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ORIGINAL RESEARCH ARTICLE

# Clinical Efficacy, Safety and Imaging Effects of Oral Valiltramiprosate in APOEε4/ε4 Homozygotes with Early Alzheimer's Disease: Results of the Phase III, Randomized, Double-Blind, Placebo-Controlled, 78-Week APOLLOE4 Trial

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## Abstract

**Background** The apolipoprotein E ε4 (APOE ε4) allele is the strongest genetic risk factor for Alzheimer's disease (AD), with homozygotes accumulating a high burden of cerebral beta-amyloid (Aβ) pathology. Valiltramiprosate/ALZ-801 is a small-molecule potent inhibitor of Aβ-oligomer formation. The efficacy, safety/tolerability, and brain volume effects of oral valiltramiprosate were evaluated in this phase III, randomized, double-blind, placebo-controlled, multi-center, 78-week trial in homozygotes with early symptomatic AD.

**Methods** The study enrolled eligible APOE4/4 subjects aged 50–80 years with Early AD (Mini-Mental State Examination [MMSE] 22–30), which included mild cognitive impairment (MCI) and mild dementia, Clinical Dementia Rating—Global Score (CDR-G) of 0.5 or 1, who were randomized 1:1 to valiltramiprosate (265 mg twice/day) or placebo. The primary outcome was AD Assessment Scale—Cognitive Subscale (ADAS-Cog13); the key secondary outcomes were CDR—Sum of Boxes (CDR-SB) and Amsterdam—Instrumental Activities of Daily Living (IADL), and a secondary outcome was Disability Assessment for Dementia (DAD). The main imaging outcome was hippocampal volume on MRI; diffusion tensor imaging (MRI-DTI) assessed microstructural tissue integrity. Amyloid-related imaging abnormalities (ARIA) were monitored with MRIs every 26 weeks.

**Results** A total of 325 participants enrolled and received study drug. At 78 weeks, the overall efficacy population did not show significant effects on ADAS-Cog13 or other clinical outcomes compared with placebo (ADAS-Cog13: 11% slowing; $p = 0.607$, $N = 320$), but showed significant slowing of hippocampal atrophy (18%, $p = 0.017$, $N = 290$). Prespecified analyses by disease severity (stratification variable) showed no significant clinical effects in mild AD (MMSE ≤26, $N = 195$). The prespecified MCI group (MMSE >26, $N = 125$) showed nominally significant positive effects on ADAS-Cog13 (52%, nominal $p = 0.041$) and DAD (96%, nominal $p = 0.016$), positive trend on CDR-SB (102%, nominal $p = 0.053$), with significant hippocampal atrophy slowing (26%, $p = 0.004$), and positive grey/white matter effects on MRI-DTI. In the MCI group, positive ADAS-Cog13 drug effects showed significant subject-level correlations with positive effects on imaging outcomes. The most common adverse events were nausea, vomiting, and decreased appetite (more than double placebo rate), with no increased risk of brain edema or microhemorrhages.

**Conclusions** The APOE4/4 Early AD population did not show significant clinical efficacy at 78 weeks but showed significant brain atrophy slowing. Prespecified analyses at the MCI stage showed nominally significant slowing of clinical decline with significant hippocampal atrophy slowing. Oral valiltramiprosate may provide a favorable benefit–risk profile and simple treatment paradigm for homozygotes with MCI. These results will inform the design of future MCI trials.

**Trial Registration** Clinicaltrials.gov: NCT04770220; EudraCT Number: 2020-005755-20.

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**Key Points**

In the primary analysis of the early Alzheimer's disease (AD) population (combined mild cognitive impairment [MCI] and mild AD), valiltramiprosate/ALZ-801 did not achieve significance on the primary or secondary clinical outcomes but showed significant slowing of hippocampal atrophy compared with placebo.

In the prespecified MCI subgroup, valiltramiprosate showed nominally significant positive effects on cognition (AD Assessment Scale—Cognitive Subscale, ADAS-Cog13) and function (Disability Assessment for Dementia, DAD), positive trend on Clinical Dementia Rating—Sum of Boxes (CDR-SB), with significant slowing of hippocampal and cortical atrophy, and significant subject-level correlations between clinical and imaging outcomes.

The overall safety profile was favorable with mild/moderate nausea as the most common adverse event and no increased risk of amyloid-related imaging abnormalities (ARIA) in this high-risk apolipoprotein E ε4 homozygous (APOE4/4) population.

Consistent with its mechanism of action, inhibiting formation of Aβ oligomers by valiltramiprosate may provide a favorable benefit–risk profile for APOE4/4 MCI patients, to be confirmed in future studies.

## 1 Introduction

Alzheimer's disease (AD) remains the sixth most common cause of mortality in the United States, affecting approximately 7 million Americans, and has an estimated prevalence of approximately 100 million individuals globally [1, 2]. The current biological definition of AD requires positive amyloid and tau biomarkers [3], with beta amyloid (Aβ) being the earliest detected pathology [4–6]. Multiple lines of evidence support the upstream role of neurotoxic soluble Aβ oligomers in AD pathogenesis. Misfolded Aβ oligomers spread through the brain, causing direct injury to neuronal membranes and synaptic impairment [7, 8]. Additionally, Aβ triggers tau hyperphosphorylation and the spreading of tau pathology across the neocortex, leading to neurodegeneration and clinical decline [9–11].

The strongest genetic risk factor for sporadic AD is carrying the ε4 allele of apolipoprotein E (APOE4), which exerts a gene-dose effect, with APOE4/4 homozygotes having a 14-fold higher AD risk [12–14]. Homozygotes carry a high burden of Aβ pathology including oligomers in brain parenchyma and in cerebral vasculature, with accelerated hippocampal atrophy and earlier onset of symptoms [9, 15–17]. APOE4/4 homozygotes are also at highest risk of amyloid-related imaging abnormalities (ARIA) representing brain edema and microhemorrhage with the class of plaque-clearing anti-amyloid antibodies [10, 18].

Valiltramiprosate/ALZ-801 is a novel, brain-penetrant, oral agent that is being evaluated in early symptomatic AD, including in the current phase III trial (ClinicalTrials.gov identifier: NCT04770220) and in a phase II trial in APOE4 carriers (NCT04693520) [19]. Valiltramiprosate is a valine-conjugated prodrug of tramiprosate that was developed to improve the pharmacokinetic variability and gastrointestinal tolerability of its active agent, tramiprosate. Tramiprosate and its sole metabolite, 3-sulfopropionic acid (3-SPA), inhibit Aβ42 aggregation, and stabilize monomers in a conformation that prevents oligomer formation [20, 21]; these findings have been reproduced by multiple independent laboratories [22, 23]. Valiltramiprosate is thought to protect neuronal membranes from the direct Aβ oligomer toxicity that can lead to synaptic dystrophy and axonal injury [7, 8] and is expected to preserve synaptic structure and function and to slow brain atrophy and cognitive decline. Oral tramiprosate was previously evaluated in a phase III trial in approximately 1000 patients with mild to moderate AD that included all APOE genotypes and did not show significant clinical effects at 78 weeks [24], but the MRI substudy showed potential slowing of hippocampal atrophy in APOE4 carriers [25]. The tramiprosate phase III study was conducted before the adoption of a biomarker-based definition of AD [3] and therefore, a large proportion of APOE4 noncarriers and about 20% of APOE4 heterozygotes may not have had amyloid pathology (making these data less informative); in contrast, >95% of APOE4/4 symptomatic individuals were likely to be amyloid-positive and provided informative data for the valiltramiprosate phase III trial design [16, 26]. In the prespecified APOE4/4 subgroup, tramiprosate showed promising dose-dependent cognitive and functional benefits that were largest in the mild subgroup [27, 28]. APOE4 carriers in the tramiprosate study had no ARIA-E events [27]. These data formed the basis for the current AD301 study design evaluating valiltramiprosate in APOE4/4 homozygotes with early AD.

Valiltramiprosate has a distinct mechanism of action that does not require microglial activation and plaque clearance and is not likely to be associated with fluid shifts. Since mean diffusivity on MRI diffusion tensor imaging (DTI) measures extracellular water diffusivity and brain water content, the combination of vMRI and DTI may allow distinction between volumetric drug effects that are due to brain edema versus preservation of neuronal elements.

Two monoclonal anti-amyloid antibodies, lecanemab and donanemab, are approved and marketed in the United States

and several other countries. Both drugs trigger microglial-mediated clearance of Aβ plaque and, to variable degrees, soluble Aβ protofibrils (large oligomers) [10, 29, 30]. Both antibodies have shown significant clinical benefits in their phase III trials in early AD [31, 32], but their clinical use faces challenges, including the risk of symptomatic or serious ARIA, frequent safety monitoring, and the need for infusion centers, limiting access to treatment. Since APOE4 is also a risk factor for cerebral amyloid angiopathy (CAA), the risk of serious ARIA is highest in APOE4/4 homozygotes [10, 18, 33–35]. ARIA rates in APOE4/4 homozygotes are approximately 33% and 41%, respectively, in the lecanemab and donanemab phase III trials [31, 32]. In the United States, both drugs carry safety boxed warnings about the risk of potentially serious ARIA; while in the European Union and United Kingdom, their approvals excluded APOE4/4 homozygotes. Although both amyloid antibodies have reported 8–10% slowing of hippocampal atrophy, there remains uncertainty around the observed increase in whole brain and white matter atrophy with several of the anti-amyloid antibodies [36–38]. Given these challenges, there remains an unmet medical need for effective and safe treatments for APOE4/4 patients with early AD. The early AD population in the current study included both mild cognitive impairment (MCI) and mild AD dementia, similar to the pivotal trials of the anti-amyloid antibodies [31, 32]. The current study in APOE4/4 homozygotes was designed to evaluate the safety and efficacy of valiltramiprosate, replicate the tramiprosate results from homozygotes with mild AD, and extend these findings to the early AD stage [27, 28, 39].

## 2 Methods

### 2.1 Study Design

This randomized, double-blind, placebo-controlled, two-arm, multi-center, 78-week phase III trial was conducted in the US, Canada, UK and six EU countries (Online Resource Table 1, see electronic supplementary material [ESM]). Trial design with the schedule of visits and enrollment per country are shown in the ESM (Online Resource Fig. 1 and Table 1). The trial schedule consisted of a screening visit, a second screening/baseline visit, and clinic visits with efficacy and safety assessments at 13-week intervals up to Week 78. The first safety visit occurred at Week 6 with a final safety follow-up visit at Week 82 (after 4 weeks off study drug). Unscheduled visits or telephone visits occurred if needed for safety reasons. Participants were randomized 1:1 to receive treatment with oral valiltramiprosate tablets, 265 mg twice daily (BID) or matching placebo for 78 weeks. There was a 2-week titration period from daily to BID dosing. The rationale for focus on the APOE4/4 AD population, the trial design, and outcome measures of the current APOLLOE4 trial were presented in a recent publication [39]. The design of this phase III trial is consistent with the current regulatory guidance from the US FDA for Early AD trials [40].

### 2.2 Study Population, Inclusion/Exclusion Criteria

This study enrolled male and female participants aged 50–80 years, with a clinical diagnosis of AD, who carried the APOE4/4 genotype, and who were at the early stage of disease (early AD), which includes MCI and mild dementia due to AD (mild AD). Participants were required to have a screening Mini-Mental State Examination (MMSE) score of 22–30, a Clinical Dementia Rating Scale—Global Score (CDR-G) of 0.5 or 1, a CDR—Memory Box score ≥0.5, a Repeatable Battery for the Assessment of Neuropsychological Status delayed memory index (RBANS-DM) ≤85, evidence of progressive memory loss over the previous 12 months, and a brain MRI that is consistent with MCI or AD. Participants were required to have appropriately treated and stable medical conditions or to be in good medical health to be able to participate in all study procedures. Participants were required to have acceptable hematology/chemistry/coagulation laboratory tests, normal TSH and B12 levels, and glomerular filtration rate (GFR) ≥40 mL/min. For participants receiving symptomatic acetylcholinesterase inhibitors (AChEi) prior to randomization, the dose had to be stable for at least the prior 3 months and to remain stable throughout the study. Main exclusion criteria were other neurodegenerative or psychiatric disorders, seizures within the last 10 years, cerebral infarct or transient ischemic attack within the last year, untreated major depression, and inadequately treated or unstable medical conditions. The exclusionary brain MRI findings included tumors, vascular malformations, cortical infarcts, more than two lacunar infarcts (each >1.5 cm), confluent white matter disease (Fazekas score >2), ARIA-E, macrohemorrhage >1 cm, and more than three superficial siderosis lesions (the latter required discussion with the Sponsor). Any number of microhemorrhages (≤1 cm) were allowed, thus participants with lesions consistent with CAA were allowed. Amyloid PET or AD fluid biomarkers were not required for enrollment, since symptomatic APOE4/4 patients have high rates of amyloid positivity [16, 17, 26].

### 2.3 Prohibited Medications

Anti-amyloid antibody use in the prior 6 months or lifetime use of any anti-amyloid vaccines were exclusionary. Prohibited medications included memantine, anticoagulants, CNS-penetrant anti-cholinergic agents, atypical anti-psychotics, and anti-epileptics (the exception was low doses of the latter two medications when used for sleep).

**Table 1** Demographic and baseline characteristics of safety population

| Characteristic | Valiltramiprosate ($N = 163$) | Placebo ($N = 162$) |
|---|---|---|
| Age, mean ± SD (years) | 68.4 ± 6.4 | 68.5 ± 5.9 |
| Sex, female, *n* (%) | 85 (52) | 82 (51) |
| Race, White, *n* (%) | 144 (88) | 145 (90) |
| Ethnicity, non-Hispanic/Latino, *n* (%) | 147 (90) | 141 (87) |
| Body mass index, mean ± SD ($kg/m^2$) | 25.8 ± 4.0 | 25.2 ± 4.5 |
| Diagnosis, MCI[a], *n* (%) | 67 (41) | 60 (37) |
| Acetylcholinesterase inhibitor use | 54 (33) | 62 (38) |
| MMSE[b], mean ± SD | | |
| Screening (Visit 1a) | 25.69 ± 2.55 | 25.52 ± 2.39 |
| Randomization (Visit 2)* | 25.34 ± 3.14 | 24.73 ± 3.49 |
| ADAS-Cog13[c], mean ± SD | 23.54 ± 8.30 | 24.31 ± 8.79 |
| CDR-SB[d], mean ± SD | 3.04 ± 1.53 | 2.97 ± 1.45 |
| Imaging parameters, mean ± SD | | |
| Bilateral hippocampal volume, (μL or $mm^3$) | 7067.3 ± 1035.1 | 6998.1 ± 990.5 |
| Cortical thickness, whole brain (mm) | 2.41 ± 0.10 | 2.41 ± 0.12 |
| Whole brain volume (mL) | 1078.4 ± 120.0 | 1069.4 ± 107.6 |
| Ventricular volume (mL) | 40.2 ± 21.5 | 42.4 ± 21.9 |
| Plasma biomarkers[e], mean ± SD | | |
| Aβ42/40 (pg/mL) | 0.053 ± 0.01 | 0.053 ± 0.01 |
| p-$tau_{181}$ (pg/mL) | 29.9 ± 30.25 | 31.5 ± 18.10 |
| Concomitant medications, *n* (%) | | |
| Lipid-modifying agents | 77 (47.2) | 81 (50.0) |
| Drugs used in diabetes | 7 (4.3) | 16 (9.9) |
| Antihypertensive agents | 60 (36.8) | 59 (35.2) |
| Renin-angiotensin agents | 51 (31.3) | 45 (27.8) |
| β-blocking agents | 27 (16.6) | 15 (9.3) |
| Calcium channel blockers | 19 (11.7) | 21 (13.0) |
| Diuretics | 11 (6.8) | 11 (6.7) |
| Other antihypertensives | 4 (2.5) | 2 (1.2) |

The safety population included all randomized participants who received at least one dose of valiltramiprosate or placebo. Values of *n* represent number of participants, and percentages were calculated using treatment group *N*

*ADAS-Cog13* Alzheimer's Disease Assessment Scale-cognitive subscale 13 item, *CDR-SB* Clinical Dementia Rating—Sum of Boxes, *MCI* mild cognitive impairment, *MMSE* Mini-Mental State Examination

[a]Mild cognitive impairment was defined as an MMSE score of 27–30. The MMSE ranges from 0 to 30; with higher scores indicating better cognition

[b]The screening period included 2 visits to ensure participant eligibility (Online Resource Fig. 1, see electronic supplementary material). A maximum of 13 weeks was allowed for the screening period (between Visit 1a and Visit 2)

[c]The 13-item ADAS-Cog13 total score ranges from 0 to 85; higher scores indicate greater impairment

[d]The CDR-SB total score ranges from 0 to 18; higher scores indicate greater impairment

[e]Plasma biomarker values that indicate amyloid positivity for the Quanterix assays are Aβ42/40 level <0.07 and p-tau181 >14.2 pg/mL

*The difference in MMSE at randomization was significant ($p = 0.041$)

## 2.4 Randomization, Block Size, Blinding and Compliance

Randomization occurred via an Interactive Response Technology (IRT) system, with a block size of four per study site. Randomization was stratified by use of AChEi (yes, no), age (50–65 years or >65 years), sex, and disease severity based on the MMSE (score ≤26 or >26). All of the site, Contract Research Organization (CRO), and Sponsor staff remained blinded to treatment allocation. No unblinding occurred during the study, except for the safety reviews by the independent safety monitoring board (DSMB) members as described in the ESM. The study drug was provided in blister packs and first dose administered under clinic staff supervision.

At the baseline and all post-baseline visits, participants and their caregivers/study partners were counseled on the target to achieve 100% compliance with study drug and to inform clinic staff if dosing had to be interrupted. Compliance was assessed and recorded at each visit by returned tablet counts. Any deviations from the prescribed dosage or drug interruptions were recorded. Samples for pharmacokinetic analysis of study drug levels were collected at each visit and analyzed after the database lock and unblinding of treatment allocation.

### 2.5 Clinical Outcomes

The primary clinical efficacy outcome was the 13-item Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog13). The two key secondary outcomes were the CDR—Sum of Boxes (CDR-SB), a cognitive/functional composite, and the functional Amsterdam—Instrumental Activities of Daily Living weighted average (A-IADLw). Higher scores on these three outcomes indicate greater deficits. The functional Disability Assessment for Dementia (DAD, used in tramiprosate trials) was a secondary outcome, where lower scores on DAD indicate greater deficits. Additional clinical outcomes included the cognitive ADAS-Cog11 and MMSE. Lower scores on MMSE indicate greater deficits.

### 2.6 Imaging Biomarker Outcomes

Imaging biomarkers included volumetric magnetic resonance imaging (vMRI) assessments at baseline and weeks 26, 52, and 78. On vMRI, bilateral hippocampal volume (HV) was the prespecified main imaging outcome, with cortical thickness as secondary, and ventricular volume and whole brain volume as additional imaging outcomes. The vMRI assessments of brain volumes were complemented with diffusion tensor imaging (MRI-DTI) to assess grey and white matter microstructural integrity at the same vMRI timepoints [5, 41, 42]. On DTI, mean water diffusivity (MD) in the grey and white matter were the prespecified DTI outcomes, with an increase in MD indicating worsening microstructural integrity. The vMRI and DTI analyses were conducted by Clario Inc.

### 2.7 Fluid Biomarkers

Fluid biomarkers included assessments of plasma biomarkers in all subjects at each visit and included Aβ42, Aβ40, p-tau$_{181}$, p-tau$_{217}$, GFAP, and NfL. Drug effects on plasma biomarkers including NfL effects and their correlations with drug effects on clinical and imaging outcomes were prespecified analyses. A CSF sub-study was planned to include CSF samples at baseline, 52, and 78 weeks in 80–100 participants. Serial assessments of the core AD plasma biomarkers (Aβ42, Aβ40, p-tau$_{181}$, p-tau$_{217}$) are currently in progress and will be reported in a future publication.

### 2.8 Safety and Safety Imaging

Safety was assessed by incidence of treatment-emergent adverse events (TEAEs) and changes in laboratory tests and ECG over 78 weeks. Safety monitoring for ARIA included safety MRI every 26 weeks using FLAIR and T2* sequences that were assessed by a central neuroradiologist (Clario Inc). Details on the imaging methods are provided in the ESM and the phase III design publication [39].

### 2.9 Trial Conduct and Safety Oversight

The trial was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization (ICH) guidelines for human research and all applicable national/local regulatory requirements. Central and local institutional review board/independent ethics committees approved the protocol and written informed consent forms. All participants, their legal representative (with participant assent), and trial partners/caregivers provided written informed consent. The Sponsor, Alzheon, designed the trial, provided trial drug, oversaw its conduct, and analyzed the data. An independent DSMB reviewed unblinded safety data every 6 months through closed safety meetings (no Sponsor or CRO staff involved), provided recommendations to the Sponsor, and reviewed the final safety data at the end of trial.

### 2.10 Statistical Methods

The study was designed to detect a statistically significant difference in the change from baseline (CBL) between the placebo and active arms on the primary clinical outcome, ADAS-Cog13, at a 2-sided $\alpha = 0.05$ at 78 weeks. The sample size estimation was based on data from the APOE4/4 mild AD subgroup of the tramiprosate phase III study that showed ~ 4.5 benefit versus placebo on the ADAS-Cog at 78 weeks [27]. A more conservative estimate was that ADAS-Cog13 would show a difference in CBL between the active and placebo arm of 2.0 to 2.5 points, with standard deviations of 8.1 and 5.6, respectively. A sample size of 125 participants per arm provided 80–90% power to show this difference at a 2-sided $\alpha = 0.05$. Assuming an early termination rate of 22%, a sample size of ~320 subjects with 125 completers/arm provided this power.

The primary efficacy population was the full analysis set (FAS), which included participants with a baseline and postbaseline efficacy measure. The primary analysis utilized a Mixed-Effect Model Repeated Measure (MMRM) model with fixed-class effect terms for sex, age group,

treatment group, disease severity (screening MMSE), use of concomitant Alzheimer's disease medications, visit, treatment-by-visit interaction, and baseline ADAS-Cog13 by treatment-by-visit interaction as covariates. The other endpoints included each measure's baseline score as covariate. Model diagnostics were performed to select either a linear or quadratic baseline term for the interaction between baseline, treatment, and visit. The MMRM model included conservative imputations for post-baseline missing data. For clinical and vMRI outcomes, the percent slowing of clinical decline or atrophy versus placebo presented in Table 2 is calculated as follows: $(-1) \times$ [Active–Placebo Difference] / [Absolute Value of Placebo Least Squares Mean (LSM) estimate] $\times$ 100. The final statistical analysis plan (SAP) specified that the key secondary endpoints, CDR-SB and A-IADLw, would be tested at the same hierarchy using the graphical approach [32, 43], with a significant effect ($p < 0.05$) achieved on either CDR-SB or A-IADL-w considered a success.

Subject-level correlations between clinical/imaging outcomes and clinical/plasma biomarker outcomes were prespecified and conducted on the CBL of a clinical outcome to CBL of the imaging or biomarker outcome at 78 weeks or the specified 26 or 52-week timepoint. The CBL for each outcome was from the MMRM model (unless specified otherwise) and used Spearman's or Pearson's correlation coefficients. Description of the imaging methods and statistical model is provided in the Online Resource (Supplementary Information, see ESM).

## 3 Results

### 3.1 Participants

A total of 6554 individuals were screened after signing informed consent at 98 sites in North America, UK, and Europe (Fig. 1). Initial screening identified 598 homozygotes with MMSE 22–30, of whom 325 fulfilled the other eligibility criteria and were randomized at 77 sites (Online Resource Table 1, see ESM). The study enrolled 325 participants, with 162 and 163 participants, respectively, in the placebo and valiltramiprosate arms who received trial drug (safety population), of whom 158 and 162 constituted the efficacy FAS, and 148 and 132, respectively, completed the study. Study discontinuation rates were 9% in the placebo and 19% in the active arm. The overall safety population was approximately 52% female, had a mean age of 68.5 years, mean MMSE of 25.6, approximately 39% with MCI and 61% with mild AD, and ~36% were on AChEi treatments. The overall baseline ADAS-Cog13 and CDR-SB were 23.9 and 3.00, respectively. Lipid-lowering agents were the most commonly used concomitant medications (~49% overall). The treatment arms showed similar demographics and baseline characteristics except for the randomization MMSE, which was lower (more impaired) in the placebo arm ($p = 0.042$), and the percent use of AChEi, which was numerically higher in the placebo arm (Table 1). The mean baseline levels of plasma Aβ42/40 (ratio = 0.053) and p-tau$_{181}$ (~31 pg/mL) shown in Table 1 confirmed the positive amyloid status of the trial population [3].

### 3.2 Clinical Endpoints

In the overall efficacy population (FAS), the primary analysis of the ADAS-Cog13 did not show significant differences between the CBL of the placebo and active arms at the 78-week endpoint (Table 2). The baseline ADAS-Cog13 mean scores in the FAS were 24.32 in the placebo arm and 23.58 in the valiltramiprosate arm, and both arms showed initial numerical improvement compared with their baselines at 13 and 26 weeks but worsened below baseline at 52 and 78 weeks (Fig. 2a). The active arm showed numerical benefit compared with placebo at 52 weeks ($p = 0.135$) but at 78 weeks the difference favoring the drug became small and non-significant (CBL LSM = −0.50, [95% CI −2.43 to +1.42]; $p = 0.607$), representing 11% slowing of cognitive decline compared with placebo. Since the primary clinical outcome did not achieve significance ($p < 0.05$), all subsequent $p$-values for the clinical scores are considered nominal, and were not adjusted for multiplicity testing.

The effects on the other clinical outcomes in the overall FAS are shown in Table 2 and in Fig. 2, panels b–d. In the FAS, the CDR-SB at 78 weeks worsened (increased) by +1.36 points in placebo and by +1.05 in the active arm (LS mean diff. 0.31 [95% CI −0.91 to +0.29]; nominal $p = 0.309$). The DAD worsened (decreased) from baseline by −9.2 points in placebo and −6.5 points in the active arm (LSM difference, 2.63 [95% CI −2.14 to +7.40]; nominal $p = 0.279$). These drug effects on CDR-SB and DAD represented, respectively, 23% and 29% slowing of functional decline versus placebo, but were not statistically significant. The A-IADLw showed no placebo–valiltramiprosate difference. Drug effects on these clinical outcomes were similar between the study regions (North America and Europe).

A prespecified analysis was performed based on the stratification variable of disease severity based on screening MMSE (MCI 27–30; mild AD ≤26; Table 2). The demographics and baseline characteristics of the MCI and mild AD subgroups are shown in Online Resource Table 2 (see ESM), and show an imbalance in the proportion of MCI subjects using AChEi drugs (higher in placebo arm). Trajectories of clinical outcomes in the prespecified MCI population are shown in Fig. 2, panels e–h. In the 125 participants with MCI (Table 2), the ADAS-Cog13 worsened (increased) by +4.10 in placebo and +1.97 in the active arm, showing a nominally significant drug–placebo difference which favored valiltramiprosate

**Table 2** Effects of valiltramiprosate on clinical and volumetric imaging outcomes at 78 weeks in overall population, MCI and mild Alzheimer's disease subgroups

| Clinical endpoints | | | | vMRI endpoints | | | |
|---|---|---|---|---|---|---|---|
| Endpoint | LSM difference (95% CI) | *p*-Value | % Slowing vs placebo | Endpoint | LSM difference (95% CI) | *p*-Value | % Slowing vs placebo |
| **Overall population (Drug, *N* = 162; Placebo, *N* = 158)** | | | | **Overall population (Drug, *N* = 145; Placebo, *N* = 145)** | | | |
| ADAS-Cog13[a] | −0.504 (−2.43, 1.42) | 0.607 | +11% Favors drug | HV,[c] µL or $mm^3$ | +74 (13, 134) | 0.017 | +18% Favors drug |
| CDR-SB[a] | −0.312 (−0.914, 0.291) | 0.309 | +23% Favors drug | CT-WB,[c] mm | +0.012 (0.005, 0.020) | 0.002 | +20% Favors drug |
| DAD[b] | +2.629 (−2.14, 7.40) | 0.279 | +29% Favors drug | WBV,[c] µL | +2821 (130.25, 5511.80) | 0.040 | +16% Favors drug |
| A-IADLw[a] | +0.011 (−5.58, 5.60) | 0.997 | 0% Favors placebo | VV,[d] µL | −1157 (−1879, −435) | 0.002 | +22% Favors drug |
| **MCI (Drug, *N* = 67; Placebo, *N* = 58)** | | | | **MCI (Drug, *N* = 61; Placebo, *N* = 52)** | | | |
| ADAS-Cog13 | −2.144 (−4.20, −0.087) | 0.041 | +52% Favors drug | HV,[c] µL or $mm^3$ | +108 (34, 182) | 0.004 | +26% Favors drug |
| CDR-SB[a] | −0.646 (−1.30, 0.009) | 0.053 | +102% Favors drug | CT-WB,[c] mm | +0.020 (0.011, 0.030) | <0.0001 | +35% Favors drug |
| DAD[b] | +6.093 (1.14, 11.05) | 0.016 | +96% Favors drug | WBV,[c] µL | +3844 (448, 7240) | 0.027 | +22% Favors drug |
| A-IADLw[b] | −3.408 (−9.45, 2.64) | 0.268 | +70% Favors drug | VV,[d] µL | −1312 (−2171, −453) | 0.003 | +29% Favors drug |
| **Mild AD (Drug, *N* = 95; Placebo, *N* = 100)** | | | | **Mild AD (Drug, *N* = 85; Placebo, *N* = 92)** | | | |
| ADAS-Cog13[a] | +0.874 (−1.13, 2.88) | 0.391 | −18% Favors placebo | HV,[c] µL or $mm^3$ | +51 (−12, 115) | 0.115 | +12% Favors drug |
| CDR-SB[a] | +0.127 (−0.490, 0.745) | 0.685 | −7% Favors placebo | CT-WB,[c] mm | +0.007 (−0.001, 0.015) | 0.099 | +11% Favors drug |
| DAD[b] | −0.533 (−5.47, 4.41) | 0.832 | −5% Favors placebo | WBV,[c] µL | +2164 (−704, 5032) | 0.139 | +12% Favors drug |
| A-IADLw[a] | +3.653 (−2.17, 9.48) | 0.218 | − 20% Favors placebo | VV,[d] µL | −1057 (−1816, −298) | 0.007 | +19% Favors drug |

Data were analyzed using a mixed-effect model repeated measure model in the full analysis set (all participants who provided a baseline and postbaseline efficacy measure) for clinical endpoints or in the imaging biomarker population (all participants who had an evaluable baseline vMRI scan, received at least one dose of trial treatment, and had at least one evaluable postbaseline vMRI assessment) for the vMRI endpoints

*ADAS-Cog13* Alzheimer's Disease Assessment—cognitive subscale 13 item, *A-IADLw* Amsterdam—Instrumental Activities of Daily Living weighted average, *CDR-SB* Clinical Dementia Rating—Sum of Boxes, *CI* confidence interval, *CT-WB* cortical thickness whole brain, *DAD* Disability Assessment for Dementia, *HV* hippocampal volume, *LSM* least squares mean, *MCI* mild cognitive impairment, *vMRI* volumetric magnetic resonance imaging, *VV* ventricular volume, *WBV* whole brain volume

[a]For the ADAS-Cog13, CDR-SB, and A-IADLw, a negative value for the LSM difference indicates benefit, and a positive value for percent slowing favors drug (valiltramiprosate). A positive value for the LSM difference indicates worsening and a negative value for percent slowing favors placebo

[b]For the DAD, a positive value for the LSM difference indicates benefit and a positive value for percent slowing favors drug (valiltramiprosate). A negative value for the LSM difference indicates worsening and a negative value for percent slowing favors placebo

[c]For HV, CT-WB, and WBV, a positive value for the LSM difference indicates benefit and a positive value for the percent slowing favors drug (valiltramiprosate)

[d]For VV, a negative value for the LSM difference indicates benefit and a positive value for the percent slowing favors drug (valiltramiprosate)

(CBL LSM difference: −2.14; 95% CI −4.20 to −0.09; nominal $p = 0.041$) and represented 52% slowing of cognitive decline compared with placebo. In this group, CDR-SB worsened (increased) by +0.63 in placebo and improved slightly (decreased) by −0.02 in the active arm with drug–placebo LSM difference of −0.65 (nominal $p = 0.053$). The DAD scores worsened (decreased) by −6.30 in placebo and by −0.2 points in the active arm with drug–placebo LSM difference of 6.09 (nominal $p = 0.016$). These valiltramiprosate effects on CDR-SB and DAD represented 102% and 96% slowing, respectively, of functional decline on drug compared with placebo. The A-IADLw drug effect directionally favored drug, representing 70% slowing of functional decline versus placebo, but was not significant (CBL LSM difference −3.41; nominal

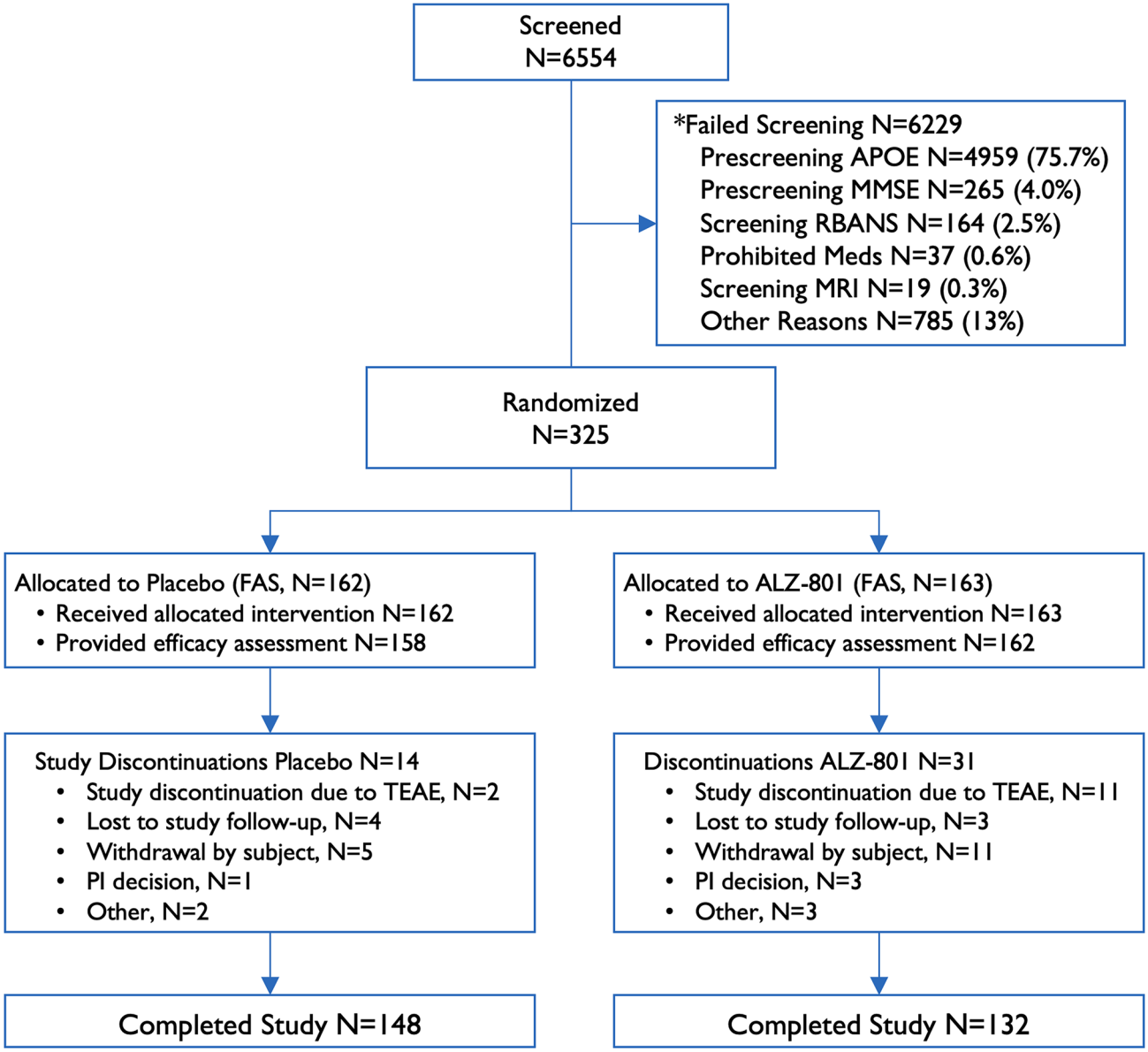



**Fig. 1** CONSORT diagram of participant disposition. *ALZ-801* valiltramiprosate, *APOE* apolipoprotein E, *FAS* full analysis set, *Meds* medications, *MMSE* Mini-Mental State Examination, *MRI* magnetic resonance imaging, *PI* principal investigator, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *TEAE* treatment-emergent adverse event

$p = 0.268$). These clinical outcomes in mild AD showed effects favoring placebo that were small and not statistically significant (Online Resource Fig. 2 panels a–d, see ESM).

Since AD pathology and symptoms occur on a continuum rather than in discrete stages, and valiltramiprosate targets soluble amyloid species that play a role early in the pathophysiological cascade, a pre-planned sensitivity analysis was conducted to evaluate progressively earlier disease stages based on the screening MMSE. In this FAS sensitivity analysis (Fig. 3), drug effects on ADAS-Cog13, CDR-SB, and DAD showed a progressive increase in the magnitude of drug effects at the earlier disease stages. On ADAS-Cog13, valiltramiprosate showed a positive trend with $p < 0.1$, starting at MMSE 26–30 with a placebo-adjusted drug effect of 1.84 ($p = 0.067$), that is larger than the 1.5–1.7 points achieved with the approved amyloid antibodies [31, 32]. On the CDR-SB, valiltramiprosate showed a positive trend starting at MMSE 24–30 with a placebo-adjusted drug effect of 0.52 ($p = 0.090$) that is larger than the ~0.5 points achieved with lecanemab [31]. Similarly, starting at MMSE 24–30, the DAD showed a positive trend favoring drug by 4.50 points (nominal $p = 0.039$). For the DAD, a drug effect of 4

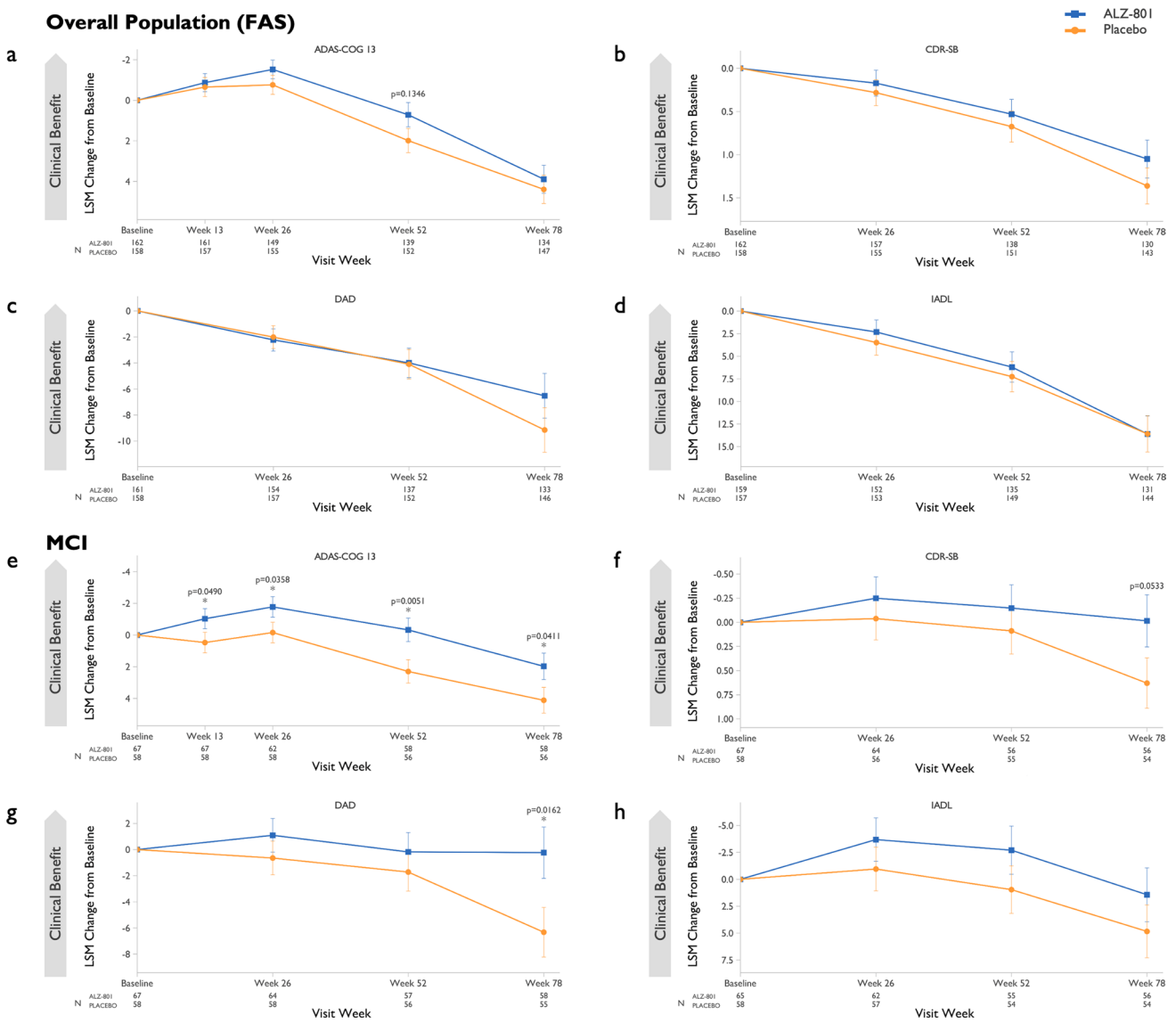


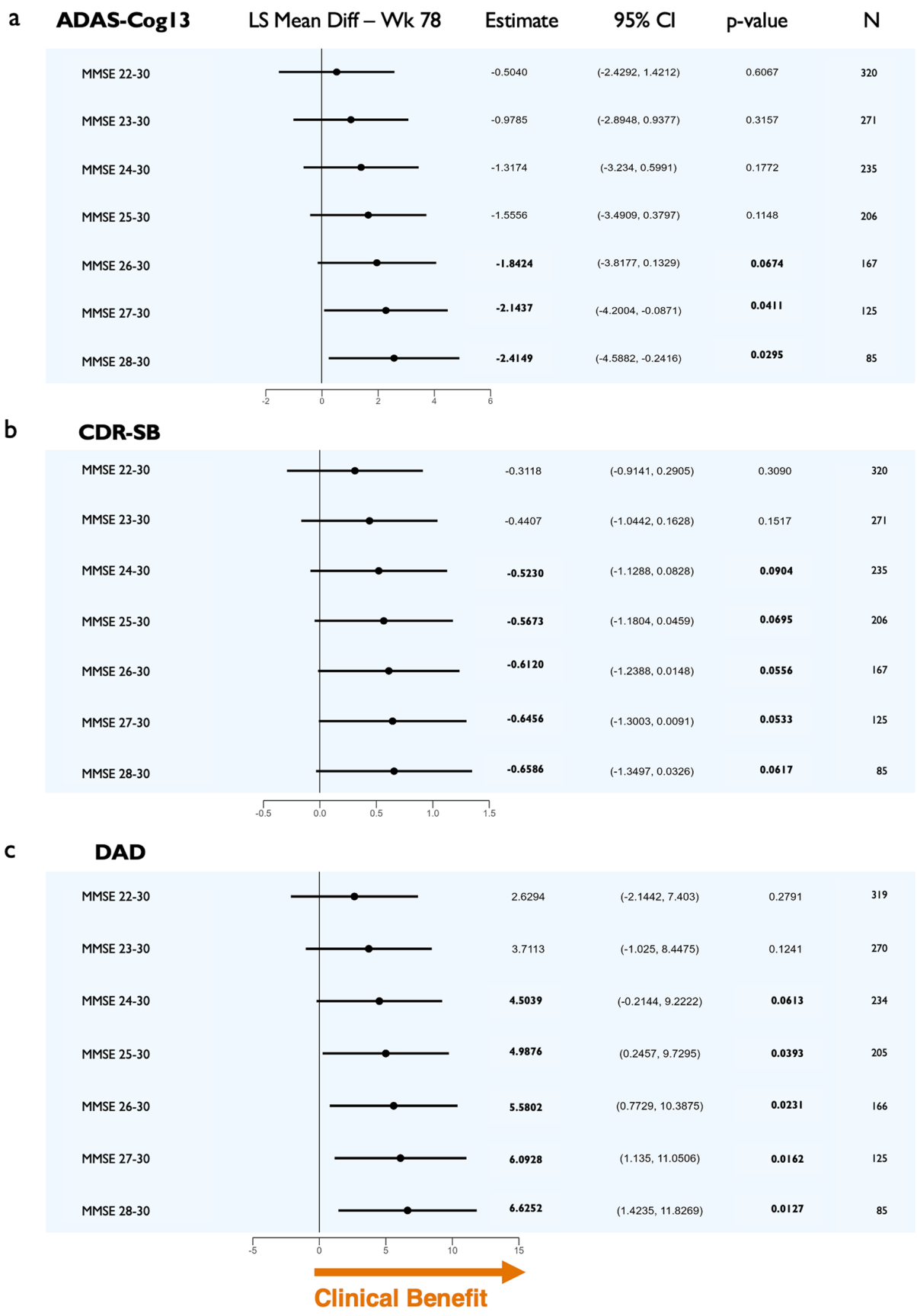

**Fig. 2** Effects of ALZ-801/valiltramiprosate on the main clinical outcomes in the overall efficacy population (FAS, full analysis set) and in participants with mild cognitive impairment (MCI). Results shown from a mixed-effect repeated measure model (MMRM); *LSM* least squares mean. **a**, **e** ADAS-Cog13 (13-item Alzheimer's Disease Assessment Scale—Cognitive Subscale); **b**, **f** CDR-SB (Clinical Dementia Rating—Sum of Boxes); **c**, **g** DAD (Disability Assessment for Dementia); **d**, **h** IADL (Amsterdam—Instrumental Activities of Daily Living weighted average)

points was considered clinically meaningful in the phase III AD trials of the anti-amyloid antibody bapineuzumab, where DAD was a co-primary outcome [44].

## 3.3 Magnetic Resonance Imaging (MRI) Results

### 3.3.1 Volumetric MRI Outcomes

In the overall imaging population ($N = 290$), valiltramiprosate effects on HV, whole brain cortical thickness, and all other secondary vMRI outcomes consistently favored valiltramiprosate over placebo by 18% to 22%, with 18% slowing ($p = 0.017$) of HV atrophy and 20% ($p = 0.002$) slowing of cortical atrophy (Table 2, Fig 4, panels a–d). In the MCI participants ($N = 113$), the vMRI effects compared with placebo were larger across all brain regions with 26% slowing of HV atrophy ($p = 0.004$) and 35% slowing of whole brain cortical thinning ($p < 0.0001$), with apparent divergence of slopes over time (Table 2, Fig. 4, panels e–f). The prespecified MCI group also showed 22% slowing of whole brain atrophy compared with placebo ($p = 0.027$) over 78 weeks (Fig. 4, panel g). In the prespecified mild AD group, both HV and CT showed directional slowing of atrophy compared to placebo (12% and 11%, respectively) but these effects


a
ADAS-Cog13
LS Mean Diff – Wk 78
Estimate
95% CI
p-value
N
MMSE 22-30 -0.5040 (-2.4292, 1.4212) 0.6067 320
MMSE 23-30 -0.9785 (-2.8948, 0.9377) 0.3157 271
MMSE 24-30 -1.3174 (-3.234, 0.5991) 0.1772 235
MMSE 25-30 -1.5556 (-3.4909, 0.3797) 0.1148 206
MMSE 26-30 -1.8424 (-3.8177, 0.1329) 0.0674 167
MMSE 27-30 -2.1437 (-4.2004, -0.0871) 0.0411 125
MMSE 28-30 -2.4149 (-4.5882, -0.2416) 0.0295 85
-2 0 2 4 6
b
CDR-SB
MMSE 22-30 -0.3118 (-0.9141, 0.2905) 0.3090 320
MMSE 23-30 -0.4407 (-1.0442, 0.1628) 0.1517 271
MMSE 24-30 -0.5230 (-1.1288, 0.0828) 0.0904 235
MMSE 25-30 -0.5673 (-1.1804, 0.0459) 0.0695 206
MMSE 26-30 -0.6120 (-1.2388, 0.0148) 0.0556 167
MMSE 27-30 -0.6456 (-1.3003, 0.0091) 0.0533 125
MMSE 28-30 -0.6586 (-1.3497, 0.0326) 0.0617 85
-0.5 0.0 0.5 1.0 1.5
c
DAD
MMSE 22-30 2.6294 (-2.1442, 7.403) 0.2791 319
MMSE 23-30 3.7113 (-1.025, 8.4475) 0.1241 270
MMSE 24-30 4.5039 (-0.2144, 9.2222) 0.0613 234
MMSE 25-30 4.9876 (0.2457, 9.7295) 0.0393 205
MMSE 26-30 5.5802 (0.7729, 10.3875) 0.0231 166
MMSE 27-30 6.0928 (1.135, 11.0506) 0.0162 125
MMSE 28-30 6.6252 (1.4235, 11.8269) 0.0127 85
-5 0 5 10 15
Clinical Benefit

◂**Fig. 3** Sensitivity analyses of the main clinical outcomes, showing placebo-adjusted point estimates in progressively earlier disease stages by screening MMSE (MMRM analysis). **a** ADAS-Cog13 (13-item Alzheimer's Disease Assessment Scale—Cognitive Subscale); **b** CDR-SB (Clinical Dementia Rating—Sum of Boxes); **c** DAD (Disability Assessment for Dementia). *LS Mean Diff – Wk 78* LSMs of drug–placebo difference at 78 weeks; Estimate: point estimate for the LS means difference; *95% CI* 95% confidence interval, *N* = number of participants at baseline for each MMSE category. The *bolded point estimates* are ones that show positive trend favoring drug with $p < 0.1$. Note: MMSE 22–30 is the full analysis set (FAS); MCI is defined as MMSE >26. *MCI* mild cognitive impairment, *MMSE* Mini-Mental State Examination, *MMRM* mixed-effect model repeated measure

were smaller than the MCI group and were not statistically significant. However, the mild AD group showed significantly less ventricular expansion (19%, nominal $p = 0.007$). The vMRI trajectories for the mild AD group are shown in Online Resource Fig. 2 (panels e–h, see ESM).

#### 3.3.2 MRI Diffusion Tensor Imaging Outcomes (Diffusion MRI, Mean Water Diffusivity)

Mean water diffusivity (MD) is a measure of microstructural tissue integrity with larger MD indicating greater abnormality [5, 41, 42]. The DTI population included 208 participants (105 active, 103 placebo); MD ($mm^2$/sec) was the main outcome. The overall population showed positive drug effects compared with placebo on several white matter tracts (lower MD), but the grey matter effects did not achieve statistical significance (Online Resource Fig. 3, see ESM). The prespecified MCI group showed positive drug effects compared with placebo on cortical grey matter (cingulate cortex, $p = 0.031$, $N = 84$) and several white matter tracts that were most significant in the genu of corpus callosum ($p = 0.003$; $N = 84$), as shown in Fig. 5 (panels a, b). The prespecified mild AD group ($N = 121$) showed positive effects in two white matter tracts but none of the grey matter effects achieved significance (Online Resource Fig. 4, panels a, b; see ESM).

#### 3.3.3 Correlations Between Imaging Biomarkers Effects and Clinical Outcomes

The prespecified MCI population that showed nominally significant clinical effects also showed significant *subject-level* correlations between drug effects on ADAS-Cog13 and CDR-SB, and drug effects on HV and cortical thickness at 78 weeks (Online Resource Table 3, see ESM). This MCI group also showed significant correlations between drug effects on each of ADAS-Cog13, CDR-SB, and HV and the drug effects on MD shown on DTI (Fig. 6).

#### 3.3.4 Plasma Neurofilament to Hippocampal Volume Correlations

Plasma neurofilament light (NfL) levels were of interest because they are considered a biomarker of neuroaxonal loss in several neurodegenerative diseases including AD [3]. In participants with MCI, the plasma NfL drug effects in the valiltramiprosate arm over 52 and 78 weeks showed significant *subject-level* correlations with vMRI effects at 78 weeks (Fig. 6), while the placebo arm did not show significant correlations over those time periods (Online Resource Table 4, see ESM).

### 3.4 Exposure and Safety

Pharmacokinetic analysis from all participants showed consistent plasma drug exposures over 78 weeks that were within the expected efficacious range based on nonclinical mechanistic studies and the tramiprosate trials (Online Resource Fig. 5, see ESM) [20, 21].

The safety profile of valiltramiprosate was consistent with the reported safety from the tramiprosate and valiltramiprosate studies in >3000 AD participants [27, 28]. The rates of nausea, decreased weight, decreased appetite, and vomiting in the valiltramiprosate arm were double those in the placebo arm (Table 3). Nausea was the most common treatment-emergent adverse event (TEAE) (valiltramiprosate, 26%; placebo, 5%) but was mostly mild to moderate in severity and transient. Nausea and vomiting primarily occurred early in the trial and showed tolerance, with <5% of participants discontinuing from the trial for this reason. Weight loss (monitored at each visit) occurred primarily at or after 26 weeks, was reversible or stabilized at a lower weight, and was manageable with nutritional supplements. The incidence of TEAEs that led to early terminations (ET) was low overall at 4% (6.7% in active arm, 1.2% in placebo), with nausea and vomiting being the only events that led to ET in more than two subjects. ECG and laboratory tests showed no safety signals. The incidence of serious TEAEs (SAEs) in valiltramiprosate and placebo arms was 8.6% and 8.0%, respectively. The system organ classes with the highest overall SAE rate of 1.8% were cardiac disorders (active 1.2%, placebo 2.5%), nervous system disorders (active 1.8%, placebo 1.9%), and injury/procedural complications (active 1.8%, placebo 1.9). Syncope ($n = 2$) was the only SAE that occurred in more than one participant. There were no deaths in the study.

Among 298 participants with serial MRIs, there were five cases of ARIA-E in each treatment arm (3.5%; Table 3). The incidence of ARIA due to hemosiderin deposition (ARIA-H) was lower in the valiltramiprosate arm than in the placebo arm. New microhemorrhages were reported in 30% of participants in the valiltramiprosate arm and in 36% of

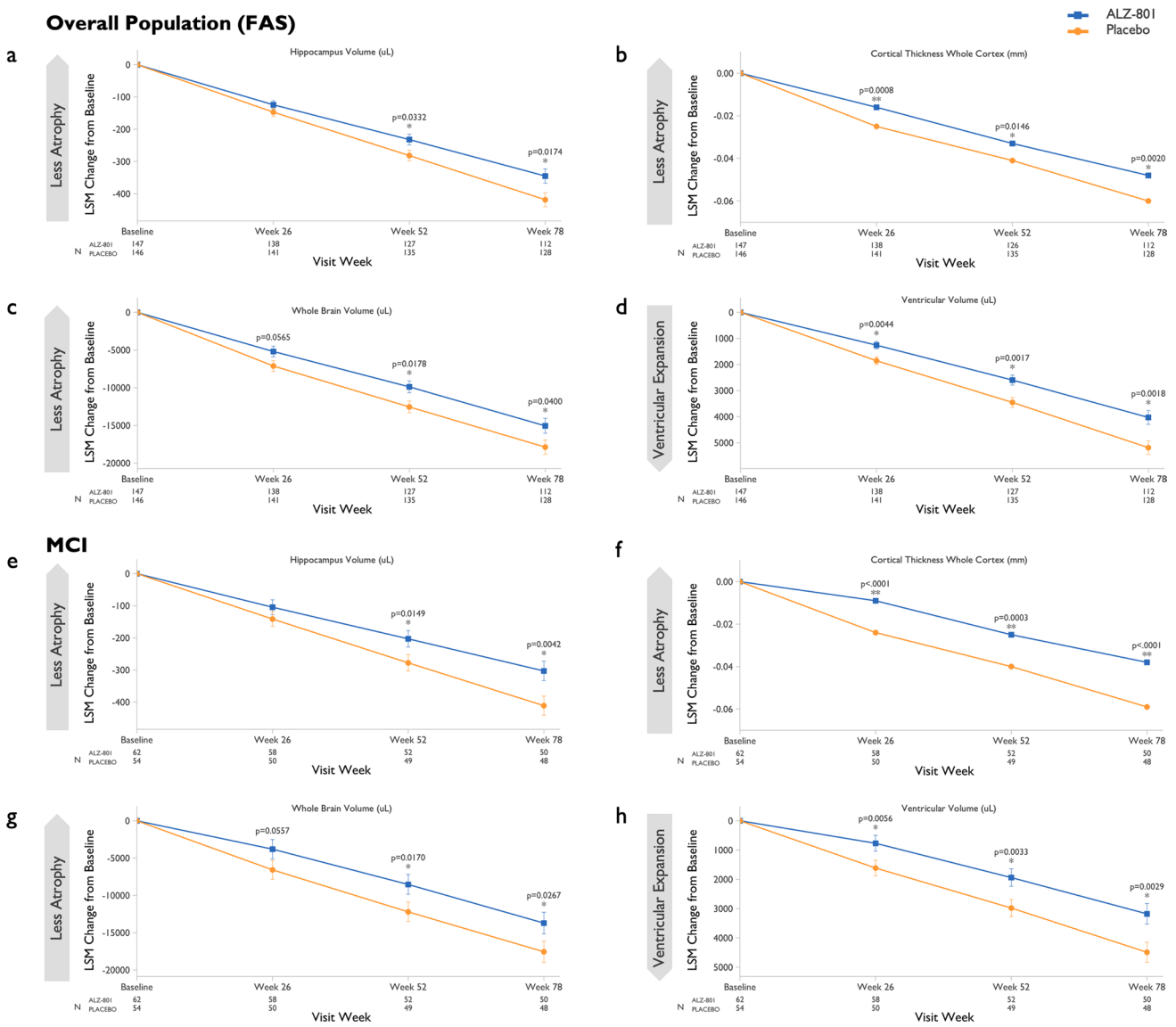



**Fig. 4** Effects of ALZ-801/valiltramiprosate on volumetric outcomes in the overall imaging population (FAS, imaging population full analysis set) and in participants with mild cognitive impairment (MCI, imaging population). Results shown from a mixed-effect repeated measure model (MMRM); *LSM* least squares mean. Note: increase in ventricular volume (expansion) indicates brain atrophy

participants in the placebo arm; siderosis was reported in 13% and 17% of participants in the valiltramiprosate and placebo arms, respectively. None of the ARIA events were symptomatic.

## 4 Discussion

This phase III trial did not achieve significance on its primary or secondary clinical outcomes in the primary analysis of the early AD population. Although the overall population showed significant slowing of atrophy in all brain compartments on vMRI, the magnitude of these effects did not translate into meaningful cognitive benefits.

The study design assumed that both the MCI and mild AD subjects would show similar degrees of clinical efficacy. However, the prespecified disease severity analysis showed that only patients at the MCI stage of disease (MMSE 27–30), comprising ~40% of the study, showed meaningful clinical efficacy. The sensitivity analysis suggested that meaningful cognitive and functional effects may be achieved with intervention at the early symptomatic stages, likely starting at MMSE ≥25. This is consistent with valiltramiprosate β-amyloid anti-aggregation mode of action preventing

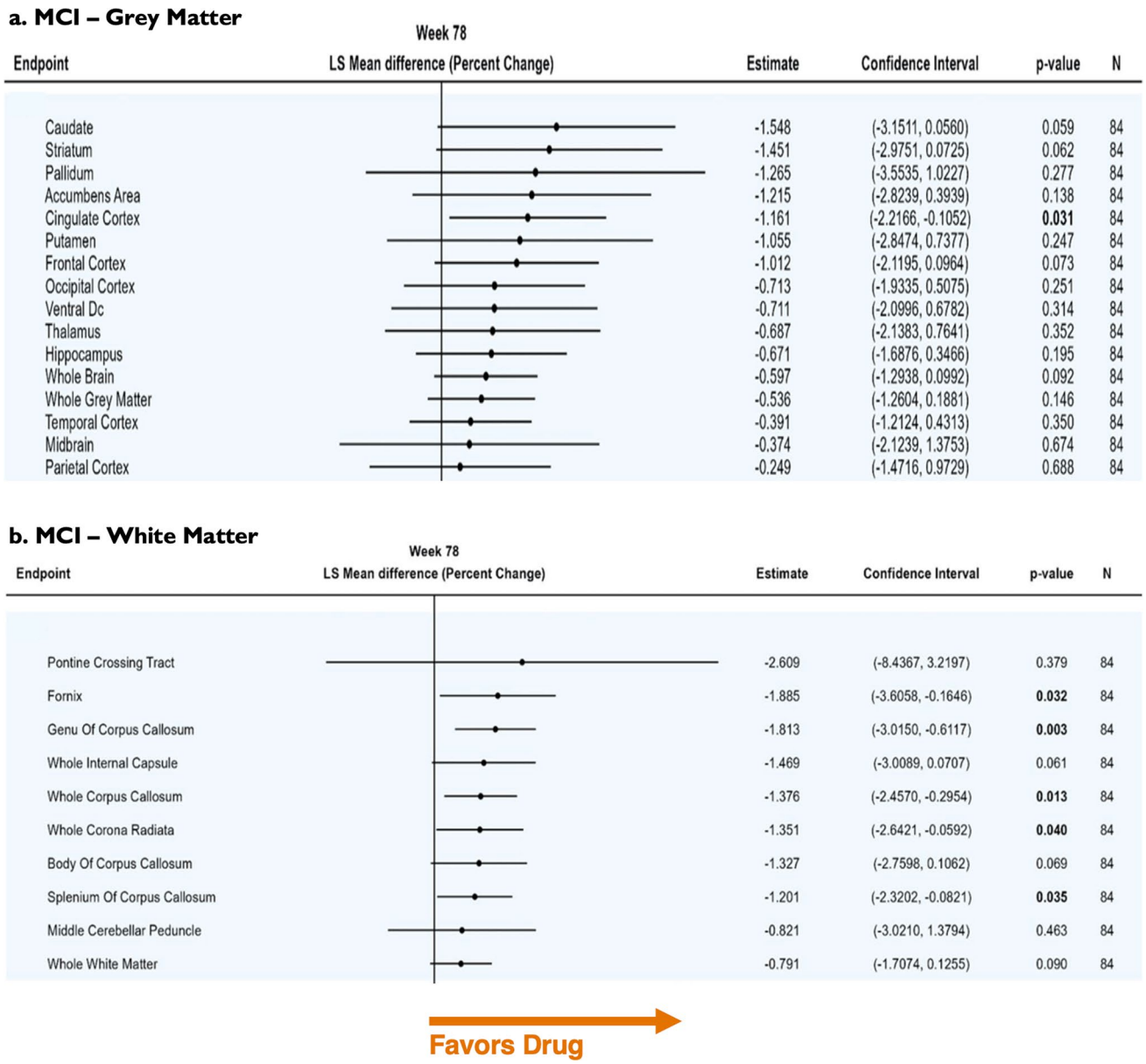



**Fig. 5** Effects of ALZ-801/valiltramiprosate on the main DTI endpoints in participants with mild cognitive impairment (MCI). Results shown from a mixed-effect repeated measure model (MMRM) in the DTI population. **a** Grey matter regions, **b** white matter tracts. *DTI* diffusion tensor imaging, a measure of mean extracellular water diffusivity in brain tissue, where lower diffusivity indicates positive drug effect, *LSM* least squares mean, *N* number of participants in DTI population

formation of soluble amyloid oligomers that play a key role early in AD pathophysiology.

It is possible that the positive clinical effects observed in the MCI group may represent a false positive effect (since the overall study was negative). However, as discussed below, the consistency of results across the cognitive, functional, and imaging effects in the prespecified MCI group with significant *subject-level* correlations between these outcomes may help alleviate this concern.

MCI participants showed consistent (nominally) significant effects on the primary cognitive and secondary functional outcomes. These clinical effects were nominally significant despite the smaller sample size of the MCI subjects ($N = 125$ instead of the planned 300 subjects). The effects on ADAS-Cog were above the accepted ~30% threshold of clinical meaningfulness in AD trials, and this translated to stabilization of function (on CDR-SB and DAD) for approximately 1.5 years.

Valiltramiprosate effects on brain volumes at the prespecified MCI stage of AD, before neuronal dystrophy and white matter disruption become extensive, show significant slowing of atrophy in the hippocampus and other analyzed

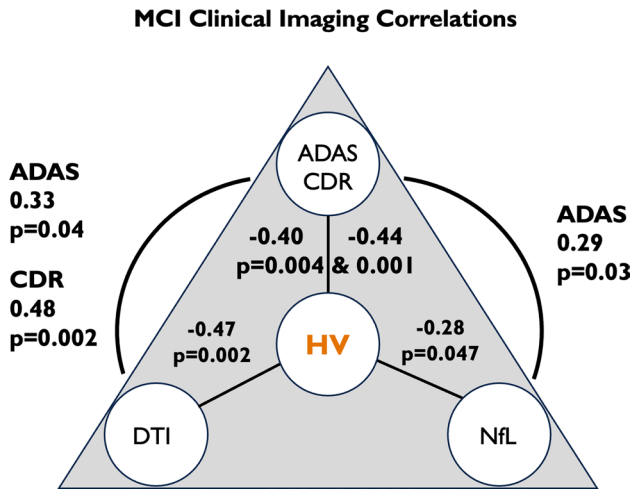



**Fig. 6** Pearson's correlations of clinical outcomes with HV, DTI, and plasma biomarker outcomes in MCI group (observed case analysis). The correlations represent Pearson's correlations of changes from baseline to 78 weeks. Correlation of +1 indicates the strongest positive relationship, −1 indicates the strongest negative relationship and 0 indicates no linear relationship. In AD trials, correlations between 0.2 and 0.29 are considered modest, between 0.30 and 0.39 are moderate strength, and ≥0.40 are considered strong correlations. The noted ADAS, CDR and HV correlations to DTI outcomes were to the frontal cortex (grey matter). The noted HV correlation to DTI outcome was to the genu of corpus callosum (white matter tract). *ADAS* Alzheimer's Disease Assessment Scale—Cognitive Subscale, *CDR-SB* Clinical Dementia Rating—Sum of Boxes, *DTI* diffusion tensor imaging, mean diffusivity, *HV* hippocampal volume, *MCI* mild cognitive impairment, *NfL* plasma level of neurofilament light chain

brain compartments. The slowing of reduction in brain volumes represented 26% deceleration of hippocampal atrophy and 35% deceleration of cortical atrophy, with both these drug effects showing significant subject-level correlations with clinical benefits. These brain volume effects are supported by the DTI results on microstructural integrity, and taken together, may suggest slowing of the underlying neurodegeneration.

An orthogonal approach to evaluating a drug's effect on the underlying AD pathophysiology is to analyze its effects on fluid biomarkers of neurodegeneration, such as NfL (the 'N' in the A/T/N biological definition of AD). In the MCI active arm, the drug effects on both ADAS-Cog13 and HV showed significant subject-level correlations with its effect on plasma NfL. Of note, the full analyses of plasma biomarkers of core AD pathologies, including Aβ42, Aβ40, and p-tau over 78 weeks, are being conducted with recent state-of-the-art assays and will be presented in a future publication.

The mild AD group in this study showed small and non-significant clinical effects favoring placebo, whereas prior tramiprosate data in APOE4/4 subjects at the mild AD stage (MMSE 22–26) showed positive drug effects at 78 weeks with a bioequivalent tramiprosate dose [27]. The observed lack of efficacy in the APOE4/4 Mild AD group in this AD301 trial compared with the tramiprosate trial may be related to lower use of symptomatic AD drugs as background therapy (42% in this study vs >95% in the tramiprosate trial).

This study has several limitations including the limited ethnic and geographic diversity of the enrolled population. Approximately 89% of the enrolled population was White, despite a dedicated outreach effort to enroll a more diverse population (especially in the US). Similarly, most of the sites were in urban areas or major metropolitan cities, with limited participation from rural areas. This may limit the generalizability of these study findings to the wider population. Another limitation is that the MCI group that showed positive drug effects comprised ~40% of the study or 125 participants, rather than the originally planned sample size of ~300 subjects. Finally, stratification by disease stage was based on clinical scores rather than biomarkers of AD pathologies such as amyloid or tau-PET scans or brain volume measures, which may have adversely influenced trial results in the mild AD group.

Despite these limitations, this study has several notable features, namely its focus on an APOE4/4 population that includes patients with high burden of CAA and small vessel disease and being one of the first AD trials to report drug effects on tissue microstructure with DTI.

The APOLLOE4 trial represents the largest placebo-controlled dataset in APOE4/4 homozygotes and is the first completed interventional phase III AD trial focused exclusively on this genotype. APOE4/4 homozygotes comprise an AD population that is typically enriched in amyloid, tau, and vascular pathologies [9–11, 15–17, 35] and that usually shows accelerated HV atrophy and clinical decline compared with other APOE genotypes [15, 45, 46].

This trial was unique among amyloid-targeting studies in allowing enrollment of homozygotes with a high burden of CAA lesions at baseline (>4 microhemorrhages, >1 superficial siderosis) who would have been excluded from recent anti-amyloid antibody trials [31, 32]. This resulted in 31% of all enrolled participants having at least one microhemorrhage and included participants with up to 160 microhemorrhages and up to five superficial siderosis lesions in the active arm at baseline. This population also had a high prevalence of cardiovascular comorbidities and small vessel white matter disease, which is more representative of APOE4/4 patients in clinical practice [5, 35].

To our knowledge, this is one of the first AD trials to incorporate brain DTI assessments. DTI measures brain water diffusivity that reflects the integrity of cortical gray matter and the white matter tracts that connect them and can, therefore, provide information about the structural network connectivity [5, 41, 42, 47].

**Table 3** Incidence of treatment-emergent adverse events in safety population, including incidence of ARIA in safety MRI population

| Adverse event category | Valiltramiprosate ($N = 163$) | Placebo ($N = 162$) |
|---|---|---|
| Number (%) of participants with at least one | | |
| Adverse event | 140 (85.9) | 137 (84.6) |
| Adverse event related to trial treatment[a] | 51 (31.3) | 16 (9.9) |
| Serious adverse event | 14 (9.0) | 13 (8.0) |
| Adverse event resulting in death | 0 | 0 |
| Adverse event leading to treatment discontinuation | 11 (6.7) | 2 (1.2) |
| Frequent adverse events in either treatment arm[b] | | |
| Nausea | 42 (25.8) | 8 (4.9) |
| COVID-19 | 34 (20.9) | 31 (19.1) |
| Weight decreased | 23 (14.1) | 12 (7.4) |
| Decreased appetite | 16 (9.8) | 3 (1.9) |
| Vomiting | 16 (9.8) | 2 (1.2) |
| Fall | 10 (6.1) | 11 (6.8) |
| Urinary tract infection | 10 (6.1) | 11 (6.8) |
| Dizziness | 9 (5.5) | 9 (5.6) |
| Headache | 9 (5.5) | 12 (7.4) |
| Cerebral microhemorrhage | 8 (4.9) | 11 (6.8) |
| ARIA category[c] | Valiltramiprosate ($N = 145$) | Placebo ($N = 145$) |
| ARIA-E (edema or effusion) | 5 (3.4) | 5 (3.4) |
| ARIA-H (microhemorrhage) | 44 (30) | 54 (36) |
| ARIA-H (siderosis) | 19 (13) | 25 (17) |
| Symptomatic ARIA-E or ARIA-H | 0 | 0 |

Data are presented as the number and percentage of participants based on the safety population (all randomized participants who received at least one dose of valiltramiprosate or placebo), unless otherwise noted

*ARIA-E* amyloid-related imaging abnormalities with vascular edema, *ARIA-H* amyloid-related imaging abnormalities with microhemorrhages or hemosiderin deposition, *MRI* magnetic resonance imaging

[a]Relatedness was assessed by the investigators

[b]Frequent adverse events are defined as events that occurred in >5% of participants in either the valiltramiprosate or placebo arm. Events are listed in decreasing order of frequency based on the valiltramiprosate arm

[c]Data are expressed as number (%) of participants based on the safety MRI population (all randomized participants who had a safety MRI assessment at baseline, received at least one dose of valiltramiprosate or placebo, and had at least one post-baseline safety MRI assessment)

A differentiating attribute of valiltramiprosate is the favorable safety profile in this high-risk APOE4/4 population with no increased risk of ARIA, allowing for infrequent MRI monitoring. This safety profile is consistent with valiltramiprosate's mode of action that does not require microglial activation and breakdown of amyloid plaques in brain parenchyma and vessel walls [20–23, 48]. Inhibition of Aβ42 monomer aggregation is thought to facilitate its removal by the brain's natural clearance mechanisms, including microglial uptake and the glymphatics, and may lower amyloid burden in both the brain parenchyma and microvessels [49–51]. This favorable neurovascular profile may also contribute to its clinical efficacy profile, making it especially suited for future trials in CAA and mixed AD with vascular dementia.

## 5 Conclusions

Valiltramiprosate, an anti-amyloid oligomer agent, showed favorable safety with no increased risk of ARIA over 78 weeks in high-risk APOE4/4 homozygotes. Valiltramiprosate did not show significant efficacy in the overall study population of homozygotes with early AD. Prespecified analyses by disease stage showed nominally significant positive clinical effects in the MCI group, but not in mild AD. The promising clinical benefits in MCI were associated with statistically significant slowing of hippocampal, cortical thickness, and whole brain atrophy. The need for early intervention in Alzheimer's pathology observed in this phase III trial is consistent with results of other interventional trials targeting amyloid and have driven the current

interest in prevention trials at the presymptomatic stage [52]. APOE4/4 homozygotes represent 10% to 15% of all AD, or approximately 1 million US patients in the US alone [53, 54], and are a therapeutically challenging population [10, 17, 18, 55]. These phase III study results suggest that valiltramiprosate provides a favorable benefit–risk profile in APOE4/4 patients with MCI and will inform the design of future confirmatory trials.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40265-025-02250-5.

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## Declarations

**Conflicts of Interest** Alzheon employees receive salary compensation and stocks and/or stock options from Alzheon Inc. The AD experts (A. Porsteinsson, M. Sabbagh, M. Doraiswamy) received consulting fees and stocks or stock options from Alzheon Inc, and multiple other pharmaceutical companies developing CNS drugs, devices, or diagnostic tests. The site investigators (D. Watson, E. MacSweeney, S. Cohen, M. Boada-Rivera) received investigator fees for this study and multiple other AD and CNS trials from various global pharmaceutical companies. S. Dickinson is an employee of Pentara Inc., which provided statistical services and receives compensation from Alzheon Inc.

**Availability of Data** The data that support the findings of this study are available from Alzheon, Inc., but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Alzheon, Inc.

**Ethics Approval** The APOLLOE4 trial was approved by Adverra Central IRB and by the required local university IRBs in the US, and by country-specific ethics committees in the UK and EU. Alzheon certifies that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

**Consent to Participate** All participants signed written informed consent to participate in the trial before screening.

**Consent to Publish** Not applicable.

**Code Availability** Not applicable.

**Author Contributions** Alzheon employees: S. Abushakra is the principal investigator on the NIA grant for the APOLLOE4 trial. S. Abushakra, A. Power, E. Liang, S. Flint, J., L. Tolar, Hey and M. Tolar designed the trial and oversaw its conduct, data analysis, data interpretation, and manuscript preparation. All other Alzheon employees contributed to one or more of the following: trial conduct and oversight, safety oversight, and data analysis and interpretation. Advisors: A. Porsteinsson and M. Sabbagh were advisors for clinical trial design, data interpretation and manuscript preparation and/or review. P.M. Doraiswamy was scientific advisor and provided manuscript reviews and critiques. D. Watson, E. McSweeney, S. Cohen, and M. Boada-Rivera were trial investigators in the United States, United Kingdom, Canada, and Europe, respectively; they contributed to the trial conduct, safety discussions, data interpretation and manuscript preparation. S. Dickson contributed to statistical methods and data analysis.



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