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Post hoc analysis of ADAMANT, a phase 2 clinical trial of active tau immunotherapy with AADvac1 in patients with Alzheimer's disease, positive for plasma p-tau217

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Abstract

Background The spread of tau pathology closely correlates with the disease course and cognitive decline in Alzheimer's disease (AD). Tau-targeting immunotherapies are being developed to stop the spread of tau pathology and thus halt disease progression. In this post hoc analysis of the ADAMANT clinical trial, we examined the performance of AADvac1, an active immunotherapy targeting the microtubule-binding region (MTBR) of tau, in a subgroup of participants with elevated plasma p-tau217, indicating AD-related neuropathological changes.

Methods ADAMANT was a 24-month, randomized, placebo-controlled, parallel-group, double-blinded, multicenter, phase 2 clinical trial in subjects with mild AD. The trial participants were randomized 3:2 to receive six doses of AADvac1 or placebo at 4-week intervals, followed by five booster doses at 14-week intervals. The primary outcome was safety. The secondary outcomes were the Clinical Dementia Rating-Sum of Boxes (CDR-SB), the Alzheimer's Disease Cooperative Study – Activities of Daily Living score for Mild Cognitive Impairment 18-item version (ADCS-ADL-MCI-18), and immunogenicity. Volumetric MRI, plasma neurofilament light (NfL), and glial fibrillary acidic protein (GFAP) were exploratory outcomes. The inclusion criterion for this post-hoc analysis was a baseline plasma p-tau217 level above the cutoff for AD.

Results Among 196 ADAMANT participants, 137 were positive for plasma p-tau217 (mean age 71.4 years, 59% women). AADvac1 was safe and well tolerated in this subgroup. AADvac1 reduced the rate of accumulation of log-plasma NfL by 56% and that of GFAP by 73%. The treatment differences in the CDR-SB and ADCS-ADL-MCI-18 scores favored AADvac1 but were not statistically significant. AADvac1 had no effect on whole-brain volume but nonsignificantly reduced the loss of brain cortical tissue in several regions. Importantly, the impact on the study outcomes was more pronounced in participants with higher anti-tau antibody levels.

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Conclusions These results suggest that AADvac1 tau immunotherapy can reduce plasma biomarkers of neurodegeneration and neuroinflammation. These findings and possible observations on brain atrophy and cognition are hypothesis-generating and warrant further evaluation in a larger clinical trial.

Trial registration EudraCT 2015–000630-30 (primary) and NCT02579252.

Keywords Alzheimer's disease, Immunotherapy, Tau, Plasma phosphorylated tau 217, Plasma biomarkers, Neurofilament light (NfL), Glial fibrillary acidic protein (GFAP), AADvac1

Background

In Alzheimer's disease (AD), neurofibrillary lesions strongly correlate with the severity and pattern of brain atrophy [1], and with the clinical phenotype and severity of cognitive impairment [2, 3]. The specific distribution of tau pathology determined by positron emission tomography (PET) is a strong indicator of the topography of future atrophy [4] and longitudinal cognitive decline [5]. These observations support the notion that the tau pathogenic process is an important target for AD therapy.

AADvac1 is an active immunotherapy that targets pathological tau proteins [6, 8]. It was developed to reduce the accumulation and spread of neurofibrillary pathology in the brain and hence slow or halt the progression of AD [7]. The phase 2 ADAMANT trial with AADvac1 demonstrated favorable safety and tolerability with the induction of high levels of IgG antibodies [8]. There was a strong positive effect on plasma neurofilament light (NfL), a marker of ongoing neurodegeneration [9–15], and a reduction in cerebrospinal fluid (CSF) tau biomarkers. However, there were no statistically significant effects on cognitive tests or volumetric magnetic resonance imaging (vMRI) findings in the full study sample. The enrollment relied mostly on MRI atrophy and as a result 30% of participants were suspected not to meet CSF biomarker criteria for AD [8, 16].

Recent progress in the development of fluid biomarker assays has shown encouraging results, indicating the diagnostic utility of plasma biomarkers [17]. Tau species phosphorylated at Thr217 (p-tau217) have the strongest association with tau PET [18] and the highest diagnostic performance [19–22], as this measure reflects a combination of tau and amyloid proteinopathies [23–29]. We used an analytically qualified ADx pTau217 Simoa assay to identify ADAMANT participants who were above the cutoff value for AD in this assay (> 0.2 pg/mL). The aim of the present post hoc analysis was to evaluate the performance of AADvac1 in plasma p-tau217 'positive' AD participants on the primary, secondary and exploratory endpoints of the study.

Methods

Study design, participants and intervention

ADAMANT was a 24-month, phase 2, randomized (3:2), placebo-controlled, parallel-group, double-blinded, multicenter clinical trial on AADvac1, sponsored by Axon Neuroscience SE [8]. The trial enrolled 196 participants at 41 sites across Europe (June 2016 and May 2019), with 193 participants composing the full analysis set (FAS) under the modified intention-to-treat principle. The inclusion criteria included a diagnosis of mild AD according to the 2011 NIA-AA criteria [30], an age range of 50–85 years, Mini-Mental State Examination (MMSE) score ≥ 20 and ≤ 26 (defining mild dementia), evidence of either medial temporal lobe atrophy or a positive cerebrospinal fluid (CSF) AD biomarker profile [8].

The subjects initially received 6 subcutaneous doses of AADvac1 or placebo at 4-week intervals, followed by 5 booster doses of AADvac1 or placebo at 14-week intervals [8]. Patients were randomized via an interactive web-based response system (Cenduit GmbH, Switzerland).

The ADAMANT study protocol was approved by the appropriate ethics committees and competent authorities [8]. The study complied with the applicable International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines and the Declaration of Helsinki. The study is registered under EudraCT 2015–000630-30 (primary record) and NCT02579252.

ADx pTau217 Simoa assay

The immunoassay for plasma p-tau217 was developed by ADx NeuroSciences using a Homebrew Simoa Assay Kit (Quanterix) with a hybridoma-based mouse monoclonal antibody (mAb) (RD-084; ADx NeuroSciences) that specifically binds phospho-tau Thr217 (capture Ab) combined with a recombinantly expressed mouse mAb (RD-073; ADx Neurosciences) that recognizes an epitope in the N-terminus of Tau (detector Ab, biotinylated). Its performance in patient samples was evaluated using discovery cohort I (42 CSF-confirmed AD patients in the prodromal or dementia stage and 35 healthy spouse controls) [31] and discovery cohort II, which included 40 CSF-confirmed AD-dementia patients and 40 age-matched healthy volunteers [32]

(see Methods in the Supplement). A cutoff value of 0.2 pg/mL for indicating AD neuropathology was identified with the aim of avoiding non-AD individuals and conferring ≥ 95% specificity in the two cohorts (Supplementary material Figure S1). The ADx pTau217 Simoa assay was shown to perform on par with other plasma p-tau217 assays in a round robin study [33]. The cutoff of 0.2 pg/mL correlates with the upper cutoff point (0.219 pg/mL) selected for an algorithm constructed for the identification of Aβ-positive, high tau-PET individuals [34].

For this post hoc analysis, all ADAMANT plasma samples were measured in one batch. The samples were thawed at room temperature and centrifuged before analysis for 8 min at 10,000*xg*.

Safety (primary outcome)

Safety was the primary outcome in the ADAMANT phase 2 study and the prespecified analyses included comparisons of the overall incidence of adverse events (AEs) and serious AEs (SAEs) between the treatments, comparisons of the incidence of AEs for each system organ class (SOC), and comparisons of the expected injection site reactions (ISRs) [8]. In this work, we replicated these analyses in the post-hoc defined plasma p-tau217 'positive' and 'negative' subgroups (see Methods in the Supplementary material).

Cognitive and functional assessment and immunogenicity (secondary outcomes)

The secondary outcomes of the ADAMANT trial included the Clinical Dementia Rating—Sum of Boxes (CDR-SB, range 0–18), the Alzheimer's Disease Cooperative Study – Activities of Daily Living Score adapted for Mild Cognitive Impairment 18-item version (ADCS-ADL-MCI-18, range 0–53), and immunogenicity. The cognitive outcomes were assessed at weeks 0, 12, 24, 38, 52, 66, 80, 94, and 104. Computerized versions of the CDR-SB and ADCS-ADL-MCI-18 scales were employed (MedAvante Virgil platform, MedAvante, NJ, USA). The tests were administered and scored by site raters [8].

For immunogenicity, the geometric mean antibody response at each postbaseline visit was calculated (see Methods in the Supplementary material).

Biomarker assessment (exploratory outcomes)

The plasma and imaging biomarkers were exploratory outcomes in the ADAMANT trial. The concentrations of NfL in plasma were measured by single molecule array (Simoa) digital ELISA, using an HD-1 Analyzer (v1.5) and the NF-Light Advantage assay kit (Quanterix) [8]. Plasma GFAP is a biomarker for astrocytosis [35, 36], and its increasing levels are associated with increasing tau tangle load [37]. It was measured using a Simoa GFAP Discovery Kit (Quanterix).

CSF biomarker measurements were described previously [8].

MRI data were collected at 3 T field strength with the whole brain as area of acquisition [8]. 3D T1 scans were normalized, and regional cortical volumes, lateral ventricles, and the whole cortex were subsequently extracted and analyzed. Whole brain volume loss was calculated with SIENA 2.6. For volume estimates, images were automatically processed with the longitudinal stream in FreeSurfer v.6.0 [8].

Statistical analysis

All analyses of efficacy endpoints presented in this work were performed on plasma p-tau217 'positive' subgroup using a mixed model for repeated measures (MMRM), with study visit treated as a categorical variable. The model was fit via restricted maximum likelihood estimation and an unstructured correlation matrix, and was adjusted for treatment status, baseline values of outcome, age, sex, years of education, baseline plasma NfL ($\log_{10}$ -transformed), baseline MMSE, ApoE4, memantine use and geographical region. Interaction effects were included between the categorical time variable and all covariates to account for the possibility that covariates may not be perfectly randomized in the selected biomarker-positive subgroup. Least-squares mean (LSM) changes from the baseline of individual outcomes were subsequently calculated, and the treatment on the outcome was determined at the 104-week study visit and at intermediate visits.

To analyze the relationship between the levels of AADvac1-induced IgG antibodies and the trial endpoints, the AADvac1-treated plasma p-tau217 'positive' study participants were categorized into low responders (below the 75th percentile, $n=60$) or high responders (above the 75th percentile, $n=22$) on the basis of the anti-tau peptide IgG antibody levels at week 24 [8], after completion of the initial the six-dose regimen when antibody levels reached the maximal value. The endpoint analyses were repeated on these subgroups each compared with the entire plasma p-tau217 'positive' placebo group. Two participants who discontinued before week 24 could not have their antibody levels evaluated and were excluded from this analysis.

All the statistical analyses were performed using R (v4.0.5) and GraphPad Prism (v8.4.3) with a significance level of 0.05 and without correction for multiple comparisons due to the exploratory nature of the analyses.

The percent slowing relative to placebo was calculated by dividing the LSM change from baseline treatment differences by the LSM change from baseline with placebo and multiplying by 100.

Results

Identification of ADAMANT study participants with plasma p-tau217-supported AD diagnosis

The demographics of the entire phase 2 ADAMANT clinical trial and participant flow have been previously published [8]. The disposition of the participants in the subgroup presented in this post hoc analysis is shown in Fig. 1. Out of 196 participants randomized in the ADAMANT trial 46 provided CSF samples either at screening or baseline. Analysis of CSF Aβ42 and p-tau181 levels revealed that only 32 participants (70%) fulfilled the inclusion criteria of p-tau181 positivity (cutoff > 60 pg/mL) [8], indicating that approximately 30% of all trial participants might not suffer from neurodegeneration caused by AD pathogenic processes.

To evaluate the treatment effect of AADvac1 in participants with confirmed AD neuropathology, the levels of plasma tau species phosphorylated at Thr217 were measured with the ADx pTau217 Simoa assay, with a positivity cutoff of 0.2 pg/mL. Among 196 randomized participants, 137 (70%) had p-tau217 levels above the cutoff, indicating a dysregulated tau and amyloid metabolism and the presence of AD neuropathological changes. In the p-tau217 biomarker-positive AD subgroup, 84 patients received AADvac1 and 53 received placebo (Supplementary material Figure S1B). Compared with the dichotomized CSF p-tau181 values, which were used as the evidence of the presence of tau pathology in the ADAMANT samples collected at screening or baseline ($n = 46$), the ADx pTau217 Simoa assay showed a sensitivity of 78% (95%CI 64–92%, a specificity of 79% (95%CI 57–100%); the positive predictive value (PPV) of 0.893 (96%CI 0,78–1,00) and the negative predictive value (NPV) of 0.611 (95%CI 0,39–0,84) (Supplementary material Figure S1C).

The baseline levels of plasma p-tau217 correlated with CSF tau phosphorylated at Thr217 (Spearman r = 0.595, $P = 0.017$), total tau (r = 0.615, $P = 0.013$) and tau phosphorylated at Thr181 (r = 0.602, $P = 0.015$), in 16 CSF samples that were collected at baseline (Supplementary

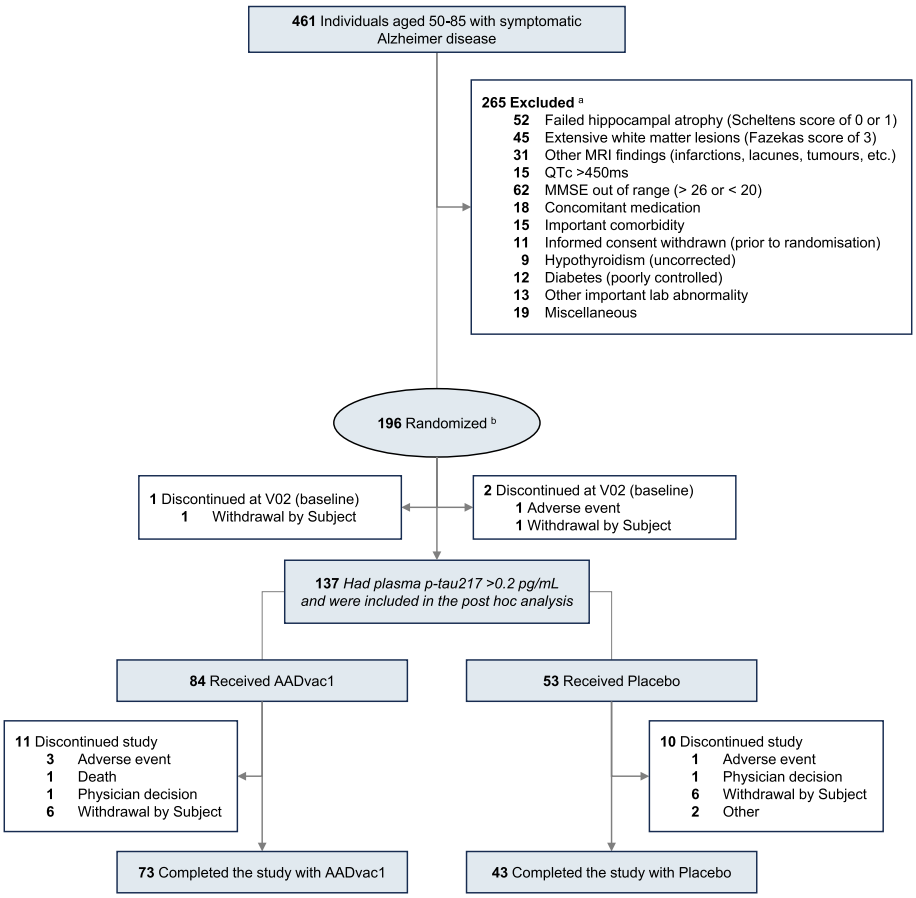

Fig. 1 Participant flow in this post hoc study on plasma p-tau217 'positive' subgroup.[a]Patients who failed screening did commonly present with multiple reasons for screening failure. [b]Safety set, includes all subjects who have received at least one dose of study treatment and who have at least one postbaseline value for safety

material Figure S2). This plasma marker did not correlate with CSF Aβ42 (r = 0.185, $p = 0.49$) or the Aβ42/40 ratio (r = −0.227, $p = 0.40$).

The baseline demographics and clinical characteristics of the plasma p-tau217 'positive' participants revealed that the treatment subgroups are balanced in most of the relevant baseline characteristics (Table 1). The subgroups differed only in the ADCS-ADL-MCI-18 score (P = 0.042), with a mean of 39.11 (SD, 7.77) points for AADvac1 and 36.04 (SD, 9.65) points for the placebo.

Safety in the plasma p-tau217 'positive' participants

In the plasma p-tau217 'positive' subgroup, treatment-emergent adverse events (AE) were observed in 86% of the participants treated with AADvac1, and 85% of participants treated with placebo (logistic regression odds ratio 1.19, $P = 0.57$). Treatment-emergent serious adverse events (SAE) were nominally less common in participants treated with AADvac1 (18%, 22 events in 15 participants) than in the placebo group (25%, 20 events in 13 participants, logistic regression odds ratio 0.75, $P = 0.49$). A trend toward a greater incidence of general disorders and administration site conditions was observed in the AADvac1 group (AADvac1 52%, placebo 36%, logistic regression odds ratio 1.90, $P = 0.055$), which was primarily due to injection site reactions (ISRs) being more common in the AADvac1 group. No statistically significant differences in the incidence of adverse events or serious adverse events were observed at the SOC or MedDRA preferred term level (Supplementary material Tables S1 and S2). The previously reported difference in the incidence of confusion [8] was not significant in this subgroup. The dropout rate was 13% (11 out of 84) in the AADvac1 group and 19% (10 out of 53) in the placebo group.

No differences in safety profile between the plasma p-tau217 'positive' and 'negative' (Supplementary material Tables S3 and S4) subgroups were observed.

Table 1 Baseline demographics and clinical characteristics of the plasma p-tau217 'positive' and 'negative' subsets of the trial participants

Characteristic	Plasma p-tau217 'positive'		Plasma p-tau217 'negative'	
	Placebo ($n = 53$)	AADvac1 ($n = 84$)	Placebo ($n = 24$)	AADvac1 ($n = 32$)
Age, mean (SD)	72.28 (6.71)	70.79 (8.26)	73.62 (7.23)	69.78
Sex, n (%)				
Women	31 (58.5)	50 (59.5)	14 (58)	11 (34)
Men	22 (41.5)	34 (40.5)	10 (42)	21 (66)
Years of education, mean (SD)	12.00 (3.06)	12.99 (3.45)	12.71 (3.88)	12.72 (3.66)
Ethnic origin	White (100%)	White (100%)	White (100%)	White (100%)
Concomitant memantine treatment, n (%) [a]	10 (19)	21 (25)	5 (21)	7 (22)
Apo E4 alleles, n (%):				
0	16 (30)	29 (34)	10 (42)	18 (56)
1	30 (57)	46 (55)	9 (37)	10 (31)
2	7 (13)	9 (11)	5 (21)	4 (13)
CDR-SB, mean (SD)	4.88 (2.62)	4.35 (2.06)	3.79 (1.74)	4.44 (2.14)
MMSE, mean (SD)	23.23 (1.93)	22.71 (1.89)	23.12 (2.03)	23.81 (1.69)
ADCS-MCI-ADL 18-item, mean (SD) [b]	36.04 (9.65)	39.11 (7.77)	39.92 (7.01)	36.0 (8.78)
Plasma p-tau217 [pg/mL], mean (SD) [c]	0.54 (0.42)	1.08 (5.23)	0.12 (0.04)	0.11 (0.06)
Plasma NfL [pg/mL], mean (SD)	22.64 (9.21)	22.59 (8.94)	22.27 (24.68)	18.45 (11.72)
Plasma GFAP [pg/mL], mean (SD)	529.8 (198.5)	582.1 (286.8)	378.0 (134.9)	335.2 (170.8)

[a] All participants were concomitantly treated with an approved acetylcholinesterase inhibitor

[b] $p = 0.009$

[c] The plasma p-tau217 'positive' AADvac1 group contains an outlier with an impossibly high plasma p-tau217 value of 48.35 pg/mL. The two treatment groups are otherwise balanced (Median (25%, 75%)), AADvac1: 0.417 pg/mL (0.329 pg/mL, 0.617 pg/mL), Placebo: 0.412 pg/mL (0.306 pg/mL, 0.635 pg/mL), see also Supplementary material Figure S1B

Cognitive and functional endpoints in plasma p-tau217 'positive' participants

The AADvac1 treatment in plasma p-tau217 'positive' participants marginally influenced the rate of decline in the CDR-SB score that was observed after 104 weeks, the treatment difference in the least-squares mean (LSM) change from baseline was −0.63 points (standard error [SE], 0.546; $P=0.25$) in favor of AADvac1 (Fig. 2A).

The sensitivity analysis of study completers, i.e. participants who completed the study and had an evaluation of the CDR-SB score at 104 weeks (n = 72 with AADvac1, $n=42$ with placebo), suggested a stronger effect of AADvac1. The treatment difference in the LSM change from baseline at 104 weeks was −0.97 points (SE, 0.543; $P=0.08$; slowing of decline by 19% [95% CI, −1.8 to 39.9]) (Fig. 2B).

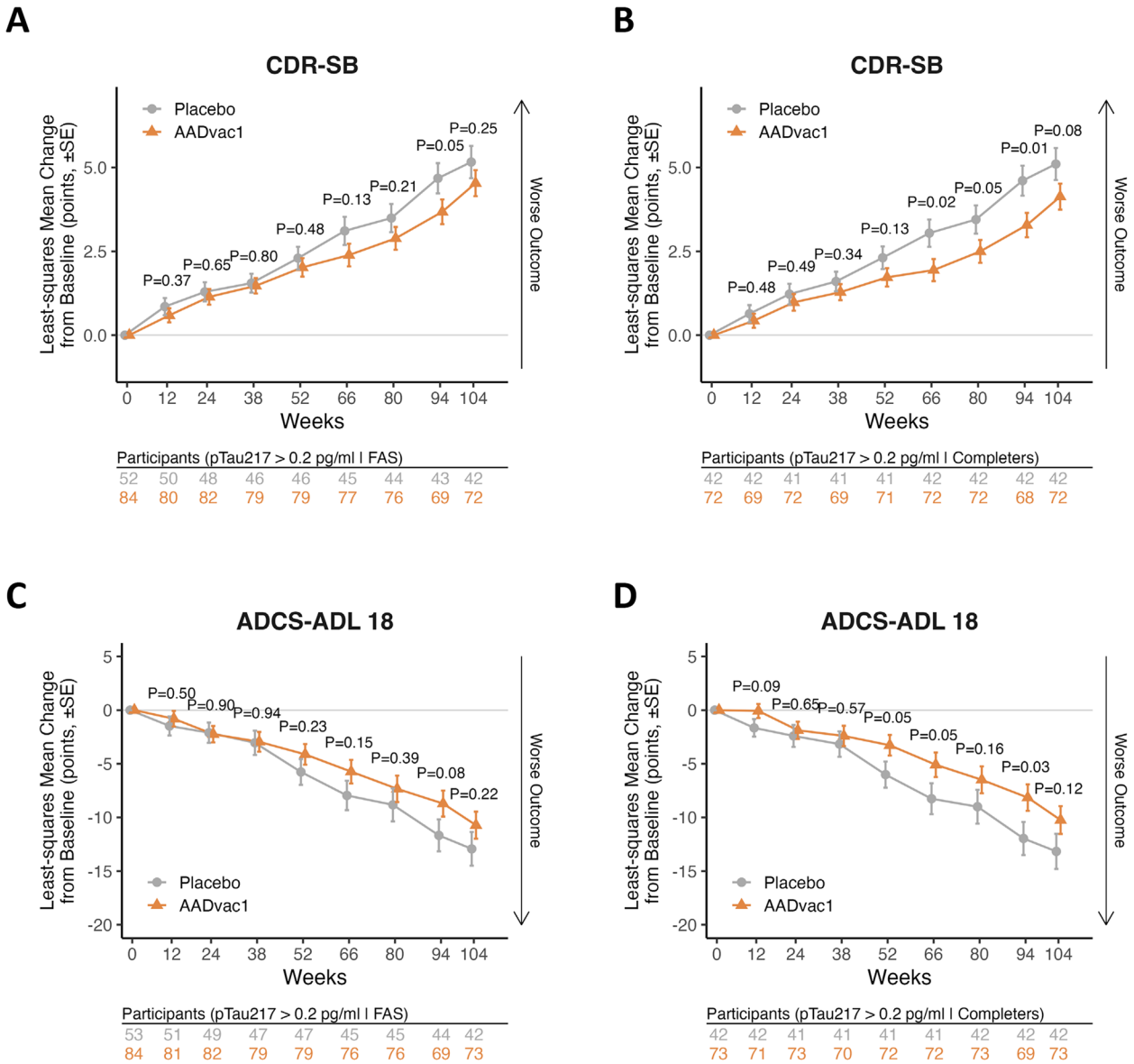

Fig. 2 Changes in key secondary endpoints (CDR-SB, ADCS-ADL-MCI-18) in plasma p-tau217 'positive' participants after AADvac1 treatment. A mixed model for repeated measures (MMRM) analysis for the CDR-SB and ADCS-ADL-MCI-18 endpoints in the plasma p-tau217 'positive' ADAMANT participants. (**A**) and (**C**), analysis of participants from the full analysis set ("FAS", $n=137$). (**B**) and (**D**), analysis of participants who had the CDR-SB ($n=114$) and ADCS-ADL-MCI-18 scores ($n=115$) evaluated at 104 weeks ('Completers'). All models were adjusted for the baseline and time-interaction effects of age, sex, geographical region, baseline MMSE score, baseline plasma NfL, and *APOE* status. Higher CDR-SB values and lower ADCS-ADL-MCI-18 values indicate worsening. The error bars indicate the standard error. The dotted line indicates the baseline

Analysis of functional status assessed by the ADCS-ADL-MCI-18 score revealed a nonsignificant difference in the LSM change from baseline between the treatment groups at 104 weeks, which was 2.2 points (SE, 1.77; $P=0.22$) in favor of AADvac1 (Fig. 2C).

The benefits of AADvac1 on the ADCS-ADL-MCI-18 score were possibly greater for study completers, the difference at 104 weeks was 2.9 points (SE, 1.84; $P=0.12$; nominal slowing of decline by 22% [95% CI, −5.2 to 49.6]) (Fig. 2D).

Antibody response to AADvac1 in plasma p-tau217 'positive' participants

The AADvac1-induced antibody response reached a geometric mean IgG titer of 1:17,494 (95% CI, 11,989 to 25,528) at week 24 (after the initial six doses) in plasma p-tau217 'positive' participants, and 1:16,985 (95% CI, 10,178 to 28,342) in the 'negative' subgroup (Supplementary material Figure S3). The response rate at week 24 was 97% for both the p-tau217 'positive' and p-tau217 'negative' subgroups.

Analysis of neuroimaging biomarkers in plasma p-tau217 'positive' participants

In plasma p-tau217 'positive' participants, no difference between in the LSM change in vMRI from baseline to 104 weeks was detected in the whole-brain volume (1.5 mm^3 [SE, 3.4], $P=0.66$) (Fig. 3A). Differences in favor of AADvac1, although not statistically significant, were observed in the cortical regions, including the whole brain cortex (the difference was 6.6 cm^3 [SE, 4.31]; nominally slowing the atrophy rate by 29% [95% CI, −8.4 to 66.7]; $P=0.13$), the temporal cortex (difference, 2.3 cm^3 [SE, 1.18]; nominally slowing atrophy by 27% [95% CI, −0.6 to 55.4]; $P=0.06$), the frontal cortex (difference, 1.9 cm^3 [SE, 1.51]; nominally slowing atrophy by 32% [95% CI, −17.6 to 81.0]; $P=0.21$) (Fig. 3B, C, D, respectively), and the occipital cortex (difference, 0.8 cm^3 [SE, 0.49], slowing atrophy by 38% [95% CI, −7.4 to 84.1]; $P=0.10$) (Supplementary material Figure S4).

Marginal, statistically nonsignificant, treatment differences were observed for the parietal cortex (difference, 1.1 cm^3 [SE, 0.99], $P=0.29$) and the left and right entorhinal cortices (0.06 cm^3 [SE, 0.038], $P=0.12$, and 0.049 cm^3 [SE, 0.041], $P=0.23$, respectively). No differences were detected for the left and right hippocampi (Supplementary material Figure S4).

Analysis of plasma biomarkers in plasma p-tau217 'positive' participants

In the biomarker-positive subgroup, AADvac1 showed a benefit on plasma NfL, as the difference between the treatment groups in the LSM change from baseline (log_{10}-transformed values) at 104 weeks was −0.139 (SE, 0.046; $P=0.003$) (Fig. 3E). This treatment difference corresponded to a decrease in the accumulation of plasma NfL by 56% (95% CI, 19.4 to 93.1, the difference in the untransformed values was −4.1 pg/mL [SE, 1.381]; $P=0.004$; Supplementary material Figure S5A).

The treatment difference in the LSM change in plasma GFAP from baseline (log_{10}-transformed values) at 104 weeks was 0.135 (SE, 0.055; $P=0.02$) (Fig. 3F), which corresponded to a mean treatment difference of 73% (95% CI, 14.2 to 131.5, the difference in the untransformed values was −77.6 pg/mL [SE, 38.8]; $P=0.05$; Supplementary material Figure S5B).

The treatment differences in the study endpoints are summarized in a forest plot in Fig. 4.

Relationship between trial endpoints and AADvac1-induced antibody levels

To evaluate the dose effect of the AADvac1-induced anti-tau antibodies on the trial endpoints, the AADvac1-treated plasma p-tau217 'positive' participants were split into high- and low-responder subgroups on the basis of the AADvac1-induced antibody levels at week 24 (see the Methods section), and each subgroup was compared with the entire placebo (one example each of clinical, vMRI and plasma endpoints is shown in Fig. 5, and the remaining data are shown in Supplementary material Figure S6).

In the high-responder subgroup, the difference from the placebo subgroup in the LSM change from baseline in CDR-SB at 104 weeks was −0.97 points (SE, 0.962; $P=0.32$) (Fig. 5A). In the low responder subgroup, the difference was −0.69 points (SE, 0.594; $P=0.25$).

The difference between the treatments in the volume loss of the temporal cortex at 104 weeks was 3.6 cm^3 (SE, 1.76; $P=0.05$; nominal slowing atrophy by 46% [95% CI, 1.8 to 89.8]) in the high-responder subgroup, and 1.9 cm^3 (SE, 1.36; $P=0.16$; 24% slowing [95% CI, −9.2 to 56.6]) in the low-responder subgroup (Fig. 5B).

The difference between the high-responder subgroup and placebo in plasma NfL (log_{10}-transformed) was 0.19 (SE, 0.076; $P=0.01$; slowing of accumulation by 87% [95% CI, 19.4 to 154.9]), and between the low-responder subgroup and placebo it was 0.13 (SE, 0.05; $P=0.01$; 57% [95% CI, 13.3 to 101.1]) (Fig. 5C). The treatment difference between the high-responder subgroup and placebo in the changes of log_{10}-transformed plasma GFAP (Fig. 5D) was 0.25 (SE, 0.087; $P=0.006$; slowing accumulation by 126% [95% CI, 39.3 to 212.5]), while the difference between the low-responder subgroup and placebo was 0.11 (SE, 0.053; $P=0.04$; slowing accumulation by 66% [95% CI, 2.5 to 130.4]) (Fig. 5D).

The treatment differences in the high- and low-responder subgroups in other endpoints including the

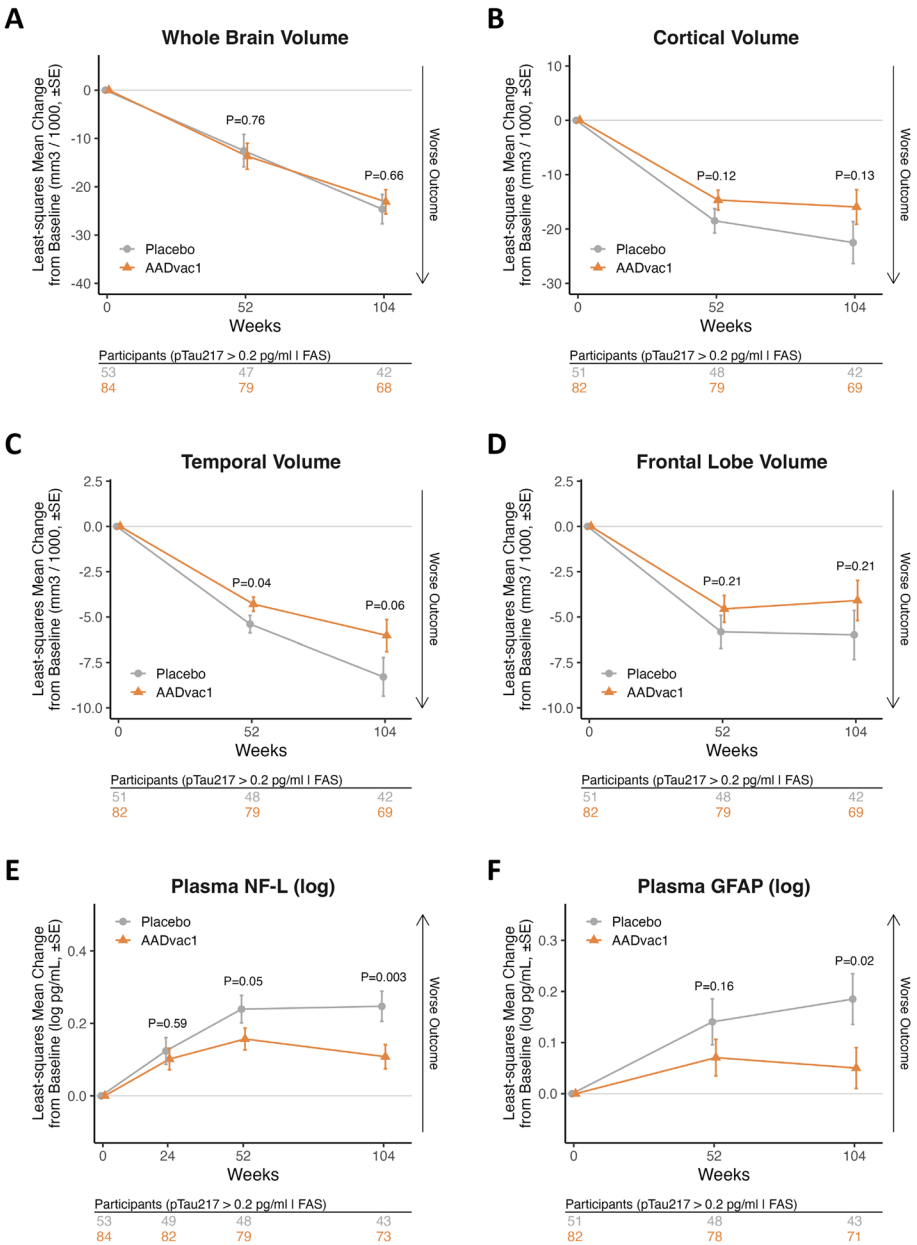

Fig. 3 Changes in neurodegeneration and astrogliosis biomarkers in plasma p-tau217 'positive' participants following AADvac1 treatment. The treatment differences in the change from baseline at week 104 in neuroimaging and plasma biomarkers in the plasma p-tau217 'positive' participants were analyzed by MMRM: (**A**), 6% (95% CI, −20.9 to 33.3, $P=0.66$) in the whole brain volume; (**B**), 29% (95% CI, −8.4 to 66.7; $P=0.13$) in the entire cortical tissue; (C), 27% (95% CI, −0.61 to 55.4; $P=0.06$) in the temporal cortex; (**D**), 32% (95% CI, −17.6 to 81.0; $P=0.21$) in the frontal cortex; (**E**), 56% (95% CI, 19.4 to 93.1, $P=0.003$) in plasma NfL (log_{10}-transformed concentrations); (**F**), 73% (95% CI, 14.2 to 131.5, $P=0.02$) in plasma GFAP (log_{10}-transformed concentrations). All the MMRM models were adjusted for variables as described in the Methods section. FAS, the positive participants were selected from the full analysis set. The error bars indicate the standard error. The dotted line indicates the baseline

ADCS-MCI-ADL-18 score, whole-brain volume, and entire cortex, are shown in Supplementary material Figure S6.

Secondary and exploratory endpoints in plasma p-tau217 'negative' participants

The baseline characteristics of the plasma p-tau217

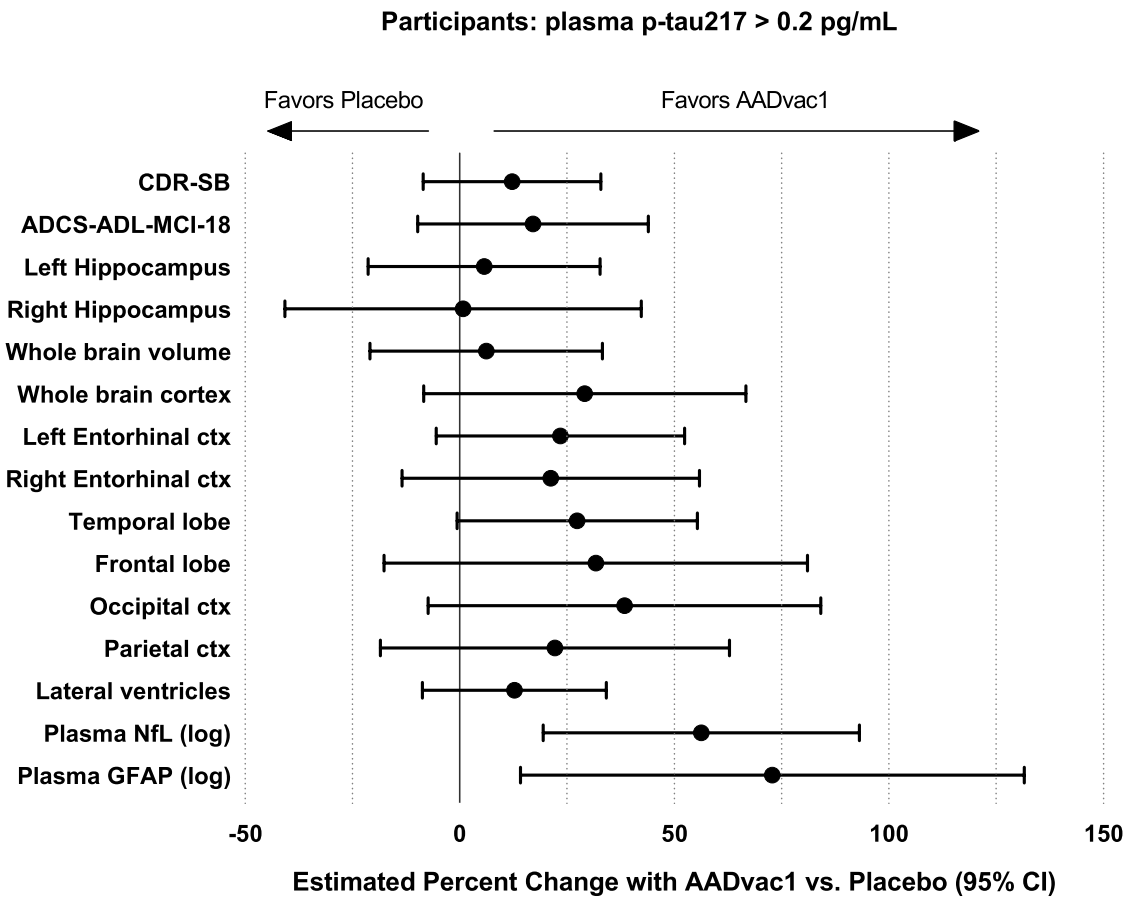

Fig. 4 Forest plot summarizing the effect of AADvac1 on outcomes in plasma p-tau217 'positive' participants. A mixed model for repeated measures (MMRM) analysis was performed for changes in cognitive, volumetric and plasma biomarker outcomes at 104 weeks. Percent differences between the AADvac1 and placebo groups were plotted along with 95% CIs (error bars). Ctx, cortex

'negative' participants are shown in Table 1. In this 'negative' subgroup, AADvac1 had no effect on the secondary outcomes or plasma biomarkers (Supplementary material Figure S7).

Discussion

This post hoc analysis of the ADAMANT trial revealed a reduction in the accumulation of plasma biomarkers of neurodegeneration (NfL) and reactive astrogliosis (GFAP) in AADvac1-treated mild AD participants positive for plasma p-tau217. From a safety standpoint, the vaccine was well tolerated in this subgroup and no clinically significant adverse findings, except injection site reactions, were associated with AADvac1.

The findings, while hypothesis generating, may be particularly noteworthy, as it has been shown that p-tau217 reflects the accumulation of both amyloid plaques and tau tangles in the brain and has the potential to become an excellent AD biomarker to identify Aβ and tau positivity comparable to key CSF- or PET-based measures [37–40]. The use of p-tau217 for supporting diagnostics and clinical trials has been strengthened by extensive clinical research on Aβ-targeting immunotherapy [34, 41, 42].

Several monoclonal antibodies targeting the N-terminal region of tau have failed to show benefit in the clinical development [43–47], which prompted discussions regarding the selection of an adequate target region on tau [48]. Recently, the microtubule-binding region (MTBR) of tau has garnered attention as a new biomarker highly specific for tangle pathology and promising for the staging of sporadic AD [49, 50], which further emphasized the importance of the MTBR of tau for therapeutic interventions. The new biomarker MTBR-tau243 offers support for the scientific rationale of the development of AADvac1 immunotherapy, which targets this region on pathological tau, inhibits tau aggregation, prevents the spread of neurofibrillary pathology [51], facilitates the removal of extracellular tau via microglia [52], and thus might affect the course of AD [53]. The antibodies recognize four epitopes in the tau MTBR, thus targeting the full spectrum of tau pathology in the human AD brain [6, 54].

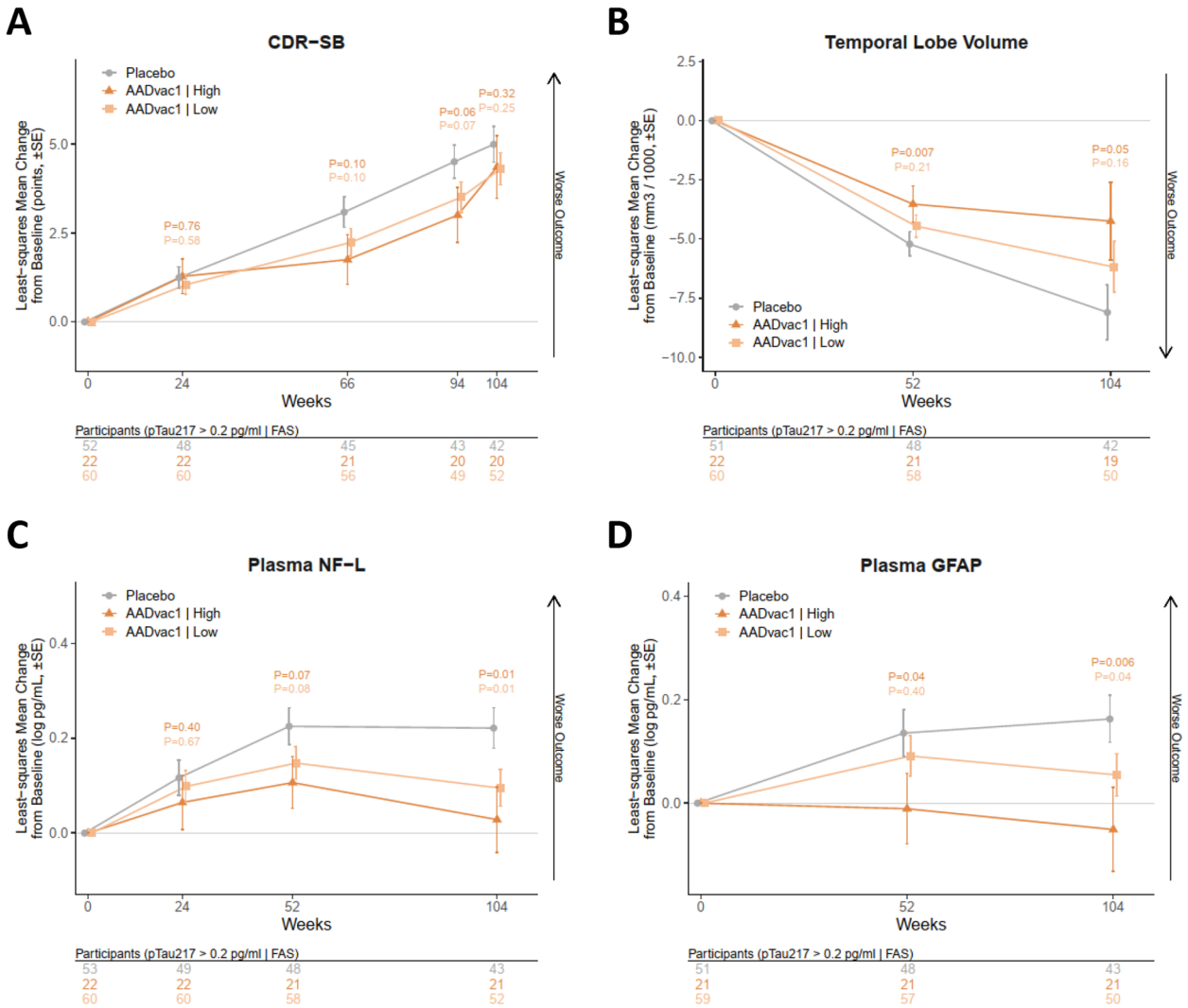

Fig. 5 Trial endpoints in plasma p-tau217 'positive' participants with high and low AADvac1-induced antibody levels Analyses of changes from baseline in the CDR-SB (**A**), temporal lobe volume (**B**), and plasma NfL (**C**) and GFAP (**D**) levels performed on two subgroups of plasma p-tau217 'positive' participants, those with high ('High', $n=22$) and low ('Low', $n=60$) AADvac1-induced antibody levels. Both responder subgroups were compared with the entire plasma p-tau217 'positive' placebo ($n=53$). The error bars indicate the standard error. The dotted line indicates the baseline. The results of the analyses of other endpoints are shown in Supplementary material Figure S6

This post hoc exploratory analysis of plasma p-tau217 'positive' ADAMANT participants suggested that AADvac1 reduced neurodegeneration and neuroinflammation in participants with AD, as measured by plasma NfL and GFAP, and might have an impact on cognition (CDR-SB), activities of daily living (ADCS-ADL-MCI-18), and rates of cortical brain atrophy measured via vMRI. While most of these treatment differences are statistically nonsignificant and measured at 104 weeks, the described effect sizes (especially in study completers) are comparable to those of the anti-amyloid monoclonal antibodies (AAMAs), donanemab (23% on the CDR-SB, 23% on the ADCS-iADL at 76 weeks) and lecanemab (22% on the CDR-SB, 40% on the ADCS-ADL-MCI at 78 weeks).

The potential for AADvac1 to reduce neurodegeneration may be reflected through NfL, which also shows promise as a marker of disease progression in AD [12, 55]. There have been contradictory results for plasma NfL with AAMAs. While lecanemab showed reduction compared with placebo after 18 months [56], there was no effect with donanemab [57]. In ADAMANT, there was a 56% reduction in the NfL accumulation rate in the AADvac1 group compared with the placebo group. This reduction may reflect slowing of the progression of neurofibrillary pathology and neurodegeneration [11].

Plasma GFAP emerged as a responsive biomarker in AAMA studies and represents a potentially informative biomarker for diagnostics and clinical trials. In cognitively impaired patients, GFAP provides information on both tau pathology and Aβ deposition [37, 58]. GFAP demonstrated good individual prediction of Braak staging of neurofibrillary pathology, providing nonoverlapping information with phospho-tau [59], and has been reported to be a predictive marker of future functional decline [60]. AADvac1 decelerated the increase in plasma GFAP levels by 73%, suggesting an effect on neurodegeneration and neuroinflammation. This conclusion is corroborated by recent data indicating a direct link between early astrocyte reactivity and synapse damage [64].

The plasma biomarker outcomes of AADvac1 might be supported by the nominal slowing, although statistically nonsignificant, of brain cortical tissue loss as measured by vMRI, which was more pronounced in participants with higher antibody response. This is of potential interest at a time when treatment effects with AAMAs are showing vMRI results indicating more atrophy and where the significance of that finding is uncertain [61, 62]. Our findings add to the characterization of MRI changes associated with various forms of immunotherapy, and thus merit further investigation and confirmation in larger clinical trials. Furthermore, the outcomes of amyloid and tau therapies support the conclusion that combining an AAMA with a tau-targeted therapy, such as AADvac1, could lead to an additive positive impact on clinical decline.

Finally, these findings support the potential utility of plasma p-tau217 in selecting participants for clinical trials in early AD [34, 63], with active tau-targeted immunotherapy directed at the microtubule-binding regions.

These analyses have several important limitations. They are undertaken post hoc to the trial's completion and must be considered hypothesis-generating. The number of participants who are evaluated in the subanalyses varies and it is not possible to control for differences in the characteristics of the treatment arms while the available sample is smaller than the parent study. The participants were all white Europeans. The analyses we have undertaken do not control for multiple comparisons and provide only nominal significance. The plasma biomarker concentrations were not corrected for the body-mass index or kidney function. The correlation analyses of plasma p-tau217 with CSF biomarkers suffer from a low number of samples. It is recognized that this plasma p-tau217 assay has yet to be fully validated against either amyloid or tau PET and that some of the subjects might not in fact be positive for tau neurofibrillary pathology. Finally, we have not tested for additional pathologies (Lewy bodies, TDP-43), which increase the disease progression rate and might cause an imbalance between the treatment arms.

Conclusions

In this study, we identified a subgroup of the phase 2 ADAMANT study participants most likely suffering from AD neuropathological changes on the basis of elevated plasma p-tau217. Analyses of outcomes in this biomarker-confirmed AD subgroup revealed possible benefits of AADvac1 on the rate of accumulation of plasma NfL and GFAP. These findings were supported by a statistically nonsignificant slowing of cortical brain atrophy in subjects receiving AADvac1. The effects on the study outcomes were more pronounced in individuals with greater antibody response. These data merit further attention in larger clinical trials.

Abbreviations

AAMA	Anti-Amyloid Monoclonal Antibody
Aβ42	Amyloid Beta 1–42
AE	Adverse Event
AD	Alzheimer's Disease
ADCS-ADL-MCI-18	Alzheimer's Disease Cooperative Study-Activities of Daily Living Score for Mild Cognitive Impairment (18-item version)
ADCS-iADL	Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory
ApoE4	Apolipoprotein E allele ε4
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CI	Confidence Interval
CSF	Cerebrospinal Fluid
FAS	Full Analysis Set
GFAP	Glial Fibrillary Acidic Protein
ISR	Injection Site Reaction
LSM	Least-Squares Mean
mAb	Monoclonal Antibody
MMSE	Mini-Mental State Examination
MMRM	Mixed Model For Repeated Measures
MTBR	Microtubule-Binding Region
NfL	Neurofilament Light
NIA-AA	National Institute on Aging and Alzheimer's Association
p-tau217	Tau Phosphorylated at Threonine 217
PET	Positron Emission Tomography
SAE	Serious Adverse Event
SE	Standard Error
Simoa	Single Molecule Assay
SOC	System Organ Class
vMRI	Volumetric Magnetic Resonance Imaging

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01620-7.

Supplementary Material 1: Figures S1–S7, Tables S1-S4, Supplementary Methods

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Authors' contributions
BK analyzed and interpreted the data, and conceived the original draft of the manuscript. NC and SK performed the statistical analysis. PN and MF participated in the design of the clinical trial and interpretation of the results. JH analyzed the plasma NfL and GFAP levels and interpreted the results. EK performed the immunogenicity analyses and contributed to the data interpretation. VP participated in the analysis of blood biomarkers and data interpretation. JV, ES and EV analyzed plasma p-tau217 and interpreted the results. HF participated in the interpretation of the data and manuscript preparation. BW contributed to the study design, interpretation of the results and manuscript preparation. NZ participated in the clinical trial design, interpretation of the results and manuscript preparation. All authors approved the submitted version of the manuscript.

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Data availability
All data and code from the present study are available to qualified investigators upon relevant requests.

Declarations

Ethics approval and consent to participate
The ADAMANT study protocol (provided with the Statistical Analysis Plan in Clinical Trial Material Supplement) was approved by the appropriate ethics committees and competent authorities [8]. All patients and their caregivers provided written informed consent before the study procedures.

Consent for publication
Not applicable.

Competing interests
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