

Phase 1 trial design for ACU193, a monoclonal antibody that selectively binds soluble A β oligomers

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2. Acumen Pharmaceuticals, Inc. – Charlottesville (USA)
3. Cogstate Ltd. – Melbourne (Australia)
4. Ixico Plc – London (United Kingdom)

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Disclosures for Eric Siemers

Chief Medical Officer

Acumen Pharmaceuticals Inc.

Consulting Agreements (2019 or later)

Acelot Inc.

Aquestive Therapeutics Inc.

Athira Pharma, Inc.

Biogen Inc.

Cogstate Ltd.

Cortexyme Inc.

Gates Ventures LLC

Hoffman La-Roche Ltd.

Indiana University

LuMind Research Down Syndrome Foundation

Partner Therapeutics Inc.

Pinteon Therapeutics Inc.

Prothena Inc.

Vaccinex, Inc.

Washington University (St. Louis)

Not-for-profit activity (unpaid)

Alzheimer's Association

Bright Focus Foundation

Huntington Study Group

Michael J. Fox Foundation

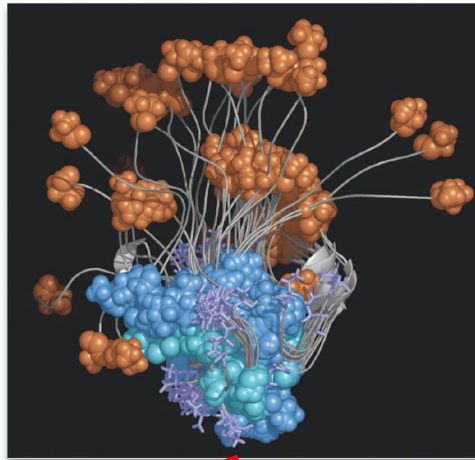
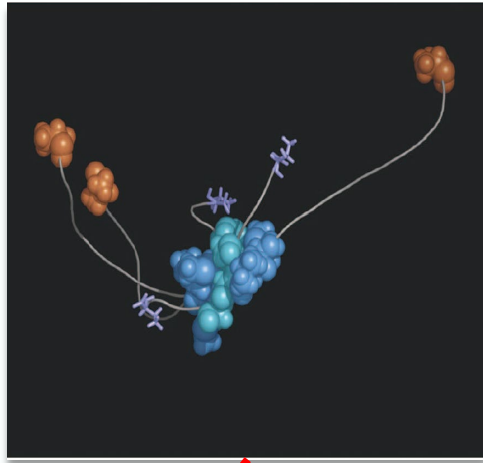
Stock positions

Shareholder: Eli Lilly and Company

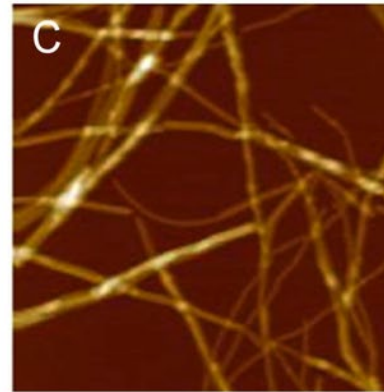
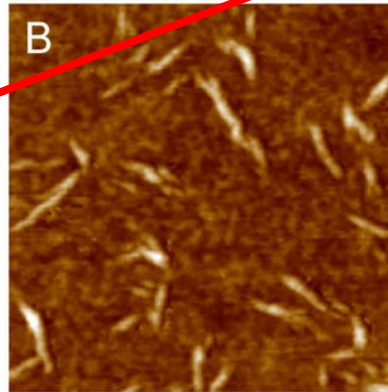
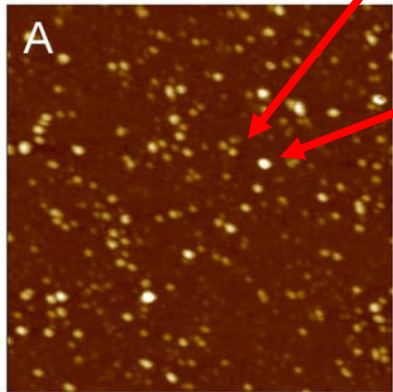
Stock options: Acumen Pharmaceuticals Inc.

Quaternary structures of A β Oligomers, protofibrils and fibrils

A β O may consist of 2 to >200 A β peptides.



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



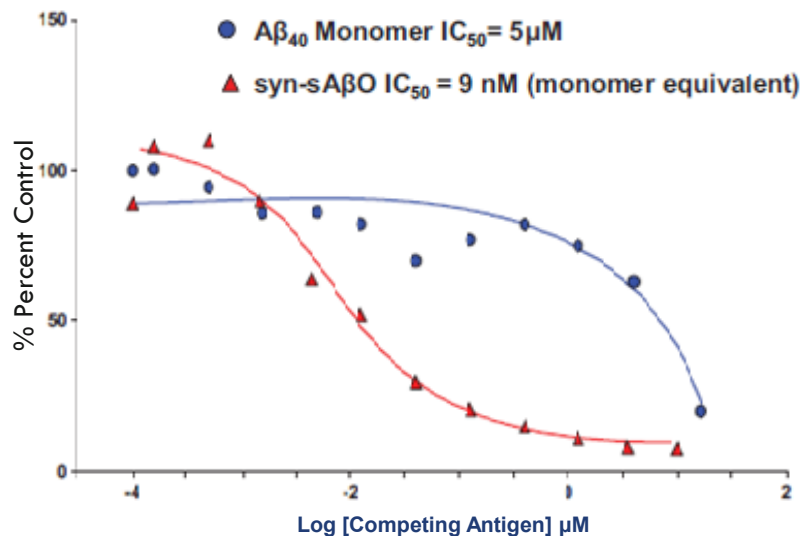
Relini et al. Misfolding of amyloidogenic proteins and their interactions with membranes *Biomolecules* 2014

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.

ACU193 is the first mAb developed to selectively target A β O_s

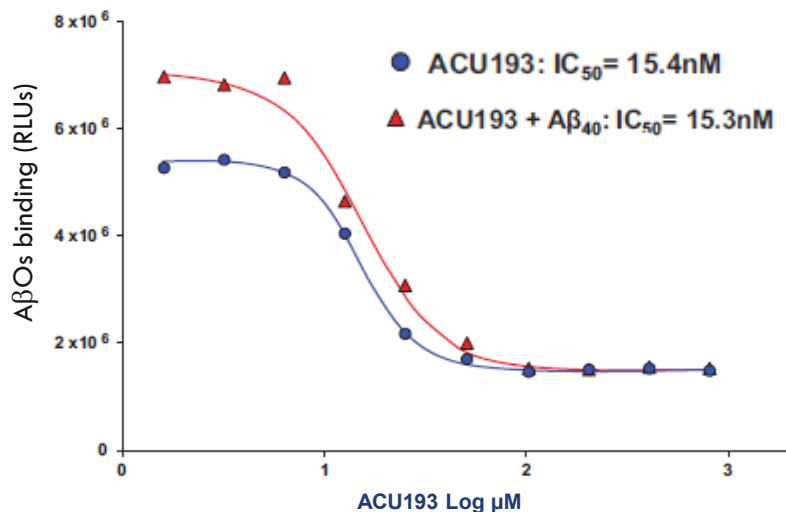
Highly selective for A β oligomers versus A β monomers

ACU193 Selectivity



Binding of ACU193 to A β O_s >500x
binding to A β monomer

ACU193 Selectivity in presence of $5 \mu M$ monomeric A β



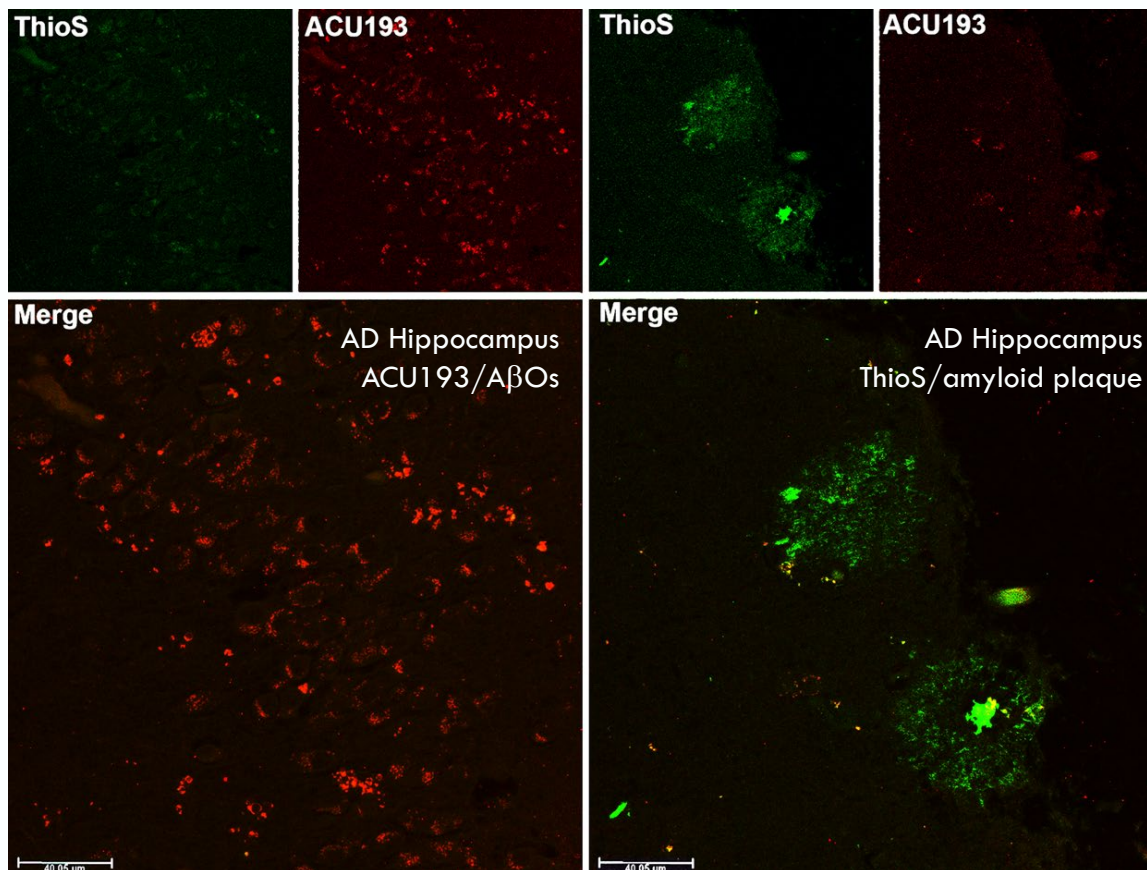
Even in the presence of a large excess of A β monomer,
binding of ACU193 to A β O_s is unchanged

ACU193 selective binding to A β O_s is preserved even in the
presence of a large excess of A β monomer

ACU193 is highly selective for A β O $_s$ versus A β plaques

ACU193 staining in human AD brain slices from hippocampus:

ACU193 (red) binds non-Thioflavin S positive A β (green)



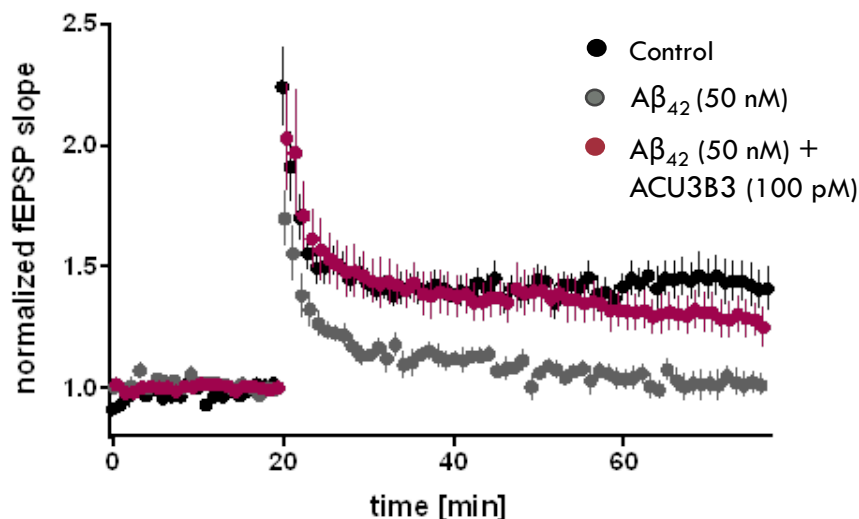
ACU193 has limited to no binding to thioflavin S positive fibrillar A β plaque in human AD brain tissue

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

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

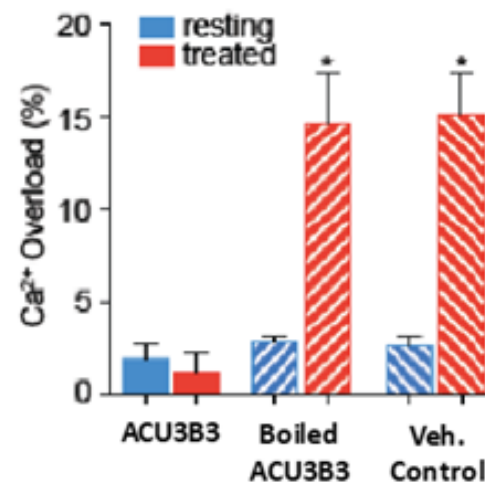
After binding to neurons, A β O disrupt Long Term Potentiation (LTP) and cause pathologic increases in intracellular calcium that is destructive to cells.

ACU3B3 prevents A β O inhibition of hippocampal LTP ex vivo



ACU3B3 prevents A β O mediated Ca²⁺ elevation in cell cultures

Primary Neuronal Cultures



ACU3B3 prevents aberrant neuronal activity caused by A β O and prevents A β O mediated disruption of calcium homeostasis in neuronal cultures

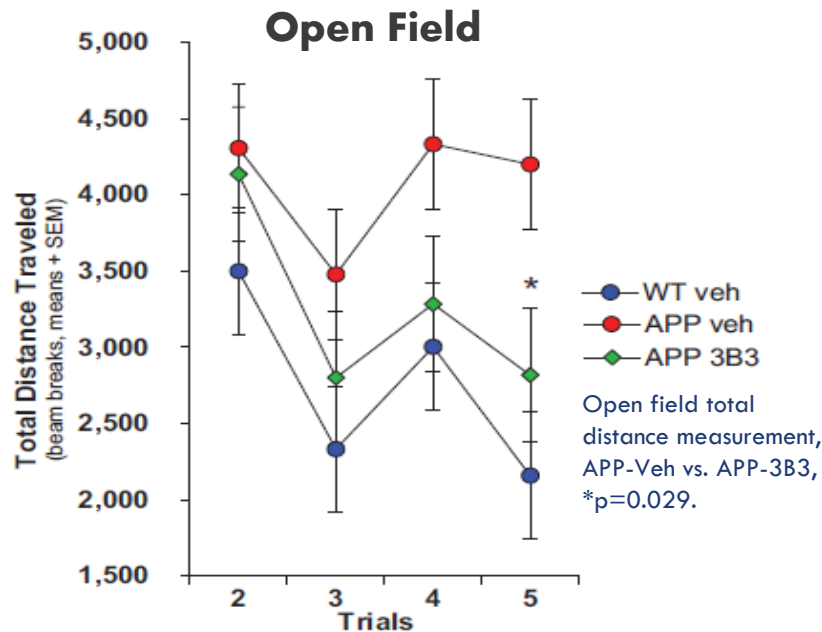
Data on File and

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

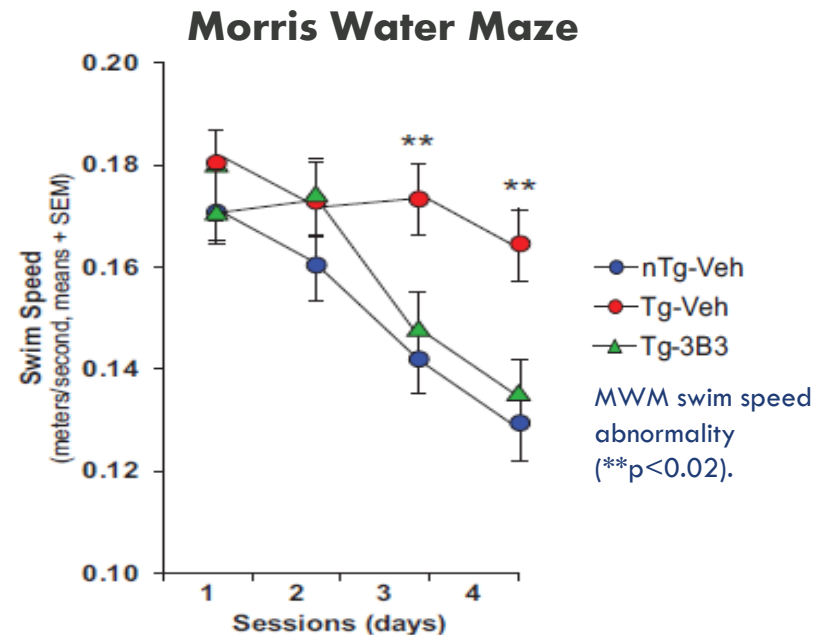
Treatment of a transgenic mouse model of AD results in reduction of behavioral deficits

Dodart JC et al. Passive immunization with the anti-A β oligomer antibody ACU-3B3 improves behavioral deficits in hAPP^{SL} tg mice. Sfn, Washington, DC 2014. Ma K. et al. Soluble A β -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



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



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

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:

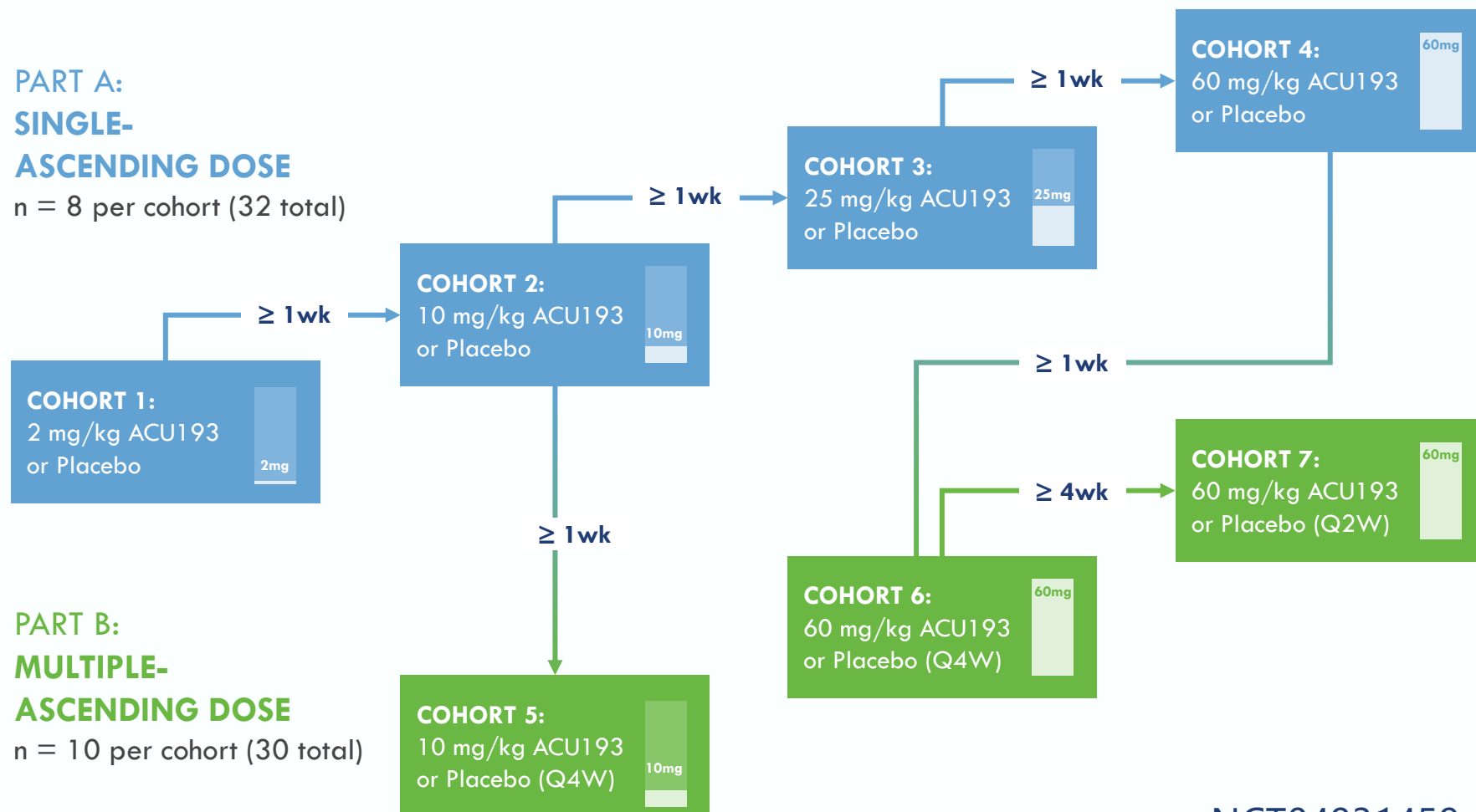
Proof of Mechanism (PoM)

- 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)



NCT04931459

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**

Arterial Spin Labelling (ASL) as an MRI outcome

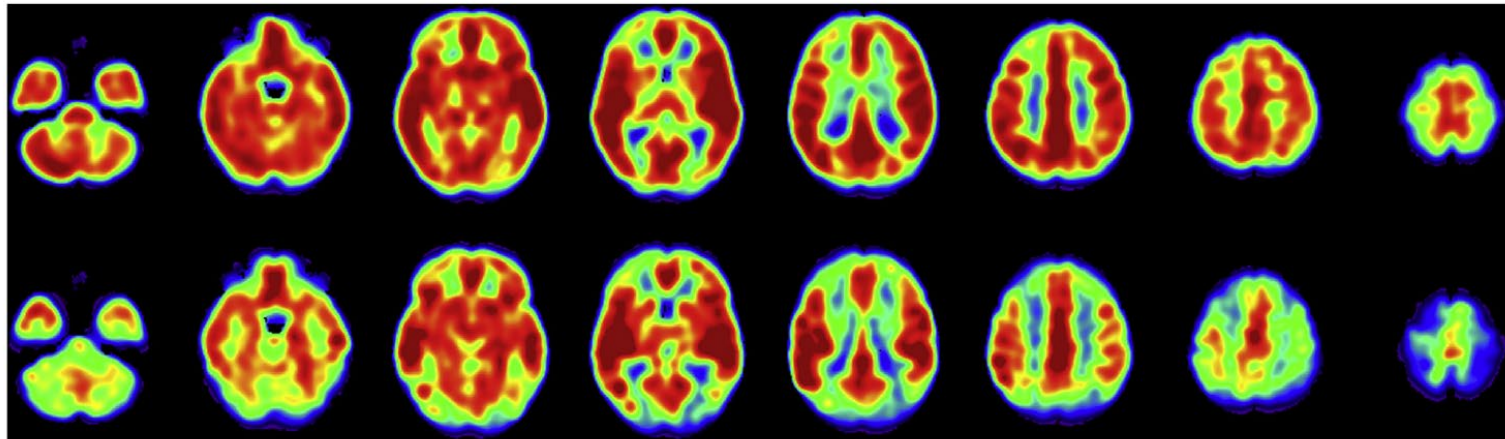


Fig. 1. Processed CBF images measured with ASL of a young and an old healthy control from our database. The top row images are from a 32 year-old woman, and the bottom row images are from an 80 year-old man. The reduction of CBF can be readily observed in widespread brain areas of the older subject compared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

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

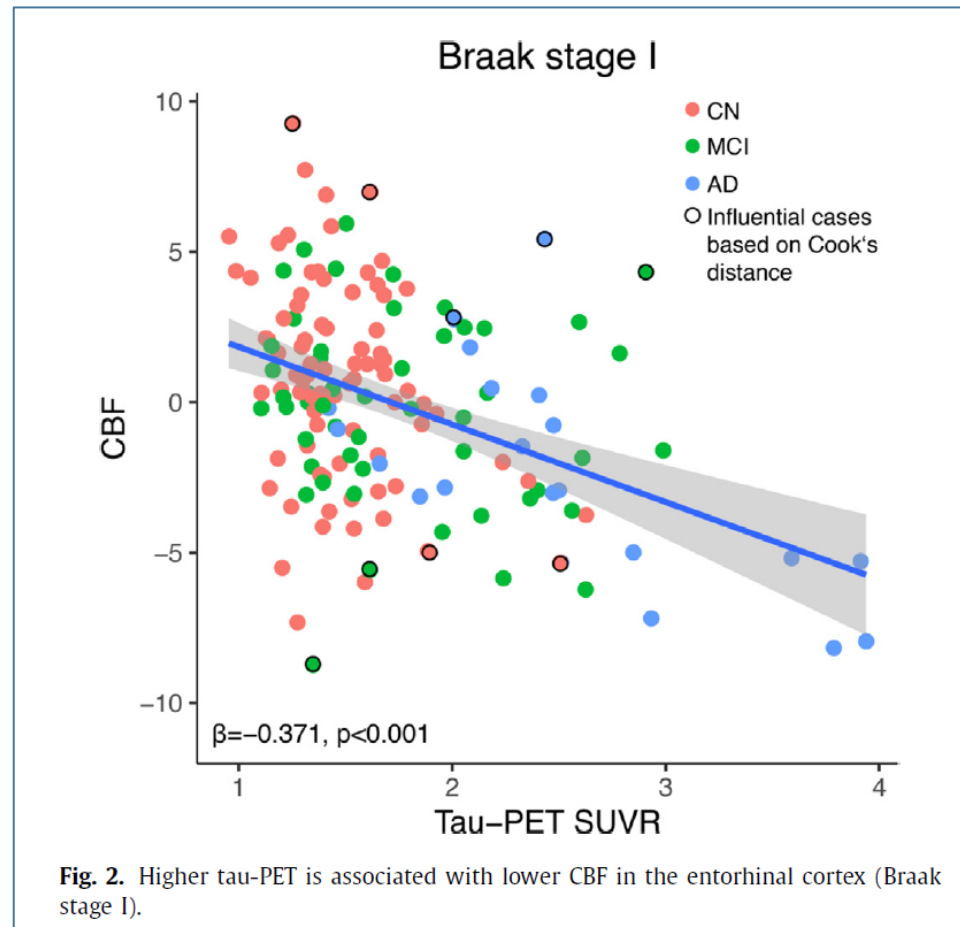
- MCI patients show hypoperfusion in parietal cortex, precuneus, posterior cingulate cortex and medial temporal lobe
- AD patients show global hypoperfusion, but especially cingulate, precuneus, parietal lobes and inferior frontal regions
- Perfusion correlates with several neuropsychological tests
- 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

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



Summary

- Non-clinical data consistent with toxicity of A β oligomers and selective binding of ACU193 to A β 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