INTERCEPT-AD, a Phase 1 Study of Sabirnetug (ACU193): Safety, Target Engagement, and Biomarker Changes

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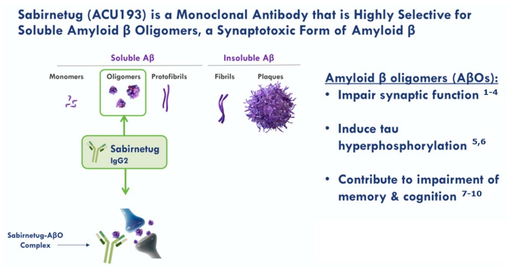
Introduction

Figure 1. Sabirnetug Binding

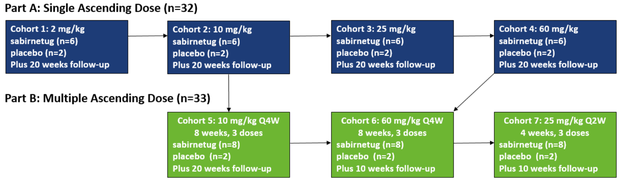


Soluble amyloid ß oligomers (AßOs) instigate neurodegeneration in Alzheimer's disease (AD). Sabirnetug (ACU193) is a humanized IgG2 subclass monoclonal antibody raised against soluble AßOs. The objective of the INTERCEPT-AD phase 1 study was to investigate safety, pharmacokinetics, target engagement, and biomarker effects of sabirnetug in a phase 1 trial of participants with early AD.

Study Design

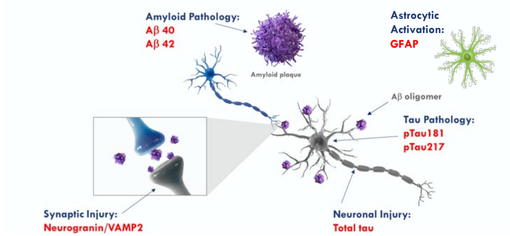
INTERCEPT-AD (NCT04931459) was a double-blind, placebo-controlled study incorporating four single ascending dose (SAD) cohorts with doses ranging from 2 mg/kg to 60 mg/kg and three multiple-ascending dose (MAD) cohorts receiving three doses of sabirnetug (10 or 60 mg/kg every four weeks [Q4W] or 25 mg/kg every two weeks [Q2W] or placebo; Figure 2). Participants had mild cognitive impairment or mild dementia and amyloid positivity was confirmed by florbetapir PET. Safety assessments included regular MRI. Target engagement was assessed in cerebrospinal fluid (CSF) and CSF and plasma were used for biomarker assessments. CSF was collected pre-dose and 7-21 days post-dose.

Figure 2. Study Design



Arrows indicate reviews conducted on data from one cohort by safety review team before initiation of treatment in the next cohort.

Figure 3. Key Biofluid Biomarkers Associated with Alzheimer's Disease Pathology

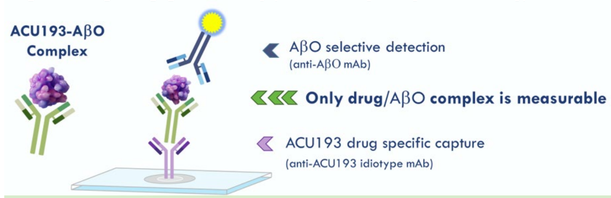


Biomarker Assay Methods

Biomarkers were measured in CSF and EDTA-plasma, before and after drug administration, at ADx NeuroSciences (CSF pTau217) and Amsterdam UMC (all other biomarkers). Participants were excluded from all biomarker analyses for the following reasons: baseline and/or endpoint lumbar puncture not done (n=9); 10 mg/kg Q4W cohort participant who received only one of three infusions (n=1). Participants were excluded from some analyses for the following reasons: values below measurable range and/or limited CSF volume (n=3); and values outside mean ± 2 standard deviations and outside published correlations with other biomarkers (n=2). P-values were calculated for differences in means using unpaired, 2-sided Student's t test and for correlations using Pearson's r test.

Target Engagement Assay Methods

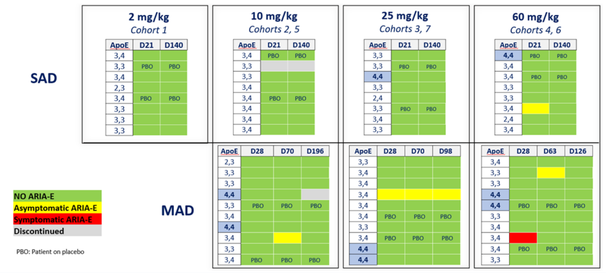
Figure 4. Target Engagement Assay (MSD S-Plex [Turbo] Immunoassay)



Novel assay configuration tailored to selectively detect sabirnetug-AβO complex in CSF as direct measure of target engagement

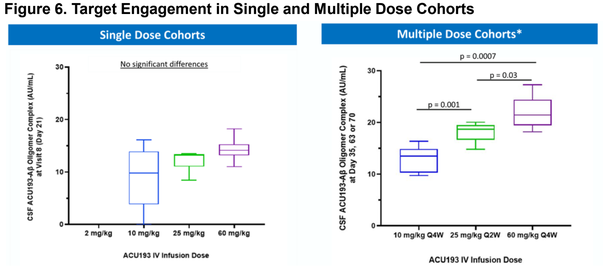
Results

Figure 5. Amyloid Related Imaging Abnormalities – Edema/Effusion (ARIA-E)



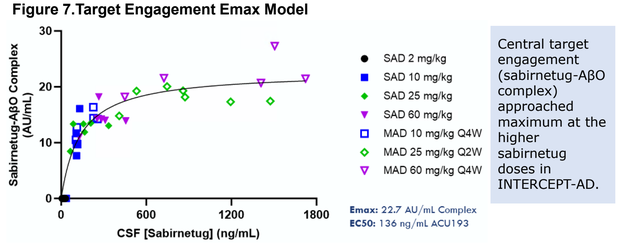
Five of 48 sabirnetug-treated participants experienced amyloid related imaging abnormalities – edema/effusion (ARIA-E). Only one instance, in a participant in the 60 mg/kg Q4W cohort, was symptomatic. None of the six apolipoprotein ε4 homozygotic participants experienced ARIA-E. Four cases of ARIA-E were in ε4 heterozygotes. One (at 60 mg/kg) was a non-carrier.

Figure 6. Target Engagement in Single and Multiple Dose Cohorts



Sabirnetug target engagement increased with increasing dose with both single and multiple dose treatment.
*One 10 mg/kg Q4W participant received only 1 dose and was therefore excluded.

Figure 7.Target Engagement Emax Model



Central target engagement (sabirnetug-AβO complex) approached maximum at the higher sabirnetug doses in INTERCEPT-AD.

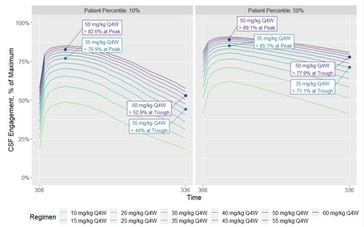
RESEARCH HIGHLIGHTS

INTERCEPT-AD: NCT04931459
ALTITUDE-AD: NCT06335173

- **Sabirnetug has a favorable safety and tolerability profile**
  - **Rates of ARIA-E were relatively low**
  - **Lack of ARIA-E in APOE ε4 homozygotic participants was of interest**
- **Dose-dependent target engagement of Aβ oligomers was demonstrated in CSF**
- **Sabirnetug significantly lowered CSF neurogranin (-13.9%) and pTau181 (-13.0%) concentrations and numerically increased Aβ 42/40 after 3 administrations of sabirnetug 60 mg/kg Q4W**
- **Reduction of the synaptic marker neurogranin correlated significantly with sabirnetug engagement with AβO target**
- **Effects on biomarkers may be both duration- and dose-dependent**
- **Long-term changes in clinical cognitive outcomes, biomarkers, and safety will be evaluated in the ongoing, placebo-controlled phase 2 ALTITUDE-AD study over 18 months.**
- **Based on safety, target engagement, and biomarker changes, sabirnetug doses in ALTITUDE-AD will be 35 mg/kg Q4W and 50 mg/kg Q4W**

Target Engagement, continued

Figure 8. Simulated Target Engagement to Aid Dose Selection for Phase 2 ALTITUDE-AD Study: 35 and 50 mg/kg Q4W



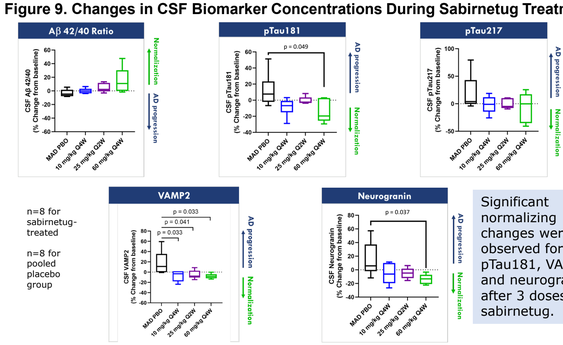
CSF target engagement was simulated at steady state for a list of doses administered Q4W.

Doses were selected with variation in participant PK/PD in mind; select doses based on participants at 50th percentile and 10th percentile.

Doses were selected with peak-trough variation in mind; select doses based on trough (end of dosing interval) CSF engagement. Notable diminishing differentiation was observed as doses increased.

Biomarkers

Figure 9. Changes in CSF Biomarker Concentrations During Sabirnetug Treatment

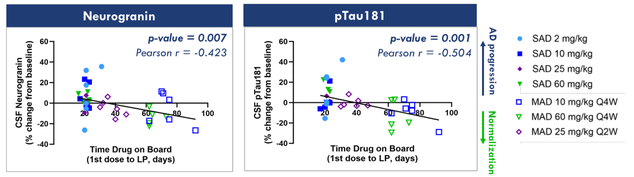


n=8 for sabirnetug-treated

n=8 for pooled placebo group

Significant normalizing changes were observed for pTau181, VAMP2, and neurogranin after 3 doses of sabirnetug.

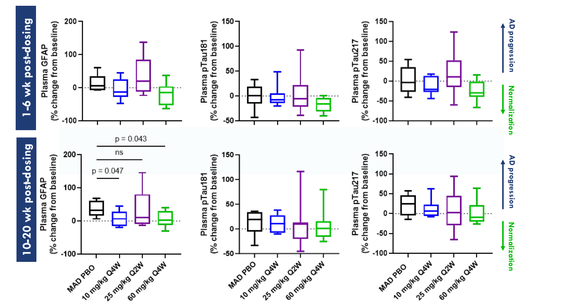
Figure 10. Duration- and Dose-Dependence of Changes in CSF Neurogranin and pTau181



Normalizing changes of CSF neurogranin & pTau181 were positively correlated with duration of drug exposure ("time drug on board"), defined as time between first sabirnetug dose and lumbar puncture (LP). Dose (magnitude & number) is another contributing factor, further substantiating observations in Figure 9.

Biomarkers, continued

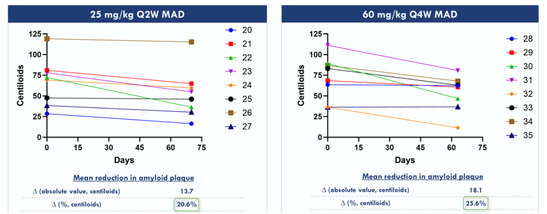
Figure 11. Post-Dose Changes in Plasma Biomarker Concentrations



After 1-6 weeks drug washout, median levels of glial fibrillary acidic protein (GFAP), pTau181, and pTau217 in 10 mg/kg Q4W & 60 mg/kg Q4W groups were lower than placebo.

After 10-20 weeks drug washout, median levels remained lower than placebo; note that placebo levels also increased at this time point.

Figure 12. Effect of Sabirnetug on Amyloid Plaque Load



Nearly all sabirnetug-treated participants in the high dose MAD cohorts showed reductions in plaque load after three doses at 63 or 70 days.

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References: 1. Lacor et al 2004 2. Lacor et al 2007 3. Townsend et al 2006 4. Batistia et al 2018 5. De Felice et al 2008 6. Zemple et al 2010. 7. Clearly et al 2005 8. Poling et al 2008 9. Cline et al 2019 10. Gobom J et al. 2021