P071 - Neflamapimod Significantly Lowers Plasma GFAP and Correlates with Clinical Benefit in Dementia with Lewy Bodies (DLB): Results from the RewinD-LB Trial

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INTRODUCTION AND OBJECTIVES

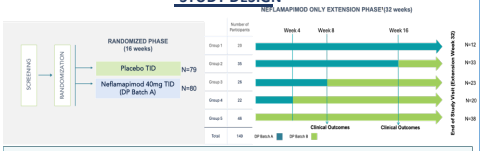
Neflamapimod, an oral p38α kinase inhibitor, targets molecular mechanisms that drive cholinergic degeneration and, in preclinical studies, has been shown to rescue basal forebrain cholinergic neuronal loss. In a retrospective analysis of stored plasma samples from a phase 2a clinical trial presented at CTAD 2024, neflamapimod treatment reduced plasma GFAP levels compared with placebo, and these reductions were correlated with clinical benefit as measured by CDR-SB.

Here, we present the plasma biomarker results from the RewinD-LB phase 2b clinical trial of neflamapimod in DLB, in which—based on the phase 2a results—plasma GFAP was prospectively defined in the Statistical Analysis Plan as the primary biomarker endpoint.

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 ≥ 27.2 pg/mL

STUDY DESIGN



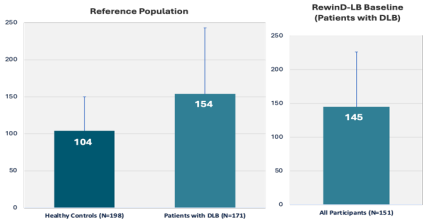
Neflamapimod Dosing Groups and Comparisons

- **Drug Product (DP) Batch A:** Batch of capsules utilized in placebo-controlled phase and initially during the extension. Did not achieve expected and targeted plasma drug concentrations.
- **DP Batch B:** introduced during the extension; achieved the targeted plasma drug concentrations.
- **Comparisons:** (1) Placebo vs DP Batch A during placebo-controlled period; (2) DP Batch B vs. DP Batch A during the extension

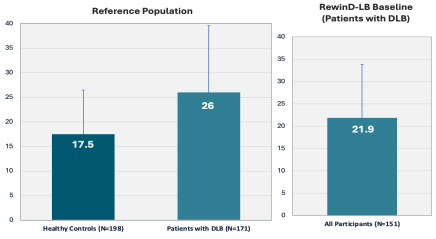
Plasma levels of GFAP and Neurofilament light chain (NfL) were determined at the neurochemistry laboratory at Amsterdam Medical Center using the Simoa Neurology 4-PLEX E (NF4PE) Advantage kit on the Simoa platform. Values reported are in pg/mL

BASELINE DATA

A. Plasma Glial Fibrillary Acidic Protein (GFAP) Levels (pg/mL)



B. Baseline Neurofilament Light Chain (NfL) Levels (pg/mL)

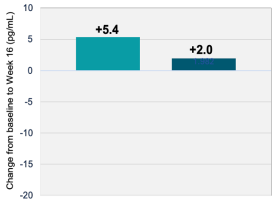


Reference ipopulation from Doeke et al (Alzheimers & Demenetia, 2025), in which the same assay was utilized in the same laboratory

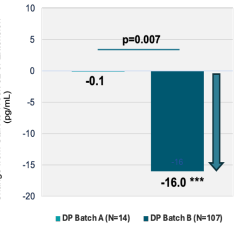
PLASMA GLIAL FIBRIALLARY ACIDIC PROTEIN (GFAP) ON-TREATMENT RESULTS

During the randomized period both placebo and neflamapimod showed small increases from baseline to week 16 in plasma GFAP (with no differences between the two treatment groups. In contrast, from the start of the Extension to Week 32 of the Extension there was a significant reduction in plasma GFAP levels in participants who received DP Batch B (i.e. achieved therapeutic plasma drug concentration (median -16.0, IQR: -35, +6.7; p<0.0001 for change from start to Week 32 of the Extension).

Median Change from Baseline to Week 16 During Placebo-Controlled Phase



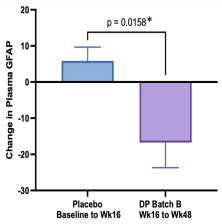
Median Change from Start to Week 32 of Extension



***P<0.0001 for change from start of extension to Week 32

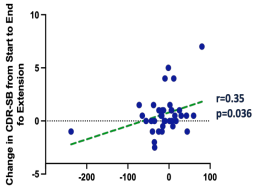
In a within-subject comparison in participants who received placebo during the randomized period and then received DP Batch B during the Extension, change in plasma GFAP over 32 weeks was significantly lower during treatment with DP Batch B compared to change in the same participants during placebo administration over 16 weeks (difference = -23.5 pg/mL, p=0.016). Further, in this cohort, change in GFAP was positively correlated to change in CDR-SB over 32 weeks (r=.35, p=0.036)).

Within Participant Comparison (N=48) of Effect on Plasma GFAP: Neflamapimod (DB Batch B) vs. Placebo



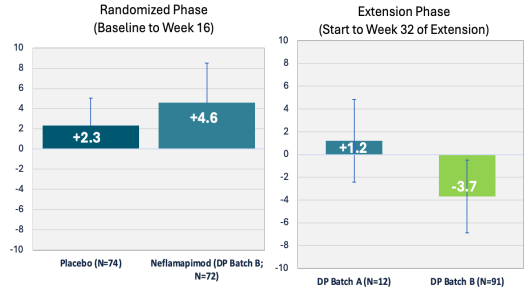
Median Difference between Neflamapimod and placebo: -23.1 pg/mL (~50% of disease-specific elevation)

During the Extension, Change in Plasma GFAP is Correlated to Treatment Response lassessed by Change in CDR-SB



PLASMA NEUROFILAMENT LIGHT CHAIN (NfL) ON-TREATMENT RESULTS

There were not apparent treatment effects with DP Batch A and a trend towards a reduction in plasma NfL levels with DP Batch B during the Extension..



CONCLUSIONS

Neflamapimod in the Rewind-LB study markedly reduced plasma GFAP levels in patients with DLB when target plasma drug concentrations are achieved, confirming the preliminary findings from phase 2a.

The magnitude of the effect is substantial, with reductions relative to placebo corresponding to approximately 50% of the disease-specific elevation in plasma GFAP (i.e., the increase observed in DLB compared with healthy controls).

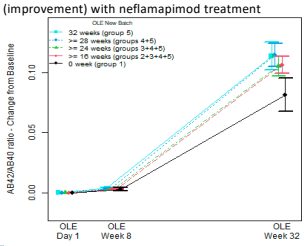
The reduction in plasma GFAP associated with neflamapimod treatment also appears clinically meaningful, as it correlates with treatment response as measured by CDR-SB

32 weeks treatment with neflamapimod also significantly increased Aβ42/40 ratio and showed a trend towards reducing NfL levels.

In line with the recent literature (e.g. Vrillon et al, 2024), and in contrast to ALS and FTD, NfL levels are only modestly elevated in patients with mild-to-moderate DLB, which provides insufficient signal to detect treatment effects in this context.

Aβ42/40 Ratio Results

During the placebo-controlled phase, there was a trend towards an increase with neflamapimod that was not seen with placebo. During the extension phase there was was significant increase (improvement) with neflamapimod treatment



P<0.001 vs. baseline for all except group 1; p=0.003 for group 1

Implications for Future Clinical Trials in DLB

Our results demonstrate the feasibility and potential of plasma GFAP, and preliminarily Aβ42/40 ratio, to detect treatment effects on neurodegenerative disease activity in DLB. In contrast, the modest elevation in plasma NfL levels compared to healthy controls and a standard deviation of 20 pg/mL (i.e.,two-thirds that for GFAP), our results indicate that plasma NfL has limited utility to detect treatment effects in DLB. For example, >300 participants would be required, with 80% power, to detect the mean 3.7 pg/mL reduction from baseline observed in our study with DP Batch B. Further to detect the maximal potential treatment effect of ~ 5 pg/mL (i.e. the elevation in DLB compared to healthy controls), 168 patients per arm would be required to detect a change from baseline.