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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,

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who have "preclinical" AD. Crenezumab is an antiamyloid monoclonal antibody that binds 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), 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