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Association of Plasma Phosphorylated Tau With the Response to Neflamapimod Treatment in Patients With Dementia With Lewy Bodies

John J. Alam, MD, Paul Maruff, PhD, Susan R. Doctrow, PhD, Hui-May Chu, PhD, Jennifer Conway, BS, Stephen N. Gomperts, MD, PhD, and Charlotte Teunissen, PhD

Correspondence
Dr. Alam
jalam@eippharma.com

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Abstract

Background and Objectives

In a proportion of patients, dementia with Lewy bodies (DLB) is associated with Alzheimer disease (AD) copathology, which is linked to accelerated cognitive decline and more extensive cortical atrophy. The objective was to evaluate the relationship between a biomarker of AD copathology, plasma tau phosphorylated at residue 181 (ptau181), and the treatment effects of the p38α kinase inhibitor neflamapimod, which targets the cholinergic degenerative process in DLB.

Methods

The AscenD-LB study was a phase 2a, randomized (1:1), 16-week, placebo-controlled clinical trial of neflamapimod in DLB, the main results of which have been published. After the study was completed (i.e., post hoc), pretreatment plasma ptau181 levels were determined and participants were grouped based on a cutoff for AD pathology of 2.2 pg/mL (established in a separate cohort to identify AD from healthy controls). Clinical outcomes for the comparison of placebo with neflamapimod 40 mg three times daily (TID; the higher and more clinically active of 2 doses studied) were analyzed using mixed models for repeated measures within each subgroup (baseline plasma ptau181 < and ≥2.2 pg/mL).

Results

Pretreatment plasma ptau181 levels were determined in eighty-five participants with mild-to-moderate DLB receiving cholinesterase inhibitors, with 45 participants below and 40 above the 2.2 pg/mL cutoff at baseline. In the 16-week treatment period, in the comparison of placebo with neflamapimod 40 mg TID, for all end points evaluated, improvements with neflamapimod treatment were greater in participants below the cutoff, compared with those above the cutoff. In addition, participants below the ptau181 cutoff at baseline showed significant improvement over placebo in an attention composite measure (+0.42, 95% CI 0.07–0.78, $p = 0.023$, $d = 0.78$), the Clinical Dementia Rating Scale Sum of Boxes (−0.60, 95% CI −1.04 to −0.06, $p = 0.031$, $d = 0.70$), the Timed Up and Go test (−3.1 seconds, 95% CI −4.7 to −1.6, $p < 0.001$, $d = 0.74$), and International Shopping List Test-Recognition (+1.4, 95% CI 0.2–2.5, $p = 0.024$, $d = 1.00$).

Discussion

Exclusion of patients with elevated plasma ptau181, potentially through excluding patients with extensive cortical neurodegeneration, enriches for a patient with DLB population that is more responsive to neflamapimod. More generally, plasma biomarkers of AD copathology at study entry should be considered as stratification variables in DLB clinical trials.

Trial Registration Information

NCT04001517 at ClinicalTrials.gov.

From the CervoMed (formerly EIP Pharma) (J.J.A., S.R.D., J.C.), Inc., Boston, MA; CogState Ltd London (P.M.), United Kingdom; Anoixis Corporation (H.-M.C.), Natick; Massachusetts Alzheimer's Disease Research Center (S.N.G.), Department of Neurology, Massachusetts General Hospital, Charlestown; and Neurochemistry Lab (C.T.), Department of Laboratory Medicine, Amsterdam Neuroscience, Neurodegeneration, Amsterdam UMC, Vrije Universiteit Amsterdam, the Netherlands.

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Glossary

AChEIs = acetylcholinesterase inhibitors; **AD** = Alzheimer disease; **DLB** = dementia with Lewy bodies; **DS** = down syndrome; **ISLT** = International Shopping List Test; **MMRM** = mixed model for repeated measures; **MMSE** = Mini-Mental Status Examination; **TID** = three times daily.

Introduction

In dementia with Lewy bodies (DLB), degeneration in the basal forebrain occurs early in the disease process and is prominent.[1,2] The resulting deficit in cholinergic neurotransmission has been proposed as the reason that patients with DLB are more responsive to acetylcholinesterase inhibitors (AChEIs) than those with Alzheimer disease (AD).[3] While most patients with DLB develop cortical atrophy, those with the least AD copathology show relatively less atrophy of the medial temporal lobe[4] than patients with AD. Conversely, patients with DLB with the evidence of AD pathology show more severe cortical atrophy,[5] including in the medial temporal lobe.[6] In addition, concomitant abnormality of AD-associated biomarkers (e.g., reduced CSF levels of amyloid beta 1–42, elevated CSF phosphorylated tau, and/or PET amyloid signal above threshold), seen in approximately 50% of patients with DLB, affects the clinical profile, including the rate of cognitive decline,[7-9] and might affect the response to AChEIs.[10] However, the practical implications of AD copathology on the management of patients with DLB in either clinical practice or clinical trials remain to be defined.

An opportunity to understand the relative contribution of basal forebrain cholinergic degeneration, relative to that of AD copathology, was afforded by a clinical trial of an investigational drug, neflamapimod, which targets the molecular mechanisms underlying the degeneration of cholinergic neurons in the basal forebrain.[11] In preclinical studies,[12] neflamapimod reversed the cholinergic neurodegenerative phenotype in the Ts2 transgenic mouse model of down syndrome (DS), an animal model that, along with the developmental defects associated with DS, develops basal forebrain cholinergic degeneration in adulthood. In the same animal model, neflamapimod improved behavioral outcomes associated with cholinergic function, while having only a modest impact on long-term potentiation in the CA1–CA3 region of the hippocampus. Furthermore, in an exploratory 16-week, phase 2a, placebo-controlled clinical trial, the AscenD-LB study,[12] neflamapimod reduced dementia severity and improved motor function, outcomes associated with basal forebrain cholinergic function in patients with DLB. In addition, the highest dose of neflamapimod (40 mg three times daily [TID]) improved cognition in that study, with the greatest benefits observed for the aspects of attention.

While the AscenD-LB study was ongoing, multiple reports from independent studies were published,[13-15] demonstrating that plasma tau phosphorylated either at position 181 (ptau181) or 217 (ptau217) predicted, in patients with preclinical or clinical AD, amyloid plaque status (by either PET or CSF), tau pathology (by PET), and/or cerebral, particularly medial temporal lobe, neurodegeneration, and atrophy. Moreover, after the AscenD-LB study was completed, Hall et al.[16] reported that in patients with DLB, the levels of plasma phosphorylated tau, either ptau181 or ptau217, could be used to predict the presence of concomitant AD pathology, assessed by either abnormal tau PET scan in temporal cortex or abnormal CSF Aβ42/Aβ40 ratio [area under the curve (AUC) > 0.78 and >0.81, respectively].[16] In addition, plasma ptau181 or ptau231 concentrations were reported to be associated with cognitive decline in a long-term (minimum 5 years of follow-up) longitudinal cohort study in patients with DLB.[17] In the latter study, similar to the findings of Hall et al., the patients with abnormal CSF Aβ42 levels had higher plasma concentrations of both ptau markers than did those with normal CSF levels and the AUC for plasma ptau181 predicting reduced CSF Aβ42 was 0.62.

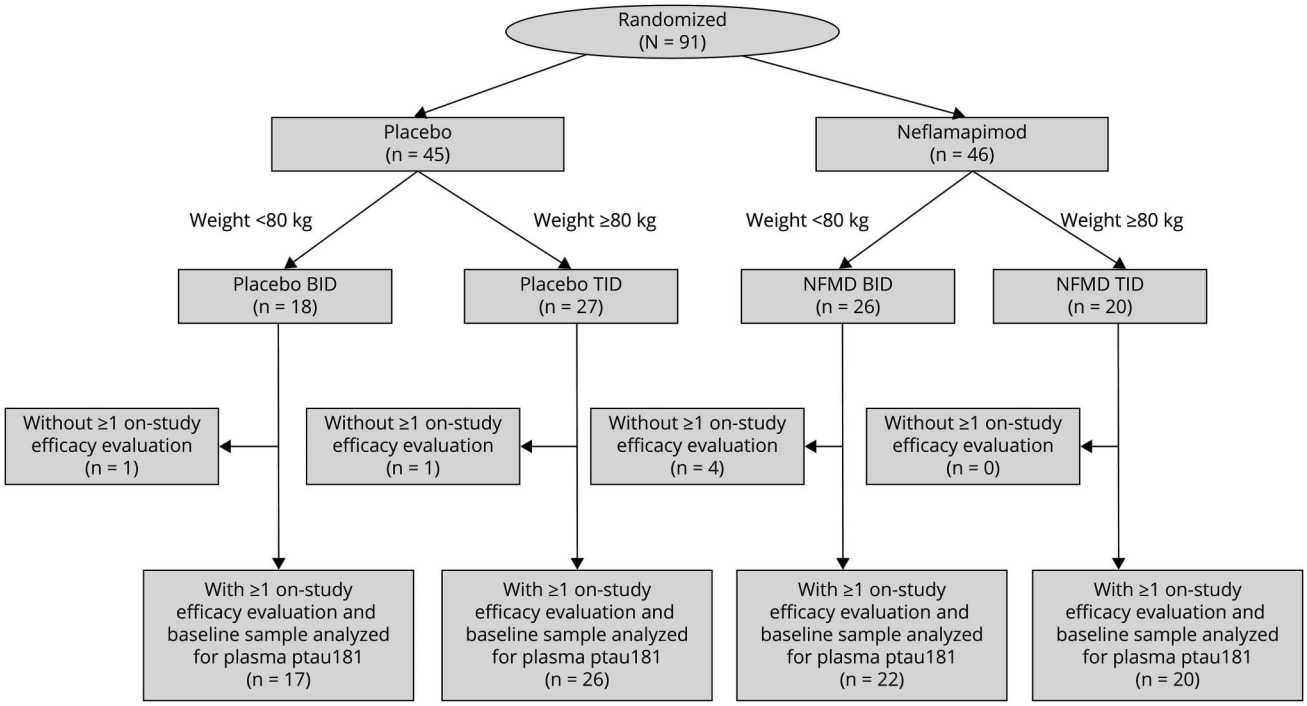
Based on these developments in the literature regarding plasma ptau as a biomarker in patients with DLB and hypothesizing that the effects of neflamapimod are dependent on the presence of AD copathology (specifically medial temporal lobe tau pathology and/or neurodegeneration), we determined the plasma levels of ptau181 in the stored pretreatment samples from the AscenD-LB clinical study and reanalyzed the efficacy outcomes after stratifying patients by whether the pretreatment plasma ptau181 level was elevated above an a priori defined cutoff. In addition to informing on the utility of ptau181 as a marker of responsiveness to neflamapimod, our findings increase the understanding of the contribution of AD pathology and cortical neurodegeneration on the clinical expression of DLB.

Methods

Participants and Study Design

The full design of the AscenD-LB study and its patient inclusion/exclusion criteria, participant characteristics, and main results were described previously.[12] In brief, AscenD-LB was a 16-week, double-blind, placebo-controlled phase 2a clinical study in 91 patients with mild-to-moderate (Mini-Mental Status Examination [MMSE], between 16 and 28) DLB, also receiving cholinesterase inhibitor therapy. Criteria for mild-to-moderate DLB were consistent with consensus clinical criteria[18]: dementia, with at least one core clinical feature of DLB and demonstrated abnormality in dopamine uptake by DaTscan (ioflupane I123 SPECT). The first

Figure 1 CONSORT Flow Diagram



participant was enrolled on September 30, 2019, and the last visit was on July 14, 2020.

As previously described,[12] the primary outcome measure of the study was a study-specific six-test neuropsychological test battery (NTB) designed to assess the cognitive domains most affected in DLB: attention (identification, detection tests), executive function (category fluency, letter fluency, one back accuracy), and visual learning (one card learning). Secondary objectives included evaluating the effects of neflamapimod on the Clinical Dementia Rating Scale, motor function (assessed by the Timed Up and Go, TUG test), and memory (assessed by International Shopping List Test [ISLT], Immediate Recall, Delayed Recall, and Recognition Index). The Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), designed to assess both cognition and function, is obtained by clinicians rating the severity of symptoms across 6 domains (memory, orientation, judgment & problem solving, community affairs, home & hobbies, and personal care) after a semistructured interview with the subject and a reliable informant (e.g. family member) on a 0–3 scale for each domain (total range 0–18, with a higher score indicating worse dementia).[19] The ISLT is a validated 12-word verbal list learning test that reports 3 scores: Immediate Recall (scored 0–36, the sum of 3 immediate recall trials), Delayed Recall (0–12, single recall, 20–25 minutes after initial trials), and Recognition (0–12, accurate recognition of the words in the original trials).[20,21] The TUG test, measuring functional mobility, monitors the time in seconds that a subject takes to rise from a chair, walk 3 meters, turn, walk back to the chair, and sit down while turning 180°.[22] The NTB and ISLT were performed at baseline and at weeks 4, 8, and 12 during treatment. The CDR-SB and TUG test were performed at baseline and at weeks 8 and 16. The MMSE was also an outcome measure of the study. However, COVID-19 pandemic restrictions on site visits to the clinical research centers led to more than third of on-study MMSE evaluations being missed or conducted remotely through video, an as-yet unvalidated approach. Because of this limitation, the on-treatment MMSE data were not evaluated in the main reporting of study results[12] nor evaluated herein.

Patients were randomized through an Interactive Response Technology (IRT, Svoboda, Inc., Conshohocken, PA) 1:1 to either neflamapimod (NFMD) 40 mg capsules or matching placebo and then, based on body weight, assigned to either a twice daily (BID) (weight < 80 kg; 40 mg BID neflamapimod or placebo BID) or three times daily (TID) (weight ≥ 80 kg; 40 mg TID neflamapimod or placebo TID) regimen.

The study protocol stated that an analysis based on stratification by an AD-associated plasma biomarker would be conducted. However, at the time, the specific biomarker and appropriate cutoffs for the presence of AD pathology in DLB were not available. Instead, plasma samples were obtained from subjects before treatment and stored until such a biomarker became available, with the intent to analyze those samples in the future for whether the AD copathology was present.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was registered at ClinicalTrials.gov (NCT04001517) on June 28, 2019, and in the EU Clinical Trials Register (EudraCT No. 2019-001566-15) June 26, 2019, and was conducted in

Table 1 Baseline Characteristics by Plasma ptau181 Status

	Baseline ptau181 < 2.2 pg/mL (N = 45)	Baseline ptau181 ≥ 2.2 pg/mL (N = 40)	*p* Value for comparison of < vs ≥ 2.2 ng/mL groups
Age (y)	71.7 (6.4)	73.9 (7.0)	0.13
Male	84%	85%	>0.2
CDR Sum of Boxes	4.5 (2.1)	5.5 (2.8)	0.048
MMSE	24 (3.4)	22 (3.6)	0.008
ISLT-Immediate	15 (6.0)	13 (5.0)	0.10
ISLT-Delayed	4 (2.5)	4 (2.4)	>0.2
ISLT-Recognition	10.4 (1.4)	10.1 (1.8)	>0.2
Timed Up and Go	13 (6.1)	13 (4.1)	>0.2
NTB *z*-score	0.13 (0.76)	−0.12 (0.73)	0.13
Fluctuating cognition	53%	65%	>0.2
Visual hallucinations	58%	58%	>0.2
REM sleep disorder	71%	60%	>0.2
Parkinsonism	80%	83%	>0.2

Mean (SD), except when shown as percentage. *p* value determined using the *t* test. For ISLT-delayed, ISLT-recognition and NTB (Neuropsychological Test Battery) *z*-score: missing data for 2 participants with ptau > 2.2 pg/mL. Also missing TUG (Timed Up and Go) test data for 1 participant with baseline ptau181 ≥ 2.2 pg/mL.

accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Applicable local/central ethics committee or IRB approvals were obtained as previously described,[12] and all participants provided written informed consent and were uncompensated. The study was performed, and this manuscript prepared in accordance with ICJME guidelines. The protocol and statistical analysis plan (SAP) may be accessed at ClinicalTrials.gov/ct2/show/study/NCT04001517.

Plasma ptau181 Measurements

The primary study completion date for the AscenD-LB study was July 2020, and the primary study analyses were completed in September 2020. Following the report in March 2021 that plasma ptau181 predicted AD copathology in DLB,[16] ptau181 levels in the stored plasma samples were assayed in August 2021 in all patients who had at least one on-study efficacy evaluation (see CONSORT flow diagram, Figure 1). Plasma ptau181 measurements were performed in the neurochemistry laboratory at the Amsterdam University Medical Centers following the instructions in the assay kit (p-Tau181 V2 kit, Quanterix, Billerica, MA) on the Simoa HD-X platform (Quanterix). In-house quality control plasma samples were assayed in duplicate at the start and end of each plate to assess within-run and between-run variations. The assay had been validated internally and, when evaluated in an in-house panel of patients with AD dementia, performed similar to the other available plasma ptau181 assays to differentiate patients with AD from healthy controls, with an AUC of 0.94 (95% CI 0.89–0.99) using a cutoff of 2.2 pg/mL.[23]

Statistical Analyses

Because the different tests in the NTB have various scales, each test score was converted to a *z*-score as previously described.[12] This enabled all tests to be equally weighted in the NTB composite *z*-score, which was calculated by averaging the *z*-scores from the components of the 6 individual tests. For greater understanding of treatment effects on the cholinergic system, an attention composite end point was also calculated, comprising only the 2 tests in the NTB that evaluate information processing speed, that is, the identification and detection tests.

Whether baseline characteristics were influenced by AD copathology was evaluated by comparing the value for each characteristic in patients with elevated (≥2.2 pg/mL) baseline plasma ptau181 than those with low (<2.2 pg/mL) plasma ptau181 using a *t* test without adjustment for multiple comparisons. With respect to evaluating treatment response, as prespecified in the study protocol, the analyses of all efficacy end points (primary, secondary, and exploratory) used a mixed model for repeated measures (MMRM) analysis method with change from baseline as the dependent variable, with study visit and baseline composite score as covariates.[12] Of note, the MMRM approach includes all time points on the study (*i.e.*, is not an end-of-treatment analysis), which were at baseline and at weeks 4, 8, and 12 for the NTB, attention, and ISLT evaluations and at baseline and at weeks 8 and 12 for the CDR-SB and TUG test. For each end point, the MMRM analysis was conducted separately for participants with baseline plasma ptau181 levels below (<) and greater than or equal to (≥) the cutoff of 2.2 pg/mL. As neflamapimod treatment effects on the cognitive end points were confined to the 40 mg TID dose group and the objective of this report was to evaluate the association of baseline plasma ptau181 with treatment response, the primary focus of this report is the results of the comparison of NFMD 40 mg TID vs all placebo, a comparison that was included in the SAP as a secondary (exploratory) analysis to evaluate dose response; however, we also conducted and report 2 sensitivity analyses of the results in patients with baseline plasma ptau181 below the cutoff, in which we compared 40 TID recipients with placebo TID and all neflamapimod (40 mg BID and 40 mg TID) with all placebo, respectively. As the current analysis was exploratory in nature and formally *post hoc*, the results are reported as mean difference between placebo and neflamapimod, with 95% confidence intervals. *p* values are also reported but to evaluate the strength of the evidence rather than to make inferences regarding efficacy. Cohen *d* effect size was also calculated for each comparison.

Data Availability

Individual participant deidentified the data that underlie the clinical trial results reported herein will be provided to

Table 2 Baseline Characteristics by Plasma ptau181 Status and Treatment Group

	Baseline ptau181 < 2.2 pg/mL		Baseline ptau181 ≥ 2.2 pg/mL	
	Placebo (N = 23)	Neflamapimod 40 mg TID (N = 11)	Placebo (N = 20)	Neflamapimod 40 mg TID (N = 9)
Age (y)	70.7 (6.0)	69.3 (5.5)	73.8 (7.5)	75.7 (6.4)
Male	87%	100%	85%	89%
CDR Sum of Boxes	4.3 (2.0)	4.3 (1.7)	6.1 (3.4)	5.2 (2.0)
MMSE	24 (3.8)	25.2 (2.2)	23 (3.6)	21.8 (3.2)
ISLT-Immediate	15 (6.0)	16.4 (4.8)	13 (4.6)	11.1 (3.2)
ISLT-Delayed	5 (2.3)	5.0 (2.4)	4 (1.8)	3.3 (2.2)
ISLT-Recognition	10.7 (1.3)	10.3 (1.4)	9.5 (2.0)	11.0 (1.1)
Timed Up and Go	14 (7.7)	12.8 (4.0)	13 (3.6)	14 (3.8)
NTB *z*-score	0.09 (0.82)	0.22 (0.74)	−0.12 (0.65)	−0.16 (0.71)
Fluctuating cognition	56%	45%	60%	67%
Visual hallucinations	65%	64%	45%	78%
REM sleep disorder	83%	73%	65%	67%
Parkinsonism	87%	82%	85%	100%

Mean (SD), except when shown as percentage. For ISLT-delayed, ISLT-recognition and NTB (Neuropsychological Test Battery) *z*-score: missing data in 1 placebo participant with ptau > 2.2 pg/mL. Also missing TUG (Timed Up and Go) test data in 1 placebo participant with baseline ptau181 ≥ 2.2 pg/mL. There were no significant differences noted between placebo and neflamapimod 40 mg TID groups in any baseline characteristic ($p > 0.05$).

investigators whose proposed use has been approved by an independent review committee on reasonable request to the corresponding author (JJA). These data will be available beginning 9 months and ending 36 months after publication. If/when neflamapimod receives marketing approval, patient-level clinical trial data will be shared through the Vivli data sharing platform (vivli.org).

Results

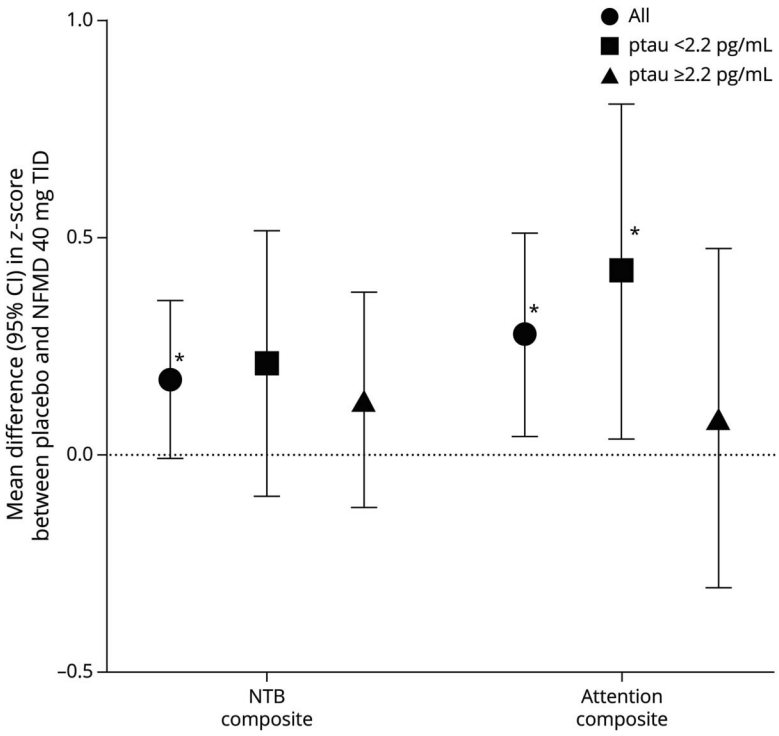
Baseline Characteristics

Baseline demographic and disease characteristics by treatment group and plasma ptau181 strata (< or ≥2.2 pg/mL) are presented in Table 1. The mean (SD) baseline plasma ptau181 was 1.6 (0.4) pg/mL in participants below the cutoff at baseline and 3.4 (1.4) in those above the cutoff. Consistent with the literature, patients with elevated plasma ptau181 (*i.e.*, those with AD copathology) had worse cognitive function, with significantly lower MMSE scores (mean 22.0 [SD = 3.6] vs 24.0 [3.4] for ptau181 < 2.2 pg/mL; $p = 0.008$) and higher CDR-SB scores (mean 5.5 [2.8] vs 4.5 [2.1] for ptau181 < 2.2 pg/mL; $p = 0.048$). The mean NTB-cognitive test battery *z*-scores and ISLT-Immediate Recall scores were also numerically lower in participants with baseline ptau181 ≥ 2.2 pg/mL, and these participants were numerically older than those with baseline ptau181 < 2.2 pg/mL, but the differences were not significant ($p = 0.13$ for NTB, $p = 0.10$ for ISLT; $p = 0.13$ for age). Notably, there were no significant differences in the profiles, with respect to "core features" of DLB (*i.e.*, fluctuating cognition, visual hallucinations, REM sleep disorder, parkinsonism), between the participants above or below the ptau181 cutoff. Within each strata (< or ≥2.2 pg/mL), there were no significant differences in any of the characteristics between placebo and neflamapimod 40 mg TID recipients (Table 2).

Treatment Effects of Neflamapimod Analyzed by Baseline Plasma ptau181

To evaluate the potential impact of AD copathology on neflamapimod treatment effect, we first conducted plasma ptau181 stratified analyses on the end points that demonstrated significant improvement, compared with placebo, in the 40 mg TID dose in the results previously reported[12]: the NTB (cognitive test battery), attention composite, CDR-SB, and TUG test. When the analyses were thus repeated, taking into account plasma ptau181 levels, the neflamapimod treatment response (i.e., the difference between neflamapimod 40 mg TID and placebo from MMRM analysis) in the patients with baseline plasma ptau181 < 2.2 pg/mL seemed to be greater than in those with baseline plasma ptau181 levels ≥2.2 pg/mL (Figures 2 and 3), with significant differences between treatment and placebo that were not observed in patients with the higher baseline plasma ptau181 levels. Specifically, in the patients with baseline ptau181 < 2.2 pg/mL, there was significant improvement, compared with placebo, in the MMRM analysis (Table 3) for the attention composite (40 mg TID-placebo difference = 0.42, 95% CI 0.07–0.78, $p = 0.023$; Cohen $d = 0.78$), CDR-SB (40 mg TID-placebo difference = −0.60, 95% CI −1.04 to −0.06, $p = 0.031$; $d = 0.70$), and TUG

Figure 2 Cognitive Outcomes in AscenD-LB Clinical Study Stratified by Baseline Plasma ptau181 Status



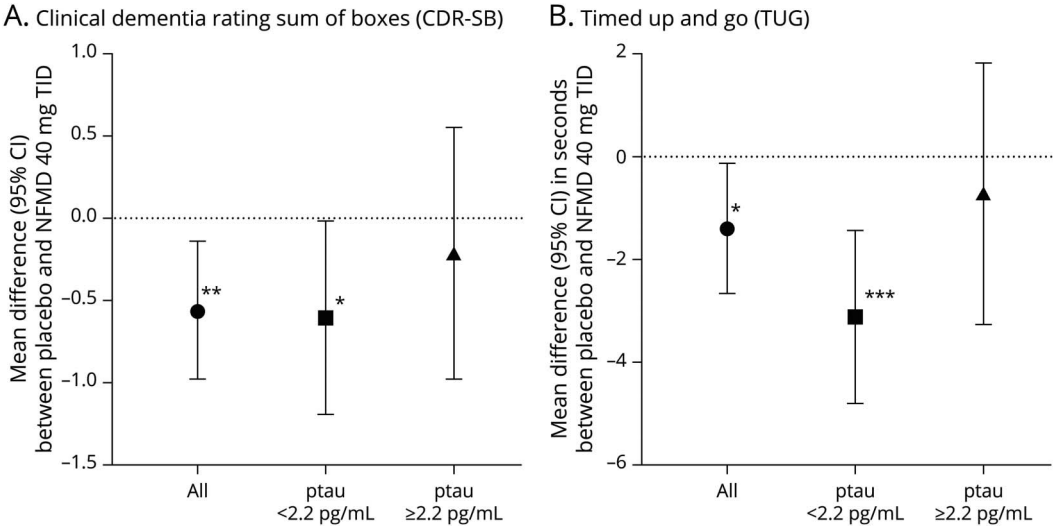
Mean difference between placebo and neflamapimod 40 mg TID, 95% CI, of analysis change from baseline using mixed model for repeated measures (MMRM) with baseline as a covariate for patients with baseline ptau181 < 2.2 pg/mL (absence of AD copathology) or ≥2.2 pg/mL (presence of AD copathology). Neuropsychological Test Battery (NTB) comprised 6 tests that individually assess attention, executive function, or visuospatial function: computerized tests from the Cogstate cognitive testing battery (detection, identification, one card learning, one back) and 2 verbal fluency tests (letter fluency test, category fluency test) that were recorded on paper. The attention composite z-score includes the results on the 2 tests within the NTB that evaluate information processing speed, detection, and identification. *p < 0.05.

test (40mg-placebo difference = −3.1 seconds, 95% CI −4.7 to −1.6, p < 0.001; d = 0.74). For the NTB, there also seemed to be a positive treatment effect in patients with baseline ptau181 < 2.2 pg/mL and one that was greater than in patients with baseline ptau181 ≥ 2.2 pg/mL but with the smaller sample size the 95% CI crosses zero (40 mg TID-placebo difference 0.21, 95% CI −0.07 to 0.49, p = 0.13; d = 0.56).

Having observed a neflamapimod treatment effect of greater magnitude in patients with baseline plasma ptau181 < 2.2 pg/mL on the aforementioned outcome measures, we then conducted analyses with stratification for ptau181 for the ISLT measures, in which there were no discernible treatment effects of neflamapimod 40 mg TID in the previously reported main results.[12] As shown in Figure 4, for the ISLT, the difference between placebo and neflamapimod 40 mg TID in the patients with baseline plasma ptau181 < 2.2 pg/mL was positive (*i.e.*, improved compared with placebo) and seems to be greater than in those with baseline plasma ptau181 levels ≥2.2 pg/mL for ISLT-Immediate Recall and for ISLT-Recognition. Specifically, when MMRM analysis was confined to patients with ptau181 < 2.2 pg/mL at baseline, a strong positive trend favoring NFMD 40 mg TID was seen for ISLT-Immediate Recall (Table 3, difference vs placebo = 2.1 words 95% CI 0.0–4.2, p = 0.053; d = 0.55) and significant positive improvement favoring NFMD 40 mg TID for ISLT-Recognition (Table 3, difference vs placebo = 1.4 words, 95% CI 0.2–2.5, p = 0.024; d = 1.00). There were no significant differences between NFMD 40 mg TID and placebo on ISLT-Delayed Recall, in either plasma ptau181 strata (Figure 3, Table 2). The pattern of an effect on Immediate Recall and Recognition, without an effect on Delayed Recall, is most consistent with an effect on executive function, which is consistent with the study results overall and a mechanism of action of neflamapimod on the cholinergic system.[12]

In addition to the comparison of 40 mg TID vs all placebo recipients, 2 sensitivity analyses were performed of the results in patients with plasma ptau181 < 2.2 pg/mL at baseline. First, because the TID dosing (either neflamapimod 40 mg or placebo matching capsules) was administered only to patients with weights ≥80 kg, MMRM analyses of the data from patients with baseline plasma ptau181 < 2.2 pg/were also conducted to compare the response only in the 2 higher weight cohorts (*i.e.*, within the patients without elevated plasma ptau181 to compare patients receiving 40 mg TID with the patients receiving placebo TID), and the results (eTable 1, links.lww.com/WNL/D91) were similar to those for the comparison of 40 mg TID with all placebo recipients. In the second sensitivity analysis, all neflamapimod recipients (*i.e.*, including patients who received the lower dose in the study of 40 mg BID) with baseline plasma ptau181 < 2.2 pg/mL were compared with all placebo recipients with baseline plasma ptau181 < 2.2 pg/mL. Given that in the previously published analysis,[12] 40 mg BID showed limited to no efficacy, while similar trends favoring neflamapimod were seen, the magnitude of the neflamapimod treatment effect compared with placebo, evaluated by Cohen d effect size, in this second

Figure 3 Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) and Timed Up and Go (TUG) Test Results in AscenD-LB Clinical Study Stratified by Baseline Plasma ptau181 Status



Mean difference between placebo and neflamapimod 40 mg TID, with 95% CI, of analysis change from baseline using mixed model for repeated measures (MMRM) with baseline as a covariate for patients with baseline ptau181 < 2.2 pg/mL (absence of AD copathology) or ≥2.2 pg/mL (presence of AD copathology). (A) Clinical Dementia Rating Sum of Boxes (CDR-SB) score. (B) Time Up and Go Test in seconds. *p < 0.05, **p < 0.01, ***p < 0.001.

sensitivity analysis was lower for all the end points (eTable 2, links.lww.com/WNL/D92; $d \leq 0.4$, except for CDR-SB, where $d = 0.58$), compared with the effect sizes presented in Table 3 (i.e., for the comparison of 40 mg TID and placebo in patients with baseline plasma ptau181 < 2.2 pg/mL).

Additional results from this clinical trial have been published,[12] and area was also available at ClinicalTrials.gov (ClinicalTrials.gov/ct2/show/results/NCT04001517).

Discussion

Data from a study of a novel therapeutic modality directed at cholinergic dysfunction and degeneration in patients with DLB[12] were reorganized and analyzed to account for pretreatment levels of plasma ptau181. The results showed that those patients without elevated plasma ptau181 levels (i.e., below a cut-off value of 2.2 ng/mL) had substantial treatment benefits in attention, dementia severity, and motor functional mobility as well as in memory. The magnitude of these benefits was moderate to large by convention (i.e., $d >$ 0.7), rendering group comparisons as statistically significant despite the relatively small sample sizes (n = 18–22 for placebo and n = 10–11 for neflamapimod, with baseline ptau181 below cutoff). More specifically, patients with DLB and plasma ptau181 levels within normal limits, in this 16-week clinical study of neflamapimod, demonstrated significant improvement over placebo on cognitive tests of attention, the CDR-SB, the TUG test measuring functional mobility, and ISLT-Recognition, a measure of memory retrieval. The finding that neflamapimod, an agent targeting cholinergic degeneration, has a beneficial treatment effect in DLB is consistent with the known prominent cholinergic deficit in the disease[1,24] as well as with several recent translational studies reporting that the strongest MRI finding associated with cognitive dysfunction in DLB is atrophy of the nucleus basalis of Meynert.[25-27] Indeed, in relation to the dementia component, the cholinergic system may be the primary site of neurodegeneration in DLB, as basal forebrain cholinergic degeneration was the major MRI finding in prodromal DLB, with cortical atrophy, starting in the inferior temporal lobe, developing as patients progressed to dementia.[2]

With respect to the association between plasma ptau181 and treatment response, it is important to note that, in DLB, such elevated plasma levels of phosphorylated tau are associated with more extensive neurodegeneration[6,7,28] and more rapid clinical disease progression.[17,29] This literature is compatible with our observation that elevated plasma ptau181 is associated with poorer cognitive function and greater dementia severity. These findings are also consistent with prior reports of pathology and/or MRI data indicating that patients with DLB and without AD copathology (cortical tau pathology and/or neuritic amyloid plaques) have minimal cortical atrophy, particularly in the medial temporal lobe.[4-6,30] Accordingly, the readiest explanation for the better outcome in subjects with plasma ptau181 < 2.2 pg/mL is that they represent a patient population having less advanced disease, particularly less extensive neuronal death and secondary cortical atrophy which, otherwise, are associated with and potentially result from AD copathology. That is, although future work will be required to differentiate between these possibilities, we expect that AD copathology is not directly modulating treatment response but, instead, that the patients in our study with ptau181 < 2.2 pg/mL have less extensive

Table 3 Clinical Outcomes in Patients With Baseline Plasma ptau181 < 2.2 pg/mL

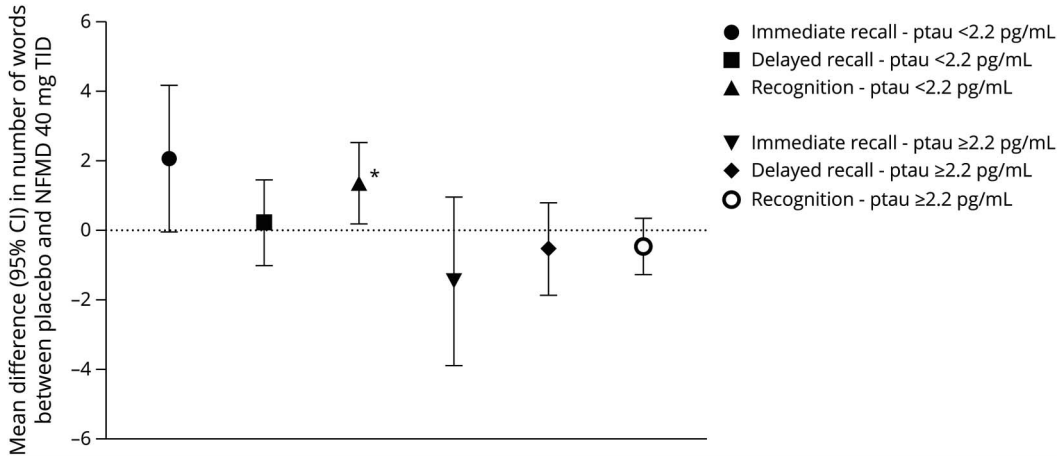
	Neflamapimod (NFMD) 40 mg TID vs placebo			
		MMRM analysis		
	N = NFMD, placebo	Difference (95% CI)	*p* Value	Cohen *d* Effect size
NTB	11, 19	0.21 (−0.07 to 0.49)	0.13	0.56
Attention	11, 18	0.42 (0.07 to 0.78)	0.023	0.78
CDR-SB	11, 22	−0.60 (−1.04 to −0.06)	0.031	0.70
Time Up and Go	11, 20	−3.1 (−4.7 to −1.6)	<0.001	0.74
ISLT-Immediate	11, 22	2.1 (0.0 to 4.2)	0.053	0.55
ISLT-Delayed	10, 21	0.2 (−1.0 to 2.4)	>0.2	0.15
ISLT-Recognition	10, 21	1.4 (0.02 to 2.5)	0.024	1.0

neurodegeneration in the cortex, that is, less irreversible neuronal loss and fixed deficits, and therefore would be more likely to show functional improvement within a 16-week treatment period. In particular, because the role of the basal forebrain cholinergic system is to modulate tasks conducted in the cortex and not to perform the tasks themselves, a finding that cortical atrophy would limit treatment response may be expected for an agent, such as neflamapimod, presumed to act on the cholinergic system. The concept that patients with DLB have partly reversible deficits, which are limited by neurodegeneration in those with AD copathology, is consistent with the results of a Tau PET study[31] in DLB. In that study, tau binding in patients with DLB was not different than in controls, except in those with AD copathology (by CSF or amyloid PET), where subtly greater tau binding was evident in the medial temporal lobe and occipital lobes. In addition, there were reductions in occipital and lateral parietal relative cerebral blood flow in patients with DLB, which are potentially reversible, compared with in controls and patients with AD, that correlated with cognitive dysfunction.

The notion that medial temporal lobe (i.e., hippocampal) neurodegeneration would limit treatment response is consistent with the preclinical results with neflamapimod as well as with the clinical findings described herein. Specifically, in DS mice that develop basal forebrain cholinergic degeneration, neflamapimod treatment restored behavioral outcomes associated with the basal forebrain cholinergic system but only modestly improved hippocampal function, evaluated as LTP in the CA1–CA3 region.[12] Of note, it has been reported that the cholinergic degenerative process is reversible in DS mice,[32] while in the hippocampus, they develop neurodegeneration and fixed structural changes.[33,34] Our results in the TUG test (Figure 3B) and ISLT-Recognition (Figure 4), showing the most prominent treatment effect differences between plasma ptau181 strata, are instructive in that regard because both measures would be expected to be influenced by the cholinergic input from the medial septal nucleus of the basal forebrain to the hippocampus.[35]

Recently, the results similar to ours with respect to the association of a plasma biomarker of AD copathology on treatment response to a novel agent were reported[36] with the PDE9 inhibitor, irsenontrine; in a 12-week, placebo-controlled phase 2 study in DLB, "amyloid-negative" patients (evidenced by a high plasma Aβ42/40 ratio) demonstrated a trend ($p = 0.053$) toward improvement in cognition, measured using the Montreal

Figure 4 International Shopping List Test (ISLT) Results in AscenD-LB Clinical Study Stratified by Baseline Plasma ptau181 Status



Mean difference between placebo and neflamapimod 40 mg TID, 95% CI, of analysis change from baseline using mixed model for repeated measures (MMRM) with baseline as a covariate for the International Shopping List Test Immediate Recall, Delayed Recall, and Recognition for patients with baseline ptau181 < 2.2 pg/mL (absence of AD copathology) or ≥2.2 pg/mL (presence of AD copathology). *$p < 0.05$, **$p < 0.01$.

Cognitive Assessment, whereas no such trends were evident in "amyloid-positive" patients. Together with our results, these findings point to the potential utility of a plasma biomarker for underlying pathology to decrease patient heterogeneity either as a covariate or by excluding patients with a concomitant, and potentially confounding, pathology. Although much work will be required to establish any one measure as a treatment response marker, we would suggest that a plasma biomarker of AD copathology is considered as a baseline stratification factor for randomization in future therapeutic clinical trials in DLB. Using stratification for such a biomarker at randomization would be particularly important in phase 2 trials because the relatively small size of the trials could not otherwise guarantee a balance among treatment groups, and the impact of cortical neurodegeneration on short-term effects may be more prominent than in longer duration clinical trials.

There are several limitations to our report. First, formally, our analysis was conducted *post hoc*, that is, after the primary study data were analyzed and reported. However, to temper this, an analysis based on baseline AD copathology status by a plasma biomarker was defined in the protocol; in addition, the cutoff was independently developed (against a panel of AD patients and controls)[23] and selected before conducting the analysis. Second, after stratification and limiting the treatment effect analysis to those participants receiving the higher neflamapimod dose, the number of patients within the subgroups is small, inherently requiring a larger study to confirm the results. Third, from a biological perspective, despite the preclinical data showing an effect on the cholinergic system and the supportive clinical associations presented herein and in a prior report,[12] without a specific biomarker or clinical end point for cholinergic degeneration and/or function, we cannot be certain that the therapeutic effects of neflamapimod are mediated by acting on cholinergic dysfunction and degeneration. This does not affect the interpretation that plasma ptau181 is useful to enrich the patient population for treatment responsiveness to neflamapimod; however, it limits the extent that the results can be interpreted, with respect to the role of the cholinergic system in disease expression and progression in DLB.

In conclusion, exclusion of patients with elevated plasma ptau181 levels in a *post hoc* analysis, potentially by excluding patients with more extensive cortical neurodegeneration, enriches for a patient with DLB population that is more responsive to neflamapimod, a therapy directed at cholinergic degeneration. More generally, plasma biomarkers of AD copathology at study entry should be considered as stratification variables in DLB clinical trials.

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Disclosure

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Appendix Authors

Name	Location	Contribution
John J. Alam, MD	CervoMed (formerly EIP Pharma), Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

Appendix *(continued)*

Name	Location	Contribution
Paul Maruff, PhD	CogState Ltd London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Susan R. Doctrow, PhD	CervoMed (formerly EIP Pharma) , Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content
Hui-May Chu, PhD	Anoixis Corporation, Natick, MA	Analysis or interpretation of data
Jennifer Conway, BS	CervoMed (formerly EIP Pharma) , Boston, MA	Analysis or interpretation of data
Stephen N. Gomperts, MD, PhD	Massachusetts Alzheimer's Disease Research Center, Department of Neurology, Massachusetts General Hospital, Charlestown, MA	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Charlotte E. Teunissen, PhD	Neurochemistry Lab, Department of Laboratory Medicine, Amsterdam Neuroscience, Neurodegeneration, Amsterdam UMC, Vrije Universiteit Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data; additional contributions: supervised validation of plasma ptau181 assay and sample testing

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Association of Plasma Phosphorylated Tau With the Response to Neflamapimod Treatment in Patients With Dementia With Lewy Bodies

John J. Alam, Paul Maruff, Susan R. Doctrow, et al.

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