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Reactions to Multiple Ascending Doses of the Microtubule Stabilizer TPI-287 in Patients With Alzheimer Disease, Progressive Supranuclear Palsy, and Corticobasal Syndrome
A Randomized Clinical Trial

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IMPORTANCE Basket-design clinical trials that allow investigation of treatment effects on different clinical syndromes that share the same molecular pathophysiology have not previously been attempted in neurodegenerative disease.

OBJECTIVE To assess the safety, tolerability, and pharmacodynamics of the microtubule stabilizer TPI-287 (abeotaxane) in Alzheimer disease (AD) or the 4-repeat tauopathies (4RT) progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS).

DESIGN, SETTING, AND PARTICIPANTS Two parallel-design, double-blind, placebo-controlled phase 1 randomized clinical trials in AD and 4RT were conducted from December 20, 2013, through May 4, 2017, at the University of California, San Francisco, and University of Alabama at Birmingham. A total of 94 patients with clinically diagnosed AD (n = 39) and 4RT (n = 55) were screened; of these, 3 refused to participate, and 10 with AD and 11 with 4RT did not meet inclusion criteria. A total of 29 patients with AD, 14 with PSP, and 30 with β-amyloid–negative CBS (determined on positron emission tomography findings) were enrolled. Data were analyzed from December 20, 2013, through May 4, 2017, based on modified intention to treat.

INTERVENTIONS Randomization was 8:3 drug to placebo in 3 sequential dose cohorts receiving 2.0, 6.3, or 20.0 mg/m^2 of intravenous TPI-287 once every 3 weeks for 9 weeks, with an optional 6-week open-label extension.

MAIN OUTCOMES AND MEASURES Primary end points were safety and tolerability (maximal tolerated dose) of TPI-287. Secondary and exploratory end points included TPI-287 levels in cerebrospinal fluid (CSF) and changes on biomarker, clinical, and neuropsychology measures.

RESULTS A total of 68 participants (38 men [56%]; median age, 65 [range, 50-85] years) were included in the modified intention-to-treat analysis, of whom 26 had AD (14 women [54%]; median age, 63 [range, 50-76] years), and 42 had 4RT (16 women [38%]; median age, 69 [range, 54-83] years). Three severe anaphylactoid reactions occurred in TPI-287–treated patients with AD, whereas none were seen in patients with 4RT, leading to a maximal tolerated dose of 6.3 mg/m^2 for AD and 20.0 mg/m^2 for 4RT. More falls (3 in the placebo group vs 11 in the TPI-287 group) and a dose-related worsening of dementia symptoms (mean [SD] in the CDR plus NACC FTLD-SB [Clinical Dementia Rating scale sum of boxes with frontotemporal dementia measures], 0.5 [1.8] in the placebo group vs 0.7 [1.6] in the TPI-287 group; median difference, 1.5 [95% CI, 0-2.5]; P = .03) were seen in patients with 4RT. Despite undetectable TPI-287 levels in CSF, CSF biomarkers demonstrated decreased chitinase-3–like protein-1 (YKL-40) levels in the 4RT treatment arm (mean [SD], −8.4 [26.0] ng/mL) compared with placebo (mean [SD], 10.4 [42.3] ng/mL; median difference, −14.6 [95% CI, −30.0 to 0.2] ng/mL; P = .048, Mann-Whitney test).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, TPI-287 was less tolerated in patients with AD than in those with 4RT owing to the presence of anaphylactoid reactions. The ability to reveal different tau therapeutic effects in various tauopathy syndromes suggests that basket trials are a valuable approach to tau therapeutic early clinical development.

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Supplemental content

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Alzheimer disease (AD), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS) are distinct neurodegenerative syndromes that are associated with pathologic accumulation of tau protein in the brain. The clinical hallmarks of each disorder are unique: memory loss in AD, postural instability with gaze palsy in PSP, and asymmetric parkinsonism in CBS.[1] Neuropathologically, AD tau aggregates consist of neurofibrillary tangles of 3- and 4-microtubule binding repeat (3R/4R) tau, whereas in PSP and corticobasal degeneration, the most common neuropathology associated with CBS, different tau aggregates consisting primarily of 4R tau accumulate in neurons and glia.[1] Although neuropathologic tau accumulation correlates with disease severity and clinical phenomenology in all 3 diseases, tau-targeted therapeutic trials mostly have included participants with a single clinical diagnosis of either AD or PSP.[2] Basket studies are clinical trials that include participants defined by a specific underlying molecular cause that may be associated with treatment response independently of clinical phenotype. In oncology, basket clinical trials with treatments targeting a common oncogenic mutation found in different cancers have provided new insights into molecular pathophysiology and evidence of treatment response.[3] To date, similar approaches have not been attempted for neurodegenerative tauopathies.

Tau is a microtubule-associated protein that promotes the assembly of tubulin, stabilizes microtubules, and regulates other cellular processes.[4] In tauopathies, tau disengages from microtubules and may contribute to instability and axonal transport deficiencies owing to a hypothesized loss of tau function.[5] Microtubule-stabilizing agents have been proposed to compensate for this loss of function when used at low doses. Tau transgenic mouse models treated with the microtubule-stabilizing agents paclitaxel[6] or epothilone D[7] had improved axonal transport and motor function and reduced tau pathology.

TPI-287 (abeotaxane) is a blood-brain barrier–penetrable microtubule stabilizer. In animal models, TPI-287 accumulates at higher concentrations in the brain than blood and reduces brain metastatic colonization of breast cancer cells. In melanoma and neuroblastoma clinical trials, the maximal tolerated dose (MTD) of TPI-287 was 125 mg/m^2.[8-10] In PS19 tau-transgenic mice, TPI-287 reduced hyperphosphorylated tau levels in brain and improved performance on the Morris Water Maze.[11] Because it is not clear which sporadic human tauopathy best corresponds to the PS19 model, we investigated the safety and tolerability of TPI-287 intravenous infusions in patients with AD, PSP, and CBS in a randomized clinical trial with a parallel-group, double-blind, placebo-controlled basket design. For funding reasons, 2 clinical trials were conducted in parallel; one in patients with AD and the other in patients with PSP or CBS (referred to as the 4-Repeat Tauopathy [4RT] trial).

Key Points

Question Do patients with different tauopathies react differently to the microtubule stabilizer TPI-287?

Findings Two parallel, double-blind, placebo-controlled randomized clinical trials of near-identical design enrolled patients with Alzheimer disease, progressive supranuclear palsy, and corticobasal syndrome. Severe hypersensitivity reactions were observed only in patients with Alzheimer disease who received TPI-287, whereas clinical worsening and biomarker changes were observed in those with progressive supranuclear palsy and corticobasal syndrome.

Meaning Although the present study does not support continued development of TPI-287 for tauopathies, the results highlight the value of measuring treatment effects in multiple clinical tauopathy syndromes at early stages of development.

Methods

Participants

Participants were evaluated at the University of California, San Francisco (UCSF), for the AD and 4RT trials and the University of Alabama at Birmingham for the 4RT trial only. Ethics approval was obtained at UCSF and University of Alabama. All participants gave written informed consent at screening. The study was overseen by an independent data and safety monitoring board and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The complete AD and 4RT trial protocols are found in Supplement 1.

Patients in the AD cohort met the National Institute on Aging–Alzheimer Association workgroups criteria for probable AD dementia and had a Mini-Mental State Examination (MMSE) score ranging from 14 to 26 (inclusive) at screening (scores range from 14 to 24, with higher scores indicating better cognitive function).[12] Patients in the PSP cohort met the National Institute of Neurological Disorders and Stroke-Society for Progressive Supranuclear Palsy probable or possible PSP criteria, as modified for the Neuroprotection and Natural History in Parkinson Plus Syndromes clinical trial.[13] Participants in the CBS cohort met the 2013 criteria for possible or probable corticobasal degeneration, CBS subtype.[14]

Exclusion criteria included history of significant peripheral neuropathy. Because as much as 30% of CBS can be caused by underlying AD pathologic features,[1,15,16] participants with CBS had an additional exclusion criterion of elevated cortical β-amyloid levels on visual read of florbetapir fluorine 18–labeled positron emission tomography (PET) scans (complete exclusion criteria list is found in the eMethods in Supplement 2).

Randomization and Masking

All participants and study personnel were masked to treatment assignment. Participants were randomly assigned (by an unblinded pharmacist) in an 8:3 ratio of TPI-287 to placebo into sequential dose panels (11 per panel) of 2.0, 6.3, and 20.0 mg/m^2. In the 4RT trial, separate doses of 2.0 mg/m^2 for PSP and CBS and of 6.3 and 20.0 mg/m^2 for combined PSP and CBS panels were enrolled. Doses were selected based on extrapolation from previous microtubule stabilizer preclinical experiments that were confirmed with TPI-287 in PS19 tau-transgenic mice.[9,11] Dose escalation rules specified that if no more than 1 of the 8 participants receiving active treatment experienced dose-limiting toxic effects during the first 4 weeks,

the dose of TPI-287 would be escalated to the next higher dose. If 2 of 8 participants in a dose panel experienced a dose-limiting toxic effect, this dose was determined to be the MTD, and no further escalation occurred. A dose-limiting toxic effect was defined as (1) any grade 3 or higher adverse event per National Cancer Institute Common Terminology Criteria for Adverse Events, (2) any grade 2 or higher adverse event in the nervous system considered clinically significant for which there is reasonable possibility that TPI-287 caused the event, or (3) any infusion-related toxic effect (eg, allergic reaction or hypersensitivity) that did not resolve with supportive care. Anaphylactoid hypersensitivity reactions were a known risk of TPI-287 and were considered adverse events of special interest.

Procedures

Study drug was provided by Cortice Biosciences, Inc, as a concentrate (10 mg/mL) and diluted in normal saline solution. Placebo infusion consisted of normal saline solution. TPI-287 was given as a 1-hour intravenous infusion once every 3 weeks during 9 weeks for a total of 4 infusions for the placebo-controlled period. An additional 6 weeks of open-label extension for a total of 3 infusions was offered to all participants. Lumbar puncture for cerebrospinal fluid (CSF) collection was performed at screening and 1 week after the last double-blind infusion. Magnetic resonance imaging (MRI) scans were performed at screening and 2 weeks after the last double-blind dose.

Study visits occurred from December 20, 2013, through May 4, 2017. After 2 patients experienced a rash, the protocol was amended in May 2014 with addition of 25 mg of intravenous diphenhydramine hydrochloride pretreatment. After an anaphylactoid hypersensitivity reaction in October 2014, the protocol was further amended with addition of 10 mg of intravenous dexamethasone and 20 mg of intravenous famotidine as pretreatment for all participants. At the time of the second amendment, 10 patients had been enrolled in the AD and 6 in the 4RT trial cohorts.

Outcomes

The primary outcome was the safety and tolerability (MTD) of TPI-287 intravenous infusions. Safety assessments included adverse effects, physical and neurological examination, weight, vital signs, electrocardiography, blood tests, CSF cell count with differential, glucose levels, total protein levels, and qualitative reads of the brain MRI. Secondary outcomes included the plasma pharmacokinetics (PK) profile of TPI-287 after a single infusion and steady state TPI-287 CSF level 1 week after completion of the fourth infusion (eMethods in Supplement 2).

Exploratory end points included the following CSF biomarkers: neurofilament light chain (NfL) (NF-light assay; Uman Diagnostics), total tau, phosphorylated tau (p-tau), and β-amyloid 1-42 (Aβ42) (INNO-BIA AlzBio3; Fujirebio). Chitinase-3-like protein 1 (YKL-40) (Quidel Corporation) was added as a post hoc biomarker based on a published hypothesis that taxanes could alter central nervous system inflammation.[7,17] The MRI methods are described in the eMethods in Supplement 2.

In the AD trial, exploratory clinical end points included the MMSE, Alzheimer Disease Assessment Scale-Cognitive,[18] and the Alzheimer Disease Cooperative Study Activities of Daily Living scale[19] scores. In the 4RT trial, exploratory outcomes included the PSP Rating Scale score,[20] Schwab and England Activities of Daily Living scale score, the sum of boxes score from the Clinical Dementia Rating (CDR) Dementia Staging Instrument plus the NACC FTLD Module (FTLD-SB [CDR scale sum of boxes with frontotemporal dementia measures]; scores range from 0 to 10.5, with higher scores indicating worse dementia),[21] MMSE, and phonemic fluency[22] scores. Mood was assessed by the Geriatric Depression Screen score.[23]

Statistical Analysis

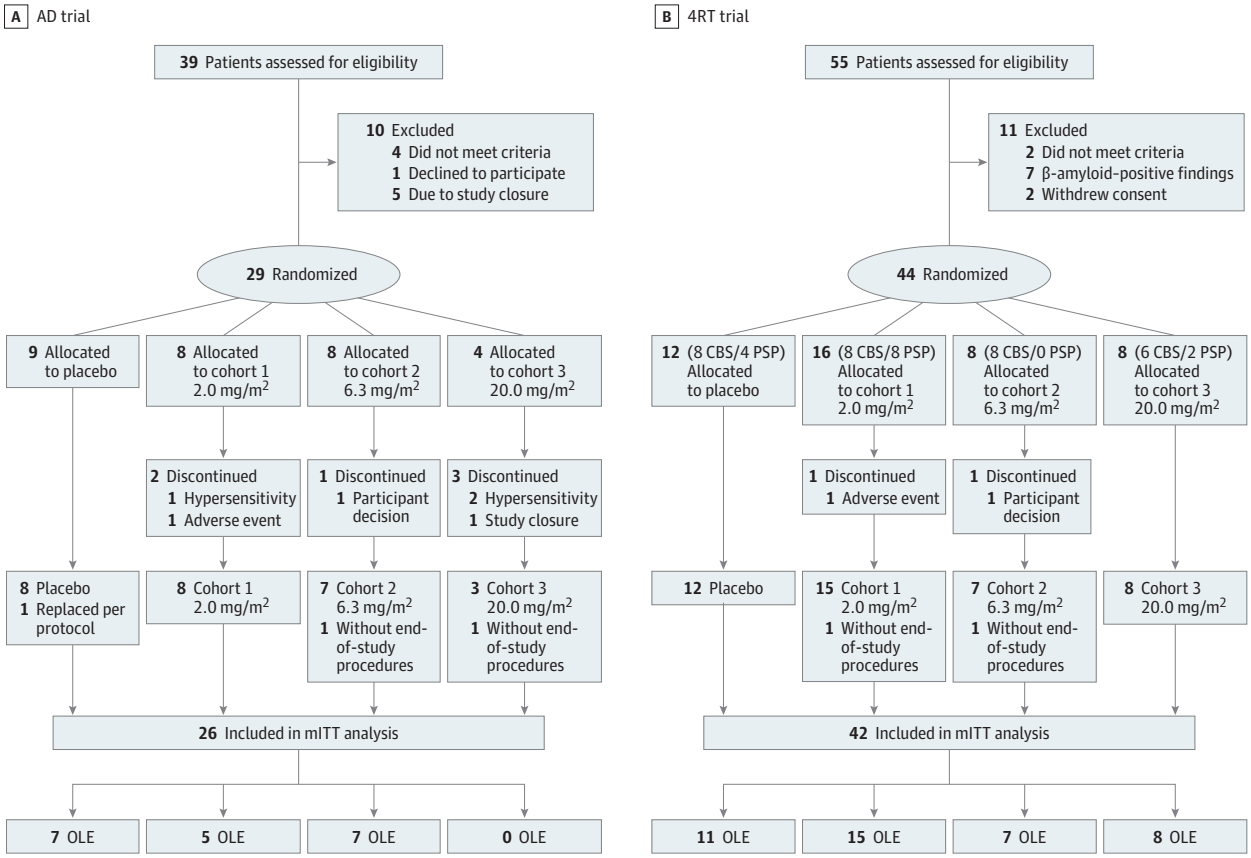
Data were analyzed from December 20, 2013, through May 4, 2017. Sample size was based on a standard phase 1, PSP, multiple ascending-dose escalation scheme[24] with 3 additional participants per panel to increase power for exploratory analyses. Data from all participants who received at least 1 infusion were included in the safety analysis.

A modified intention-to-treat analysis of all participants who received 2 or more infusions and had end-of-study efficacy assessments was used for the secondary and exploratory outcomes. A previous study[25] showed no differences between PSP and CBS in decline on the PSP Rating Scale or Schwab and England Activities of Daily Living score during 6 and 12 months, and in our study, CBS and PSP were combined for exploratory analyses. Baseline demographic variables and baseline to end-of-study outcome differences between treatment and placebo arms were analyzed with a Shapiro-Wilk normality test, and nonparametric tests were used as appropriate. For outcome differences between treatment and placebo arms, median difference and 95% CI were assessed by Mann-Whitney test and Hodges-Lehmann method. Differences between treatment dose panels and placebo were compared with a Kruskal-Wallis test with post hoc Dunn test and Benjamini-Hochberg correction. The significance level was set to 2-sided $P \leq .05$. Statistical analyses were conducted using Stata, version 13.1 (StataCorp LLC)

Results

A total of 94 patients (39 in the AD trial and 55 in the 4RT trial) were screened from local and national referrals; 29 with AD and 44 with 4RT were randomized to TPI-287 or placebo, and all were included in the safety analysis (**Figure 1**). In the AD trial, only 4 patients were randomized to the high-dose panel before the trial was terminated for safety reasons. A total of 68 patients (38 men [56%] and 30 women [44%]; median age, 65 [range, 50-85] years), including 26 patients with AD (14 women [54%]; median age, 63 [range, 50-76] years) and 42 with 4RT (16 women [38%]; median age, 69 [range, 54-83] years), had sufficient data to be included in the modified intention-to-treat analysis. In the modified intention-to-treat population, baseline characteristics did not differ between the placebo and treatment arms in the 2 trials except for lower CDR plus NACC FTLD-SB scores in the CBS low-dose panel (median, 0 [range, 0-4.0]) compared with the medium- (median, 4.0 [range, 0-10.5]) and high-dose (median, 4.0 [range, 2.5-

Figure 1. Trial Profile



AD indicates Alzheimer disease; CBS, corticobasal syndrome; mITT, modified intention to treat; OLE, open-label extension; PSP, progressive supranuclear palsy; and 4RT, 4-Repeat Tauopathy.

7.0]) panels (**Table 1**). Post hoc analyses demonstrated expected differences in CSF β-amyloid, p-tau, and NfL levels among the 3 diagnostic cohorts. The AD cohort had the lowest Aβ42 level (mean [SD], 283 [72] pg/mL) compared with the PSP and CBS cohorts (mean [SD], 462 [135] and 519 [132] pg/mL, respectively). Levels of p-tau were highest in the AD cohort (mean [SD], 64 [25] pg/mL) compared with the PSP and CBS cohorts (mean [SD], 26 [7] and 28 [7] pg/mL, respectively). Levels of NfL were highest in the CBS cohort (mean [SD], 6097 [3552] pg/mL) compared with the AD and PSP cohorts (mean [SD], 2643 [1102] and 3482 [1717] pg/mL, respectively) (**Figure 2**A and the eFigure in Supplement 2). Post hoc analysis of baseline volumetric MRI measurements in each diagnostic cohort demonstrated atrophy in expected regions, including the temporal parietal lobes for AD, frontal white matter for CBS, and midbrain pontine white matter for PSP (Figure 2B).

Adverse events are listed in **Table 2**. No safety signals were reported on laboratory assessments, weight, vital signs, electrocardiography, physical and/or neurological examination findings, or MRI for both trials. In the AD trial, all 3 serious adverse events (15%) were anaphylactoid reactions (narrative descriptions are given in the eResults in Supplement 2) that occurred in the treatment arm. Because 2 anaphylactoid reactions occurred early in the high-dose panel, the AD trial was stopped for safety considerations. In the 4RT trial, no serious adverse events or anaphylactoid reactions were reported, although more participants in the treatment arm experienced falls (11 of 32 [34%]) compared with the placebo arm (2 of 12 [17%]; $\chi^2 = 1.3$; $P = .16$). Patients in the treatment arms for both trials reported a higher incidence of headaches, dizziness, constipation, diarrhea, and nausea. Five participants in the AD trial discontinued early, 3 owing to anaphylactoid reactions that resulted in serious adverse events and 1 owing to mild infusion-related rash and 1 owing to withdrawal of consent. In the 4RT trial, 1 participant withdrew owing to a mild infusion-related rash and another withdrew owing to disease burden.

Pharmacokinetics data were available on 14 patients in the AD cohort and 38 in the 4RT trial cohort (eTable in Supplement 2). Plasma TPI-287 concentrations were highest from 30 to 60 minutes after the infusion, with dose-dependent increases seen across dose panels at 5 and 60 minutes after infusion (mean [SD] peak 60-minute postinfusion plasma concentration after 20-mg/m^2 dose: 75.4 [17.3] ng/mL in the AD cohort and 59.5 [15.5] ng/mL in the 4RT trial cohort). No steady-state CSF concentrations of TPI-287 were detectable 1 week after the last infusion, although plasma TPI-287 concentrations were measurable in highest-dose panel in the 4RT trial cohort at this time (mean [SD], 1.1 [2.1] ng/mL).

Table 1. Baseline Clinical and Demographic Characteristics of the Study Population in mITT Analysis[a]

Characteristic	Study Cohort by Treatment Randomization, Median (Range)										
	AD Trial					4RT Trial					
		TPI-287					TPI-287				
	Placebo (n = 8)	2.0 mg/m^2 (n = 8)	6.3 mg/m^2 (n = 7)	20.0 mg/m^2 (n = 3)	All (n = 18)	Placebo (n = 12)	PSP, 2.0 mg/m^2 (n = 8)	CBS, 2.0 mg/m^2 (n = 7)	CBS, 6.3 mg/m^2 (n = 7)	CBS, 20.0 mg/m^2 (n = 8)	All (n = 30)
Age, y	54.5 (50-74)	64.0 (50-76)	63.0 (54-74)	72.0 (59-76)	63.5 (50-76)	65.5 (54-77)	70.0 (61-83)	70.0 (55-76)	69.0 (62-78)	65.0 (57-78)	69.0 (55-83)
Sex, No.											
Male	3	5	3	1	9	6	4	4	5	7	20
Female	5	3	4	2	9	6	4	3	2	1	10
MMSE score[b]	21.0 (17-23)	23.5 (14-26)	24.0 (17-26)	23.0 (14-24)	23.5 (14-26)	26.5 (15-30)	26.5 (18-30)	27.0 (21-30)	24.0 (21-27)	23.0 (19-30)[c]	26.0 (18-30)[c]
ADAS-Cog score[d]	40.5 (27-59)	31.5 (28-48)	40.0 (34-52)	32.0 (24-40)[c]	37.0 (24-52)	NA	NA	NA	NA	NA	NA
ADCS-ADL score[e]	64.5 (33-76)	67.5 (55-73)	61 (51-74)	72 (26-78)	67.5 (26-78)	NA	NA	NA	NA	NA	NA
GDS score[f]	2.5 (1-10)	1.5 (0-7)	4.0 (0-8)	1.0 (0-12)	0 (2-12)	5.0 (1-7)	6.0 (2-11)	4.0 (1-12)	6.0 (1-7)	1.0 (0-7)	4.0 (0-12)
PSPRS score[g]	NA	NA	NA	NA	NA	25.5 (3-69)	37.5 (28-54)	25.0 (14-41)	25.0 (10-61)	29.0 (24-38)	30.0 (10-61)
SEADL score[h]	NA	NA	NA	NA	NA	40 (10-100)	20 (10-50)	60 (30-100)	60 (10-90)	50 (30-80)	45 (10-100)
CDR plus NACC FTLD-SB score[i]	NA	NA	NA	NA	NA	2.5 (1-7.5)	4.5 (0-6.5)	0 (0-4)	4.0 (0-10.5)	4.0 (2.5-7)	4.0 (0-10.5)
PF score[j]	NA	NA	NA	NA	NA	18.5 (4-55)	17.5 (0-37)	19.0 (7-36)	15.0 (8-35)	11.5 (2-35)	17.5 (0-37)
CSF levels											
Aβ42, pg/mL	280.5 (188-320)	305 (149-487)[c]	271.5 (230-350)	259 (124-325)	291 (124-487)[c]	625 (410-767)[c]	377 (248-628)	438 (312-547)	446 (268-644)	498 (280-669)	444 (248-669)
t-tau, pg/mL	113.5 (61-172)	100.5 (49-232)[c]	110.0 (89-162)	104.0 (58-177)	101.0 (49-232)[c]	69.0 (42-141)[c]	50.5 (35-76)	63.0 (50-75)	71.0 (39-100)	75.0 (42-121)	63.0 (35-121)
p-tau, pg/mL	57.5 (41-87)	76.0 (34-128)[c]	61.5 (34-80)	76.0 (26-81)	66.0 (26-128)[c]	29.0 (17-39)[c]	24.5 (19-39)	25.0 (18-39)	30.0 (19-42)	27.0 (13-41)	26.0 (13-42)
NfL, pg/mL	2497 (1844-3315)	2006 (1440-5700)[c]	2589 (1419-3923)	4410 (1723-5212)	2373 (1419-5700)[c]	3630 (1053-14681)	4182 (1354-6810)	6105 (734-7365)	3538 (1101-9460)	6815 (948-12 694)	4611 (734-12 694)
YKL-40, ng/mL	264 (209-414)	235.5 (143-531)[c]	296 (197-444)	324 (247-427)	288 (143-531)[c]	271 (190-642)	288 (209-309)	250 (143-300)	354 (280-669)	372 (170-521)	296 (143-521)

Abbreviations: Aβ42, β-amyloid 1-42; AD, Alzheimer disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living; CBS, corticobasal syndrome; CDR plus NACC FTLD-SB, Clinical Dementia Rating Scale sum of boxes with frontotemporal dementia measures; CSF, cerebrospinal fluid; GDS, Geriatric Depression Screen; mITT, modified intention to treat; MMSE, Mini-Mental State Examination; NA, not applicable; NfL, neurofilament light chain; PF, phonemic fluency; PSP, progressive supranuclear palsy; PSPRS, Progressive Supranuclear Palsy Rating Scale; p-tau, phosphorylated tau; 4RT, 4-Repeat Tauopathy; SEADL, Schwab and England Activities of Daily Living; t-tau, total tau; YKL-40, chitinase-3–like protein 1.

[a] Data are from mITT analysis of individuals who received 2 or more infusions and had end-of-study assessment data. Unless otherwise indicated, data are expressed as median (range).

[b] Scores range from 14 to 26, with higher scores indicating better cognition.

[c] One participant was missing data.

[d] Scores range from 24 to 59 with higher scores indicating more severe impairment.

[e] Scores range from 33 to 78, with higher scores indicating less severe impairment.

[f] Scores range from 0 to 12, with higher scores indicating worse depression.

[g] Scores range from 3 to 69, with higher scores indicating worse disability.

[h] Scores range from 10 to 100, with higher scores indicating better activities of daily living function.

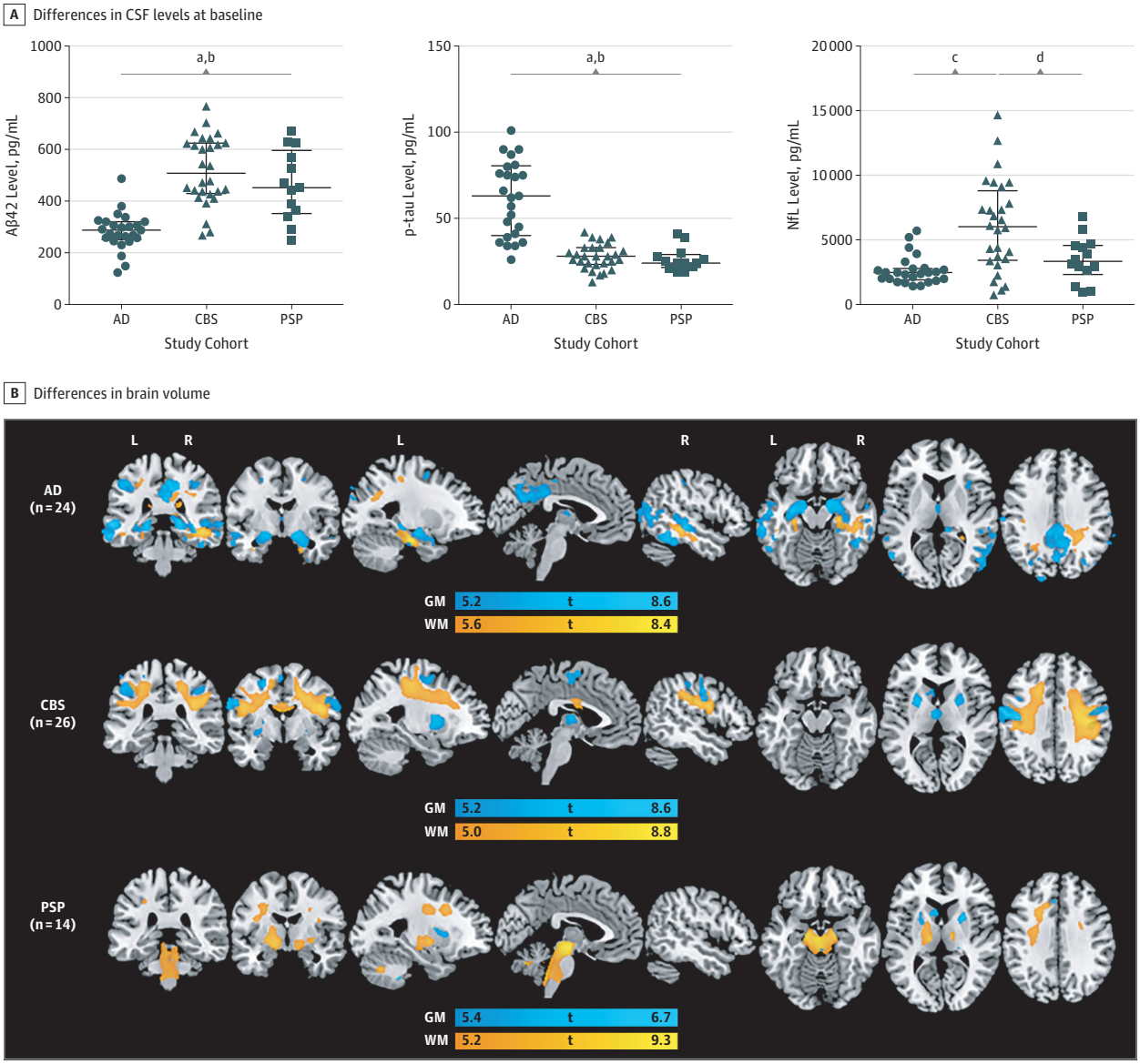
[i] Scores range from 0 to 10.5, with higher scores indicating worse dementia.

[j] Scores range from 0 to 37, with higher scores indicating better phonemic fluency.

For the exploratory CSF biomarker end points, no differences were found in rate of change between treatment and placebo arms in the AD or 4RT trial cohort. Post hoc exploratory analysis demonstrated a reduction in YKL-40 levels in the 4RT cohort treatment arm (median [range], −15 [49 to 76] ng/mL) compared with the placebo arm (median [range], 4 [−30 to 134] ng/mL; median difference, −14.6 [95% CI, −30.0 to 0.2] ng/mL; P = .048) (**Table 3**). No treatment-related differences were noted in the exploratory imaging end points.

For exploratory clinical end points in the AD trial, less decline in MMSE scores was observed in the treatment (median [range], 0 [−4 to 4]) compared with the placebo arms (median [range], −3 [−4 to 1]; median difference, 2.0 [95% CI, 0-4.0]; P = .04) (median and range are given in Table 3). In the 4RT trial, a more severe worsening in CDR plus NACC FTLD-SB score was observed in the 4RT treatment arm (median [range], 0.5 [−3 to 5]) compared with the placebo arm (median [range], −0.75 [−3 to 3]; median difference, 1.5 [95% CI, 0-2.5]; P = .03), with a dose-dependent trend for greater worsening with higher dose. A slight worsening of Geriatric Depression Screen in the 4RT treatment arm (median [range], 1 [−8 to 6]) compared with placebo (median

Figure 2. Baseline Cerebrospinal Fluid Biomarker and Volumetric Magnetic Resonance Imaging Measurements



Data are expressed as medians with 25% and 75% quartile bars. A, Differences in cerebrospinal fluid (CSF) levels of β-amyloid 1-42 (Aβ42), phosphorylated tau (p-tau), and neurofilament light chain (NfL) at baseline among diagnostic groups with Alzheimer disease (AD), corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP). B, Differences in brain volume among AD, CBS, and PSP compared with a group of 44 age- and sex-matched healthy control participants. All maps thresholded at $P < .05$ (familywise error).

GM indicates gray matter; WM, white matter. Color scale bars indicate t scores.

[a] $P < .001$ compared with CBS cohort.

[b] $P < .001$ compared with PSP cohort.

[c] $P = .001$ compared with CBS cohort.

[d] $P = .03$ compared with PSP cohort.

[range], −1 [−4 to 1]; median difference, 2.0 [95% CI, 0-3.0]; $P = .03$) was also observed.

Discussion

In a basket-design randomized clinical trial that recruited patients with the tauopathies AD, PSP, or β-amyloid PET-negative CBS, we examined the safety, tolerability, PK, pharmacodynamic effects, and clinical effects of the microtubule stabilizer TPI-287. Treatment-related immune hypersensitivity reactions that resulted in serious adverse effects were observed in patients with AD but not in those with PSP or CBS, leading to an MTD of 6.3 mg/m^2 for patients with AD, whereas a higher dose of 20.0 mg/m^2 was tolerated in patients with PSP and CBS. Of note, hypersensitivity reactions continued to occur in our AD cohort even after the addition of dexamethasone and antihistamine pretreatment, which may reflect stronger genetic links to the innate immune system in AD than in primary tauopathies.[26] Instead, a notable increase in falls

Table 2. Adverse Events in More Than 5% of Study Participants[a]

	Study Cohort by Treatment Arm, No. (%)								
	AD Trial			4RT Trial					
				PSP		CBS		Combined	
Adverse Event	TPI-287 (n = 20)	Placebo (n = 9)	All (n = 29)	TPI-287 (n = 10)	Placebo (n = 4)	TPI-287 (n = 22)	Placebo (n = 8)	All (n = 44)	All (n = 73)
Fall	2 (10)	0	2 (7)	7 (70)	1 (25)	4 (18)	1 (13)	13 (30)	15 (21)
Headache	5 (25)	0	5 (17)	0	0	7 (32)	2 (25)	9 (20)	14 (19)
Flushing	2 (10)	0	2 (7)	1 (10)	0	5 (23)	1 (13)	7 (16)	9 (12)
Rash	2 (10)	0	2 (7)	2 (20)	0	3 (14)	2 (25)	7 (16)	9 (12)
Back pain	0	2 (22)	2 (7)	2 (20)	0	1 (5)	2 (25)	5 (11)	7 (10)
UTI	0	0	0	4 (40)	1 (25)	0	1 (13)	6 (14)	6 (8)
Constipation	3 (15)	0	3 (10)	0	0	2 (9)	1 (13)	3 (7)	6 (8)
Dizziness	2 (10)	0	2 (7)	1 (10)	0	3 (14)	0	4 (9)	6 (8)
URI	0	0	0	2 (20)	0	2 (9)	1 (13)	5 (11)	5 (7)
Insomnia	0	0	0	0	0	2 (9)	3 (38)	5 (11)	5 (7)
Diarrhea	2 (10)	0	2 (7)	1 (10)	0	1 (5)	0	2 (5)	4 (5)
Fatigue	0	0	0	1 (10)	0	3 (14)	0	4 (9)	4 (5)
Itching	2 (10)	0	2 (7)	1 (10)	0	1 (5)	0	2 (5)	4 (5)
GI tract upset	1 (5)	0	1 (3)	0	0	2 (9)	0	2 (5)	3 (4)
Nausea	2 (10)	0	2 (7)	0	0	1 (5)	0	1 (2)	3 (4)
Hypersensitivity[b]	3 (15)	0	3 (10)	0	0	0	0	0	3 (4)

Abbreviations: AD, Alzheimer disease; CBS, corticobasal syndrome; GI, gastrointestinal; PSP, progressive supranuclear palsy; 4RT, 4-Repeat Tauopathy; URI, upper respiratory tract infection; UTI, urinary tract infection.

[a] Data are from the safety population who were randomized and received at least 1 infusion.

[b] Constitutes an adverse event of special interest.

occurred among patients with PSP in the treatment arm compared with the placebo arm, and a dose-related worsening of global cognitive status on the CDR plus NACC FTLD-SB occurred in the 4RT trial cohort treated with TPI-287. These findings demonstrate that patients with different tauopathies can experience different safety profiles when exposed to the same tau-directed therapy.

The human serum PK profile of TPI-287 has been previously described.[8] Similar to that study, the highest plasma TPI-287 concentrations were observed 30 to 60 minutes after infusion start.[8] Animal models have demonstrated excellent TPI-287 blood-brain barrier penetration and persistently elevated brain parenchymal concentrations exceeding plasma levels 96 hours after infusion.[9] However, CSF TPI-287 levels were not detectable 7 days after the final infusion. Nonetheless, treatment-related decreases in CSF YKL-40 levels in the 4RT trial treatment group suggest that TPI-287 had central nervous system activity. One possible explanation for our inability to detect TPI-287 in CSF might be that it remained in the brain parenchyma owing to its high hydrophobicity.

Although the AD treatment group showed a smaller decline in MMSE scores compared with the placebo group, this outcome was likely driven by the greater-than-expected decline of 2.1 points in the placebo group during 11 weeks and was not an effect of TPI-287.[27] Therefore, the treatment differences should not be interpreted as meaningful. Annualized CDR plus NACC FTLD-SB change scores for FTLD syndromes have been estimated to be 3.5.[21] The 4RT trial demonstrated no clear change in the CDR plus NACC FTLD-SB score in the placebo group but did show worsening scores in a dose-dependent fashion during 11 weeks (higher doses led to greater decline). The dose-dependent worsening in CDR plus NACC FTLD-SB in the 4RT trial combined with more frequent falls as an adverse event, which may be a result of subclinical taxane toxic effects in peripheral nerves, do not support further development of TPI-287 for PSP or CBS.

To the best of our knowledge, this study is the first placebo-controlled randomized clinical trial for β-amyloid PET–negative CBS. The pathologic heterogeneity of CBS—with as many as one-third of cases possibly caused by underlying AD pathology, approximately one-half by underlying 4R tauopathies (roughly 3:1, corticobasal degeneration to PSP), and the remaining by TDP-43 proteinopathy, dementia with Lewy bodies, or other diseases—has complicated clinical trial planning.[1,15,16] We attempted to exclude CBS due to AD pathologic changes using β-amyloid PET. Baseline biomarker analyses suggested that the enrollment criteria were able to accurately identify patients with each of the different tauopathies. The AD cohort had the lowest CSF Aβ42 concentrations and highest p-tau concentrations compared with the PSP and CBS cohorts, similar to previous observations.[28] Together, these results suggest that recruitment of patients with different tauopathies in a single trial is feasible and the diagnostic criteria used are reliable. In future studies, the addition of tau PET tracers such as [^{18}F]flortaucipir may further refine CBS recruitment accuracy.[29]

The basket design used for this clinical trial revealed differences in adverse events that might reflect differences in the cause of different tauopathy syndromes. Genome-wide association studies have demonstrated genetic overlap between AD and immune-mediated diseases, with many late-onset AD risk

Table 3. Change in Exploratory Outcomes From Baseline to End of Study in mITT Analysis[a]

Characteristic	Study Cohort by Treatment Arm, Median (Range)										
	AD Trial					4RT Trial					
		TPI-287					TPI-287				
	Placebo (n = 8)	2.0 mg/m^2 (n = 8)	6.3 mg/m^2 (n = 7)	20.0 mg/m^2 (n = 3)	All (n = 18)	Placebo (n = 12)	PSP, 2.0 mg/m^2 (n = 8)	CBS, 2.0 mg/m^2 (n = 7)	CBS, 6.3 mg/m^2 (n = 7)	CBS, 20.0 mg/m^2 (n = 8)	All (n = 30)
Clinical											
MMSE score[b]	−3.0 (−4 to 1)	0 (−4 to 4)	0 (−4 to 4)	0 (−3 to 1)	0 (−4 to 4)[c]	0.5 (−3 to 4)	−0.5 (−9 to 6)	−1.0 (−4 to 2)	1.0 (−3 to 4)	0 (−3 to 4)[d]	0 (−9 to 6)[d]
ADAS-Cog score[e]	1.5 (−6 to 8)	−3.5 (−12 to 6)	−3.0 (−9 to 9)	3.5 (0 to 7)[d]	−2.0 (−12 to 9)[d]	NA	NA	NA	NA	NA	NA
PSPRS score[f]	NA	NA	NA	NA	NA	1.0 (−11 to 8)	1.0 (−9 to 14)	1.0 (−17 to 9)	−3.0 (1 to 8)	2.5 (−10 to 15)	1.0 (−17 to 15)
ADCS-ADL score[g]	−0.5 (−12 to 7)	2.0 (−25 to 12)	−6.0 (−15 to 3)	−3.0 (−11 to −1)	−4.0 (−25 to 12)	NA	NA	NA	NA	NA	NA
SEADL score[h]	NA	NA	NA	NA	NA	0 (−20 to 30)	5.0 (−20 to 40)	−10 (−30 to 10)	0 (−20 to 10)	5.0 (−20 to 20)	0 (−30 to 40)
GDS score[i]	−0.5 (−6 to 2)	0 (−2 to 1)	−0 (−4 to 1)	0 (0 to 1)	0 (−4 to 1)	−1.0 (−4 to 1)	1.5 (−8 to 6)	1.0 (−3 to 2)	−1.0 (−3 to 6)	1.5 (−1 to 6)	1 (−8 to 6)[j]
CDR plus NACC FTLD-SB score[k]	NA	NA	NA	NA	NA	−0.75 (−3 to 3)	0.5 (−1 to 2.5)	0 (−3 to 0.5)	0 (1 to 3.5)	1.25 (−2.5 to 5)	0.5 (−3 to 5)[j]
PF score[l]	NA	NA	NA	NA	NA	0 (−10 to 9)	−0.5 (−4 to 8)	−1.0 (−6 to 6)	−5.0 (−10 to 3)	2.5 (−4 to 6)	−1.0 (−10 to 8)
CSF levels											
Aβ42, pg/mL	−3.5 (−22 to 5)	−8.0 (−23 to 61)[d]	−2.0 (−50 to 17)[d]	−4.0 (−22 to 1)	−6.0 (−50 to 61)[m]	−33.0 (−77 to 42)	−36.0 (−66 to 17)	−18.0 (−76 to 121)	−1.0 (−50 to 72)	−4.0 (−40 to 59)	−11.5 (−76 to 121)
t-tau, pg/mL	1.5 (−24 to 10)	1.0 (−15 to 14)[d]	−5.0 (−25 to 11)[d]	−6.0 (−24 to 26)	−3.0 (−25 to 26)[m]	−4.0 (−9 to 5)	2.0 (−6 to 12)	−2.0 (−18 to 9)	−1.0 (−14 to 25)	1.0 (−14 to 5)	1.0 (−18 to 25)
p-tau, pg/mL	6.5 (−35 to 29)	−5.0 (−18 to 17)[d]	−4.0 (−26 to 15)[d]	0 (−21 to 26)	−3.0 (−26 to 26)[m]	1.0 (−9 to 12)	0.5 (−8 to 7)	−4.0 (−12 to 3)	2.0 (−15 to 7)	−0.5 (−7 to 5)	0 (−15 to 7)
NfL, pg/mL	−0.5 (−141 to 256)	−5.0 (−159 to 370)[d]	81.5 (−474 to 310)[d]	−21.0 (−132 to 72)	10.5 (−474 to 370)[m]	92.0 (−575 to 1856)	148.0 (−464 to 1267)	−161.0 (−578 to 105)	−143.0 (−2162 to 265)	−36.0 (−2114 to 2304)	67.0 (−2162 to 2304)
YKL-40, ng/mL	−30.5 (−37 to 20)	−3.0 (−94 to 18)[d]	0.5 (−44 to 26)[d]	17.0 (−42 to 30)	0.5 (−94 to 30)[m]	4.0 (−30 to 134)	−19.0 (−34 to 76)	−23.0 (−49 to 29)	−4.0 (−23 to 46)	−14.0 (−26 to 7)	−15.0 (−49 to 76)[n]

Abbreviations: Aβ42, β-amyloid 1-42; AD, Alzheimer disease; ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive; ADCS-ADL, Alzheimer Disease Cooperative Study Activities of Daily Living; CBS, corticobasal syndrome; CDR plus NACC FTLD-SB, Clinical Dementia Rating Scale sum of boxes with frontotemporal dementia measures; CSF, cerebrospinal fluid; GDS, Geriatric Depression Screen; mITT, modified intention to treat; MMSE, Mini-Mental State Examination; NA, not applicable; NfL, neurofilament light chain; PF, phonemic fluency; PSP, progressive supranuclear palsy; PSPRS, Progressive Supranuclear Palsy Rating Scale; p-tau, phosphorylated tau; 4RT, 4-Repeat Tauopathy; SEADL, Schwab and England Activities of Daily Living; t-tau, total tau; YKL-40, chitinase-3–like protein 1.

[a] Data are from mITT analysis of individuals who received 2 or more infusions and had end-of-study assessment data.

[b] Scores range from −9 to 6, with positive scores indicating a worsening from baseline and negative scores indicating an improvement from baseline.

[c] P = .04, treatment group compared with placebo.

[d] One participant was missing data.

[e] Scores range from −12 to 9, with positive scores indicating a worsening from baseline and negative scores an improvement from baseline.

[f] Scores range from −17 to 15, with negative scores indicating improvement in disability and positive scores indicating worsening disability from baseline.

[g] Scores range from −25 to 12, with negative scores indicating a worsening in activity of daily living function from baseline and positive scores indicating an improvement.

[h] Scores range from −30 to 40, with negative scores indicating a worsening in activity of daily living function from baseline and positive scores indicating an improvement.

[i] Scores range from −8 to 6, with negative scores indicating an improvement in depressive symptoms since baseline and positive scores indicating a worsening.

[j] P = .03, treatment group compared with placebo.

[k] Scores range from −3 to 5, with negative scores indicating an improvement in dementia rating since baseline and positive scores indicating worsening dementia.

[l] Scores range from −10 to 9, with negative scores indicating worse phonemic fluency since baseline and positive scores indicating improved phonemic fluency.

[m] Two participants were missing data.

[n] P = .045, treatment group compared with placebo.

genes being highly expressed in microglia and astrocytes.[26,30] Meanwhile, most risk factor polymorphisms identified in corticobasal degeneration and PSP genome-wide association studies do not involve the immune system.[26,31] Our finding of more

severe hypersensitivity reactions in the AD cohort suggests clinically meaningful differences between immune system function in AD compared with CBS and PSP.

Limitations

Our study has important limitations. Although the blood-brain barrier penetration of TPI-287 in animal models has been previously reported,[9] we were not able to measure steady state concentrations of TPI-287 in CSF 7 days after multiple infusions. The absence of a target engagement biomarker that would show microtubule stabilization or other downstream pharmacodynamic biomarkers related to tau function limited our ability to determine whether TPI-287 engaged its molecular target or exerted influence on tau pathophysiology. Therefore, despite evidence of central nervous system biological activity reflected by CSF YKL-40 changes and adverse cognitive effects, the biological hypothesis that TPI-287 bound to central nervous system microtubules was not tested, and we could not comment on the potential for disease modification. Future clinical trials of microtubule stabilizers will need better pharmacodynamic biomarkers to be successful.

Conclusions

This study demonstrates the potential value of conducting basket clinical trials comparing the effects of tau-directed therapies in AD and the primary tauopathies PSP and β-amyloid PET-negative CBS. These studies may reveal important differences in safety, tolerability, and potential efficacy between neurodegenerative syndromes that share underlying tau pathologic features.

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