Development of a non-fibrillic amyloid-beta oligomer selective positron emission tomography imaging diagnostic for Alzheimer.

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Principal Investigators

KLEIN, WILLIAM L

Institution

ACUMEN PHARMACEUTICALS, INC.

Contact information of lead PI
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USA

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Research Abstract

In the United States in 2015 an estimated 5.3 million people suffered from Alzheimer’s disease

(AD), with as many as 50% being undiagnosed (Alzheimer’s Association 2015). Three stages of AD are proposed (National Institute on Aging and the Alzheimer’s Association 2011): preclinical AD, mild cognitive impairment (MCI) due to AD, and dementia due to AD. The preclinical stage is proposed to begin 20 or more years before symptoms appear. Today, many researchers believe that treatments to slow or stop AD will be most effective if administered during the preclinical or MIC stages. However, new biomarker tests are needed to identify individuals at these early stages. These biomarker tests will also be essential for monitoring treatment effects. Current biomarker tests for AD are based on the levels of total amyloid beta (A?), mainly monomer, in cerebrospinal fluid (CSF), levels of tau and phosphorylated tau in CSF, or the levels of fibrillic amyloid plaques in the brain. However, many researchers now regard non-fibrillic A? oligomers (A?o), in contrast to monomeric or fibrillic A?, as the primary A? toxins that cause acute cognitive deficits and induce the chronic neuronal degeneration of AD (tau abnormalities, synapse loss, oxidative damage, etc.). A non-invasive method to detect and quantify A?o could provide a valuable biomarker test to identify early stage AD patients and for monitoring the effect of therapies. Preliminary studies suggest that an A?o selective antibody-positron emission tomography (PET) probe may enable the in vivo detection and quantification of A?o. ACU193 is a proprietary, affinity matured, humanized, monoclonal antibody exhibiting high selectivity for A?o versus monomeric and fibrillic A?. In AD mouse models, ACU193 crosses the blood-brain barrier and forms complexes with A?o in the brain. ACU193 exhibits excellent pharmacokinetics, biodistribution and brain penetration in four animal species. Protein binding studies show excellent selectivity for A?o. Exploratory toxicity studies in monkeys reveal an excellent safety profile for ACU193. Thus, ACU193 is an ideal candidate for testing the potential utility of an A?o antibody PET probe for the in vivo detection and quantification of A?o. The objective of this Phase 1 STTR application is to prepare and optimize an ACU193-PET probe and demonstrate that it provides a sensitive and selective in vitro A?o-dependent signal from transgenic AD mouse model tissues and human AD brain tissues. The underlying hypothesis is that a sensitive and highly A?o selective PET probe can be made using ACU193 labeled with 64Cu. If in vitro sensitivity and selectivity are achieved, the Phase 1 study will also evaluate the sensitivity of the probe in vivo in a transgenic AD mouse mode. Overall success in this program would provide a non-invasive method for detecting and quantifying A?o in vivo, and support its development as an AD diagnostic tool for monitoring disease progression and the effects of treatment and as a research tool that would enable a better understanding of the etiology of AD.

Further information available at:

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