RESEARCH ARTICLE

AZP2006 in Progressive Supranuclear Palsy: Outcomes from a Phase 2a Multicenter, Randomized Trial, and Open-Label Extension on Safety, Biomarkers, and Disease Progression

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ABSTRACT: Objectives: The aim was to evaluate the safety, tolerability, pharmacokinetics, and potential clinical efficacy of AZP2006, an oral pleiotropic drug modulating progranulin levels, in patients with progressive supranuclear palsy (PSP), a rare tauopathy.

Methods: A randomized, double-blind, placebo-controlled, parallel-group trial was conducted at three sites in France. Eligible participants (age 40–80 years, diagnosed with probable or possible PSP) were randomized to receive AZP2006 (60 mg once per day [QD] or 80/50 mg QD [80 mg for 10 days followed by 50 mg]) or placebo for 12 weeks. Assessments included safety, pharmacokinetics (plasma and whole blood), pharmacodynamics (cerebrospinal fluid and plasma biomarkers), and exploratory clinical efficacy (PSP rating scale, clinical global impression, and activities of daily living). Approximately 2 years post-trial, an open-label extension (OLE) enrolled 15 patients who received active treatment (AZP2006) for 6 months.

Results: Forty-one patients were screened, 36 randomized, and 34 completed the study. AZP2006 demonstrated acceptable tolerability and safety with no treatment-related serious adverse events. Pharmacokinetic analysis confirmed rapid absorption, a long half-life (60 mg: 764.3 hours; 80/50 mg: 684.7 hours), and steady-state by day 45 (60 mg) and day 28 (80/50 mg). Biomarker analyses indicated blood–brain barrier crossing, target engagement, and stabilized progranulin levels. Trends in efficacy favored slower disease progression in AZP2006 groups. The OLE demonstrated a slowed progression of the disease and revealed no notable safety concerns.

Conclusions: AZP2006 was well-tolerated and demonstrated favorable trends in biomarker and clinical outcomes. These preliminary signals support further investigation to determine whether a meaningful clinical benefit can be achieved in PSP with AZP2006. © 2025 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: lysosome; progranulin; progressive supranuclear palsy; tauopathy

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disorder marked by rigidity, postural instability, gaze palsy, and cognitive deficits. It progresses rapidly, increasing disability, care dependence, and mortality within a few years.[1,2] Although the cause of PSP remains unknown, neuropathologically it is characterized

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by the accumulation of τ immunoreactive neurofibrillary tangles (NFTs) in the basal ganglia, brainstem, and cerebellar nuclei, as well as neuronal loss and gliosis with tufted astrocytes.[3-6] Genetic studies have shown a strong association with the gene coding the microtubule associated protein τ (MAPT),[7-9] and PSP is considered as a primary tauopathy.[4]

In PSP, τ becomes hyperphosphorylated, detaching from microtubules (loss of function) and forming toxic filaments (gain of function). No disease-modifying therapy exists, and dopaminergic treatments are ineffective.[1,10,11] Although τ-targeted immunotherapies showed target engagement, they failed to demonstrate efficacy.[12-14] Alternative approaches are urgently needed to address PSP's underlying pathology and reduce its burden. Unlike passive or active τ immunotherapies, which have targeted extracellular τ species late in the disease cascade, AZP2006 targets lysosomal dysfunction and facilitates the clearance of multiple pathogenic proteins, including hyperphosphorylated τ, at an earlier stage. This pleiotropic mechanism involves restoring progranulin-prosaposin (PGRN-PSAP) –mediated lysosomal integrity, thereby enhancing proteolysis of diverse aggregates such as τ, α-synuclein, and potentially TDP-43, and reducing associated neuroinflammation. Therefore, AZP2006 addresses τ pathology indirectly by improving lysosomal clearance while simultaneously impacting other co-pathologies that may drive disease progression in PSP.

Lysosomal dysfunction is now seen as a key factor in tauopathies like Alzheimer's, frontotemporal dementia, and PSP. When lysosomes, responsible for degrading cellular waste, fail to clear τ proteins effectively, τ accumulates, worsening cell stress and further damaging lysosomes. T itself can impair lysosomal function, causing membrane rupture and cell death. This vicious cycle accelerates neurodegeneration, making lysosomal repair a promising therapeutic target.

AZP2006 is a small molecule therapeutic that targets lysosomal dysfunction and τ pathology through its unique stabilization of the PGRN-PSAP complex.[15] By binding PSAP and the PGRN-PSAP complex with high affinity, AZP2006 acts as a molecular chaperone, enhancing intracellular and extracellular trafficking of this intact complex via sortilin (PGRN), M6PR (PSAP), and LRP1 (PSAP) receptors. This dual mechanism promotes lysosomal delivery of PGRN, a critical neurotrophic factor for lysosomal function. The consequent enrichment of the lysosomal compartment with functional PSAP and PGRN augments its overall proteolytic capacity and reinforces membrane integrity, thereby promoting the effective catabolism of pathological protein aggregates, including hyperphosphorylated τ, a hallmark of tauopathies like progressive PSP and Alzheimer's disease. Preclinical evidence demonstrates that AZP2006-mediated stabilization of the PGRN-PSAP axis not only mitigates neuroinflammation and neuronal loss, but also improves cognitive deficits in tauopathy models.[15] Notably, silencing PSAP or PGRN abolishes these neuroprotective effects, underscoring the centrality of this pathway in AZP2006's therapeutic action. By restoring lysosomal integrity and promoting the clearance of misfolded proteins AZP2006 directly addresses core pathogenic processes in tauopathies such as PSP, AZP2006 represents a disease-modifying strategy that addresses core pathological mechanisms in neurodegenerative tauopathies.

Phase 1 trials confirmed safety and described its pharmacokinetics, including a long half-life and a primary non-active metabolite, AZP2045. These mechanisms position AZP2006 as a promising PSP therapy.[16] Through its unique combination of mechanisms linked to PGRN, AZP2006 is positioned as a comprehensive and potentially impactful therapeutic candidate for PSP, addressing various aspects of the complex pathophysiology associated with this neurodegenerative disorder.

The objective of this phase 2a/proof-of-concept clinical trial was, therefore, to investigate the safety, tolerability, and pharmacokinetics of AZP2006, and provide potential evidence of target-engagement and efficacy in PSP patients.

Materials and Methods

Trial Design and Participants

This was a randomized, double-blind, placebo-controlled, parallel-group, phase 2a trial conducted at three trial sites in France (ClinicalTrials.gov Identifier: NCT04008355).

Ethics approval followed Helsinki and Good Clinical Practice guidelines. Eligible patients (age 40–80, probable/possible PSP per Movement Disorder Society [MDS]-PSP criteria,[17] symptom onset ≤5 years, and stable medication ≥30 days) were included. Key exclusions were Mini Mental State Examination <20, head trauma or cerebrovascular disease within the previous 1 year, malignancy, abnormal electrocardiogram (ECG), significant lab abnormalities, or safety concerns. Dopaminergic medications (eg, levodopa, dopamine agonists) were permitted if maintained at stable dose for ≥30 days before baseline. Patients were randomized (1:1:1) to receive 60 mg AZP2006/day, 80 mg AZP2006/day (10-day loading dose, then 50 mg/day), or placebo via a stratified web response system. The 60 mg dose aimed for optimal plasma concentration, whereas 80/50 mg accelerated steady state. Treatment lasted 12 weeks, followed by a 3-month drug-free follow-up. An open-label

extension (OLE) enrolled phase 2a patients for 6 months (60 mg/day) under adjusted eligibility criteria. The randomized period of the trial spanned from June 2020 to July 2022, followed by the OLE phase conducted from May 30, 2023 to July 22, 2024. "Adjusted eligibility" in the OLE referred to removal of certain acute exclusion criteria used in the randomized phase (eg, recent head trauma, unstable comorbidities) to allow participation of patients with stable chronic conditions, whereas retaining core inclusion criteria for PSP diagnosis and safety. The primary objective of the OLE was to gather long-term safety data, continue monitoring for efficacy signals, and ethically, to provide the active treatment to patients in need. Because of delays in regulatory approval, the start of the OLE was postponed by several months, resulting in some patients transitioning as late as 2.5 years after their final phase 2a visit.

Interventions were administered orally once daily in the morning under fasting conditions. AZP2006, formulated as a disulphate salt in aqueous solutions (6.25, 7.5, and 10 mg/mL for 50, 60, and 80 mg doses, respectively), was dispensed in 10 mL amber glass vials. The first dose (day 1) was administered at an inpatient facility with 10-hour post-dose observation. Subsequent doses were taken daily within a $\pm$ 30-min window, with compliance verified via patient diaries. After the end-of-treatment visit (day 84), participants underwent a 12-week recovery period and follow-up visit. During inpatient monitoring, safety assessments included serial vital signs, ECGs, adverse event surveillance, and observation for potential acute central nervous system effects, hypersensitivity, or gastrointestinal intolerance.

Centralized biomarker analyses were conducted, with blood and cerebrospinal fluid (CSF) pre-dose samples collected at baseline and on day 84. Pharmacodynamic analyses of biomarkers (PGRN, neurofilament light chain [NfL]) were conducted on plasma and CSF samples, with CSF also analyzed for τ and phosphorylated-τ (T181). Efficacy was evaluated using the PSP Rating Scale (PSPRS), Schwab and England Activities of Daily Living (ADL), Clinical Global Impression (CGI), and Montreal Cognitive Assessment (MoCA) scales at baseline, day 84, and the end of the trial. Adverse events (AEs) and safety parameters were monitored throughout.

Primary outcomes focused on safety (AEs, laboratory values, ECGs, vital signs, and ophthalmologic exams) and pharmacokinetics of AZP2006 and AZP2045. Secondary and exploratory outcomes included pharmacodynamic biomarker changes and efficacy measures. The ophthalmologic exam comprised best-corrected visual acuity testing, oculomotor examination, slit-lamp biomicroscopy, funduscopy, and intraocular pressure measurement. This was included to monitor potential visual or oculomotor effects given PSP's ocular manifestations and to detect rare drug-related retinal or optic nerve changes.

Statistical Analysis

No formal statistical hypotheses or sample size calculations were performed. A sample size of 36 patients (12 per group) with a 10% drop-out rate was chosen for feasibility and deemed sufficient to meet trial objectives. Continuous variables were summarized using descriptive statistics, while categorical data were presented as counts and percentages. The safety analysis set included all patients who received at least one dose, and pharmacokinetic analyses were performed for those with valid concentration data and no significant protocol deviations. AEs, coded using the MedDRA dictionary (version 25.0), were summarized by system organ class (SOC) and preferred term (PT), with reports detailing event counts and patient percentages. Biomarker trends were analyzed graphically and with statistical tests, including one-way analysis of variance (ANOVA), Hodges-Lehmann estimators, and Wilcoxon rank-sum tests ($P = 0.05$). Efficacy measures, such as PSPRS, were evaluated using t-tests and Dunnett tests ($P = 0.05$) for baseline, within-group, and between-group comparisons, with clinical worsening defined as a $\geq$ 6-point PSPRS increase.[11]

Results

A total of 41 patients were initially screened at three sites in France, and 36 patients were randomized and included in the trial between June 8, 2020 and July 18, 2022, of which 34 completed the trial (see Fig. S1).

Demographics were comparable across groups (mean, age 68; BMI, 28.17). Ethnicity data was not collected because of regulations. See Table 1 for demographics and baseline characteristics.

The PSPRS, consisting of 28 items in six areas, demonstrated a mean (standard deviation [SD]) baseline total score of 40.8 (14.8) across the three groups. The mean (SD) Schwab and England ADL scale scores at baseline for the 60 mg AZP2006, 80/50 mg AZP2006, and placebo groups were 50.8 (26.0), 54.5 (19.2), and 55.8 (19.8), respectively. The CGI-S score, assessing the severity of psychopathology, was similar across treatment groups at baseline, with an overall mean (SD) score of 4.3 (1.3). The mean (SD) MoCA scale total score was 21.9 (3.9), with 58% of patients exhibiting mild cognitive impairment. Table 3 provides the details.

The mean (SD) time from PSP diagnosis to inclusion in the trial varied across treatment groups: 4.0 (1.80) years for the 60 mg AZP2006 group, 2.7 (1.26) years for the 80/50 mg AZP2006 group, and 4.1 (1.45) years for the placebo group. The overall mean (SD) duration of PSP was 3.6 (1.6) years. The two-sided Dunnett adjusted *P*-value for the dose effect was 0.988 for the 60 mg AZP2006 group and 0.082 for the 80/50 mg AZP2006 group, indicating a significant difference in

TABLE 1 *Demographic and baseline characteristics.*

		AZP2006 60 mg	AZP2006 80/50 mg	Placebo	All
		N = 13	N = 11	N = 12	N = 36
Sex, no.		13	11	12	36
Female	n (%)	8 (62)	6 (55)	5 (42)	19 (53)
Male	n (%)	5 (39)	5 (46)	7 (58)	17 (47)
Age (y)	Mean (SD)	67 (6)	67 (6)	70 (6)	68 (6)
	Median	67.0	68	72	69
	[Min; Max]	[58; 78]	[58; 79]	[60; 80]	[58; 80]
Age in class (y)	N	13	11	12	36
40–64 y	n (%)	4 (31)	4 (36)	2 (17)	10 (28)
65–74 y	n (%)	7 (54)	6 (55)	7 (58)	20 (56)
≥75 y	n (%)	2 (15)	1 (9)	3 (25)	6 (17)
Disease duration	Mean (SD)	4.0 (1.80)	2.7 (1.26)	4.1 (1.45)	3.6 (1.6)
PSPRS total score	N	13	11	12	36
	Mean (SD)	45.6 (19)	38.7 (14)	37.5 (8)	40.8 (15)
	Median	40	40	39	40
MMSE score	N	13	11	12	36
	Mean (SD)	26.8 (2)	26.5 (3)	25.8 (2)	26.4 (2)
	Median	27	26	26	26
MoCA score	N	13	11	12	36
	Mean (SD)	21.8 (4)	22.5 (4)	21.6 (4)	21.9 (4)
	Median	22	22	22	22
Schwab and England ADL score	N	13	11	12	36
	Mean (SD)	50.8 (26)	54.5 (19)	55.8 (20)	53.6 (22)
	Median	40	50	60	50
MDS-UPDRS score	N	13	11	12	36
	Mean (SD)	90.5 (35)	77.6 (25)	72.3 (16)	80.5 (27)
	Median	87	84	78	83
CGI score	N	13	11	12	36
	Mean (SD)	4.5 (1)	4.4 (1)	4.1 (2)	4.3 (1)
	Median	4	5	5	5

Abbreviations: N, number of patients; SD, standard deviation; Min, minimum; Max, maximum; PSPRS, Progressive Supranuclear Palsy Rating Scale; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; ADL, Activities of Daily Living; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating; CGI, Clinical Global Impression.

disease duration among the treatment groups. During the OLE, 15 participants (47% female, 53% male) with a mean age of 69.8 years (range, 61–78), were enrolled. The mean time from PSP diagnosis to OLE inclusion was 5.1 years (range, 2–11 years).

In the double-blind period, most patients reported at least one AE (92%, 100%, and 83% of patients in the 60 mg AZP2006 group, 80/50 mg AZP2006 group, and placebo group, respectively). The most frequently reported AEs were fall (22.0% overall), weight decreased (16.7% overall), urinary tract infections (13.9% overall), and hypertension (13.9% overall), although most were mild in severity. Only one treatment related AE was reported (vision blurred in 1 participant in the placebo

group). Serious AEs (SAEs) were reported in 30.8% of patients in the 60 mg AZP2006 group, 18.2% in the 80/50 mg AZP2006 group, and 25.0% in the placebo group, with no particular trends or specific frequencies throughout the trial for PT or SOC, nor severity and relatedness to AZP2006. No SAE was considered to be treatment-related. Two deaths were reported in the 60 mg AZP2006 group because of aspiration pneumonia, one on day 4 and one on day 184 (during follow-up period), neither of which was related to AZP2006. Overall, laboratory evaluations, ECGs, vital signs, and ophthalmologic examinations showed no remarkable changes relative to baseline, or across trial arms. In the OLE period, 93.3% of participants experienced an AE. Four SAEs occurred, including one fatal event, none of the SAEs, including the death, were considered treatment-related. Table 2 presents safety outcomes from both trial periods. ECG abnormalities were defined as new clinically significant changes from baseline (eg, arrhythmias, corrected QT, prolongation >450 ms). Laboratory abnormalities were predefined as values exceeding Grade 2 Common Terminology Criteria for Adverse Events thresholds for hematology, liver enzymes, renal function, or electrolytes.

Blood and CSF samples were analyzed for all participants, except for CSF in two individuals and blood/plasma in four individuals. These exceptions were because of delayed sample delivery to the laboratory, resulting in data that were deemed analytically unreliable and, therefore, excluded from the final analysis. Plasma pharmacokinetics (Fig. 1) showed a similar pattern of AZP2006 concentrations for both the 60 mg group and the 80/50 mg group, with maximum concentrations reached at 0.5 hour post-dose on day 1 and day 84. Following C_{max}, on day 1 plasma concentrations declined rapidly up to approximately 4.0 hours post-dose except for a small rebound at 2.0 hours post-dose observed only for the 60 mg AZP2006 group. On day 84, concentrations declined after C_{max} at a moderate rate in both treatment groups up to approximately 3.0 hours post-dose and continued to decrease at a similar rate up to approximately 10.0 hours post-dose for the 60 mg AZP2006 group, whereas in contrast declining sharply between 3.0 hours and 5.0 hours, followed by a moderate rebound up to 8.0 hours post-dose for the 80/50 mg AZP2006 group. Plasma concentrations remained quantifiable at 24.0 hours post-dose on both day 1 and day 84, with geometric mean half-life ($t_{½}$) for the 60 mg AZP2006 group and the 80/50 mg AZP2006 group of 9.5 and 7.5 hours on day 1 and 746.3 hours and 684.7 hours on day 84.

AZP2006 concentrations in whole blood were similar to plasma levels, with C_{max} reached at 2.0 hours (60 mg) and 1.0 to 10.0 hours (80/50 mg) on day 1. C_{max} was higher for the 80 mg group initially, but similar between groups by day 84. Geometric mean t½ values were approximately 10 hours on day 1 and approximately 720 hours on day 84, with slower declines in the 60 mg group post-C_{max} by day 84.

Similar plasma concentrations were observed for the AZP2045 metabolite on both day 1 and day 84, with higher C_{max} noted for the 80/50 mg AZP2006 dose. The plasma concentrations declined rapidly up to 4.0 hours post-dose on day 1, followed by a slower decline up to 24 hours post-dose for both groups, whereas geometric mean half-life ($t_{½}$) for AZP2045 was 8.0 hours for the 60 mg AZP2006 group and 10.5 hours for the 80/50 mg AZP2006 group on day 1, and 2228.6 and 1609.8 hours on day 84, respectively, with whole blood concentrations showing similar profiles to plasma.

TABLE 2 *Summary of safety outcomes.*

	Double-blind period				OLE period
	AZP2006 60 mg, N = 13	**AZP2006 80/50 mg, N = 11**	**Placebo, N = 12**	**All, N = 36**	**AZP2006 60 mg, N = 15**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Adverse event	12 (92.31)	11 (100.00)	10 (83.33)	33 (91.67)	14 (93.3)
Serious adverse event	4 (30.77)	2 (18.18)	3 (25.00)	9 (25.00)	4 (26.7)
Non-treatment–emergent adverse event	11 (84.62)	6 (54.55)	5 (41.67)	22 (61.11)	10 (66.7)
Non-treatment–emergent serious adverse event	2 (15.38)	1 (9.09)	1 (8.33)	4 (11.11)	1 (6.7)
Treatment-emergent adverse event	12 (92.31)	11 (100.00)	10 (83.33)	33 (91.67)	11 (73.3)
Treatment-unrelated deaths	2	0	0	2	1
Treatment-related deaths	0	0	0	0	0

Abbreviation: OLE, open-label extension.

TABLE 3 *Summary of PSPRS, CGI-S score, Schwab and England ADL scale score, and MoCA scale.*

			AZP2006 60 mg	AZP2006 80/50 mg	Placebo
PSPRS	Baseline	Mean (SD)	45.6 (19)	38.7 (14.3)	37.5 (8.3)
	EOT	Mean (SD)	48.3 (17.1)	41.2 (11.5)	44.5 (12)
CGI-S	Baseline	Mean (SD)	4.5 (1)	4.4 (1)	4.1 (2)
	EOT	Mean (SD)	4.7 (1)	4.4 (1)	4.5 (1)
	FUP	Mean (SD)	4.9 (1)	5.0 (1)	5.2 (1)
Schwab and England	Baseline	Mean (SD)	50.8 (26)	54.5 (19)	55.8 (20)
ADL score	EOT	Mean (SD)	45.0 (25)	52.7 (21)	52.7 (23)
	FUP	Mean (SD)	43.6 (25)	48.9 (20)	44.0 (21)
MoCA scale	Baseline	Mean	21.8	22.5	21.6
	EOT-baseline	Mean	18.1	21.5	20.8
	FUP	Mean	16.6	21.7	21.8

Abbreviations: PSPRS, Progressive Supranuclear Palsy Rating Scale; CGI, Clinical Global Impression; ADL, Activities of Daily Living; MoCA, Montreal Cognitive Assessment; EOT, end of trial; SD, standard deviation; FUP, follow-up.

For both plasma and whole blood, steady-state concentrations of AZP2006 and AZP2045 appeared to have been reached by day 45 with the 60 mg AZP2006 group and by day 28 for the 80/50 mg AZP2006 group.

For the evaluation of AZP2006 and AZP2045 in CSF, neither AZP2006 nor the metabolite were detected in either group on day 1. On day 84, AZP2006 concentrations were 1.3 to 1.6-fold higher in the 80/50 mg AZP2006 group than the 60 mg AZP2006 group (ie, ~0.13 vs. 0.21 ng/mL).

Most patients showed quantifiable levels of total τ in CSF at baseline and end of treatment (EOT). Within-group comparisons of CSF-τ protein levels revealed statistically significant relative changes from baseline for both the AZP2006 60 mg group (Wilcoxon signed-rank test, $P = 0.016$) and the pooled treatment groups ($P = 0.023$), whereas between-group comparisons showed no statistically significant differences in relative change from baseline between AZP2006-treated groups and placebo. For phosphorylated-τ (T181), baseline mean from AZP2006 60 mg was 48.1 (SD, 16.3) and end of study mean was 44.0 (SD, 20), whereas baseline mean for placebo was 62.2 (SD, 23.7) and end of study mean was 57.8 (SD, 19.7). For CSF NfL, baseline mean from AZP2006 60 mg was 2149 (SD, 351) and end of study mean was 2480 (SD, 1131), whereas baseline mean for placebo was 2607 (SD, 2050) and end of study mean was 2472 (SD, 2164). Between-group comparisons of relative change from baseline in CSF NfL did not show statistically significant differences between AZP2006-treated groups and placebo (one-way ANOVA, $P > 0.05$). The direction of change indicated a slight increase in the 60 mg group, stability in placebo, and no consistent trend in the 80/50 mg group, consistent with the short study duration and the exploratory nature of this endpoint.

Levels of PGRN in CSF remained stable in both the 60 mg and 80/50 mg AZP2006 groups, indicating potential target related effect, compared to a statistically significant reduction of the relative change from baseline observed in the placebo group (−0.46 [0.54]; $P = 0.016$, Wilcoxon signed rank test). In plasma, PGRN levels were higher at EOT than baseline for the 60 mg and 80/50 mg AZP2006 groups (mean [SD] change from baseline at EOT of 12.17 [25.37] and 13.95 [32.29], respectively) but not for placebo (−0.49 [13.38]) (Fig. S2).

The efficacy analyses demonstrated an increase in mean PSPRS score for all groups (60 mg AZP2006, 80/50 mg AZP2006, and placebo) from baseline to both EOT and follow-up (FUP). Within-group comparisons revealed statistically significant changes for 60 mg and placebo groups at EOT, and for all groups at FUP. The placebo group exhibited a higher mean change from baseline at both EOT and FUP compared to the 60 and 80/50 mg AZP2006 groups (Fig. 2).

Clinical worsening was observed across groups, but the estimates of the difference between placebo and each AZP2006 group were not statistically significant for either EOT or FUP.

The CGI scale (Table 3) indicated stable severity scores for the 60 and 80/50 mg AZP2006 groups at EOT, with a more prominent increase observed in the placebo group. At FUP, the deterioration indicated by CGI score was more pronounced in the placebo group than in the 60 and 80/50 mg AZP2006 groups.

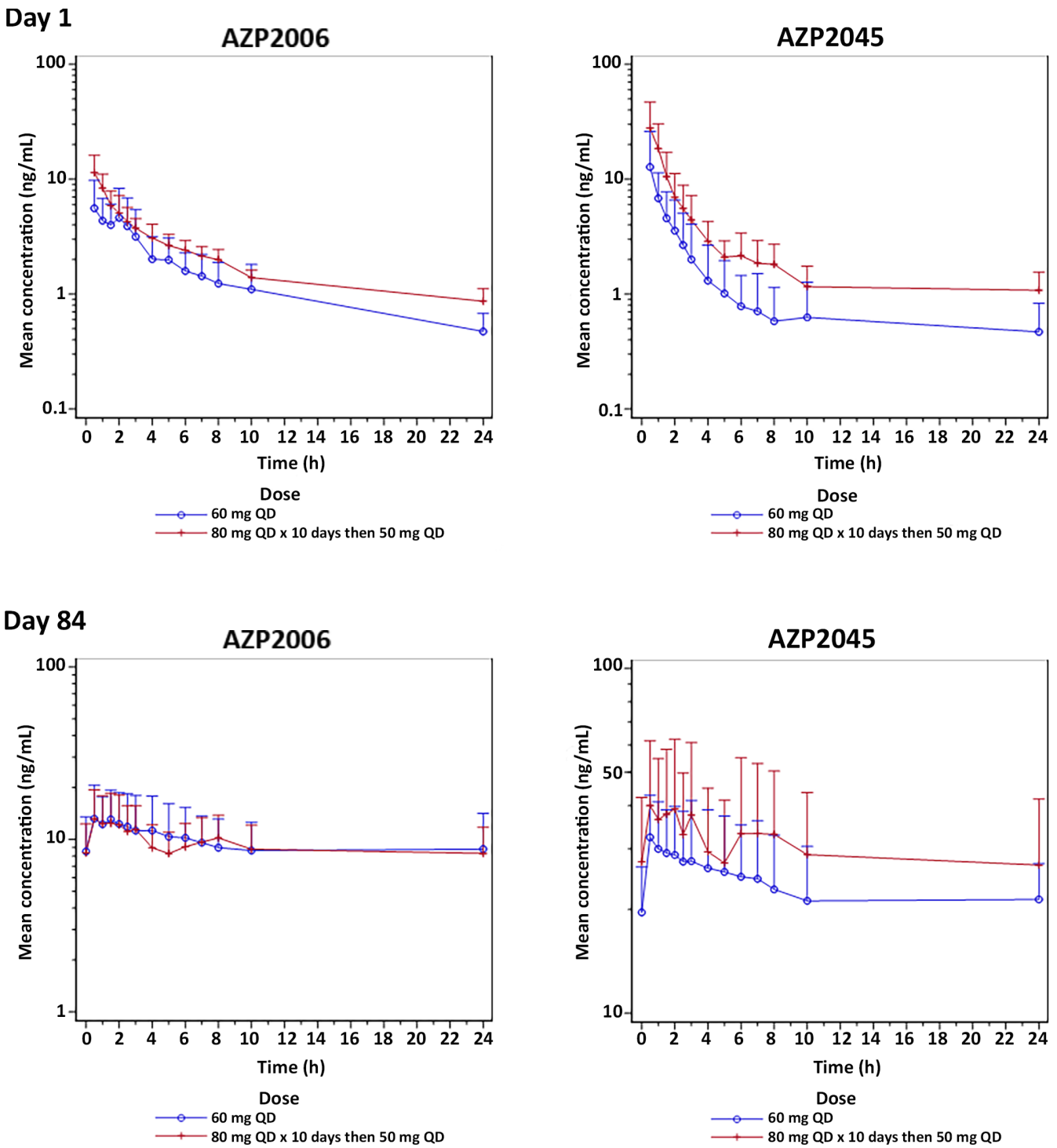

FIG. 1. Mean (+standard deviation) AZP2006 and AZP2045 (M2 metabolite) plasma concentrations versus time profiles (0–24 hours) on day 1 and on day 84 by treatment group (log-linear scale). QD, once per day. [Color figure can be viewed at wileyonlinelibrary.com]

The Schwab and England ADL score (Table 3) indicated a decline in functioning for all groups at EOT and FUP versus baseline, with the deterioration less pronounced in the 80/50 mg AZP2006 group compared to the other groups.

The MoCA score (Table 3) showed a decline in all groups at EOT and FUP, with the 60 mg group exhibiting a more prominent decline than the 80/50 mg and placebo groups at both time points.

Approximately 2 years after the completion of the phase 2a trial, 15 patients enrolled in the OLE, of whom 12 completed the 6-month treatment course. One patient died during the OLE because of a cause unrelated to the study drug. No remarkable safety events were observed

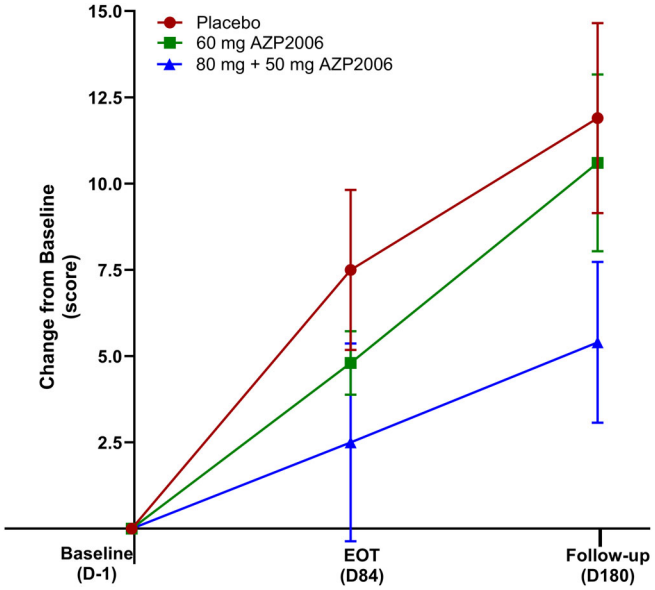

FIG. 2. Mean (+standard deviation) of the score of change from baseline (D-1) in the Progressive Supranuclear Palsy Rating Scale (PSPRS). EOT, end of treatment; D180, end of 6-month follow-up. [Color figure can be viewed at wileyonlinelibrary.com]

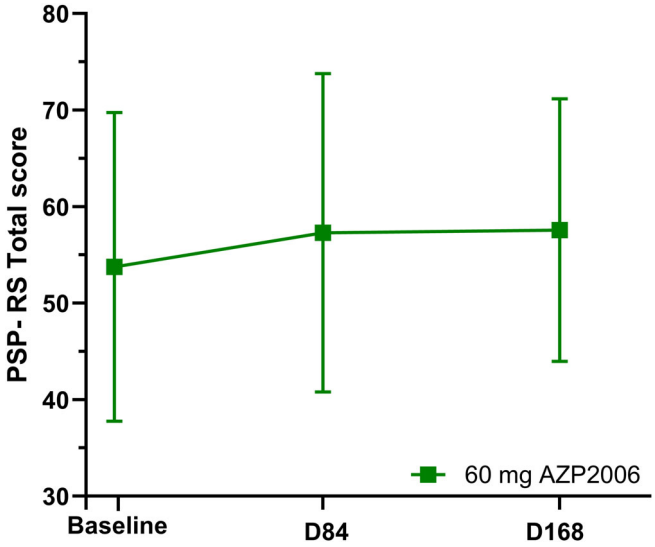

FIG. 3. Progressive Supranuclear Palsy Rating Scale (PSPRS) total score of the open label extension during the treatment with AZP2006. [Color figure can be viewed at wileyonlinelibrary.com]

during the OLE, specifically, no treatment-related SAEs were observed. At the end of the OLE, the change from baseline in PSPRS for the 12 patients were − 2, −1, −1, 0, 0, 2, 2, 3, 7, 10, 11, and 15 points (Fig. 3).

Discussion

The trial has provided valuable insights into the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of AZP2006 in patients with PSP. The 60 mg dose cohort consistently showed worse disease severity scores at baseline, which may be attributed to the small sample size in this trial, however, overall the attributes well balanced in other aspects. The 3-month exposure was associated with a favorable safety profile, and there were no safety concerns. The 6-month OLE confirmed this favorable safety profile. The pharmacokinetic data were consistent with those previously described in phase 1 clinical development of AZP2006 in healthy volunteers when administered in the fasted state, although the phase 1 multiple dose study used a 10-day dosing regimen and steady-state was not reached for any dose level.[16] The ability of AZP2006 to cross the blood–brain barrier, as demonstrated by its presence in the CSF and the reported modulations of PGRN concentrations in both CSF and plasma, suggests effective target engagement. Exploratory efficacy analysis using the PSPRS suggested a trend toward slowed disease progression in treated participants. Although preliminary signals warrant further investigation into potential clinical benefit, interpretation is limited by several factors. Participants had a disease duration of approximately 3 to 4 years at baseline, and a subset may have approached a ceiling effect. Notably, eight participants in the OLE phase showed near-complete stabilization for over 6 months, without clear evidence of ceiling limitation. However, potential selection bias in the OLE, where only participants with stable conditions could continue, must be considered before concluding on potential benefits. It is important to note that, this trial was not powered for efficacy endpoints and the outcomes presented should be interpreted based on observed trends rather than statistical differences between groups. Although inferential statistical analyses were conducted, the study's small sample size and limited power reduce the reliability of such comparisons. Consequently, greater emphasis was placed on descriptive analyses and patient-level evaluations to identify potential trends and account for confounding factors, such as ceiling effects or selection-bias during the OLE, before drawing any conclusions.

Most patients had mild-to-moderate adverse events unrelated to AZP2006. SAEs occurred across all groups, but were not drug-related. Two deaths (60 mg group) from pneumonia aspiration were attributed to underlying conditions. Two deaths in the 60 mg group because of pneumonia aspiration were both considered to be related to the patients' underlying clinical condition rather than to administration of AZP2006. Importantly, there were no significant differences in abnormal values for any safety parameter between groups. The pharmacokinetic results confirmed the long t½ of AZP2006 and its metabolite, AZP2045, allowing for a long period of availability in both plasma and whole blood, and also showed that steady-state for both

AZP2006 and AZP2045 was achieved sooner with the loading dose (ie, the 80/50 mg AZP2006 group) than without (ie, the 60 mg AZP2006 group). The availability of both AZP2006 and AZP2045 in CSF confirm that both pass the blood–brain barrier, and the observed concentrations are comparable to those indicative of efficacy in in vitro and in vivo models.[9]

The mechanism of action of AZP2006 centers around the stabilization of PGRN, a lysosomal crucial protein involved in regulating neuroinflammation and reducing neuronal burden. Unlike interventions that involve the blockade of PGRN receptor uptake, the anticipated effect of AZP2006 is not to markedly elevate PGRN levels in the CSF, and as expected, the observed changes in plasma and CSF PGRN levels during the trial were relatively modest. The subtle but consistent changes in PGRN concentrations are aligned with the targeted mechanism of modulation by AZP2006 in the context of neuroinflammatory processes. Particularly, the lesser decline in CSF PGRN levels among treated patients is in accordance with the drug's target engagement and its potential neuroprotective properties. The proposed mechanism involves optimizing lysosomal recycling to prevent PGRN loss, which is crucial given the association of lower PGRN levels with adverse outcomes in neurodegeneration.[18,19] The suggestion that PSP, as a proteinopathy, may be in part a lysosomal disease[20] underscores the drug's potential by improving lysosomal function and preventing the accumulation of extracellular proteins. The relatively rapid decrease of PGRN in the placebo group was surprising, and we cannot exclude fluctuations attributed to chance. The mechanistic explanation related to the impact of AZP2006 on the pathophysiology of PSP is, however, supported by the median levels in the placebo group, which remained lower than the AZP2006 groups, suggesting a potential drug effect. Previous studies have associated PGRN decline with dementia and mutations in neurodegenerative conditions,[21,22] including PSP.[23] Changes observed in plasma PGRN levels in both treated groups, although remaining stable in the placebo group, are also supportive of target engagement. Despite uncertainties about the specific causes of PGRN changes, the trial results highlight the promising neuroprotective aspect of AZP2006.

The observed discrepancy—where the 60 mg group showed a statistically significant τ reduction, whereas the 80/50 mg group exhibited the largest PGRN increases—may reflect differential sensitivity of these biomarkers to dose, pharmacokinetic steady-state dynamics, or engagement of parallel mechanisms. Preclinical evidence suggests that AZP2006 can influence additional pathogenic proteins (eg, TDP-43, amyloid β) and neuroinflammatory pathways, which may be differentially modulated at each dose. These findings underscore the importance of incorporating broader biomarker panels such as inflammatory cytokines or other proteinopathy markers in future studies to more comprehensively characterize its pleiotropic effects.

This trial was not powered to assess AZP2006 efficacy on disease progression, as the 12-week duration was too short and the sample size too small. However, considering the long t½ of AZP2006 and its metabolite AZP2045, we pre-planned a long-term FUP of 6 months to detect any safety or efficacy signal in the longer term. At the end of this period there was a trend toward a slower progression of PSPRS scores in the 80/50 mg AZP2006 group.

An important limitation of the OLE study is that patients eligible for inclusion were likely those with relatively slow disease progression. This could be because they were still alive and able to attend visits 2.5 years after the phase 2a study, suggesting slower progression. This factor may have influenced the observed outcomes, as patients with more advanced disease may have been excluded from the OLE. Despite this potential bias, the OLE study provided a unique opportunity to assess the effects of AZP2006 in the same patient population at two distinct time points, with different stages and severities of disease. The observed stabilization in later-stage PSP, despite a few outliers, suggests that the drug may have efficacy across a range of disease stages. OLE participants had baseline PSPRS scores between 50 and 60, which were still well below the potential ceiling effect of the PSPRS, further supporting the drug's potential impact. Natural history studies have shown that disease progression continues linearly well beyond these scores,[24] which adds to the evidence for AZP2006's efficacy. Although the results are encouraging, they must be interpreted with caution because of the potential biases, the small sample size, and the lack of non-confirmatory design of the OLE. However, these consistent findings of disease stability across two time points underscore the need for larger studies to confirm these promising results. Although definitive conclusions cannot be drawn from this data alone, the signal of a potential clinical effect of AZP2006, combined with evidence of target engagement, is promising and warrants further investigation in future clinical trials.

The trial is not without its limitations. Moreover, the small sample size raises concerns about the generalizability of the findings, and the lack of statistical power to detect efficacy outcomes emphasizes the exploratory nature of the efficacy analysis. To establish a more robust efficacy signal, future studies should include a larger sample size, and a trial design explicitly powered to detect treatment effects. Another limitation is the relatively short treatment duration of 3 months, which may not capture the full spectrum of disease progression in PSP. Longer treatment periods, ideally extending to at least 1 year, are crucial for detecting meaningful changes in patient status, especially in the placebo group in which increased divergence in patient status compared to AZP2006-treated

patients may be expected over a longer term. This extended duration would provide a more accurate assessment of the potential of AZP2006 to delay the progression of PSP, allowing for a more comprehensive evaluation of its efficacy.

Author Roles: (1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.
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C.M.: 1C, 2B, 3B.
L.-L.M.: 1C, 2B.
J.-P.B.: 1C, 2B.
D.D.: 1A, 3B.
S.S.: 1C, 2B.
N.C.: 1C, 2B.
G.H.: 2C, 3B.
M.L.: 1C, 2B.
G.M.: 1C, 2B.
N.C.: 1A, 2C.
A.B.: 1B, 2C.
O.D.: 2C, 3B.
C.E.: 2C, 3B.
A.K.: 1A, 1B, 2A, 2C, 3A, 3B.
P.V.: 1A, 1B, 2C, 3A, 3B.
L.D.: 1A, 1C, 2A, 2B, 2C, 3B.

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Data Availability Statement

Data collected for this trial, including individual participant data, and additional trial information can be made available on reasonable request to the corresponding author.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.