Sabirnetug biomarker treatment responses: exploratory evaluation of the CNS Disease Panel NULISAseq™

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Introduction

Pharmacodynamic biomarker changes are critical for understanding a drug's mechanism of action and the timing of therapeutic effects in Alzheimer's disease (AD) and other neurological conditions.

We applied the NULISAseq™ (NULISA) High-Sensitivity Immuno-PCR Platform to assess its utility in clinical trials and to further characterize neuronal protein changes associated with sabirnetug (ACU193) treatment.

Using the CNS Disease Panel (v1)—which includes analytes reflecting amyloid and tau pathology, synaptic function, neuroinflammation, and neurodegeneration—we conducted an initial evaluation to:

- Assess the analytical and clinical performance of the NULISA platform
- Examine correlations and directionality among key amyloid/tau/neurodegeneration [AT/N)] biomarkers
- Confirm concordance with ELISA and Lumipulse© assays
- Extend insights into sabirnetug pharmacodynamics using samples from INTERCEPT-AD, a phase 1, randomized, double-blind, placebo-controlled study of sabirnetug (ACU193) in early symptomatic AD

Figure 1. Biomarkers Reflect AD Pathology

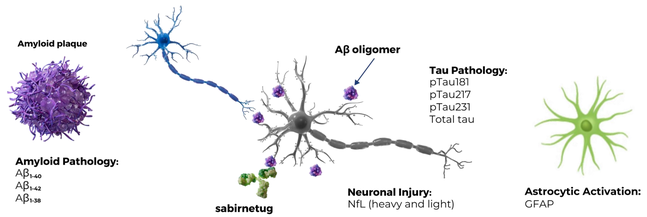
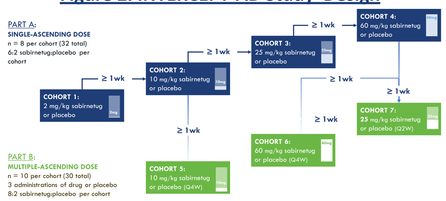


Figure 1. Biofluid biomarkers provide biologic diagnosis and pharmacodynamic readouts of Alzheimer's disease pathology. CSF and blood biomarkers reflect key AD pathophysiology (amyloid, tau, neurodegeneration/glial responses) and can be used for biologic diagnosis and to monitor treatment-associated changes in clinical studies. Marker examples shown align with AT(N) biology and include amyloid-β (Aβ) species/ratios, phosphorylated tau proteoforms, neurofilament (NfL), and glial fibrillary acidic protein (GFAP).

Methods

Figure 2. INTERCEPT-AD Study Design. 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).[1,2] The study was conducted in two parts: (A) single-ascending dose (SAD, top, blue) and (B) multiple-ascending dose (MAD, bottom, green). The dosing regimen and sample sizes for each of the 7 cohorts are shown in the schematic. Biobanked CSF (3 F/T) and plasma (1 F/T) samples were obtained 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 and 7. Q2W = every 2 weeks; Q4W = every 4 weeks. Data from 22 SAD participants and 21 MAD participants was used. F/T = freeze thaw cycle.

Figure 2. INTERCEPT-AD Study Design



Novel application: CNS-focused proteomic profiling for pharmacodynamic assessment

Figure 3. NULISA technology. NULISA utilizes sequential immunocomplex capture-and-release mechanism with next-generation sequencing (NGS) as the readout method.[3,4] The capture and detection antibodies are conjugated to DNA fragments containing antibody-specific barcodes and a polyA-containing oligonucleotide and a biotin-modified oligonucleotide, respectively. The immunocomplex of the target protein with both antibodies is captured by oligo-dT beads and recaptured with streptavidin-coated beads followed by addition of ligation reaction mix containing DNA ligase and a DNA ligator sequence containing a unique sample barcode. The ligation of the DNA fragments attached to the paired antibodies generates DNA reporter molecules containing a unique pair of barcodes, which are then quantified by NGS. Figure from NULISA.[4]

Figure 3. NULISA Technology

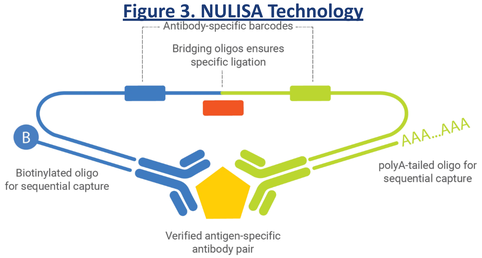


Figure 4. ARGO HT system workflow. The ARGO HT System is a NULISA-compatible fully automated, high-throughput precision proteomics platform.[4] ARGO HT integrates qPCR for pulled NGS library creation, sequencing platform, and NULISA analysis software. NULISA technology and ARGO HT System were utilized for biomarker detection and quantification in INTERCEPT-AD pre- and post-dose EDTA-plasma and CSF samples (n = 86 each). The CNS Disease Panel (v1) measuring 127 protein analytes was used. Figure adapted from NULISA.[4]

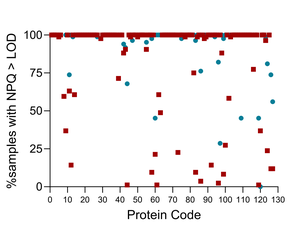
Figure 4. Sample Processing and Analysis Using ARGO HT Platform

Acumen bioanalytical databank.
The results were reported to Acumen as normalized NULISA Protein Quantification (NPQ) units. Acumen generated a bioanalytical databank to assess sabirnetug treatment effects. The percent change in NPQ values was determined for each participant in the SAD and MAD treatment and placebo groups and used for statistical analyses. Statistical methods are described in the caption of each figure. Samples with NPQ lower than the limit of detection (LOD) were excluded.

References: 1. Siemers et al. *J Prev Alzheimers Dis,* 2025;12(1):100005. 2. Cline, et al. *J Prev Alzheimers Dis*, 2025;1(4):100082. 3. Feng et al. *Nat Commun*, 2023;14(1):7238.
4. NULISA™ Platform, https://alamarbio.com/technology/nulisa-platform/

Results

Figure 5. Multiplexed Analyte Detectability in CSF and Plasma



B

% Samples with NPQ > LOD		
Biomarker	**Plasma (%)**	**CSF (%)**
Aβ42	100	98.8
BDNF	100	14
pSNCA-129	100	14
pTau-217	98.8	100
pTDP43-409	81.4	2.3
SNCB	45.3	100
UCHL1	0	36

Figure 5. Analyte detectability in human CSF and EDTA-plasma samples. A: Percentage of the 84 INTERCEPT-AD samples with detectable levels (NPQ > LOD) for the 127 proteins in the NULISA CNS Disease Panel v1. Samples are representative of all dose groups. The variability was verified using internal plate controls (2 plates, 3 samples per plate). Median %CV (p5, p95) was 0.72% (0.29, 1.9). B: Examples for gene IDs with differential detectability in CSF and plasma. *Aβ = β-amyloid, BDNF = Brain-Derived Neurotrophic Factor, NPQ = NULISA protein quantification, pSNCA-129 = Phosphorylated Alpha-Synuclein at Serine 129, pTau-217 = Phosphorylated Tau at Threonine 217, pTDP43-409 = Phosphorylated TAR DNA-Binding Protein 43 at Serine 409, SNCB = Beta-Synuclein, UCHL1 = Ubiquitin C-Terminal Hydrolase L1*

Figure 6. Multiple AT(N) Biomarkers are Highly Correlated in Early AD

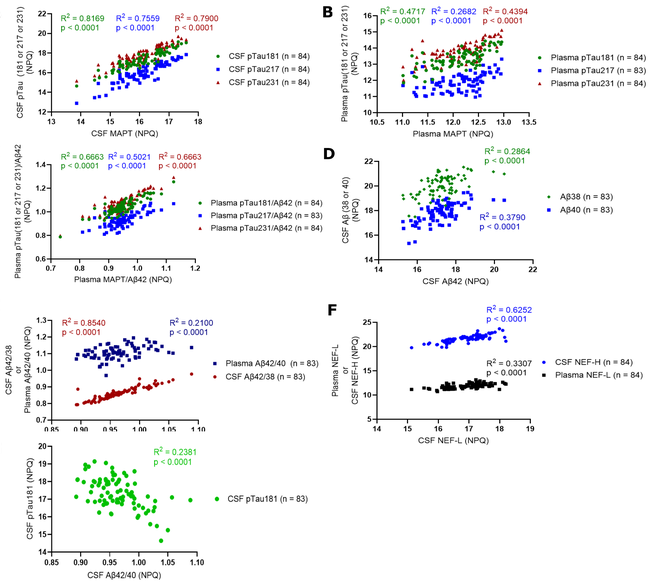


Figure 6. AT(N) biomarker correlations in CSF and plasma in early AD. Spearman correlations were conducted to determine the relationships between CSF and EDTA-plasma biomarkers and their ratios using NPQ values from the NULISA platform. Correlations between the different phospho-tau PTM variants/MAPT ratios are stronger in CSF (R^2: 0.7559-0.8169) (A) than in EDTA-plasma (R^2: 0.2682-0.4717) (B). In EDTA-plasma, ratios between phospho-tau variants/Aβ42 and MAPT/Aβ42 were moderately correlated (R^2: 0.5021-0.6663) (C). Weak to moderate correlations were seen between CSF Aβ42 and Aβ40 (R^2 = 0.3790) and Aβ42 and Aβ38 (R^2 = 0.2864) (D). A strong correlation was seen between CSF Aβ42/Aβ40 and CSF Aβ42/Aβ38 (R^2 = 0.8540), but there was only a weak correlation between CSF and EDTA-plasma Aβ42/Aβ40 (R^2 = 0.2100) (E). The correlation between neurofilament NEF-L and NEF-H was moderate in CSF (R^2 = 0.6252) but there was a weak correlation between CSF and EDTA-plasma NEF-L (R^2 = 0.3307) (F). A weak to moderate correlation was also seen between CSF Aβ42/Aβ40 and pTau181 (R^2 = 0.2381) (G). The total number of subjects analyzed is noted in parentheses for each analyte. *Aβ = β-amyloid; MAPT= total tau; NF; = neurofilament; NPQ = NULISA Protein Quantification; pTau = phosphorylated tau; PTM = post translationally modified.*

Figure 7. Demonstrated platform concordance between NULISA, ELISA, and Lumipulse

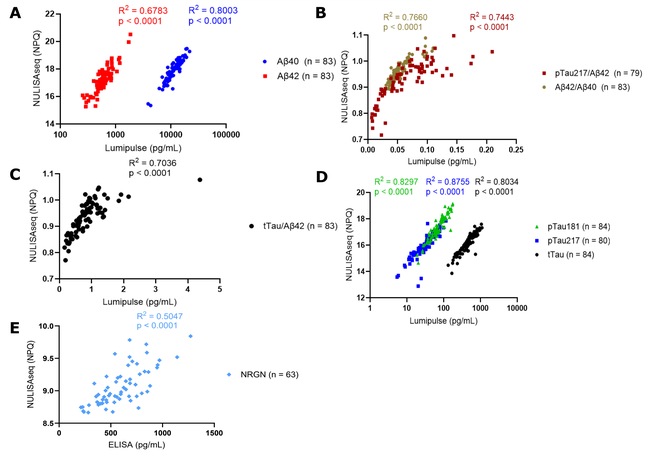


Figure 7. Correlations between NULISA, ELISA, and Lumipulse CSF biomarker data. Spearman correlations were conducted to determine the relationships between NULISA NPQ values and data previously reported in INTERCEPT-AD[2] with ELISA and Lumipulse. Aβ and tau variants and their ratios showed strong correlations across platforms ($R^2 \geq 0.6783$) (A-D). A moderate correlation was found for neurogranin (R^2 = 0.5047) (E). The number of participants analyzed is noted in parentheses for each analyte. *Aβ = β-amyloid; MAPT = total tau; NPQ = NULISA protein quantification; pTau = phosphorylated tau*

Figure 8. Acute sabirnetug treatment effects on AT(N) markers

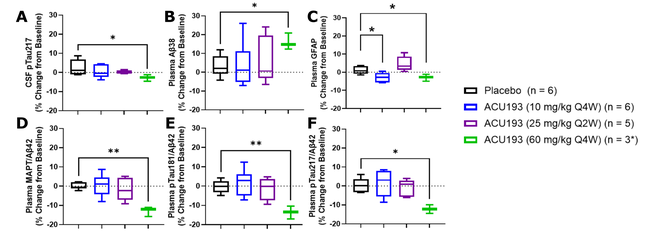


Figure 8. Statistical trends of treatment effects on CSF and plasma biomarkers. Welch's t-tests were conducted between MAD placebo cohorts and each MAD treatment group to explore potential treatment effects in CSF and EDTA-plasma biomarkers analyzed using NULISA. No adjustments were made for multiple comparisons; therefore, all statistical significance is considered nominal. Nominal treatment effects were seen for pTau217 in CSF (A). In plasma, nominal treatment effects were observed for Aβ38 (B) and GFAP (C), as well as ratios MAPT/Aβ42 (D), pTau181/Aβ42 (E), and pTau217/Aβ42 (F; n = 2 for the 60 mg/kg cohort). * = $p < 0.05$; ** = $p < 0.01$; **** = $p < 0.0001$
MAD = Multiple Ascending Dose. MAPT = total Tau. Q2W = Every 2 weeks. Q4W = Every 4 weeks.

RESEARCH HIGHLIGHTS

- By deploying NULISA for pharmacodynamic profiling we established a novel framework for detecting multiple low and high abundance CNS biomarkers that accurately track sabirnetug treatment effects in INTERCEPT-AD.
- The AT(N) biomarkers measured with NULISA in INTERCEPT-AD samples exhibit cross-platform concordance with ELISA and Lumipulse CSF data, highlighting the analytical alignment
- NULISA measurements show that multiple tau phosphorylation sites and/or Aβ proteoforms exhibit mutual biological relationships in early AD.
- A dedicated bioanalytical databank was created from this study, enabling follow-up exploratory analyses using larger sample sets derived from the ongoing phase 2 ALTITUDE-AD study.