INTERCEPT-AD Biomarker Results: Early effect of sabirnetug treatment on synaptic biomarkers in Alzheimer's disease

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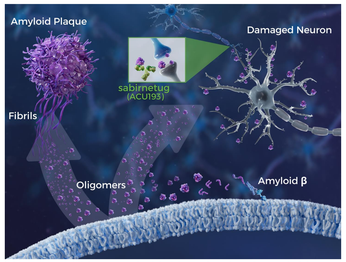
Introduction



- Soluble amyloid β oligomers (AβOs) accumulate early in Alzheimer's disease (AD) and trigger synaptic dysfunction.
- Sabirnetug (ACU193) is a humanized IgG2 monoclonal antibody selective for AβOs.
- Sabirnetug's proposed mechanism of action is to block AβO impairment of neuronal synapses.
- Sabirnetug pharmacodynamics were assessed in the INTERCEPT-AD phase 1 study of mild cognitive impairment (MCI) and mild dementia due to AD (NCT04931459).[1]
- *Objective: Analysis of pharmacodynamic changes in cerebrospinal fluid (CSF) synaptic biomarkers in study participants with early symptomatic AD, following sabirnetug treatment.*

Figure 1. Sabirnetug is highly selective for soluble, synaptotoxic amyloid β oligomers (AβOs). Amyloid beta (Aβ) peptides, including 1-42 and 1-40, are generated from the amyloid precursor protein (APP) localized to neuronal membranes, through enzymatic cleavages. Due to their amphiphilic nature, Aβ monomers readily aggregate to oligomers (and protofibrils) and larger insoluble amyloid fibrils, the primary component of amyloid plaques. Soluble AβOs reach neuronal synapses via diffusion and AβO accumulation may depend on synaptic activity and receptor binding. The synaptic toxicity of AβOs is elicited through several mechanisms that disrupt normal synaptic function, including tau hyperphosphorylation, calcium dysregulation, and inhibition of long-term potentiation, ultimately contributing to the early stages of neurodegeneration and cognitive impairment associated with AD.[2]

Methods

INTERCEPT-AD Trial Design

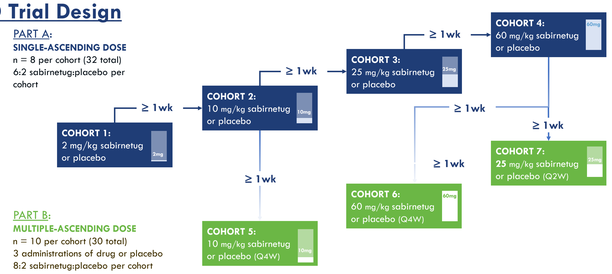
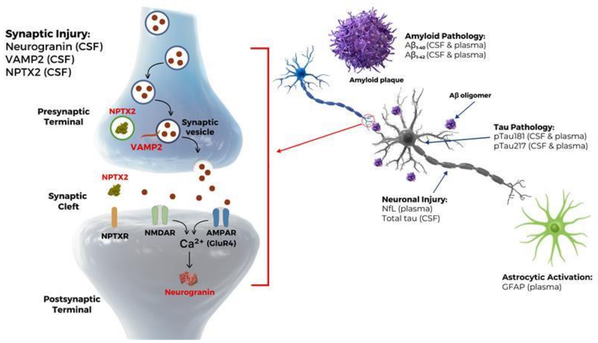


Figure 2. INTERCEPT-AD was a phase 1 clinical trial testing the safety, pharmacokinetics, and pharmacodynamics of sabirnetug in MCI and mild dementia due to AD (NCT04931459). The study was conducted in two parts: (A) single-ascending dose (SAD, top, blue) & (B) multiple-ascending dose (MAD, bottom, green). The dosing regimen and sample sizes for each of the 7 cohorts are shown in the schematic. CSF was drawn from each study participant at two timepoints: (1) before the first dose, and (2) 21 days after the dose for SAD cohorts, 14 days after the last dose for MAD cohort 5, and 7 days after the last dose for MAD cohorts 6 & 7. *Q2W = every 2 weeks; Q4W = every 4 weeks.*

Key Biomarkers Measured in INTERCEPT-AD Included Indicators of Synaptic Injury



- **Neurogranin:** a post-synaptic, Ca^{2+}/calmodulin dependent protein located in dendritic spines that is involved in long-term potentiation & depression. CSF neurogranin levels are **increased in AD.**[3-5]
- **VAMP2:** a component of synaptic vesicles, functioning in pre-synaptic neurotransmitter release and the post-synaptic vesicle trafficking of glutamate receptor subunits. CSF VAMP2 levels are **increased in AD.**[3,6,7]
- **Neuronal pentraxin 2 (NPTX2):** a pre-synaptic protein that acts on post-synaptic excitatory synapses. The role of NPTX2 in disease progression is under investigation.[8-15]

Figure 3. In INTERCEPT-AD, multiple ATX(N) biomarkers (A = Aβ pathway, T = tau-mediated pathophysiology, X = additional pathophysiological mechanisms such as synaptic dysfunction, N = neurodegeneration[2]) were measured in CSF and EDTA-plasma. These biomarkers are indicated in the graphic above. **Biomarkers for which data are presented in this poster are highlighted in red (left inset):** A synapse is enlarged to show the neuronal localization of the three synaptic biomarkers measured in CSF: neurogranin (P75 truncated form measured), vesicle associated membrane protein 2 (VAMP2), and neuronal pentraxin 2 (NPTX2). Figure adapted from Das et al. Alzheimers Res Ther, 2023.[9] Neurogranin was measured via ELISA (EUROIMMUN), VAMP2 via ELISA (ADx prototype), and NPTX2 via ELISA (Fujirebio). All assays were run at Amsterdam UMC. Results for $Aβ_{1-42}/Aβ_{1-40}$ & the tau proteoforms in CSF were presented at the 2024 AD/PD™ meeting in Lisbon, Portugal. Results for the sabirnetug-associated changes in ATX(N) biomarker levels in plasma were presented at the AAIC 2024 meeting. Statistical methods are described in the caption of each figure.

Results

Sabirnetug-Associated Changes in CSF Synaptic Biomarkers Neurogranin & VAMP2 Indicate Downstream Pharmacology After 3 Doses

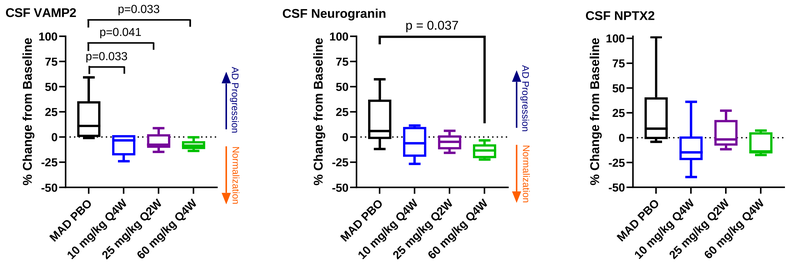


Figure 4. Synaptic biomarkers measured in CSF in the multiple ascending dose (MAD) cohorts. Box and whisker plots show median (line), interquartile range (boxes), and minimum/maximum (whiskers). Nominally significant p-values from unpaired, two-tailed Student's t-test without correction for multiple comparisons (α = 0.05) are listed above the plots. n = 8 subjects/treated group; 6 subjects in pooled placebo (PBO).

- **Sabirnetug administration was associated with lower CSF levels of the synaptic injury markers VAMP2 & neurogranin compared to baseline in MAD cohorts.**
- **In placebo-treated groups, levels of VAMP2 & neurogranin increased from baseline over the time of the study.**
- **No significant effect of sabirnetug on NPTX2 levels was observed.**
- **No sabirnetug-dependent trends were observed for any biomarker in the single-ascending dose (SAD) cohorts (not shown).**

Decreases in CSF VAMP2 and Neurogranin Correlate with Time of Drug Exposure

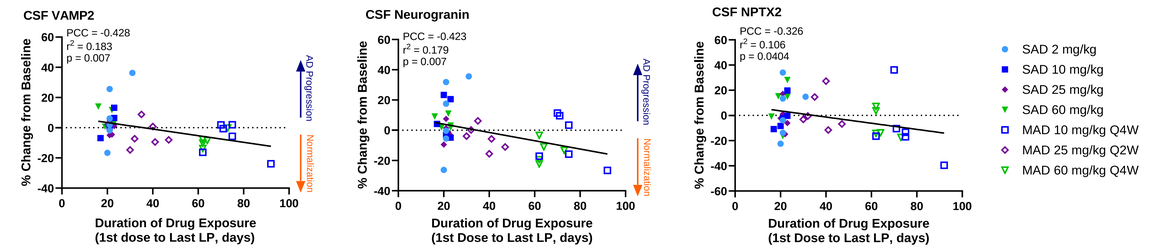


Figure 5. The decrease of VAMP2 and neurogranin following sabirnetug treatment significantly correlates with increased duration of drug exposure. (p = 0.007 for both analytes, R^2 = 0.183 and 0.179, PCC = -0.428, -0.423 for VAMP2 and neurogranin, respectively). The linear regression analysis plots show correlations between percent change from baseline of each biomarker concentration in CSF and the sabirnetug treatment duration, defined here as duration from first dose to last CSF collection by lumbar puncture (LP). Correlation plots present data points from individual subjects with lines from linear regressions. Pearson's correlation coefficient (PCC), r^2, and p-values for linear trends were calculated for all treated cohorts together.

Changes in CSF Synaptic Biomarker Concentrations Do Not Correlate with Amyloid Plaque Reduction

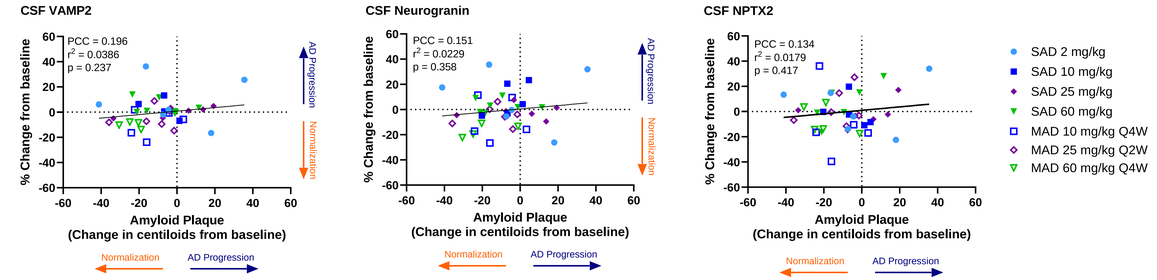


Figure 6. The changes in the CSF synaptic biomarker levels do not correlate with plaque reduction. No statistically significant correlation with plaque change is observed for any synaptic marker. Correlation plots present data points from individual subjects with lines from linear regressions. Pearson's correlation coefficient (PCC), r^2, and p-values for linear trends were calculated for all treated cohorts together. The changes in amyloid plaque load were determined by Positron Emission Tomography (PET) with florbetapir. PET was performed at screening and at day 42 for participants in SAD cohorts and days 70, 63, 70 (14, 7, and 42 days after last dose) in the MAD cohorts 5, 6, and 7, respectively. PET signal indicating amyloid plaque levels in the global cortical area was quantified using standardized uptake value ratio (SUVr) values, converted to the Centiloid scale using the formula Centiloids = (SUVr*174.5415856813) - 183.210370061647.

RESEARCH HIGHLIGHTS

- In INTERCEPT-AD, lower levels of CSF synaptic injury biomarkers relative to baseline were observed after just three administrations of sabirnetug versus placebo.[16]
  - VAMP2 concentrations decreased from baseline in all three MAD cohorts versus placebo. Decreases in neurogranin were most notable at the highest administered dose.
  - These changes are consistent with sabirnetug nonclinical data demonstrating interruption of AβO synaptic binding[17] and may suggest rapid synaptic protection by sabirnetug.
- The decreases in CSF VAMP2 and neurogranin correlated with time of drug exposure but not with amyloid plaque reduction in this small sample.
- Long term changes in biomarker levels, amyloid deposition, and clinical efficacy of sabirnetug will be evaluated over 18 months in the ongoing ALTITUDE-AD phase 2 study (NCT06335173).

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