Results Of A Phase 2 Study Of Neflamapimod 80mg Twice-daily In Dementia With Lewy Bodies

Tuesday-0020

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This study met its primary safety, tolerability, and pharmacokinetic objectives Neflamapimod 80mg BID was well tolerated with no new safety signals identified. Trough plasma concentrations was modestly increased relative to 40mg TID, demonstrating this regimen may be a twice daily alternative to achieve target plasma drug concentrations

INTRODUCTION

Background: In a phase 2a study, neflamapimod 40 mg twice daily (BID) was largely ineffective, whereas 40 mg three-times-daily (TID) showed clinical activity. In a phase 2b study, the neflamapimod batch used during the randomized phase ("Batch A") of phase 2b achieved lower-than-target plasma drug concentrations (C_{trough} mean=4.0 ng/mL; target=5.0 ng/mL). Batch A did not significantly improve outcomes during the randomized phase. A new batch introduced during the Extension ("Batch B"), achieved target concentrations (C_{trough} mean=5.1 ng/mL) and significantly improved CDR-SB, ADCS-CGIC, and plasma glial fibrillary acidic protein (GFAP) compared to Batch A during the Extension and to placebo in within-participant analyses across phases. Here, we report the first clinical data for neflamapimod 80 mg BID

Objectives

- The primary objective was to assess safety, tolerability, and pharmacokinetics.
- Secondary objectives evaluated clinical activity using the ADNI-Executive Function composite, CDR-SB, and Timed Up and Go test (TUG).
- In addition, behavior activity was evaluated using Mild Behavioural Impairment Check list (MBI-C)

Design

- 24-week open label treatment with two 40mg capsules of neflamapimod administered with meals, that is, 160mg a day.
- Participants met consensus clinical criteria for DLB with MoCA ≥18 or CDR Global Score ≤1.0.
- NCT06815965 (clinicaltrials.gov)

BASELINE

	Neflamapimod 80mg BID
Number of Participants	26
Age (M, SD)	72.1 (6.8)
Male	17 (65.4%)
MoCA (M, SD)	23.5 (3.7)
CDR-SB (M, SD)	3.6 (2.2)
Core Clinical Criteria:	
Cognitive fluctuations	22 (84.6%)
Visual Hallucinations	16 (61.4%)
REM sleep behavioral disorder	20 (76.9%)
Parkinsonism	18 (69.2%)
Receiving acetyl cholinesterase inhibitor therapy	13 (50%)
Screening plasma ptau181 level (pg/mL)	27.8 (11.3)
Number (%) with screening plasma ptau181<21 pg/mL	7(27%)

Plasma ptau181 measurements were performed in the neurochemistry laboratory at the Amsterdam University Medical Centers following the instructions in the assay kit (p-Tau181 V2.1 kit,Quanterix, Billerica, MA) on the Simoa HD-X platform.

SAFETY

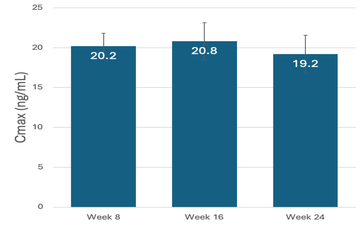
- Neflamapimod 80mg BID was generally well tolerated, with no new safety signals identified.
- The most common treatment-emergent adverse events were asthenia (8 participants, 30.1%) and falls (6 participants, 23.1%)
- One participant discontinued early due elevations in ALT and AST(Grade 3 elevation without bilirubin increase); values normalized after discontinuation. Concomitant medications known to affect liver enzymes may have contributed

PHARMACOKINETICS

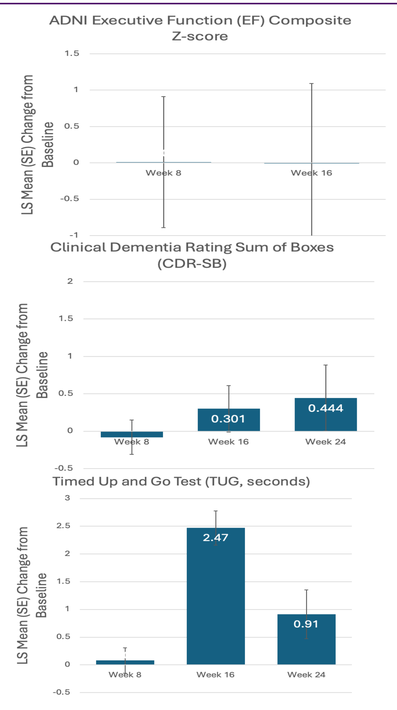
Trough Plasma Drug Concentration (C_{trough}, ng/mL)

Mean	SD	Q1	Median	Q3
5.72	1.61	4.51	5.36	6.54

Peak Plasma Drug Concentration (C_{max}, ng/mL)



CLINICAL ENDPOINTS



Least square mean (LSM) by visit from Mixed Model for Repeated Measure (MMRM).

MBI-C was evaluated only at baseline and Week 24. The mean MBI-C total score decreased from 17.9 at baseline to 15.7 at Week 24, corresponding to an LS mean change from baseline of −2.4 points (SE 1.37), suggesting an improvement in behavioral symptoms.

CONCLUSIONS

- Neflamapimod 80 mg BID was generally well tolerated over 24 weeks in participants with DLB.
- The regimen achieved target trough plasma concentrations predicted to optimize p38α inhibition, though the increase in C_{trough} from 40mg TID was less than dose-proportional (12% increase in C_{trough} vs. 33% increase in daily dose)
- Executive function and mobility were generally maintained over 24 weeks, while there was mild decline in global cognition and function (CDR-SB) and potentially an improvement in behavioral symptoms.
- Evaluation of treatment effects on clinical endpoints limited by lack of a placebo control and most participants (73%) having AD co-pathology, a patient population that has not been responsive to neflamapimod treatment in prior clinical studies
- Evaluation of other exploratory clinical endpoints, plasma biomarker and MRI data are ongoing

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