INTERCEPT-AD: ACU193 CSF pharmacokinetics in early Alzheimer's disease

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Background

ACU193 is a humanized, affinity matured, IgG2 subclass monoclonal antibody with high selectivity for soluble Amyloid beta oligomers (sAβOs). A multi-center, randomized, placebo-controlled, double-blind, single- and multiple-dose phase 1 study INTERCEPT-AD (NCT04931459) investigated the safety, tolerability, and pharmacokinetics (PK) of intravenous ACU193 in individuals with early AD (mild cognitive impairment or mild dementia due to AD). We report here the ACU193 PK in cerebrospinal fluid (CSF) and its correlation with dose and dose regimen and serum PK.

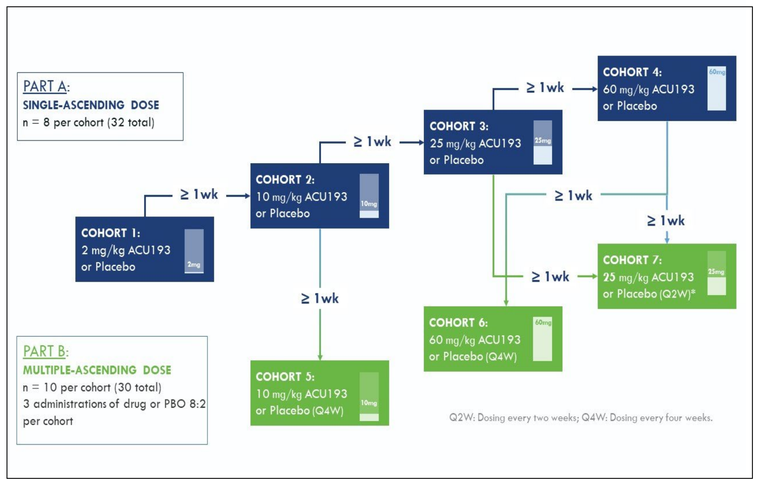

Figure 1. INTERCEPT-AD dosing regimens
INTERCEPT-AD is a two-part (Parts A and B) randomized, double-blind, placebo--controlled, single-ascending dose (SAD)/multiple-ascending dose (MAD) study in individuals with early AD. For Part A, 32 eligible participants were randomized in a 6:2 ratio (ACU193 [n=6] and placebo [n=2]) into one of four cohorts to receive a single dose of ACU193 or placebo. For Part B, 30 eligible participants were randomized in an 8:2 ratio (ACU193 [n=8] and placebo [n=2]) into one of three cohorts to receive a total of three doses of ACU193 or placebo. In order to maintain participant safety, a sequential dosing scheme was followed for each cohort. Dosing began at least one week after all participants in preceding cohort have received one administration of study drug and safety data have been reviewed by the internal blinded safety team.

Methods

Sixty-two participants with early AD were enrolled into one of seven cohorts: either single ascending dose (SAD; 2, 10, 25, or 60 mg/kg) or multiple ascending dose (MAD; 10 or 60 mg/kg every four weeks [Q4W] or 25 mg/kg every two weeks [Q2W] for a total of three infusions). CSF samples were collected at baseline and 5 to 37 days post the last dose. CSF ACU193 concentrations were measured by the Meso Scale Diagnostics (MSD) laboratory using an S-PLEX immunoassay that measures both bound and unbound (free) ACU193 (i.e., total drug). Serum ACU193 concentrations were determined by an electrochemiluminescence (ECL) immunoassay that measures only the unbound form of ACU193 (i.e., free drug) with Aβ-derived diffusible ligands (ADDLs; i.e., synthetic sAβOs) as capture. CSF ACU193 concentrations were correlated with serum ACU193 concentrations for matched visits for each participant. Correlation of ACU193 CSF PK with dose and dose regimen and CSF sampling time was also assessed.

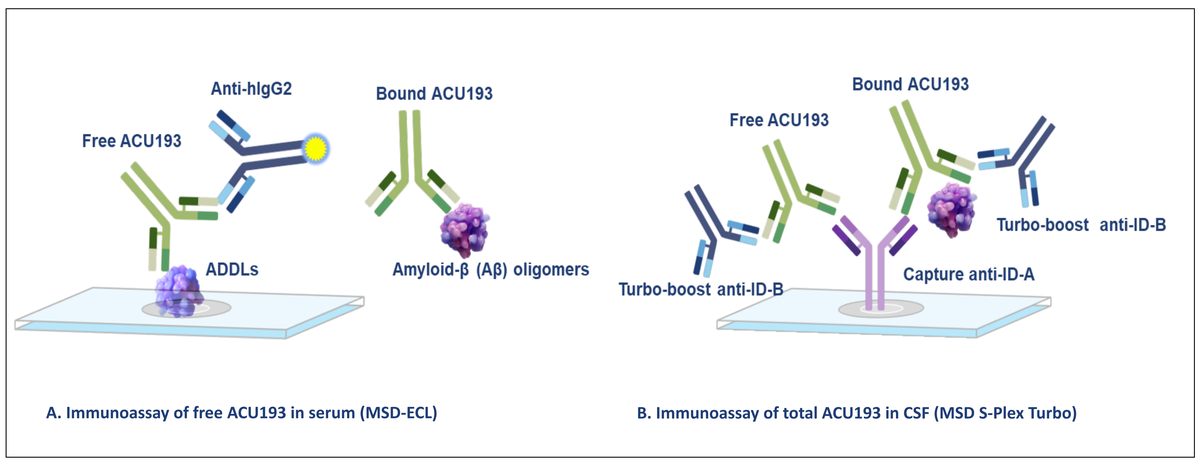

Figure 2. Immunoassays of free ACU193 in serum and total ACU193 in CSF
(A). To measure ACU193 IgG2 in human serum, a sandwich immunoassay is performed using a pre-coated and stabilized Standard Bind MSD MULTIARRAY® 96-well plate with the synthetic sAβO preparation ADDLs (Amyloid-beta Derived Diffusible Ligands)[1] and a SULFO-TAG labeled mouse anti-human IgG2 MAb antibody for detection. The pre-coated plate was incubated with calibrators, QC and serum samples under a 1/200 MRD in assay buffer. After incubation with detection antibody, MSD GOLD Read Buffer is added, and the plate is read on the MSD QuickPlex SQ 120 Plate Reader. Only immunoreactive form of ACU193 (free) is measured with this assay format. The amyloid-β (Aβ) oligomers bound form of ACU193 can't bind to ADDLs pre-coated on the plate due to the occupation of oligomer binding sites on the drug.[2]
(B). Total ACU193 levels in CSF are measured using ultrasensitive MSD S-PLEX assay kits employing a sandwich immunoassay format using monoclonal antibodies and ECL detection in MSD's Contract Services. The biotinylated anti-ID antibody (anti-ID A) is coated on the MSD GOLD™ S-PLEX SECTOR Plate and incubated with diluted calibrators, QCs and CSF samples. After washing, the plate is added with the detection antibody Turbo-boost anti-ID B. Turbo tag is added to the washed plate to enhance electrogenerated chemiluminescence. The resulting plated is read on MSD plate reader by addition of read buffer. Both free ACU193 and bound ACU193 are detectable with this format, indicating that total drug is measured in CSF. The lower limit of quantification (LLOQ) of 6 pg/mL is achieved through the S-Plex Turbo method.

Results

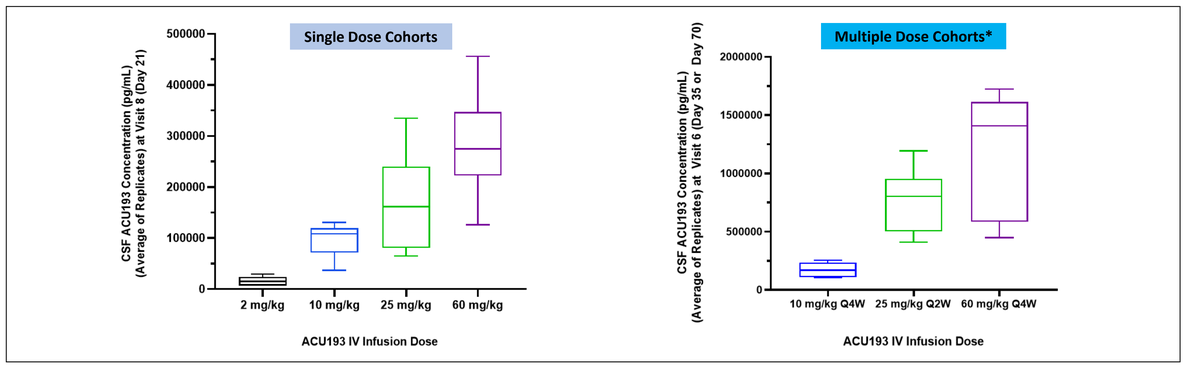

Figure 3. Dose and dose-regimen proportional CSF exposure.
CSF samples were collected through lumbar puncture (LP) procedures at pre-treatment (baseline) and 21±3 days post-treatment in SAD cohorts. CSF samples were collected at baseline and 14±3 days since last dose for cohort 5, 7±3 days since last dose for cohorts 6 and 7 in MAD cohorts. CSF total drug level was determined using the verified MSD S-Plex Turbo assay with all available CSF samples from pre-treatment and post-treatment. Each sample was analyzed in duplicate on the plate and the average concentration was reported. There were no detectable (below LLOQ) concentrations in all pre-treatment and placebo samples. In SAD cohorts, the mean CSF ACU193 concentration was 15,728 pg/mL, 97,981 pg/mL, 169,514 pg/mL and 282,662 pg/mL for cohort 1, cohort 2, cohort 3 and cohort 4, respectively. In MAD cohorts, the mean CSF ACU193 concentration was 148,867 pg/mL, 1,161,628 pg/mL, and 869,821 pg/mL for cohort 5, cohort 6, and cohort 7, respectively. The mean concentration data shows the dose and dose-regimen proportional CSF exposure for single dose and multiple dose ACU193 administration. *One patient from Cohort 5 (10 mg/kg Q4W) excluded because only received one administration of drug (discontinued after lacunar infarct).

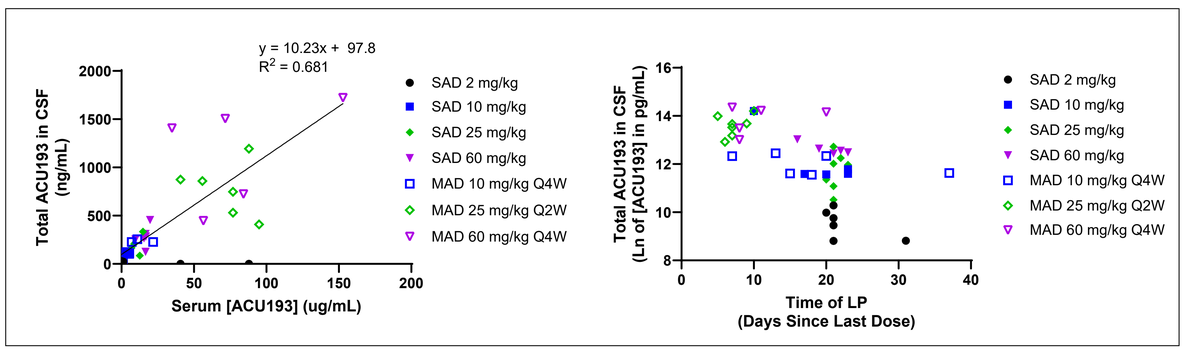

Figure 4. Correlation between CSF total ACU193 concentration and serum free ACU193 concentration for single dose and multiple dose ACU193 administration.
Scatter Plot of CSF total ACU193 Concentration (in pg/mL) versus Serum ACU193 Concentration (in ng/mL) for Cohorts 1-7 Placebo and ACU193 Subjects including all doses and all regimens. The relationship of CSF PK responses to serum exposure based on either a determined or estimated drug level temporally proximal to the timing of the LP was determined. In SAD cohorts, mean CSF to serum ACU193 percent ratios were 1.71, 3.25, 2.40 and 1.83% for cohort 1, cohort 2, cohort 3, and cohort 4, respectively. In MAD cohorts, mean CSF to serum ACU193 percent ratios were 2.20, 1.79 and 1.65% for cohort 5, cohort 6, and cohort 7, respectively.
We thank B2S Life Sciences for production and qualification of the ADDL coated plates and MSD's Contract Services for development and sample testing of the S-Plex assay.

Figure 5. Individual subjects plot of CSF total ACU193 concentration (LN) versus days since last dose profiles for all cohorts.
Individual total CSF ACU193 concentrations of post-treatment (Ln) and days since last dose (16-31 days for SAD cohorts and 5-37 days for MAD cohorts) were plotted. A trend of drug elimination was observed over the days since the last dose for all cohorts. Given the limit of sample size and time points of sampling, the elimination phase of the drug in CSF could not be well characterized.

Conclusions

Measurable exposures of ACU193 were detected in CSF and increased in a dose-related manner following single and multiple dose administration. There was a modest correlation between 'total' CSF ACU193 concentrations and 'free' serum ACU193 concentrations for both SAD and MAD regimens. A negative correlation was shown between CSF ACU193 concentration and CSF sampling time post last dose.

References
1. Chromy, B.A., Nowak, R.J., Lambert, M.P., et al. Self-assembly of Abeta(1-42) into globular neurotoxins. Biochemistry 42 (44), 12749-12760 (2003).
2. Hampel, H., Hardy, J., Blennow, K. et al. The Amyloid-β Pathway in Alzheimer's Disease. Mol Psychiatry 26, 5481–5503 (2021).

RESEARCH HIGHLIGHTS

- An ultra-sensitive CSF-PK assay was developed and verified to analyze ACU193 drug concentrations in the central nervous system of participants in the INTERCEPT-AD trial.
- ACU193 CSF PK is characterized by dose-proportional exposure in both SAD and MAD cohorts.
- A decrease in CSF ACU193 concentration over time since last dose demonstrated the clearance of ACU193 from the central nervous system.

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