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PERSPECTIVE

The path forward in Alzheimer's disease therapeutics: Reevaluating the amyloid cascade hypothesis

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Abstract

Development of disease-modifying treatments for Alzheimer's disease (AD) has been challenging, with no drugs approved to date. The failures of several amyloid-targeted programs have led many to dismiss the amyloid beta (Aβ) hypothesis of AD. An anti-amyloid antibody aducanumab recently showed modest but significant efficacy in a phase 3 trial, providing important validation of amyloid as a therapeutic target. However, the inconsistent results observed with aducanumab may be explained by the limited brain penetration and lack of selectivity for the soluble Aβ oligomers, which are implicated as upstream drivers of neurodegeneration by multiple studies. Development of agents that can effectively inhibit Aβ oligomer formation or block their toxicity is therefore warranted. An ideal drug would cross the blood-brain barrier efficiently and achieve sustained brain levels that can continuously prevent oligomer formation or inhibit their toxicity. A late-stage candidate with these attributes is ALZ-801, an oral drug with a favorable safety profile and high brain penetration that can robustly inhibit Aβ oligomer formation. An upcoming phase 3 trial with ALZ-801 in APOE4/4 homozygous patients with early AD will effectively test this amyloid oligomer hypothesis.

KEYWORDS

Alzheimer's disease, Amyloid cascade hypothesis, Amyloid oligomers, APOE4 genotype, ALZ-801, Antiamyloid antibodies, Aducanumab, BAN2401, β-secretase inhibitors

1 | INTRODUCTION

The past 2 decades have been very challenging for Alzheimer's disease (AD) drug development, with no drugs approved that can slow or stop the progressive clinical decline. In 2018, the US Food and Drug Administration (FDA) approved 59 new drugs [1], but the last new drug for AD was approved in 2003. The failures of several antiamyloid immunotherapies and β-secretase inhibitor (BACEi) programs have raised doubts about the role of amyloid beta (Aβ) in AD pathogenesis, despite compelling evidence from genetics, neuropathology, and clinical biomarker studies.

The recent announcement that aducanumab showed significant efficacy in the phase 3 EMERGE trial in early AD subjects was a decisive development for the Alzheimer's field and validates amyloid as a therapeutic target.[2] However, the clinical effects of aducanumab even at the highest dose were modest, with 23% benefit on the primary outcome, the Clinical Dementia Rating-Sum of Boxes. A second identical phase 3 ENGAGE trial of aducanumab failed to achieve this primary

endpoint. Low brain penetration of aducanumab and the lack of selectivity for soluble amyloid oligomers versus insoluble aggregated fibrils and plaque, may explain the limited and inconsistent efficacy signal.

These aducanumab results, and the failed amyloid-targeted programs, provide insights that can help us fine-tune the mechanistic targets and therapeutic strategies to achieve a more meaningful clinical efficacy. To date, none of the clinical programs have appropriately evaluated the amyloid cascade hypothesis because they did not address the critical pathogenic role of amyloid oligomers. We believe that the failures of anti-amyloid trials were related to drug development challenges and do not negate the compelling science supporting soluble amyloid oligomers as therapeutic targets. We now have an opportunity to learn from the recent programs and apply these lessons for a more selective and effective approach to preventing amyloid toxicity in AD.

The three critical issues for amyloid-targeted therapies are (1) what is the pathogenic form of amyloid that must be inhibited or removed to slow the disease progression, (2) does the therapeutic agent effectively enter the brain, engage the target, and achieve brain concentrations sufficient to elicit the desired biological response, and (3) what is the optimal study population and stage of the disease that best allow for confirmation of efficacy. We will discuss these issues in the following sections and propose a path forward for successful drug development for AD.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed genetic, biomarker and clinical studies evaluating the role of Aβ oligomers in the pathogenesis of familial and sporadic AD.
2. Interpretation: Soluble Aβ oligomers cause synaptic toxicity and neurodegeneration, and inhibition of formation or removal of soluble oligomers, rather than insoluble fibrils or plaques, is the key to clinical efficacy.
3. Future directions: (A) Development of therapeutic agents highly selective for Aβ oligomers that efficiently cross the blood-brain barrier and achieve sustained brain levels that prevent oligomer toxicity. (B) Development of assays that detect Aβ oligomers in cerebrospinal fluid and their response to therapy. (C) Evaluation of treatments in AD populations enriched with Aβ oligomers, such as carriers of APOE4 genotype. (D) ALZ-801, an oral drug with favorable safety and high brain penetration that fully inhibits Aβ oligomer formation, will be evaluated in Phase 3 trial in patients with early AD who are homozygous for APOE4 genotype.

2 | SHORTCOMINGS OF CLINICAL TRIALS IN AD

The following drug development issues have affected clinical trials in AD, including the recently failed phase 3 programs:

1. Targeting of amyloid species not associated with neurotoxicity – Aβ monomers or plaques
2. Lack of robust and sustained inhibition of soluble Aβ oligomers, which may ultimately prove to be the most important amyloid species involved in events leading to neurodegeneration
3. Poor selectivity of antiamyloid antibodies for neurotoxic soluble Aβ oligomer species versus monomers, insoluble amyloid fibrils, and plaques
4. Poor brain penetration of antiamyloid antibodies as a class, resulting in suboptimal drug levels in the brain, below the sustained levels needed to continuously prevent the formation or effective removal of Aβ oligomers
5. Patient heterogeneity due to concomitant neuropathologies other than amyloid and tau, resulting in higher variability of clinical decline and biomarker changes

For the aforementioned reasons, these failed programs did not provide an adequate test of the amyloid hypothesis and do not invalidate the rationale for therapies selectively directed at Aβ oligomers.

3 | MULTIPLE LINES OF EVIDENCE SUGGEST CENTRAL ROLE OF Aβ OLIGOMERS IN AD PATHOGENESIS

3.1 | Genetic and biomarker data support causative role of amyloid in early- and late-onset AD

The central and early role of amyloid in AD pathogenesis has been confirmed by genetic and biomarker studies in both familial (early-onset) and sporadic (late-onset) AD. Dominant mutations related to processing of the amyloid precursor protein (APP) lead to increased amyloid production and cause early-onset familial AD.[3] Individuals with Down syndrome who have APP gene triplication show excess amyloid production and develop early-onset dementia.[4,5] In contrast, the Icelandic mutation, an APP genetic variant leading to approximately 40% decrease in amyloid production,[6] is associated with decreased AD risk, suggesting that increased Aβ production or its impaired clearance are the initial triggers of AD pathogenesis.

Large genome-wide association studies also show that genetic variants affecting APP and Aβ processing are associated with a high risk for late-onset AD if they increase Aβ monomer production.[7,8] Finally, longitudinal clinical biomarker studies show that the appearance of brain amyloid deposits precedes tau pathology and is required for disease progression and neurodegeneration in patients with AD.[9]

3.2 | Soluble Aβ oligomers are pathogenic forms of amyloid associated with neurodegeneration

The issue of which pathological marker best correlates with clinical progression in AD has been intensely debated over the last 4 decades. In 1968, Blessed et al.[10] reported that neurofibrillary tangles seemed to correlate with clinical symptoms, but not amyloid plaques. This observation has since been reproduced in other data sets. The AD Neuroimaging Initiative data showed that amyloid plaque burden, detected by amyloid positron emission tomography (PET) imaging, does not correlate with clinical progression.[11] However, this observation depends on the form of amyloid being evaluated because the presence of Aβ is a known prerequisite for disease progression.[12]

When Aβ oligomers were isolated from the brains of patients with AD,[13,14] their levels were shown to closely correlate with the onset of disease progression and the severity of clinical symptoms.[15–17] In addition, Aβ oligomers were shown to cause a high degree of synaptic toxicity when compared with other forms of brain amyloid.[18–22] In contrast, Aβ plaque load does not seem to correlate with clinical progression or response to treatments, as suggested by the aducanumab and BAN2401 clinical data. In both aducanumab phase 3 trials the low dose achieved robust plaque reduction but failed to show significant clinical efficacy,[2] suggesting a lack of correlation between amyloid plaque removal and clinical benefit. In the phase 1b PRIME trial of aducanumab, the consistent dose-response on amyloid plaque reduction also did not translate into a dose-response for clinical efficacy.[23] Therefore, amyloid plaque is unlikely to be the correct therapeutic target but may be a protective mechanism by which soluble Aβ oligomers are sequestered to neutralize their toxicity.[18,21] It is plausible that due to the relative lack of selectivity and limited brain penetration of aducanumab, only a sustained exposure to the highest dose reaches sufficient exposure in the brain to reduce soluble Aβ oligomers and lead to clinical efficacy.

3.3 | Osaka and Arctic amyloid mutations provide strong genetic support for the role of Aβ oligomers, rather than plaque, in AD pathogenesis

Several AD groups have elucidated the upstream and early role of Aβ oligomers in the pathogenesis of AD.[15–22] Aβ oligomers derived from postmortem brains of patients with AD have been shown to cause acute synaptic neurotoxicity and inhibition of long-term potentiation, an established model of memory formation.[19,21,22] Aβ oligomers also induce dysregulation of neurotransmitter receptors, in particular the N-methyl-D-aspartate receptor, dystrophy of synapses, and dysfunction of networks in *in vivo* models.[24,25]

The strongest evidence for the crucial pathogenic role of Aβ oligomers in AD comes from two familial mutations that lead to early-onset AD symptoms. The first, the Osaka variant, is an APP mutation associated with enhanced Aβ oligomer production but with very limited plaque pathology; yet, these patients develop early cognitive symptoms of AD dementia.[26] The second, the Arctic variant, is an APP mutation, which leads to increased production of soluble Aβ protofibrils (large oligomers) and early-onset AD symptoms,[27] and it is also associated with low amyloid plaque burden on imaging.[28] The Arctic mutation provided the basis for the development of BAN2401,[29] an antiamyloid antibody directed at soluble protofibrils (i.e., large Aβ oligomers). The stark discrepancy between the increased Aβ oligomer production resulting in toxicity and early disease onset, and the minimal plaque burden associated with these mutations, suggests that the soluble and insoluble amyloid forms may not be in equilibrium in the human brain and that targeting monomers or plaques in patients with AD may not reduce the burden of pathogenic Aβ oligomers.

Compelling evidence for Aβ oligomer toxicity in patients with AD opens new avenues of research and drug discovery,[13,14] and supports the inhibition, or selective removal, of Aβ oligomers as a logical therapeutic approach in AD. With the exception of BAN2401,[29,30] none of the AD immunotherapies evaluated in the late-stage clinical trials are reported to be highly selective for Aβ oligomers over monomers or insoluble fibrils and plaques.[31]

Inhibition of Aβ oligomer formation with a small molecule, or its removal with a selective antibody, is an approach that has shown potentially meaningful efficacy in early-stage trials. Both BAN2401 and ALZ-801/tramiprosate have shown efficacy signals in subgroup analyses of carriers of the apolipoprotein ε4 allele (*APOE4*) with early or mild AD.[30,32,33] APOE4 carriers, especially patients with homozygous APOE4/4 AD, have a high burden of Aβ oligomers,[17,19,34] their cognitive status declines more rapidly,[35,36] and have less variability in their clinical characteristics. ALZ-801/tramiprosate, which inhibits the formation of Aβ oligomers without binding amyloid plaques,[37,38] has excellent brain penetration of approximately 40% of plasma levels.[39] ALZ-801 achieves concentrations in the brains of patients with AD, which were shown to fully inhibit the formation of Aβ oligomers, from dimers to dodecamers, in an *in vitro* assay,[37,39] and may provide the ultimate test of the amyloid oligomer hypothesis.

4 | FAILED PHASE 3 CLINICAL TRIALS WERE DIRECTED AT Aβ MONOMERS OR INSOLUBLE FIBRILS AND PLAQUES

One therapeutic approach has focused on lowering the production of Aβ monomers using BACEi or γ-secretase inhibitors and modulators. Several BACEi drugs, which reduced the production of Aβ monomers by >70%, failed to demonstrate clinical benefits in phase 3 trials in symptomatic and prodromal AD.[40,41] Solanezumab, an antibody designed to clear amyloid monomers from the brain, also failed to show clinical benefit in mild AD.[42] Collectively, these studies suggest that even marked Aβ monomer reduction in the brain is unlikely to be a successful approach for treatment of symptomatic early or prodromal AD. However, lower levels of Aβ monomer reduction that avoid side effects, together with intervention at the presymptomatic stage of AD over an extended period of time, may still be beneficial.

Most antiamyloid antibodies were designed to bind and clear insoluble amyloid plaques. Studies with bapineuzumab, the first amyloid immunotherapy evaluated in phase 3 trials, failed to show clinical efficacy and also showed no significant effects on amyloid PET imaging or cerebrospinal fluid (CSF) Aβ biomarkers.[43] In contrast, the second-generation antiamyloid antibodies, namely aducanumab and BAN2401,[2,23,30] showed reduction and even complete removal of amyloid plaques on PET imaging. Aducanumab has shown significant but modest efficacy in one Phase 3 trial while failing in the second Phase 3 trial.[2] BAN2401 showed preliminary efficacy in a large Phase 2 trial.[30] However, in both of these programs, the dose-response on plaque reduction did not translate into a dose-response on clinical endpoints. BAN2401 is reported to have higher affinity for soluble Aβ protofibrils (large Aβ oligomers) than insoluble fibrils or plaques[29,30] and, indeed, showed lower rates of vasogenic edema in patients with AD. These data suggest that preferential binding of BAN2401 to Aβ oligomers versus plaques may underlie its preliminary, but promising, efficacy signals and lower risk of vasogenic edema in a recently completed phase 2 study.[30] BAN2401 is now being evaluated in a large phase 3 trial. These results further suggest that targeting neurotoxic soluble Aβ oligomers may be the key to therapeutic success.

5 | ANTIAMYLOID IMMUNOTHERAPIES SHOW POOR BRAIN PENETRATION AND HIGH RISK OF VASOGENIC EDEMA

The development of antiamyloid monoclonal antibodies for the treatment of AD has faced substantial challenges with respect to their efficacy and/or safety profiles. As a class, antibody therapies have very limited blood-brain barrier penetration: it is estimated that only <1.5% of an administered dose enters the brain.[23,29,42–45] Antibodies that bind Aβ plaque have a propensity to cause amyloid-related imaging abnormalities with effusion or edema (ARIA-E) and amyloid-related imaging abnormalities with hemosiderin deposits (ARIA-H), particularly in APOE4 carriers who have a higher burden of vascular amyloid.[46] ARIA is likely related to antibody-mediated removal of vascular amyloid, resulting in inflammation and leakage of plasma and/or blood from small vessels in the brain.[46] In addition, most immunotherapies are administered as intravenous infusions, which are inconvenient for patients and may be associated with infusion-related adverse reactions.

In a phase 2 study, BAN2401 showed the largest clinical benefit at the highest administered dose of 10 mg/kg twice a month and the efficacy signal seemed more robust in APOE4 carriers than in noncarriers.[30] However, at this dose, ARIA-E events occurred in approximately 15% of patients and included some serious adverse events.[30] This safety risk led European regulators to prohibit the highest dose in APOE4 carriers, who had the highest incidence of vasogenic edema. Of note, this is the same dose that is being evaluated in a phase 3 AD trial.

The events of ARIA-E and ARIA-H may be asymptomatic in most patients, yet approximately 30% present with clinical symptoms that may include seizures and other serious adverse effects.[23,30] Consequently, the US Food and Drug Administration and the European Medicines Agency require quarterly monitoring with magnetic resonance imaging in clinical trials of antiamyloid antibodies, which adds to the patient burden in these trials. Because the doses of plaque-clearing antibodies that showed preliminary efficacy in phase 2 trials are associated with a higher incidence of vasogenic edema,[2,30] a consistent challenge with these antibodies has been the almost nonexistent therapeutic window, especially in APOE4 carriers. This may limit the use of higher, and potentially more efficacious, doses. In contrast, small molecules such as ALZ-801, which do not bind Aβ plaques,[38] can avoid the risk of ARIA even in APOE4 carriers, allowing higher dosing to achieve the maximum potential efficacy.[33,39]

6 | AD THERAPEUTICS MUST BE EVALUATED IN WELL-DEFINED PATIENT POPULATIONS WITH EARLY DISEASE

Patients with AD are known to have concomitant neuropathologies in addition to amyloid and tau, which may impact their clinical course and response to treatments. In addition, pathologies unrelated to AD may mimic the clinical picture of AD, such as the recently reported limbic-predominant age-related TDP-43 encephalopathy, also called "LATE encephalopathy".[47,48] This heterogeneity contributes to misdiagnosis and high variability in clinical course and biomarker changes in AD trials. To improve the chances of success and provide maximum benefit to patients, it is critical to adopt a precision medicine approach in AD management, similar to the successful approach to drug development that has been applied in oncology. We need to study well-defined AD populations with well-characterized pathology and genetics.

A focus on APOE4 carriers, especially AD patients with homozygous APOE4/4 genotype, is a logical approach because they are known to carry a high burden of Aβ oligomers,[17,19,34] decline more rapidly at the early stages of AD,[35,36] and have less variability in their clinical presentation. Due to this lesser variability, programs that initially focus on APOE4/4 patients may have a higher chance of success. Positive data in trials of APOE4/4 homozygotes may then inform studies in APOE4 heterozygotes and noncarrier AD populations. Because APOE4/4 patients are also at higher risk of developing vasogenic edema with compounds that clear amyloid plaques, agents selective for Aβ oligomers would be ideal for this population.[32] Aβ oligomers are thought to play an upstream role in AD pathogenesis; therefore, efficacy trials should intervene as early as possible in the disease process and initially include patients with symptoms of early or mild AD. This concept extends to even earlier intervention at the presymptomatic stage, as in the current prevention trials in individuals at high risk for AD, namely, carriers of APOE4 genotype and autosomal dominant AD mutations. An oral agent with favorable long-term safety that inhibits neurotoxic Aβ oligomers would be an ideal candidate as a preventive treatment in such high-risk individuals.

7 | ALZ-801 PROGRAM PROVIDES EFFECTIVE TEST OF AMYLOID HYPOTHESIS BY SELECTIVELY AND ROBUSTLY INHIBITING FORMATION OF ALL Aβ OLIGOMERS WITH BRAIN-PENETRANT SMALL-MOLECULE DRUGS

An example of a small-molecule drug that fulfills the aforementioned criteria is ALZ-801. ALZ-801 is an oral agent that selectively and dose-dependently inhibits the formation of neurotoxic soluble Aβ oligomers, from dimers to dodecamers,[37] without affecting insoluble Aβ plaques or fibrils.[38] In addition, the recently described active metabolite of ALZ-801, 3-SPA, has also shown potent antioligomer activity *in vitro* and was found to be endogenously present in the human brain.[49] Multiple molecules of tramiprosate and its active metabolite, 3-SPA, interact reversibly with the Aβ42 monomer at specific sites, preventing its misfolding and stabilizing the monomer in a conformation that prevents its aggregation into Aβ oligomers.[37,49]

ALZ-801 has shown favorable pharmaceutical properties in preclinical and clinical studies. The ALZ-801 tablet shows consistent oral absorption and sustained plasma and CSF levels, with approximately 40% brain penetration at steady state, which is important to achieve the full inhibition of oligomer formation and clinical efficacy.[37,39,49]

Favorable long-term safety of ALZ-801 has been established in more than 1600 patients with AD treated with tramiprosate for up to 1.5 years and in 400 patients treated for up to 2.5 years.[32,33] The main adverse events were mild to moderate nausea and vomiting. The substantially optimized ALZ-801 prodrug provides improved gastrointestinal absorption, tolerability, and brain penetration.[39] Importantly, no ARIA-E was observed in 426 patients in the tramiprosate phase 3 studies, even in APOE4 carriers.[32] Therefore, ALZ-801 has no requirements for magnetic resonance imaging monitoring.

In prespecified subgroup analyses of phase 3 data in mild to moderate AD, tramiprosate showed meaningful clinical effects in APOE4 carriers, especially APOE4/4 homozygotes.[32,33] The preferential efficacy signal of ALZ-801 in this group provides biological plausibility because the APOE4/4 genotype is associated with higher burden of Aβ oligomers in patients with AD than in noncarriers, even with comparable plaque load.[17,19,34] This distinct biology of APOE4/4 patients with AD and the fact that ALZ-801 inhibits Aβ oligomers provide a biological rationale for focusing on APOE4/4 homozygotes in the initial phase 3 trial.

The planned phase 3 study of ALZ-801 will enroll APOE4/4 patients with early AD and will include a single active dose that can achieve targeted CSF drug levels, similar to those achieved in CSF of patients with AD in the tramiprosate trials. These CSF drug levels of ALZ-801/tramiprosate are several times higher than the concentrations needed for the full inhibition of Aβ oligomer formation in the *in vitro* assay.[37,49] The extrapolation from *in vitro* to human studies regarding CSF concentrations of ALZ-801 necessary for full inhibition of formation of Aβ oligomers will be evaluated in the phase 3 study using currently available Aβ oligomer CSF assays, as well as future improved techniques as they become available.

For Aβ oligomer–targeted agents that either inhibit their formation or promote their clearance, the use of a validated CSF Aβ oligomer assay is important to assess target engagement of the selected clinical dose. Several investigational immunoassays of CSF Aβ oligomers that show selectivity to Aβ oligomers over monomers have been developed,[20,50] and one was recently used to evaluate CSF Aβ oligomers from crenezumab phase 2 studies in mild to moderate AD.[51] Using this immunoassay, crenezumab caused ~40–50% decrease in CSF Aβ oligomers in the two antibody arms versus 13% in the placebo arm. Although a higher proportion of patients showed decreased CSF levels of Aβ oligomers in the two active arms, the mean Aβ oligomer concentrations were not significantly different between the active and placebo arms. These results suggest that crenezumab treatment did not provide the necessary reduction of Aβ oligomers and may explain the failure of crenezumab phase 3 trials in early AD. More robust reduction of Aβ oligomers may be required to provide clinical benefit at this stage of the disease.

Several BACEi treatments have been evaluated in patients with AD at doses that produce >50% reduction in standard assays of CSF Aβ40 and Aβ42, which predominantly detect Aβ monomers. A robust reduction in monomeric Aβ would be expected to result in a reduction of oligomeric Aβ; however, no data on CSF Aβ oligomer levels have been reported from the BACEi programs. To date, four BACEi drugs evaluated in late-stage trials showed cognitive worsening during the treatment.[41] One potential explanation for this finding is that alternate forms of N-terminally truncated Aβ may be produced from APP in a β-secretase–independent pathway, as recently reported by two groups.[52–54] These alternate Aβ peptides were reported to form highly toxic Aβ oligomers.[54] Therefore, Aβ oligomer assays for Aβ40 and Aβ42 in BACEi studies may not correlate with clinical benefit for this class of drugs.

A limitation of currently available CSF Aβ oligomer immunoassays is that they use antibodies directed at specific epitopes on Aβ and do not capture all forms of Aβ oligomers.[20,50] The combined use of multiple immunoassays may be needed to provide a more complete assessment of Aβ oligomer burden in patients with AD. Highly sensitive techniques such as ion mobility spectrometry–mass spectrometry provide improved characterization of the full range of Aβ oligomeric species,[37] and the development of Aβ oligomer assays should remain a priority for AD drug development.

8 | CONCLUSIONS

There is a large body of evidence supporting the crucial role of neurotoxic soluble Aβ oligomers, rather than insoluble plaques or monomers, in AD pathogenesis. Candidate drugs directed at Aβ oligomers have a strong scientific and mechanistic rationale based on genetic evidence, neuropathological studies, and data from clinical trials. Selective and sufficient inhibition of neurotoxic Aβ oligomers has not been achieved with any of the antiamyloid antibodies or BACEi programs that have

failed in large phase 3 trials, while agents that effectively target soluble Aβ oligomers have not been evaluated in adequately designed phase 3 trials.

Antiamyloid antibodies have limited brain penetration and may not reach and sustain brain concentrations to effectively remove Aβ oligomers. In contrast, oral agents with good brain penetration can achieve those target brain concentrations. Another advantage of agents that selectively target Aβ oligomers is the lower risk of vasogenic edema and its potential complications. Finally, focusing on APOE4/4 carriers in AD efficacy trials assures patient population that is enriched with Aβ oligomers and has relatively uniform neuropathology, which will decrease variability in clinical and biomarker changes and improve the chance of success.

The aducanumab phase 3 EMERGE trial has provided the first large-scale clinical validation of the biological rationale and utility of targeting amyloid in patients with early AD. BAN2401, an antiamyloid antibody, which preferentially targets soluble Aβ protofibrils (large Aβ oligomers), has also shown preliminary but promising efficacy in a phase 2 trial and is currently in phase 3 testing. ALZ-801, an oral tablet, which fully inhibits formation of Aβ oligomers without plaque binding, has shown promising efficacy signals in prespecified subgroup analyses. Both BAN2401 and ALZ-801 show larger efficacy signals in APOE4 carriers, who have a high burden of Aβ oligomers. The upcoming phase 3 trial with ALZ-801, an agent that can robustly inhibit the formation of neurotoxic Aβ oligomers in the human brain, will enroll APOE4/4 homozygous patients with early AD, therefore, providing an opportunity to effectively test the refined amyloid oligomer hypothesis.

Looking ahead to the future of Aβ oligomer–directed programs, it becomes clear that there is a pressing need for a reliable Aβ oligomer assay to assess the full spectrum of soluble oligomers in CSF, which would serve as a pharmacodynamic marker of the drug effect and target engagement. Such an Aβ oligomer assay will be helpful in screening and selecting drug candidates that show Aβ oligomer inhibition and allow rational dose selection in other AD subpopulations, who may carry a lower oligomer burden, such as APOE4 heterozygotes, noncarriers, and at-risk patients with presymptomatic AD. Based on their Aβ oligomer burden, these patients may require lower doses.

In the face of repeated failures of amyloid immunotherapies and BACEi programs and the large unmet need for safe and effective AD treatments, it is imperative to pursue alternative therapeutic strategies. As the large body of evidence consistently points to soluble Aβ oligomers as upstream culprits in AD pathogenesis, it is logical and prudent to pursue Aβ oligomer inhibitors as potential AD treatments. The probability of success in clinical trials can be further improved by using drug doses that inhibit Aβ oligomers in validated CSF assays and by focusing on APOE4 carriers at the early clinical stages of disease.

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