ACU193-sAβO Complex Measurement in CSF: Additional Analyses Using a Sensitive Assay of Target Engagement for the sAβO-Selective Antibody ACU193 in INTERCEPT-AD

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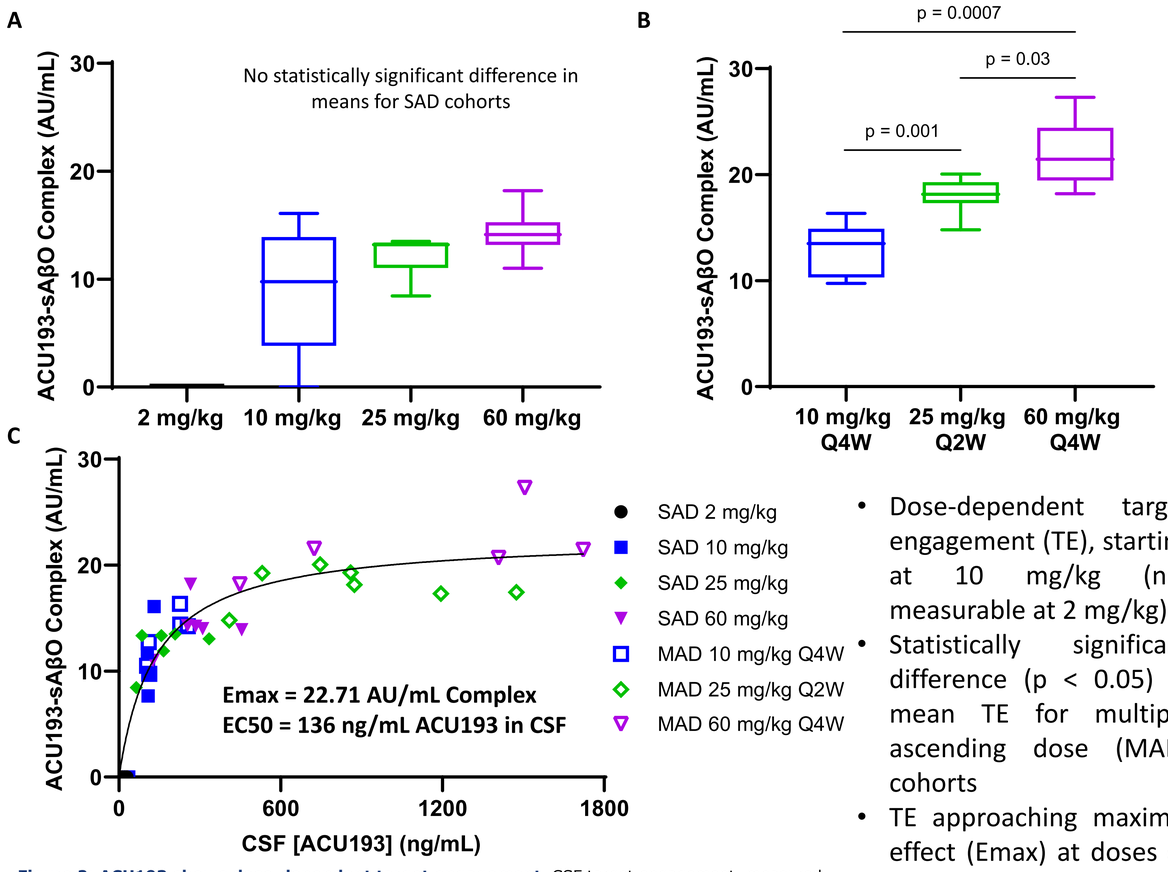
Background

ACU193 is a humanized monoclonal antibody selective for **soluble amyloid β oligomers (sAβOs)**, which accumulate early in Alzheimer's disease (AD) pathogenesis and trigger many aspects of AD neuropathology and cognitive decline. The ability of ACU193 to engage its intended sAβO target was recently tested in the INTERCEPT-AD phase 1 study in early AD.

Figure 1. ACU193 targets sAβOs, which have been shown *in vitro* to bind neuronal synapses and elicit synaptic damage, in addition to many other facets of AD pathology.[1]

Target Engagement of ACU193 was investigated in the Phase 1 study INTERCEPT-AD by measurement of ACU193-sAβO complexes in cerebrospinal fluid



- Dose-dependent target engagement (TE), starting at 10 mg/kg (not measurable at 2 mg/kg)
- Statistically significant difference ($p < 0.05$) in mean TE for multiple ascending dose (MAD) cohorts
- TE approaching maximal effect (Emax) at doses of 25 mg/kg Q2W & 60 mg/kg Q4W

Figure 2: ACU193 shows dose-dependent target engagement. CSF target engagement, measured as ACU193-sAβO complex levels, per single ascending dose (SAD; A) and multiple ascending dose (MAD; B) cohorts. Statistical significance in differences in means between cohorts tested by Student's t test. C) CSF exposure of ACU193 plotted vs. ACU193-AβO complex levels. An Emax model (E = Emax * C/(EC50 + C)) was fit to the data. One additional CSF sample tested since data presented at 2023 AAIC.[1]

Methods

Trial Design:
Dosing & Lumbar Puncture Schedule

INTERCEPT-AD was a Phase 1, randomized, placebo-controlled study with two parts:

1. SAD Cohort: randomized in 6:2 ratio to ACU193 (2, 10, 25, 60 mg/kg) or placebo
2. MAD Cohort: randomized in 8:2 ratio to ACU193 (10 or 60 mg/kg Q4W, 25 mg/kg Q2W) or placebo

Table 1: Endpoint LP Schedule

	Dose	LP (Days after Last Dose)*
Single Ascending Dose (SAD)	2 mg/kg	21 ± 3
	10 mg/kg	
	25 mg/kg	
	60 mg/kg	
Multiple Ascending Dose (MAD)	10 mg/kg Q4W	14 ± 3
	25 mg/kg Q2W	7 ± 3
	60 mg/kg Q4W	

**per protocol*

Two lumbar punctures (LPs) were performed per study participant:

1. Baseline (pre-dose)
2. Endpoint (post-last dose) – see Table 1 for endpoint LP schedule

Target Engagement Assay Format

MSD S-Plex (Turbo) Immunoassay

- The target engagement assay was built on the ultrasensitive MSD S-Plex (Turbo) immunoassay platform (right)
- Use of an ACU193-specific capture antibody and an sAβO selective detection antibody yielded an assay that was specific and selective for the ACU193-sAβO complex in human CSF

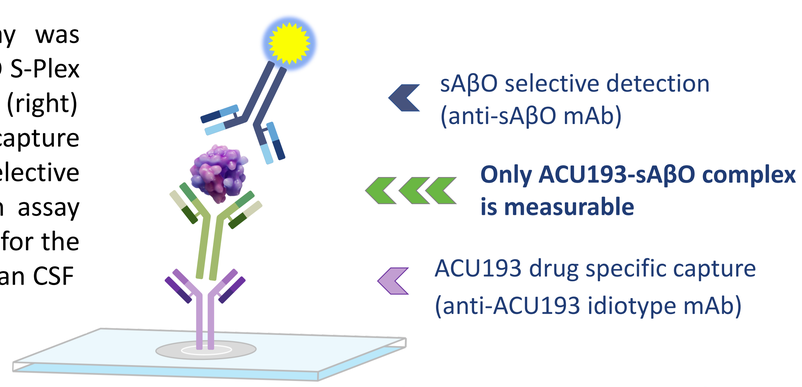


Figure 3: Target engagement assay format.

Results

ACU193-sAβO complex levels decrease in CSF with increasing time since last dose

- Despite variations in dosing per cohort, a study-wide analysis shows a downward trend in TE (measured by ACU193-sAβO complex levels) with increasing time between last dose and LP
- Plotted results visually suggest that sampling CSF within 11 days of last dose yields the highest TE measures in this specific study design

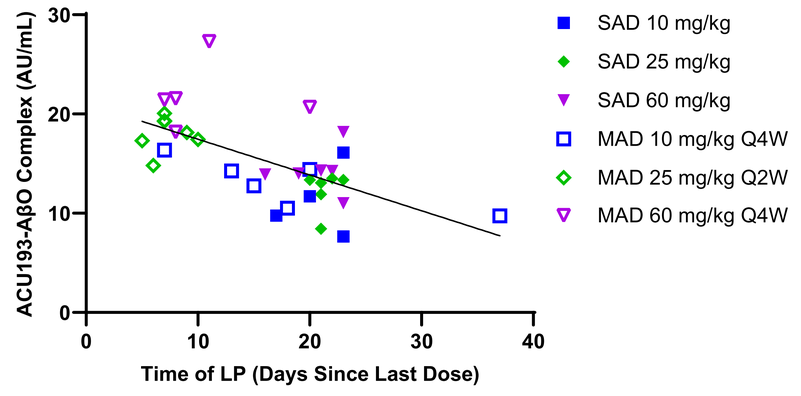


Figure 4: Relationship between ACU193-sAβO complex levels and time between last dose and lumbar puncture (LP). Time of LP since the last dose was plotted vs. ACU193-sAβO complex levels. Linear regression was applied to the data. Planned LP timing is shown in Table 1; actual LP timing is plotted and varied from 5-37 days post-dose.

Amyloid plaque reduction increases with increasing CSF ACU193-sAβO complex levels

Despite variations in dosing and time between last dose and PET imaging, a study-wide analysis shows a statistically significant negative correlation between TE & change in plaque burden, i.e., plaque reduction increases with increasing ACU193-sAβO levels in CSF

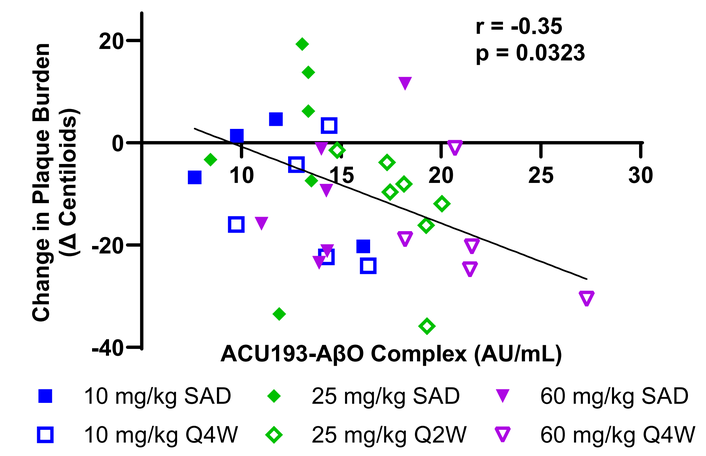
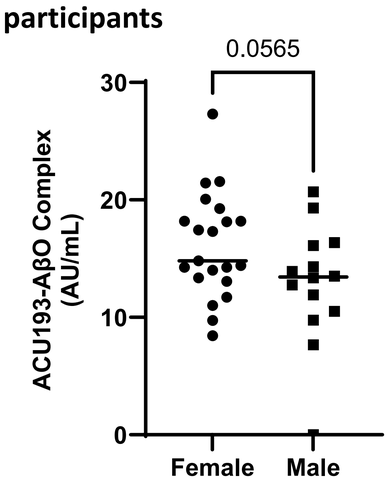


Figure 5: Relationship between ACU193-sAβO complex levels and change in plaque burden. Amyloid plaque burden measured via florbetapir positron emission tomography (PET) at baseline and 42 (SAD), 14 (10 mg/kg Q4W), 7 (60 mg/kg Q4W), or 42 days (25 mg/kg Q2W) after the last dose. The Pearson correlation coefficient (r) was obtained between target engagement results (ACU193-sAβO complex levels) and change from baseline in centiloid levels for global cortical area

Average CSF ACU193-sAβO complex levels are greater for female than male participants



- Mean ACU193-sAβO levels were numerically greater for female participants than male
- This difference was not statistically significant at $\alpha = 0.05$

No correlation with, or impact on, target engagement and the following measures:

- APOE4 genotype
- ARIA
- Baseline Centiloids for amyloid PET imaging (florbetapir)

Figure 6: Target engagement levels separated by gender. Levels plotted for all cohorts except for 2 mg/kg, where target engagement was below the assay's level of quantitation for all samples. Statistical significance for difference in means tested via t test.

References

1. Cline EN, Bicca MA, Viola KL, Klein WL. The Amyloid-beta Oligomer Hypothesis: Beginning of the Third Decade. J Alzheimers Dis. 2018;64(s1):S567-S61.
2. Siemers ER, Feaster HT, Skljarevski V, Sundell K, Sethuraman G et al. (2023, July 16-20). A Phase I Trial of Oligomer Targeting ACU193 in Early Alzheimer's Disease. Developing Topics platform presentation at Alzheimer's Association International Conference, Amsterdam, Netherlands.

Acknowledgements

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RESEARCH HIGHLIGHTS

- Measurement of ACU193-sAβO complex levels in CSF provided a practical approach for measuring central target engagement of the sAβO-selective antibody ACU193.
- Target engagement levels were measurable & dose-dependent ≥ 10 mg/kg ACU193 in CSF sampled 5-37 days after the last dose and levels decreased with time after last dose. Target engagement increased with increasing plaque reduction.