Design of a phase 3 clinical trial of the oral p38a kinase inhibitor neflamapimod in patients with dementia with Lewy bodies (DLB)

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BACKGROUND

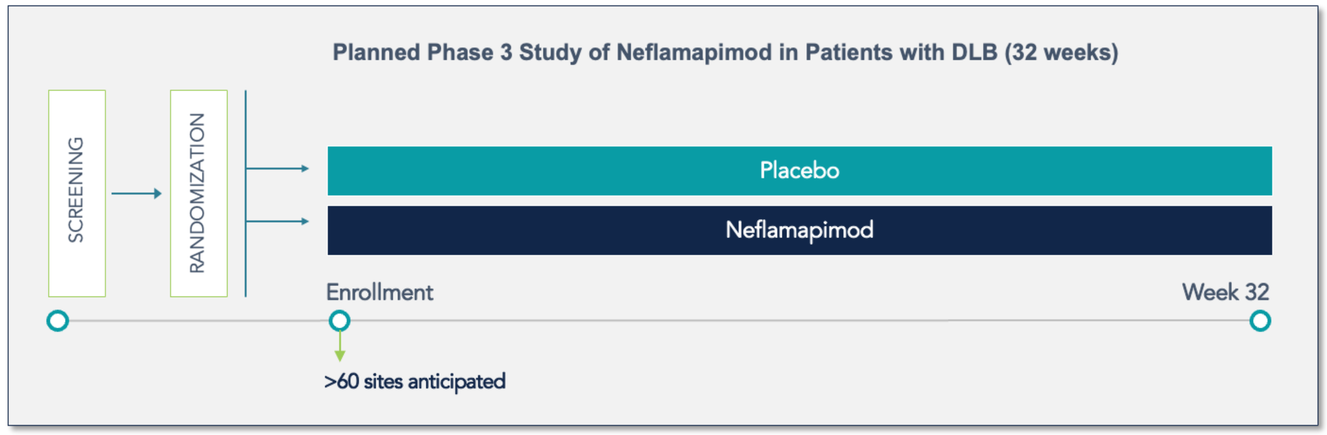
- **Brain-penetrant p38a inhibitor.** Oral small molecule in development as a potential disease-modifying treatment for dementia with Lewy bodies (DLB)
- **Targets inflammatory signaling.** Inhibits p38a-dependent interleukin-1β signaling and its downstream effects (Alam et al, *Cells*, 2026)
- **Preclinical evidence of neuronal rescue.** Reverses basal forebrain (BF) cholinergic pathology and improves associated behavioral outcomes (Jiang et al, *Nat Comm*, 2022)
- **Clinical evidence in DLB.** Phase 2 studies show signals on CDR-SB and plasma glial fibrillary acidic protein (GFAP), with supportive basal forebrain MRI findings (Jiang et al, *Nat Comm*, 2022; Alam et al, *Neurology*, 2023; Taylor et al, *Alzheimer's Research & Therapy, 2026)*
- **Regulatory Authority Alignment**. Alignment obtained with US FDA, European Medicines Agency, MHRA (UK) and PMDA (Japan) on key parameters of a Phase 3 trial of neflamapimod in DLB

OBJECTIVES

To review the clinical data obtained in Phase 2 study that supports key design elements of the Phase 3 clinical trial

Choice of Dosing Regimen

Dose	Percent of patients who achieve $C_{trough} \geq 4$ ng/mL	Clinical Activity
40 mg BID (Phase 2a only)	25%	**None**: No discernible activity
40 mg TID (Phase 2a)	2 of 2 participants with available data C_{trough} not systemically evaluated in Phase 2a	**Significant**: Improvement on CDR-SB vs. placebo in overall population; greater effect with 40mg TID and in participants w/o AD co-pathology
40 mg TID, Batch A (Phase 2b)	50%	**Active in target-exposure group**: CDR-SB in participants w/o AD co-pathology
40 mg TID, Batch B (Phase 2b)	>75%	**Broad improvement**: CDR-SB, CGIC, plasma GFAP, MRI; magnitude of clinical effect greater in participants w/o AD co-pathology
100 mg BID, New formulation	>90% (estimated)	To be confirmed, expected to be higher than observed in Phase 2a and Batch B in Phase 2b



KEY PARAMETERS

- DLB by consensus criteria, enriched for patients without AD co-pathology **(pTau181 < 21 pg/mL)**
- Primary endpoint: **Change in CDR-SB**
- Approximately **300 participants**

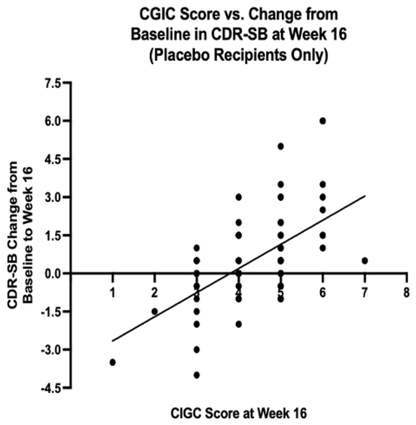
Primary Outcome Measure: Change in CDR-SB

- The Phase 2b, CDR-SB and CGIC were the only endpoints that showed worsening in placebo group. Other endpoints showed improvement

Placebo Group Results in Phase 2b Study

	Mean (SD) Change Over 16 Weeks	p-value
CDR-SB (N=77)	+0.59 (SD=1.76)	0.004
ADCS-CGC (N=77)	4.5 (1.5)*	N/A
Timed Up and Go (sec) N=75	-0.61 (3.97)	0.18
Neuropsychological Test Battery (NTB) z-score (N=62)	+0.17 (0.52)	0.02 (improvement)
Dementia Cognitive Fluctuation Scale	0.4 (2.8)	NS
International Shopping List Test	0,.2 (4.2)	NS
NPI-10 N=75	-1.7 (12.9)	NS)
UPDRS Part III (Motor)	-0.9 (11.7)	85.5 (9.2)

*Absolute value – mean score > 4 reflects worsening



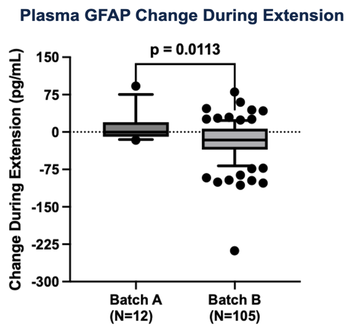
Clinician's Global Impression of Change (CGIC) Scoring:

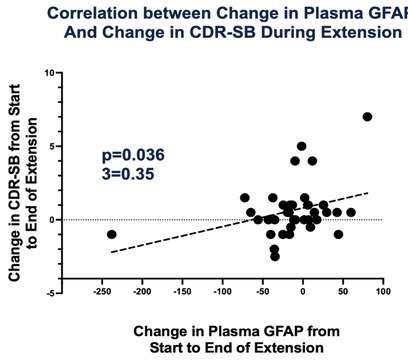
1. Marked Improvement
2. Moderate Improvement
3. Minimal Improvement
4. Neutral
5. Minimal Worsening
6. Moderate Worsening
7. Marked Worsening

N=76; note: multiple individuals at given datapoint are not shown in the figure

Plasma Biomarker

- Plasma glial fibrillary GFAP correlated to cognitive decline and MRI atrophy measures in natural history studies, and neflamapimod reduced plasma GFAP in Phase 2b extension (Batch B), an effect that was correlated to CDR-SB outcomes

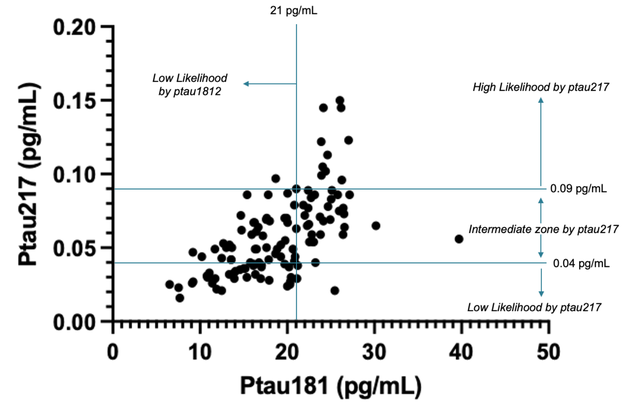




pTau181 to Screen for AD co-pathology

	Least Square Mean (SE) Change at Week 16 of Randomized Phase		Treatment Effect	
Population	**Placebo**	**Neflamapimod**	**Placebo-Neflamapimod Difference**	**95% CI**
All (mITT)	0.410 (0.239) N=77	0.273 (0.247) N=74	-0.137	(-0.699, 0.425,)
p-tau181 <25.2 pg/mL	0.362 (0.282) N=68	0.223 (0.247) N=62	-0.139	(-0.769, 0.491)
p-tau181 <23 pg/mL	0.360 (0.288) N=56	-0.154 (0.306) N=54	-0.514	(-1.156, 0.128)
p-tau181 <21 pg/mL	0.660 (0.340) N=45	-0.044 (0.356) N=46	-0.704	(-1.424, 0.012)

Ptau181 (Simoa®) vs. ptau217 (Simoa – Lucent® AD)



Imaging (MRI) Biomarker

In Phase 2b, effects demonstrated on BF atrophy and functional connectivity (right BF to default mode network, DMN); the latter was inversely correlated to CDR-SB

