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

November 2021

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This presentation discusses Acumen's investigational drug ACU193 that is in an early Phase 1 First in Humans clinical study. ACU193 has not been approved for marketing by the U.S. Food and Drug Administration or any regulatory authority.

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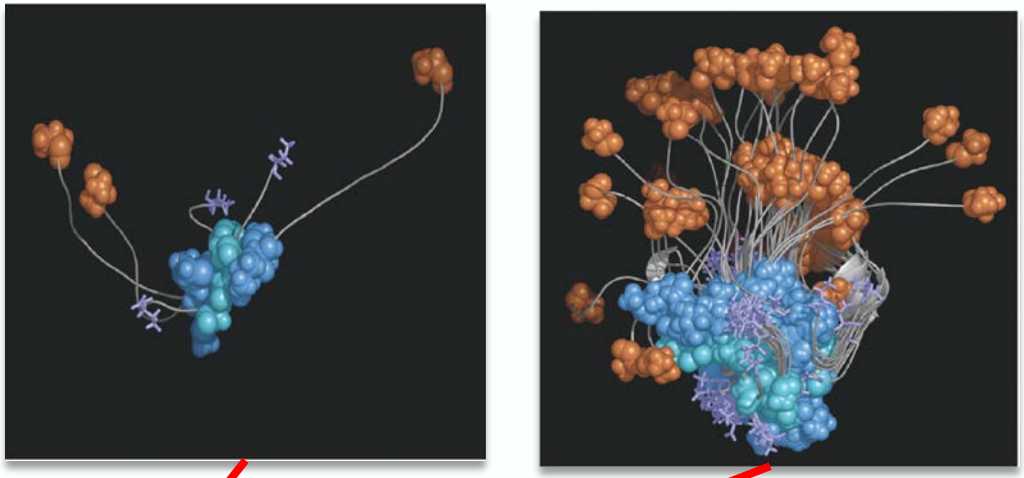
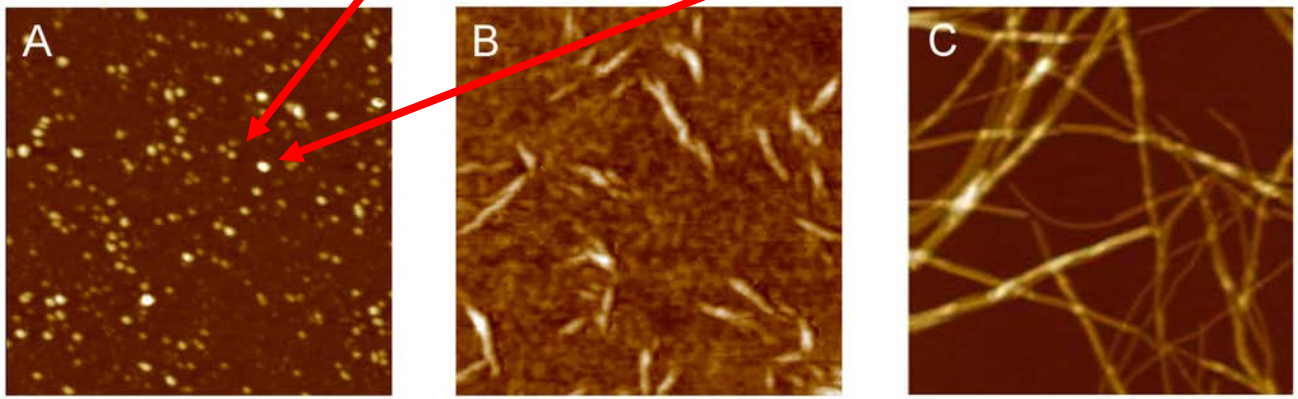
Quaternary structures of Aβ Oligomers, protofibrils and fibrils

AβOs may consist of 2 to >200 Aβ peptides.



Kelley et al. Simulating oligomerization at experimental concentrations and long timescales: A Markov state model approach. J Chem Physics 2008.



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.

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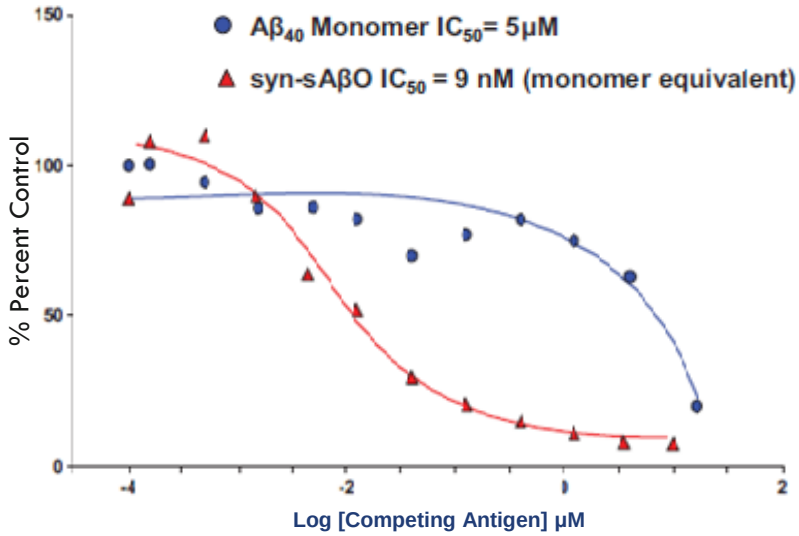
ACU193 is the first mAb developed to selectively target AβOs

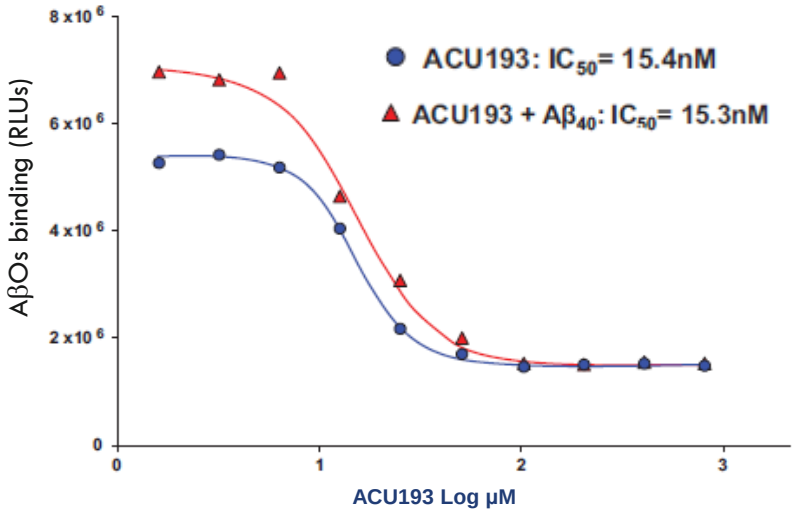
Highly selective for Aβ oligomers versus Aβ monomers

ACU193 Selectivity



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

ACU193 Selectivity in presence of 5μM monomeric Aβ



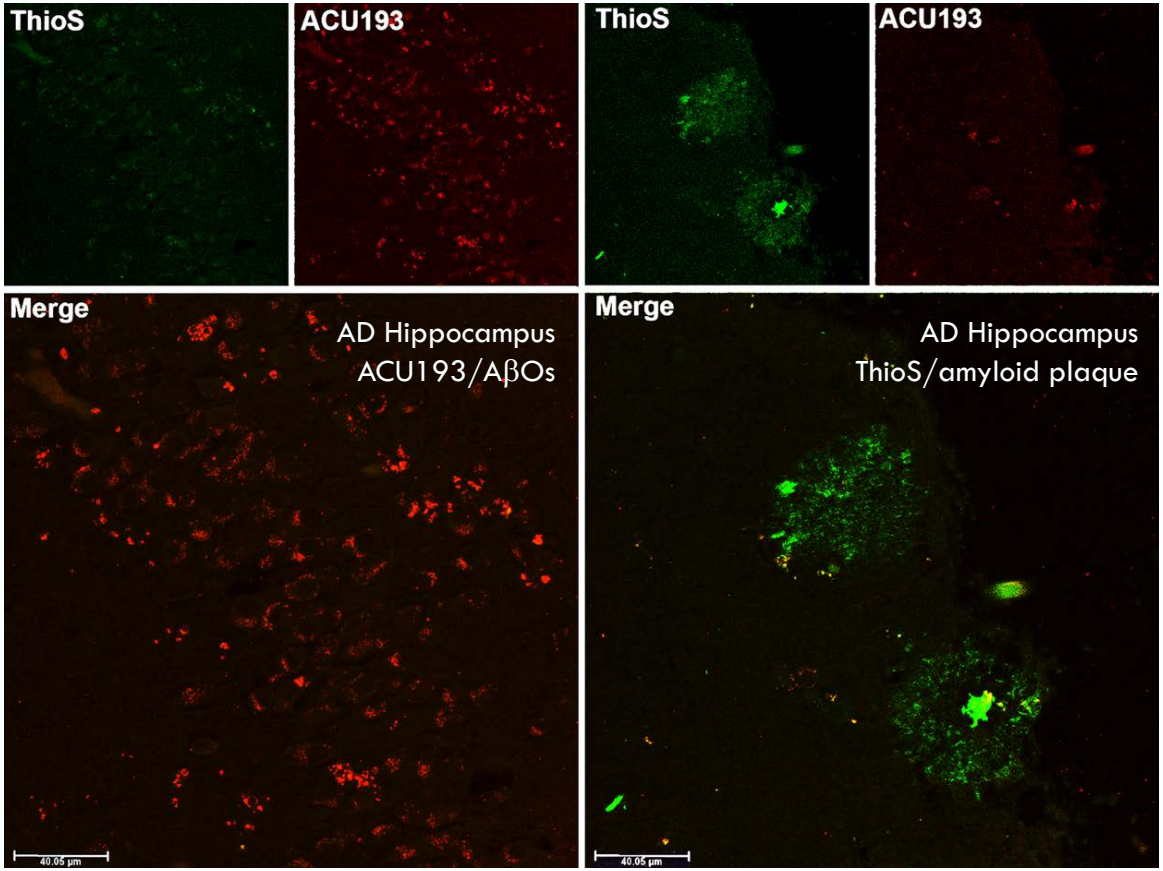
Even in the presence of a large excess of Aβ monomer, binding of ACU193 to AβOs is unchanged

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)



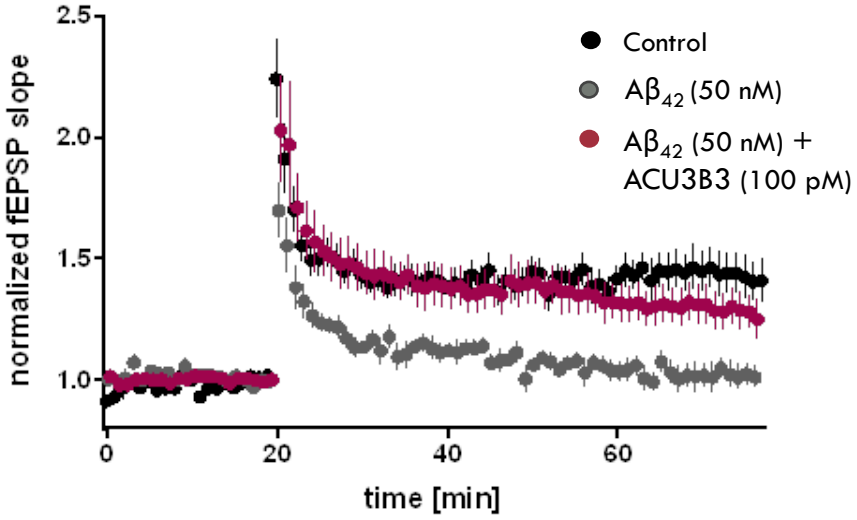
ACU193 has limited to no binding to thioflavin S positive fibrillar Aβ plaque in human AD brain tissue

Cline E. et al. Synaptic intervention in Alzheimer's disease: soluble Aβ oligomer directed ACU193 monoclonal antibody therapeutic for treatment of early Alzheimer's disease. J. Prevent. Alzheimer's Dis., 6 (Supplement 1) (2019), p. S151.

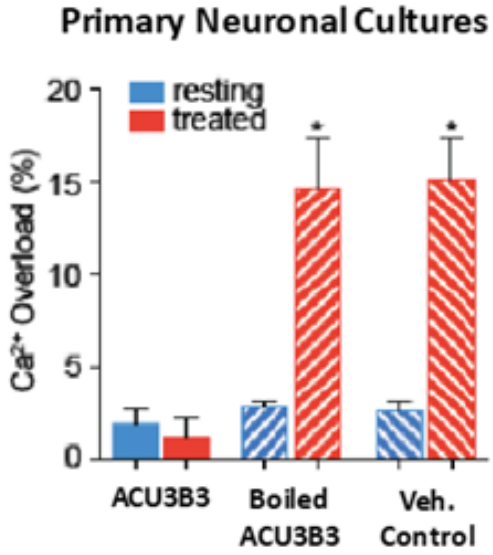
AβOs bind to neurons and are toxic; the murine IgG1 parent of ACU193 (ACU3B3) prevents toxicity

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*



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

Data on File and

Wang X. et al. An acute functional screen identifies an effective antibody targeting amyloid-beta oligomers based on calcium imaging. Sci Rep. 2018;8(1):4634

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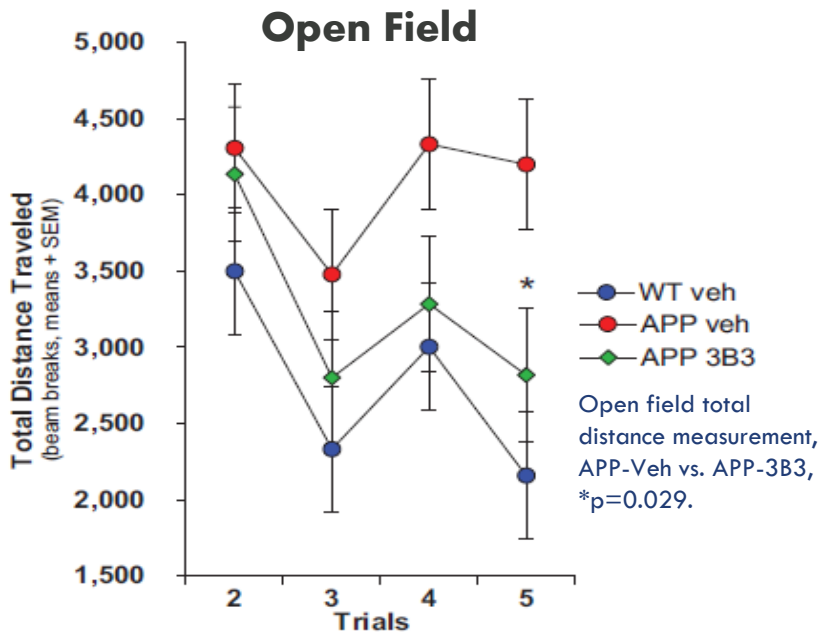
Treatment of a transgenic mouse model of AD results in reduction of behavioral deficits

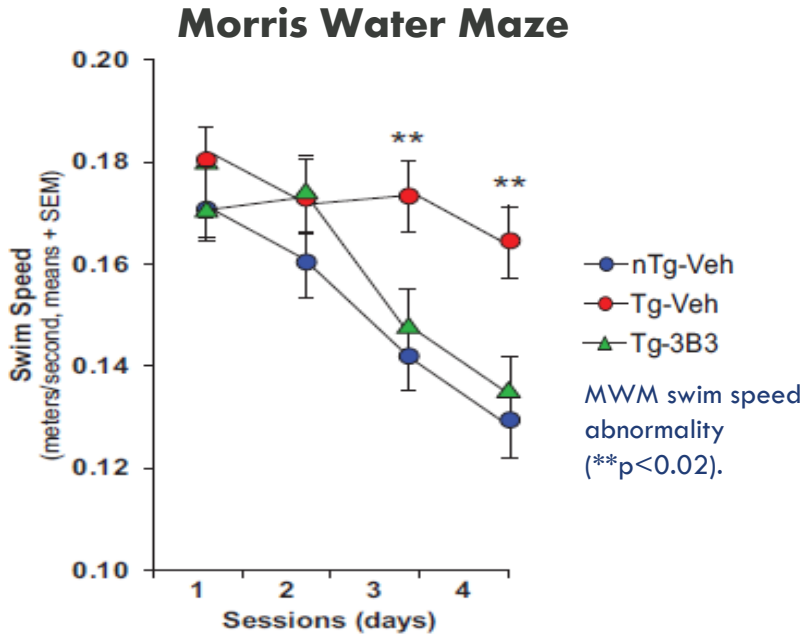
Dodart JC et al. Passive immunization with the anti-Aβ oligomer antibody ACU-3B3 improves behavioral deficits in hAPPSL tg mice. SfN, Washington, DC 2014. Ma K. et al. Soluble Aβ-Oligomer–Selective Antibody ACU3B3 Reduces Amyloid Pathology & Improves Multiple Behavioral Domains in a Mouse Model of AD. Alz&Dement.15, (7S Part 11 P2-063).1Jul2019 and Data on File

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



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

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



MWM swim speed abnormality (**p<0.02).

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

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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
2mg

≥ 1wk

COHORT 2:
10 mg/kg ACU193
or Placebo
10mg

≥ 1wk

COHORT 3:
25 mg/kg ACU193
or Placebo
25mg

≥ 1wk

COHORT 4:
60 mg/kg ACU193
or Placebo
60mg

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

≥ 1wk

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

≥ 1wk

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

≥ 4wk

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

NCT04931459

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Cogstate

Cogstate computerized test battery

Test	Domains tested	Time (minutes)
International shopping list test (immediate)	Immediate recall	5
Cogstate brief battery	Attention, working memory, learning	15
International shopping list test (delayed)	Delayed recall	1
Groton maze learning test	Executive function	7
International digit-symbol substitution test	Processing speed	3
		Total = 31

Frequency of administration and sensitivity of battery offers improved possibility to observe effects

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Arterial Spin Labelling (ASL) as an MRI outcome

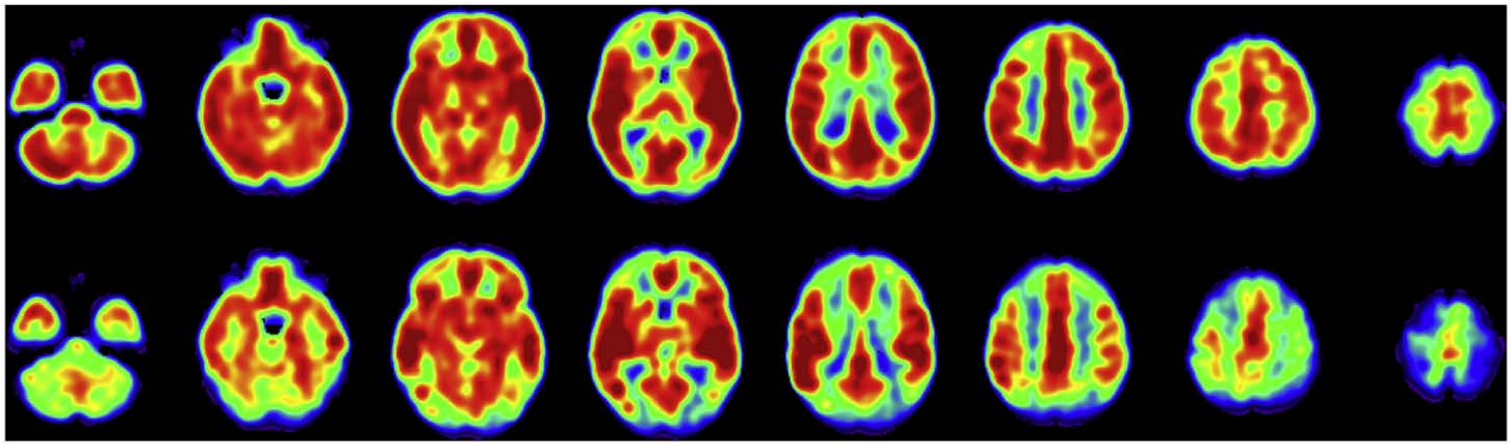

Fig. 1. Processed CBF images measured with ASL of a young and an old healthy control from our database. The top row images are from a 32 year-old woman, and the bottom row images are from an 80 year-old man. The reduction of CBF can be readily observed in widespread brain areas of the older subject compared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

* *N. Zhang et al. Cerebral blood flow measured by arterial spin labeling MRI at resting state in normal aging and Alzheimer's disease. Neuroscience and Behavioral Reviews 72 (2017) 168-175*

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

Anna Rubinski[a], Duygu Tosun[b], Nicolai Franzmeier[a], Julia Neitzel[a], Lukas Frontzkowski[a], Michael Weiner[b], Michael Ewers[a,c,*]

Neurobiology of Aging 102 (2021) 111–118

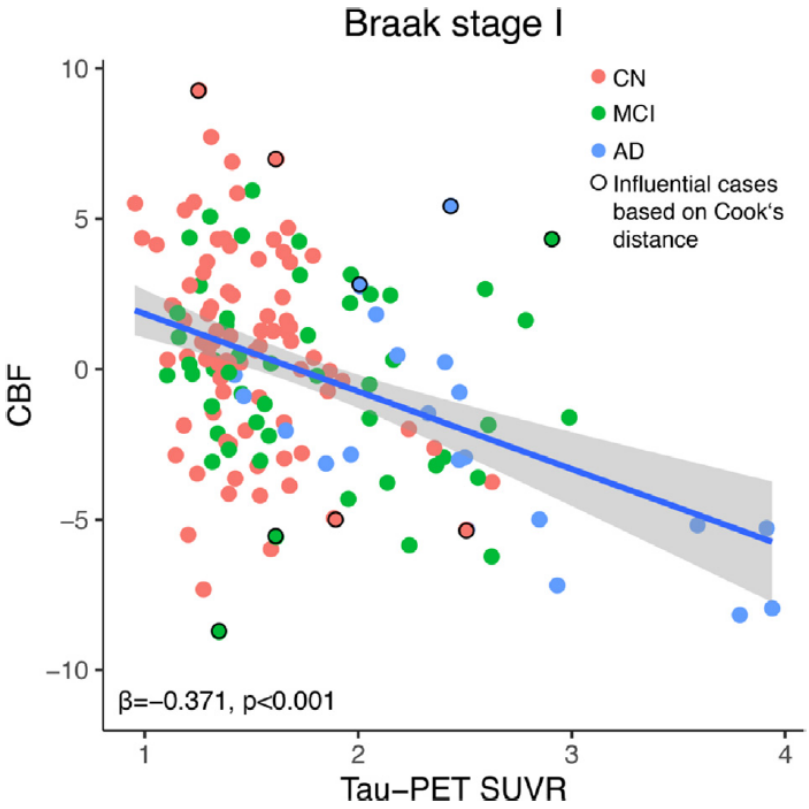

Fig. 2. Higher tau-PET is associated with lower CBF in the entorhinal cortex (Braak stage I).

Summary

- Non-clinical data consistent with toxicity of Aβ oligomers and selective binding of ACU193 to Aβ oligomers
- Enrollment in a Phase 1study 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