The A3 Study: Ante-Amyloid Prevention of Alzheimers disease

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Country

USA

Title of project or programme

The A3 Study: Ante-Amyloid Prevention of Alzheimers disease

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NIH (NIA)

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Research Abstract

SUMMARY This is an application for NIH support of a public-private-philanthropic partnership to conduct a novel prevention trial aimed at initiating anti-amyloid therapy prior to the current threshold for “amyloid positivity” (A?+). We propose the Ante-Amyloid prevention of Alzheimer’s disease (AD)—the “A3” Study—in clinically normal older individuals with “non-elevated” amyloid levels on screening PET who are at increased risk for further A? accumulation. The A3 Study will leverage the large number of eager participants who screen-fail for current secondary prevention trials (A4 and EARLY/“A5” trials) on the basis of non-elevated amyloid levels on screening Amyloid PET scans (florbetapir SUVr). We will utilize an Age x APOE x Amyloid PET SUVr risk algorithm to identify and enroll 600 individuals between the ages of 60-75 who are not yet at the threshold for A?+, but who show intermediate levels of SUVr (A?i) and are at the highest risk for progressing to A?+. Our preliminary data suggest these A?i participants will demonstrate significant increases in A? accumulation over 2-4 years, as well as show evidence of neocortical tau spreading, cortical thinning, and even subtle declines on cognitive testing as they progress towards A?+. Our ultimate goal is to facilitate primary prevention trials in AD. The A3 design will test an oral treatment (BACE inhibitor) at a stage of A? accumulation that is estimated to be 5 years earlier than current secondary prevention trials (“pre-preclinical AD”). There are several BACE inhibitors currently in large-scale trials at later stages of AD that show robust lowering of A? production, with good safety profiles suitable for initiating trials in this very early at-risk population. The A3 Study design is a Phase 2b/3 double-blind, randomized, 3-arm, 4 year trial with a BACE inhibitor at 2 doses vs. placebo (n=200 per arm). The primary outcome will be rate of A? deposition on serial Amyloid PET imaging, with additional outcomes using Tau PET imaging, CSF assays, volumetric MRI, and sensitive cognitive measures. We aim to build a “chain of evidence” that will link the slowing of very early A? accumulation to the prevention of neurodegeneration and cognitive decline that occurs in the later stages of preclinical AD. Similar to the A4 Study, the A3 Study will be a public-private-philanthropic partnership with our industry partner providing the majority of the financial support for the study conduct. We have selected 3 potential industry partners. A therapeutic selection committee will make the final choice of the BACE inhibitor and industry partner based on the up-to-date efficacy and safety data provided by the sponsors. This study will provide critical longitudinal biomarker and cognitive data that will also inform the design of future prevention trials. The A3 Study also has the potential to support regulatory approval for an even-earlier at-risk population, in combination with cognitive endpoint trials at later stages of preclinical or prodromal AD. We hope the A3 Study will serve to catalyze the next era of prevention trials to help move our field towards the primary prevention of AD.

Lay Summary

NARRATIVE The A3 Study is a public-private partnership that will test a drug aimed at reducing the production of amyloid, one of the hallmark pathologies of Alzheimer’s disease (AD), in individuals who are not (yet) “amyloid-positive.” The A3 Study is the first of its kind trial that will attempt to prevent the build-up of amyloid in the brain of asymptomatic older individuals with the ultimate goal of slowing the progression of tangle pathology, nerve cell loss, and eventual memory decline and dementia due to Alzheimer’s disease. This trial has enormous potential to impact public health, as 10,000 baby boomers enter the age of risk for AD every day in the United States.

Further information available at:

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Investments > €500k

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United States of America

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