Sabirnetug and ALTITUDE-AD – what do the results mean for the oligomer hypothesis?

What is sabirnetug?

Sabirnetug, formerly known as ACU193, is a humanized monoclonal IgG2 antibody developed by Acumen Pharmaceuticals for the treatment of Alzheimer's disease. It originates from the murine antibody 3B3, which was generated by immunizing mice with synthetic, soluble Aβ42 aggregates known as ADDLs (amyloid-β-derived diffusible ligands). The antibody was subsequently humanized and affinity-matured through a research collaboration between Acumen and Merck.

According to Acumen, sabirnetug selectively binds to a broad range of soluble Aβ oligomers, which the company describes as particularly toxic and disease-driving forms of Aβ. The company has reported a more than 500-fold preference for oligomers over monomers in competitive ELISA assays, lower reactivity toward fibrils, and limited or no binding to amyloid plaques in tissue analyses. The intended mechanism of action is to prevent oligomers from binding to and damaging neuronal synapses, rather than primarily removing plaques.

Sabirnetug was generally well tolerated in the Phase 1 INTERCEPT-AD study and was subsequently evaluated in the Phase 2 ALTITUDE-AD study, which investigated its clinical efficacy in patients with early Alzheimer's disease.

What did ALTITUDE-AD show?

Sabirnetug demonstrated no clinical benefit in ALTITUDE-AD at the doses investigated in patients with early Alzheimer's disease. The study enrolled 542 participants and failed to meet both its primary endpoint, change in iADRS at 18 months, and its key secondary endpoints, including CDR-SB. According to Acumen, no meaningful difference was observed between the treatment groups and placebo.

At the same time, amyloid plaque burden was statistically significantly reduced at both dose levels. ARIA-E, referring to amyloid-related edema or fluid accumulation detected by magnetic resonance imaging (MRI), was reported in approximately 10 percent of sabirnetug-treated participants.

Based on the study results, Acumen has announced that development of sabirnetug will be discontinued.

Was the outcome expected?

There were already scientific reasons to question how selective sabirnetug actually is for disease-relevant oligomers. In a 2022 publication (Sandberg et al., https://link.springer.com/article/10.1186/s13195-022-01141-1), we discussed the

distinction between selectivity for multivalent Aβ aggregates and specificity for a structure unique to oligomers. We also highlighted that the available data for ACU193 and its predecessor, the murine antibody, did not unequivocally support the latter characterization.

It is important to note that this was a mechanistic concern, not evidence that the clinical trial would fail. The outcome brings this concern back into focus but does not establish which property of the antibody or treatment was decisive for the result.

Does this disprove the oligomer hypothesis?

No, certainly not on the basis of this study alone. The result provides evidence against the specific therapeutic strategy pursued with sabirnetug. The antibody binds soluble Aβ aggregates, but published tissue analyses also demonstrate reactivity toward plaque-associated Aβ. ALTITUDE-AD therefore does not represent a definitive test of exclusive binding to a defined oligomer-specific structure. The observed effects on plaques in the study are consistent with this observation.

It would therefore be an overstatement to claim that the study disproves the oligomer hypothesis. The key question remains which Aβ species need to be targeted, to what extent, and at which stage of the disease to achieve meaningful clinical benefit. This has yet to be established, although preclinical data suggest that oligomers are by far the most toxic forms of Aβ and therefore represent attractive therapeutic targets.

How selective is sabirnetug?

Preference for oligomers is not the same as oligomer specificity. The antibody lineage underlying sabirnetug has been associated with the flexible N-terminal region of Aβ, which is accessible in several different forms of Aβ, including fibrils and plaque-associated Aβ. Reported selectivity varies across analytical methods and also depends on who performs the analyses.

The binding profile and clinical results support the conclusion that the observed binding preference depends substantially on avidity for multivalent aggregates, rather than on recognition of a unique oligomer-specific conformation. Tissue analyses using an independently produced version of sabirnetug demonstrated clear plaque-associated binding. Taken together, the findings suggest that sabirnetug is more similar to lecanemab than has been communicated, although it has a different immunoglobulin subclass (IgG2 rather than IgG1).

Why is avidity relevant?

Affinity describes the strength of binding between an individual antigen-binding site on an antibody (the paratope) and the structure on the target protein that it recognizes (the epitope). Avidity describes the enhanced overall binding strength resulting from multiple interactions and rebinding, for example when an antibody binds to an aggregate containing numerous accessible epitopes.

An antibody can therefore bind substantially more strongly to aggregates than to free monomers without recognizing an oligomer-specific structure. This makes assay format, epitope density, and aggregate size central to the interpretation of results: a high oligomer-to-monomer binding ratio does not, in itself, demonstrate conformational specificity.

What could explain the failure?

Insufficient exposure at the relevant target structure and inadequate effects on the most disease-relevant Aβ species are possible explanations, although neither has been established. For an antibody with broader aggregate reactivity, binding to abundant Aβ deposits may divert the antibody away from rare toxic oligomers. Limited penetration into the brain could further compound this limitation.

Sabirnetug's IgG2 format also has lower effector function, including effects on cells such as microglia, than the IgG1 format used by antibodies including lecanemab, donanemab, and PMN310. This may influence the balance between neutralization, immune cell-mediated clearance, and inflammation. However, it would be incorrect to equate IgG2 with a complete absence of clearance or to assume that IgG1 would have resolved the problem. Gantenerumab is also an IgG1 antibody and likewise failed to meet its primary clinical endpoints despite some effects on amyloid plaques.

How does PMN310 differ from sabirnetug?

PMN310, an antibody being developed by ProMIS Neurosciences, represents a scientifically relevant alternative approach to achieving greater oligomer selectivity. The antibody was developed against an epitope around amino acids 13–16 of Aβ, near the end of the N-terminal region, which generally extends from amino acids 1 to 16.

Published preclinical data demonstrate binding to soluble Aβ aggregates derived from Alzheimer's disease brains, with no detectable staining of amyloid plaques or vascular amyloid under the conditions investigated. This represents a more pronounced distinction from sabirnetug than can be claimed for most other anti-Aβ antibodies.

PMN310 and sabirnetug therefore represent different therapeutic approaches rather than interchangeable treatments. The outcome of sabirnetug does not determine the outcome of PMN310. Its safety and clinical value must be assessed on the basis of its own unblinded clinical trial results.

How selective Is PMN310 for oligomers?

PMN310 does not bind to plaques and has demonstrated low monomer reactivity in published analyses. However, an absolute claim of zero binding goes beyond what the available data support. Published findings are consistent with a weak interaction with Aβ40 monomers but do not quantify the affinity or establish its significance in vivo.

According to ProMIS, unblinded 12-month results from PRECISE-AD are expected during the first quarter of 2027. The study is a randomized, double-blind, placebo-controlled Phase 1b trial involving 144 participants with early Alzheimer's disease.

The six-month results presented to date are blinded and pooled across active treatment and placebo. No cases of ARIA-E were reported among 136 evaluable participants at the relevant data cutoff, and biomarker changes were presented. However, these findings cannot yet be attributed to PMN310 or used to establish a treatment effect.

How does ALZ-201 differ from these antibodies?

ALZ-201 was developed to recognize an oligomer-specific conformation, rather than merely exhibiting preferential binding to larger Aβ aggregates through avidity. This represents a different binding strategy from that underlying sabirnetug and lecanemab.

The antibody binds strongly to a unique epitope on the oligomer structure, rather than to the N-terminal region. Accordingly, we observe no detectable binding to either monomeric or fibrillar Aβ.

Is there evidence supporting the relevance of the target structure?

Yes, from a preclinical experiment using brain extracts from individuals with Alzheimer's disease. The extracts were immunodepleted using ALZ-201 before exposure to primary mouse neurons. The treatment reduced damage to dendritic and synaptic structures, despite no statistically significant reduction in the measured total amount of Aβ.

The study is available here: https://link.springer.com/article/10.1186/s13195-022-01141-1

The findings support the conclusion that ALZ-201 removed a low-abundance but biologically significant Aβ component. However, the exact naturally occurring target structure could not be unequivocally identified in the study, and the experiment does not constitute evidence of clinical efficacy in patients. This must be investigated in clinical studies.

Does ALZ-101 have the same binding profile?

ALZ-101 is based on the same stabilized oligomer technology, but the antibody response, and consequently the binding profile, is broader than that of a single monoclonal antibody.

Nevertheless, animal data support a strongly oligomer-directed response, and binding studies demonstrate that the epitope recognized by these antibodies is the same as that recognized by ALZ-201.

The weaker response toward the N-terminal region observed in animals appears to be absent in patients. However, the available evidence remains limited, and some N-terminal reactivity among a small percentage of the generated antibodies cannot be ruled out. Such reactivity is not expected to have any mechanistic impact.

What did the Phase 1 study of ALZ-101 show?

The study supported continued development based on its tolerability and immunogenicity results but did not demonstrate statistically significant clinical efficacy, which was not the study's objective.

A total of 32 participants received the investigational treatment or placebo across the different parts of the study. No serious adverse drug reactions were reported, and clear IgG responses were induced in nearly all vaccinated participants.

Potential signals of efficacy were observed, but these are hypothesis-generating only and should not be interpreted as confirmed disease modification. No statistically significant differences versus placebo were demonstrated for the predefined CSF biomarkers or the cognitive and functional endpoints in the randomized part of the study.

During longer-term follow-up, numerical differences were observed in several measures, including tau, NfL, and ADCOMS, supporting further clinical development.

The results have been published and are available here:
https://link.springer.com/article/10.1186/s13195-026-02082-9

What is the status of ADVANCE?

ADVANCE (ALZ-C-002) is Alzinova's planned Phase 2a study of ALZ-101, with preparations underway ahead of the enrollment of the first participant.

Approximately 120 participants with early Alzheimer's disease are planned to be enrolled. The study will be conducted in the United States, the European Union, and the United Kingdom.

Updated study documentation has been submitted to the FDA, and seven US clinical trial sites have been selected. Enrollment of the first participant is targeted for around the turn of 2026/2027.