments. **Objectives:** This is a preliminary report of the distribution of NTK biomarkers across AD stages (unimpaired, MCI, dementia) by biomarker profile (pTau/Aβ42). **Methods:** Three hundred CSF samples were obtained from N = 206 adults ages 50-92 (M = 70.7, SD = 8.3; 51.4% female) participating in the Wisconsin Registry for Alzheimer's Prevention (WRAP) or the Wisconsin Alzheimer's Disease Research Center (WADRC); n = 47 were diagnosed with Alzheimer's clinical syndrome (dementia-ADcs), n = 40 had mild cognitive impairment (MCI), while n = 115 were cognitively unimpaired (CN), and n = 4 had non-AD related cognitive impairments. Clinical diagnosis was determined by consensus conference based on NIA-AA criteria (2011) without reference to biomarkers. CSF samples were acquired with a uniform preanalytic protocol between 2010 and 2018. Samples were assayed in batches at the Clinical Neurochemistry Laboratory at the Sahlgrenska Academy of the University of Gothenburg. IVD markers of Aβ42, pTau and tTau were assayed on a cobas e 601 analyzer. The exploratory NTK panel was assayed on a cobas e 411 analyzer and consisted of several markers of neuronal degradation (neurogranin, NFL, and α-synuclein) and inflammation (GFAP, YKL-40, IL6, S100, and sTREM) (not commercially available). A subset of participants (n = 82) underwent dynamic PiB-PET imaging. Amyloid+/- status, ascertained by visual reads of parametric distribution volume ratio images, was used as the standard of comparison for a ROC analysis to derive an optimal pTau/Aβ42 threshold with 92% positive agreement. This cut-point was then applied to all participants with CSF data. Because this is an initial subsample of a larger ongoing project, the results reported here are descriptive. We compared biomarker levels across clinical groups and pTau/Aβ42 biomarker status. We also describe trends in biomarker concentrations across age by pTau/Aβ42 biomarker status in individuals with multiple CSF samples (n = 58). **Results:** The pTau/Ab42 to PIB ROC area under the curve was 0.98. A cut-off of 0.033 resulted in a 98% negative agreement. 44/47 (94%) dementia-ADcs, 13/40 (33%) MCI, and 30/115 (26%) CN participants were identified as pTau/Aβ42 positive. Although biomarker distributions tended to overlap across groups, we observed several trends in biomarker levels by clinical stage and pTau/Aβ42 status. As expected, Aβ42 level was clearly differentiated by pTau/Aβ42 status, although levels declined slightly across clinical stage in both groups. Tau indicators and their ratios exhibited stepwise differences across clinical stage among pTau/Aβ42 positive participants but remained low in pTau/Aβ42 negative participants. Neurogranin moderately increased with pTau/Aβ42 status, but appeared unrelated to clinical stage. In contrast, NFL and α-synuclein were related to pTau/Aβ42 status and clinical stage; impaired pTau/Aβ42 positive participants had higher levels than pTau/Aβ42 negative or CN participants. Inflammatory biomarkers (GFAP, s100, sTREM2, and YKL40) followed a similar pattern. Biomarker levels appeared to increase in the presence of impairment among pTau/Aβ42 positive participants; inflammatory biomarker levels remained relatively stable among pTau/Aβ42 negative participants. IL6 was unrelated to either clinical stage or amyloid status. Participants with longitudinal CSF samples were divided into stably positive (n = 34) and stably negative (n = 18) pTau/Aβ42 groups (n = 6 converted from negative to positive over the course of the study and are not reported on here). 90% were cognitively unimpaired at their last visit. CSF levels of tTau, GFAP, NFL, sTREM2, s100, and YKL40 (and to a lesser extent α-synuclein and neurogranin) appeared to increase with age, although these changes were more noticeable among pTau/Aβ42 negative participants. Aβ42 values remained steadily low among pTau/Aβ42 positive participants but varied considerably with age in pTau/Aβ42 negative participants. **Conclusion:** The NTK panel is designed to cover a broad spectrum of pathophysiologies known to play a role in neurodegenerative diseases to identify individuals in the early stages of AD as well as individuals with mixed pathologies. This is the first study to compare all currently available NTK biomarkers across the AD spectrum by CSF pTau/Ab42 status. Although results are preliminary, core AD biomarkers were differentiated by CSF pTau/Aβ42 early in AD progression while biomarkers for neurodegeneration and inflammation were differentiated by CSF pTau/Aβ42 during symptomatic phases.

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

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

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

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

burst cognitive data are critical before they are considered as appropriate primary analysis models for AD clinical trials. The hierarchical MMRM or LME models optimizes the increased reliability of the clustered weekly data. Our study demonstrates that these hierarchical models are superior to the two-stage traditional MMRM/LME models, and could be considered as a primary endpoint analysis model in AD clinical trials. **Funding:**The DIAN observational study is supported by grant U19 AG032438, PI Randall Bateman. The DIAN-TU study is supported NIH U01 AG042791-01A1; PI: Randall Bateman, MD; NIA R01 AG059798; PI: Eric McDade. The ARC smartphone application is supported by funds from An Anonymous Foundation, the GHR foundation, and R01AG057840; PI: Jason Hassenstab.

OC34: SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF RDN-929: A POTENT AND SELECTIVE HDAC-COREST COMPLEX INHIBITOR FOR THE TREATMENT OF SYNAPTOPATHIES.

J. Michael RYAN (1), Christine VOORS-PETTE (2), Christel ROMEIJN (2), Minh VO (3), Magnus IVARSSON (1), Berkely A. LYNCH (1), Antonella PIRONE (1), Michael C. HEWITT (1), Nathan O. FULLER (1), Amy DIRICO (1), Steven P. SWEENEY (1) *((1) Rodin Therapeutics, United States, (2) QPS, Netherlands, (3) Certara, United States)*

Background: RDN-929 is a potent and selective inhibitor of the HDAC-CoREST complex that is being developed as a potential therapy for neurologic diseases driven by synaptic loss or dysfunction. Post-translational modification of histones, through HDAC modulation, have been shown to be important regulators of neuronal gene expression and synaptic function. Pre-clinical proof of concept has been demonstrated in mouse models of dendritic spine density, coincidence of synaptic proteins and hippocampal long-term potentiation [Fuller, 2019]. As such, inhibition of the HDAC-CoREST complex may play a key role in targeting synaptic structure and function and provide a new therapeutic approach for treating multiple synaptopathies. **Objectives:** The objectives of this first-in-human study were to determine the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of RDN-929, a small molecule inhibitor of the HDAC-CoREST complex. **Methods:** A Phase 1, double-blind, randomized, placebo-controlled trial was performed in healthy young and older subjects at a single center. This initial human trial of orally-administered RDN-929 consisted of 84 subjects enrolled into 3 parts: (1) healthy young male subjects aged 18-54 years (n= 48) who received either placebo, or 2, 10, 30, 100, 250 or 500 mg as a single dose, (2) healthy older male and female subjects aged 55-80 years (n=12) who received a single 100 mg dose following an overnight fast and second 100 mg dose following a high fat, high calorie meal, and (3) healthy older male and female subjects aged 55-80 years (n=24) who received either placebo, or 30, 100 or 300 mg once daily doses for twelve (12) days. Serial plasma PK samples were collected for all subjects in all Parts. Part 3 subjects also underwent cerebral spinal fluid (CSF) sampling by lumbar puncture for PK and PD analysis. In Parts 1 and 3, target engagement was assessed by analysis of peripheral blood mononuclear cell (PBMC) histone acetylation. **Results:** RDN-929 was safe and well-tolerated over the dose range tested from 2 to 500 mg as a single oral dose and from 30 to 300 mg when given once daily for twelve (12) days. No dose-limiting toxicities were identified and no SAEs were reported. All AEs recorded were of mild severity with the exception of one moderate severity headache reported in Part 3. No subject discontinued due to an AE. There were no RDN-929 dose-related changes observed for vital signs, hematologic assessments, clinical chemistries, coagulation parameters or ECG parameters. RDN-929 was rapidly absorbed and exposure increased slightly less than proportionally over the single dose range of 2 to 500 mg. Steady state concentration was reached after four (4) days of once daily dosing with no significant accumulation in RDN-929 exposure observed. Co-administration of RDN-929 with a high-fat meal increased RDN-929 peak and total exposure by 1.4 and 1.7 fold, respectively. RDN-929 CSF concentrations increased with increasing dose at levels that cover the targeted therapeutic range predicted by mouse spine density models. RDN-929 administration produced a significant increase in PBMC histone acetylation compared to placebo in Parts 1 and 3. **Conclusion:** RDN-929 administered orally as a single dose up to 500 mg and multiple daily doses up to 300 mg in healthy young males and healthy older males and females demonstrates an excellent safety, tolerability and PK profile. The significant increases observed in PBMC histone acetylation confirm peripheral target engagement. These initial data suggest that RDN-929 represents a novel, brain-penetrant, complex-selective HDAC inhibitor with a safety profile that is supportive of further clinical development in patient populations characterized by synaptic loss or dysfunction. **References:** Fuller, N. O., Pirone, A., Lynch, B. A., Hewitt, M. C., Quinton, M. S., McKee, T. D., & Ivarsson, M. (2019). CoREST Complex-Selective Histone Deacetylase Inhibitors Show Prosynaptic Effects and an Improved Safety Profile To Enable Treatment of Synaptopathies. ACS Chemical Neuroscience, 10, 1729-1743.

OC35: A PHASE 2 TRIAL OF GRF6019 IN MILD-TO-MODERATE ALZHEIMER'S DISEASE.

Jonas HANNESTAD (1), Tiffanie PEDERSON (1), Whitney CHAO (1), Katie KOBORSI (1), Vicki KLUTZARITZ (1), Steven BRAITHWAITE (1), Suzanne HENDRIX (2), Karoly NIKOLICH (1) *((1)Alkahest, United States, (2) Pentara Corporation, United States)*

Background: The proprietary plasma protein fraction GRF6019 shows multiple benefits in aged mice. Functional benefits include improved memory and increased cortical activity; morphological benefits include increased synaptic density and neurogenesis, and reduced neuroinflammation. In mice, daily administration of GRF6019 for 5 or 7 consecutive days produced benefits lasting up to 3 months. Therefore, a similar dosing regimen was chosen for Alkahest's first clinical trial in Alzheimer's disease, ALK6019-201 (NCT03520998), which evaluated the safety and tolerability of two dose levels of GRF6019 in mild-to-moderate AD. **Methods:** The main inclusion criteria were: age 60-90; probable AD according to NIA-AA criteria; Mini Mental State Examination (MMSE) score 12-24. The main exclusion criteria were: any neurological disorder other than AD; > 2 lacunar strokes on Magnetic Resonance Imaging (MRI); change in the dose of cholinesterase inhibitor or memantine in the last 3 months. Each subject had a baseline visit, two 5-day inpatient dosing periods each followed by a 3-month treatment-free period, for a total study duration of 6 months. Subjects were randomized in a 1:1 ratio to receive either 100 mL or 250 mL of GRF6019 per day for five days, and dose allocation was blinded to subjects, caregivers, raters, and investigators. There was no placebo control arm. The primary endpoint was safety and tolerability, while secondary endpoints included the AD Assessment Scale-Cognitive Subscale (ADAS-Cog), the Clinical Dementia Rating Scale (CDR), the AD Cooperative Study Activities of Daily Living (ADCS-ADL), the MMSE, and the Savonix Mobile Battery.

Exploratory endpoints included blood and cerebrospinal fluid biomarkers, and structural and functional MRI. The study was conducted at 9 U.S. sites between March 2018 and May 2019. **Results:** 89 subjects were screened, 52 subjects were randomized, 51 subjects received at least one dose, 43 subjects completed the first 5-day dosing period, and 40 subjects completed both dosing periods. Among the 51 subjects dosed, there were a total of 81 adverse events, of which 28 were assessed as related to study drug. The most common adverse events were mild headaches, infusion site reactions, transient lab abnormalities, and transient blood pressure changes. There were two serious adverse events; one was a hypersensitivity reaction assessed as related to GRF6019, while the other was related to a history of deep venous thrombosis (a pre-existing condition). There were no deaths. The baseline demographics and level of cognitive and functional impairment for all subjects who were randomized (n=52) are summarized in Table 1. Over the course of the 6-month study period, there was no significant cognitive or functional decline as measured by the ADAS-Cog, the ADCS-ADL, and the CDR-SB. The expected decline over a 6-month period in AD subjects of similar baseline severity who received placebo in other trials is a 2- to 3-point worsening on the ADAS-Cog and a 3- to 4-point worsening on the ADCS-ADL. **Conclusions:** This Phase 2 trial in AD demonstrates that daily infusions with up to 250 mL of the plasma protein fraction GRF6019 for 5 consecutive days is safe and well-tolerated in this population. Furthermore, progression of disease in GRF6019-treated subjects was slower than what would be expected in this population. Based on these data, the benefit-risk of continued clinical development of plasma protein fractions in AD is favorable, and a placebo-controlled Phase 2b trial is currently being planned.

OC36: HOPE4MCI TRIAL: TARGETING REDUCTION OF HIPPOCAMPAL OVERACTIVITY TO TREAT MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE WITH AGB101.

Sharon ROSENZWEIG-LIPSON (1), Russell BARTON (1), Michela GALLAGHER (2), Richard MOHS (1) *((1) AgeneBio, Inc, United States, (2) Johns Hopkins University, United States)*

Background: No effective therapies exist to halt or reverse Alzheimer's disease (AD). With a predicted prevalence of AD cases rising to >100 million worldwide by 2050, the need for such therapies is urgent. The prevalence of patients with AD dementia, who represent the greatest human and economic burden, could be dramatically reduced by preventing or delaying progression in early phases of the disease, such as Mild Cognitive Impairment (MCI) due to AD (prodromal AD). There is now strong evidence from preclinical models and human patients that neuronal circuits become hyperactive in prodromal AD contributing to the accumulation and spread of Alzheimer's pathology and to subsequent cognitive decline. Hippocampal hyperactivity is most pronounced in patients with amnestic MCI and deposited amyloid as determined by amyloid PET imaging (MCI due to AD). AgeneBio is developing therapeutics to reduce hippocampal overactivity and slow progression to Alzheimer's dementia. Extensive clinical and preclinical data support the hypothesis that neural overactivity is a critical driver of AD neuropathology, including the deposition of amyloid and spread of tau along connectional pathways. AGB101 (low dose levetiracetam) demonstrates efficacy on a range of molecular, synaptic, electrophysiological, functional and behavioral endpoints across models (age-related memory impairment, amyloid, tau) and species (flies, mice, rats, aMCI in humans). In a Phase 2 study measuring hippocampal activity during a pattern separation memory test in patients with aMCI, AGB101 normalized hippocampal activity and improved performance on this highly specific memory assessment of hippocampal function. The HOPE4MCI trial (currently in progress) is investigating the effects of AGB101 (220 mg) vs placebo in patients with MCI due to AD. **Objectives:** Primary objective: To assess the efficacy of AGB101 (low-dose levetiracetam, 220 mg, extended release tablet) compared to placebo in subjects with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) using Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores. Secondary objectives: To assess the efficacy of AGB101 compared to placebo on: 1) FAQ and MMSE scores, 2) neuronal injury, as measured by a change in the entorhinal cortex thickness. Additional secondary objectives: To assess the efficacy of AGB101 compared to placebo on: 1) CDR (global, memory box), BPS-O task, and ISLT scores, 2) hippocampal volume, 3) the levels of tau protein in the brain using the tau PET ([18F]MK-6240). **Methods:** This is a multicenter, randomized, double-blind, placebo-controlled, 78-week, fixed-dose study evaluating AGB101 versus placebo as a treatment for slowing the progression of MCI due to AD. A total of 830 subjects will be randomized (415/treatment group). Inclusion criteria: Subjects must meet all of the following inclusion criteria at screening: 1) Subjects between 55 and 85 years old (inclusive) in good general health; 2) Have a study partner who has sufficient contact with the subject to be able to provide assessment of memory changes, who can accompany the subject to the screening and all major clinic visits for the duration of those visits, and who is able to provide an independent evaluation of the subject's functioning. 3) Have MCI due to AD as defined by all of the following criteria and consistent with the National Institute on Aging-Alzheimer's Association criteria. - MMSE scores between 24 and 30 (inclusive), - A memory complaint reported by the subject or his/her study partner. - Evidence of lower memory performance based on the delayed recall portion of the ISLT.- A Clinical Dementia Rating (CDR) score of 0.5 with a memory box score of ≥ 0.5. - Essentially preserved activities of daily living. - Cognitive decline not primarily caused by vascular, traumatic, or medical problems (alternative causes of cognitive decline are ruled out). 4) Evidence of an amyloid-positive PET scan. **Results:** The HOPE4MCI trial is currently underway. Sites are currently enrolling in the US and Canada with plans to expand to Europe. Up to date subject demographics, screen failure information, safety and dropout information will be presented at the meeting. **Conclusions:** HOPE4MCI represents the first and only Phase 3 clinical trial targeting the reduction of hippocampal overactivity for slowing the progression of MCI due to AD. The HOPE4MCI trial is supported, in part, by R01AG061091 to RM and R01AG048349 to MG.

Late Breaking News

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

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

Background: Approximately 2.4 million patients with dementia in the US alone experience delusions and hallucinations associated with dementia-related psychosis (DRP). Occurrence of DRP symptoms is further associated with poor outcomes such as increased likelihood of nursing home placement, progression to severe dementia, increased morbidity, and mortality. No available therapies have been approved for treatment of DRP. Pimavanserin is an atypical antipsychotic that acts as an inverse agonist/antagonist at the 5-HT2A receptor. Its efficacy and safety in treating hallucinations and delusions has been demonstrated in patients with Parkinson disease psychosis, with or without cognitive impairment. Additionally, in a short-term study in Alzheimer disease psychosis, pimavanserin has shown significant efficacy and favorable tolerability. The present study seeks to investigate the use of pimavanserin across a broad population of patients with dementia-related psychosis. **Objectives:** The aim of HARMONY study (NCT03325556) is to evaluate the efficacy and safety of pimavanserin for treatment of delusions and hallucinations associated with DRP in a broad spectrum of dementias including Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), Alzheimer's disease (AD), frontotemporal degeneration spectrum disorders (FTD), and vascular dementia (VaD). **Methods:** HARMONY is a Phase 3, placebo-controlled, randomized withdrawal study. The relapse-prevention design was chosen to allow for systematic evaluation of long-term efficacy in a clinically relevant manner. Participants with dementia and moderate to severe psychosis were enrolled. Eligible patients received pimavanserin 34 mg once daily for 12 weeks during the open-label period, with a possibility of dose adjustment to 20 mg within the first 4 weeks. After 12 weeks, participants who sustained a clinically meaningful improvement relative to open-label baseline (≥30% reduction on the SAPS-H+D Total Score AND a CGI-I score of 1=very much improved or 2=much improved) at both Weeks 8 and 12 were randomized 1:1 in a double-blind fashion to continued pimavanserin or to placebo, for up to 26 weeks. Patients were monitored for re-occurrence of psychotic symptoms in the double-blind period. The primary endpoint was time from randomization to relapse of psychosis. **Results:** Overall, 794 patients were screened during approximately 24 months study enrollment. A total of 392 patients were enrolled into the open-label treatment period with the following distribution of dementia subtypes: 66.8% AD, 14.3% PDD, 9.7% VaD, 7.4% DLB, and 1.8% FTD. Most of the patients achieved sustained improvement, suggesting robust response rates, with fewer than 21% of eligible patients failing to meet sustained response criteria. Pimavanserin was well tolerated, and more than 90% of patients remaining on the initial 34-mg dose and fewer than 10% having dose reduced to 20 mg. Over 61% of eligible patients were randomized into the double-blind phase of the study. At the time of interim analysis, 40 patients were judged by the independent adjudication committee to have reached study criteria for relapse, 19 patients were arbitrated as discontinued due to other reasons, 70 patients were ongoing, and 65 patients had completed 6-month double-blind treatment. The study was stopped early for efficacy when the result of the prespecified interim analysis revealed highly statistically significant benefit of pimavanserin treatment over placebo (1-sided $P<0.0033$) in delaying time to relapse. Selected results from the open-label portion of the trial will be presented, including demographics of the study population, response rates overall and by dementia subtype, safety information and reasons for discontinuations. Additionally, interim analysis primary efficacy results, including hazard ratio, will be presented. Further data from the double-blind relapse population may be presented as available. **Conclusions:** There currently are no approved therapies for the treatment of DRP. Variable and only modest efficacy, along with safety concerns, complicate the off-label use of available antipsychotics, leaving a high unmet need for safe and effective treatment for this debilitating condition. The HARMONY study evaluated pimavanserin's potential to address this need by employing a randomized withdrawal design with clinically meaningful endpoints. In the open-label portion of the trial, pimavanserin was well tolerated, with robust treatment response across dementia subtypes. The statistically significant superiority for pimavanserin over placebo in time to relapse of DRP during the subsequent double-blind period supports efficacy and durability of effect of pimavanserin in this patient population.

LB2: MASUPIRDINE (SUVN-502), A 5-HT6 RECEPTOR ANTAGONIST IN COMBINATION WITH DONEPEZIL AND MEMANTINE IN MODERATE ALZHEIMER'S PATIENTS: STUDY OUTCOMES FROM A PHASE-2 STUDY.

Jeffrey CUMMINGS (1,2), Alireza ATRI (3), Ramakrishna NIROGI (4), John IENI (4), Vinod GOYAL (4), Pradeep JAYARAJAN (4), Jyothsna RAVULA (4), Satish JETTA (4), Venkat JASTI (4) *((1) Department of Brain Health, School of Integrated Health Sciences, University of Nevada; Cleveland Clinic, Lou Ruvo Center for Brain Health, United States, (2) Cleveland Clinic, Lou Ruvo Center for Brain Health, United States, (3) Banner Sun Health Research Institute, Banner Health, United States, (4) Suven Life Sciences, India)*

Background: Masupirdine (SUVN-502) is a selective 5-hydroxytryptamine-6 (5-HT6) receptor antagonist being investigated for the symptomatic treatment of moderate Alzheimer's disease (AD). Animal data show that masupirdine has potential to improve cognitive performance. Phase-1 studies of masupirdine in healthy humans suggest favorable properties including once daily oral treatment and a lack of food, gender and age effect. Masupirdine added to background treatment with donepezil and memantine was evaluated in moderate AD subjects in a double-blind placebo controlled, randomized, 26-week treatment phase-2 study. **Objectives:** To evaluate the efficacy and safety of masupirdine in combination with donepezil and memantine for the symptomatic treatment of moderate AD. **Methods:** In this phase-2 study, a total of 564 moderate AD patients with MMSE scores between 12–20 receiving stable doses of donepezil and memantine were randomized (1:1:1) to receive either 50 mg or 100 mg of masupirdine, or placebo once daily for 26 weeks. The primary efficacy endpoint was change from baseline in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog 11). Secondary efficacy endpoints included CDR-SB, ADCS-ADL, NPI, C-SDD and MMSE. The efficacy endpoints were analyzed using MMRM of the modified intent-to-treat (mITT) and the evaluable population (EP). Safety was assessed by recording

adverse events and laboratory measurements, vital signs, electrocardiograms, physical and neurological examinations and C-SSRS. **Results:** Out of 564 randomized patients, 183 assigned to placebo, 184 who received 50 mg masupirdine, and 176 who received 100 mg masupirdine were included in the final analysis. Patient baseline characteristics were consistent with moderate AD with MMSE scores ranging from 12-20. The mean (SD) age of patients was 73.6 (7.46) years and the mean (SD) duration of AD diagnosis was 3.73 (2.7) years. Two-thirds of the patients were ApoE-4 carriers. Masupirdine was well-tolerated in patients with moderate AD. The study missed its primary and secondary efficacy endpoints . Triple therapy of Masupirdine + Donepezil + Memantine resulted in unique and unconventional datasets. Masupirdine is the first and the only 5-HT6 receptor antagonist which was evaluated as triple therapy. Post-hoc and hypothesis-generating observations of interest emerged from the detailed data analyses. In the exploratory subgroup analysis, masupirdine treatment arms showed significant improvement in cognitive functions in subjects stratified by memantine regimen, memantine plasma concentrations and memantine treatment duration. Improvement in the behavioral and psychological symptoms was also observed with masupirdine in NPI domains. The primary, secondary and exploratory efficacy analysis and safety outcomes of the study will be presented. **Conclusions:** Masupirdine is safe and well tolerated. The current study involving Triple therapy of Masupirdine + Donepezil + Memantine missed its primary and secondary efficacy endpoints. Post-hoc and hypothesis-generating observations of interest emerged from the detailed data analyses. These findings support further exploration of the potential of masupirdine.

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

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

methodologies will inform trial designs for the future testing of other repurposable RAS-targeting drug candidates the urgency of which continue to grow with the continuous emergence of supportive data for the angiotensin hypothesis in AD. **Key words:** losartan, Alzheimer, intervention, angiotensin II, MRI, RCT.

LB4: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL DESIGN, PROSPECTIVE, PHASE II CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF GV1001, A NOVEL PEPTIDE MIMICKING HUMAN TELOMERASE REVERSE TRANSCRIPTASE, FOR THE TREATMENT OF MODERATE TO SEVERE ALZHEIMER'S DISEASE.
Seong-Ho KOH (1), Seong Hye CHOI (2), Jee Hyang JEONG (3), Chan Nyoung LEE (4), Young Soon YANG (5), Ae Young LEE (6), Jae-Hong LEE (7), Kyung Won PARK (8), Hyun Jeong HAN (9), Byeong Cha KIM (10), Jin Se PARK (11), Jee-Young LEE (12), Sangjae KIM (13) *((1) Hanyang University Guri Hospital, Korea, Republic of, (2) Inha University Hospital, Korea, Republic of, (3) Ewha Womans University Mokdong Hospital, Korea, Republic of, (4) Korea University Anam Hospital, Korea, Republic of, (5) Veterans Health Service Medical Center, Korea, Republic of, (6) Chungnam National University Hospital, Korea, Republic of, (7) Asan Medical Center, Korea, Republic of, (8) Dong-A University Hospital, Korea, Republic of, (9) Myongji Hospital, Korea, Republic of, (10) Chonnam National University Hospital, Korea, Republic of, (11) Inje University Haeundae Paik Hospital, Korea, Republic of, (12) Seoul National University Boramae Medical Center, Korea, Republic of, (13) Teloid Inc., United States)*

Background: GV1001 is a peptide of 16 aminoacids from human telomerase reverse transcriptase (hTERT), corresponds to a fragment from the catalytic site of telomerase. GV1001 has been shown to inhibit neurotoxicity, apoptosis, and production of reactive oxygen species in neural cells by mimicking the extra-telomeric functions of hTERT. In both mild (early stage) and severe (late stage) Alzheimer's Disease (AD) mouse models, GV1001 has been shown to improve cognitive function and memory, as well as significantly reduce the amount of amyloid beta and tau proteins. The multifunctional effect of GV1001 makes it a promising therapeutic option for the treatment for AD. **Objectives:** To evaluate the safety and efficacy of GV1001 in patients with moderate to severe AD. **Methods:** Patients 55 to 85 years of age, Korean-Mini-Mental State Examination (K-MMSE) score ≤ 19, were recruited and randomized to treatment with Group 1 (GV1001 0.56 mg), Group 2 (GV1001 1.12 mg), or placebo (normal saline) in a 1:1:1 ratio. The intervention course was 24 weeks, study treatment (GV1001 0.56 mg, GV1001 1.12 mg, or placebo) was administered by subcutaneous (SC) injection every week for 4 weeks (4 times) followed by SC administration every 2 weeks through Week 24 (10 times) for a total of 14 SC administrations of study treatment. Primary outcome was change from baseline(CFB) in Severe Impairment battery (SIB) and secondary endpoints were CFB in K-MMSE, Geriatric Depression Scale (GDS), Clinical Dementia Rating-Sum of Boxes(CDR-SB), AD Cooperative Study-Activities of Daily Living(ADCS-ADL), and Neuropsychiatric Inventory(NPI). Adverse events, relevant laboratory, and vital signs were assessed. **Results:** A total of 90 participants from 11 sites were included (Group 1, Group 2 and Placebo: n = 30). At week 24, a statistically significant difference in the mean CFB in SIB score was seen in GV1001 treatment Groups 1 and 2 vs the control group for the full analysis population ($p < 0.05$). There was also a significant improvement in the mean CFB in ADCS-ADL at week 24 in all GV1001 treatment Groups vs control group ($p < 0.05$). There were no statistically significant differences found in other secondary outcome measures. Adverse event (AE) reporting was similar across all three groups. No treatment-emergent AEs were considered to be related to the study drug. **Conclusion:** The results indicate that GV1001 was effective and well tolerated without safety concerns, and may provide potential beneficial effects in patients with AD. Further investigation will be required to confirm these observations in a large-scale and longer-term clinical evaluation. TRIAL REGISTRATION: ClinicalTrials.gov, NCT03184467 Registered on 12 June 2017.

LB5: ORAL MICROBIAL DYSBIOSIS AND AMYLOID PATHOLOGY IN COGNITIVELY NORMAL SUBJECTS.
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Background: Inflammation and dysbiosis could contribute to Alzheimer's disease pathogenesis. We previously have shown that periodontal disease, a dysbiotic condition is associated with lower cognition, and brain amyloid pathology. **Objectives:** Based on our prior studies, we hypothesize that elderly cognitively normal people with CSF biomarker evidence for amyloid pathology would have subgingival microbiota enriched in periodontal bacteria compared to those with less biomarker evidence. We will also examine the effect of subgingival periodontal dysbiosis on the continuous measures of amyloid pathology. **Methods:** Subgingival bacterial composition was assessed using 16S rRNA sequencing in 26 subjects with higher (normal) CSF Ab42 (Ab>=600pg/ml) and 22 subjects with lower (amyloid positive) CSF Ab42 (Ab<600pg/ml). We used Linear discriminant effect size analysis (LEfSe) and univariate analysis of variance adjusted for relevant covariates (ApoE, age, smoking) to determine the bacterial taxa different between our groups. To determine the predictive effect of high/low dysbiotic index on CSF Ab42, 2-way analysis of variance was used with the relevant covariances (age, BMI, APOE). Dysbiotic index (DI) was defined as a ratio of periodontal bacteria (Porphyromonas, Treponema and Tannerella) to healthy bacteria (Rothia and Corynebacterium). Hi vs. low DI was classified by dichotomizing the DI scores using the upper vs. lower half with the cut-point of 3 (<3 vs. 3+). **Results:** LEfSe showed that subgingival samples of subjects with low CSF Ab42 were enriched in bacterial taxa characteristic of periodontal disease such as genera Prevotella, Porphyromonas, Alloprevotella, and Fretibacterium while subjects with high CSF Ab42 were enriched in bacterial taxa belonging to genera characteristic of periodontal health such as Corynebacterium, Actinomyces, Leptotrichia, and Capnocytophaga. The subgingival dysbiotic index (DI) was statistically significant lower in subjects with high CSF Ab42 compared to those with low CSF Ab42 even after adjustment for age, ApoE and smoking (Adjusted log means±SE: 0.26±0.15 vs. 0.82±0.18; F=4.80, p=0.03). In 2-way analysis of variance, with high/low DI and APOE4 as independent variables, we found that there was a significant interaction between DI and APOE on CSF Ab42. Among

APOE4- subjects, those with high DI (n=13) vs those with low DI [(n=13) had significantly lower CSF Ab42 (adjusted means±SE: 600.48±47.07 vs. 885.25±47.07; F=17.48 p<0.001)]. Moreover, there was a significant inverse correlation between DI and CSF Ab (partial R=-0.52, p=0.01). However, in APOE4+ subjects the CSF Ab42 was not different between the 2 DI groups (low DI: n=13; adjusted means±SE: 572.07±56.43 vs. high DI: n=9; 582.26±68.25; F=0.13, p=0.91). **Conclusion:** These results add to our understanding of a relationship between oral bacteria and brain Ab. Our results also show that the oral bacterial effect on CSF Ab may be APOE dependent or best recognized in E4 negative. Periodontal disease is a prevalent condition that can be treated non-invasively. Therefore, to further determine the roles of specific oral bacteria in Alzheimer's disease pathogenesis, longitudinal and interventional studies are warranted.

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

Background: Previous research has indicated that miR-107 may play important roles in both metabolism and AD pathogenesis that may be modulated by "fibrates" (PPAR-alpha agonists). Fibrates increase miR-107 expression, leading to down-regulation of BACE1 protein. We evaluated the safety and efficacy of gemfibrozil administration in predementia Alzheimer's disease in a parallel-design, double-blind, placebo-controlled clinical trial funded by NIH/NIA R01 AG042419 and registered on clinicaltrials.gov NCT02045056. **Methods:** Patients with pAD, MCI, or early AD (CDR 0.5) were randomized to receive gemfibrozil (600 mg twice daily) for 48 weeks or placebo. Primary endpoints included: 1) safety of administration of gemfibrozil in the specific study population, 2) CSF levels of gemfibrozil to demonstrate target engagement, and 3) change in miR-107 expression and CSF A-beta levels. Exploratory outcome measures included change in ptau-181, MRI hippocampal volume, fasting glucose and lipid levels among others. **Results:** There were no significant differences in frequency and/or occurrence of AEs classified by MeDRA classification in treatment (63%) versus placebo (53%) arms of the study (p=0.37). No serious adverse events related to the study medication were observed. CSF levels of gemfibrozil were reliably detected in the treatment group only at the end of treatment study visit. Change in A-beta42 and ptau-181 CSF levels between baseline and week 48 were not significantly different between active treatment and placebo arms of the study (p=0.34 & p=0.18, respectively). A nonspecific trend towards reduction in hippocampal atrophy in the treatment versus placebo group was seen (p=0.15). Change in glucose and lipid levels across study visits demonstrate favorable metabolic changes in the gemfibrozil treatment versus placebo arms of the study. **Conclusions:** While the primary outcome measures were negative, positive trends associated with gemfibrozil treatment included reductions in CSF A-beta42, CSF ptau-181 and rate of hippocampal atrophy. Gemfibrozil showed excellent CSF penetration and was safe for administration in the elderly population at risk for Alzheimer's disease including those in the prodromal state of mild cognitive impairment. Further secondary and subgroup analyses are underway to explore the outcome measures and metabolic influences of gemfibrozil on risk for dementia in this predementia population.

LB7: ONE-MONTH ORAL TREATMENT WITH PTI-125, A NEW DRUG CANDIDATE, REDUCES CSF AND PLASMA BIOMARKERS OF ALZHEIMER'S DISEASE.
Lindsay BURNS (1), Hoau-Yan WANG (2), Zhe PEI (2), Kuo-Chieh LEE (2), Carrie CROWLEY (2), Michael MARSMAN (2), Nadav FRIEDMANN (2) *((1) Cassava Sciences, Inc., United States, (2) City of New York School of Medicine, United States)*

Background: PTI-125 is an oral small molecule drug candidate that binds and reverses an altered conformation of the scaffolding protein filamin A (FLNA) found in Alzheimer's disease (AD) brain. Altered FLNA links to the α7-nicotinic acetylcholine receptor (α7nAChR) to allow Aβ42's toxic signaling through this receptor to hyperphosphorylate tau. Altered FLNA also links to toll-like receptor 4 (TLR4) to enable Aβ-induced persistent activation of this receptor and inflammatory cytokine release. Restoring the native shape of FLNA prevents or reverses FLNA's linkages to α7nAChR and TLR4, thereby blocking Aβ42's activation of these receptors. The result is reduced tau hyperphosphorylation and neuroinflammation, with multiple functional improvements demonstrated in transgenic mice and postmortem AD brain tissue. PTI-125 was safe and well-tolerated in a Phase I trial in healthy volunteers. **Objective:** Safety, pharmacokinetics (PK), and CSF and plasma biomarkers were assessed in a Phase 2a clinical trial of mild-to-moderate AD patients following treatment for 28 days. Target engagement and mechanism of action were assessed in patient lymphocytes by measuring 1) the reversal of FLNA's altered conformation, 2) linkages of FLNA with α7nAChR or TLR4, and 3) levels of Aβ42 bound to α7nAChR or CD14, the co-receptor for TLR4. **Methods:** In this open-label, Phase 2a trial conducted in the US, 12 patients with mild-to-moderate AD received PTI-125 in 100 mg oral tablets b.i.d. for 28 days. Key inclusion criteria were MMSE ≥ 16 and ≤ 24, age 50-85 and CSF total tau/Aβ42 ratio ≥ 0.30. Safety was assessed by ECGs, clinical labs, adverse event (AE) monitoring and physical examinations. Blood samples for PK analysis were collected over 12 h on Days 1 and 28. CSF samples were collected at screening and on Day 28. Blood samples for plasma and lymphocyte biomarkers were collected on Days 1 (pre-dose), 14 and 28. CSF and plasma biomarkers were analyzed using commercial ELISA kits. Biomarkers assessed AD pathology (pT181-tau, total tau and Aβ42), neurodegeneration (neurofilament light chain [NfL] and neurogranin), and neuroinflammation (YKL-40, IL-6, IL-1β and TNFα). Cytokines were not measured in plasma. CSF and plasma samples were stored at -80°C, thawed and treated with protease and phosphatase inhibitors prior to aliquoting and refreezing until analysis. For each ELISA biomarker, pre-dose and Day 28 samples were tested in triplicate in the same ELISA plate. Values were adjusted to a regression analysis run on standards, and background for chromogen blanks and the no-CSF controls was subtracted. R2 values for regression analyses ranged from 0.85 to 0.99. Plasma levels of phosphorylated tau were assessed by immunoprecipitation of tau with anti-tau followed by immunoblotting of three different phospho-epitopes elevated in AD (pT181-tau, pS202-tau and pT231-tau). Changes in conformation of FLNA in lymphocytes were measured by isoelectric focusing point (pI). FLNA linkages to α7nAChR and TLR4 were assessed by immunoblot detection of α7nAChR and TLR4 in anti-FLNA immunoprecipitates from lymphocytes. Aβ42 complexed with α7nAChR or CD14 was also measured

by co-immunoprecipitation. **Results:** PTI-125 was safe and well-tolerated in all patients, consistent with a previous Phase I trial. Plasma half-life was approximately 4.5 h. Approximately 30% drug accumulation was observed by comparing AUC0-12 on Day 28 vs. Day 1. Consistent with the drug's mechanism of action and preclinical data, PTI-125 reduced CSF biomarkers of AD pathology, neurodegeneration and neuroinflammation from baseline to Day 28. T-tau, neurogranin, and NfL decreased by 20%, 32% and 22%, respectively. P-tau (pT181) decreased 34%, evidence that PTI-125 suppresses tau hyperphosphorylation induced by Aβ42's signaling through α7nAChR. CSF biomarkers of neuroinflammation (YKL-40, IL-6, IL-1β and TNFα) decreased by 5-14%. Biomarker effects were seen in all patients and were similar in plasma. Aβ42 increased slightly – a desirable result because low Aβ42 in CSF and plasma indicates AD. This increase, significant only in plasma, is consistent with PTI-125's 1,000-fold reduction of Aβ42's femtomolar binding affinity to α7nAChR. All reductions of CSF and plasma biomarkers were at least $p \leq 0.001$ by paired t test. Target engagement was shown in lymphocytes by a shift in FLNA's conformation from aberrant to native: 93% of FLNA was aberrant on Day 1 vs. 40% on Day 28. As a result, FLNA linkages with α7nAChR and TLR4, and Aβ42 complexes with α7nAChR and CD14, were all significantly reduced by PTI-125 treatment. **Conclusions:** This first-in-patient trial with PTI-125 demonstrated reductions in both CSF and plasma biomarkers of AD pathology, neurodegeneration, and neuroinflammation. All patients responded to treatment. The magnitude and consistency of reductions in established, objective biomarkers imply that PTI-125 treatment counteracted disease processes and reduced the rate of neurodegeneration. These encouraging early results support PTI-125 as a new, highly differentiated and potentially disease-modifying treatment for AD. This work was funded by NIA grant AG060878.

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

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

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

Background: Highly sensitive and specific plasma biomarkers for Alzheimer's disease (AD) have the potential to improve diagnostic accuracy in the clinic and facilitate research studies including enrollment in prevention and treatment trials. Blood-based biomarkers of AD pathology will be needed to

screen the general population when prevention treatments for AD become available, as cerebrospinal fluid (CSF) and PET scan approaches are not feasible. Total tau (t-tau) and some phosphorylated tau (phospho-tau or p-tau) isoform levels are significantly increased in AD CSF. However, relatively poor correlations between plasma tau and CSF tau levels have been a challenge in developing plasma tau as a biomarker for AD. Recent reports using immunoassays suggest more promising developments; for example, some reports indicate slight plasma total-tau increases in mild cognitive impairment (MCI) and AD, and several studies demonstrated plasma phospho-tau at threonine 181 (pT181) increases in AD at MCI and moderate stages. However, AD diagnosis using blood t-tau and pT181 has been restricted to the symptomatic stages of AD and with moderate levels of accuracy. Recent advances in blood amyloid-beta biomarkers measures by mass spectrometry (MS) have transformed the approach to AD clinical research. We sought to determine the relationship of blood tau-based measures to CNS measures of AD pathology and clinical stage of dementia using similar MS-based approaches. **Objectives:** 1) To determine the potential utility of plasma phosphorylated tau (phospho-tau or p-tau) isoforms to detect AD pathology and clinical stages of AD dementia. 2) To assess CSF and plasma tau isoform profile relationships to inform about the biology of tau in AD. 3) To design a MS assay for potential use as a reference method for plasma tau and phospho-tau quantitation. **Methods:** Plasma collected from the tau Stable Isotope Labeling Kinetics (SILK) study were pooled for each participant in order to obtain large volumes and detect minor tau species and phospho-tau isoforms in plasma by MS. The plasma tau isoform profile was compared to matching CSF tau isoform profiles, amyloid status, and clinical stage of AD dementia for each participant. This discovery cohort includes 34 participants selected according to their amyloid status. Amongst them, 15 amyloid positive participants had various Clinical Dementia Rating (CDR) scores of 0 (5 participants), 0.5 (8 participants), and 1 (2 participants). All preclinical AD participants (amyloid positive, CDR=0) had tau PET AV-1451 SUVR measures not significantly different from amyloid negative participants. Total-tau (t-tau) and phosphorylated tau peptides at T181, T217 and S202 detected in plasma extracts were quantified by MS. Absolute levels of tau and phospho-tau along with p-tau/t-tau ratios were measured and compared to results obtained from matching CSF. **Results:** Similar to CSF tau, plasma tau was truncated. As previously reported, no correlation was found between CSF and plasma total-tau levels. Similarly, we found no correlation between CSF and plasma pS202. In contrast, CSF and plasma pT217 measures (absolute level and pT217/T217 ratio) were highly correlated (r=0.78), and a lower correlation was determined for those of pT181 (r=0.68). Further, pT217 and pT181 were highly specific for amyloid plaque AD pathology (AUROC=0.99 and 0.95 for pT217 and pT181 levels and 0.98 and 0.98 for pT217/T217 and pT181/T181 ratios respectively). **Conclusions:** The results of this study demonstrate higher phosphorylation status of CNS tau on T217 and T181 compared to peripheral tau. This makes AD-specific tau modification detectable in plasma despite the major contribution of peripheral tau to overall plasma tau level. This finding appears to support the use of plasma pT217 and pT181 as blood biomarkers of AD pathology even at the asymptomatic stage.

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

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

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

Background: Research and clinical work in agitation has been hampered by a lack of agreed upon definition for agitation. In the absence of a gold standard, clinical response has been measured as a function of overall clinical impression, or improvement on either agitation specific rating scales or agitation domains of general psychopathological measures. In 2015, the International Psychogeriatric Association (IPA) Agitation Definition Working Group developed a definition for agitation to help facilitate research in the field. Important features of the definition are the requirement of distress due to the behaviours, and the breakdown of agitation into three domains: excessive motor activity (EMA), verbal aggression (VA), and physical aggression (PA). However, despite the development of the criteria, there are no definition specific measurements, nor any information on how to measure meaningful change using the new definition. **Objectives:** To describe the modified Delphi process for the mapping of items from the Cohen Mansfield Agitation Inventory (CMAI) and the Neuropsychiatric Inventory Clinician rating (NPI-C), onto IPA agitation definition domains to generate derivative measurement instruments, the CMAI-R and and NPI-R. To assess psychometric properties of these derivative instruments and to estimate a minimal clinically important difference (MCID) in agitation, when compared to the Clinician Global Impression of Change (ADCS-CGIC) in participants from a multi-center observational study. **Methods:** The modified Delphi process included clinicians (N=7) and researchers (N=2) with expertise in agitation in dementia. As a first, step, items from the CMAI and the NPI-C were reviewed by ZI for relevance to any of the three domains: EMA, VA, or PA. For the CMAI, all items were included, and for the NPI-C, all questions from the agitation, aggression, aberrant motor activity, abnormal vocalizations, disinhibition, and irritability/lability domains were included. As a next step, all relevant questions were incorporated into an online survey and rated by the Delphi Panel as 1 (none), 2 (weak), or 3 (strong) for association to each of the three IPA definition domains. For each item, if mean score was ≥2.5, the item was included and applied to the corresponding domain, and if <1.5, the item was discarded. Items with scores from 1.5-2.5 were retained for further discussion. These residual items were discussed via teleconference and assigned to a domain if 80% consensus was reached. Items that did not distinctly map onto one domain were discarded. To determine the association with parent and derivative change scores and MCID, data were analysed for 262 participants in the multi-centre French A3C study, an observational cohort of clinic and nursing home patients with Alzheimer's Disease (AD) dementia and clinically significant agitation. The CMAI, NPI-C and ADCS-CGIC were assessed on all participants at baseline and 3 months. MCID was estimated as the CMAI, CMAI-R, or NPI-R scale change score between baseline and 3 months that predicted an ADCS-CGIC score of 1 or 2 (Marked or Moderate Improvement) at the 3-month study timepoint. Sensitivity, Specificity, and Area Under the ROC Curve (AUC) were calculated for each using the Youden Point. **Results:** The correlation between the CMAI and CMAI-R was 0.84. For the original CMAI, a -4 point change captured the MCID with a sensitivity of 76% and specificity of 89% (AUC 0.82). For the derivative CMAI-R, a -2 point change captures MCID with a sensitivity of 76% and specificity of 89% (AUC 0.82). For the derivative NPI-R, a -4 point change captured the MCID with a sensitivity of 79% and a specificity of 90% (AUC 0.85). The AUCs were not significantly different between CMAI-R and NPI-R. **Conclusion:** The CMAI-R had comparable psychometric properties to the parent CMAI, and to the NPI-R. These findings demonstrate the utility of derivative scales in capturing improvement in agitation in those with clinically significant symptoms. IPA agitation domain-specific measures are an important advance in measurement and management of agitation in dementia. In the absence of current gold standard outcome, these results may optimize future clinical trials of treatments for agitation symptoms in AD. Next steps include assessing the contribution of each individual domain in MCID for agitation.

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

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

Research Institute, Gerontopole, Exhonit Therapeutics SA, Avid Radiopharmaceuticals Inc.

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

Background: The Clinical Dementia Rating (CDR) is an instrument used to detect the presence or absence and, when present, the severity of dementia symptoms. It assesses change from previously attained levels in 6 cognitive and functional domains. The CDR is widely used in observational studies of Alzheimer disease and in clinical trials, both as a screening measure and a primary outcome. It has established reliability and is able to identify even very mild symptoms of dementia with high diagnostic accuracy based on neuropathogical examination. To determine the CDR, an experienced clinician conducts semi-structured interviews with the individual and with a study partner to assess change from prior levels of performance to determine the presence or absence of dementia and its severity. Although all available information is synthesized to generate the global CDR score using an established algorithm, it is likely that specific questions are more sensitive to disease stage than others. The current study seeks to use Item Response Theory (IRT) to identify specific items from the semi-structured interviews that contribute most to CDR staging to produce a shorter version of the CDR without compromising its reliability, and to facilitate the development of an online CDR (eCDR). A shortened version will ultimately aid in its deployment as a screening instrument in the general population and accelerate enrollment into clinical and observational studies. **Objectives:**To evaluate the difficulty, discrimination, and information levels of each item in the CDR and identify the most informative items or the need to exclude some least-informative items. To develop the best fitting IRT models for predicting cognitive impairment and validate its performance using existing measures: CDR global and box scores. **Methods:** Baseline data from 2894 participants enrolled in the Washington University Memory and Aging project who had a global CDR no greater than 1 were analyzed in this study. Items were modeled as ordinal variables containing 2-5 response options. Confirmatory factor analysis was performed to compare various IRT models to identify the best fitting model for further measure development/refinement. The tested models included (1) a unidimensional IRT model with all items contributing to a general factor; (2) a multidimensional IRT model with six correlated factors for 6 domains in the CDR; (3) a bi-factor model with a general factor indicated by all items and six factors corresponding to the 6 domains of the CDR. The general factor was specified to be independent of the domain specific factors, while the correlations between the domain specific factors were estimated; and (4) same bi-factor model as in (3) but with separate factors for study participants and their informants nested within each domain. The difficulty and discrimination parameters of each item were examined, and item information curves were compared across items to select the most informative items. General factor scores and domain specific factor scores were generated using the best fitting model, and their relationship with the CDR global and box scores were evaluated using 10 fold cross-validation. **Results:** Among the 2894 participants, 46% were CDR 0, 32% were CDR 0.5 and 22% were CDR 1. Sixty-four items from the CDR with available data were included in IRT models. The Home and Hobbies domain only has one item with data available and therefore was excluded from the IRT analysis. The fourth model (bi-factor model with correlated domain and participants/informant specific factors) provided the best representation of the factor structure of the CDR. Moderate correlations were observed among Community Affairs, Memory, Orientation, and Judgement and Problem Solving domains, while the Personal Care domain was less correlated with other domains. Of the original 64 items, 53 that demonstrated high discriminative power and factor loadings were kept in the final bi-factor model for estimation of general factor scores and domain specific factor scores. These estimated scores were highly predictive of the CDR global and box scores: volume under the surface (VUS) of 0.94 for the overall factors in predicting global CDR, VUS of 0.82, 0.87, 0.91, 0.85 and 0.96 for the domain specific factor scores in predicting Community Affairs, Judgement and Problem-Solving, Memory, Orientation, and Personal Care domain box scores respectively. **Conclusion:** The IRT analysis indicates that majority of the items in the CDR discriminate well at mild and very mild levels of cognitive impairment, which is consistent with the reliability of the CDR. A small number of least-informative items could be excluded to reduce the burden on study participants and clinicians. The shortened version of the CDR still demonstrated very high classification accuracy and is well suited for development of an online CDR (eCDR). The general and domain specific factor scores estimated from the bi-factor model potentially could be used as a continuous outcome (as opposed to an ordinal ranking of CDR) in clinical trials to increase the sensitivity in detecting cognitive decline.

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

Background: Cognitive decline, the hallmark of dementia and Alzheimer's disease, is caused by the loss of nerve cells and synaptic dysfunction. NA-831 is an endogenous small molecule that exhibits neuroprotection, neurogenesis, and cognitive protective properties across a range of disease models. In the Phase 1 studies, no adverse effects were observed. It is well-tolerated up to 100 mg/day in healthy volunteers. Predictable pharmacokinetics including dose-dependent exposure linearity and low variability. **Method:** A randomized clinical trial of NA- 831 was performed in a total of 56 patients: 32 Alzheimer patients with MCI, and 24 patients with early onset of Alzheimer's disease over 24 weeks, with an additional follow-up over 24 weeks. The patients with MCI received 10 mg of NA-831 or placebo orally per day. The patients with mild and moderate Alzheimer's disease received 30 mg of NA-831 or placebo orally per day. The study was conducted in accordance with the Declaration of Helsinki and ICH and GCP guidelines. Inclusion criteria included: (a) male or female, at 55-80 years of age at screening, (b) For MCI patients, MMSE score ≥20. For patients with mild and moderate Alzheimer's disease, MMSE score> 17 (c) Center for Epidemiological Studies-Depression (CES-D) score <27. Patients were randomly assigned to NA-831 at a daily dosage of 10 mg- 30 mg or matched placebo (1:1). The primary outcome measures were the changes in ADAS-Cog-13, Brief Cognitive Rating Scale (BCRS) and Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus)

after 24 weeks. **Result:** Based on the BCRS, the effects of NA-831 were apparent after 12 weeks of treatment (p=0.001), with the significant improvement in: fatigue, anxiety, irritability, affective lability, disturbance to waking, daytime drowsiness, headache, and nocturnal sleep. NA-831 showed a significant improvement for patients with MCI with ADAS-Cog-13 score change of an average of 3.4 as compared to the placebo (p=0.01). In addition, NA-831 showed a significant improvement for patients with mild and moderate Alzheimer's disease, with ADAS-Cog-13 score change of an average of 4.1 as compared to the placebo (p=0.001). CIBIC-Plus showed 79.3% vs. 21.7 % patients improved; P = 0.01). NA-831 was well-tolerated at high dosage up to 50 mg per day. No adverse effects were observed. **Conclusion:** Over the 24 week treatment period, NA-831 was effective for improving cognitive and global functioning in patients with mild cognitive impairment. As an endogenous compound, NA-831 is well-tolerated and has excellent safety profile. **Future Studies:** The company plans to start two phase 3 programs: (1) the TREATMENT Phase 3 clinical trial on 465 patients with mild and moderate Alzheimer' disease taking one capsule of 30 mg per day orally over 52 weeks; (2) the PREVENTION Phase 3 clinical trial on 585 asymptomatic subjects taking one capsule of 10 mg per day over 104 weeks.

LB15: THE CHARIOT-PRO SUBSTUDY: BASELINE CHARACTERISTICS OF THE FULLY ENROLLED COHORT.

Gerald NOVAK (1), Susan BAKER (1), Chi UDEH-MOMO (2), Geraint PRICE (2), Tam WATERMEYER (3), Celeste LOOTS (2), Natalia REGLINSKA-MATVEYEV (3), Luc BRACOUD (4), Craig RITCHIE (3), Lefkos MIDDLETON (2) *((1) Janssen R&D, United States, (2) Imperial College London, United Kingdom, (3) University of Edinburgh, United Kingdom, (4) Bioclinica, France)*

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

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

Objectives: [18F]PI-2620 is a novel tau PET-tracer that accumulates in regions of tau pathology. The study objective was to evaluate regional tau deposition using [18F]PI-2620 PET tracer in a sub-study of the elenbecestat MissionAD program in patients with MCI due to AD or mild AD dementia and to correlate it to the amount of amyloid-beta deposition as determined by Neuraceq PET in this unique patient population. **Methods:** Patient sub-study inclusion criteria were: MCI due to AD or mild AD dementia including: MMSE ≥ 24, CDR global score of 0.5, CDR Memory Box score ≥ 0.5, and impaired episodic memory confirmed by a list learning task. All subjects were amyloid PET positive by visual read of Neuraceq PET scan. Neuraceq composite SUVr (cSUVr) was calculated using the mean SUVR from frontal, parietal, lateral temporal, anterior and posterior cingulate and occipital cortex. The study population was divided into 4 groups based on Neuraceq cSUVr levels. The lowest threshold, cSUVr =1.25, was determined from 2 SD above a group of 70 young healthy controls (age: 20-40). The 2nd threshold 1.48 was determined from the Phase 3 histopathology data as the point that differentiated low/sparse plaques from moderate/frequent plaques. The Neuraceq positive group, cSUVr > 1.48, was divided in half to create two equal size groups. These groups are designated very low, low, intermediate and high amyloid-beta. [18F]PI-2620 PET scans were obtained from 60-90 min p.i.. Individual MRI-based subregions including hippocampus (HC), parahippocampus (PHC), amygdala, fusiform gyrus and others were investigated by SUVr analysis. Cerebellar cortex was used as reference region (vermis and anterior cerebellar gray matter contiguous to the vermis was excluded). Z-score maps were generated using a template of n=10 healthy control subjects for comparison. In a region-by-region comparison between the HC and MissionAD subjects, SUVr mean +3 SD was used. Visual assessment of [18F]PI-2620 tau PET scans was performed as well. Scans with uptake above cerebellar background in mesial-temporal, temporo-parietal and cortical regions were considered positive. **Results:** 78 visually amyloid-beta positive subjects were included in the tau PET substudy. Tau PET scans of 77 subjects were evaluable (mean age 75.9 ± 6.5 yrs). The MMSE in the tau PET group was 27.0±1.7; CDR-SB was 2.34±0.97. [18F]PI-2620 accumulation was observed in 52% and 61% by visual and quantitative assessment, respectively, in the overall population. 38 subjects were positive both visually and quantitatively (49%), 9 subjects were only positive quantitatively (12%) and 2 subjects were visually positive only. 28 subjects were negative both visually and quantitatively (36%). A third of the apparent tau positive cases had isolated mesial temporal uptake consistent with early disease. A strong correlation was seen between amyloid-beta load and [18F] PI-2620 accumulation. All subjects with very low amyloid-beta (cSUVr < 1.25) were visually tau PET negative. 19% of Subjects in the low amyloid "grey-zone" (1.25 ≤ cSUVr ≤ 1.48) were visually tau PET positive. 48% of subjects with intermediate amyloid-beta 1.48<cSUVr ≤ 1.73 and 79% of subjects with high amyloid-beta cSUVr > 1.73 were found tau PET positive. **Conclusion:** Tau PET positivity was highly associated with amyloid-beta load. The lowest amyloid load with positive [18F]PI-2620 deposition in this population was cSUVr = 1.43. The subjects recruited in the MissionAD tau PET substudy represents a very early AD population.

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

Background: Existing mild cognitive impairment (MCI) guidelines suggest no treatment. This conclusion stems from performance on standardized tests. Might data from patients or their carers on the symptoms that they experience, and their importance, suggest a different understanding? The SymptomGuide® Dementia app (SG-D) tackles the heterogenous manifestations of cognitive impairment by allowing users (patients and/or caregivers) to identify, describe, and track their most important symptoms. Since its web launch in 2006, over 4000 users have created individualized profiles, from a menu now grown through clinician, patient and caregiver input to 67 symptoms. These many symptoms highlight how the heterogeneity of cognitive impairment challenges measurement and treatment. **Objective:** Using a novel supervised staging algorithm, we explored, in the SG-D database, how symptom characteristics and patterns varied across degrees of cognitive impairment. **Methods:** Staging: We analyzed baseline profiles recorded from 2006-05-15 to 2018-11-15. Patient age and symptoms formed inputs to a supervised Support Vector Machine learning algorithm to classify profiles as either MCI, or Mild, Moderate or Severe dementia. We trained the algorithm using symptom profiles from a memory clinic and two dementia clinical trials that each used Goal Attainment Scaling. (See poster 00164 for details on the algorithm training and performance of the model.) Analysis: Across stages, we compared symptom tracking frequency and descriptions (each symptom lists 8-12 descriptors of specific manifestations; users can also add their own). We also analyzed symptom potency. Users can rank symptoms by importance from 1 (least important) to N (most important; the number of symptoms tracked). We calculated individual potency rankings as a weighted rank (rank/N) for each user's symptoms. Descriptive statistics were calculated as percentages, means ± standard deviations, or medians [25-75th percentiles], as appropriate. **Results:** Of 4213 users, data were insufficient for staging on 304 (7.2%; no age provided, and/or only one symptom) yielding 3909 baseline profiles. The staging algorithm classified 916 MCI, 1592 Mild, 514 Moderate and 876 Severe profiles. Average patient age generally increased with stage: 71±13, 74±13, 81±13, and 78±13, for MCI, Mild, Moderate and Severe, respectively. MCI profiles tracked fewer symptoms (median 2) versus profiles in Mild (5), Moderate (7), and Severe (4) dementia. The most frequently tracked MCI symptoms were Recent Memory (33.4% of profiles), Verbal Repetition (22.8%), and Language Difficulty (15.6%). Eight of the 10 most frequently tracked symptoms were common to both MCI and Mild profiles. Insensitivity and Social Withdrawal ranked higher in MCI, versus Comprehension, and Sleep Disturbances in Mild. Symptom overlap decreased with increasing severity: 5/10 and 1/10 of the top MCI symptoms were shared with Moderate and Severe profiles, respectively. Language Difficulty

was the symptom shared by MCI (15.6% of profiles) and Severe dementia (14.4%) but was distinguishable in its specific descriptions. At the descriptor level, Language Difficulty in MCI most often referred to "Complains of not being able to say what they mean" versus "Has trouble explaining a thought or idea" or "Relies on others to guess what they mean" in Severe. The most important symptoms typically were among the least frequent. For example, the top three symptoms tracked among all profiles were Travel, Hobbies/Games and Looking After Grandchildren. Their median weighted ranks were 0.90, 0.83 and 0.82, but were tracked only in 4.2%, 8.4% and 2.0% of profiles, respectively. Only Impaired Initiative was both frequent (14.3%) and potent (median weighted rank 0.75). This discrepancy between frequency and potency was consistent across stages. The most important symptoms ranked by MCI profiles were Inappropriate Language (median rank 1; 4.0%), Incontinence (1; 1.1%), and Operating Gadgets/Appliances (1; 1.0%). Across all stages, four symptoms were common to all top 10 most important: Hobbies/Games, Looking After Grandchildren, Operating Gadgets/Appliances and Travel. In contrast, no symptoms among the top 10 were the most frequent at any stage. **Conclusion:** In complex illnesses with cognitive impairment, involving patients and their families/caregivers through individualized symptom tracking is self-evidently clinically meaningful. Here, we used an online cognitive symptom tracking tool to gain insights into what is most important to people with cognitive impairment and their caregivers at each stage. We found a high degree of overlap in the most frequent MCI and Mild dementia symptoms. In contrast there was little overlap between MCI and later stage dementia. Across all stages, symptom potency was inversely related to symptom frequency. The most important symptoms consistently concerned leisure and family. Online tracking can help clinicians to take a personalized approach towards management of patients with cognitive impairment. These findings will inform further research in MCI.

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

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

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

Background: Synaptic loss is an early and robust pathology in Alzheimer disease (AD) and the major structural correlate of cognitive impairment. In a small preliminary study using [11C] UCB-J–PET we have previously shown significant reductions in hippocampal SV2A specific binding as a marker of synaptic density in participants with AD (Chen M, et al. Assessing synaptic density in Alzheimer disease with synaptic vesicle glycoprotein 2A positron emission tomographic imaging. JAMA Neurol. 2018;75:1215). However, postmortem studies have suggested more widespread neocortical reductions in synaptic density in AD. **Methods:** In the present study we measured SV2A binding in a larger sample of participants with early AD and cognitively normal (CN) individuals. Participants were scanned on the HRRT after bolus injection of [11C]UCB-J. We first re-examined and compared the suitability of reference regions (the white matter of centrum semiovale [CS]—which we previously used—versus cerebellum [Cb]) in a subset of participants who had undergone arterial blood sampling for 1-tissue compartment (1TC) modeling to estimate the distribution volume VT. We compared VT between groups for Cb and CS. We then generated parametric images of BPND for the full participant sample using SRTM2 and CS as the reference region. DVR with a CS reference region (DVRCS) = BPND+1. Finally, DVR with a Cb reference region (DVRCb) of each voxel was computed from DVRCS as (BPND+1)/(BPND[Cb]+1). **Results:** The study sample consisted of 34 participants with early AD (MMSE = 23.1±4.1, CDR = 0.5-1.0), who were all Aβ+ by [11C]Pittsburgh Compound B [11C]PiB) PET and spanned the disease stages from amnestic Mild Cognitive Impairment (aMCI, n = 14) to mild dementia (n = 20); and 19 who were CN (MMSE = 29.3±1.1, CDR = 0) and confirmed Aβ– by [11C]PiB PET. In the subset of participants (18 AD, 12 CN) with arterial blood sampling, values of VT were very similar between groups for CS and Cb, supporting the validity of both reference regions. Moreover, values of DVRCb converted from DVRCS (obtained from SRTM2) were very highly correlated with values of DVRCb obtained with the 1TC model across all brain regions. Finally, values of DVRCb showed considerably

lower variability than DVRCS across brain regions of interest, suggesting it's practical superiority in AD studies. Our primary analysis of group differences in SV2A binding demonstrated a significant effect of group ($F(1,51) = 33.4$, $P < 0.00001$) and group*region ($F(10,510) = 2.4$, $P = 0.01$) as predictors of SV2A binding (DVRCb). Post-hoc comparisons revealed significant group differences in all medial temporal regions, as well as more broadly in neocortical regions. SV2A reductions in AD compared to CN participants were most pronounced in the hippocampus (DVRCb –17.3%, $P < 0.00001$; BPND –19.8%) and entorhinal cortex (DVRCb –15.7%, $P < 0.00001$; BPND–17.6%) but were also present in the parahippocampal cortex, amygdala, lateral temporal cortex, prefrontal cortex, posterior cingulate cortex/precuneus, lateral parietal cortex, and pericentral cortex. These reductions were largely maintained after correction for volume loss and were more extensive than decreases in gray matter volume. **Conclusion:** We observed widespread reductions of synaptic density with [11C]UCB-J PET in medial temporal and neocortical brain regions in early AD compared to CN participants. Most of these reductions were maintained after PVC and thus are not attributable solely to gray matter tissue loss. Further longitudinal studies are needed to characterize the temporal course of synaptic alterations in AD in relation to amyloid and tau deposition, as well as the associations with cognitive and functional change. Future studies will continue to evaluate the utility of SV2A PET for tracking AD progression and for monitoring potential therapies.

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

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

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

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

LB22: CUT POINTS FOR COGNITIVE DECLINE USING MMSE DEFINE BASELINE AND LONGITUDINAL DIFFERENCES IN BOTH CLINICAL AND PATHOLOGICAL ALZHEIMER'S DISEASE BIOMARKERS. James DOECKE (1), Marcela CESPEDES (1), Cai GILLIS (2), Nancy MASEREJIAN (2), Pierrick BOURGEAT (3), Chris FOWLER (4), Victor VILLEMAGNE (5), Qiao-Xin LI (4), Steven COLLINS (4), Stephanie RAINEY-SMITH (6, 7), Paul MARUFF (4), Ralph MARTINS (6, 8, 9), David AMES (10), Colin MASTERS (4) *((1) Australian e-Health Research Centre, CSIRO, Australia, (2) Biogen, United States, (3) Australian e-Health Research Centre, CSIRO, Brisbane, QLD, Australia., Australia, (4) The Florey Institute, The University of Melbourne, Australia, (5) Austin Health, Department of Molecular Imaging and Therapy, Center for PET, Australia, (6) Sir James McCusker Alzheimer's Disease Research Unit (Hollywood Private Hospital), Australia, (7) Centre of Excellence for Alzheimer's disease Research and Care, School of Medical and Health Sciences, Edith Cowan University, Australia, (8) Department of Biomedical Sciences, Macquarie University, Australia, (9) School of Psychiatry and Clinical Neurosciences, University of Western Australia, Australia, (10) National Ageing Research Institute, Australia)*

Background: Heterogeneity of disease progression among patients with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) has been observed in multiple observational and clinical studies. Prior work has examined classifying progression into "fast" or "slow" based on change in MMSE score over time. However, definitions of what qualifies as fast and slow progression have varied among studies. Understanding how decline in MMSE score is related to future disease progression has the potential to inform how other pathological and clinical measures, are associated with more severe decline. **Objectives:** In this study, we examined prespecified cut-points of MMSE score change over 18 months to determine how these cut-points were associated with baseline and annual rates of change in other cognitive and clinical measures. **Methods:** Amyloid positive participants (classified as either PET-Aβ+ via a Centiloid value of greater than 20, or a CSF Aβ42 (INNOTEST) value of less than 544ng/L) diagnosed with either MCI or AD from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing were included in the study. Cognitive decline groups were defined as either fast: those participants with a six point or greater loss on the MMSE over a period of 18-months; moderate: those participants with a loss of at least three but less than six points on the MMSE over a period of 18-months; and slow: those participants with a loss on the MMSE of less than three points over 18-months. Unadjusted pairwise comparisons between cognitive decline groups (slow vs. fast decliners, moderate vs. fast decliners) at

baseline were performed using Welch's T-test. For longitudinal comparisons of imaging and cognitive measures between cognitive decline groups, Linear Mixed Effects models (LME) with a random intercept was used. **Results:** In our study, a total of 52 participants were classified as fast decliners, 56 participants were classified as moderate decliners and 74 participants were classified as slow decliners. No participants were in two or more groups. Compared with moderate and slow decliners at baseline, fast decliners had lower mean grey matter values (slow decliners: 444.49 [SD: 23.71], moderate decliners: 434.75 [SD:22.8], p=0.02 & fast decliners: 419.69 [SD: 23.57], p=0.0001); lower mean hippocampal volume (compared with slow decliners only, slow decliners: 5.38 [SD:0.58], fast decliners: 4.65 [SD: 0.77], p=0.0002); lower mean levels of CSF Aβ42 (compared with slow decliners only, slow decliners: 698.44 [SD: 146.49], fast decliners: 512.33 [SD: 50.71], p=0.0007); higher mean CDR Sum of Boxes (CDR-SB) score (slow decliners: 1.05 [SD: 1.07], moderate decliners: 2.74 [SD: 2.2], p<0.0001 & fast decliners: 4.64 [SD: 3.3], p<0.0001); and higher mean AIBL Preclinical Alzheimer's Cognitive Composite (AIBL PACC) scores (slow decliners: -4.39 [SD: 2.75], moderate decliners: -5.9 [SD: 2.6], p=0.002 & fast decliners: -8.36 [SD: 3.04], p<0.0001). Fast, moderate and slow decliners were not significantly different in age, gender, level of education, or APOE ε4 allele status (p>0.05). Annual rates of decline were significantly worse for fast decliners compared to moderate and slow decliners in relation to AIBL PACC score (slow decliners: β: -0.022 [SE:0.02], moderate decliners: β: -0.357 [SE:0.04], fast decliners: β: -0.719 [SE: 0.13], p<0.0001) and CDR-SB (slow decliners: β: 0.025 [SE: 0.02], moderate decliners: β: 0.254 [SE: 0.03], fast decliners: β: 0.579 [SE: 0.03], p<0.0001). Amongst the imaging measures, beta coefficients representing group-wise rates of atrophy for ventricular volume showed the strongest stepwise increases (slow decliners: β: 0.066 [SE: 0.01], moderate decliners: β: 0.154 [SE: 0.02], fast decliners: β: 0.176 [SE: 0.19], p<0.002). Given the majority of participants had only one follow up, values from testing other imaging measures were not stable, and as such are not shown here. Group-wise comparisons from the LME assessments are shown adjusted for age, gender and APOE ε4 allele status, and are conservative estimates given the relative group sample sizes. **Conclusion:** Classifying individuals as fast, moderate and slow decliners by change in MMSE score over 18 months, indicated significant differences among these groups both at baseline and for rate of change in cognitive and imaging measures. These findings suggest that these markers may be useful in identifying those individuals that will have a clinically meaningful change in a short period of time.

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

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

ADAS-cog score. **Conclusions:** This work highlights a new technology that can significantly decrease the time required to run clinical trials in AD. Unlearn's model, which can generate digital twin control subjects, can provide purely synthetic controls for single-arm exploratory trials or supplementary control data for pivotal trials. Both of these applications significantly reduce the number of trial subjects, reducing recruitment time and bringing new therapeutics to market more rapidly.

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