Overview of product candidate ACU193 and the ongoing Phase-1 INTERCEPT-AD trial

November 2021
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Quaternary structures of Aβ Oligomers, protofibrils and fibrils

AβOs may consist of 2 to >200 Aβ peptides.


Relini et al. Misfolding of amyloidogenic proteins and their interactions with membranes Biomolecules 2014

Figure 3. Atomic force microscopy images of representative steps of amyloid aggregation: (A) oligomers; (B) protofibrils; (C) mature fibrils. Scan size 1.0 μm. Z range (A) 8.0 nm; (B) 15 nm; (C) 20 nm.
**ACU193 is the first mAb developed to selectively target AβOs**

Highly selective for Aβ oligomers versus Aβ monomers

ACU193 Selectivity

![Graph showing ACU193 selectivity](image)

Binding of ACU193 to AβOs >500x binding to Aβ monomer

ACU193 Selectivity in presence of 5μM monomeric Aβ

![Graph showing ACU193 selectivity in presence of 5μM monomeric Aβ](image)

Even in the presence of a large excess of Aβ monomer, binding of ACU193 to AβOs is unchanged

ACU193 selective binding to AβOs is preserved even in the presence of a large excess of Aβ monomer

Data On File
**ACU193 is highly selective for AβOs versus Aβ plaques**

ACU193 staining in human AD brain slices from hippocampus:

ACU193 (red) binds non-Thioflavin S positive Aβ (green)

ACU193 has limited to no binding to thioflavin S positive fibrillar Aβ plaque in human AD brain tissue

AβOs bind to neurons and are toxic; the murine IgG1 parent of ACU193 (ACU3B3) prevents toxicity

After binding to neurons, AβOs disrupt Long Term Potentiation (LTP) and cause pathologic increases in intracellular calcium that is destructive to cells.

ACU3B3 prevents AβO inhibition of hippocampal LTP ex vivo

Data on File and

ACU3B3 prevents AβO mediated Ca2+ elevation in cell cultures

ACU3B3 prevents aberrant neuronal activity caused by AβOs and prevents AβO mediated disruption of calcium homeostasis in neuronal cultures
Treatment of a transgenic mouse model of AD results in reduction of behavioral deficits


Murine parent of ACU193 (3B3) was used to treat younger mice with depositing plaque or older mice with abundant plaque

**Open Field**

- Deficits in younger (5-7 months) transgenic mice are markedly reduced with treatment

**Morris Water Maze**

- Deficits in older (9-10 months) transgenic mice are markedly reduced with treatment

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Open field total distance measurement, APP-Veh vs. APP-3B3, \(^*p=0.029\).

MWM swim speed abnormality (\(^{**}p<0.02\)).
Phase 1 overview

TRIAL DESIGN: Randomized Placebo Controlled Phase 1
- Part A: Single-Ascending Dose
- Part B: Multiple-Ascending Doses

ENROLLMENT CRITERIA: Early AD
- Mild Cognitive Impairment and Mild Dementia due to AD (amyloid positive by PET)

TRIAL OBJECTIVES: Proof of Mechanism (PoM)
- Safety and tolerability
- Pharmacokinetics
- Target Engagement
- Exploratory cognition and biomarkers
Randomized Placebo Controlled Phase 1 in Early AD patients: INTERCEPT-AD

PART A:
SINGLE-ASCENDING DOSE
n = 8 per cohort (32 total)

COHORT 1:
2 mg/kg ACU193 or Placebo

COHORT 2:
10 mg/kg ACU193 or Placebo

COHORT 3:
25 mg/kg ACU193 or Placebo

COHORT 4:
60 mg/kg ACU193 or Placebo

≥ 1wk

PART B:
MULTIPLE-ASCENDING DOSE
n = 10 per cohort (30 total)

COHORT 5:
10 mg/kg ACU193 or Placebo (Q4W)

COHORT 6:
60 mg/kg ACU193 or Placebo (Q4W)

COHORT 7:
60 mg/kg ACU193 or Placebo (Q2W)

≥ 1wk

≥ 4wk

NCT04931459
## Cogstate computerized test battery

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<td>Attention, working memory, learning</td>
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Arterial Spin Labelling (ASL) as an MRI outcome

MCI patients show hypoperfusion in parietal cortex, precuneus, posterior cingulate cortex and medial temporal lobe.

AD patients show global hypoperfusion, but especially cingulate, precuneus, parietal lobes and inferior frontal regions.

Perfusion correlates with several neuropsychological tests.

Hypoperfusion can be improved in middle and posterior cingulate cortex with cholinesterase inhibitors and was associated with improvement in ADAS-cog scores.

Fig. 1. Processed CBF images measured with ASL of a young and an old healthy control from our database. The top row images are from a 32 year-old woman, and the bottom row images are from an 80 year-old man. The reduction of CBF can be readily observed in widespread brain areas of the older subject compared with the younger subject.

Acumen believes additional literature supports use of ASL to assess hypoperfusion in AD:

- MCI patients show hypoperfusion in parietal cortex, precuneus, posterior cingulate cortex and medial temporal lobe.
- AD patients show global hypoperfusion, but especially cingulate, precuneus, parietal lobes and inferior frontal regions.
- Perfusion correlates with several neuropsychological tests.
- Hypoperfusion can be improved in middle and posterior cingulate cortex with cholinesterase inhibitors and was associated with improvement in ADAS-cog scores.

Lower cerebral perfusion is associated with tau-PET in the entorhinal cortex across the Alzheimer’s continuum

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*Neurobiology of Aging 102 (2021) 111–118

Fig. 2. Higher tau-PET is associated with lower CBF in the entorhinal cortex (Braak stage I).
Summary

- Non-clinical data consistent with toxicity of Aβ oligomers and selective binding of ACU193 to Aβ oligomers
- Enrollment in a Phase 1 study assessing safety and target engagement is ongoing
- Although unlikely with this small sample size, the possibility of improvement in cognition and cerebral blood flow will also be assessed as exploratory outcomes in the Phase 1 study
Thank you!

- Study participants and study partners
- ACU-001 sites
- Acumen collaborators