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RESEARCH ARTICLE

APOLLOE4 Phase 3 study of oral ALZ-801/valiltramiprosate in *APOE* ε4/ε4 homozygotes with early Alzheimer's disease: Trial design and baseline characteristics

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Abstract

INTRODUCTION: The approved amyloid antibodies for early Alzheimer's disease (AD) carry a boxed warning about the risk of amyloid-related imaging abnormalities (ARIAs) that are highest in apolipoprotein E (*APOE*) ε4/ε4 homozygotes. ALZ-801/valiltramiprosate, an oral brain-penetrant amyloid beta oligomer inhibitor is being evaluated in *APOE* ε4/ε4 homozygotes with early AD.

METHODS: This Phase 3 randomized, double-blind, placebo-controlled, 78-week study of ALZ-801 administered as 265 mg twice per day tablets, enrolled 50- to 80-year-old homozygotes with Mini-Mental State Examination (MMSE) ≥ 22 and Clinical Dementia Rating–Global Score 0.5 or 1.0. The study is powered to detect a 2.0 to 2.5 drug–placebo difference on the Alzheimer's Disease Assessment Scale 13-item Cognitive subscale primary outcome with 150 subjects/arm. The key secondary outcomes are Clinical Dementia Rating–Sum of Boxes and Instrumental Activities of Daily Living; volumetric magnetic resonance imaging and fluid biomarkers are additional outcomes.

RESULTS: The APOLLOE4 Phase 3 trial enrolled 325 subjects with a mean age of 69 years, 51% female, MMSE 25.6, and 65% mild cognitive impairment. Topline results are expected in 2024.

DISCUSSION: APOLLOE4 is the first disease-modification AD trial focused on *APOE* ε4/ε4 homozygotes. Oral ALZ-801 has the potential to be the first effective and safe anti-amyloid treatment for the high-risk *APOE* ε4/ε4 population.

KEYWORDS
ALZ-801, Alzheimer's disease, amyloid beta, amyloid beta oligomers, anti-aggregation agents, anti-oligomer agents, apolipoprotein E, apolipoprotein E ε4/ε4 homozygotes, disease modification, valiltramiprosate

Highlights

- The APOLLOE4 Phase 3, placebo-controlled, 78-week study is designed to evaluate the efficacy and safety of ALZ-801 265 mg twice per day in early Alzheimer's disease (AD) subjects with the apolipoprotein E (*APOE*) ε4/ε4 genotype.
- The enrolled early AD population ($N = 325$) has 51% females, a mean age = 69 years, and a mean Mini-Mental State Examination = 25.6, with the majority being mild cognitive impairment subjects, a similar disease stage to the lecanemab Phase 3 AD trial (Clarity AD).
- The primary outcome is the cognitive Alzheimer's Disease Assessment Scale 13-item Cognitive subscale, with two functional measures as key secondary outcomes (Clinical Dementia Rating–Sum of Boxes, Amsterdam-Instrumental Activities of Daily Living), and with hippocampal volume and fluid biomarkers as additional outcomes.
- The study is unique in allowing a large number of microhemorrhages or siderosis at baseline magnetic resonance imaging, lesions that indicate concomitant cerebral amyloid angiopathy (CAA).
- At baseline, 32% of the enrolled population had at least 1 microhemorrhage, 24% had 1 to 4, and 8% had > 4 microhemorrhages; 10% had at least 1 siderosis lesion; with more males than females having microhemorrhages (63% vs. 37%) and siderosis (68% vs. 32%).
- Study results will become available in the second half of 2024 and, if positive, ALZ-801 may become the first oral drug to demonstrate a favorable benefit/risk profile in *APOE* ε4/ε4 AD subjects.

1 | BACKGROUND

The approval of the first wave of anti-amyloid antibodies has ushered in the era of disease modification in Alzheimer's disease (AD), with a new treatment landscape starting to take shape. Over the past decade, a wide range of drug targets has been tested in clinical trials[1]; however, only agents that target amyloid beta (Aβ) have demonstrated clinical efficacy as disease-modifying treatments.[2] The US Food and Drug Administration (FDA) has approved two anti-amyloid antibodies for the treatment of early AD. Aducanumab (aduhelm) received accelerated approval based on its amyloid plaque–clearing effects,[3] but its commercialization was discontinued. Lecanemab (leqembi) received traditional approval based on a positive Phase 3 trial showing ≈ 30% benefit over placebo on composite and cognitive outcomes.[4] A third antibody, donanemab, is under regulatory review based on a Phase 3 trial showing ≈ 35% to 36% benefit on a composite and cognitive outcome in subjects with low–medium tau levels.[5]

The FDA-approved antibodies carry a boxed warning about the risk of amyloid-related imaging abnormalities (ARIAs) with edema (ARIA-E) or hemorrhage (ARIA-H).[6,7] Differences in ARIA risk among these antibodies are likely related to their distinct binding profiles to soluble versus aggregated Aβ species,[8,9] which can explain their unique benefit/risk profiles.[10] Across these antibodies, apolipoprotein E (*APOE*) ε4/ε4 homozygotes are at the highest risk of ARIAs ranging from 33% with lecanemab to 41% with donanemab and 67% with aducanumab.[11]

Elevated ARIA risk in carriers of *APOE* ε4 is related to the higher burden of cerebral amyloid angiopathy (CAA) in *APOE* ε4 carriers and especially in homozygotes,[12] because the *APOE* ε4 genotype is a major risk factor for both AD and CAA. ARIAs are thought to be a manifestation of microglial activation and inflammation induced by antibody binding to amyloid aggregates in leptomeningeal and penetrating cortical arterioles.[13,14] Indeed, a microglial-activating TREM2 antibody was recently associated with symptomatic ARIA in *APOE* ε4/ε4 homozygotes (NCT04592874).[15] *APOE* ε4/ε4 AD patients represent a population with an unmet need for a safe disease-modifying treatment (DMT) that does not induce ARIAs.

1.1 | ALZ-801 mechanism of action—inhibition of Aβ oligomer formation

ALZ-801/valiltramiprosate is a novel small-molecule oral agent being evaluated in early AD patients as a potential DMT. ALZ-801 is a prodrug composed of tramiprosate conjugated to valine, which provides increased oral bioavailability, a more consistent pharmacokinetic profile, and improved gastrointestinal tolerability compared to tramiprosate.[16] Tramiprosate, the active agent in ALZ-801, was

developed as an Aβ anti-aggregation agent, with positive effects in preclinical AD models[17] and showed dose-dependent inhibition of oligomer formation that is mediated by electrostatic interactions between drug and Aβ monomers that stabilize monomers and inhibit their misfolding and aggregation into toxic oligomers.[18]

The ALZ-801 265 mg twice daily (BID) dose used in ongoing studies delivers brain exposures that provide > 90% inhibition of oligomer formation[19] and is bioequivalent to tramiprosate 150 mg BID that showed promising efficacy in *APOE* ε4 carriers.[20,21] A Phase 2 biomarker trial of ALZ-801 in *APOE* ε4/ε4 and *APOE* ε3/ε4 subjects (carriers) showed a significant reduction of plasma phosphorylated tau $(p\text{-tau})_{181}$ starting at 13 weeks and sustained at the 2-year primary endpoint.[22] This was accompanied by significant plasma Aβ42 reduction from baseline at 2 years, suggesting clearance of Aβ42 from brain to plasma.[22] These biomarker effects can be explained by ALZ-801 maintaining Aβ42 in monomeric form and allowing its clearance via the brain's homeostatic pathways.[23]

1.2 | Rationale for focus on *APOE* ε4/ε4 homozygotes with early AD

The APOLLOE4 trial was designed to evaluate ALZ-801 effects in *APOE* ε4/ε4 individuals with mild cognitive impairment (MCI) or mild AD collectively called early AD, to replicate prior efficacy signals from tramiprosate Phase 3 studies. These studies enrolled ≈ 2000 subjects with a clinical diagnosis of mild-to-moderate AD without biomarker confirmation and included all *APOE* genotypes, of which ≈ 65% were *APOE* ε4 carriers. The completed North American trial did not show efficacy, but analysis by *APOE* ε4 genotype showed consistent efficacy signals for *APOE* ε4/ε4 homozygotes.[20,21] The *APOE* ε4/ε4 subgroup with mild AD showed positive dose-dependent effects on two co-primary outcomes, the 11-item Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog11) and the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB) at the high dose (Figure 1), and on the Disability Assessment for Dementia (DAD). Tramiprosate safety across both trials in > 2000 AD patients was favorable but was associated with high rates of nausea and vomiting.[20,21] Incidence and severity of nausea were minimized with the pro-drug valiltramiprosate.[16] No ARIA-E was detected in 426 subjects who had serial magnetic resonance imaging (MRI).[20]

RESEARCH IN CONTEXT

1. **Systematic review**: The currently US Food and Drug Administration (FDA)-approved anti-amyloid antibodies cause amyloid-related imaging abnormalities (ARIAs) that may be symptomatic and serious, with apolipoprotein E (*APOE*) ε4/ε4 homozygotes showing the highest incidence and severity of ARIAs, leading to a boxed warning in their US drug labels. ARIAs are related to the presence of underlying cerebral amyloid angiopathy (CAA). Because *APOE* ε4/ε4 is a risk factor for both Alzheimer's disease (AD) and CAA, *APOE* ε4/ε4 homozygotes have a high burden of CAA that predisposes them to severe and recurrent ARIAs. Therefore, *APOE* ε4/ε4 AD patients have an unmet need for a safe and effective disease-modifying treatment. ALZ-801 is being developed for early AD in *APOE* ε4/ε4 homozygotes as the initial indication.
2. **Interpretation**: The APOLLOE4 Phase 3 study is consistent with the revised FDA guidance for early AD and is designed to detect 2.0 to 2.5 points on the primary cognitive outcome, Alzheimer's Disease Assessment Scale 13-item Cognitive subscale (ADAS-Cog13). This effect will be supported by two key secondary functional outcomes. The disease stage of the APOLLOE4 trial is similar to that of lecanemab with ≈ 65% being at the mild cognitive impairment and 35% at the mild AD stages. Unlike amyloid-antibody trials, APOLLOE4 allows subjects with a large burden of CAA lesions. Compared to ARIA rates in the placebo arm of antibody trials, no increased risk of ARIAs has been detected in the blinded safety reviews to date.
3. **Future directions**: If APOLLOE4 achieves significance on the primary ADAS-Cog13 outcome, this effect will be larger than the effects of approved antibodies, and its clinical meaningfulness will be supported by one of the functional outcomes. Subject-level correlations of clinical effects to imaging and plasma biomarker outcomes could also support a disease-modifying profile. Positive efficacy coupled with favorable safety, no increased risk of ARIAs, and a convenient oral formulation would represent a favorable benefit/risk profile to support regulatory filings. A positive Phase 3 trial could also unlock further development opportunities for *APOE* ε4 carriers with symptomatic and pre-symptomatic AD.

2 | METHODS

2.1 | Study design and inclusion/exclusion criteria

The APOLLOE4 trial design is summarized in Figure 2. Study AD301 is a Phase 3 randomized, double-blind, placebo-controlled, parallel-arm, multicenter study of 78 weeks' duration enrolling *APOE* ε4/ε4 individuals with MCI or mild AD (National Institute on Aging–Alzheimer's Association clinical criteria). The primary outcome is the ADAS 13-item Cognitive subscale (ADAS-Cog13), and two key secondary outcomes are CDR-SB and Amsterdam-Instrumental Activities of Daily Living (A-IADL). The other outcomes are volumetric MRI measures, plasma core AD biomarkers (all subjects), and cerebrospinal fluid (CSF) biomarkers (subgroup). Subjects were ages 50 to 80 years with Mini-Mental State Examination (MMSE) ≥ 22, Clinical Dementia Rating–Global Score

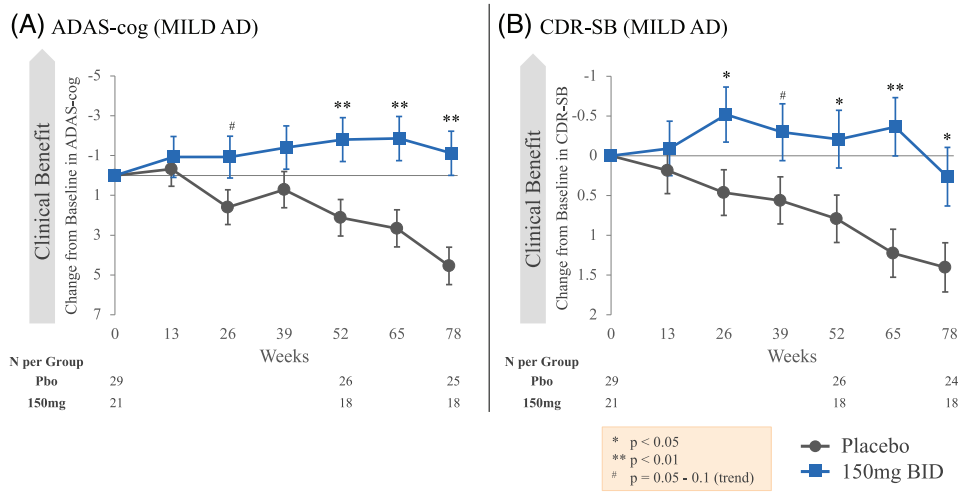

FIGURE 1 Effects of tramiprosate in *APOE* ε4/ε4 mild AD subjects at 78 weeks: subgroup analysis from tramiprosate Phase 3 Trial. Figure from Abushakra 2017 (reprinted with permission), shows the results of MMRM analyses in *APOE* ε4/ε4 group with MMSE 22–26. In the North American Phase 3 trial. Tramiprosate doses: 100 mg BID or 150 mg BID. AD, Alzheimer's disease; ADAS-Cog11, Alzheimer's Disease Assessment Scale-Cognitive subscale; *APOE*, apolipoprotein E; BID, twice per day; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMRM, mixed models for repeated measures; MMSE, Mini-Mental State Examination

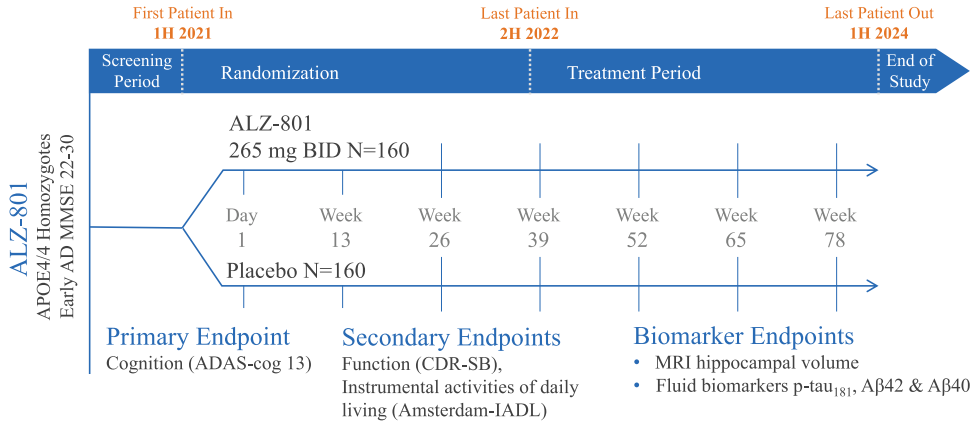

FIGURE 2 ALZ-801 Phase 3 study design in *APOE* ε4/ε4 subjects with early AD (APOLLOE4). *Note*: The study was designed to enroll between 150 and 160 patients per arm, and 325 were actually enrolled. AD, Alzheimer's disease; ADAS-Cog13, Alzheimer's Disease Assessment Scale 13-item Cognitive subscale; A-IADL, Amsterdam Instrumental Activities of Daily Living; *APOE*, apolipoprotein E; BID, twice per day; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging

(CDR-G) = 0.5 or 1.0, and on stable acetylcholinesterase inhibitors (ChEi) or none. Memantine and anticoagulants were not permitted. ARIA-E, large macrohemorrhage, and severe white matter disease (WMD) on MRI were exclusionary.

2.2 | Protocol and informed consent approvals and study conduct

The trial is being conducted under the ALZ-801 IND #125760 at the US FDA, and appropriate clinical trial applications were approved in Canada, the Czech Republic, France, Germany, Iceland, the Netherlands, Spain, and the UK. The trial was approved by a central institutional review board (IRB), country-specific IRB/independent ethics committees (EC), and local IRB/EC as required. The trial is conducted in accordance with the International Council for Harmonization Guideline (ICH) for Good Clinical Practice and all applicable national and local regulatory requirements. Subjects or a subject's legal representative (with subject's assent) provided informed consent (IC), and all caregivers provided their IC for their role as study partners. All informed consent forms were approved by the appropriate IRB/EC.

The sponsor, Alzheon, designed the trial in collaboration with academic advisors, provided the blinded study drug, and provided direct oversight of the clinical research organization and all vendors. The study is being conducted at 78 trial sites across North America and Europe. The study has an independent data and safety monitoring

board (DSMB) that meets every 6 months and reviews unblinded safety data. ADAS-Cog and CDR tests are reviewed by the central ratings group (Medavante-ProPhase) that also provides all rater training, scale translation, and rater oversight. Different raters are assigned for the ADAS-Cog and CDR assessments. MRIs are read and analyzed by central neuroradiologists (Bioclinica/Clario, Inc.). Plasma and CSF samples for biomarker analyses are stored for batched central analyses after the database lock.

2.3 | Outreach to underrepresented populations

There was a dedicated effort in the United States to enroll subjects from underrepresented populations to maximize the diversity, equity, and inclusiveness of the study. Sites were identified in cities with large communities of Hispanics and non-Hispanic Black subjects. We also engaged local referring physicians from these backgrounds to attract individuals from these communities. We identified and included trial sites from smaller cities that attract individuals from surrounding rural areas. Sites were allotted specific budgets to allow wider outreach in their communities. We also reached out to major academic medical centers in metropolitan areas with large ethnically diverse communities (Atlanta, Chicago, Dallas, San Francisco, and San Diego). However, several medical centers had major delays in trial initiation partially due to prioritizing clinical care during the COVID-19 pandemic leading to delays of ≈ 1 year. These challenges impacted enrollment from these communities. Details of screening/randomization and schedule of visits/assessments are provided in the supporting information, Sections 1 and 2.

2.4 | Statistical assumptions, study powering, and subject stratification

The study is powered to detect a 2.0 to 2.5 point difference in the Change from Baseline (CBL) of ADAS-Cog13 between placebo and ALZ-801 at 78 weeks. This assumes a within-treatment standard deviation of approximately ± 8.1 in the ALZ-801 arm and ± 5.6 in the placebo arm. A sample size of 125 subjects per arm provides 80% to 90% power to show this difference at a two-sided significance level of $\alpha = 0.05$. A total of 300 enrolled subjects was projected to provide ≈ 125 completers per arm, assuming a drop-out rate between 17% and 22% over 78 weeks. Randomization was stratified by sex, age (50–65, or > 65 years), disease stage (MMSE ≤ 26 or > 26), and use of ChEi.

2.5 | Efficacy analysis of primary, secondary, and other outcomes

The primary analysis uses the full analysis set (FAS), defined as subjects who provide a baseline efficacy measure, receive at least one dose of the study drug, and provide any post-baseline measure. Analysis of the ADAS-Cog primary outcome, and all clinical efficacy and volumetric imaging (vMRI) outcomes, will use a likelihood-based mixed model for repeated measures on observed cases. Model terms include treatment, stratification factors of age group, sex, baseline MMSE, use of ChEi, measure's baseline value, visit (VISIT), and treatment-by-visit interaction. If ADAS-Cog13 achieves significance, CDR-SB and A-IADL (key secondary outcomes) will be tested at the same hierarchy level with a graphical testing approach to control for Type 1 errors.

Details of the statistical model, vMRI outcomes, fluid biomarkers, and pharmacokinetic analyses are detailed in the supporting information, Sections 3–6.

2.6 | Safety and ARIA analyses

Safety will be evaluated in all subjects who receive a dose of the study drug and include incidence of treatment emergent adverse events, laboratory tests, and MRI findings, including detailed ARIA analyses.

3 | RESULTS

3.1 | Enrolled population characteristics

Approximately 6500 individuals were screened to identify ≈ 650 *APOE* ε4/ε4 homozygotes, of whom 325 fulfilled all inclusion/exclusion criteria, were randomized, and received the study drug. Enrollment started in May 2021 and completed in December 2022. Tables 1 and 2 summarize the baseline demographics and clinical characteristics of the enrolled population, respectively. The APOLLOE4 trial population had a mean age of 69 years, evenly split between females and males, with 91% White and 9% Hispanic or non-White subjects. Approximately 13% of 152 US subjects were Hispanic or non-White, despite instituting outreach strategies to enroll a more diverse population. The modest result of the outreach efforts was partially related to the challenges faced by research sites during the COVID-19 pandemic. More extensive outreach to diverse groups will be planned in future trials. The population's mean MMSE was 25.6, the mean CDR-G was 0.58, the majority (65%) had MCI, 35% had mild AD, and 35% were on ChEi treatment.

Because *APOE* ε4 is also associated with hyperlipidemia and increased cardiovascular disease (CVD) risk, the prevalence of hyperlipidemia and CVD risk factors was analyzed (Table 1). Almost half of enrolled subjects (48%) have hyperlipidemia with 42% and 26% receiving statins and anti-platelet agents, respectively. Hypertension is reported in 38% of subjects with 37% receiving anti-hypertensives.

3.2 | Fluid biomarker and imaging populations

Approximately 310 subjects provided serial plasma samples for biomarkers, and ≈ 45 subjects provided serial CSF samples. A total of 313 subjects were enrolled with MRI scans and 12 had computed tomography scans. The MRI criteria in this study were more

TABLE 1 Enrolled population: demographics, baseline characteristics, and comorbid conditions.

	APOLLOE4 trial Enrolled population N = 325		
Age (years)	68.5 (6.1)	**RBANS-DM**	59 (14)
% Female	51%	**Cholinesterase inhibitor use**	35%
% Non-White or Hispanic	9%	**Statin use**	42%
Years of education	15 (3)	**Antihypertensives**	37%
MMSE at screening	25.6 (2.5)	**Antiplatelet use**	26%
MCI	65%	**Hyperlipidemia**	48%
Mild AD	35%	**Hypertension**	38%
MMSE > 26	39%	**Obesity/BMI > 30 kg/m^2**	14%
MMSE = 22–26	61%	**CAD**	10%
CDR-G	0.58 (0.18)	**Diabetes**	9%

Note: Data are represented by mean (SD) for continuous variables and number (%) for categorical variables.
Abbreviations: AD, Alzheimer's disease; BMI, body mass index; CAD, coronary artery disease; CDR-G, Clinical Dementia Rating–Global Score; MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment; RBANS-DM, Repeatable Battery for the Assessment of Neuropsychological Status-delayed memory index; SD, standard deviation.

TABLE 2 Baseline clinical test scores of enrolled population.

	APOLLOE4 trial Enrolled population N = 325
ADAS-Cog13	24.0 (8.5)
A-IADL-W	16.7 (19.6)
CDR-SB	3.0 (1.5)
ADAS-Cog11	14.8 (6.1)
DAD	36.0 (5.2)
NPI-12 total	5.5 (7.8)
NPI-12 total distress	3.3 (4.7)
QoL-AD informant	38.7 (6.0)
QoL-AD subject	39.5 (5.3)

Note: Data are represented by mean (SD).
Abbreviations: ADAS-Cog11, Alzheimer's Disease Assessment Scale 11-item version; ADAS-Cog 13, Alzheimer's Disease Assessment Scale 13-item Cognitive subscale; A-IADL-W, Amsterdam Instrumental Activities of Daily Living weighted average score; CDR-SB, Clinical Dementia Rating–Sum of Boxes; DAD, Disability Assessment for Dementia; NPI-12, 12-item version of Neuropsychiatric Inventory; QoL-AD, Quality of Life in Alzheimer's Disease; SD, standard deviation.

permissive than amyloid-antibody trials by allowing subjects with any number of microhemorrhages (MHs) and several siderosis lesions. MRI findings that are suggestive of CAA were analyzed and showed a high prevalence of CAA with 32% having > 1 MH, 24% having 1 to 4 MH, 8% having > 4 MH, 4% having > 10 MH, and 10% with siderosis (Table 3). Most subjects (> 90%) have WMD with most showing punctate distribution (Fazekas score 1). WMD prevalence was similar in men and women while CAA prevalence was markedly higher in males for both MH and siderosis (Table 3). The male–female difference in MH prevalence is especially prominent in the moderate and severe categories (5–10 MH and > 10 MH) with 22 men versus 5 women having > 5 MH. The prevalence of siderosis is 68% in men versus 32% in women.

4 | DISCUSSION

The APOLLOE4 Phase 3 trial enrolled subjects at the early symptomatic stage of AD (early AD) similar to the approved antibody lecanemab, but with a larger percentage of MCI subjects and a slightly younger mean age than lecanemab's Phase 3 Clarity AD trial.[4] The ALZ-801 Phase 2 single-arm open-label biomarker study that enrolled *APOE* ε4 carriers (NCT04693520) has a similar mean age and baseline MMSE to APOLLOE4,[22] making the Phase 2 biomarker and clinical data particularly relevant to this Phase 3 trial.

4.1 | Genetically defined AD population

Since the introduction of the A/T/N biomarker framework for AD clinical research,[24] trials of amyloid-targeting DMT now require evidence of amyloid pathology by either amyloid positron emission tomography (PET) scans, CSF, or more recently plasma biomarkers.[25] The *APOE* ε4 allele is the strongest genetic risk factor for sporadic AD, with a single ε4 allele increasing risk 4-fold, and double alleles increasing risk by ≈ 12-fold.[26,27] Not surprisingly, *APOE* ε4/ε4 homozygotes have shown early and accelerated amyloid accumulation at the presymptomatic and early symptomatic stages of AD.[28,29]

In the ALZ-801 Phase 2 trial in *APOE* ε4 carriers with early AD, 31 of 32 screened homozygotes had either low (abnormal) Aβ42/40 ratio, historically positive amyloid PET, or both.[22] In a clinical trial of the amyloid antibody solanezumab, the *APOE* ε4/ε4 mild AD group had positive amyloid PET scans in > 95% of these subjects.[30] Because APOLLOE4 enrolled symptomatic *APOE* ε4/ε4 homozygotes who are expected to

TABLE 3 APOLLOE4 imaging population: baseline prevalence of microhemorrhages (MH), siderosis, and other CAA lesions.

	MRI population *N* = 313	Females *N* = 161 (51%)	Males *N* = 152 (49%)
MH > 0	101 (32%)	37 (37%)	64 (63%)
MH (1–4)	74 (24%)	32 (43%)	42 (57%)
MH 5–10	13 (4%)	1 (8%)	12 (92%)
MH >10	14 (4%)	4 (29%)	10 (71%)
Macrohemorrhages	2 (1%)	0 (0%)	2 (100%)
Superficial siderosis	31 (10%)	10 (32%)	21 (68%)
Periventricular WMD	263 (94%)	135 (51%)	128 (49%)
Deep WMD	256 (92%)	134 (52%)	123 (48%)

Notes: Number of subjects and % of MRI population who had ARIA-H lesions; macrohemorrhage defined as size > 10 mm; majority WMD Fazekas score = 1 (mild). The most common MH location is occipital > frontal. The most common siderosis location is frontal > occipital; the mean lesion size is 1.6 cm. ARIA-E at screening MRI was exclusionary.
Abbreviations: ARIA-E, amyloid-related imaging abnormalities with edema; ARIA-H, amyloid-related imaging abnormalities with hemorrhages; CAA, cerebral amyloid angiopathy; MRI, magnetic resonance imaging; WMD, white matter disease.

have > 95% amyloid positivity, amyloid PET scans were not required for inclusion. The study population is, therefore, simply defined by clinical tests that indicate early symptomatic AD and a blood test for the *APOE ε4/ε4* genotype, which would facilitate its use in clinical practice upon regulatory approval.

4.2 | ADAS-Cog13 as the single primary outcome

A large number of studies underscore the distinct amnestic phenotype of AD in *APOE ε4* carriers, especially in homozygotes. These studies include neuropsychological tests, amyloid PET, tau PET imaging, functional and vMRI,[31–34] and brain/CSF transcriptomic and proteomic profiles.[35] The convergence of these multiple lines of evidence from *APOE ε4* carriers points to accelerated amyloid pathology, hippocampal hypometabolism, early tau deposition with a preference for medial temporal lobes (MTL), and accelerated hippocampal atrophy. This distinct regional pattern of pathology manifests as early and prominent deficits in episodic memory especially affecting delayed memory and word recall.

The ADAS-Cog13 is a comprehensive battery of 13 cognitive domains and skills that include immediate and delayed memory tests (word recall). It is a sensitive measure of hippocampal-dependent memory tasks and is therefore well suited to this population.[36] From a regulatory perspective, designating ADAS-Cog as the single primary outcome in this early symptomatic population is consistent with the FDA guidance on developing treatments for early AD.[37]

4.3 | CDR-SB and IADL as key secondary outcomes

One approach to demonstrating the clinical relevance of cognitive effects is the inclusion of composite and functional outcomes, the CDR-SB[38] and the A-IADL,[39] to investigate the impact of cognitive benefits on daily function. The A-IADL is increasingly used in current AD trials to assess daily activities and includes the use of modern technologies such as computers and cell phones, which is relevant for this relatively younger APOLLOE4 population.[40] The CDR-SB was used as a single composite cognitive/functional outcome in pivotal trials of the approved antibodies[3,4] and their effects can provide a reference point for ALZ-801 efficacy. Of note, the triad of ADAS-Cog, CDR-SB, and IADL show a consistent pattern of drug effects within each trial,[3–5,41,42] and together appear to accurately reflect the degree of clinical efficacy of several antibodies (Figure 3).

4.4 | Imaging and fluid biomarker outcomes

The imaging MRI biomarkers include the assessment of hippocampal atrophy and cortical thickness.[34] Significant drug effects on hippocampal atrophy may indicate neuroprotection and further support the clinical outcomes. The plasma biomarker effects are expected to replicate the ALZ-801 effects on Aβ42 and p-tau$_{181}$ observed in the Phase 2 biomarker study and would indicate target engagement.[22] Because there is longer experience with the CSF assays for AD biomarkers, the CSF biomarker effects on Aβ42, Aβ40, p-tau$_{181}$, and p-tau$_{217}$ in the sub-study will add value for assessing target engagement.

4.5 | Baseline burden of CAA and Phase 3 blinded safety profile

The APOLLOE4 Phase 3 trial is unique in allowing enrollment of subjects with moderate to severe burden of CAA, which together with *APOE ε4* status is a known risk factor for symptomatic or severe ARIAs.[11] The burden of CAA in AD is reported to be influenced by both *APOE ε4* status and sex.[43,44] The majority also had mild WMD, which may be related to deficient glymphatic clearance,[23,45] and a high prevalence of hyperlipidemia and hypertension, which may have contributed to WMD. In APOLLOE4, no symptomatic ARIA events have

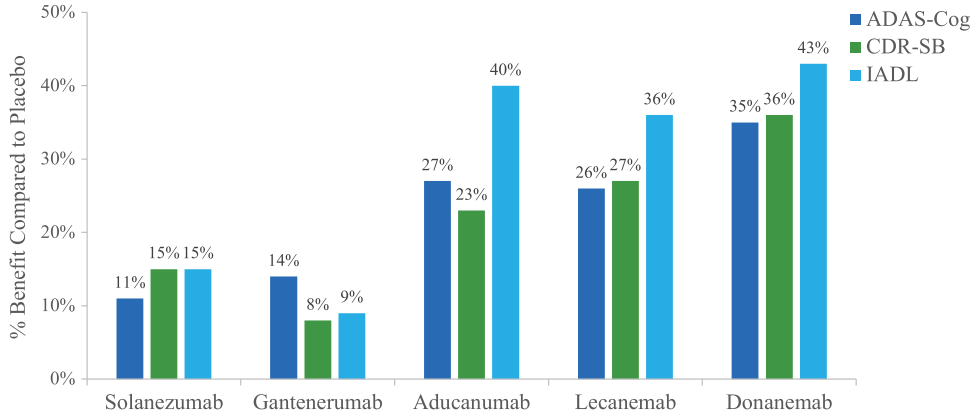

FIGURE 3 Summary of amyloid antibody effects on ADAS-Cog, CDR-SB, and IADL scales in Phase 3 trials in early or mild AD. % Benefit compared to placebo is mean change from baseline/baseline x 100. Solanezumab: Phase 3 trial in mild AD[41]; gantenerumab: average of two Phase 3 Trials in Early AD[42]; aducanumab: data shown for the positive Emerge Phase 3 trial in Early AD[3]; lecanemab Phase 3 Early AD trial[4]; donanemab Trailblazer-2 Phase 3 Early AD Trial, in low-medium tau population[5]. AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SB, Clinical Dementia Rating–Sum of Boxes; IADL, Instrumental Activities of Daily Living

been reported to date. The overall blinded safety profile in the APOLLOE4 trial is similar to the ALZ-801 Phase 2 study and tramiprosate combined safety dataset.[21,22] The most common treatment emergent adverse event in the current ALZ-801 studies is mild nausea.

4.6 | Conclusions and future directions

When the APOLLOE4 results become available later this year, this will be the first completed trial focusing solely on *APOE* ε4/ε4 AD patients. This study is unique in allowing subjects with a large burden of CAA, who would otherwise be at high risk of severe or recurrent ARIAs with amyloid antibodies.[2,10,11] The inclusion of subjects with CAA is possible because ALZ-801/tramiprosate had not shown ARIAs in prior AD studies that included ≈ 1000 *APOE* ε4 heterozygotes and > 250 *APOE* ε4/ε4 homozygotes. Based on the low ARIA risk in *APOE* ε4 carriers and the promising Phase 2 biomarker effects suggesting enhanced brain Aβ clearance, ALZ-801 will be an attractive candidate for CAA patients who have few treatments in development; thus, dedicated CAA studies are warranted.

In the APOLLOE4 Phase 3 trial, statistically significant effects on ADAS-Cog13 accompanied by significant effects on CDR-SB or the Instrumental-ADL would demonstrate that ALZ-801's cognitive benefits can indeed impact daily function and are, therefore, clinically meaningful.

Significant correlations of the plasma (or CSF) biomarker effects including plasma p-tau$_{181}$ and other p-tau isoforms[25,46] to clinical effects may provide valuable insights into the mechanism of ALZ-801 efficacy, while significant correlations of cognitive benefit to slowing of hippocampal atrophy would suggest improved synaptic plasticity or neuroprotective effects. Importantly, the correlations of plasma (or CSF) biomarkers, volumetric imaging, and clinical efficacy outcomes in the placebo arm are likely to provide valuable insights into the unique *APOE* ε4/ε4 biology in AD. These correlations may also identify plasma biomarkers that are harbingers of accelerated pathology and clinical disease progression and can become suitable enrichment biomarkers. Similarly, plasma and/or imaging biomarkers that show robust correlations to ALZ-801 benefits and clinical stabilization may become valuable surrogate outcomes for future trials in pre-symptomatic AD.[47,48] Because pre-symptomatic *APOE* ε4/ε4 homozygotes are at the highest risk of clinical disease progression, the development of preventive treatments for this population is a high priority.

An important consideration for prevention trials in presymptomatic *APOE* ε4/ε4 individuals is the reported influence of racial background on the risk of disease progression, and appropriate trial stratification becomes important. In contrast, the APOLLOE4 trial enrolled subjects who have already showed progressive cognitive decline and disease progression. Nevertheless, the effect of ethnic background on the clinical and biomarker effects of ALZ-801 will be analyzed in this and any future trials. A Phase 3 long-term extension study (AD351, NCT06304883) was initiated to allow subjects completing the core trial to receive active drug for an additional 52 weeks, while subjects and study staff remain blinded to treatment assignment in the core study. In addition to evaluating long-term safety and maintenance of benefits over 2.5 years, the long-term extension will allow an analysis of clinical efficacy with a "delayed-start approach," comparing the active–active arm to the placebo–active arm in the extension study.

The *APOE* ε4/ε4 population constitutes 10% to 15% of the 6.7 million individuals living with AD in the United States alone.[49] *APOE* ε4/ε4 AD patients have a pressing need for an effective and safe treatment that avoids the risk of serious ARIAs and its challenging and burdensome clinical management. Indeed, the unique biological phenotype of *APOE* ε4/ε4 homozygotes was recently highlighted in a meta-analysis of fluid biomarker datasets with clinical–pathologic correlations, showing high prevalence of AD pathology in *APOE* ε4/ε4 individuals at the presymptomatic phase,[50] highlighting the importance of prevention approaches in this AD population.

The APOLLOE4 Phase 3 trial has the potential to demonstrate the meaningful clinical benefits of ALZ-801 with favorable safety and long-term tolerability. ALZ-801 has the additional advantages of a convenient oral formulation, a simple dosing regimen, limited MRI monitoring, and potentially wider accessibility to patients from diverse communities and geographies.

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CONFLICT OF INTEREST STATEMENT

Drs. Susan Abushakra, Aidan Power, Earvin Liang, J. Patrick Kesslak, John A. Hey, Susan Flint, Rosalind McLaine, and Martin Tolar are employees and own stocks or stock options in Alzheon Inc.; Drs. Anton P. Porsteinsson, Marwan Sabbagh, and Merce Boada are advisors to several companies developing AD drugs. Drs. David Watson, Emer MacSweeney, and Merce Boada are investigators in the Phase 3 study and are active investigators in multiple AD clinical trials with various mechanisms of action. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Prior to the start of any study procedures, an informed consent was obtained from all study participants and their study partners.

TRIAL REGISTRATION

An Efficacy and Safety Study of ALZ-801 in APOE4/4 Early AD Subjects (APOLLOE4). Clinicaltrials.gov NCT04770220; EudraCT Number: 2020-005755-20. Sponsor: Alzheon Inc.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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