Effects of neflamapimod (p38α kinase inhibitor) on clinical progression in patients with dementia with Lewy bodies (DLB) without Alzheimer's disease (AD) Co-Pathology

LS Honig[1], SN Gomperts[2], JP Taylor[3], ND Prins[4], A Gardner[5], K Blackburn[5], JJ Alam[5], JE Galvin[6]

1. Columbia University Irving Medical Center – New York, NY (United States) 2. Massachusetts General Hospital – Charlestown, MA (United States) 3. Newcastle University - Newcastle Upon Tyne (United Kingdom 4. Brain Research Center, Amsterdam (Netherlands) 5. CervoMed – Boston, MA (United States) 6. Miller School of Medicine – Miami, FL (United States)

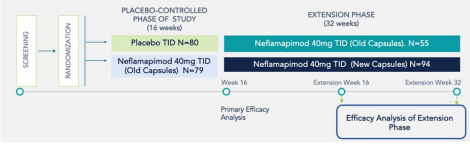
INTRODUCTION AND OBJECTIVES

RewinD-LB phase 2b study (NCT05869669) was initiated to confirm phase 2a results in DLB (Jiang et al, 2022) in which neflamapimod demonstrated positive effects on multiple clinical endpoints, most prominently in patients without evidence of AD co-pathology (assessed by plasma ptau181).

DESIGN

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 (*i.e.*, excluded patients with AD co-pathology)



Dosing Groups and Comparisons

OLD CAPSULES: Neflamapimod capsules produced in Oct'2020. Only batch utilized in placebo-controlled phase, where it did not achieve expected and targeted plasma drug concentration. Also utilized in a subset of participants (N=55) in the Extension, where it effectively served as a "low dose control" arm.

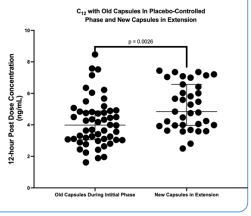
NEW CAPSULES: Neflamapimod capsules produced in Mar'2023. Only utilized in a subset of participants during the Extension (N=94), where it was introduced over time, achieved expected plasma drug concentrations, and served as the active control arm.

BASELINE CHARACTERISTICS

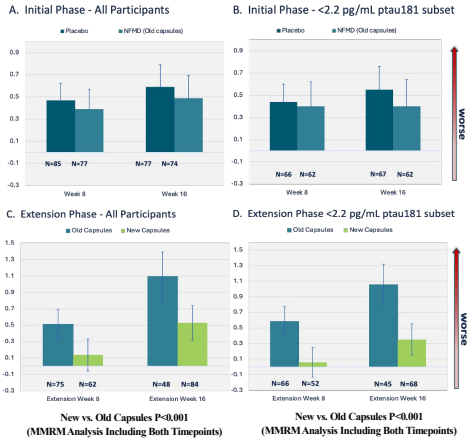
	Initial Phase		Extension Phase	
	Placebo	Neflamapimod	Neflamapimod (Old Capsules)	Neflamapimod (New Capsules)
Number of Participants	79	80	55	94
Age	70.7 (5.8)	72.1 (6.4)	70.9 (6.4)	71.8 (6.1)
Male	67 (83.8%)	69 (87.3%)	48 (87.3%)	80 (85.1%)
MMSE	23.3 (4.6)	23.6 (4.3)	23.8 (3.7)	23.4 (4.8)
CDR-SB	4.23 (1.71)	4.45 (2.17)	4.87 (2.41)	4.79 (2.45)
DCFS	10.0 (3.0)	10.0 (3.2)	9.6 (3.4)	10.0 (3.1)
ISLT Immediate	14.8 (5.9)	13.0 (5.0)	13.5 (5.2)	13.8 (5.7)
ISLT Recognition	10.4 (1.8)	10.4 (1.7)	10.6 (1.7)	10.2 (1.8)
TUG	14.9 (13.4)	12.7 (6.2)	12.0 (4.2)	13.9 (13.7)
NPI-12	16.7 (18.3)	14.0 (14.0)	13.6 (16.4)	14.3 (14.7)
Core Clinical Criteria:				
Cognitive fluctuations	59 (73.8%)	59 (74.7%)	32 (58.2%)	77 (81.9%)
Visual Hallucinations	45 (56.3%)	43 (54.4%)	26 (47.3%)	54 (57.4%)
REM sleep behavioral disorder	64 (80.0%)	60 (75.9%)	46 (83.6%)	69 (73.4%)
Parkinsonism	68 (85.0%)	70 (88.6%)	46 (83.6%)	85 (90.4%)
Background Therapy				
AChEI alone*	52 (65.0%)	50 (63.3%)	36 (65.4%)	46 (61.3%)
Memantine (with or without AChEI therapy)	11 (13.8%)	12 (15.2%)	9 (16.4%)	14 (18.7%)
No background therapy	17 (21.3%)	17 (21.5%)	10 (18.2%)	15 (20.0%)

PHARMACOKINETICS

During the placebo-controlled phase, with the Old Capsules, the median 12-hour post-dose neflamapimod drug concentration (C12) was 4.0 ng/mL (interquartile range: 3.1, 4.9 ng/mL; N=53), which was below the expected 5.0 ng/mL for a dose of neflamapimod 40mg TID derived from a population PK analysis of prior clinical studies. During the Extension with the New Capsules, the median C12 was 5.1 ng/mL (interquartile range: 4.0, 6.8 ng/mL; N=36). Neflamapimod drug concentration determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method at Charles River Laboratories Edinburgh Ltd



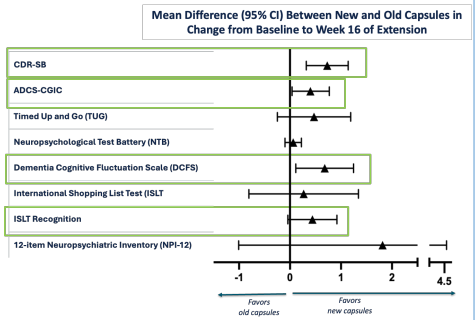
PRIMARY OUTCOME MEASURE – CHANGE IN CDR-SB



New vs. Old Capsules P<0.001 (MMRM Analysis Including Both Timepoints)

New vs. Old Capsules P<0.001 (MMRM Analysis Including Both Timepoints)

SUMMARY OF STATISTICAL ANALYSES[1] OF PRIMARY, SECONDARY AND EXPLORATORY ENDPOINTS IN EXTENSION PHASE

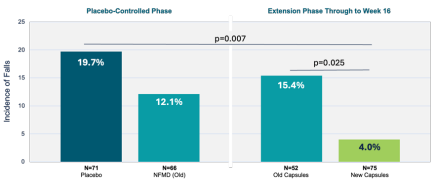


[1] Except for CGIC, Linear Mixed-Effects Model for Repeated Measures (MMRM) with baseline CDR-SB, Sex, Age and MMSE as covariates; CIGC analyzed by t-test. Signs (-/+) adjusted as necessary so that (+) difference reflects better outcome.

SAFETY

- The incidence of discontinuation due to treatment-emergent adverse events (TEAEs) was 4% with neflamapimod and 1% with placebo during the Initial phase, and 4% with Old Capsules and 2% with New Capsules through to Week 16 of the Extension.
- The incidence of TEAEs was low (only falls seen at >10% incidence in either phase) and, except for falls, similarly distributed across treatment arms. For falls, the incidence was lower with New Capsules:

Incidence of Falls in Participants with Screening Plasma ptau181 < 2.2 pg/mL

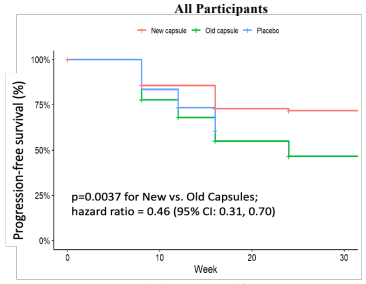


CONCLUSIONS

- The clear differences in clinical activity between New and Old Capsules is consistent with the hypothesis that the absence of difference between placebo and neflamapimod treatment were the result of not having achieved pharmacologically active plasma drug concentrations in the placebo-controlled phase of the study
- Once target plasma drug concentrations are achieved, neflamapimod during the extension demonstrates a meaningful effect on clinical progression, assessed by CDR-SB and CGIC, in patients with DLB who do not have AD co-pathology by plasma ptau181

KAPLAN-MEIER ANALYSIS OF CLINICALL RELEVANT PROGRESSION (≥ 1.5 POINT INCREASE IN CDR-SB) THROUGH TO WEEK 32

All Participants

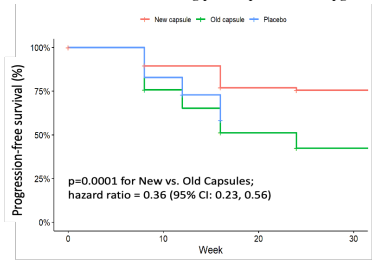


Number of Participants at Risk of Progressing*

	Week 8	Week 16	Week 24	Week 32
New	126	107	62	39
Old	117	68	26	15
Placebo	79	57		

*In a Kaplan-Meier analysis, once a participant progresses on, or discontinues a treatment, they are no longer included in number at risk for that treatment

Subset with screening plasma ptau181 < 2.2 pg/mL



Number at Participants at Risk of Progressing*

	Week 8	Week 16	Week 24	Week 32
New	105	93	53	36
Old	99	56	23	15
Placebo	70	50		

*In a Kaplan-Meier analysis, once a participant progresses on, or discontinues a treatment, they are no longer included in number at risk for that treatment

ACKNOWLEDGEMENTS AND FUNDING

Patients, caregivers, study investigators and clinical site staff involved with the RewinD-LB study (see https://clinicaltrials.gov/study/NCT05869669 for locations)

Clinical project teams at Worldwide Clinical Trials and CervoMed, Inc.

Members of the Data Safety Monitoring Board (DSMB) for the RewinD-LB study: Kenneth Rockwood MD, FRCPC, FRCP, FCAHS (Chair), Jennifer Goldman MD MS, Janet Wittes, PhD

Primary funding source: National Institutes of Aging (NIA) Grant #R01AG080536