Impact of AD Co-Pathology on Response to Neflamapimod Treatment in Patients with Dementia with Lewy Bodies

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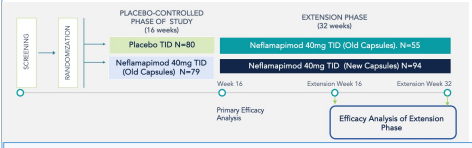
INTRODUCTION AND OBJECTIVES

Neflamapimod, an oral drug that targets basal forebrain cholinergic dysfunction and degeneration was recently reported (AD/PD 2025) in patients with DLB without AD co-pathology to slow clinical progression, assessed by CDR-SB in the RewinD-LB Phase 2b Study. Exclusion criteria for AD co-pathology (≥ 2.4 pg/mL plasma ptau181 at screening) in RewinD-LB was based on evaluation of data from an AD dementia cohort that indicated 90% specificity for AD co-pathology. Herein, we compared the effect of different cut-offs, 2.2 pg/mL, and 1.8 pg/mL (the Youden's cut-off for either CSF ptau181 or CSF tau in the AUMC DLB cohort) on the primary outcome measures. The correlation between plasma ptau181 and ptau217 was also evaluated in samples obtained in phase study.

DESIGN AND METHODS

PATIENTS

- 159 patients with dementia with Lewy bodies by consensus clinical criteria
- CDR global score of 0.5 or 1.0 at baseline
- Excluded patients with plasma ptau181 ≥ 2.4 pg/mL

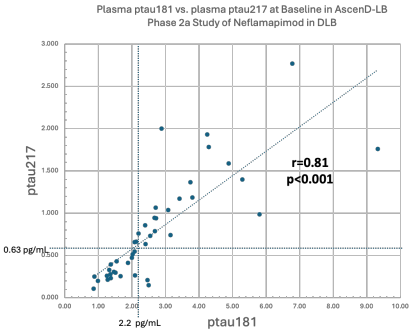


Dosing Groups and Comparisons

- Pharmacokinetic measurements in the placebo-controlled phase, in which only Old Capsules were utilized, showed that expected plasma neflamapimod concentrations were not achieved during the first 16 weeks of the study.
- With introduction during the Extension Phase of a new batch of capsules that achieved the targeted plasma drug concentrations, the effects of neflamapimod with New Capsules (N=94; extension "active drug arm") could be compared against outcomes in participants who continued to receive Old Capsules (N=55; extension "control arm").

Plasma ptau181 and ptau217 (ALZPath) were evaluated on Simoa® platform.

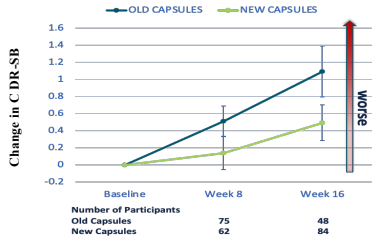
CORRELATION BETWEEN PLASMA PTAU181 AND PTAU217 IN PATIENTS WITH DLB



Utilizing published cutoffs for ptau217 (0.63 pg/mL) and ptau181 (2.2 pg/mL) there is 92% concordance for presence or absence of AD co-pathology. Similar results have been obtained in an analysis of plasma ptau217 and ptau181 in the subset with plasma ptau181 > 1.8 pg/mL in the RewinD-LB study.

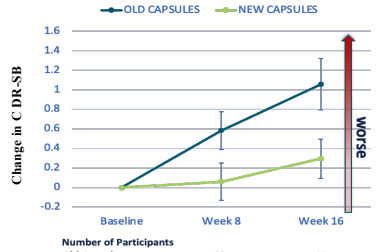
CHANGE IN CDR-SB DURING EXTENSION PHASE BY SCREENING $PTAU_{181}$ CUTOFF

All Participants 9screening ptau181 < 2.4 pg/mL)



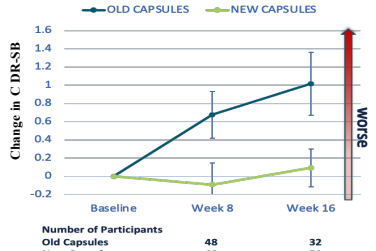
Number of Participants		
Old Capsules	75	48
New Capsules	62	84

Participants w/screening plasma ptau181 < 2.2 pg/mL



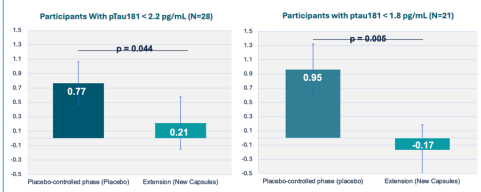
Number of Participants		
Old Capsules	66	45
New Capsules	52	67

Participants w/screening plasma ptau181 < 1.8 pg/mL



Number of Participants		
Old Capsules	48	32
New Capsules	40	51

Within-participant Comparison of Change in CDR-SB Over 16 Weeks in Participants Who Received Placebo in Initial Phase and Then New Capsules

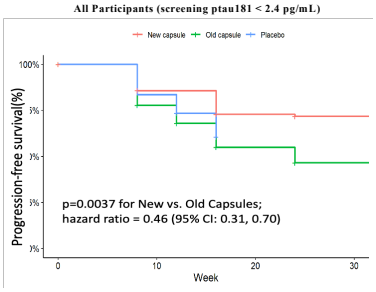


CONCLUSIONS

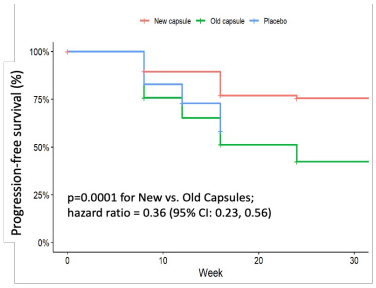
- The results further demonstrate that neflamapimod beneficially impacts clinical progression in patients with DLB and confirm with larger participant numbers the phase 2a finding that AD co-pathology impacts response to neflamapimod treatment.
- The established ptau181 cutoff of 2.2 pg/mL for AD also appears to be the optimal cutoff to maximize neflamapimod treatment response without screening out a large proportion of individuals who do not have A co-pathology
- Plasma ptau217 and plasma ptau181 provide largely concordant results when utilized to identify AD Co-Pathology in patients with DLB.

KAPLAN-MEIER ANALYSIS OF TIME TO CLINICALLY RELEVANT PROGRESSION ≥ 1.5 POINT INCREASE IN CDR-SB) BY $PTAU_{181}$ CUTOFF

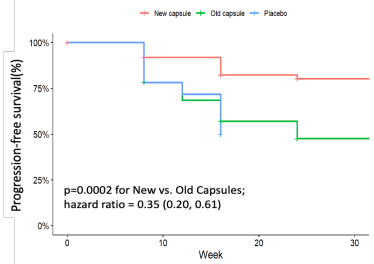
All Participants (screening ptau181 < 2.4 pg/mL)



Participants with screening ptau181 < 2.2 pg/mL



Participants with screening ptau181 < 1.8 pg/mL



Note: Kaplan-Meir survival curve analysis utilizing data from both placebo-controlled and extension phase ; participants when switched to new treatment (e.g. new capsules)