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The DIAN-TU Next Generation Alzheimer's prevention trial: adaptive design and disease progression model

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Abstract

INTRODUCTION—The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) trial is an adaptive platform trial testing multiple drugs to slow or prevent the progression of Alzheimer's disease in autosomal dominant Alzheimer's disease (ADAD) families. With completion of enrollment of the first two drug arms, the DIAN-TU now plans to add new drugs to the platform, designated as the Next Generation Prevention Trial (NexGen).

METHODS—In collaboration with ADAD families, philanthropic organizations, academic leaders, the DIAN-TU Pharma Consortium, the NIH, and regulatory colleagues, the DIAN-TU developed innovative clinical study designs for the DIAN-TU NexGen trial.

RESULTS—Our expanded trials toolbox consists of a Disease Progression Model for ADAD, primary endpoint DIAN-TU cognitive performance composite, biomarker development, self-

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administered cognitive assessments, adaptive dose adjustments, and blinded data collection through the last participant completion.

CONCLUSION—These steps represent elements to improve efficacy of the adaptive platform trial and a continued effort to optimize prevention and treatment trials in ADAD.

Keywords

Alzheimer's disease; Alzheimer's Prevention Trial; Adaptive Clinical Trial; Biomarkers; Disease Progression Model; Cognitive Composite; Dose Adjustment; DIAN-TU; Amyloid; Tau; Autosomal Dominant Alzheimer's Disease

1. Introduction

Alzheimer's disease (AD) is a growing public and financial healthcare crisis. AD afflicts over 5 million people in the United States, with an expected increase to 13.8 million by the year 2050 (1). The costs for care of patients with AD and other dementias in 2015 was $226 billion, which is predicted to increase beyond a trillion dollar annual cost by 2050 unless disease modifying treatments are developed. Because of the severity and increasing prevalence of the disease, better treatments and prevention are urgently needed.

Development of highly effective AD treatments has been hampered by the lack of surrogate biomarkers, slow course of cognitive and clinical decline, variability in clinical phenotype, and variability when measuring cognition and functional impairments in AD. These challenges are especially difficult since validated diagnosis of AD in the absence of symptoms has not yet been achieved. Prevention trials thus must be long and large due to inability to predict if and when cognitive symptoms will start, lack of functional impairment and difficulties identifying an at-risk study population prior to symptomatic cognitive decline.

In order to address key AD prevention trial design challenges in a population almost certain to develop AD – the autosomal dominant AD (ADAD) population – a public-private partnership was formed in 2010 to facilitate collaborative discussions between industry (the DIAN-TU Pharma Consortium, dian-tu.wustl.edu/en/pharma-consortium-members), ADAD families, the Alzheimer's Association, U.S. National Institute on Aging, regulators including FDA and EMA, and researchers (DIAN Observational Study, API, A4, CAP and others). Through these discussions, the DIAN-TU designed and executed a pioneering prevention trial for the ADAD population. The DIAN-TU Trial (DIAN-TU-001, www.clinicaltrials.gov) is also a public-private partnership supported by Eli Lilly, Roche, Alzheimer's Association, NIA, Avid Radiopharmaceuticals, GHR Foundation, Fidelity Biosciences Research Initiative, Cogstate and Bracket. Because the ADAD population is almost certain to develop cognitive impairment, at a younger and predictable age, several of the challenges inherent in conducting prevention trials of late-onset, sporadic AD are mitigated.

1.1 Autosomal Dominant Alzheimer's Disease

ADAD is caused by mutations in the *APP, PSEN1* or *PSEN2* genes, which lead to early-onset AD. Because of the almost certain risk of developing AD and the predictability of the

age at symptom onset (2, 3), ADAD represents a uniquely informative population for clinical trials. Unlike sporadic AD (SAD), the clinical onset of symptoms can be predicted throughout the lifespan, allowing drug trials to start years or even decades before symptoms occur (4). Potential therapeutic drugs were developed using cellular and animal models of identified ADAD mutations (5-8). These pre-clinical studies led to the development of agents used in anti-Aβ drug trials reaching clinical phase studies (9-15). While some remain in phase 3 trials, several have been discontinued due to adverse events (AEs) (16), worsened outcomes (17, 18), or lack of benefit (16, (19). Of concern, many of these trials failed to show target engagement of the proposed drug, largely due to lack of studies that adequately incorporated biomarkers (14, 15). Results from recent trials involving anti-Aβ antibodies (e.g. gantenerumab, crenezumab, solanezumab and aducanumab) have suggested that a greater magnitude of target engagement is critical and that treatment instituted earlier in the disease is possible and necessary for cognitive benefit (14, 20-23).

For families known to carry ADAD mutations, prevention and treatment trials using novel therapies offer the potential to delay or even prevent dementia in asymptomatic individuals and improve mild symptoms or mitigate symptom progression. Due to the younger age, higher capability of CNS repair, earlier stage of disease and Aβ as a likely initiator of ADAD, the ADAD population is expected to provide an efficient and, compared to sporadic AD, relatively rapid test for anti-Aβ therapeutics. The relative homogeneity of the DIAN-TU trial population, fewer comorbidities, low attrition to date, and the success in recruitment and completion of trial measures make the DIAN-TU trial and this patient population ideal for testing disease modifying therapies.

1.2 Relationship to Sporadic AD

Changes in cognitive, clinical, biochemical and structural measures in ADAD are similar to SAD (2, 24, 25). This suggests a common pathophysiology and provides rationale that treatment trials in ADAD are likely to provide insight into common treatments with the much more prevalent SAD. Prior studies of statins in familial hyperlipidemia (26) demonstrated a remarkable normalization of cholesterol deposits, which predicted improvements of lifespan by treatment of hypercholesterolemia in the general population by several decades (27). This is a historical precedent to what may be possible in ADAD and its relationship to SAD.

Three decades of accumulated research evidence supports the hypothesis that alterations in Aβ metabolism are necessary to cause AD (28, 29). In both SAD and ADAD, the presence of β-amyloidosis has been associated with cognitive decline in symptomatic individuals (30-32). In ADAD, cerebral amyloidosis correlates with worse baseline performance on multiple cognitive composites and predicts greater decline over time in global cognition, working memory, and Mini-Mental State Examination (MMSE) in symptomatic mutation carriers (32). Recent data from the DIAN observational study suggests that even in asymptomatic mutation carriers, the ratio of total tau to CSF $A\beta_{1-42}$ is associated with longitudinal declines in episodic memory, language and global cognition (33). Similar results have been seen outside of ADAD populations, in which Aβ-positive healthy older adults show decline in episodic memory when compared with Aβ-negative healthy older

adults (30, 31). In contrast, an Icelandic mutation that reduces amyloidogenic processing of APP and also mildly decreases Aβ aggregation is protective against AD and age-related cognitive decline (34, 35). Together these data strengthen support for the amyloid hypothesis and the value of finding therapeutics targeting Aβ to treat both ADAD and SAD.

Regarding tau pathology, there is evidence in preclinical and clinical studies supporting a temporal relationship between Aβ plaque deposition and neurofibrillary tangles (NFT) development specifically in AD such that the development of Aβ plaques contributes the subsequent spread of NFT outside of the entorhinal cortex and hippocampus (36-38). In the aging process, NFTs can be seen starting in the 4th decade and appear to primarily develop in the entorhinal cortex and hippocampal areas (39) before the development of significant Aβ plaque. In the aging brain the spread of NFT pathology appears to be limited in the absence of coexisting Aβ pathology (40-42). Based on autopsy series of patients, the distribution of NFT pathology appears similar between ADAD and SAD (43). Further, recent studies in the DIAN have demonstrated similar distributions of tau PET signals in ADAD and SAD (44). Thus, the distribution and type of tau pathology among ADAD and SAD are analogous. Ongoing studies will clarify the role of aging in NFT development and further characterize tau pathology associated with cognitive and clinical impairment.

In SAD a dynamic sequence of biomarker changes has been proposed (24, 45) with cerebral amyloidosis being one of the first detectable changes, followed by measures of neurodegeneration and lastly cognitive and functional decline. Longitudinal and cross-sectional studies in ADAD (4, 46, 47) have supported the same relationship. Although further studies are required in both populations, the temporal order and progression of pathophysiological, cognitive and clinical changes are shared in ADAD and SAD (3).

2. The DIAN-TU Alzheimer's Disease Prevention Trial Platform

The DIAN-TU platform (NCT01760005; See Figure 1) was launched to accelerate identification of effective drugs for prevention and treatment of ADAD (48, 49). In 2012, a phase 2/3 double-blind, randomized, pooled-placebo controlled two-year biomarker trial began by testing two drugs – solanezumab (an anti-soluble Aβ antibody) and gantenerumab (an anti-fibrillar Aβ antibody). The study transitioned within the DIAN-TU platform to the Adaptive Prevention Trial in 2014 as a four-year Phase 3 cognitive endpoint trial to determine whether Aβ antibody administration demonstrating central nervous system (CNS) biomarker target engagement is able to prevent cognitive decline in cognitively normal individuals. The DIAN-TU trial is now operational in 7 countries (Australia, Canada, France, Italy, Spain, UK and US), 26 sites, and 4 languages (English, French, Italian and Spanish) (See Figure 2). Full enrollment of the first two drug arms has been achieved with a high assessment completion rate and low attrition. The DIAN-TU trial is one of five ongoing trials aiming to prevent or delay the onset and progression of AD (50).

2.1 DIAN-TU Next Generation

As enrollment for the first two arms was completed in late 2015, the DIAN-TU is preparing to launch two new drug arms as the Next Generation (NexGen) Prevention Trial (see Figure 1). The NexGen trial will be a multi-center, double blind, randomized, pooled-placebo

controlled, four-year cognitive composite endpoint registration study of two potential disease modifying therapies in 160 mutation carriers at risk for or with mild symptomatic ADAD. The NexGen trial proposes to test the ability of a beta secretase inhibitor (BACEi), gamma-secretase modulator, and other novel Aβ or tau-based therapies to slow or prevent cognitive decline in asymptomatic (CDR 0) to mildly symptomatic (CDR 0.5 or 1) ADAD mutation carriers in the range of −15 to +10 years with respect to estimated years to symptom onset (EYO). The DIAN-TU anticipates future development of AD specific pathophysiology interventions which may include combination treatments. Each drug program will include at least 80 mutation carrier subjects who receive either drug or placebo randomized 3:1. Cognitive benefit will be determined over 4 plus years with the primary outcome being the DIAN-TU cognitive composite and secondary outcomes including multiple cognitive and clinical measures and cerebrospinal fluid and imaging biomarkers.

The NexGen trial goals are to enable rapid testing of novel approaches, inform if dementia can be prevented or delayed in ADAD subjects, provide publicly accessible data and biological samples for research, and develop surrogate biomarkers to accelerate future AD trials. NexGen working groups evaluated additional designs that allow the platform to test drugs with diverse mechanisms of action more quickly. Significant innovations that may be implemented include: an ADAD Disease Progression Model (DPM) to detect changes in cognition with fewer participants compared to traditional Mixed Effects Model for Repeated Measures (MMRM), self-administered cognitive testing, a pre-defined dose escalation algorithm to safely maximize target engagement, adaptive trial design that includes both early biomarker and later cognitive interim analyses to inform early efficacy or futility, and novel imaging (e.g. Tau PET and diffusion basis spectrum imaging MRI).

3. Methods and Results

3.1 Primary Endpoint – DIAN-TU Cognitive Composite

Utilizing the latest DIAN observational data limited to participants meeting DIAN-TU trial eligibility criteria, we developed a cognitive composite using sensitive and reliable tests that together represent cognitive domains affected in AD – particularly in the very early stages – including episodic memory, executive functioning, processing speed, and mental status. The DIAN-TU cognitive composite consists of the delayed recall score from the International Shopping List Test, the Logical Memory delayed recall score from the Wechsler Memory Scale-Revised, the Digit Symbol Coding test total score from the Wechsler Adult Intelligence Scale-Revised, and the MMSE total score. These measures were selected based on their psychometric characteristics (reduced ceiling and floor effects, relatively low variability), sensitivity to subtle declines prior to clinical diagnosis, and face-validity as indicators of the cognitive phenotype of AD. Since the DIAN-TU is a multi-site international study, translations were necessary. Translation of the test stimuli for the International Shopping List Test followed procedures described in Lim and colleagues (2012)(51), which selects stimulus words representing commonly available items in the language and culture of interest. A similar procedure was followed for translation of the paragraph used in the WMS-R Logical Memory test, wherein translations represent an adaptation of the content rather than a word-by-word translation (Acevedo et al., 2012) (52).

This process relies on multiple reviews and revisions during translations with native speakers with the ultimate goal of achieving conceptual and cross-cultural equivalence. Power analyses indicate the DIAN-TU composite is sensitive to decline and produces feasible sample size requirements to detect prescribed effect sizes.

We have vetted our composite by taking advantage of the longitudinal database from the DIAN observational study cohort (See Figure 3). These analyses have shown that the proposed DIAN-TU Cognitive Composite can detect declines up to 10 years prior to estimated age of symptom onset. The composite has good distributional characteristics across the trial range of EYO and good separation of mutation carriers and non-carriers years prior to symptom onset. The DIAN-TU Cognitive Composite is a valid indicator of the cognitive phenotype of AD and is directly comparable to cognitive endpoints of other secondary prevention clinical trials in AD, thus allowing future comparisons of clinical trial outcomes between ADAD and SAD. For example, the Anti-Amyloid in Asymptomatic Alzheimer's disease (A4) trial has chosen an endpoint that includes measures of episodic memory (verbal list learning [Free and Cued Selective Reminding Test] and paragraph recall [Logical Memory]), complex attention (Digit Symbol Coding) and a general cognitive screen (MMSE) (21).

3.2 Primary Analysis – ADAD Disease Progression Model

Traditional trial designs in AD have focused on comparing the absolute change from baseline in a cognitive measure at a fixed time post randomization. This creates considerable variability because patients vary in their stage of disease at study entry and in their rates of decline. Historically, staging disease in sporadic AD populations has been challenging due to heterogeneity at baseline and in the longitudinal trajectories of patients enrolled in therapeutic trials. Additionally, analyses focused on absolute changes at a pre-defined time point only weakly incorporate the longitudinal changes in progression. This results in trials with low power to demonstrate clinically important effects and increases the likelihood of type II error. Moreover, while clinically significant change may be clearly measurable in mild-moderate AD, preclinical or very mild stages will require mechanisms to detect small changes in outcomes that have meaningful downstream impacts.

The DIAN observational study has identified highly predictable and consistent changes that occur decades before onset of clinical symptoms (4), and we have used this valuable information to create a DPM that dramatically improves our ability to detect drug effects in DIAN-TU trials. In subjects who are not yet symptomatic, we can estimate accurately and reliably the number of years until symptom onset (3). With longitudinal follow up we are continuously able to gather a more comprehensive understanding of the rate of cognitive decline across the spectrum of EYO and how these declines manifest across different cognitive domains. One important finding from the analyses of the longitudinal data from the DIAN observational study is that the disease progression in the cognitive composite in mutation carriers is non-linear (Figure 4, left panel). Therefore, we have developed a cognitive endpoint non-linear mixed effects model with EYO as the measure of time for each subject, not time from randomization (manuscript in preparation). The model estimates the expected rate of cognitive decline for untreated mutation carriers. By incorporating two

important random effects for each individual – a subject's EYO and a subject's baseline cognitive performance – the rate of decline becomes more homogeneous and with much less variability (Figure 4, right panel). Within this disease progression model we develop a *proportional* disease modification parameter for treatments relative to placebo subjects. This parameter is identified more precisely by the entire longitudinal data for treated and placebo subjects.

While we assume that the expected proportion of the change in the cognitive measure under a treatment relative to placebo is constant across EYO, the expected absolute difference in the cognitive readout for drug treatment relative to placebo will vary depending on the EYO of the subject and the duration of treatment. Figure 5 provides an illustration of hypothetical proportional changes to the disease progression and the gradual increase in the absolute effect for a range of EYO entry points based on a treatment effect over the four-year duration of the trial. The percent slowing of the progression rate in Figure 5 ranges from 0-70% encompassing reported cognitive and clinical effects of Aβ immunotherapies; 34% reduction in cognitive decline for solanezumab (22) and 66%-75% reduction in MMSE and CDR for aducanumab (21). Importantly, the estimated standard deviation of a single visit in the DIAN-TU cognitive composite is 0.33 (Estimate of the disease progression model fit to the observational cohort from data freeze 9). Thus, a change in the DIAN-TU cognitive composite over time of 0.25 creates a statistical "effect" size of 0.25/0.33 = 0.756. For a 1-unit change in the cognitive composite this corresponds to a statistical effect size of 1.0/0.33 = 3. Thus, effect sizes of 0.756 for asymptomatic and 3 for symptomatic are quite large in the DIAN population. For a drug which causes 50% slowing of the rate of decline, treatment effect sizes of 0.756/2 = 0.378 and 3/2 = 1.5 are statistically achievable with sample sizes from 80 to 140 subjects with 4 plus years of follow-up.

Importantly, the DPM provides for very high power to determine whether a treatment slows the rate of decline in a randomized trial. The DPM shows dramatically increased power compared to a mixed model for repeated measures (MMRM), that has weak measures of the treatment effect over time and a weak allowance for capturing the influential covariate, EYO. For example, with 60 mutation carrier treatment subjects and 40 mutation carrier placebo participants enrolled, the power to determine superiority when there is a 30% slowing of disease progression, is 0.24 for the MMRM and 0.90 for the proposed DPM. Additionally, the precision of this model allows more timely decisions of superiority and futility for treatments with clear benefit or minimal to no benefit.

3.3 DIAN-TU NexGen Secondary Outcome Measures

A wide range of secondary analyses will be conducted, including efficacy analysis using MMRM to compare to the DPM and analyses of additional individual cognitive and clinical tests. Modeling for both the primary and secondary analyses will adjust for well-established risk factors and covariates such as baseline age, *APOE4* status, education and gene mutation type. Analyses will be done on functional measures of activities of daily living, all biomarker measures (e.g. CSF $A\beta_{1-40}$, $A\beta_{1-42}$, tau and p-tau181, regional amyloid PET, volumetric MRI, and Tau PET), and on the incidence of CDR conversion from baseline.

3.3.1 Exploratory Self-Administered Internet-Based Cognitive Assessments— It is expected that the reliability of the observations of the subtle changes over time increases with the number of measurements used to estimate that change. An exploratory aim for secondary analysis in the NexGen trial will be to introduce self-administered brief cognitive assessments using a validated Internet-based testing portal. The self-administered battery will include the computerized measures that comprise the 12-minute Cogstate Brief Battery, which is a component of the larger cognitive assessment battery currently in use in DIAN-TU. The overall goal is to collect more frequent cognitive assessments to test the hypothesis that this will increase reliability of the measurement of subtle cognitive change without substantially increasing study costs and burden for DIAN-TU participants. To our knowledge, this is the first trial design to incorporate self-administered assessments in a clinical trial investigating an AD disease-modifying agent.

3.3.2 Biomarker Effects of DIAN-TU Trial Drugs—Convergence and consensus in the field has generated significant support for biomarkers in AD prevention trials (2, 53). The DIAN observational study was established as the first international registry and longitudinal study of ADAD to determine the temporal course of biomarker changes relative to AD symptom onset as well as to support clinical trials in this largely asymptomatic population. Discovery and validation of AD biomarkers for identifying individuals most likely to respond to treatments, measuring responses to treatments, and predicting clinical benefit of treatments (surrogate biomarkers), are a high priority to increase the efficiency of trials for AD.

3.3.2.1 **Tracking Target Engagement:** Drugs are developed to target pathological proteins and processes (e.g. increased Aβ production and/or deposition), and the efficacy with which they engage the target can be assessed with biomarkers. The DIAN-TU NexGen trial is testing two drugs in parallel to assess target engagement using primary biomarker readouts including amyloid PET imaging for anti-Aβ antibodies and CSF $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ for BACE inhibitors.

3.3.2.2 **Finding a Surrogate Biomarker for AD Clinical Trials:** From inception, the DIAN-TU trial has assessed many biomarkers. Should a drug demonstrate cognitive benefit it will be possible to analyze which biomarkers best predicted therapeutic efficacy, findings of particular benefit for future AD trials. The need for predictive biomarkers is especially important in slowly progressive disorders like AD, without which prevention trials will necessarily be large, long, and expensive (54). The inclusion of multiple biomarkers will allow for the analysis of multiple potential responses to therapies and also better reflect the array of biomarker used to predict progression from the observational study.

As there is not yet an established predictive biomarker for AD, we have included a diverse panel of imaging and fluid AD biomarkers to determine drugs' impact on different aspects of the pathobiology including atrophy (MRI), connectivity (functional MRI), metabolism (FDG PET), amyloid pathology (amyloid PET), tau pathology (tau PET), vascular factors (MRI white matter), and biochemical changes (CSF). Novel CSF markers of synaptic dysfunction and neurodegeneration, imaging markers including tau PET and MRI diffusion sequences to better understand Amyloid Related Imaging Abnormalities (ARIA) will be

implemented. Exploratory biofluid and imaging analyses include measurement of CSF tau, ptau, VILIP-1 (visinin-like protein 1, neuronal injury/degeneration) (55) and NGRN (neurogranin, [post-] synaptic dysfunction) (56-58). Potential future exploratory biomarkers evaluated independently at trial completion include CSF synaptosomal-associated protein-25 (SNAP-25, [pre-] synaptic dysfunction) (59) and neurofilament light chain (NfL, axonal injury) (60) and plasma tau (neuronal injury/ degeneration) (61).

In particular, inclusion of tau PET imaging for the DIAN-TU NexGen drug arms will significantly enhance the trial and provide an opportunity to maximize understanding of the role of tau in AD. Inflection of CSF tau appears to predict the clinically critical cognitive decline in AD. Quantification of aggregated brain tau will be used as a secondary outcome measure to: determine whether therapeutics lowering amyloid in pre-symptomatic and mild AD can decrease insoluble brain tau levels and whether treatment timing influences the outcome; quantify the rate of aggregated brain tau changes in placebo treated ADAD participants in various stages of disease; test the hypothesis that aggregated tau levels can predict progression from asymptomatic to symptomatic AD; and analyze tau PET dynamics in the context of other imaging and CSF biomarkers in mutation carriers and non-carriers.

3.3.2.3 Biomarker Analyses and Understanding Adverse Events: Extensive characterization of DIAN-TU participants may also elucidate mechanisms of amyloid related imaging abnormalities (ARIA) that have been increased in frequency by some amyloid therapeutics. The DIAN observational cohort has demonstrated normal brain MRIs until the time of transition to symptomatic AD, at which point atrophy, white matter disease, and microhemorrhages (MHE) begin to manifest (62). Prevalence of MHE in the DIAN observational cohort is 15% overall with only 2.9% having greater than one MHE. The lack of other age and disease related comorbidities that are risk factors for MHE in the DIAN population allows us to characterize ARIA related to AD and to drug effects. To do so in greater detail, we will employ diffusion basis spectrum imaging (DBSI), a novel form of DTI analysis, permitting separation of free water (edema) from cellular infiltrate more consistent with possible inflammatory processes (63, 64).

3.3.2.4 A Community Resource: As the DIAN-TU trial is a public-private partnership with funding from the NIH, data and samples will serve as a resource for researchers. The trial will generate a repository of CSF and blood samples, imaging data and biomarker results providing a resource for qualified investigators to help develop novel and better-validated AD clinical trial biomarkers.

3.4 Dose Adjustment Algorithm

As a critical component of the adaptive platform trial design, combined safety/biomarker-target analyses at years one and two will enable dosing decisions to maximize biomarker target engagement. Although dose optimization is conventionally performed during phase I/II studies, we propose an opportunity for dose adjustment in DIAN-TU NexGen for multiple reasons. First, doses identified in phase I/II studies of amyloid specific agents have not consistently translated to target engagement and efficacy in larger, later phase studies (23, 65). Second, with early evidence of biomarker target engagement we ensure that

decisions are made quickly and thereby avoid the mistake of identifying a sub-therapeutic dose after four years, preventing the loss of precious time and resources. Third, the current DIAN-TU population has had few drug-related AEs indicating higher doses may be tolerated in this younger population. By starting with or progressing to higher doses in NexGen and then performing an early safety/biomarker analysis at year one, we will be well positioned to assess the appropriate dose in the ADAD population.

A dose escalation algorithm would account for safety signals and biomarker target engagement at interim analyses of both NexGen drugs, with precise cutoffs and safety profiles tailored to each compound based on preclinical and clinical data. After one year of drug and placebo exposure, a drug not meeting a minimal acceptable change in CSF Aβ or decrease in amyloid PET accumulation compared to baseline may be offered an opportunity to increase dose (provided there is also an acceptable safety profile). A clinical safety and biomarker interim analysis by an unblinded team will determine whether drug dosage should increase, decrease, continue at current dose, or be dropped due to futility of low biomarker engagement.

3.5 Interim Analyses

Due to significant power gains from the ADAD DPM, it may be possible to declare early success in the NexGen trial. Thus, interim analyses of cognitive outcomes are proposed when the last enrolled participant in a treatment cohort reaches two years and three years of follow-up. At each interim a regimen may be stopped for futility if the experimental therapy demonstrates a lack of efficacy (probability of at least a 20% slowing of cognitive decline is less than 5%) or stopped early due to demonstration of cognitive efficacy (the primary analysis using only the interim data showing statistically superior slowing of progression). If neither of these decisions is reached then the regimen will continue to the next interim analysis or the final analysis when the last participant has completed four years of treatment. A detailed stopping boundary for the interim efficacy analyses will be developed.

Biomarker interim analysis at year one will examine change from baseline for a drug's primary biomarker of target engagement. For drug programs that have a dose escalation at year one, a year two evaluation of safety and biomarker engagement will be performed similar to year one. However, dose-escalated drug programs that still have not safely demonstrated high impact on their biomarker of CNS target engagement at year two will be discontinued.

3.6 Extended Randomized Follow-up

Due to the extended periods of monitoring needed for cognitive change in prevention trials, any additional data on cognitive changes due to drug effects are highly valuable in determining the potential for drugs to slow or delay cognitive loss. We simulated collecting and analyzing all randomized data collected in the DIAN-TU trial from first patient in to last patient visit by having all participants continue randomized treatment until trial completion. Depending on the assumptions of trial enrollment duration and effect size, various improvements in power ranged from 1% to 30%. For example, a trial with a drug showing 30% slowing of disease progression (60 active to 40 placebo in mutation carrier subjects)

has a 60% chance of demonstrating efficacy with exactly four years of follow-up, whereas the same scenario allowing randomized participants to continue until the last subject reaches four years has 90% power. The valuable data collected beyond the four-year point provides highly informative measures to better estimate drug effects. These improvements in power take no additional time for the trial, and can be implemented with modest costs of follow-up.

3.7 NexGen Drug Candidates and Combination Therapy

Diversifying the drug portfolio has been a longstanding DIAN-TU trial platform goal to increase the likelihood of finding an effective therapy and mitigating the inherent risk of individual drug failure due to unpredicted toxicity, lack of availability or lack of efficacy. Two therapeutics will be chosen from the DIAN-TU Therapy Evaluation Committee imminent use category and are likely to include a class to target Aβ production. Future therapeutics tested in the DIAN-TU platform may include tau-based treatments and other non-Aβ targets.

An original goal of NexGen trial design included testing of combination therapy to delay onset and progression of AD. Preclinical data suggest combining therapeutics targeting the amyloid cascade (anti-Aβ and BACEi) significantly enhances reduction of amyloid load and plaque number beyond either monotherapy alone (66, 67). The existing and NexGen arms will be testing individual therapeutics that are a possible first combination (68-71), and the DIAN-TU trial platform's multiple monotherapies and pooled placebo allow an opportunity to test combinations alongside monotherapy. Moreover, the platform provides a unique opportunity for companies to work together minimizing complicated licensing and contracts. However, as yet there has been no disease modifying combination nominated for consideration by the DIAN-TU Therapy Evaluation Committee. Thus, combination therapy remains a desirable future aim of the DIAN-TU platform.

3.8 Engaging ADAD Participants

There is a growing movement to include patient-centered outcomes in the drug development process. The DIAN-TU uses surveys (72), webinars and an annual ADAD Family Conference (http://dian-tu.wustl.edu/en/adad-family-conference) to gather feedback on trial design and risk tolerance in the ADAD community. Pooled placebo and ability of individuals with undisclosed mutation status to participate in the trial – two central features of the original trial design – were incorporated as a direct result of patient engagement. Pooling data across placebo subjects from different drug arms provides participants with a 75% chance of receiving active drug rather than 50% in traditional 1:1 randomization. However, pooled placebo requires special attention to issues of equivalence and comparability. For example, sensitivity analyses are used to confirm that placebo groups across arms can be combined for the purpose of pooled placebo analyses. Further operational similarities across arms in the DIAN-TU trial support similarity in enrollment, assessments, and duration of the study. Inspired by ADAD families, the DIAN-TU NexGen design aims to test more drugs more quickly by decreasing required participant number using the ADAD DPM, declaring futility or success earlier, and maximizing dose and effect size via the dose adjustment algorithm.

Because ADAD is a rare disease, we have implemented multiple outreach strategies to recruit and engage eligible participants through the DIAN observational study, DIAN Expanded Registry (DIAN EXR) and referrals from partnering clinicians and sites with over 3500 potential participants identified. The DIAN-TU EXR offers exploratory genetic counseling and exome sequencing for families with early onset AD but without confirmation of an ADAD mutation. It is possible that through the EXR, meaningful information such as remote cognitive testing could be captured. Similar programs such as the Brain Health Registry, www.brainhealthregistry.org, are underway in the aging population. However, no such registry exists in ADAD. Additionally, with the platform design of the DIAN-TU trial there will be times enrollment is on hold. During these periods the EXR could continue to capture cognitive assessments and other data that might be helpful at the start of new drug arms such as those proposed in the NexGen trial.

4. Discussion

A therapy delaying the onset of AD dementia by five years that is introduced by 2025 would reduce the number of expected cases by 42% by 2050 and save the United States $367 billion annually on costs of care (73). While a treatment advance in the ADAD population would have to be tested in sporadic AD, we believe the data supports that DIAN-TU trial outcomes may be utilized as supportive or as one of two pivotal trials to demonstrate effectiveness in sporadic AD. A full evaluation of the comparability between ADAD and sporadic AD is underway with large ongoing observational studies in ADNI, NACC and DIAN, which will help inform about the translatability between ADAD and sporadic AD.

In support of the U.S. National Alzheimer's Project Act plan of finding an effective disease modifying therapy by 2025, the DIAN-TU NexGen trial design was developed through collaborations with DIAN-TU NexGen and Pharma Consortium members, DIAN and DIAN-TU subjects, patient groups (Alzheimer's Association and ADAD Family Forum), academic, clinical trial and statistics experts. Central themes emerged including a focus on the adaptive trial platform to minimize cycle time, ensure maximal learning from the limited population of ADAD participants and increase the chance of finding a treatment that provides cognitive benefit. The trial becomes stronger as more regimens are added, and regular interims with more stringent definitions of failure and success allow faster decision-making. Substantial power gains are achieved by using the disease progression model. The NexGen trial aims for a larger effect size by employing a drug-specific dose escalation algorithm to maximize target engagement, biomarker changes and cognitive benefit over time. Finally, the trial will provide additional value to the Alzheimer's field by investigating a comprehensive array of fluid and imaging biomarkers and cognitive tests. Inherent limitations include the possibility of small effects in a small sample size and as yet no clear relationship between biomarker changes and clinical efficacy.

The DIAN-TU NexGen trial will benefit from time and cost saving efficiencies established by the existing DIAN-TU platform operations and infrastructure. We have accounted for the common risks of choosing a single unproven drug in a long-term prevention trial, subject enrollment and retention, selection of cognitive outcomes, and power to detect a clinically

significant drug effect. If the DIAN-TU trial successfully identifies an effective therapeutic or surrogate biomarker, the impact on patients, societies and economies may be substantial.

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Highlights

- We describe innovative trial design features of interest for AD adaptive or prevention trials
- DIAN observational study data were used to model ADAD cognitive decline
- The DIAN-TU cognitive composite is sensitive to early cognitive changes in ADAD
- The disease progression model significantly improves power over traditional analytical methods
- DIAN-TU NexGen trial will test therapeutics to prevent or slow cognitive decline due to ADAD

Research in Context

1. Systematic review: The authors reviewed articles and books pertaining to clinical trial design and held numerous in person and teleconference meetings with a variety of experts including clinicians, researchers, statisticians, patient advocates, and regulatory, clinical development, imaging and informatics professionals.

2. Interpretation: This article outlines innovative trial design features that may be implemented in the DIAN-TU NexGen trial and considered by others developing adaptive trials for Alzheimer's or related diseases. We developed a mathematical model for the DIAN observational study that provides a clear and consistent pattern of disease progression for ADAD mutation carriers; the model fit provides a powerful way to simulate future subjects in the DIAN-TU trial and significant improvements in power over traditional analytical methods.

3. Future directions: Launch of the DIAN-TU NexGen trial will enable testing of new therapeutics to determine if one or more is able to prevent or slow cognitive decline due to autosomal dominant AD.

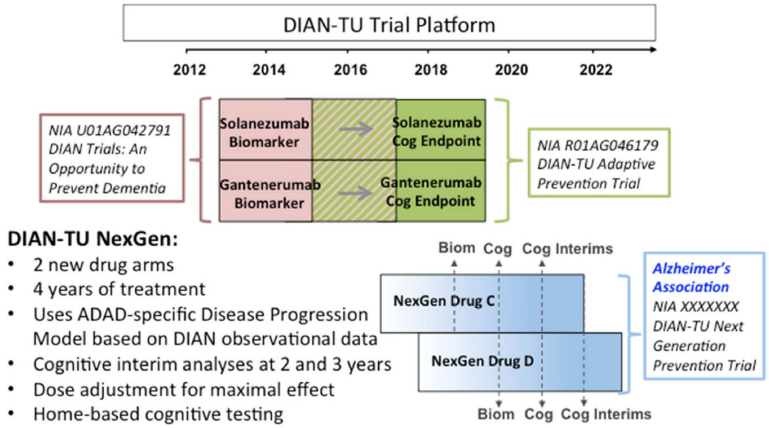

Figure 1.

Existing and proposed structure of the DIAN-TU trial platform including the Next Generation Prevention Trial. Pink indicates enrollment of the first two arms, pink and green the biomarker phase, and green denotes graduation to a cognitive endpoint. In this article we describe design considerations for the two NexGen arms including proposed interim analyses based on biomarkers and performance on the DIAN-TU cognitive composite.

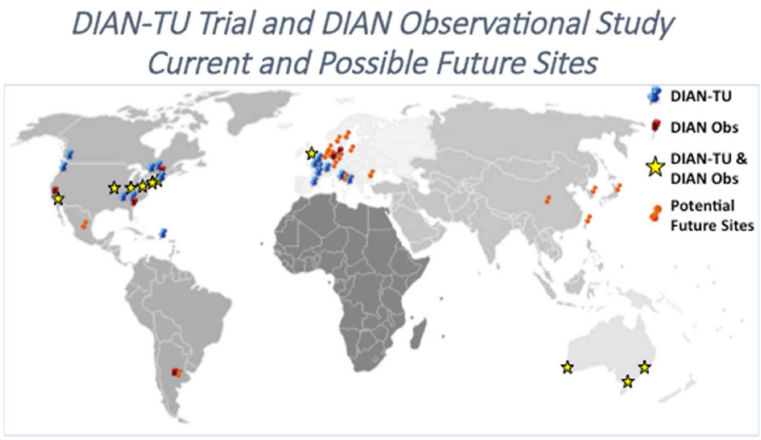

Figure 2.

Current and possible future DIAN-TU and DIAN Observational study sites. The trial is active at 26 sites in 7 countries.

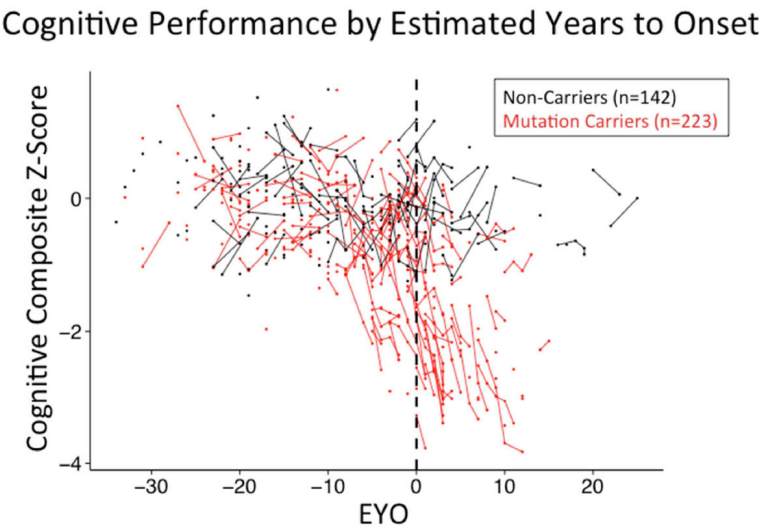

Figure 3.

DIAN-TU Cognitive Composite performance by estimated year to symptom onset in Mutation Carriers (red, n=223) and Non-Carriers (black, n=142) from the DIAN Observational Study Data Freeze 9. The four components of the test include Logical Memory Delayed Recall, DIAN Word List Test (comparable to International Shopping List Test used in DIAN-TU), Digit Symbol Coding and MMSE.

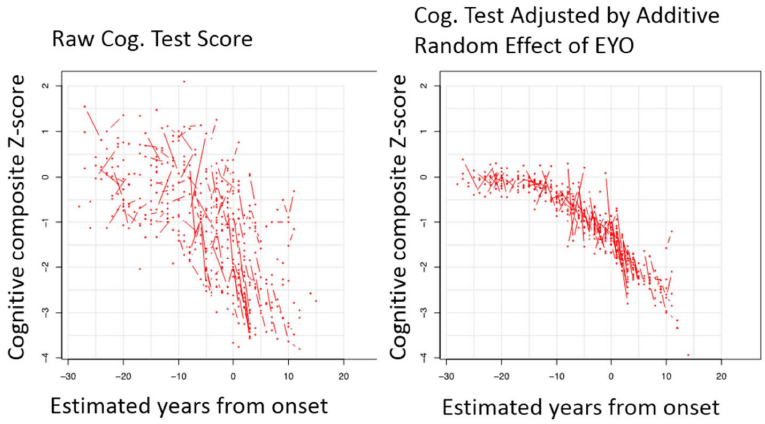

Figure 4.

Longitudinal and Cross-Sectional Cognitive Performance in Mutation Carriers. Disease progression modeling demonstrating the dramatic improvement in variance for cognitive decline (right panel) after accounting for subject level EYO and subject level baseline cognitive performance.

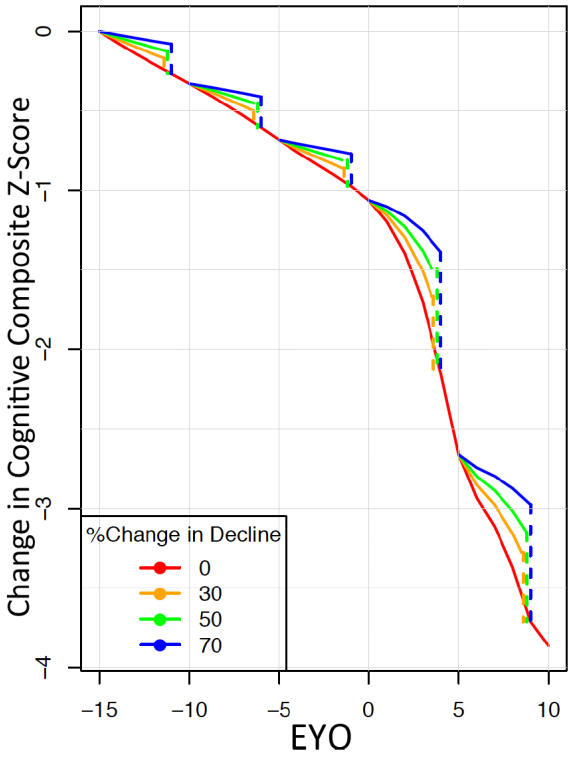

Figure 5.

Proportional hypothetical treatment effects yield different absolute changes depending on EYO. The red line represents the natural (i.e. placebo) rate of cognitive decline across EYO. The colored lines illustrate different levels of slowing disease progression based on drug effect across EYO.