ACU-193: Soluble Aβ-Oligomer Selective Immunotherapy for Alzheimer’s Disease

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Abstract

Soluble amyloid-beta (Abeta) oligomers are now widely recognized as a key culprit in Alzheimer’s disease. They inhibit synaptic function, triggering early memory deficits and initiating nerve cell degeneration. They are able to directly initiate downstream pathological events in Alzheimer’s disease. ACU-193 is a fully humanized, IgG2 monoclonal antibody that binds synaptotoxic soluble Abeta oligomers (also called Abeta-derived diffusible ligands, ADDLs) with high affinity and selectivity, and is distinct from other antibodies binding to Abeta (e.g., bapineuzumab, solanezumab, crenezumab, gantenerumab), which are designed to lower the Abeta load in the brain. Nanomolar affinity for soluble Abeta oligomer binding has been measured by various methods, with insignificant binding to Abeta monomers, or amyloid plaques and vascular amyloid in the brain. ACU-193 shows no cross-reactive binding to other proteins. ACU-193 is expected to improve synaptic function and memory of Alzheimer patients. Efficacy of ACU-193 in vitro has been demonstrated in neuronal cell cultures. Abeta soluble oligomer engagement and efficacy of ACU-193 in vivo has been demonstrated in a transgenic mouse model of Alzheimer’s disease. ACU-193 exhibits linear, dose-dependent pharmacokinetics, biodistribution, and brain penetration typical for therapeutic antibodies. Exploratory safety and toxicity studies in monkeys revealed an overall excellent safety profile for ACU-193. Clinical development plans for ACU-193 reflect the availability of biomarker assays and the expectation that behavioral efficacy is achieved relatively quickly. It is anticipated that initial evidence for efficacy will be obtained in a Phase Ib study of relatively short duration and cost.
ACU-193 Summary

- Aβ immunotherapy that specifically targets soluble Aβ oligomers, the most synaptotoxic Aβ species.
  - >500x selectivity for soluble Aβ oligomers versus monomeric Aβ, amyloid plaques or vascular amyloid.

- Expected to deliver acute symptomatic benefits and chronic disease modification benefits:
  - ACU-193 is expected to show behavior benefits within 3 months
  - POC for acute clinical benefits via Aricept/Memantine like clinical trials

- Expected to work as a stand-alone therapy or in combination with other Aβ and/or Tau directed therapies.

- In vitro and in vivo efficacy demonstrated:
  - Excellent PK/PD, BBB penetration
  - Safety properties demonstrated
  - CMC production cell lines and analytics established
ACU-193 is the result of an 8-year, multi-$M$ partnership with Merck

Aβ Species in Humans: Aβ Oligomers are the Most Toxic Yet the Least Prevalent Aβ Species

Significant changes in Aβ42 monomer and/or amyloid levels required to change levels of soluble Aβ oligomers!

ACU-193: an Anti-soluble Aβ Oligomer Antibody Drug Candidate

- Humanized, affinity-matured, IgG2 mAb with selectivity for soluble Aβ oligomers (>500 fold over Aβ monomers and fibrils)
- **In vitro** efficacy: inhibition of binding of soluble Aβ oligomers to hippocampal neurons (mean IC\textsubscript{50} = 17 nM)
- **In vivo** target engagement: minimum efficacious dose in Tg2576 mice of 10 mg/kg.
- **In vivo** efficacy: molecular and behavioral in Tg2576 mice.
- Excellent PK, biodistribution and brain penetration in Tg2576 mice, rats, and rhesus monkeys.
- Excellent safety profile in exploratory studies in rhesus monkeys.
- CMC: efficient production cell lines (>1 g/L) and the necessary analytics established.
- Established companion diagnostic biomarker and pharmacodynamic assay (soluble Aβ oligomers and antibody–ligand complex in CSF).
- Composition of matter and use patents filed 2010 (WO 2012/009442)
Mission

Demonstrate acute beneficial behavioral efficacy in MAD phase Ib/IIa trial

Pursuing parallel paths to achieve mission:
- Seeking partnership with larger Pharma-Co with committed funding and expertise
- Venture financing and self-development

Management

Franz F. Hefti, PhD, CEO

William F. Goure, PhD, COO

Key Advisors:
- Grant A. Krafft, PhD, Scientific Advisor
- Daniel J. O’Connell, MBA, Bus Dev. Advisor
- CMC, Regulatory, Clinical consultants

For additional information see: www.acumenpharm.com
Brain Penetration and Target Engagement in Tg2576 Mice

Levels of ACU-193/Ab-oligo complexes in the brain 24 hrs after IV injection of ACU-193

Tg2576 Female Mice

Tg2576 Male Mice

Minimal Efficacious Dose: 10 mg/kg
**In Vivo Efficacy: Decrease in Locomotor Activity in Tg2576 mice**

ACU-193 treatment results in significant decrease in locomotor activity after 14 and 21 days.

Excess of locomotor activity in Tg2576 used as behavioral readout (King & Arendash, 2002; Gil-Bea et al., 2007).

W = Wild Type; T = Tg2576
ACU-193 PK and Safety Summary

• PK Studies in rats, dogs, Tg2576 mice, and rhesus monkeys.
  – Linear, dose-dependent increases of antibody levels in plasma, CSF and brains.
  – Half-life in rhesus monkeys approximately 11 days
  – CSF and brain levels similar to values obtained with competitive Aβ-antibodies
  – Biodistribution similar to competitive Aβ-antibody in rhesus monkeys

• Overall excellent safety profile
  – Non-GLP studies in rhesus monkeys at high dose level (100 mpk; IV).
  – No microhemorrhage risk detected in Tg2576 mice.
ACU-193 CMC Status

- Stable production cell lines established:
  - Productivity of $\geq 1$ g/L
  - Protein quality and expression stability confirmed

- Preliminary manufacturing process established:
  - Fed-batch shake flask: titer of $\sim 1.8$ g/L with lead clone
  - Purification: Overall yield of $\sim 80$
  - Current cell line and process achieves clinical grade product quality

- Formulation suitable for refrigerated storage and IV administration established.
Companion Diagnostic Assay for CSF Levels of Soluble Aβ Oligomers

Highly selective and sensitive ELISA assay for Aβ oligomers developed

- >5000x selectivity for Aβ-oligomers
- Cross reactivity with monomer ≈ 0.05%
  - LOQ = 0.42 pg/ml
  - LOD = 0.04 pg/ml
- Commercially available assay format