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Featured Article

The Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease Trial: A study of crenezumab versus placebo in preclinical *PSEN1* E280A mutation carriers to evaluate efficacy and safety in the treatment of autosomal-dominant Alzheimer's disease, including a placebo-treated noncarrier cohort

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Abstract

Introduction: Autosomal-dominant Alzheimer's disease (ADAD) represents a crucial population for identifying prevention strategies that might modify disease course for cognitively unimpaired individuals at high imminent risk for developing symptoms due to Alzheimer's disease (AD), that is, who have "preclinical" AD. Crenezumab is an antiamyloid monoclonal antibody that binds

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monomeric and aggregated forms of amyloid β, with highest affinity for oligomers; it is in development for early stages of sporadic AD and for ADAD.

Methods: This is a prospective, randomized, double-blind, placebo-controlled phase 2 study of the efficacy of crenezumab versus placebo in asymptomatic *PSEN1* E280A mutation carriers from family kindreds with ADAD in Colombia. Participants were randomized to receive either crenezumab or placebo for 260 weeks. The study was designed to enroll a planned total of 300 participants, including 200 preclinical mutation carriers (approximately 100 treatment, 100 placebo) and an additional control group of mutation noncarriers from the same family kindreds included to mask mutation carrier status (100 placebo only). The primary outcome is change in the Alzheimer's Prevention Initiative ADAD Composite Cognitive Test Score from baseline to week 260. Secondary outcomes include time to progression to mild cognitive impairment due to AD or dementia due to AD; changes in dementia severity, memory, and overall neurocognitive functioning; and changes in amyloid–positron emission tomography, fluorodeoxyglucose–positron emission tomography, magnetic resonance imaging volumes, and cerebrospinal fluid levels of β amyloid, tau, and p-tau. Safety and tolerability are assessed.

Results: Two hundred fifty-two participants were enrolled between December 2013 and February 2017.

Discussion: We describe the first large-scale, potentially label-enabling clinical trial of a preclinical treatment for ADAD. Results from this trial will inform on the efficacy of crenezumab for delaying onset of, slowing decline in, or preventing cognitive impairment in individuals with preclinical ADAD and will foster an improved understanding of AD biomarkers and their relationship to clinical outcomes.

Keywords: Alzheimer's disease; Autosomal-dominant Alzheimer's disease; Preclinical Alzheimer's disease; Prevention; Clinical trial; Crenezumab; Alzheimer's Prevention Initiative

1. Introduction

1.1. The Alzheimer's Prevention Initiative

In 2010, Banner Alzheimer's Institute established the Alzheimer's Prevention Initiative (API) to (1) evaluate potential Alzheimer's disease (AD)–modifying treatments in cognitively unimpaired people who are at high risk for symptoms of AD; (2) develop new cognitive outcomes; (3) assess whether biomarker effects correlate with clinical benefit ("theragnostic" utility, i.e., the treatment's biomarker effects are "reasonably likely to predict a clinical benefit," a criterion that regulatory agencies consider when asked to qualify a biomarker as a surrogate end point; clinical end point, in clinical research, is a disease, symptom, or sign that constitutes one of the target outcomes of the trial or its participants), whether baseline biomarkers are associated with treatment effects ("predictive" utility), and whether baseline biomarkers predict clinical course ("prognostic" utility); (4) help establish the regulatory approval pathway needed for "preclinical" AD treatments; (5) provide improved tests of the amyloid hypothesis than clinical trials in clinical or later preclinical (e.g., amyloid-positive only) stages of AD; (6) provide prevention registries as shared resources; and (7) establish data and sample sharing plans to advance the field. This is the first of a series of API trials designed to systematically address each of these aims in addition to trial-specific aims.

1.2. AD and the amyloid hypothesis

AD is the most common form of disabling cognitive impairment in older people and has a devastating social impact [1,2]. Postulated elements of the pathogenic cascade include accumulation of amyloid β (Aβ) peptides in monomeric, oligomeric, and fibrillar Aβ species; aggregation and phosphorylation of tau; neuroinflammation; synaptic dysfunction; and neuronal loss. Accumulation of soluble Aβ42 oligomers and/or Aβ42 fibrils may play a critical, early role in the development of AD [3].

1.3. Autosomal-dominant Alzheimer's disease

Autosomal-dominant Alzheimer's disease (ADAD) accounts for 1%–2% of all AD cases [4]. Mutations of the presenilin1 (*PSEN1*), presenilin2 (*PSEN2*), and amyloid precursor protein (*APP*) genes are inherited as fully penetrant, autosomal-dominant traits typically resulting in AD symptoms by age 65 years [4,5]. Although there are genetic and biological differences between ADAD and sporadic AD, they have similar neuropathological and clinical features. Sporadic AD has been associated with reduced Aβ42 clearance and ADAD with increased Aβ42 production; however, the biochemical consequences are similar, with brain accumulation of Aβ playing an early role. Both forms of the disease might respond to treatments affecting Aβ [6].

1.4. Rationale for preclinical AD trials in ADAD

Treatments targeting this pathogenic cascade include those interfering with production, accumulation, or toxic sequelae of Aβ species [7]. We hypothesize that, to have their greatest benefit, AD-modifying treatments may need to be started before the onset of clinical symptoms, at which

point fibrillar Aβ is plateauing, tau pathology is apparent, and there is irreversible synaptic or neuronal loss [8,9]. Delaying the onset of symptoms by 5 years, at least in sporadic AD, could reduce dementia cases by 50% [10]. Because progression to mild cognitive impairment (MCI) and dementia is certain, people inheriting ADAD mutations offer a compelling group for assessing the efficacy of putative prevention strategies. We sought to conduct a study large enough to address both clinical and biomarker outcomes in a relatively homogeneous population of cognitively unimpaired mutation carriers at certain risk of developing AD dementia but lacking overt symptoms, that is, with "preclinical AD" [11].

1.5. The Paisa mutation and the Antioquia kindreds

A Colombian family with early-onset ADAD was described in 1987 [12] with a *PSEN1* mutation at codon 280 (E280A) [13]. Additional families with this mutation have been identified [14], living primarily in Antioquia, Colombia. Analysis of markers surrounding the *PSEN1* gene supports the existence of a founder effect [13].

The most frequent clinical presentation in this kindred is gradual memory loss, followed by changes in behavior and language impairment [15,16]. The cognitive profile of *PSEN1* E280A AD does not differ substantially from that of sporadic AD [17]. Median age of onset was 44 years (95% CI 43–45) for MCI and 49 years (95% CI 49–50) for dementia. Carriers died at a median age of 59 years (58–61) [16]. The age at onset of fibrillar Aβ deposition was 28 years [18] in a pattern of deposition similar to that seen in sporadic AD. Functional and structural magnetic resonance imaging showed characteristic patterns of regional activation and deactivation as well as reduced regional gray matter volumes in mutation carriers versus controls (mean age 37 years) [19–21]. These findings suggested that we could design a trial with sufficient power to characterize brain changes in asymptomatic carriers of a single mutation from the same kindred [22,23].

1.6. The Neurosciences Group of Antioquia and the API Colombia Registry

Neurosciences Group of Antioquia (GNA), sometimes together with API, has conducted clinical, cognitive, genetic, postmortem, and other studies of families affected with ADAD for over 20 years. Planning for the trial began in 2008 and it was introduced to the affected families in 2010. Since 2010, GNA has enrolled family members into the API Colombia Registry as a research preenrollment mechanism that was approved by the local Ethics Committee.

1.7. Selection of crenezumab

A Treatment Selection Advisory Committee vetted candidate agents based on target engagement and safety and tolerability data. Family members were presented masked profiles of representative agents under consideration and asked their preference (e.g., anti-Aβ or other mechanism, route of administration, known clinical effects, availability). They preferred an anti-Aβ agent with the optimal tradeoff between potency and safety, preferably administered orally or subcutaneously (SC). Crenezumab was selected based on its profile and Genentech's willingness to share API's general scientific goals.

Crenezumab is a fully humanized IgG4 monoclonal antibody to Aβ1–40 and Aβ1–42 in monomeric and aggregated forms. *In vitro*, crenezumab binds with highest affinity to oligomers, inhibits oligomer-induced neuronal toxicity, promotes oligomer disaggregation, and promotes removal via microglial phagocytosis, with minimal inflammatory activation of microglia [24,25]. A murine antibody precursor to crenezumab administered systemically reduced plaque load and improved memory performance in a murine model of AD [25]. Crenezumab was designed with an IgG4 backbone to reduce Fcγ receptor binding affinity compared to IgG1 antibodies; this lower effector function was to minimize inflammation at brain vasculature and lower the risk of localized microvascular damage and amyloid-related imaging abnormalities observed in other anti-Aβ trials [25–27]. These properties suggested that crenezumab could offer clinical efficacy with reduced risk of toxicity and potentially modify AD disease progression [25]. Unpublished data available at the time from two ongoing phase 2 trials in patients with sporadic AD indicated sufficient safety and tolerability to warrant use in this at-risk population. (The phase 2 trials, as well as a phase 1 trial, were subsequently completed, confirming the safety and tolerability profile known at the time of agent selection, and suggested a signal of efficacy at the higher of the 2 doses tested [15 mg/kg intravenously every 4 weeks] while also showing lack of benefit of the lower dose of 300 mg SC every 2 weeks in persons with AD dementia.) [28–30].

2. Methods

Description of this study protocol conforms to the 2013 Standard Protocol Items: Recommendations for Interventional Trials [31,32]. A checklist of Standard Protocol Items: Recommendations for Interventional Trials items and their corresponding page numbers can be found in Supplementary Table 1.

2.1. Design

This is a prospective, randomized, double-blind, placebo-controlled, parallel-group adaptive study of the efficacy of crenezumab versus placebo in individuals who carry the *PSEN1* E280A autosomal-dominant mutation and do not meet criteria for MCI or dementia due to AD [33,34]. The trial is registered in clinicaltrials.gov as "A study of crenezumab versus placebo in preclinical *PSEN1*

E280A mutation carriers to evaluate efficacy and safety in the treatment of autosomal-dominant Alzheimer's disease, including a placebo-treated noncarrier cohort" (NCT01998841, date of registration: November 22, 2013).

The study is conducted at a single research site at the University of Antioquia in Medellin, Colombia, with satellite sites for drug administration and safety monitoring for participants residing at a distance from Medellin. Enrollment began in December 2013 and concluded in February 2017.

PSEN1 E280A mutation carriers meeting study eligibility criteria were randomized to one of two treatment groups: crenezumab or placebo, both administered SC at a research site every 2 weeks. To maintain genotype blind and to have a genetic kindred control, a cohort of *PSEN1* E280A noncarrier kindred family members were also enrolled into the study in a double-blinded fashion and administered placebo only. This is essentially a two-part study: (1) a 260-week, double-blind, randomized, placebo-controlled, clinical trial to study the efficacy of crenezumab in an expected total of 200 preclinical individuals with a *PSEN1* E280A mutation by comparing change, on drug versus placebo, in a cognitive composite score, other clinical outcomes, and biomarker measures; and (2) a 260-week, double-blind, nonrandomized, nested, cohort study, including the carriers and expected total of 100 noncarriers receiving placebo, allowing comparison of cross-sectional and longitudinal data.

The study duration for individual participants was planned to be up to 280 weeks, including a 6-week screening period; a 260-week, double-blind treatment period; and a 14-week (last visit 16 weeks after the last dose of study drug) safety follow-up period to allow for clinical follow-up after treatment discontinuation. The study design originally incorporated a decision-making interim analysis after the last participant enrolled received 104 weeks of treatment, continuing the trial only if specified criteria were met. Based on ongoing review of all data from the field, we decided subsequently that the interim analysis will be restricted to an assessment of overwhelming efficacy or reverse efficacy, such as impaired performance on cognitive testing not evident on routine safety review.

2.2. Objectives

The primary objective of this trial is to evaluate the efficacy of crenezumab treatment compared with placebo for up to 260 weeks on change in cognitive function in preclinical *PSEN1* E280A autosomal-dominant mutation carriers.

Secondary objectives are to evaluate the ability of crenezumab to do the following in *PSEN1* E280A mutation carriers:

- Increase time to progression to MCI or dementia due to AD
- Increase time to progression to a Clinical Dementia Rating global score >0
- Reduce increase in the Clinical Dementia Rating Sum of Boxes
- Reduce cerebral fibrillar amyloid burden using florbetapir positron emission tomography
- Reduce decline in regional cerebral metabolic rate of glucose using fluorodeoxyglucose–positron emission tomography
- Reduce brain atrophy as measured by volumetric magnetic resonance imaging
- Affect cerebrospinal fluid β amyloid, total tau, and p-tau

Safety objectives are to assess the safety and tolerability of crenezumab.

Pharmacokinetic and pharmacodynamic objectives are to collect sparse pharmacokinetic samples to confirm exposure to crenezumab and explore the pharmacodynamic response measured by plasma beta amyloid.

Exploratory objectives are to:

- Assess the effect of crenezumab on other clinical measures of efficacy and AD biomarkers
- Explore pharmacogenetic influences on crenezumab's effects
- Explore effects of genetic variation on crenezumab's effects
- Examine clinical and biomarker changes in noncarriers with those seen in carriers treated with placebo
- Relate crenezumab's biomarker effects to clinical outcomes and examine predictive and prognostic utility of baseline characteristics

2.3. Treatment group assignments

At the time the study was implemented, the community standard was for individuals not to learn their *PSEN1* genotype, and there were no options for clinical genetic testing or disclosure; provisions will be made to offer this information outside the context of the trial if community standards change. A dynamic randomization design was used with age ($\leq$38 or $>$38), education ($<$9 or $\geq$9 years), apolipoprotein E4 status, and Clinical Dementia Rating total (0 or $>$0) as balancing factors. Mutation carriers were randomized to crenezumab or placebo in a 1:1 ratio; mutation noncarriers were assigned to placebo only. Efforts to promote adherence and retention include a program to ensure ready access to medical care in the event of unanticipated health concerns and a program to offer education and support to all affected family kindred members regardless of trial participation. Participants who stop treatment are invited to continue in the trial.

2.4. Dosing

The original dose was 300 mg (2 $\times$ 1 mL SC injections). Treatment is continued in participants who develop MCI or dementia due to AD to examine impact of treatment on the overall trajectory of illness.

Stable doses of maintenance medications are permitted except for those that may significantly affect cognition. Intermittent or short-term use of these medications may be allowed if medically necessary. Cholinesterase inhibitors and/or memantine are prohibited except in participants enrolled in the study who develop AD dementia.

2.5. Inclusion and exclusion criteria

Table 1 indicates pertinent criteria, some of which were amended during the trial (see Section 3.2).

2.6. Clinical outcomes and effectiveness measures

The clinical and cognitive outcome measures (Table 2) were selected primarily from those used by GNA over 20 years since the design rested on these data. Change in the API ADAD Composite Cognitive Test score from baseline to week 260 is the primary outcome measure [49]. Secondary outcome measures address changes in salient clinical and biomarker measures. Measurement and analysis plans for biomarkers will be finalized as late as possible to benefit from new developments in the field, for example, specific regions of interest and methods for measuring change in amyloid positron emission tomography measures. Key cognitive and global rating sessions are audio-recorded and monitored centrally for quality assurance and improvement.

The Schedule of Events is shown in Table 3. Every 6 months, an investigator documents whether the participant has progressed to MCI or dementia and, if so, whether the pattern is consistent with AD. Where progression is judged to have occurred, information for that participant as well as for a participant who has not progressed is presented in a blinded fashion to the Progression Adjudication Committee for review according to a charter. If the investigator and the committee disagree, the committee opinion is used for end-point determination and the investigator's opinion governs clinical management.

All data are managed and stored in a secure fashion and reviewed by external study monitors for accuracy and completeness according to the standards of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and health authority requirements.

2.7. Statistical analysis plan

Analyses planned for the study include the following: A limited interim analysis of the cohort of carriers will occur after all participants have completed the week 104 assessment. The initially planned primary analysis was to occur after all participants completed week 260. The study is powered to compare the mean change from baseline over 260 weeks in the API Composite Cognitive Battery between the active group and the placebo. Assuming a 25%

Table 1
Inclusion and exclusion criteria

Inclusion criteria
- Membership in *PSEN1* E280A mutation carrier kindred
- *PSEN1* E280A mutation carrier or noncarrier status has been confirmed by separate laboratory
- Men and women, age ≥30 years and ≤60 years
- **MMSE ≥ 26** (changed to MMSE of ≥24 for participants with <9 years of education, or MMSE of ≥26 for those with ≥9 years of education)
- Does not meet criteria for dementia due to AD [34]
- Does not meet criteria for MCI due to AD [33] as defined by cutoff scores on the Subjective Memory Checklist, CERAD Word List Recall, and FAST
- If female, and not documented to be surgically sterile, willing to undergo pregnancy tests per protocol
- For women who are not surgically sterile, agreement to remain abstinent or use two methods of contraception
- For men with partners of childbearing potential, agreement to remain abstinent or use a condom
- Study partner who agrees to participate in the study and is capable of and willing to accompany the participant to all visits
- **Serum TSH and B12 within normal range** (changed to also allow values out of range if judged not to be clinically significant)

Exclusion criteria
- Has significant medical, psychiatric, or neurological condition or disorder
- History of stroke
- **Body weight <40 or >120 kg** (lower limit changed to 45 kg)
- Clinically significant depression
- History of seizures (excluding febrile seizures of childhood or other isolated seizure episodes that were not due to epilepsy)
- Brain MRI results at baseline showing
  - evidence of amyloid-related imaging abnormality–edema, infection, significant cerebral vascular pathology, clinically significant lacunar infarct, multiple lacunes, cortical infarct, or focal lesions
  - more than four cerebral microhemorrhages
  - single area of superficial siderosis or prior cerebral macrohemorrhage
- Clinically significant screening blood laboratory abnormalities
- **Positive urine test for drugs of abuse at screening** (changed to allow for one additional screening; a second positive test [except for cannabinoids] would result in exclusion)
- Use of any other medications with the potential to significantly affect cognition

Abbreviations: AD, Alzheimer's disease; FAST, Functional Assessment Staging Test; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PSEN1, presenilin 1; RNA, ribonucleic acid; MMSE, Mini–Mental Status Examination; TSH, thyroid-stimulating hormone.

NOTE. Bolded font criteria represent key amendments.

Table 2
Specific outcome measures and instruments

Primary outcome measure
- API Cognitive Composite Test (derived from elements of the following)
  - Word List: Recall [35–37]
  - Multilingual Naming Test [38]
  - Consortium to Establish a Registry for Alzheimer's Disease Constructional Praxis Test [36]
  - Mini–Mental State Examination (for Orientation to Time) [39]
  - Ravens Progressive Matrices [40]

Secondary outcome measures
- Clinical
  - Time to progression to mild cognitive impairment or dementia due to Alzheimer's disease [33]
  - Clinical Dementia Rating (global score and sum of boxes) [41]
- Biomarkers
  - Cerebral fibrillar amyloid burden measured by florbetapir positron emission tomography (PET)
  - Regional cerebral metabolic rate of glucose using fluorodeoxyglucose (FDG)-PET
  - Volumetric magnetic resonance imaging
  - Cerebrospinal fluid (CSF) levels of β amyloid, p-tau, and total tau
- Safety
  - Safety laboratories
  - Electrocardiogram
  - Magnetic resonance imaging
  - Suicidality Assessment (Copyright Pfizer Inc. and Janssen Alzheimer Immunotherapy; used with permission)
  - Physical and neurological examination
  - Vital signs
- Pharmacokinetic/pharmacodynamic measures (PK/PD)
  - PK: CSF and serum crenezumab concentrations at protocol-specified time points (trough serum concentrations are assessed at steady state)
  - PD: plasma Aβ1–40 and Aβ1–42 concentrations

Exploratory outcome measures
- Clinical
  - Trail Making Test [42], Mini–Mental State Examination [39]
  - Repeatable Battery for the Assessment of Neuropsychological Status [43]
  - Free and Cued Selective Reminding Task (FCSRT) [44]
  - Scores of each of the components of the API Composite Cognitive Battery
  - Neuropsychiatric Inventory [45,46]
  - Geriatric Depression Scale [47]
  - Functional Assessment Staging of Alzheimer's Disease [48]
  - Subjective Memory Checklist [16]
- Fluid biomarkers
  - Cerebrospinal fluid levels of other Aβ species
  - Changes in other blood and cerebral spinal fluid measures
- Imaging biomarkers
  - Analysis of regions of interest not selected in secondary end point
- Other
  - Changes in primary, secondary, and exploratory outcomes in carriers and noncarriers as function of APOE and genetic variations

Abbreviations: API, Alzheimer's Prevention Initiative; Aβ, amyloid β; APOE, apolipoprotein E.

dropout rate, two-sided testing at the 0.05 level, a placebo group coefficient of variance of 65% for the week 260 change scores (=100% × standard deviation of placebo participant change scores/mean of placebo participant change scores), and 100 participants per arm, the study will have at least 80% power to detect a true effect of 30% reduction of the mean decline in the placebo group. The assumed placebo group coefficient of variance of 65% is based on an unpublished analysis of the Colombian Registry data.

Although the total recruitment of 252 fell short of the planned 300 participants, the impact to power is expected to be offset by a lower-than-planned attrition rate and the change to a "common close" design. The common close specifies that treatment assigned at randomization and blinded study assessments are maintained until the common close, defined as 260 weeks after the last participant is randomized. This design will add approximately 25% more observations toward the primary analysis without delaying the time to primary analysis.

2.8. Human subjects considerations

Informed consent was obtained from all participants and study partners for experimentation with human subjects. An approved companion guide to the informed consent form was used, and family members/other partners were involved in the consenting process. Provisions are in place to assess loss of capacity in individuals who develop cognitive impairment, in which case assent will be used. Consent and assent procedures are conducted in accordance with local ethics committee standards. The trial was approved by the Colombian Health Authority, Instituto Nacional de Vigilancia de Medicamento y Alimentos. An independent data monitoring committee that includes a representative from the National Institute on Aging (NIA) oversees safety data and will be

Table 3
Schedule of assessments (abridged)

Time point	Screening	Baseline (W1)	Q2 weeks after BL	W4	Q12 weeks after BL up to W52	W16	W26	W38	W52	Q26 weeks after W52	W104	W260	W274
Medical history	X												
Physical and neurological examination	X	X			X		X	X	X	X	X	X	X
Criteria for MCI/AD	X						X		X	X	X	X	
GDS	X						X		X	X	X	X	
Subjective memory checklist	X						X		X	X	X	X	
Screening cognitive battery	X												
Composite cognitive battery		X			X		X		X	X	X	X	X
Extended cognitive battery		X					X		X	X	X	X	
CDR		X					X		X	X	X	X	
FAST	X						X		X	X	X	X	
NPI		X					X		X	X	X	X	
Suicidality assessment		X			X		X	X	X	X	X	X	
Safety laboratories	X	X		X	X		X	X	X	X	X	X	X
DNA (APOE, PSEN1); optional DNA for repository	X												
ECG	X	X		X	X	X	X		X		X	X	
PK, PD, and exploratory serum, plasma, RNA samples		X		X	X	X	X	X	X	X	X	X	X
ATA sample		X					X		X	X	X	X	X
Urine screen for drugs of abuse	X								X		X	X	
Serum pregnancy test	X												
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication		X	X	X	X	X	X	X	X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Interval medical history and adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test		X	X	X	X	X	X	X	X	X	X	X	X
Brain MRI	X				X		X	X	X	X	X	X	
Lumbar puncture for CSF samples (optional)		X									X	X	
Fibrillar amyloid PET imaging	X										X	X	
FDG PET	X				X						X	X	X

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein; ATA, antitherapeutic antibody; CDR, Clinical Dementia Rating Scale; CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; ECG, electrocardiogram; FAST, Functional Assessment Staging Test; FDG, fluorodeoxyglucose; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NPI, Neuropsychiatric Inventory; PD, pharmacodynamic; PET, positron emission tomography; PK, pharmacokinetic; PSEN1, presenilin 1; RNA, ribonucleic acid.

responsible for the interim analysis. Safety and tolerability concerns are assessed every 2 weeks for each participant.

3. Discussion

3.1. Main aims

The study is designed to have adequate statistical power to evaluate the impact of crenezumab on cognition using a novel composite cognitive battery that was characterized in this cohort. We expect that some participants treated with placebo will progress to MCI, and a smaller number may progress to dementia. We aim to demonstrate whether crenezumab has the ability to slow the progression of AD symptoms as well as biomarker measures of AD pathology and neurodegeneration in ADAD mutation carriers.

3.2. Study protocol amendments

Several protocol modifications were made, approved by the ethics committees and Instituto Nacional de Vigilancia de Medicamento y Alimentos, and communicated to participants via revised, approved consent forms. Specifically, during enrollment into our trial, the phase 2 trials of crenezumab in persons with sporadic AD dementia were completed, after which we increased the dose of crenezumab to 720 mg (2×2.4 mL SC injections) to approximate the exposure levels of the high intravenous dose given in phase 2. The protocol amendment was submitted to Instituto Nacional de Vigilancia de Medicamento y Alimentos in August 2014 and approved in May 2015.

Selected inclusion/exclusion criteria were amended, reflecting pragmatic accommodations to common issues in the community and the need to recruit persons representative of the population at risk. Specifically, the Mini–Mental Status Examination criterion was revised to allow an education-adjusted cutoff, based on the observation that some prospective participants had low Mini–Mental Status Examination scores but no evidence of progressive cognitive decline and review of historical data showing that such individuals did not experience cognitive decline. Because slightly low

vitamin B12 and slightly elevated thyroid-stimulating hormone levels are prevalent in this community, the exclusion criteria for these were modified to allow inclusion of participants with clinically insignificant abnormal levels. The exclusion criterion for a positive urine test for drugs of abuse at screening was changed to allow for one additional screening; a second positive test (except for cannabinoids) would result in exclusion. Cannabinoid use is prohibited 24 hours before cognitive testing or scans. The use of low doses of anticholinergic antidepressants for depression and sleep disorders, originally exclusionary, was later permitted, as such drugs are widely used for these reasons.

We have sought permission to change to a common close study design (see Section 2.7) to enhance the power of the study and also maintain the genetic blind until the end of the study.

3.3. Recruitment

A recruitment campaign promoted awareness of the trial and the Registry, including earned media coverage, advertisements, letters to physicians, educational programs, additional interviews of affected families, and reviews of hospital and church records. The Registry expanded from 2096 in 2012 to 5846 by 2017, including over 1100 mutation carriers. A small team unblinded to genotype referred registrants to the trial, achieving the goal of having 67% of trial participants being mutation carriers, while also averting the otherwise-likely possibility of an early imbalance of noncarriers to carriers enrolled.

At the time the decision was made to increase the dose, enrollment into the trial was slowed deliberately to allow time for Health Authority approval of the higher dose amendment and maximize the number of participants exposed to the higher dose.

3.4. Study population

The inclusion and exclusion criteria limit the study population to *PSEN1* E280A autosomal-dominant mutation carriers likely to be in a "preclinical" stage of AD [11]. The lower age limit of 30 years will likely be associated with a high likelihood of brain amyloid accumulation, although not all participants will have moderate or greater fibrillar beta amyloid accumulation yet [19]. Including individuals with less-than-moderate amyloid accumulation may help to further probe the amyloid hypothesis as well as address the predictive utility of this biomarker. Neither participants nor investigators are provided information about their biomarker findings other than clinical magnetic resonance imaging interpretations.

3.5. Measuring cognitive decline in preclinical AD

Traditional cognitive outcome measures used in trials in clinically impaired persons with AD are not appropriate in preclinical treatment trials owing to their ceiling effects and general lack of sensitivity. Rather than selecting a single cognitive measure that has been reported to measure change in a preclinical stage of AD, or a measure of cognitive decline that distinguishes between at-risk groups, we conducted longitudinal analyses in two independent cohorts to empirically derive a composite cognitive battery that is sensitive to preclinical decline for use in ADAD [49] and sporadic AD treatment trials [50], meeting FDA's proposed criteria for an "intermediate clinical end point" [51]. We found that the decline in our composite cognitive test scores (1) is sensitive to subsequent progression to clinical stages of sporadic AD; (2) is sensitive to preclinical decline in *PSEN1* E280A mutation carriers aged 30 years and older [51] who would not have cognitive decline for any other reason other than ADAD; (3) has the ability to control for practice and age effects using data from either ADAD mutation noncarriers or those who remain cognitively normal during a specified time period; and (4) is consistent in independent analyses/cohorts.

3.6. Theragnostic biomarker development

Showing biomarker/efficacy correlations in the Colombia ADAD study could provide a unique opportunity to define specific biomarker changes as reasonably likely surrogate end points. Future accelerated approval using biomarker data likely would have to be confirmed with longer term clinical follow-up as well as showing that biomarker changes correlating with cognitive benefit in ADAD are also correlated with cognitive benefit in sporadic AD.

3.7. Process

Funding is provided by grants from the NIA, philanthropy, and Genentech/Roche, a public-private partnership created to maximize public benefit beyond usual specific trial-related aims. The trial is jointly governed by representatives from Genentech/Roche, Banner Alzheimer's Institute, NIA, and GNA. An Ethics and Cultural Sensitivities Committee was created to advise on issues such as genetic disclosure, participant compensation, access to health care or legal assistance, and post-trial plans. The trial design was also vetted by numerous academic and industry stakeholders, industry, patient and family advocates, and community leaders in Colombia and members of the kindred themselves. In the originally funded NIA proposal, a substudy of ADAD mutation carriers was proposed in the United States. However, the subsequent launch of the Dominantly Inherited Alzheimer's Network trial provided ADAD families in the United States an opportunity to participate in trials, with larger sample sizes. We decided to focus our efforts and resources on the kindreds in Colombia and refer any US ADAD kindreds known to us to the Dominantly Inherited Alzheimer's Network trial. To optimize coordination among the various preclinical trials that have emerged since API was launched, the Collaboration for Alzheimer's Prevention was convened with API as a partner [52].

3.8. Data and sample sharing

The trial sponsors have created a precedent-setting agreement that commits us to sharing trial data within a specified time frame after the trial is completed, as well as sharing, to the extent possible, remaining biological samples. We have committed to publishing full results from the trial as well as sharing them with trial participants. We have endorsed a new principle, articulated by Collaboration for Alzheimer's Prevention [53], and are exploring the feasibility of sharing prerandomization data.

3.9. Other considerations

We anticipate further developments in the field and will respond accordingly. If the results warrant approval for marketing by Heath Authorities, provisions will be made for all participants to have post-trial access to treatment. A point of contact for public and/or scientific inquiries will be established.

4. Summary

We described our preclinical trial to assess the impact of crenezumab in cognitively unimpaired persons with ADAD, designed to address whether active treatment can delay the onset of, slow, or prevent cognitive decline. Study participants do not meet criteria for MCI or dementia due to AD at enrollment and are thus in a preclinical phase of AD based on being at high risk for developing symptomatic AD due to their genetic status. In addition to addressing a series of specific and exploratory hypotheses, we intend to maximize the scientific impact of the trial through theragnostic, predictive, and prognostic biomarker development aims, data and sample sharing, and development of a large registry that can be used for other studies. This is the first and precedent-setting study in a series of API trials intended to provide a foundation for the accelerated evaluation of prevention therapies in unimpaired persons at risk for AD.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2018.02.002.

RESEARCH IN CONTEXT

1. Systematic review: The "Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease (API ADAD) Colombia Trial" is the first potentially label-enabling trial with an anti-amyloid therapy for prevention of autosomal-dominant Alzheimer's disease.
2. Interpretation: Its design and primary outcome may be potentially label enabling.
3. Future directions: Since it was conceived and launched, the API ADAD has helped pave the way for other preclinical trials, specifically the so-called TOMMORROW Trial, the Anti-Amyloid Against Alzheimer's (A4) Trial, and the two API Generation Program trials.

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