Review

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ADVANCING ALZHEIMER'S DISEASE TREATMENT: LESSONS FROM CTAD 2018

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Abstract

The 2018 Clinical Trials on Alzheimer's Disease (CTAD) conference showcased recent successes and failures in trials of Alzheimer's disease treatments. More importantly, the conference provided opportunities for investigators to share what they have learned from those studies with the goal of designing future trials with a greater likelihood of success. Data from studies of novel and non-amyloid treatment approaches were also shared, including neuroprotective and regenerative strategies and those that target neuroinflammation and synaptic function. New tools to improve the efficiency and productivity of clinical trials were described, including biomarkers and machine learning algorithms for predictive modeling.

Key words: Alzheimer's disease, clinical trials, therapeutics, recruitment, predictive modeling

Introduction

The Clinical Trials on Alzheimer's Disease (CTAD) conference, held each year since 2008, has become a major venue for clinical trialists and other researchers from academia and industry to share learnings from recent clinical trials and learn about new therapeutics and diagnostics in development. Convened in Barcelona, Spain in October, 2018, CTAD welcomed approximately 1200 delegates from around the world to share data from studies conducted across the spectrum of development, ranging from early stage studies of novel therapeutics targeting a range of mechanisms, to results from later stage trials including those that failed to show efficacy. Investigators shared information on the pathophysiological underpinnings of these studies, clinical and biomarker results, as well as experiences with participant recruitment, outcome measures, trial design, and data management and analysis.

Gaining insight from negative trials

A central goal of the conference is to advance the development of effective treatments for Alzheimer's disease (AD) by applying lessons learned in ongoing clinical trials as well as completed trials, including those that failed to demonstrate efficacy or that were terminated for other reasons. For example, beta-secretase inhibitors (BACEi) emerged in recent years as one of the most promising classes of drugs for treatment of AD. However, disappointing results from multiple Phase 3 clinical trials have tempered some of the optimism surrounding BACE inhibition, prompting investigators from multiple companies developing drugs in this class to come together and jointly examine the potential benefits and risks of BACE inhibition.

BACE1 is an enzyme that cleaves the amyloid precursor protein as the first step in the production of Aβ peptide, the primary constituent of amyloid plaques in the AD brain. In animal models of AD, BACE1 deletion reduced production of Aβ and plaque load, and improved cognition (1). Last year, Merck terminated a study of the BACE1 inhibitor verubecestat in mild to moderate AD when an interim analysis showed that the drug was ineffective at slowing the rate of cognitive decline (2). Reasoning that the drug might be more effective if given earlier in the disease process, before substantial buildup of plaque, the company continued their trial in prodromal AD. But in February 2018, the company stopped the trial after an independent data monitoring committee determined that there was no evidence of efficacy. Even more troubling, data presented at CTAD2018 showed that verubecestat treatment in prodromal AD was associated with worsening on all clinical measures and an increase in adverse events (3).

These results raise many unanswered questions. For example, the rapid onset of cognitive worsening might be related to a dramatic lowering of Aβ or to an off-target activity of the drug. Notable, the rapid loss of Aβ may have deleterious effects on neurotransmission or synaptic function (4). Key questions include whether the negative effect was related to dose, duration of treatment, or the specific population enrolled in the trial.

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To promote open sharing of data from the many trials conducted by academic and industry scientists, the Alzheimer's Association sponsored an emergency session at CTAD to explore emerging results from other BACE inhibitor trials, including Janssen's EARLY trial of atabecestat in preclinical AD, which was terminated in May 2018 because of elevations in a liver enzyme seen in about a third of patients. Although the levels returned to baseline, Janssen determined that the benefit risk profile of the drug was not appropriate for a preventive treatment. A preliminary analysis of data from the study suggested that there was a rapid-onset, dose-related worsening on cognitive measures. Data were also presented from a Phase 2 study of Lilly's BACEi LY3202626, another study that was terminated early due to a low probability of success; these data also suggested adverse effects on cognition. Importantly, many of these trials have collected rich biomarker and imaging data, which will be analyzed in the coming months along with cognitive and clinical data to see what else can be learned. The newly formed Alzheimer's Clinical Trials Consortium (ACTC) could serve as a neutral party to analyze data across multiple studies.

In a separate symposium, a panel explored whether BACE1 is a suitable drug target for the prevention and treatment of AD. Possible reasons for the disappointing results seen in many of the BACEi trials could be related to treatment starting too late or using doses that are too high. Indeed, it was suggested that BACE1 inhibition may be ideal for primary prevention and that dominantly inherited AD is a predictable model in which to study such interventions. The Dominantly Inherited Alzheimer's Network (DIAN) and the Alzheimer's Prevention Initiative (API) have shown that amyloid accumulation becomes significant as much as 15 years before symptoms appear in people with autosomal dominant forms of AD (5, 6), which gives investigators the opportunity to decide when and how to intervene using adaptive designs.

New data from ongoing trials

CTAD also provided sponsors the opportunity to share updated information on ongoing trials, especially of Phase 3 trials of amyloid targeting monoclonal antibodies. Highly anticipated data were presented to support claims presented earlier in 2018 suggesting disease-modifying effects for the anti-amyloid monoclonal antibody BAN2401, currently being developed jointly by Eisai and Biogen. The BAN2401 antibody is specifically aimed at species of the Aβ protein called protofibrils that are thought to be most toxic to brain cells. Top line results from the phase 2 study 201 indicated that the drug may slow cognitive decline and reduce plaque buildup in the brains of people with early AD. However, the data initially presented left unanswered questions about the degree to which participants' APOE4 status may have skewed results of the study.

The reason for concern was that in the middle of study 201, health authorities decided that APOE4 carriers should no longer be randomized to the highest dose of BAN2401 because of the risk of developing amyloid-related imaging abnormalities (ARIA). This change led to an imbalance in the number of APOE4 carriers in the high-dose group, which was also the group showing the greatest treatment effect. At CTAD, investigators presented data from additional subgroup analyses as well as cerebrospinal fluid (CSF) biomarker results that were not previously available, which lent some support to Eisai's theory that apparent treatment effects are driven by the drug itself and not to an imbalance of APOE4 carriers. Moreover, positron emission tomography (PET) imaging studies indicate that treatment with BAN2401 results in significant clearance of brain amyloid accompanied by favorable clinical effects. Nonetheless, some critics of the research remained uneasy about the complex trial design and unconvinced that concerns about the imbalance of APOE4 carriers had been laid to rest by the subgroup analyses. There was general enthusiasm for launching Phase 3 studies to provide definitive answers.

Revisiting older treatment strategies

At CTAD2018, vaccination re-emerged as a promising treatment strategy with data from a Phase 2a study of UB-311, an active anti-amyloid immunotherapy vaccine with the potential to prevent AD (7). Vaccination against amyloid is not a new idea. In 1999, Schenk and colleagues demonstrated in mice that active vaccination against neurotoxic forms of Aβ reduced levels of Aβ in the brain and improved performance on memory tasks (8). But a subsequent clinical trial of AN-1792, a vaccine against Aβ42, was terminated in 2002 because of an increased incidence of encephalitis, elicited by the production of cytotoxic T cells (9). The sponsor of the UB-311 study, United Neuroscience, Inc, has developed a platform that uses synthetic peptides to generate endogenous target-specific antibodies against a variety of antigens. UB-311 is a fully synthetic peptide vaccine that comprises two Aβ1-14 peptides fused to T-helper cell peptides in order to elicit a strong antibody response against Aβ while avoiding a cytotoxic T cell response (10). Data presented at CTAD showed no serious adverse events among 42 participants randomized to receive 7 doses of drug or placebo over 60 weeks, followed by 18 weeks of observations. Additional data from extensive biomarker, safety, and immunogenicity studies are expected by the end of 2019.

Another treatment approach, plasma exchange, has a long history in the treatment of other conditions and has recently emerged as a promising strategy against AD. Barcelona-based Grifols, S.A. reported encouraging

results from a phase 2b/3 study of plasma exchange with albumin replacement in patients with moderate AD (AMBAR study) (11).

Grifols has been investigating the clinical use of plasma exchange with albumin replacement for the past 15 years. In an earlier pilot study, they showed that the technique resulted in a decrease in plasma Aβ, an increase in cerebrospinal fluid levels of Aβ, and improvements on clinical and functional neuroimaging measures. For the AMBAR study, they randomized nearly 350 participants with mild to moderate dementia to either placebo or one of three treatment groups. A sham procedure delivered to the placebo group simulated plasmapheresis so that patients, caregivers, and raters were all blind to whether the participant was receiving active treatment or placebo. The study was conducted at 41 sites in Spain and the United States.

All three treatment groups started the trial with conventional total plasma exchange with albumin replacement (TPE) once per week for two months followed by low-volume plasma exchange (LVPE) once per month for 12 months, with either a low (20 mg) or high (40 mg) dose of albumin. Two of the treatment groups also received an intravenous infusion of immunoglobulin (IVIG) to replace endogenous immunoglobulins. One group did not receive IVIG as an extra check on the safety of this product. Cognition, function and AD biomarkers were assessed at baseline, after the 2 months of TPE, and at 6, 9, 12, and 14 months. CSF biomarkers, magnetic resonance imaging (MRI), and fluorodeoxyglucose PET (FDG-PET) studies were conducted less frequently.

Participants in all three treatment arms showed a slowing of decline compared to placebo on both cognitive and functional measures, although the results were not statistically significant. However, when the results were reanalyzed with participants divided according to their baseline mini-mental status exam (MMSE) scores, patients with mild dementia (MMSE 22-26) showed no benefits from the treatment, while those with moderate dementia (MMSE 18-21) showed 61% slowing of decline on both the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale. Safety was also assessed, and while the treated groups had a higher incidence of adverse events compared to placebo, the treatment was judged to be safe and well-tolerated. Nearly three quarters of participants (72%) completed the study despite the substantial burden of the trial.

The apparent strength of the effect in moderate but not mild AD patients was surprising and will be under further investigation. Future analyses of biomarkers and imaging studies and at least one additional clinical trial are planned to follow-up on this observation.

Continued interest in non-amyloid treatment strategies

The observed association of type 2 diabetes mellitus (T2D) with increased AD risk (12), along with preclinical studies that demonstrated improvement of brain function and synaptic health in mice treated with insulin has sparked interest in insulin as a treatment (13). Intranasal delivery of insulin results in rapid uptake in the central nervous system (14) and has been shown to improve memory and other cognitive measures in individuals with amnestic mild cognitive impairment (aMCI) or mild-to-moderate AD (15-17). Craft and colleagues at the Wake Forest School of Medicine in Winston-Salem, North Carolina, presented data from a multi-site Phase 2/3 study of intranasal insulin in patients with mild cognitive impairment (MCI) or mild AD (18).

For this trial, 289 participants at 26 US sites were randomized to receive either insulin or placebo daily for 12 months. The first 49 participants used Kurve Technology's ViaNase ™ device to deliver the drug; however frequent malfunctions led the investigators to discontinue use of that device in favor of the newly-developed Precision Olfactory Delivery™ device (POD) from Impel NeuroPharma. Assessments were made at baseline and at three-month intervals until the end of the study, when participants were offered open-label insulin treatment for another 6 months. A change in cognitive function from baseline to 12 months served as the primary endpoint; secondary endpoints included assessments of daily function, imaging, and biomarker studies.

Although the study failed to show effectiveness of intranasal insulin delivered with the POD on any of the outcome measures, a pattern suggestive of benefit in the participants who used the ViaNase device was noted. Further analyses of the data, including analyses of the open-label extension and other pre-specified responder analyses are forthcoming, said Craft.

Interesting results were presented from a Phase 3 trial of another novel treatment strategy, this one using GV-971, a marine-derived oligosaccharide that has been shown to inhibit the formation of beta amyloid fibrils, reduce neuroinflammation, and affect the gut microbiota (19). The 36-week randomized controlled multicenter trial conducted by Shanghai's Green Valley Pharmaceutical Company in 788 people diagnosed with mild-to-moderate AD demonstrated statistically significant improvements in cognition (assessed with the ADAS-cog) as early as week four, and continued improvement for the duration of the study. A non-significant trend towards improvement on the Clinicians Interview-Based Impression of Change (CIBIC+) was also observed. No improvements were seen on other secondary outcomes including measures of activities of daily living and neuropsychiatric symptoms. FDG-PET, an imaging study of brain metabolism, also showed no significant effects.

The treatment was safe and well-tolerated.

A third innovative treatment strategy was presented by investigators from the Rocky Mountain Alzheimer's Disease Center in Colorado (20). Based on the observation that people with rheumatoid arthritis have a reduced risk of AD, they hypothesized that cytokines produced by the innate immune system may be neuroprotective. To test this hypothesis, they injected transgenic AD mice with granulocyte-macrophage colony-stimulating factor (GM-CSF) and showed that it reduced brain amyloid by 40% after only seven days and reversed cognitive impairment in 14 days. They also reviewed data from bone-marrow transplant patients who had been given Leukine (also known as sargramostim), a recombinant form of human GM-CSF, and found that these patients showed significantly improved cognitive function. These data provided the rationale to test sargramostim in a placebo-controlled pilot study in patients with mild-to-moderate AD. Study participants who received a subcutaneous injection 5 days a week for three weeks showed a reduction in amyloid that correlated with an improvement in the mini-mental state examination (MMSE) score and no sign of ARIA. They are now planning a six-month trial of GM-CSF/sargramostim in mild-to-moderate AD.

A novel regenerative treatment that promotes neurogenesis in the brain is also in development as a first-in-class therapeutic for MCI and mild AD. Allopregnanolone (allo), a naturally occurring substance and metabolite of progesterone, has both regenerative and neuroprotective properties (21). Moreover, investigators at the Center for Innovation in Brain Science at the University of Arizona have demonstrated that allo induced neurogenesis and a change in synaptic connectivity and restored cognitive function in mice (22). At CTAD, they reported results from a multiple-dose Phase 1b/2a study in participants with MCI or mild AD (23). While there was no statistically significant improvement in cognition, there was a trend in the right direction for improvements in executive function. No sex differences were seen and the treatment was well tolerated. They are now planning a Phase 2 randomized controlled trial that will enroll 200 mild AD patients to receive 4 mg of allo for 72 weeks.

Developing new tools to accelerate AD drug development

Developing new AD therapeutics requires not only a full pipeline of diverse agents, but novel and efficient analytic tools and trial designs as well. At CTAD, investigators described tools ranging from low to high tech that are being applied to studies testing a diverse set of therapeutic agents. At the low-tech end, for example, investigators at the Wake Forest School of Medicine are using mass mailings and the internet to identify potential participants for the COSMOS-Mind study, which is examining the potential of cocoa-flavanol extract to improve cognition in older adults (24). Interested participants were sent recruitment materials, contacted to confirm interest, screened via telephone, and if eligible, were then enrolled and randomized. Participants are assessed annually using a telephone-based cognitive composite outcome measure. Although results of the study will not be available for several years, the study has already demonstrated the feasibility of conducting a large, simple, cost-effective, and geographically diverse trial over the telephone, and has shown that older adults are willing to volunteer for telephone-based assessments.

At the other end of the technology spectrum, a machine learning algorithm has been developed by IQVIA to help identify prodromal AD patients in the general population (25). In the United States alone, there are currently 150 clinical trials seeking about 70,000 participants, making recruitment an enormous challenge. Moreover, the landscape has become more complicated as the number of procedures involved in trials has increased by about 70% and the number of countries conducting trials has more than doubled. IQVIA's approach is to leverage huge healthcare datasets to build a predictive algorithm. To build the model, they used data from an initial cohort of more than 405 million subjects divided into a positive cohort (those with AD or who had been prescribed AD symptomatic drugs) and a control cohort (a matched sample of patients without an AD diagnosis or AD treatment). Using 24 months of medical history data from no more than 3 years prior to the AD diagnosis, they identified features such as diagnostic procedures, medical interventions, concomitant pathologies, and other characteristics that differentiated those with AD from those without AD across. They then compared the performance of different algorithms across different age groups and ranked risk factors for each age group based on the predictive value of that risk factor in that age group.

Predictive modeling can also enable precision medicine, according to data presented by Ariana Pharma in Paris, France. As part of the development of ANAVEX®2-73, an orally available selective sigma-1 receptor agonist, Ariana used an unbiased, data-driven machine learning platform that integrated clinical and genomic data to identify four key drivers of the response to the drug, including polymorphisms of two genes. This allowed them to extend their small open label study in a selected population, strengthening their hypothesis for this particular drug and supporting the notion that such precision pharmacology approaches can be used to identify patients who will benefit from particular drugs across a wide range of neurodegenerative diseases (26).

New biomarkers are also needed to increase the efficiency and productivity of trials. Speakers at CTAD described recent advances in the development of plasma biomarkers, which offer advantages for screening and diagnosis in terms of reduced cost and much greater

availability to large populations. The Trial-Ready Cohort for Preclinical/Prodromal AD (TRC-PAD) project, funded by the National Institute on Aging will incorporate three different plasma biomarker assay platforms, enabling multi-center comparative field testing of the assessment tools (27). Ultrasensitive immunoassays for amyloid beta oligomers in CSF were also described, which offer the ability to demonstrate target engagement in clinical trials with a small number of participants. The Yale PET center has also recently developed a ligand for synaptic PET imaging, which could offer the first in vivo measure of synaptic density as an outcome measure in clinical trials of disease-modifying therapies, particularly those targeting synapses.

Take home lessons

CTAD 2018 offered a vision of new and better drugs, improved methods for identifying individuals in the earliest stages of disease, and improved diagnostic and staging tools, all aimed at providing better and more personalized treatment approaches for the millions of people living with or at risk of developing AD. The conference also highlighted lessons learned from completed and ongoing clinical trials that can be applied to future trials to improve the efficiency of those trials and accelerate the discovery and development of effective treatments for AD. While there is continued optimism regarding the potential efficacy of amyloid-targeting agents, disappointing results from many trials as well as increased understanding of the pathogenetic mechanisms that contribute to AD strongly supports pursuit of treatments targeting alternative mechanisms. Combination therapies that target multiple mechanisms may be needed, as well as treatments that address comorbid conditions that contribute to dementia. Other lessons learned at CTAD 2018 include:

- Blood-based methods of detecting early markers of AD pathology have matured to the point of being ready for use in clinical trials but may still need to be refined for use in clinical care.
- Incorporating a wide range of biomarkers into all clinical trials is essential to ensure that the maximum amount of information is provided by those trials.
- Repurposing treatments that have been used for other diseases offers advantages in drug development since human safety data may be available.
- To reduce the cost and expand access to clinical trials, remote assessments via telephone provide a feasible approach for testing cognition and detecting cognitive decline over time.
- Extensive data in electronic medical records and genetics studies can be leveraged to predict risk of developing dementia, enable recruitment of presymptomatic individuals into clinical trials, and guide personalized approaches to treatment.

The next CTAD meeting, which will be held in San Diego December 4th through 7th, 2019 will build on each of these ideas. In addition to early reports on novel therapeutic strategies, we anticipate updates on the major industry and academic trials, validation data on leading biomarker candidates (including plasma markers of brain amyloid and neurodegeneration), and reports on new approaches to recruitment, retention, and improving diversity in AD clinical trials. We also expect to see Phase 2 results from highly anticipated tau-targeting therapeutics.

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References

1. Hu X, Das B, Hou H, He W, Yan R. BACE1 deletion in the adult mouse reverses preformed amyloid deposition and improves cognitive functions. J Exp Med 2018;215:927-940.
2. Egan MF, Kost J, Tariot PN, et al. Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer's Disease. N Engl J Med 2018;378:1691-1703.
3. Egan MF, Voss T, Mukai Y, et al. Results from the APECS trial. J Prev Alzheimers Dis 2018;5:S1.
4. Vassar R. Editorial: Implications for BACE1 Inhibitor Clinical Trials: Adult Conditional BACE1 Knockout Mice Exhibit Axonal Organization Defects in the Hippocampus. J Prev Alzheimers Dis 2019;6:78-84.
5. Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012;367:795-804.
6. Fagan AM, Xiong C, Jasielec MS, et al. Longitudinal change in CSF biomarkers in autosomal-dominant Alzheimer's disease. Sci Transl Med 2014;6:226ra230.
7. Verma A, Yu HJ, Chen H-C, Wang CY. Active anti-amyloid immunotherapy with UB-311 vaccine: design, baseline data and study update of a Phase IIA, randomized, double-blind, placebo-controlled, 3-arm parallel-group, multicenter study. J Prev Alzheimers Dis 2018;5:S10.
8. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 1999;400:173-177.
9. Check E. Nerve inflammation halts trial for Alzheimer's drug. Nature 2002;415:462.
10. Wang CY, Wang PN, Chiu MJ, et al. UB-311, a novel UBITh((R)) amyloid beta peptide vaccine for mild Alzheimer's disease. Alzheimers Dement (N Y) 2017;3:262-272.
11. Paez A. AMBAR (Alzheimer's Management by Albumin Replacement) Phase IIB/III Results. . J Prev Alzheimers Dis 2018;5:S8.
12. Neth BJ, Craft S. Insulin Resistance and Alzheimer's Disease: Bioenergetic Linkages. Front Aging Neurosci 2017;9:345.
13. De Felice FG, Vieira MN, Bomfim TR, et al. Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of Abeta oligomers. Proc Natl Acad Sci U S A 2009;106:1971-1976.
14. Salameh TS, Bullock KM, Hujoel IA, et al. Central Nervous System Delivery of Intranasal Insulin: Mechanisms of Uptake and Effects on Cognition. J Alzheimers Dis 2015;47:715-728.
15. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol 2012;69:29-38.
16. Reger MA, Watson GS, Green PS, et al. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. J Alzheimers Dis 2008;13:323-331.
17. Reger MA, Watson GS, Green PS, et al. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology 2008;70:440-448.
18. Craft S, Raman R, Chow T, et al. Primary results from a Phase II/III trial of intranasal insulin: A novel multi-target molecule and delivery mode for AD therapeutics. J Prev Alzheimers Dis 2018;5:S9.
19. Xiao S, Zhang Z, Geng M. Phase 3 clinical trial for a novel oligosaccharide targeting multiple A-beta fragments in patients with mild-moderate AD in China J Prev Alzheimers Dis 2018;5:S10.
20. Potter H, Woodcock JH, Boyd T, et al. Interim safety and efficacy results

of pilot trial of GM-CSF/Sargramostim in mild to moderate AD. J Prev Alzheimers Dis 2018;5:S15.
21. Irwin RW, Brinton RD. Allopregnanolone as regenerative therapeutic for Alzheimer's disease: translational development and clinical promise. Prog Neurobiol 2014;113:40-55.
22. Irwin RW, Wang JM, Chen S, Brinton RD. Neuroregenerative mechanisms of allopregnanolone in Alzheimer's disease. Front Endocrinol (Lausanne) 2011;2:117.
23. Brinton RD, Hernandez GD, Kono N, et al. Allopregnanolone regenerative therapeutic for mild cognitive impairment and mild Alzheimer's disease: Phase 1B/2A outcomes update. J Prev Alzheimers Dis 2018;5:S12.
24. Baker LD, Espeland MA, Rapp SR, et al. Cocoa supplement and multivitamin outcomes study of cognitive functin (COSMOS-MIND): Design of a large randomized clinical trial. J Prev Alzheimers Dis 2018;5:S20.
25. Uspenskaya-Cadoz O, Alamuri C, Khinda S, et al. Machine learning algorithm helps identify non-diagnosed prodromal Alzheimer's disease patients in general population. J Prev Alzheimers Dis 2018;5:S21.
26. Hampel H, Afshar M, Parmentier F, et al. Longitudinal 148-week extension study for Anavex(R)2-73 Phase 2A Alzheimer's disease demonstrates maintained activities of daily living score (ADCS-ADL) and reduced cognitive decline (MMSE) for patient cohort on high drug concentration and confirms role of patient selection biomarkers. J Prev Alzheimers Dis 2018;5:S43.
27. Jimenez-Maggiora GA, Raman R, Rafii MS, Sperling RA, Cummings JL, Aisen PS. TRC-PAD: Accelerating participant recruitment in AD clinical trials through innovation. J Prev Alzheimers Dis 2018;5:S31.