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A new horizon in Alzheimer's disease: targeting highly neurotoxic amyloid-β oligomers (AβOs)

Acumen Pharmaceuticals is developing ACU193 as the first clinical-stage therapeutic to selectively target toxic soluble amyloid-β oligomers (AβOs), which are an early and persistent driver of Alzheimer's disease-related neurodegeneration.

Alzheimer's disease (AD) is the major cause of dementia, accounting for 60–80% of all cases. More than 50 million people globally live with the disease, and as populations age the number of AD patients is expected to increase to up to 150 million by 2050[1], placing an enormous burden on patients, their families and the health-care system. New treatments are needed that go beyond the limited symptomatic relief provided by most current AD drugs, and that offer a differentiated option from approved and under-review disease-modifying therapies (DMTs).

Acumen Pharmaceuticals, headquartered in Charlottesville, VA, brings decades of collective experience in AD drug research and development to bear on this challenge, and is evaluating a potential best-in-class treatment in the new era of DMTs for AD. Its scientific founders pioneered research on AβOs, which a growing body of evidence indicates are early and persistent triggers of AD pathology, though they remain an under-explored therapeutic target. ACU193 is the first clinical-stage antibody designed to selectively target AβOs with the goal of demonstrating improved safety and efficacy compared to existing therapies and those in development for AD. Acumen has generated positive data in one of the most robust phase 1 trials in the AD space, and plans to initiate a phase 2 study in the first half of 2024 which has the potential of becoming phase 3-eligible.

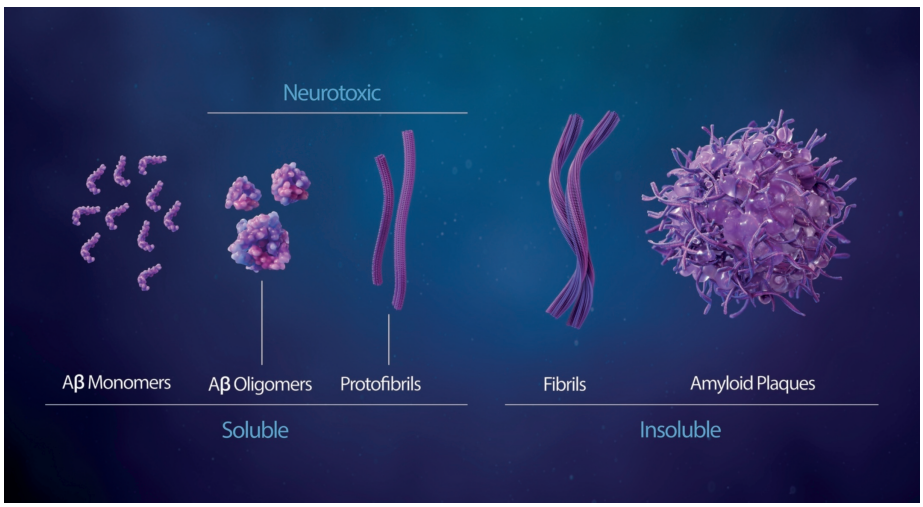

Fig. 1 | The five dominant species of amyloid-β (Aβ) and potential immunotherapeutic targets. Monoclonal antibodies (mAbs) have been developed against different species of Aβ. ACU193 is the first clinical-stage mAb to selectively target toxic soluble Aβ oligomers.

Rethinking the biology of AD

Ever since Alois Alzheimer first described the neurological changes that characterize the disease that now bears his name, amyloid plaques have been a central focus of AD research. By the early 1990s, the amyloid cascade hypothesis had emerged, proposing that AD is fundamentally caused by deposition of Aβ protein. The cascade component of the hypothesis captures the idea that the production of Aβ not only leads to amyloid plaques, but also has other downstream effects including hyperphosphorylation of tau protein (p-tau) that forms neurofibrillary tangles, causing neuronal cell death and contributing to cognitive impairment and dementia. Intracellular neurofibrillary tangles, along with extracellular amyloid plaques, are considered pathological hallmarks of AD.

Over the past three decades, research has established a clear causal linkage between AD and elevated brain levels of amyloid plaques and the component Aβ peptide. At the same time, the understanding of the role of the Aβ peptide has evolved. Initially, the amyloid cascade hypothesis considered Aβ monomers and their accumulation into amyloid plaques as a driver leading to AD; but over time, the fact that Aβ monomers and plaques are not, by themselves, primary causes of the neurodegeneration and cognitive impairment seen in AD has become more apparent.

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Of the five dominant species of Aβ (Fig. 1), the intermediate soluble AβOs have been recognized as a highly toxic form—based on their propensity to bind neuronal synapses, disrupting their normal function and contributing to tau hyperphosphorylation—and as a potentially important therapeutic target. Acumen is now developing a monoclonal antibody ACU193 as the first clinical-stage therapeutic to specifically target AβOs and thereby inhibit their harmful effects.

AD therapeutics—the current landscape

The huge toll that AD places on patients, their families and health-care systems around the world, and the need for better therapies, have ensured that investment in the search for new and improved AD therapeutics has been pronounced for decades. As of 2022, there were 143 agents in 172 clinical trials for AD worldwide, with 31 agents in phase 3, 94 in phase 2, and 30 in phase 1[2]. Across all agents, 68% are being developed as DMTs, with two-thirds of these being small molecules and one-third biologics.

These agents in development have a wide variety of mechanisms of action and targets, from metabolic, inflammatory and oxidative factors to vasculature and synaptic plasticity. But by far the largest class of DMTs—containing approximately 30% of all agents—is represented by amyloid-targeting therapeutics, reflecting the continued importance of the amyloid cascade hypothesis in AD drug development.

Developing effective anti-amyloid therapeutics has proven complex however, with numerous phase 3 drug failures. The most promise has been seen with amyloid-directed mAbs, but it should be noted that this is not a monolithic class and approved and in-review candidates differ in their mechanisms of action and the species of Aβ they target.

These setbacks have understandably caused some despondency in the AD community, said Steven DeKosky, deputy director of the

McKnight Brain Institute at the University of Florida's Department of Neurology and a member of Acumen's scientific advisory board. Yet, as DeKosky noted, recent years have provided more cause for optimism, with evidence that some Aβ- or amyloid plaque-targeting drugs can slow cognitive decline, resulting in some high-profile approvals for new AD drugs.

In July 2023, Leqembi (lecanemab; Eisai and Biogen), a DMT mAb that binds to amyloid protofibrils, was granted traditional approval by the US Food and Drug Administration (FDA), based on phase 3 data indicating a 27% slowing of cognitive decline. Donanemab (Eli Lilly), an amyloid plaque-targeting mAb, has completed a phase 3 trial and was undergoing regulatory review at the time of writing.

Based on learnings in the field over the past two decades, recent clinical trial designs have helped define development pathways for regulatory approval, including greater use of newly developed biomarkers for patient selection. In fact, use of biomarkers for patient selection is an important advance for the field, especially for earlier-stage patients with mild cognitive impairment and mild dementia who appear to be more likely to respond to DMTs.

ACU193: new target, new therapeutic possibilities

Acumen Pharmaceuticals is building on these advances with the development of ACU193 as a novel DMT. Crucially, by selectively targeting the highly toxic AβOs rather than Aβ monomers or downstream fibrils and plaques (Fig. 2), ACU193 has the potential to deliver greater benefits and an improved safety profile compared with recently approved anti-amyloid AD mAbs and other agents in development.

ACU193 has completed the phase 1 INTERCEPT-AD trial[3], with positive results reported at the Alzheimer's Association International Conference in July 2023 and further detailed analyses presented at the Clinical Trials on Alzheimer's Disease conference in October 2023. The 60 patients with early AD who were recruited and completed INTERCEPT-AD were split into single-ascending dose and multiple-ascending dose cohorts, receiving ACU193 at dose levels of 2, 10, 25 and 60 mg/kg. ACU193 was well tolerated and resulted in no drug-related serious adverse events.

Amyloid plaque-targeting mAbs have been associated with a significant incidence of the treatment-emergent adverse event known as amyloid-related imaging abnormalities-edema (ARIA-E), which occurs after the removal of amyloid plaques around blood vessels. In lecanemab trials, for example, almost 13% of patients experienced ARIA-E , and in donanemab trials, approximately 24% of patients experienced ARIA-E. ARIA-E causes symptoms in about 20% of patients who develop this radiologic finding. ACU193, which selectively targets AβOs, appears to have minimal if any binding to plaque, and based on data in the INTERCEPT-AD trial, may have a lower rate of ARIA-E compared with amyloid-plaque-directed treatments.

In addition to meeting these primary safety objectives, INTERCEPT-AD also met secondary outcomes that helped establish clinical proof-of-mechanism for ACU193, including direct target engagement of AβOs in the cerebrospinal fluid in a dose-proportional manner, rapid, dose-related, statistically significant amyloid plaque reduction observed in higher dose cohorts, and pharmacokinetics that established ACU193's activity in the central nervous system.

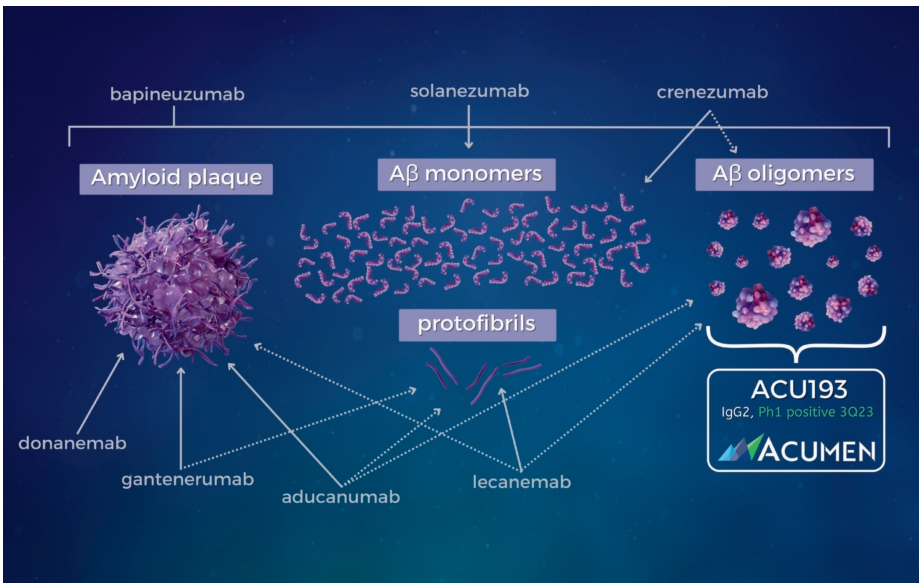

Fig. 2 | ACU193 versus other anti-amyloid monoclonal antibodies. ACU193's high selectivity for amyloid-β (Aβ) oligomers, combined with an expected low rate of amyloid-related imaging abnormalities, is anticipated to provide a better safety and efficacy profile compared with other anti-amyloid monoclonal antibodies. 3Q23, third-quarter 2023; IgG2, immunoglobulin G2; Ph1, phase 1.

These findings demonstrated that ACU193 approached maximal central-target engagement of toxic AβOs beyond expected levels with repeated dosing at 25 mg/kg and 60 mg/kg, establishing a broad therapeutic index and a path to dosing every 4 weeks.

In the phase 1 trial, ACU193 demonstrated rapid, dose-related and statistically significant (p=0.01) amyloid plaque reduction in higher dose cohorts: a 25% reduction at day 63 in cohorts receiving 60 mg/kg once every 4 weeks, and a 20% reduction at day 70 in cohorts receiving 25 mg/kg every 2 weeks. This plaque-reduction effect, in addition to target engagement with AβOs, is a promising finding given the apparent relationship between robust plaque reduction and slowing of cognitive decline in studies of other antibody therapies for AD.

Underscoring the novelty of ACU193's differentiated mechanism of action and the robustness of its phase 1 trial design and dataset, Acumen developed the first assay to evaluate target engagement on an AβO-targeting antibody in order to evaluate target engagement of ACU193. The findings demonstrated significant, dose-related central-target engagement as measured by the ACU193–AβO complex in cerebrospinal fluid. Overall low levels of ARIA-E were observed. Among 48 patients treated with ACU193, there were five cases of ARIA-E reported, one of which was symptomatic; no ARIA-E was observed in any of the six participants with two copies of the *APOE4* gene.

Looking beyond INTERCEPT-AD, Acumen is currently preparing to launch a registration-quality phase 2/3 trial of ACU193, which will feature interim analyses to guide the decision about transitioning from phase 2 to a phase 3 registration trial.

The amyloid cascade hypothesis of AD pathogenesis has historically been treated as a monolithic hypothesis, fostering the notion that approaches targeting Aβ monomers or amyloid plaques as a single therapeutic strategy were equivalent—a view that may have contributed to some of the failures of earlier amyloid-targeting therapies. Yet as the different pathological roles of distinct Aβ species have become clearer, the possibility of selectively targeting specific types of Aβ, as with ACU193's targeting of Aβ oligomers, has opened the possibility of new, more effective and safer treatments for the devastation wrought by AD. Acumen Pharmaceuticals is dedicated to leading the way in bringing this future to fruition.

1. Alzheimer's Association. *Alzheimers Dement.* **19**, 1598–1695 (2023). https://doi.org/10.1002/alz.13016
2. Cummings, J. et al. *Alzheimers Dement.* **8**, e12295 (2022). https://doi.org/10.1002/trc2.12295
3. Siemers, E. et al. *J. Prev. Alzheimers Dis.* **10**, 19–24 (2023). https://doi.org/10.14283/jpad.2022.93

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