Safety and efficacy of tilavonemab in progressive supranuclear palsy: a phase 2, randomised, placebo-controlled trial

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*Listed in the appendix

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See Online for appendix

Summary

Background Progressive supranuclear palsy is a neurodegenerative disorder associated with tau protein aggregation. Tilavonemab (ABBV-8E12) is a monoclonal antibody that binds to the N-terminus of human tau. We assessed the safety and efficacy of tilavonemab for the treatment of progressive supranuclear palsy.

Methods We did a phase 2, multicentre, randomised, placebo-controlled, double-blind study at 66 hospitals and clinics in Australia, Canada, France, Germany, Italy, Japan, Spain, and the USA. Participants (aged ≥40 years) diagnosed with possible or probable progressive supranuclear palsy who were symptomatic for less than 5 years, had a reliable study partner, and were able to walk five steps with minimal assistance, were randomly assigned (1:1:1) by interactive response technology to tilavonemab 2000 mg, tilavonemab 4000 mg, or matching placebo administered intravenously on days 1, 15, and 29, then every 28 days through to the end of the 52-week treatment period. Randomisation was done by the randomisation specialist of the study sponsor, who did not otherwise participate in the study. The sponsor, investigators, and participants were unaware of treatment allocations. The primary endpoint was the change from baseline to week 52 in the Progressive Supranuclear Palsy Rating Scale (PSPRS) total score in the intention-to-treat population. Adverse events were monitored in participants who received at least one dose of study drug. Prespecified interim futility criteria were based on a model-based effect size of 0 or lower when 60 participants had completed the 52-week treatment period and 0·12 or lower when 120 participants had completed the 52-week treatment period. This study is registered at ClinicalTrials.gov, number NCT02985879.

Findings Between Dec 12, 2016, and Dec 31, 2018, 466 participants were screened, 378 were randomised. The study was terminated on July 3, 2019, after prespecified futility criteria were met at the second interim analysis. A total of 377 participants received at least one dose of study drug and were included in the efficacy and safety analyses (2000 mg, n=126; 4000 mg, n=125; placebo, n=126). Least squares mean change from baseline to week 52 in PSPRS was similar in all groups (between-group difference *vs* placebo: 2000 mg, 0·0 [95% CI –2·6 to 2·6], effect size 0·000, p>0·99; 4000 mg, 1·0 [–1·6 to 3·6], –0·105, p=0·46). Most participants reported at least one adverse event (2000 mg, 111 [88%]; 4000 mg, 111 [89%]; placebo, 108 [86%]). Fall was the most common adverse event (2000 mg, 42 [33%]; 4000 mg, 54 [43%]; placebo, 49 [39%]). Proportions of patients with serious adverse events were similar among groups (2000 mg, 29 [23%]; 4000 mg, 34 [27%]; placebo, 33 [26%]). Fall was the most common treatment-emergent serious adverse event (2000 mg, five [4%]; 4000 mg, six [5%]; placebo, six [5%]). 26 deaths occurred during the study (2000 mg, nine [7%]; 4000 mg, nine [7%]; placebo, eight [6%]) but none was drug related.

Interpretation A similar safety profile was seen in all treatment groups. No beneficial treatment effects were recorded. Although this study did not provide evidence of efficacy in progressive supranuclear palsy, the findings provide potentially useful information for future investigations of passive immunisation using tau antibodies for progressive supranuclear palsy.

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Introduction

Tauopathies are disorders of tau protein aggregation that are heterogeneous in biochemistry, morphology, and clinical presentation.[1] Strategies targeting tau as a therapeutic intervention include active immunisation (which elicits an immune response) and passive immunisation (which entails delivery of preformed antibodies). These strategies have shown promise in reducing tau pathology in transgenic mouse models of tauopathies.[2–4]

Progressive supranuclear palsy is a tauopathy characterised by degeneration in the cerebral cortex, basal ganglia, and brainstem. It is associated with abnormal tau protein folding and aggregation, in particular the 4R tau isoform.[1,5] Progressive supranuclear palsy is a progressive neurodegenerative disorder that is ultimately fatal. Mean survival from symptom onset is approximately 6·8–8·0 years.[6,7] Progressive supranuclear palsy has an estimated prevalence of 10·7–17·9 cases per 100 000 people.[8,9]

Research in context

Evidence before this study

We searched PubMed between Jan 1, 1950, and Nov 1, 2020, with the terms "progressive supranuclear palsy", "tauopathies", "anti-tau antibody", and "neurofilament light chain", and we filtered our search by "clinical trials", "randomised controlled trials", "meta-analyses", and "review articles". We did not restrict our search by language. The search term "progressive supranuclear palsy" with the filter "clinical trial" yielded 119 results. According to these searches, research on participants with progressive supranuclear palsy has increased over the past two decades, particularly after the establishment of diagnostic criteria in the mid-1990s. We found no evidence in the peer-reviewed literature of a phase 2 clinical trial of an anti-tau antibody for progressive supranuclear palsy, although another tau antibody (gosuranemab) has been tested in people with progressive supranuclear palsy (NCT03068468). We found published clinical trials for other investigational treatments for progressive supranuclear palsy, including a benzothiazole (riluzole; NCT00211224), an octapeptide thought to stabilise microtubules (davunetide; NCT01110720), and a small-molecule glycogen synthase kinase 3 inhibitor (tideglusib; NCT01049399). To date, no treatment trials of progressive supranuclear palsy have shown efficacy in slowing progression of this disorder.

Added value of this study

To our knowledge, our report is the first publication of phase 2 trial results of an anti-tau antibody. Although we did not detect a treatment effect of tilavonemab in progressive supranuclear palsy, a similar safety profile was seen in all treatment groups. Analysis of biomarker data indicated that tilavonemab modifies levels of CSF free tau and plasma total tau.

Implications of all the available evidence

Although target engagement was noted in CSF, efficacy was not shown in participants with progressive supranuclear palsy. These results provide potentially important information for future investigations of tau-directed antibody therapy and potential biomarkers in progressive supranuclear palsy. Investigations of antibodies that bind to other tau epitopes, earlier interventions in the progressive supranuclear palsy disease process, or both could be warranted. Clinical trials of tilavonemab for the treatment of Alzheimer's disease are ongoing (NCT02880956, NCT03712787).

Early signs of progressive supranuclear palsy largely overlap with those of Parkinson's disease until onset of slowing of vertical saccades, vertical gaze palsy, or postural instability (which presents early in the course of progressive supranuclear palsy).[5,10,11] No biomarkers have been validated that can reliably differentiate early progressive supranuclear palsy from other neurodegenerative disorders or that can show pharmacodynamic effects of investigational therapies.[12] Due to the symptomatic overlap with Parkinson's disease and paucity of diagnostic biomarkers, early diagnosis of progressive supranuclear palsy is challenging.[5,12] No drugs are approved for progressive supranuclear palsy. Treatment focuses on symptom management, but symptomatic therapies typically have limited evidence of efficacy.[10,12,13]

Tilavonemab (ABBV-8E12) is a monoclonal antibody that binds to the N-terminus of human tau.[14] In transgenic mice expressing mutated human tau, anti-tau antibody reduced loss of brain volume, slowed progression of tau pathology, and increased cognitive performance.[14,15] In a phase 1, placebo-controlled, single ascending dose study in people with progressive supranuclear palsy (NCT02494024), tilavonemab showed an acceptable safety and tolerability profile.[16] These results allowed for dose escalation up to 50 mg/kg and supported repeat-dose testing in a larger cohort.[16] On the basis of these findings, we investigated the safety and efficacy of tilavonemab in individuals with a diagnosis of possible or probable progressive supranuclear palsy in the Arise phase 2 randomised clinical trial.

Methods

Study design and participants

We did a phase 2, randomised, double-blind, placebo-controlled, parallel-group, multicentre trial. Participants were enrolled at 66 study sites in Australia, Canada, France, Germany, Italy, Japan, Spain, and the USA. Eligible participants were men or women aged 40 years or older who met the National Institute of Neurological Disorders and Stroke and the Society for Progressive Supranuclear Palsy (NINDS-SPSP) criteria for possible or probable progressive supranuclear palsy;[11] had symptoms of progressive supranuclear palsy for less than 5 years; could walk five steps with minimal assistance; and had an identified reliable study partner (eg, caregiver, family member, social worker, or friend). Full inclusion and exclusion criteria are listed in the appendix (pp 4–6).

All participants and their respective study partners were required to provide written informed consent before screening or any study-specific procedures. The study received independent ethics committee or institutional review board approval at each study site before initiation. The study adhered to all applicable local regulations, was done in accordance with Good Clinical Practice, as outlined by the International Conference on Harmonisation, and complied with ethical standards described in the Declaration of Helsinki.

Randomisation and masking

Participants with progressive supranuclear palsy were randomly assigned (1:1:1) tilavonemab 2000 mg, tilavonemab

4000 mg, or matching placebo. Randomisation was stratified by study site, except in Japan because of the limited number of participants in this country. Study sites were added in Japan after initiation of the study in other countries, and randomisation at Japanese sites was prepared separately to maintain the original randomisation schedule.

Randomisation was done by Bioclinica (Princeton, NJ, USA) using a central interactive web response system that randomly allocated treatment assignment to participants who were eligible for enrolment. Block randomisation codes (block size of three) were generated by the randomisation specialist of the study sponsor, who did not participate in any other study activities. The sponsor, investigators, and participants were unaware of assigned treatments during the study treatment and follow-up periods. Blinded clinical assessments were done by the study investigators, and the sponsor did blinded safety reviews. Blinded analysis of MRI scans was done by IXICO (London, UK).

Procedures

The study comprised an 8-week screening period (with two screening visits between days –56 and –8), a 52-week double-blind treatment period (including visits for efficacy measurements at weeks 0 [randomisation], 12, 24, 36, and 52), and a 20-week post-treatment follow-up period (visits at weeks 60 and 68; appendix p 13). Tilavonemab (AbbVie, Worchester, MA, USA [manufacturer of the antibody]; Vetter Pharma, Ravensburg, Germany [manufacturer of the antibody-containing drug product]) was administered intravenously, with the duration of infusion dependent on the most recent measure of participant weight as assessed throughout the screening and treatment periods (appendix p 7). Participants received infusions on days 1, 15, and 29, and every 28 days thereafter for the remainder of the double-blind treatment period. They were monitored on-site for at least 2 h after the first four infusions, and for at least 30 min after each subsequent infusion. The first 30 enrolled participants in all countries except Japan comprised cohort 1. The first nine participants enrolled in Japan comprised cohort J1. Participants in cohort 1 and cohort J1 underwent more frequent pharmacokinetic and biomarker assessments than did the overall participant population.

The Progressive Supranuclear Palsy Rating Scale (PSPRS) was assessed at the first screening visit, before the first dose (baseline; week 0), and at treatment weeks 12, 24, 36, and 52. The Unified Parkinson's Disease Rating Scale (UPDRS) part II (activities of daily living), the Schwab and England Activities of Daily Living (SEADL) scale, and the Progressive Supranuclear Palsy Quality of Life (PSP-QoL) scale were all assessed at the first screening visit and weeks 0 (baseline), 12, 24, 36, and 52. Clinical Global Impression of Change (CGI-C) and Clinical Global Impression of Severity (CGI-S) were assessed at weeks 8, 12, 20, 24, 32, 36, 48, and 52; CGI-S was assessed additionally at both screening visits and week 0. MRI was done at the first screening visit and at weeks 12, 24, and 52 in all participants, and additionally at week 2 in cohorts 1 and J1. Safety was monitored throughout the study. Blood samples for pharmacokinetic analysis were obtained at weeks 0 (baseline), 2, 4, 12, 24, 36, and 52, and at the two post-treatment follow-up visits. Cohort 1 and cohort J1 had additional pharmacokinetic blood samples collected at weeks 1, 8, 13, 14, and 16. Serum samples for biomarker analysis were obtained for all treated participants at the first screening visit and at weeks 28, 48, and 52, and additionally at week 12 in cohorts 1 and J1 only. CSF samples for biomarker analysis were collected via lumbar puncture at the first screening visit and at week 52 in all participants, and additionally at week 14 in cohorts 1 and J1 only.

Outcomes

The primary efficacy outcome was change from baseline (predose on the first day of treatment) to week 52 in the PSPRS total score. The PSPRS is a 28-item method to measure progression of progressive supranuclear palsy, with higher scores indicating more severe disease.[6] Key secondary efficacy outcomes were the change from baseline to week 52 in SEADL score, UPDRS part II score, and midbrain volumetric MRI; and the CGI-C score at week 52. Additional secondary outcomes were change from baseline to week 52 in CGI-S, PSP-QoL, PSPRS domain scores, volumetric MRI in representative brain regions (the third ventricle, whole brain, frontal lobe, superior cerebellar peduncle, and brainstem; appendix p 2),[17,18] the Progressive Supranuclear Palsy Staging System (PSP-SS) score, and PSPRS item 26. Safety events included reports of treatment-emergent adverse events and serious adverse events. Safety events were monitored throughout the duration of study drug treatment and for 20 weeks after the last dose and were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0. Pharmacokinetic and biomarker outcomes and antibody characterisation methods are listed in the appendix (pp 2–3).

Statistical analysis

Sample size calculations were done using simulations with East (version 6.3.1; Cytel, Waltham, MA, USA). A sample size of approximately 330 participants (roughly 110 participants in each of the three treatment groups) was designed to have overall 90% power (from either dose) to detect a treatment effect at the two doses (Cohen's effect size of 0·56 for the 4000 mg dose and 0·28 for the 2000 mg dose) on the primary efficacy endpoint (SD 10·27) based on published data.[19,20] The Bonferroni method was used for multiplicity control due to multiple comparisons between the two doses and placebo groups, so the overall type I error rate (α) for the primary endpoint was controlled at the two-sided 5% level. An assumption was made of a no-data rate of 25% at week 52.

The change from baseline to week 52 in all efficacy assessments was analysed using a mixed-effect repeated-measure model. Degrees of freedom were estimated using Satterthwaite's approximation. Summary statistics of pharmacokinetic parameters were provided by treatment groups. ANCOVA was done to assess dose proportionality. For CSF biomarker assessment, ANCOVA was done at weeks 14 and 52. For plasma biomarkers, ANCOVA was done at weeks 28, 48, and 52 using a likelihood-based, mixed-effect repeated measure model. Due to non-symmetry in the probability distribution, logarithmic transformation was done. Estimates of central value on original scale were provided through back-transformation of least squares means for the logarithms. Comparisons between groups were calculated as ratios of the estimates of central values. Hypothesis testing for all assessments was done at the 0·05 significance level. Statistical analyses were done using SAS version 9.3 or higher (SAS Institute, Cary, NC, USA) under the Unix operating system.

Efficacy analyses were done in the intention-to-treat (ITT) dataset. The safety analysis was done in the safety dataset. Both ITT and safety datasets included all randomly assigned participants who received at least one dose of study drug. The ITT dataset was analysed by treatment assigned at randomisation whereas the safety data set was analysed by actual treatment received.

Two futility analyses were planned: the first was done after 60 participants completed the 52-week treatment period; the second was done when 120 participants completed the 52-week treatment period. Futility analyses were done using a mixed-effect repeated-measure analysis of changes in PSPRS total score from baseline to week 52. The threshold for interim futility analyses was a model-based treatment effect size of 0 or lower at the first analysis or 0·12 or lower at the second analysis.

The study was overseen by a data monitoring committee (DMC), which comprised four external clinicians, one external pharmacokineticist, and one external statistician. No DMC members were employees of the sponsor or involved in other study activities. The DMC reviewed unblinded efficacy and safety data and made recommendations to the sponsor.

This trial is registered with ClinicalTrials.gov, NCT02985879.

Role of the funding source

The funder of the study participated in study design, study research, data collection, data analysis, data interpretation, and writing, review, and approval of the report. All authors had full access to the data, participated in the development and review of the report, had full responsibility for the content, and approved the report for submission for publication.

Results

Between Dec 12, 2016, and Dec 31, 2018, 466 participants were screened for the study, of whom 88 were excluded, mainly because they did not meet criteria or withdrew consent (figure 1). 378 participants were randomly allocated tilavonemab 2000 mg (n=127), tilavonemab 4000 mg (125), or placebo (126). One participant allocated tilavonemab 2000 mg was not treated due to withdrawing from the study because of a severe adverse event (atrial fibrillation) that occurred before the first dose of study drug and is not included in this analysis.

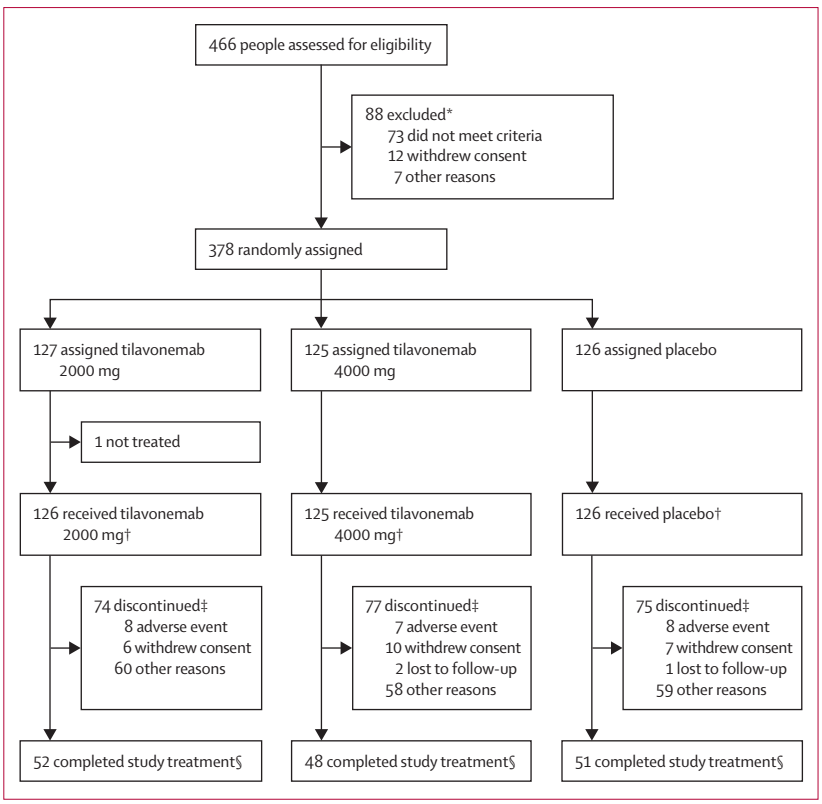

Figure 1: **Trial profile**
*Participants could have more than one reason for exclusion. †Includes all randomised participants who received one or more dose of study drug (intention-to-treat and safety populations). ‡Primary reasons for study drug discontinuation in all participants who received one or more dose of study drug. §Completed study drug treatment to week 52.

151 participants completed study drug treatment at week 52, of whom 52 were assigned tilavonemab 2000 mg, 48 were allocated tilavonemab 4000 mg, and 51 were assigned placebo (figure 1). Mean study drug exposure was 301·4 (SD 75·0) days for the tilavonemab 2000 mg group, 296·9 (77·7) days for the tilavonemab 4000 mg group, and 300·9 (78·6) days for the placebo group (appendix p 8). Antibody characteristics are described in the appendix (p 9).

The two interim analyses were done by the DMC. Based on its review, the DMC recommended to the sponsor that the trial was futile according to prespecified criteria at the second interim analysis (model-based effect size ≤0·12). Therefore, this study was terminated early by the sponsor on July 3, 2019. At study termination, 377 participants had been randomly assigned and

	Tilavonemab 2000 mg (n=126)	Tilavonemab 4000 mg (n=125)	Placebo (n=126)
Age, years	68·3 (7·2)	70·0 (6·8)	68·1 (6·2)
>65 years	83 (66%)	94 (75%)	82 (65%)
Sex			
Male	77 (61%)	69 (55%)	73 (58%)
Female	49 (39%)	56 (45%)	53 (42%)
Race			
White	106 (84%)	109 (87%)	109 (87%)
Other	20 (16%)	16 (13%)	17 (13%)
Weight, kg	76·5 (16·7)	75·4 (17·4)	77·2 (15·4)
Body-mass index, kg/m²	26·7 (4·2)	26·7 (4·7)	27·0 (4·3)*
Progressive supranuclear palsy duration, years			
Symptom onset to baseline	3·4 (1·4)	3·4 (1·4)	3·4 (1·2)
Diagnosis to baseline	1·4 (1·0)	1·3 (1·1)	1·4 (1·1)
PSPRS total score	36·5 (12·0)	35·9 (11·0)	36·7 (11·5)
UPDRS part II score	18·6 (7·1)	18·0 (6·6)	18·2 (7·1)
SEADL score	56·8 (22·3)	55·9 (20·7)	57·3 (21·6)
CGI-S score	3·8 (1·0)	3·8 (0·9)	3·8 (1·0)
PSP-QoL score	33·4 (18·8)	34·8 (16·4)	32·4 (16·8)
PSPRS domain scores			
History	7·4 (2·9)	7·4 (2·9)	7·4 (3·3)
Mentation	3·5 (2·5)	3·5 (2·4)	3·7 (2·7)
Bulbar	2·7 (1·4)	2·6 (1·5)	2·7 (1·4)
Ocular motor	8·7 (3·4)	8·1 (3·3)	8·8 (3·5)
Limb motor	4·8 (2·3)	4·6 (2·3)	4·5 (2·2)
Gait or midline	9·5 (4·4)	9·7 (4·0)	9·5 (4·0)
Volumetric MRI, mm³			
Midbrain	6766 (954)†	6788 (1062)†	6805 (1288)‡
Whole brain	1 071 371 (105 995)§	1 051 924 (104 156)¶	1 075 685 (116 559)‖
Third ventricle	2484 (828)†	2582 (826)†	2543 (965)‡
Frontal lobes	156 468 (19 688)**	154 132 (16 337)††	158 785 (21 973)‡‡
Superior cerebellar peduncle	652 (148)§§	660 (131)§§	662 (152)¶¶
Brainstem	24 771 (3256)**	24 389 (3238)††	24 971 (4431)‡‡
PSP-SS score	4·0 (1·8)	4·0 (1·9)	4·0 (1·9)
Concomitant PSP medication‖‖‖‖			
Dopaminergic agents	75 (60%)	92 (74%)	77 (61%)
Antidementia drugs	12 (10%)	6 (5%)	9 (7%)
Antidepressants	8 (6%)	7 (6%)	5 (4%)

Data are n (%) or mean (SD). CGI-S=Clinical Global Impression of Severity. PSP=progressive supranuclear palsy. PSP-QoL=Progressive Supranuclear Palsy Quality of Life Scale. PSPRS=Progressive Supranuclear Palsy Rating Scale. PSP-SS=Progressive Supranuclear Palsy Staging System. SEADL=Schwab and England Activities of Daily Living Scale. UPDRS=Unified Parkinson's Disease Rating Scale. *n=125. †n=122. ‡n=121. §n=113. ¶n=115. ‖n=110. **n=104. ††n=100. ‡‡n=103. §§n=119. ¶¶n=118. ‖‖‖‖>3% total in the overall study population, concomitant with the study drug.

Table 1: **Baseline demographics and characteristics**

received at least one dose of study drug. Participants still undergoing treatment were not able to continue treatment after study termination. Premature discontinuation visits were scheduled for all participants who did not have an opportunity to complete study drug treatment.

Study completion rates and primary reasons for discontinuation were similar across the treatment groups. The most common primary reason for study drug discontinuation was other (60 [48%] in the tilavonemab 2000 mg group, 58 [46%] in the tilavonemab 4000 mg group, and 59 [47%] in the placebo group), which mainly comprised discontinuation due to study termination. The numbers of participants who discontinued study drug primarily because of adverse events (participants could have multiple reasons for discontinuation) were similar between groups (eight [6%] in the tilavonemab 2000 mg group, seven [6%] in the tilavonemab 4000 mg group, and eight [6%] in the placebo group).

Demographics and clinical characteristics were similar between treatment groups (table 1). 219 (58%) of 377 participants were male, 324 (86%) were white, and 259 (69%) were aged older than 65 years. In all treatment groups, time between symptom onset and progressive supranuclear palsy diagnosis was approximately 2 years. 244 (65%) participants were receiving concomitant dopaminergic therapy.

All treatment groups showed similar symptomatic severity, with no differences between participants receiving tilavonemab and those receiving placebo. Change from baseline in PSPRS total score was similar between treatment groups at all visits up to week 52 (figure 2). The least squares mean change from baseline to week 52 was 10·5 (SE 1·0) for tilavonemab 2000 mg, 11·4 (1·0) for tilavonemab 4000 mg, and 10·5 (1·0) for placebo. The least squares mean difference in change from baseline to week 52 versus placebo for tilavonemab 2000 mg was 0·0 (95% CI –2·6 to 2·6; p>0·99; effect size 0·000) and for tilavonemab 4000 mg was 1·0 (–1·6 to 3·6; p=0·46; effect size –0·105).

Change from baseline to week 52 in UPDRS part II or SEADL scores did not differ between treatment groups (figure 3). Compared with placebo, for UPDRS part II, the least squares mean difference in change from baseline to week 52 was 0·2 (95% CI –1·5 to 1·9; p=0·81; effect size –0·039) for tilavonemab 2000 mg and was 1·4 (–0·3 to 3·2; p=0·10; effect size –0·243) for tilavonemab 4000 mg. Compared with placebo, for SEADL, the least squares mean difference in change from baseline to week 52 was 2·5 (95% CI –2·5 to 7·5; p=0·32; effect size 0·145) for tilavonemab 2000 mg and was 0·1 (–4·9 to 5·0; p=0·97; effect size 0·005) for tilavonemab 4000 mg. The CGI-C score at week 52 was also similar between treatment groups (figure 3). Compared with placebo, the least squares mean difference in CGI-C score was 0·0 (95% CI –0·4 to 0·3; p=0·76; effect size 0·058) for tilavonemab 2000 mg and was –0·1 (–0·4 to 0·2; p=0·41; effect size 0·140) for tilavonemab 4000 mg. No differences between treatment groups were noted in change from baseline to week 52 in volumetric MRI measures at the midbrain (figure 3). Compared with placebo, the least squares mean difference was –7·2 mm³ (95% CI –33·9 to 19·5; p=0·60; effect size –0·089) for tilavonemab 2000 mg and was –6·3 mm³ (–33·0 to 20·4; p=0·64; effect size –0·079) for tilavonemab 4000 mg. Comparison of tilavonemab activity in brain regions affected by progressive supranuclear palsy (appendix p 14) showed no

differences in whole brain atrophy, or atrophy as measured at the third ventricle. All groups had reductions in brain volume from baseline to week 52, indicating continued disease progression (appendix p 14). Other secondary outcome data are presented in the appendix (p 10).

An overview of adverse events is presented in table 2. 111 (88%) participants in the tilavonemab 2000 mg group, 111 (89%) in the tilavonemab 4000 mg group, and 108 (86%) in the placebo group had an adverse event during the study. Serious adverse events occurred in about a quarter of participants in each group (29 [23%] for tilavonemab 2000 mg, 34 [27%] for tilavonemab 4000 mg, and 33 [26%] for placebo). Adverse events considered possibly drug related were reported in 34 (27%) people in the tilavonemab 2000 mg group, 36 (29%) in the tilavonemab 4000 mg group, and 38 (30%) in the placebo group. Adverse events leading to discontinuation (participants could have multiple reasons for discontinuation) were similar between groups, with nine (7%) in the tilavonemab 2000 mg group, seven (6%) in the tilavonemab 4000 mg group, and ten (8%) in the placebo group. Severity of treatment-emergent adverse events was similar between groups.

The most common treatment-emergent adverse events were fall (42 [33%] in the tilavonemab 2000 mg group, 54 [43%] in the tilavonemab 4000 mg group, and 49 [39%] in the placebo group), contusions (16 [13%], 24 [19%], and 17 [14%], respectively), and skin lacerations (19 [15%], 21 [17%], and 19 [15%], respectively). The most common treatment-emergent serious adverse event was fall, with five (4%) reported in the tilavonemab 2000 mg group, six (5%) in the tilavonemab 4000 mg group, and six (5%) in the placebo group.

26 (7%) deaths were reported through the follow-up period, nine (7%) in the tilavonemab 2000 mg group, nine (7%) in the tilavonemab 4000 mg group, and eight (6%) in the placebo group (table 2). No deaths were considered by investigators to be related to the study drug; some patients had more than one event resulting in death. Fatal adverse events (MedDRA preferred term) were death (four [13%]; two tilavonemab 2000 mg, one tilavonemab 4000 mg, and one placebo), progressive supranuclear palsy (three [10%]; one tilavonemab 4000 mg, two placebo), respiratory failure (two [7%]; one each tilavonemab 2000 mg and 4000 mg), aspiration pneumonia (two [7%]; one each tilavonemab 2000 mg and placebo), mycoplasmal pneumonia (one [3%]; tilavonemab 2000 mg), pneumonia (one [3%]; placebo), disease progression (one [3%]; tilavonemab 4000 mg), intestinal obstruction (one [3%]; placebo), spinal stroke (one [3%]; tilavonemab 4000 mg), gastrointestinal haemorrhage (one [3%]; tilavonemab 2000 mg), suicide (one [3%]; tilavonemab 2000 mg), gunshot wound (one [3%]; tilavonemab 2000 mg), dehydration (one [3%]; placebo), malnutrition (one [3%]; placebo), respiratory arrest (one [3%]; placebo), respiratory distress (one [3%]; tilavonemab 4000 mg), cardiorespiratory arrest (one [3%]; tilavonemab 4000 mg), acute respiratory distress syndrome (one [3%]; tilavonemab 2000 mg), congestive cardiac failure (one [3%]; tilavonemab 2000 mg), brain midline shift (one [3%]; tilavonemab 4000 mg), subdural haematoma (one [3%]; tilavonemab 4000 mg), leukocytosis (one [3%]; tilavonemab 4000 mg), and cardiopulmonary failure (one [3%]; placebo).

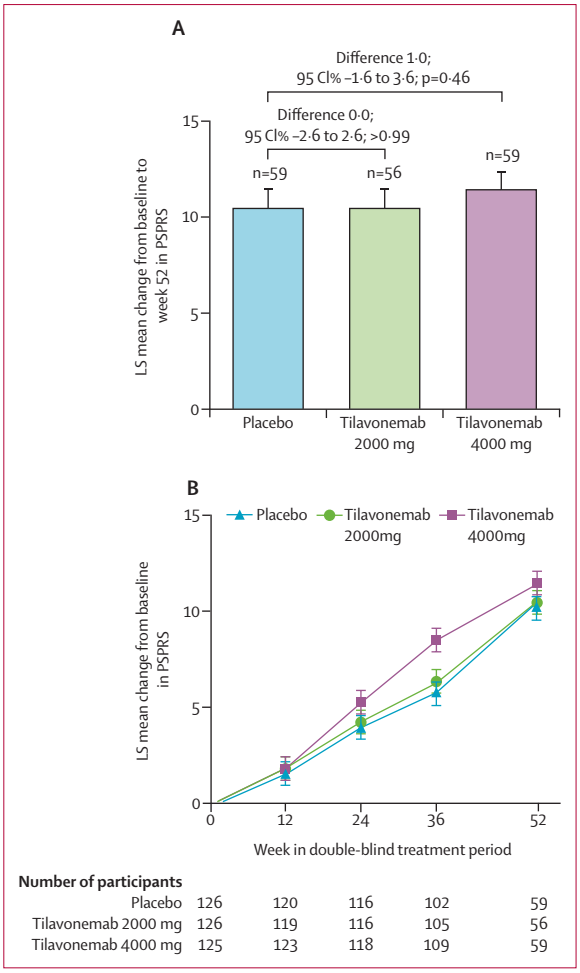

Figure 2: **Change from baseline to week 52 in PSPRS in the intention-to-treat dataset**

(A) Change in PSPRS from baseline to week 52. (B) Change in PSPRS from baseline throughout the study. Error bars represent SE in both panels. The increase in PSPRS at week 36 for the tilavonemab 4000 mg group relative to placebo and 2000 mg groups was not maintained to week 52. Numbers of participants for different scales vary because missing data differ between assessments. LS=least squares. PSPRS=Progressive Supranuclear Palsy Rating Scale.

Participants who completed the 52-week treatment period were eligible to enter a long-term extension study (NCT03391765). The extension study was terminated when the main study met prespecified futility criteria. Participants' disposition and summary safety data are presented in the appendix (pp 11, 15). Reported safety events were consistent with those documented in the main study.

Assessments of tilavonemab pharmacokinetic parameters are reported in the appendix (p 12). During the fifth dose-interval (week 12–16), steady-state tilavonemab

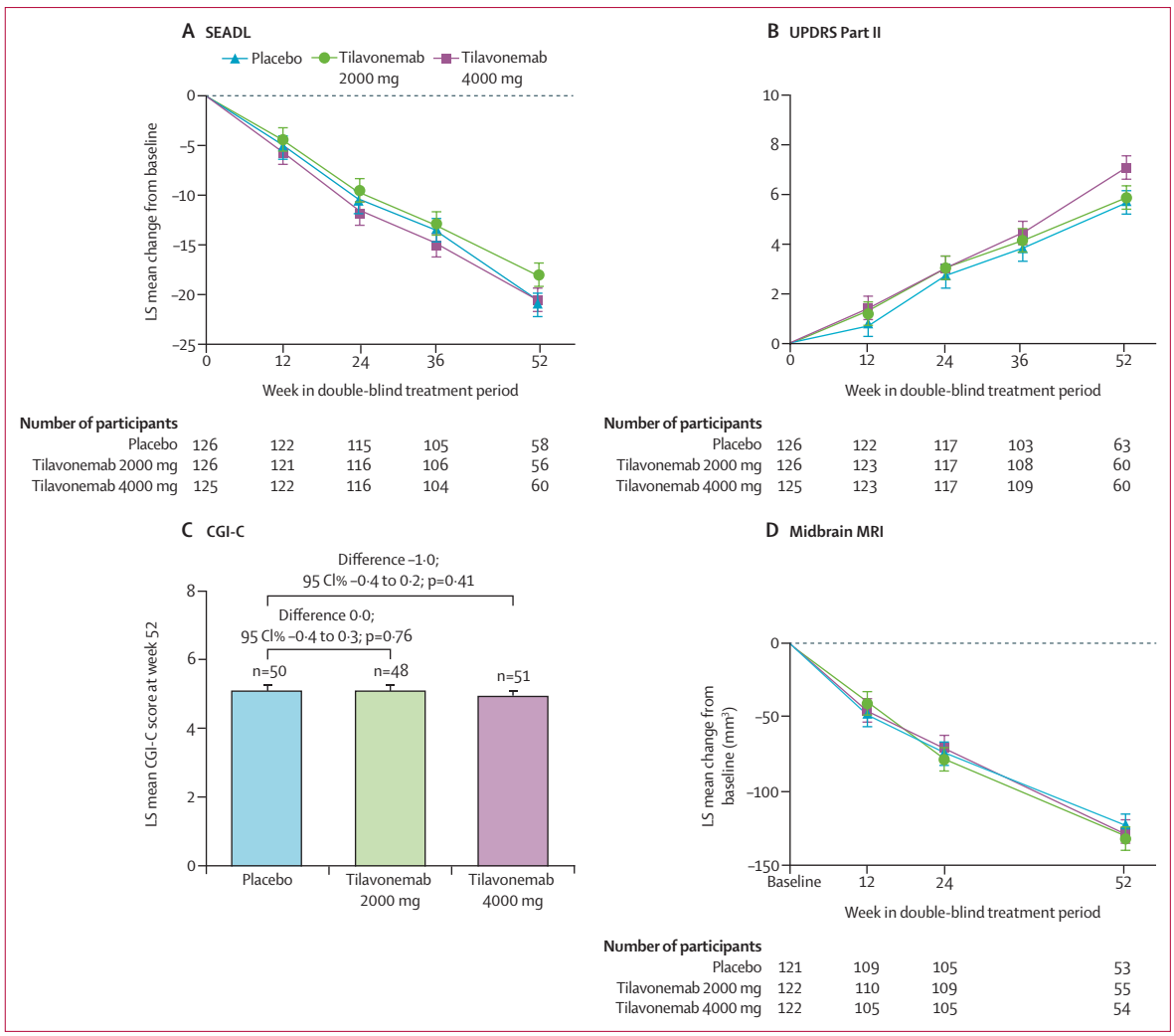

Figure 3: **Key secondary endpoints in the intention-to-treat dataset**
(A) Change from baseline throughout the study in SEADL score. (B) Change from baseline throughout the study in UPDRS part II score. (C) CGI-C score at week 52. (D) Change from baseline throughout the study in midbrain MRI volume. Error bars represent SE. Baseline MRI values were measured at the first screening visit. Numbers of participants for different scales vary because missing data differ between assessments. CGI-C=Clinical Global Impression of Change. LS=least squares. SEADL=Schwab and England Activities of Daily Living Scale. UPDRS=Unified Parkinson's Disease Rating Scale Part II.

absorption was similar for 2000 mg and 4000 mg doses (median [IQR] time to maximum plasma concentration [T_{max}], 4·1 [IQR 3·2–5·5] h for tilavonemab 2000 mg, and 4·0 [3·3–5·4] h for tilavonemab 4000 mg). Maximum concentration (C_{max}) and area under the concentration–time curve (AUC_{tau}) were dose-proportional. The geometric mean C_{max} for tilavonemab 2000 mg was 1057 (coefficient of variation 52·2) µg/mL and for tilavonemab 4000 mg it was 2258 (22·3) µg/mL; the AUC_{tau} for tilavonemab 2000 mg was 14164 (26·0) µg×day/mL and for the 4000 mg dose it was 29271 (35·8) µg×day/mL.

Concentrations of tau are shown in the appendix (p 16). CSF free tau was significantly lower in both tilavonemab treatment groups relative to placebo at week 52. The ratio of central value of treatment to placebo (antilogarithm of least squares mean difference based on the logarithmic scale of original values) was 0·6 (95% CI 0·5–0·8; p<0·0001), with an estimated effect (percent difference from placebo) of –38·0% for tilavonemab 2000 mg, and was 0·5 (0·4–0·6; p<0·0001; percent difference from placebo –46·3%) for tilavonemab 4000 mg. At week 52, compared with placebo, plasma total tau was significantly higher in participants treated with tilavonemab 2000 mg (ratio of central value 15·4, 95% CI 11·6–20·6; p<0·0001; estimated effect 1444·0%) and in those treated with tilavonemab 4000 mg (15·5, 11·6–20·6; p<0·0001; estimated effect 1446·3%). Compared with placebo, at week 52, no treatment effects were detected in CSF total tau for tilavonemab 2000 mg (ratio of central value 1·1, 95% CI 0·9–1·3; p=0·30; estimated effect 9·9%) and for tilavonemab 4000 mg (1·0, 0·8–1·2; p=0·96; estimated effect –0·5%).

Concentrations of neurofilament light chain (NFL) are shown in the appendix (p 17). At week 52, CSF NFL concentrations were similar in all treatment groups. For tilavonemab 2000 mg, the ratio of central values compared with placebo was 1·0 (95% CI 0·8–1·1; p=0·56; estimated effect –4·2%) and for tilavonemab 4000 mg it was 1·0 (0·9–1·2; p=0·99; estimated effect –0·1%). Plasma NFL concentrations were also similar between groups at week 52. For tilavonemab 2000 mg, the ratio of central values was 0·9 (95% CI 0·7–1·0; p=0·091; estimated effect –15·0%) and for tilavonemab 4000 mg it was 0·9 (0·8–1·1; p=0·29; estimated effect –9·7%).

Discussion

The findings of our phase 2 study showed no beneficial treatment effect of tilavonemab in people with progressive supranuclear palsy, and the study was terminated by the sponsor after a prespecified interim futility analysis. The most common adverse events reported during the study were consistent with the complications of progressive supranuclear palsy. Severity of treatment-emergent adverse events was similar between treatment groups. Pharmacokinetic analyses indicated that tilavonemab absorption occurs at similar rates, regardless of dose, and that C_{max} increases in a dose-dependent manner. Biomarker analyses indicated that tilavonemab successfully binds to the target, because treatment with tilavonemab resulted in reduced concentrations of CSF free tau.

Tilavonemab pharmacokinetic and biomarker assessments accord with findings from transgenic mouse and phase 1 studies.[16,21] The dosing interval used in our study is supported by phase 1 data that indicate tilavonemab has a harmonic mean plasma half-life of 27–37 days.[16] Similar to our study findings, phase 1 pharmacokinetic results indicated that tilavonemab AUC is dose-dependent at concentrations up to 50 mg/kg (approximately equivalent to 4000 mg assuming an average weight of 80 kg). This dose-proportionality extends to the amount of tilavonemab present in CSF, with the ratio of CSF:plasma tilavonemab ranging from 0·2% to 0·4%.[16] Biomarker results from our study indicated that the tilavonemab doses assessed were sufficient to engage CSF tau, as shown by a decrease of CSF free tau (ie, tau not bound by antibodies) with tilavonemab treatment. Of note, treatment with tilavonemab resulted in increased plasma total tau, consistent with results from transgenic mice.[21] These findings most likely indicate either prolongation of the half-life of antibody-bound plasma tau or that treatment would increase the peripheral tau pool according to the peripheral sink hypothesis.[21,22]

Although our phase 2 results investigating the anti-tau monoclonal antibody tilavonemab in participants with progressive supranuclear palsy are, to our knowledge, the first to be published, they are not the only such investigation. The phase 2 study PASSPORT (NCT03068468) assessed the N-terminal anti-tau antibody gosuranemab for treatment of progressive supranuclear palsy. After PASSPORT did not show efficacy (as measured by change in PSPRS total score), development of gosuranemab for progressive supranuclear palsy was discontinued.[23,24] As with our tilavonemab study, no concerning safety signals were noted in PASSPORT.[23,25]

Our study enrolled a sufficient number of participants with possible or probable progressive supranuclear palsy to be adequately powered to detect relevant effect sizes.[19] Statistical power was limited by early study termination, which was due to a small treatment effect size seen at the second interim futility analysis. Our study did not show tilavonemab efficacy in slowing progressive supranuclear palsy progression based on multiple clinical endpoints.

	Tilavonemab 2000 mg (n=126)	Tilavonemab 4000 mg (n=125)	Placebo (n=126)
Any adverse event	111 (88%)	111 (89%)	108 (86%)
Possibly drug-related adverse event	34 (27%)	36 (29%)	38 (30%)
Severe adverse events*	25 (20%)	25 (20%)	33 (26%)
Serious adverse events†	29 (23%)	34 (27%)	33 (26%)
Maximum treatment-emergent adverse event severity			
Mild	42 (33%)	36 (29%)	38 (30%)
Moderate	44 (35%)	50 (40%)	37 (29%)
Severe	25 (20%)	25 (20%)	33 (26%)
Adverse events leading to study drug discontinuation	9 (7%)	7 (6%)	10 (8%)
Deaths	9 (7%)	9 (7%)	8 (6%)
Treatment-emergent adverse events, MedDRA preferred term‡			
Fall	42 (33%)	54 (43%)	49 (39%)
Contusion	16 (13%)	24 (19%)	17 (14%)
Skin laceration	19 (15%)	21 (17%)	19 (15%)
Urinary tract infection	13 (10%)	19 (15%)	17 (14%)
Skin abrasion	11 (9%)	8 (6%)	15 (12%)
Weight decreased	10 (8%)	13 (10%)	11 (9%)
Depression	10 (8%)	3 (2%)	8 (6%)
Diarrhoea	10 (8%)	8 (6%)	6 (5%)
Constipation	9 (7%)	6 (5%)	7 (6%)
Fatigue	9 (7%)	4 (3%)	2 (2%)
Headache	9 (7%)	4 (3%)	8 (6%)
Rib fracture	6 (5%)	8 (6%)	4 (3%)
Insomnia	6 (5%)	8 (6%)	5 (4%)
Nasopharyngitis	6 (5%)	6 (5%)	4 (3%)
Cough	6 (5%)	5 (4%)	9 (7%)
Upper respiratory tract infection	5 (4%)	6 (5%)	8 (6%)
Pneumonia	4 (3%)	4 (3%)	8 (6%)
Rash	4 (3%)	3 (2%)	8 (6%)
Musculoskeletal pain	3 (2%)	8 (6%)	8 (6%)
Treatment-emergent serious adverse events, MedDRA preferred term§			
Fall	5 (4%)	6 (5%)	6 (5%)
Pneumonia	1 (1%)	3 (2%)	4 (3%)

Data are n (%). MedDRA=Medical Dictionary for Regulatory Activities. *Events causing considerable interference with usual activities and can be incapacitating or life-threatening. †Events resulting in death, that are life-threatening, that result in admission to hospital or prolong a hospital stay, are a congenital anomaly, or that result in a condition that substantially interferes with activities of daily living. ‡Occurring in >4% of participants overall. §Occurring in >2% of participants overall.

Table 2: **Adverse events**

The profile of recruited participants was representative of people with progressive supranuclear palsy and of individuals enrolled in other studies of progressive supranuclear palsy. Demographic characteristics, including participant's age and time from symptom onset to diagnosis, are in line with those reported in a population-based survey of people with progressive supranuclear palsy.[8] Disease progression, as measured by change from baseline in PSPRS scores, accorded with progression rates reported in both clinical practice and clinical trials.[6,17] Likewise, brain atrophy, as measured by changes in midbrain volumetric MRI, was similar to changes noted in other studies and consistent with expected changes due to disease progression.[18]

Several clinical trials that were adequately powered to show disease-modifying effects among participants with progressive supranuclear palsy have not shown efficacy, but the assessment of efficacy was limited by the paucity of a robust pharmacodynamic biomarker.[26–28] Researchers on a phase 2/3 clinical trial of davunetide (NCT01110720) concluded that an absence of pharmacokinetic analysis and of a known biomarker for davunetide activity made it difficult to determine whether davunetide entered the CNS or engaged its intended target.[27] A similar conclusion was reached after the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) study of riluzole (NCT00211224).[26] Additional analysis from the NNIPPS study investigated use of MRI as a measure of severity of progressive supranuclear palsy and presented criteria for MRI scan rating.[29] A phase 2 trial of the glycogen synthase kinase 3 inhibitor tideglusib (NCT01049399)[28] reported changes in PSPRS scores similar to those reported in our study of tilavonemab.

Several potential explanations could account for the lack of efficacy seen in our study, which might warrant further research in people with progressive supranuclear palsy. In vitro and in vivo characterisation of the anti-tau antibody HJ8.5 suggested an extracellular mechanism of action for clearing tau aggregates from the brain.[14,15] Treatment with HJ8.5 resulted in improved cognition and slowed progression of neurodegeneration in mouse models of tauopathies.[14,15,21,30] However, less evidence is available to show that extracellular tau could be important to disease progression in progressive supranuclear palsy.[31,32] There are no ideal animal models of progressive supranuclear palsy.[33] Additionally, anti-tau antibody chimerisation has been shown to alter antibody activity.[34] Therefore, extrapolation from preclinical models could be of little predictive value.[14,15] Some potential indicators of antibody activity and progression of progressive supranuclear palsy, including levels of free tau in plasma, and measures of phosphorylated tau were not included in our study. Additional work to characterise tilavonemab activity in people with tauopathies is ongoing.

Possibly, tilavonemab might not target the specific tau species that drives spreading of pathology and neurodegeneration in progressive supranuclear palsy, because N-terminal antibodies have not detected specific tau cleavage species in vitro,[35] and volumetric MRI results from our study indicate that tilavonemab treatment does not reduce brain atrophy in participants with progressive supranuclear palsy over time. Although results from our study indicate that tilavonemab engages its target in the CSF, it is possible that not enough tilavonemab enters the CNS to elicit a therapeutic effect.

Our study included participants with either possible or probable progressive supranuclear palsy, to allow for greater sensitivity in early diagnosis of this disorder.[11,36] The NINDS-SPSP criteria for possible and probable progressive supranuclear palsy are both highly specific to progressive supranuclear palsy,[11,36,37] so misdiagnosis is not a concern. However, a paucity of diagnostic biomarkers for progressive supranuclear palsy can lead to delays in diagnosis,[12] which is evident by the approximately 2-year difference between symptom onset and diagnosis we recorded. Thus, intervention testing in participants with progressive supranuclear palsy might have been initiated too late in the disease course in our study to reliably mitigate disease progression. We did not analyse post-mortem samples from participants or investigate outcomes based on disease severity. Additionally, we relied on the NINDS-SPSP diagnostic criteria, which only identify patients who present with Richardson syndrome at the time of diagnosis, and we, therefore, did not differentiate between other phenotypes of progressive supranuclear palsy.[5,10,11,38] Despite similar initial symptom severity, evidence suggests that people with the parkinsonism phenotype of supranuclear palsy progress more slowly than do those with the Richardson syndrome phenotype.[39] Future studies should differentiate between progressive supranuclear palsy phenotypes.

In our phase 2 study in progressive supranuclear palsy, administration of tilavonemab—a monoclonal antibody that binds an epitope containing amino acids 25–30 at the N-terminus of tau in doses high enough to bind 50% or more of tau in the CSF—did not affect progression of the disorder. Although tilavonemab did not show efficacy for treatment of progressive supranuclear palsy, a similar safety profile was seen in all treatment groups. Pharmacokinetic results showed a maximum concentration that is dose-dependent, and biomarker analyses indicated that tilavonemab binds its target. Results from our study provide important information on the trajectory of clinical and biomarker endpoints in individuals with progressive supranuclear palsy that could help to guide further investigations of tau-directed therapies in progressive supranuclear palsy.

Contributors

GUH, NM, DW, BR-M, H-KL, KB, DR, and HF contributed to the idea for the study and study design. GUH, IL, NM, DW, HZ, H-KL, ZJ, NF, and HF were involved in data acquisition. DW, HZ, H-KL, and ZJ did the statistical analysis. GUH, IL, NM, DW, BR-M, H-KL, ZJ, NF, KB, MG, DR, and HF contributed to data interpretation. All authors had access to and verified the data; participated in the development, review, and approval of the manuscript; and approved the final manuscript.

Declaration of interests

GUH has served as a consultant or scientific adviser for AbbVie, during the conduct of the study; and has served as a consultant for Alzprotect, Asceneuron, Biogen, Biohaven, Lundbeck, Novartis, Roche, Sanofi, and UCB, outside of the submitted work; has received honoraria for scientific presentations from AbbVie, Biogen, Bial, Roche, Teva, UCB, and Zambon, outside of the submitted work; and has received research support from the German Center for Neurodegenerative Diseases, Deutsche Forschungsgemeinschaft (HO2402/6-2 Heisenberg programme; HO2402/18-1 MSAomics), the German Federal Ministry of Education and Research (01KU1403A EpiPD; 01EK1605A HitTau), the NOMIS foundation (FTLD project), ParkinsonFonds Germany, the EU/EFPIA/Innovative Medicines Initiative Joint Undertaking (grant no 116060), and VolkswagenStiftung/Lower Saxony Ministry for Science/Petermax-Müller Foundation (Etiology and Therapy of Synucleinopathies and Tauopathies), outside of the submitted work. IL has received grants from the Michael J Fox Foundation, during the conduct of the study; grants from the National Institutes of Health, the Parkinson Study Group, the Lewy Body Association, and AbbVie, Biogen, Roche, outside of the submitted work; and has been a participant on the Lundbeck Advisory Board. DW, HZ, BR-M, H-KL, ZJ, NF, KB, MG, and HF are employees of AbbVie and hold AbbVie stock or stock options. NM is a former employee of AbbVie and is currently employed by AveXis, a Novartis company. DR is a former employee of AbbVie and is currently employed by Levo Therapeutics.

Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials they fund. This commitment includes access to anonymised, individual and trial-level data (analysis datasets), and other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous independent scientific research, and will be provided after review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered.

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