The Oral P38a Kinase Inhibitor Neflamapimod Slows The Rate Of Clinical Worsening In Dementia With Lewy Bodies (DLB)

P1-001

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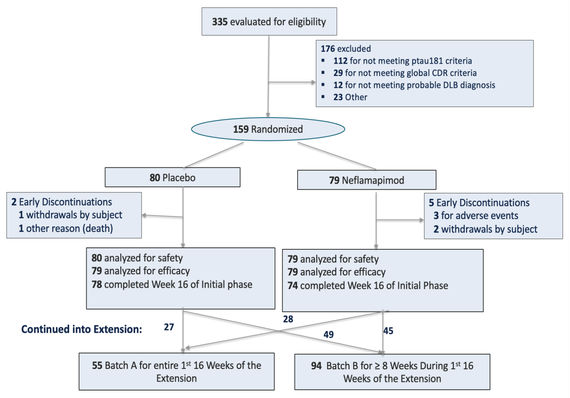
In a 159-patient randomized trial in dementia with Lewy bodies, neflamapimod did not replicate phase 2a results in which it improved outcomes on CDR-SB versus placebo. In exploratory analyses of the current study, there was evidence that neflamapimod slowed worsening on CDR-SB in patients with low plasma p-tau181and higher plasma drug concentrations, key lessons ahead of advancing into phase 3 development.

INTRODUCTION

Phase 2b 16-Week Placebo-Controlled Clinical Trial, with 32-Week Neflamapimod Only Extension



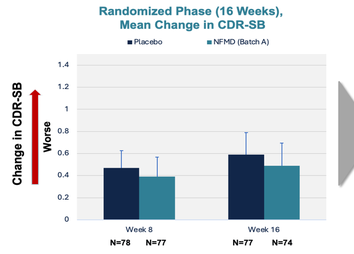
Baseline Characteristics

- All participants met consensus clinical criteria for probable DLB

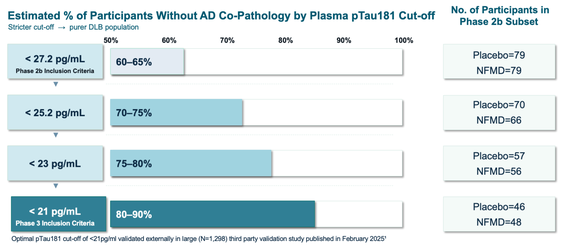
	Placebo	Neflamapimod
Number of Participants	79	80
Age (M, SD)	70.7 (5.8)	72.1 (6.4)
Male	67 (83.8%)	69 (87.3%)
MMSE (M, SD)	23.3 (4.6)	23.6 (4.3)
CDR-SB (M, SD)	4.23 (1.71)	4.45 (2.17)
ISLT Immediate (M, SD)	14.8 (5.9)	13.0 (5.0)
Core Clinical Criteria:		
Cognitive fluctuations	59 (73.8%)	59 (74.7%)
Visual Hallucinations	45 (56.3%)	43 (54.4%)
REM sleep behavioral disorder	64 (80.0%)	60 (75.9%)
Parkinsonism	68 (85.0%)	70 (88.6%)
Background Therapy		
AChEI alone*	52 (65.0%)	50 (63.3%)
Memantine (with or without AChEI)	11 (13.8%)	12 (15.2%)
No background therapy	17 (21.3%)	17 (21.5%)
Screening plasma ptau181 level (pg/mL)	19.1 (5.2)	18.9 (4.9)
Number (%) with screening plasma ptau181<21 pg/mL	46 (61%)	48 (60%)

RESULTS

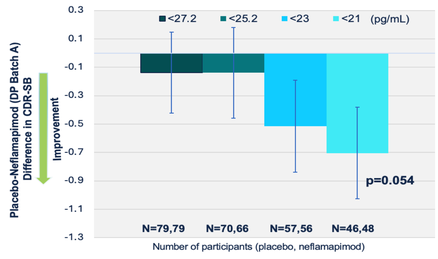
Primary Endpoint Results



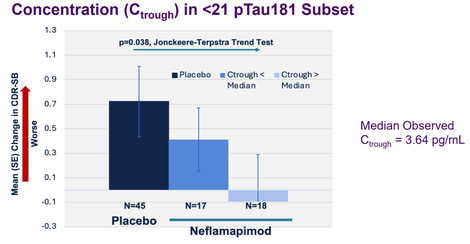
The Phase 2a clinical study findings were not replicated. However, **a higher proportion of patients with AD co-pathology** than targeted were included and neflamapimod **drug product did not achieve expected plasma drug concentrations.**



Neflamapimod Effect vs. Placebo on Change in CDR-SB by Plasma pTau181 Cutoff (MMRM Analysis)

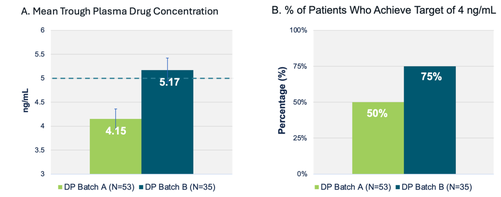


Change in CDR-SB During Placebo Controlled Phase by Trough Plasma Drug Concentration (C_{trough}) in <21 pTau181 Subset



Median Observed C_{trough} = 3.64 pg/mL

Neflamapimod Plasma Drug Concentration Were Lower Than Expected with Batch A During Randomized Phase and At Expected Levels with Batch B During the Extension Phase



With Achieving Expected Plasma Drug Concentrations, Batch B Demonstrates Improvement on Change in CDR-SB in Within-Participant Comparison to Placebo

pTau181 Cut-off	<27.2 pg/mL	<25.2 pg/mL	<23 pg/mL	<21 pg/mL
Number of Participants	32	28	24	21
NFMD-Placebo Difference	**-0.08**	**-0.55**	**-0.71**	**-1.11**
P-value NFMD vs. Placebo	p=0.9	p=0.044	p=0.034	p=0.005

CONCLUSIONS

- The Phase 2a study demonstrated improvement versus placebo on CDR-SB, particularly in participants with "pure" DLB (without AD co-pathology); this effect was not replicated in the current study.
- Exploratory analyses identified treatment effects favoring neflamapimod on CDR-SB during the placebo-controlled period among participants with low screening plasma p-tau181 (<21 pg/mL) and among those with trough plasma concentrations (C_{trough}) above the study median. These findings suggest that the negative primary outcome was driven by inclusion of a higher-than-targeted proportion of participants with AD co-pathology and lower-than-expected neflamapimod exposure.
- The optimal Phase 3 population is DLB without AD co-pathology, defined by plasma p-tau181 <21 pg/mL (v2.1 Simoa assay), a threshold recently identified as the high- sensitive cutoff for AD pathology (Doecke et al., 2025).
- The findings with Batch B further support that lower-than-expected neflamapimod exposure contributed to the primary result, as well support the choice of 50mg TID as the dose for phase 3.

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