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Original Article

# INTERCEPT-AD, a phase 1 study of intravenous sabirnetug in participants with mild cognitive impairment or mild dementia due to Alzheimer's disease

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ABSTRACT

*Background:* Soluble species of multimeric amyloid-beta including globular amyloid-beta oligomers (A$\beta$Os) and linear amyloid-beta protofibrils are toxic to neurons. Sabirnetug (ACU193) is a humanized monoclonal antibody, raised against globular species of soluble A$\beta$O, that has over 650-fold greater binding affinity for A$\beta$Os over monomers and appears to have relatively little binding to amyloid plaque.
*Objectives:* To assess safety, pharmacokinetics, and exploratory measures including target engagement, biomarker effects, and clinical efficacy of sabirnetug in participants with early symptomatic Alzheimer's disease (AD; defined as mild cognitive impairment and mild dementia due to AD).
*Design:* Randomized, double-blind, placebo-controlled, ascending dose first-in-human phase 1 study.
*Setting:* Fifteen study centers in the United States.
*Participants:* Sixty-five participants with early symptomatic AD.
*Intervention:* Participants received one infusion of sabirnetug 2 mg/kg, 10 mg/kg, 25 mg/kg, 60 mg/kg, or placebo (Part A) or three infusions of sabirnetug 10 mg/kg, 25 mg/kg, 60 mg/kg, or placebo (Part B).
*Measurements:* Safety, tolerability, serum pharmacokinetics, and central target engagement of single and multiple doses of sabirnetug, cerebrospinal fluid (CSF) concentrations of sabirnetug, and amyloid plaque load, as determined by positron emission tomography.
*Results:* Sabirnetug was generally well tolerated. A larger percentage of participants receiving sabirnetug (56.3%) versus placebo (42.9%) had at least one treatment emergent adverse event, with approximately 29% in each group considered related to study drug. Most events were mild-to-moderate in severity. Of 48 participants given sabirnetug, five developed amyloid related imaging abnormalities – edema/effusion, including one instance that was mildly symptomatic in a participant who had received one dose sabirnetug 60 mg/kg. Notably, none of the six *apolipoprotein E ε4* homozygotes who received sabirnetug developed amyloid related imaging abnormalities – edema/effusion or – hemorrhage/hemosiderin deposition. Infusion reactions, such as rash, pain, or erythema, were not frequent (6.3% for sabirnetug versus 0.0% for placebo). Sabirnetug exposure was dose proportional in both serum and CSF. Target engagement, defined as drug bound to A$\beta$Os in CSF, was shown to be dose and exposure dependent. Over three months, approximately 25% and 20% reduction in amyloid plaques, respectively, were observed in participants receiving three infusions of sabirnetug 60 mg/kg every four weeks and 25 mg/kg every two weeks.
*Conclusions:* The Phase 1 INTERCEPT-AD study provided safety, tolerability, dosing, and target engagement data that supported the design of the ongoing ALTITUDE-AD study (NCT06335173).

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