LB31 - Results of the Phase 2b Trial of Neflamapimod in Dementia with Lewy Bodies

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Thursday, December 4, 2:10 p.m. PT

Disclosures

- Neflamapimod is an investigational drug
- J. Alam, A. Gardner, and K. Blackburn are employees of CervoMed Inc, the company developing neflamapimod
- S.N. Gomperts and J-P Taylor each have acted as a consultant for CervoMed Inc
- The other co-authors have no disclosures to declare

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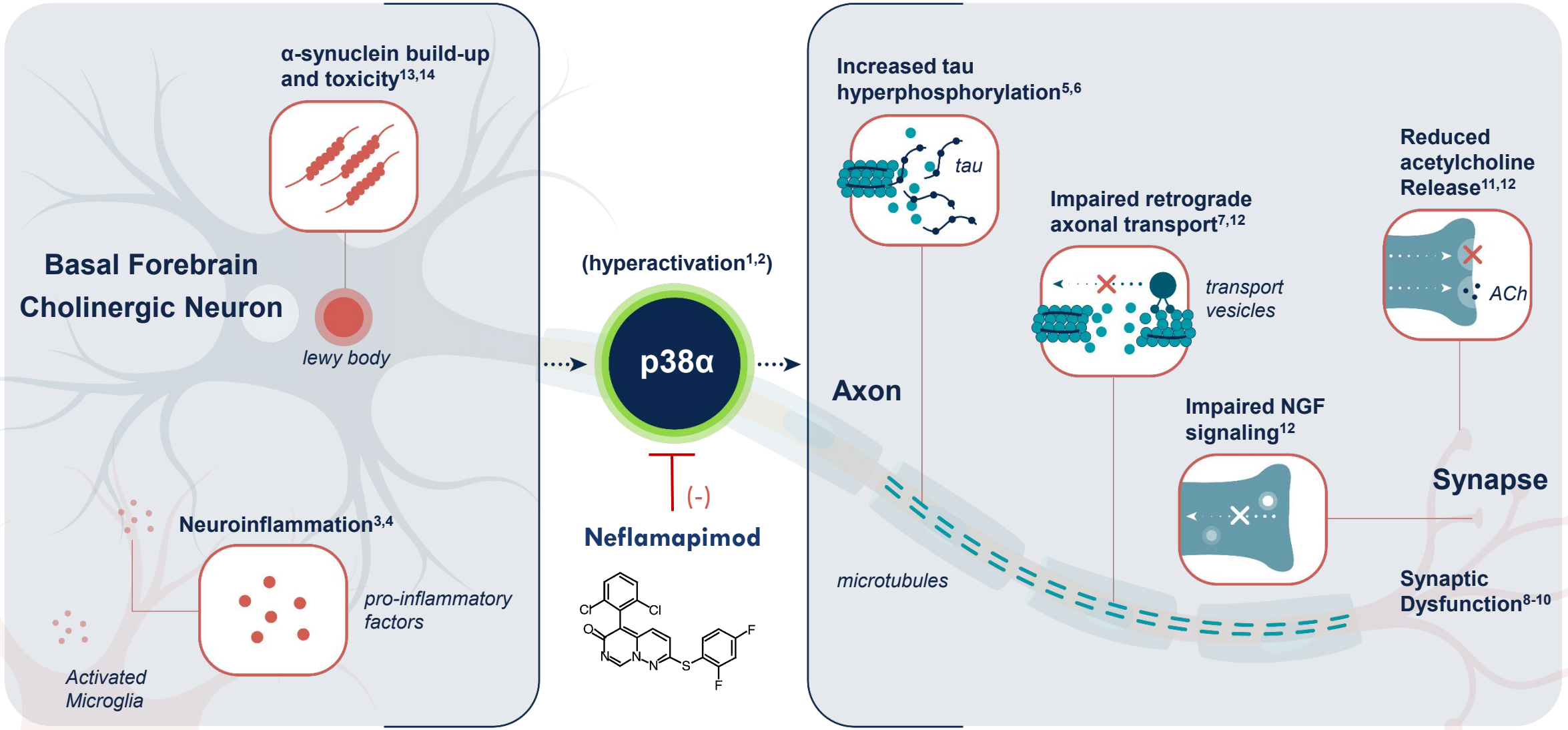
Dementia with Lewy Bodies (DLB): Background

- High unmet need
  - Significant impact on quality of life and caregiver burden
  - Progresses more rapidly than AD, with average time from diagnosis to requiring nursing home care being 2 years
- Progressive α-synucleinopathy characterised by widespread cortical and subcortical Lewy bodies
  - AD co-pathology is common in up to ~50%
- Clinical diagnostic criteria are highly specific
- In early stages, a major driver of disease expression and progression is dysfunction and degeneration of basal forebrain cholinergic neurons

Neflamapimod is An Oral p38α Kinase Inhibitor That Targets Dysfunction and Degeneration of Acetylcholine-Producing Neurons



References: 1. Asih, 2020 2. Son I, 2023 3. Prieto, 2015 4. Yang , 2023 5. Stefanoska , 2022 6. Yeganeh, 2025 7. Gibbs, 2018 8. Scali 2003 9. Ehrlich, 2012 10. Gamage, 2023 11. Jiang, 2022 12. Alam & Nixon, 2023. 13. Borland, 2022 14. Yang, 2025.

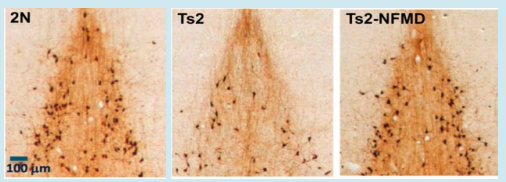
Positive Preclinical and Phase 2a (AscenD-LB) Data Validate Drug Target and Support Advancement to Phase 2b

Preclinical — *Disease processes in basal forebrain reversed*

When administered in mice that develop basal forebrain cholinergic degeneration, neflamapimod:

- ✓ Reduced Rab5 activity and tau phosphorylation
- ✓ Reversed loss of cholinergic (ChaT+) neurons in the basal forebrain; and
- ✓ Normalized performance in behavioral tests of cholinergic function[1]

Cholinergic Neurons in Basal Forebrain

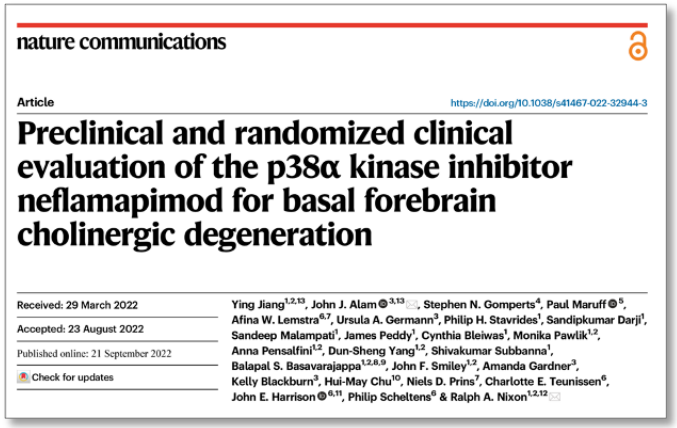


Neflamapimod preserved cholinergic neurons in the basal forebrains of mice

Phase 2a Clinical — *Improvement on multiple clinical endpoints*

In AscenD-LB, a 91-patient, 16-week, placebo-controlled Phase 2a trial in patients with DLB, neflamapimod:

- ✓ Significantly improved dementia severity (assessed by Clinical Dementia Rating Sum-of Boxes, CDR-SB, p=0.023 vs. placebo)
- ✓ Significantly improved gait (assessed by Timed Up and Go, TUG, *p*=0.044 vs. placebo)
- ✓ Reduced levels of plasma biomarker of neurodegeneration (glial fibrillary acidic protein (GFAP))
- ✓ Improved response in patients with a low likelihood of having AD co-pathology (defined by plasma pTau181)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Preclinical and randomized clinical evaluation of the p38α kinase inhibitor neflamapimod for basal forebrain cholinergic degeneration

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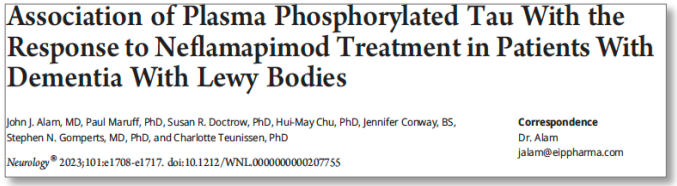
Association of Plasma Phosphorylated Tau With the Response to Neflamapimod Treatment in Patients With Dementia With Lewy Bodies

John J. Alam, MD, Paul Maruff, PhD, Susan R. Doctrow, PhD, Hui-May Chu, PhD, Jennifer Conway, BS, Stephen N. Gomperts, MD, PhD, and Charlotte Teunissen, PhD

Neurology® 2023;101:e1708-e1717. doi:10.1212/WNL.0000000000207755

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Alam & Nixon, *Molecular Neurodegeneration*, 2023. *1.* Nature Communications, 13: 5308 (2022). https://www.nature.com/articles/s41467-022-32944-3
2. Neurology® 2023;101:e1708-e1717. doi:10.1212/WNL.0000000000207755

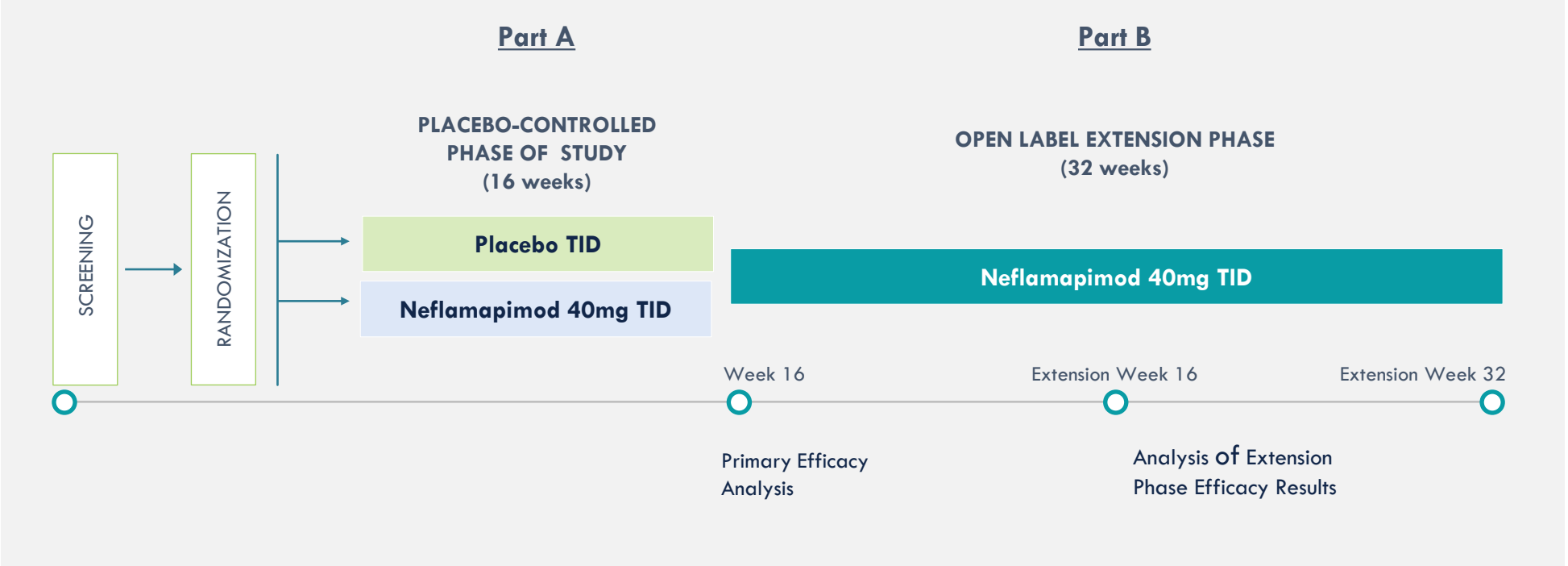
RewinD-LB Phase 2b Study in DLB: A Two-Part Study Design

PATIENTS

- 159 patients with dementia with Lewy bodies by consensus clinical criteria
- CDR global score of 0.5 or 1.0 at baseline
- Baseline plasma pTau181 < 27.2 pg/mL (Simoa v2.1)

SELECTED KEY CLINICAL OUTCOME MEASURES

- **Primary**: Clinical Dementia Rating Sum of Boxes (CDR-SB)
- **Secondary**: Clinical Global Impression of Change (CGIC), Timed Up and Go, Neuropsychological Test Battery



Plasma pTau181 Levels Were Used to Enrich Study Enrollment for Patients without AD Co-Pathology

Inclusion criteria in RewinD-LB was <27.2 pg/mL[1]	At the time RewinD-LB was initiated (mid-2023), and based on a limited data set, **27.2 pg/ml was estimated to be the optimal cutoff for AD co-pathology in patients with DLB**
New Research Supports More Stringent Cut-Off	Large (N=1298) validation study, published in June 2025[2], indicated that a **pTau181 cutoff of 21.0 pg/mL is optimal to identify patients with low likelihood of AD pathology** in AD and non-AD dementia by CSF criteria
Clinical Data Demonstrates Accentuated Effect	Sensitivity analysis of current results conducted in Phase 2b (post-hoc for randomized data, and prospectively defined for extension data) **supports utilizing a pTau181 cut of 21 pg/mL**

Efficacy Analysis Populations:

(1) **mITT[1] – All participants with ≥ 1 on-treatment evaluation**

(2) **< 21 pg/mL ptau181 subset**

DLB patients with low likelihood of AD co-pathology (i.e., “pure” DLB; pTau181 <21 pg/ml) account for ~50% of all DLB patients

[1] Modified intention-to-treat population

Baseline Characteristics: Similar Across Study Phases, Patient Subsets, and Drug Batches

	Randomized Phase		Extension Phase (All Participants)		Extension Phase (<21 pg/mL subset)	
	Placebo	NFMD (DP Batch A)	DP Batch A	DP Batch B	DP Batch A	DP Batch B
Number of Participants	79	80	55	94	38	55
Age	70.7 (5.8)	72.1 (6.4)	70.9 (6.4)	71.8 (6.1)	69.9 (6.18)	70.6 (6.42)
Male	67 (83.8%)	69 (87.3%)	48 (87.3%)	80 (85.1%)	30 (83.3%)	52 (94.5%)
MMSE	23.3 (4.6)	23.6 (4.3)	23.8 (3.7)	23.4 (4.8)	23.6 (3.63)	24.1 (4.21)
CDR-SB	4.23 (1.71)	4.45 (2.17)	4.87 (2.41)	4.79 (2.45)	4.22 (2.04)	4.22 (1.73)
ISLT Immediate	14.8 (5.9)	13.0 (5.0)	13.5 (5.2)	13.8 (5.7)	13.1 (4.45)	14.6 (5.41)
Core Clinical Criteria:						
Cognitive fluctuations	59 (73.8%)	59 (74.7%)	32 (58.2%)	77 (81.9%)	20 (55.6%)	48 (87.3%)
Visual Hallucinations	45 (56.3%)	43 (54.4%)	26 (47.3%)	54 (57.4%)	17 (47.2%)	33 (60.0%)
REM sleep behavioral disorder	64 (80.0%)	60 (75.9%)	46 (83.6%)	69 (73.4%)	29 (80.6%)	42 (76.4%)
Parkinsonism	68 (85.0%)	70 (88.6%)	46 (83.6%)	85 (90.4%)	30 (83.3%)	49 (89.1%)
Background Therapy						
AChEI alone*	52 (65.0%)	50 (63.3%)	36 (65.4%)	46 (61.3%)	25 (69.4%)	34 (61.8%)
Memantine (with or without AChEI therapy)	11 (13.8%)	12 (15.2%)	9 (16.4%)	14 (18.7%)	7 (19.4%)	11 (20.0%)
No background therapy	17 (21.3%)	17 (21.5%)	10 (18.2%)	5 (20.0%)	4 (11.1%)	10 (18.2%)

*AChEI – acetyl cholinesterase inhibitor

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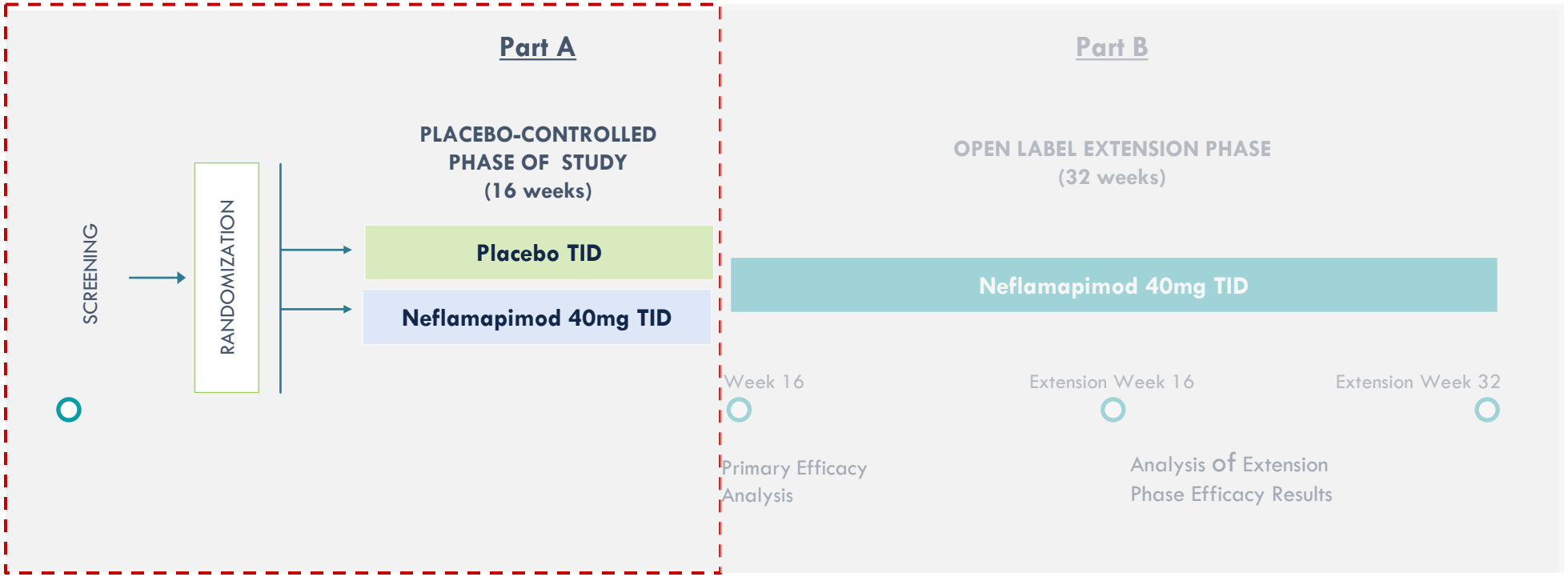

No Significant Differences between Placebo and Neflamapimod in Primary Outcome Measures Were Observed During Placebo-Controlled Phase of Study

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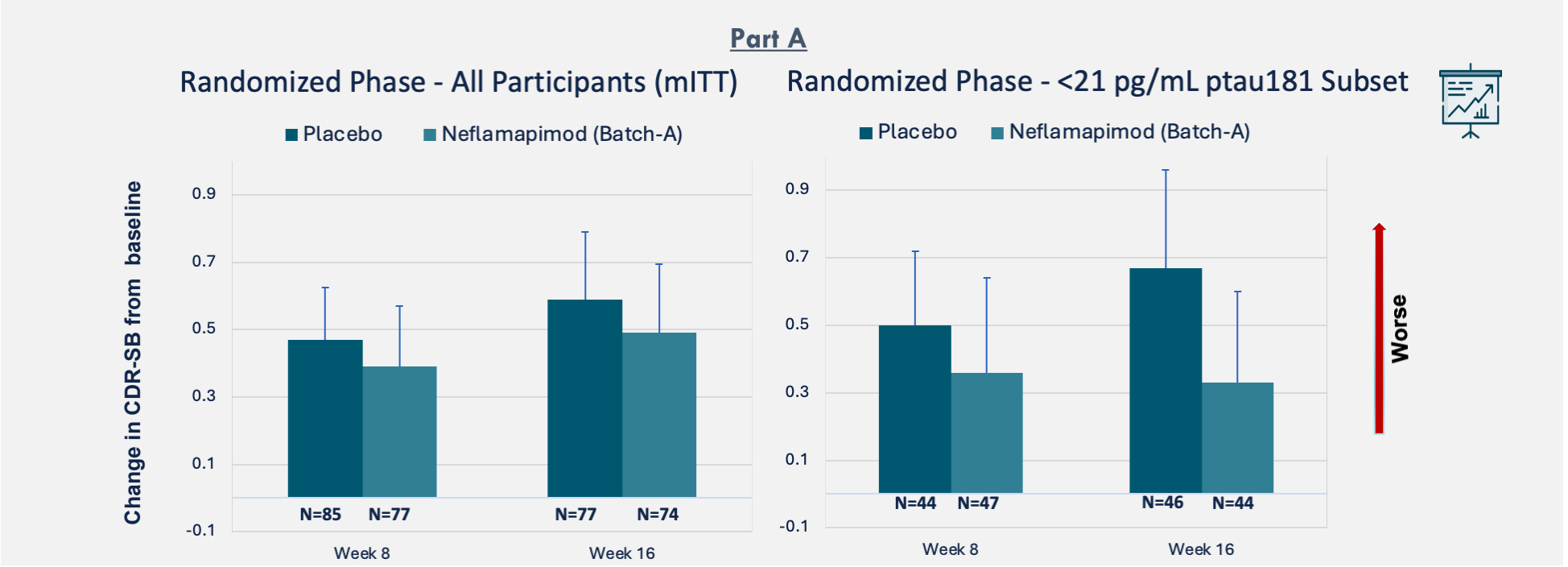

Batch of capsules utilized in placebo-controlled phase and initially during the extension, Drug Product Batch A (DP Batch A), did not achieve expected and targeted plasma drug concentrations

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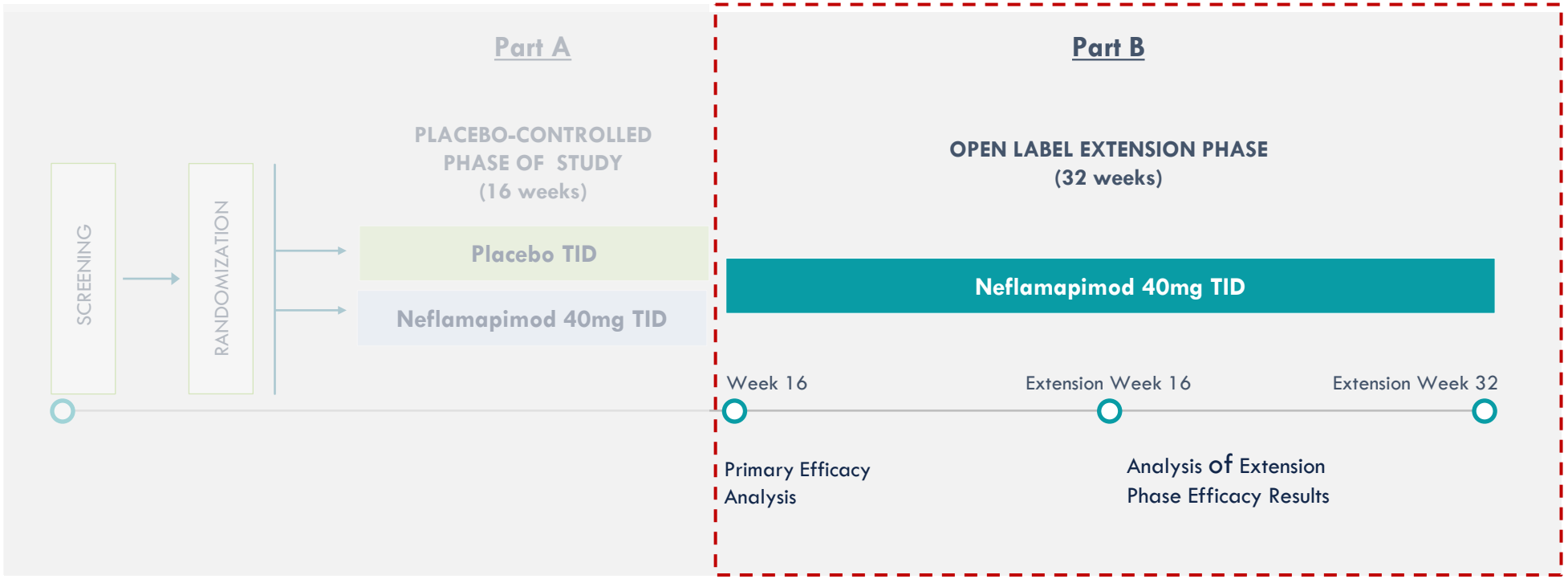
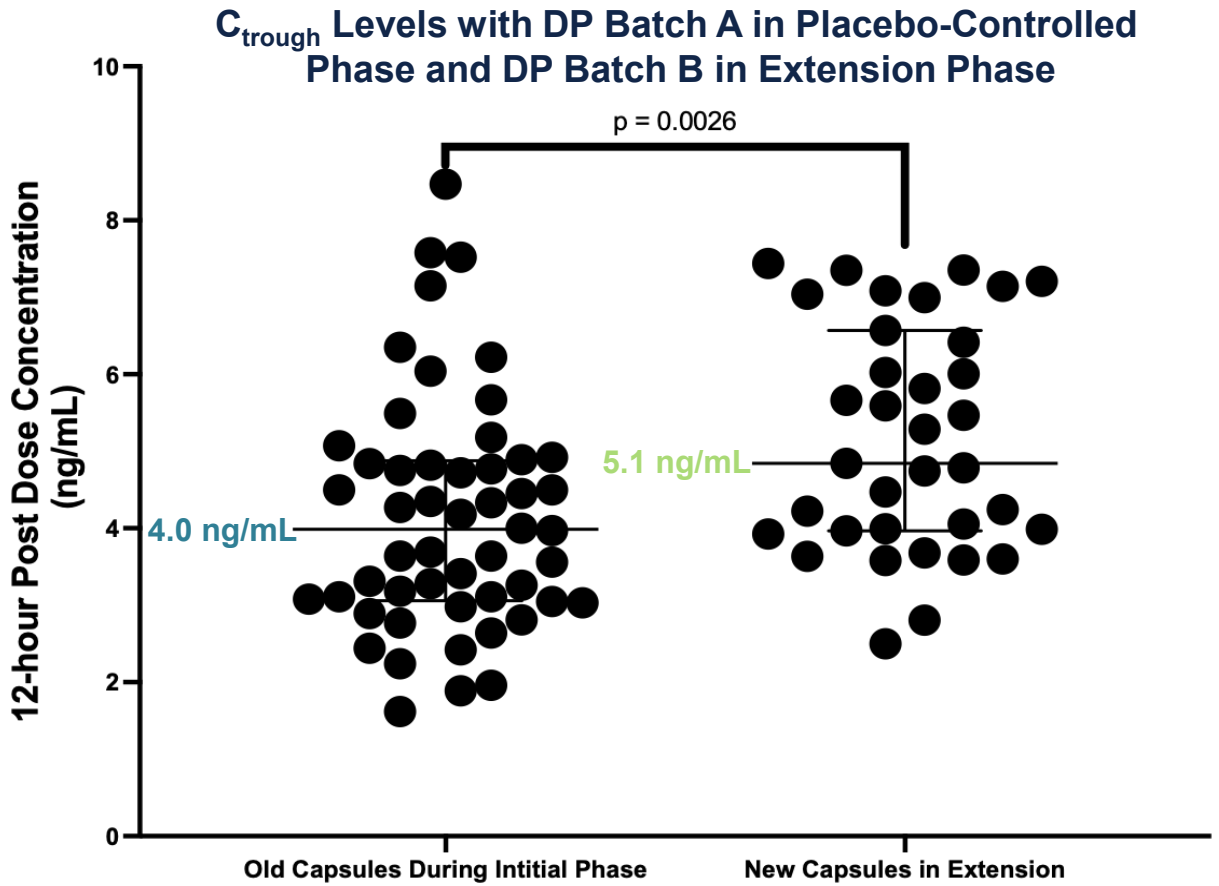


Pre-planned introduction of a new batch of drug product during the extension (DP Batch B) achieved expected and targeted plasma drug concentrations

Mean Plasma Drug Trough Concentration Was Significantly Higher with DP Batch B than in DP Batch A

- Mean plasma drug trough concentration (C_{trough}) of DP Batch A was below expected 5.0 ng/ml and similar to that seen with the lower and ineffective dose tested in Phase 2a trial

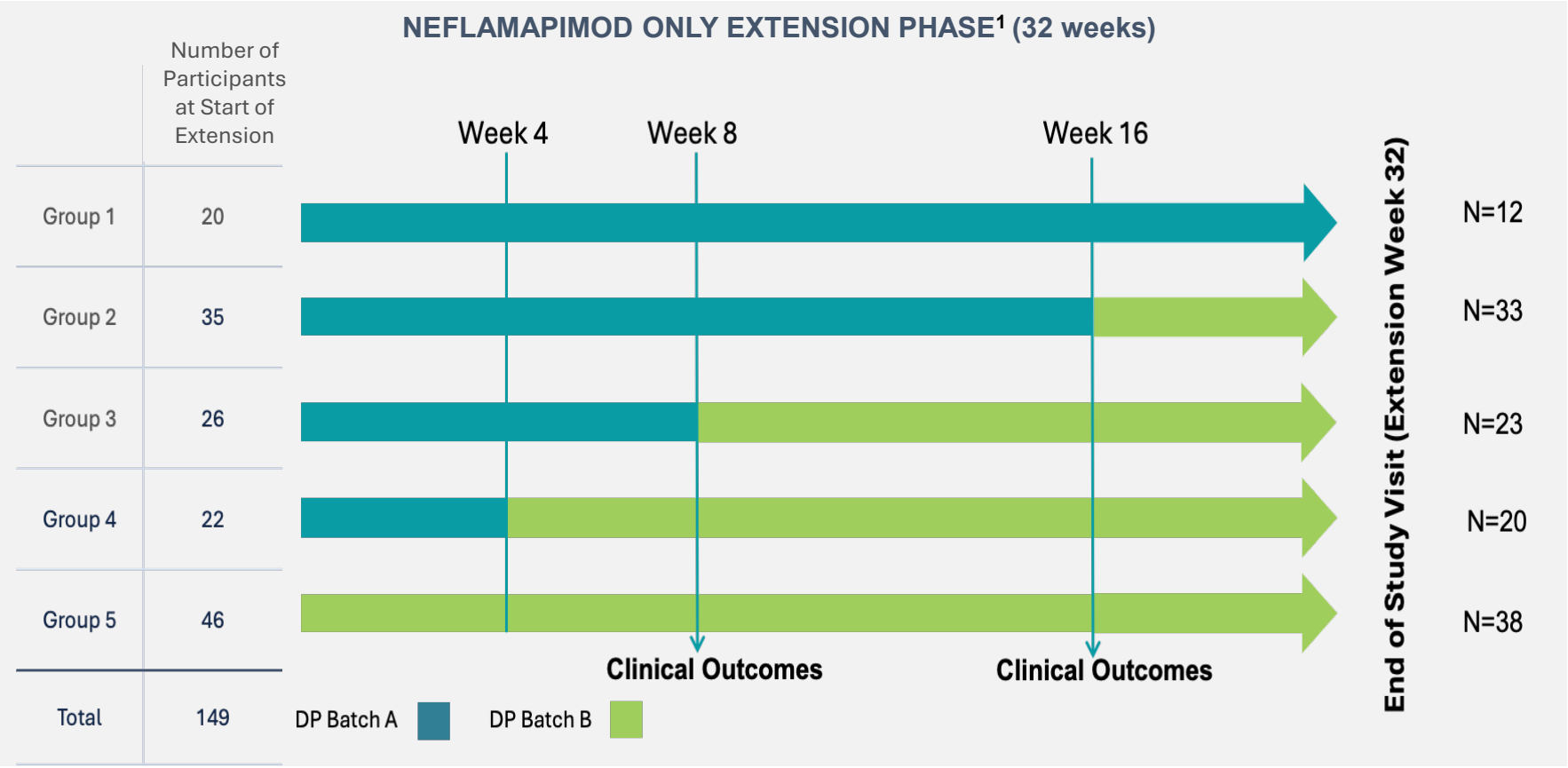
- During the Extension Phase, DP Batch B achieved targeted and expected C_{trough} levels



Lower than expected plasma drug concentrations demonstrated with DP Batch A resulted in effectively underdosing participants during the Placebo-Controlled Phase

1. Derived from a population PK analysis of prior clinical studies

Introduction of New Batch of Neflamapimod (DP Batch B) Achieved Target Drug Concentrations and Enabled Robust Extension-Phase Analyses

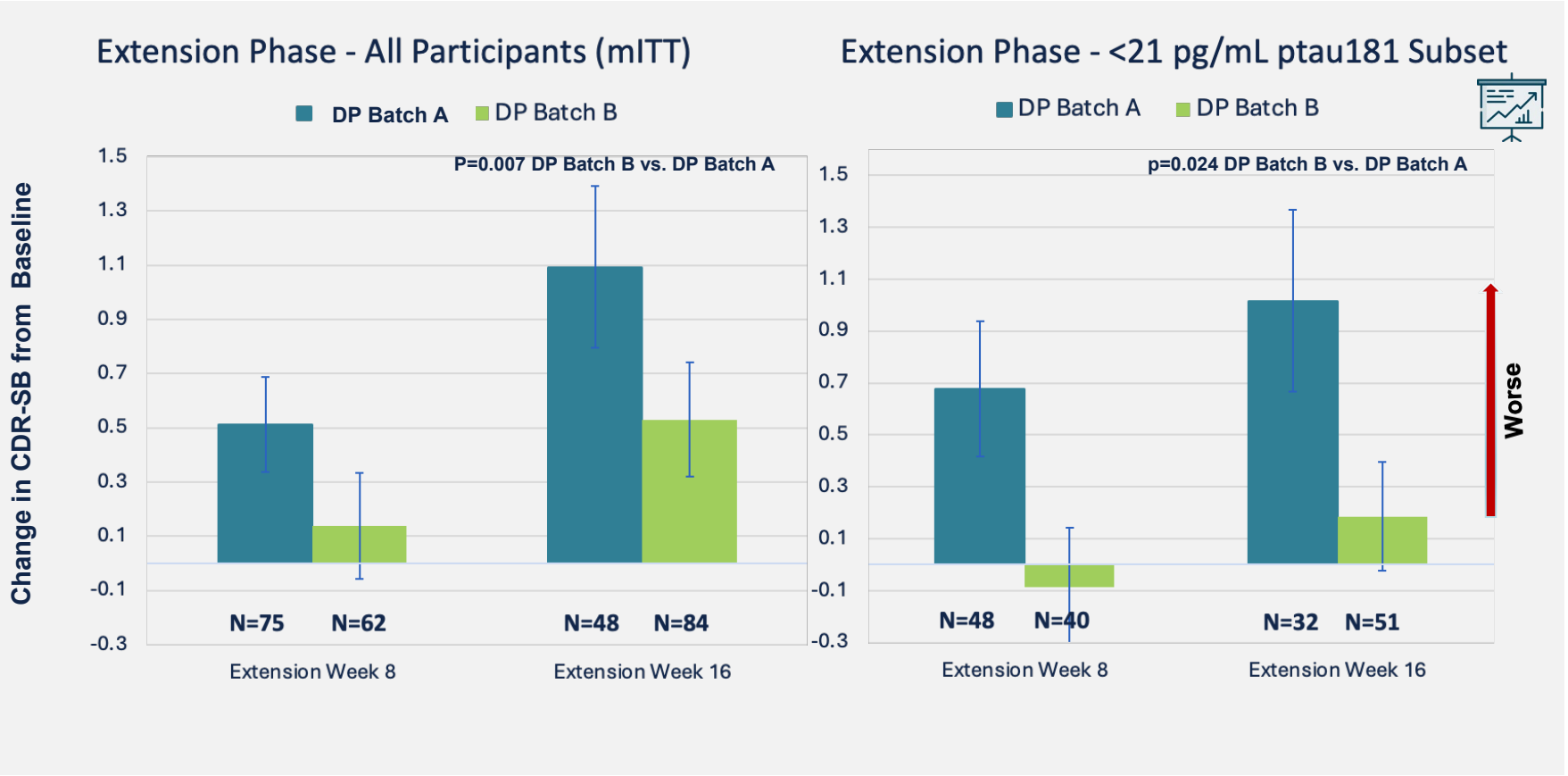


Neflamapimod Dosing Groups and Comparisons

- **DP Batch A:** Did not achieve expected and targeted plasma drug concentrations
- **DP Batch B:** Planned introduction of new batch 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; (3) Placebo vs. DP Batch B (within subject comparison)

Participants were all aware that they were receiving neflamapimod in the Extension Phase (i.e., treatment was open label), but neither they nor study site personnel were aware if they were receiving DP Batch A or DP Batch B

Significant Effect on Primary Outcome Measure (CDR-SB) Over 16 Weeks When Target Plasma Concentrations Achieved with DP Batch B



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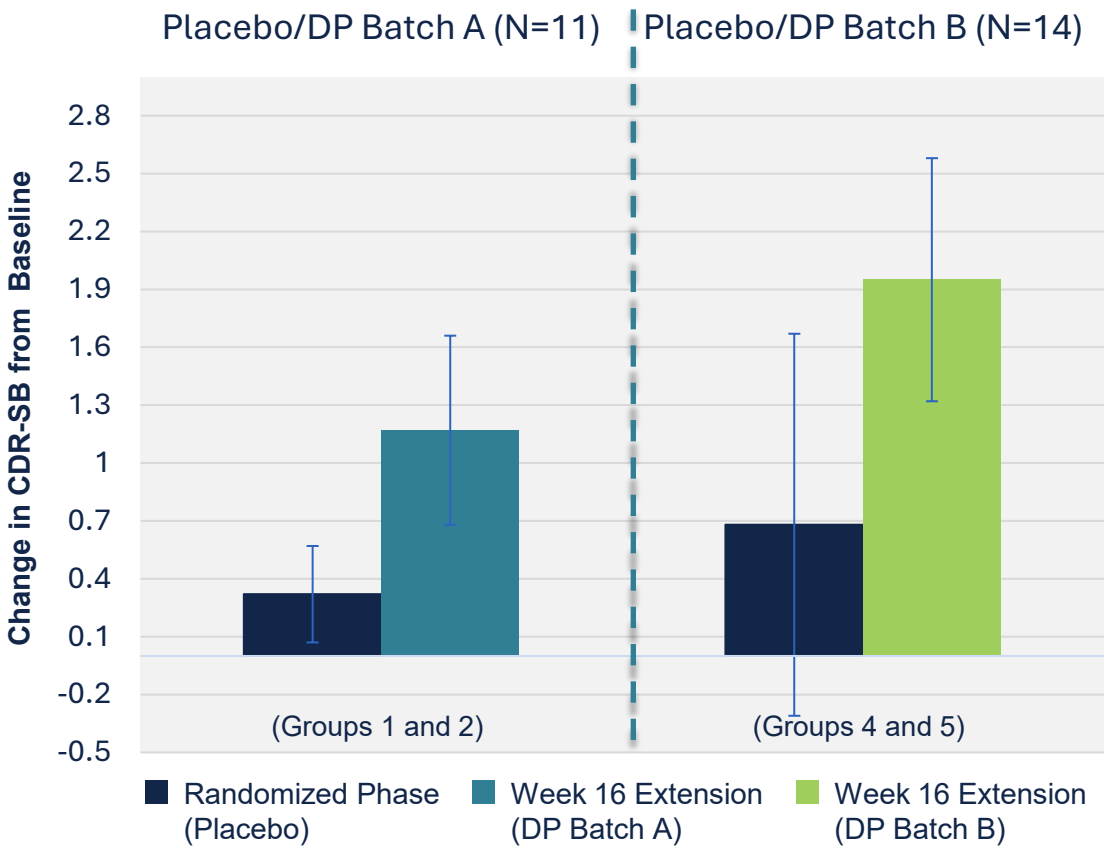
- Significant effect on clinical progression when target plasma concentrations were achieved, most prominently in patients with low likelihood of having AD co-pathology
- At week 16, mean change was 52% lower with DP Batch B compared to DP Batch A in all participants and 82% lower in <21 pg/mL subset

Linear Mixed-Effects Model for Repeated Measures (MMRM) with baseline CDR-SB, Sex, Age and Mini-Mental State Examination (MMSE) as covariates

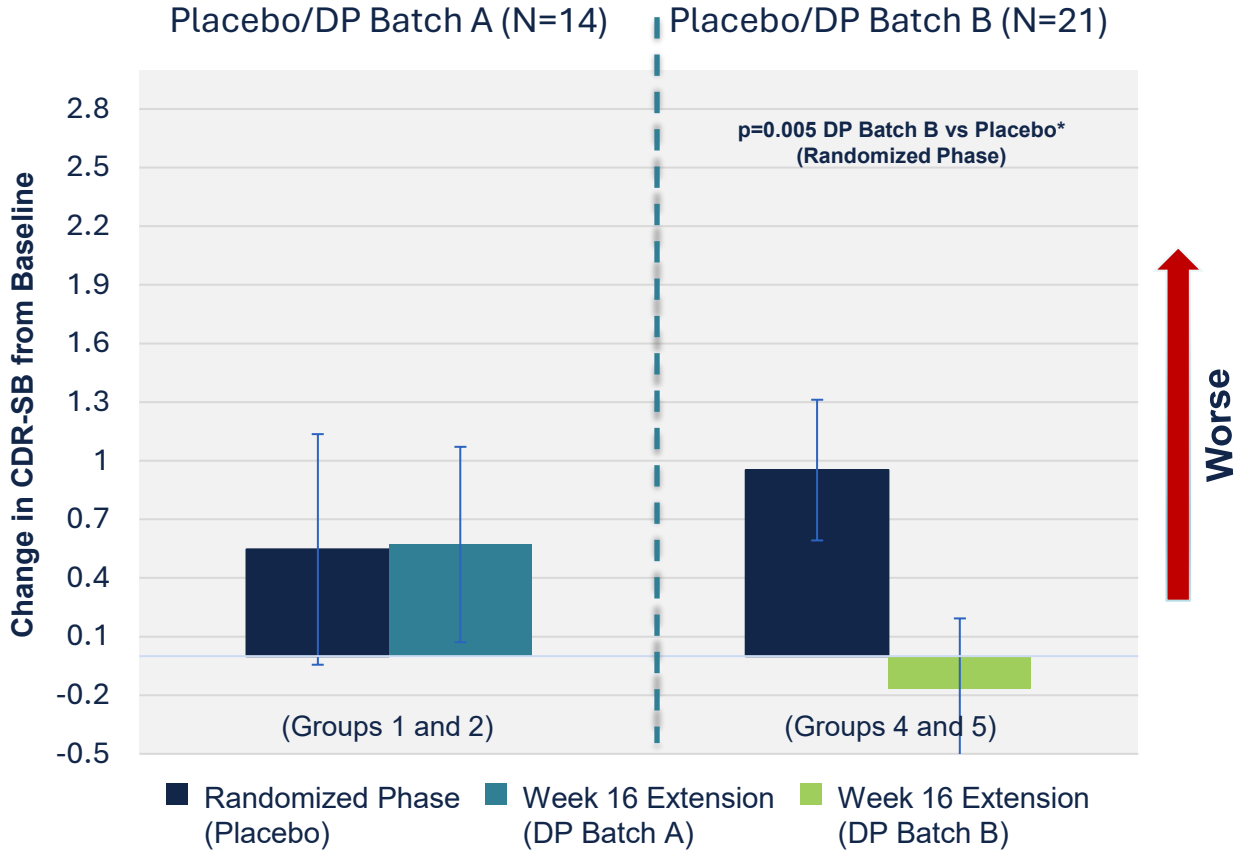
Within-Subject Analysis of Change in CDR-SB Confirms Significant Clinical Effect; Most Prominently in Patients with Low Likelihood of AD Co-Pathology

Change in CDR-SB in During Either Randomized Phase or 16 Weeks of Extension Phase

≥21 pg/mL pTau 181



<u>≤21 pg/mL pTau181</u>

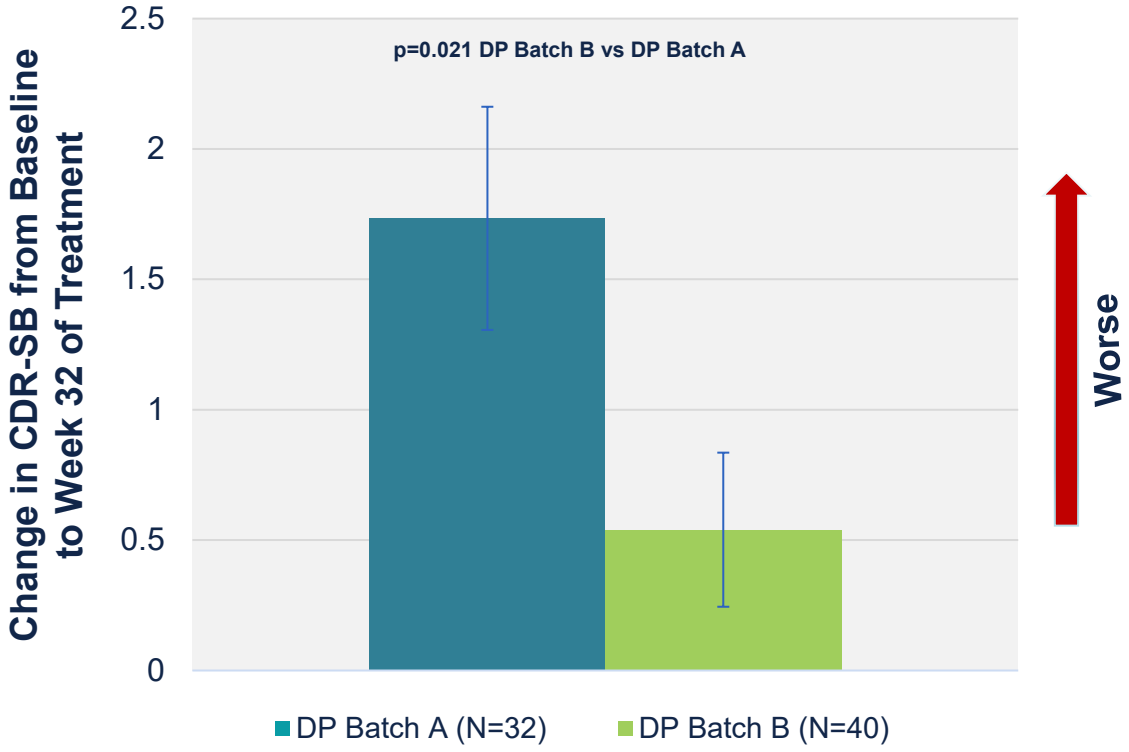


* For within-participant comparison vs. placebo (Mann-Whitney U test); median difference =-1.5 favoring DP Batch B

Includes only participants who received placebo during randomized phase and completed first 16 weeks of Extension Phase

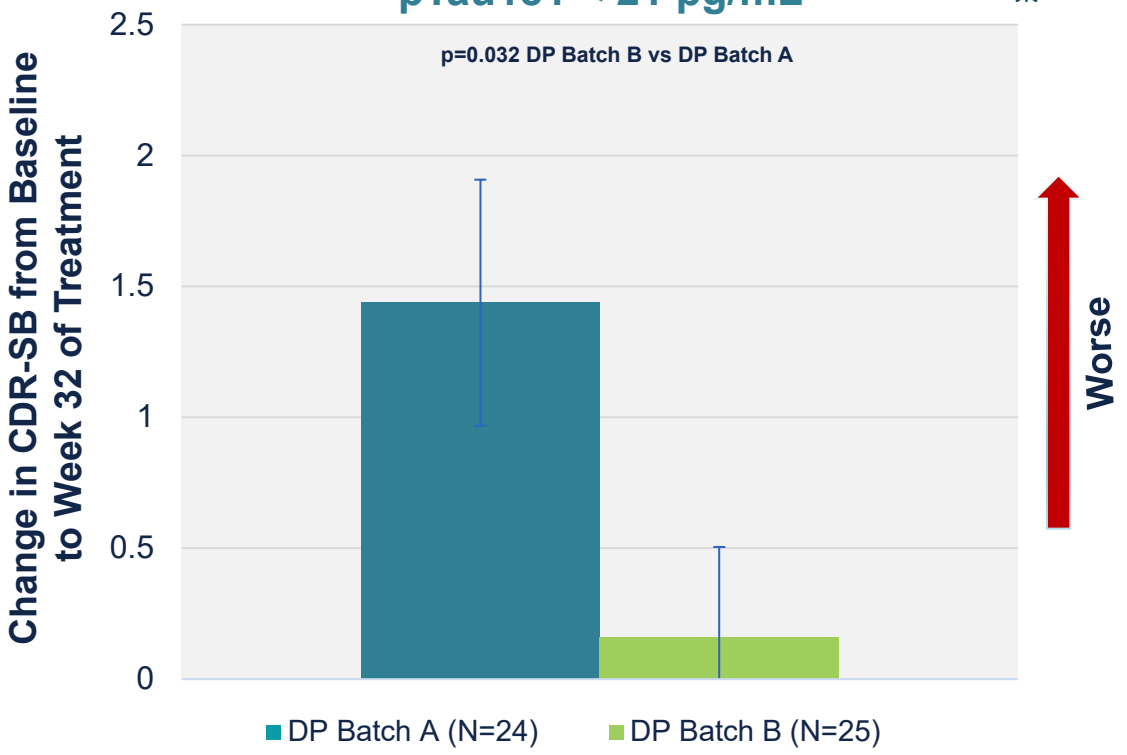
Clinical Effect Observed by CDR-SB Is Durable Out to 32 Weeks of Treatment

All Participants (mITT)



Difference: -1.12, representing a 65% reduction in CDR-SB change when targeted plasma drug concentration achieved

Participants with Screening Plasma pTau181 < 21 pg/mL

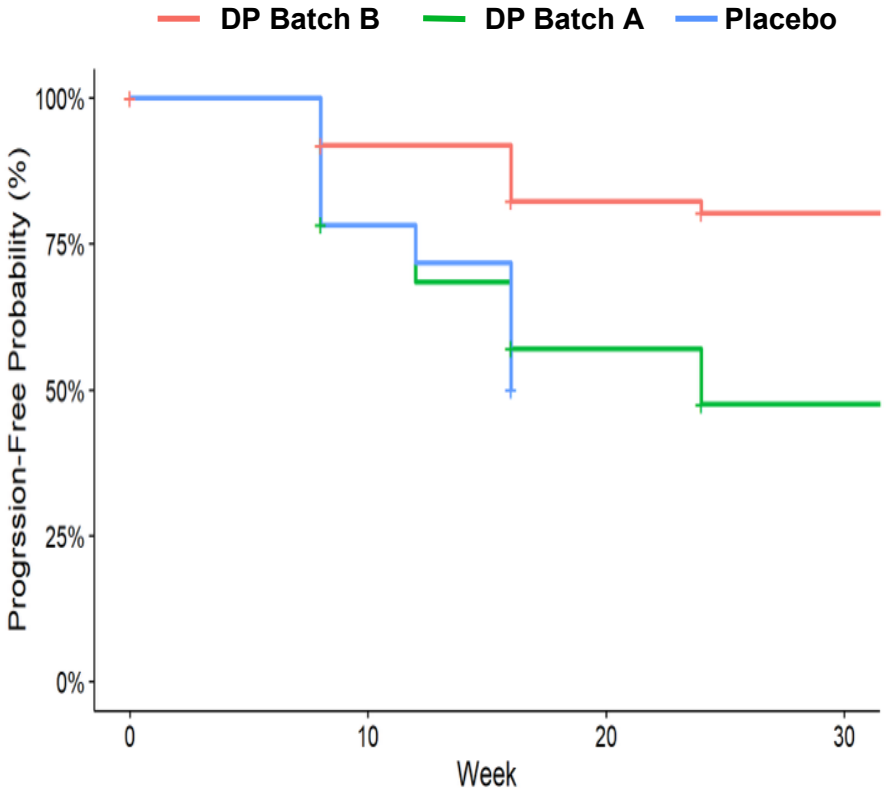


Difference: -1.2, representing a 89% reduction in CDR-SB change when targeted plasma drug concentration achieved

Note: NFMD/AA group includes patients who started neflamapimod at study start and completed the 1st 16 weeks of the extension, as well Extension Phase Group 1 patients who completed the Extension Phase. The mean change in the 12 Group 1 patients who completed the 32-week Extension was +1.5 points; the other 8 Group 1 patients discontinued early.

Risk of Clinical Progression (≥ 1.5 Pt Increase in CDR-SB) Reduced and Time to Progression Increased with Neflamapimod in Patients

Participants with Screening Plasma pTau181 < 21 pg/mL



Number at Risk

	Week 8	Week 16	Week 24
DP Batch B	74	67	41
DP Batch A	69	42	18
Placebo	46	33	

Risk of Progression			
	Hazard Ratio (95% confidence interval)	% Reduction in Risk	P-value
DP Batch B vs. DP Batch A	0.33 (0.19,0.58)	67%	<0.001
DP Batch B vs. Placebo	0.25 (0.13, 0.47)	75%	<0.001

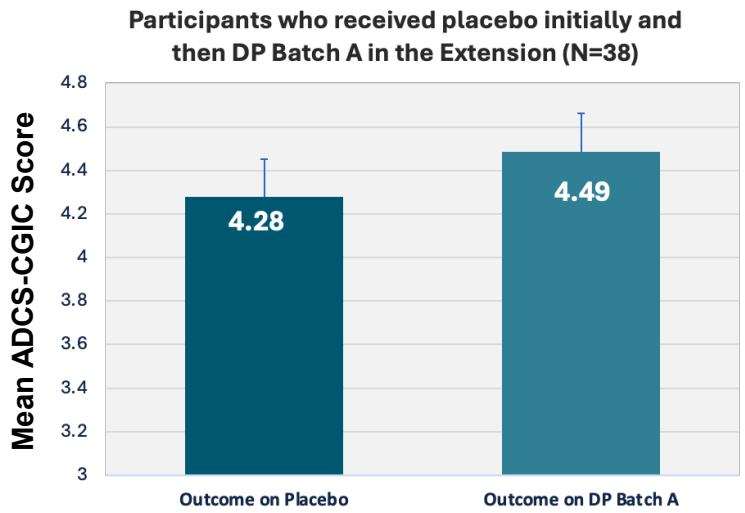
Median Time to Progression	
Placebo	16 Weeks
DP Batch A	24 Weeks
DP Batch B	Not Reached (Projected: ~1.5 years)

1. Progression defined as ≥1.5-point increase in CDR-SB. 2. Kaplan-Meier survival curve analysis utilizing data from both placebo-controlled and extension phase.

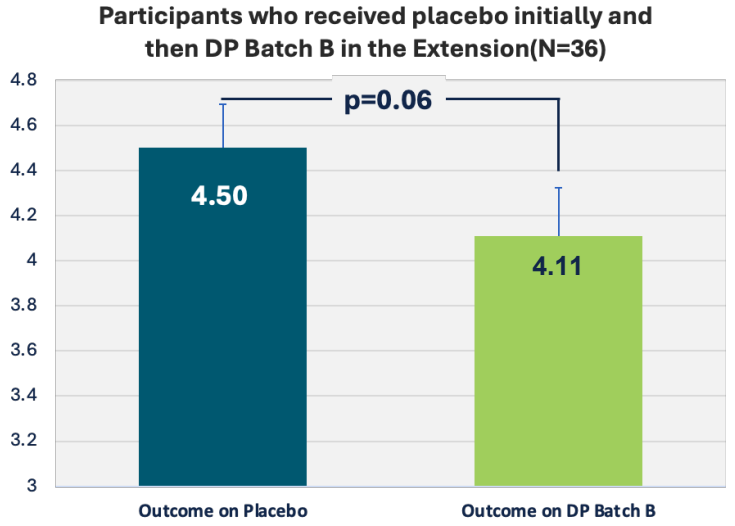
Positive Effects on ADCS-CGIC Achieved and Corroborate CDR-SB Results

All Participants

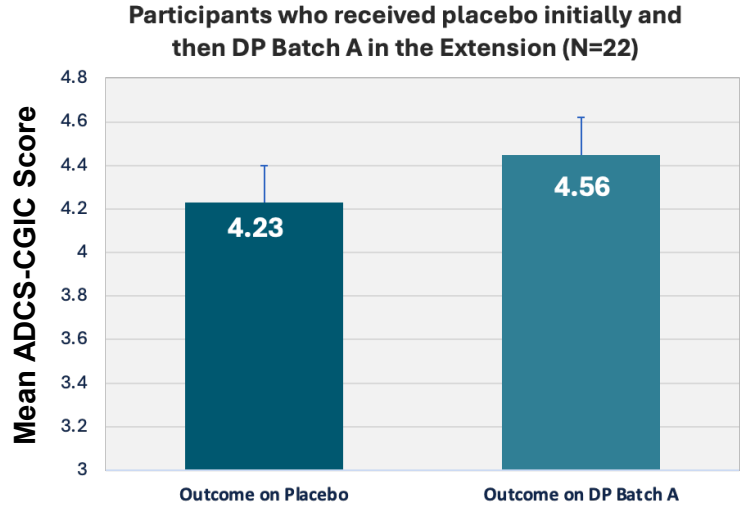
Target Concentration Not Achieved

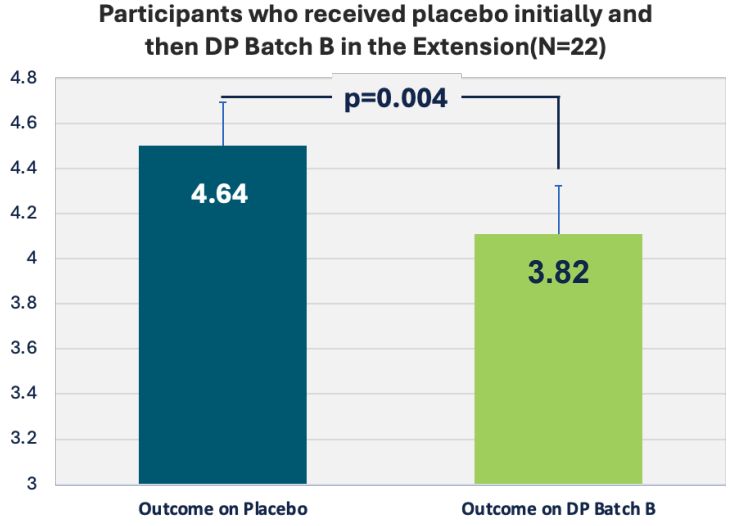


Target Concentration Achieved



Participants with Low Likelihood of AD Pathology (Screening plasma pTau181 <21 pg/mL)



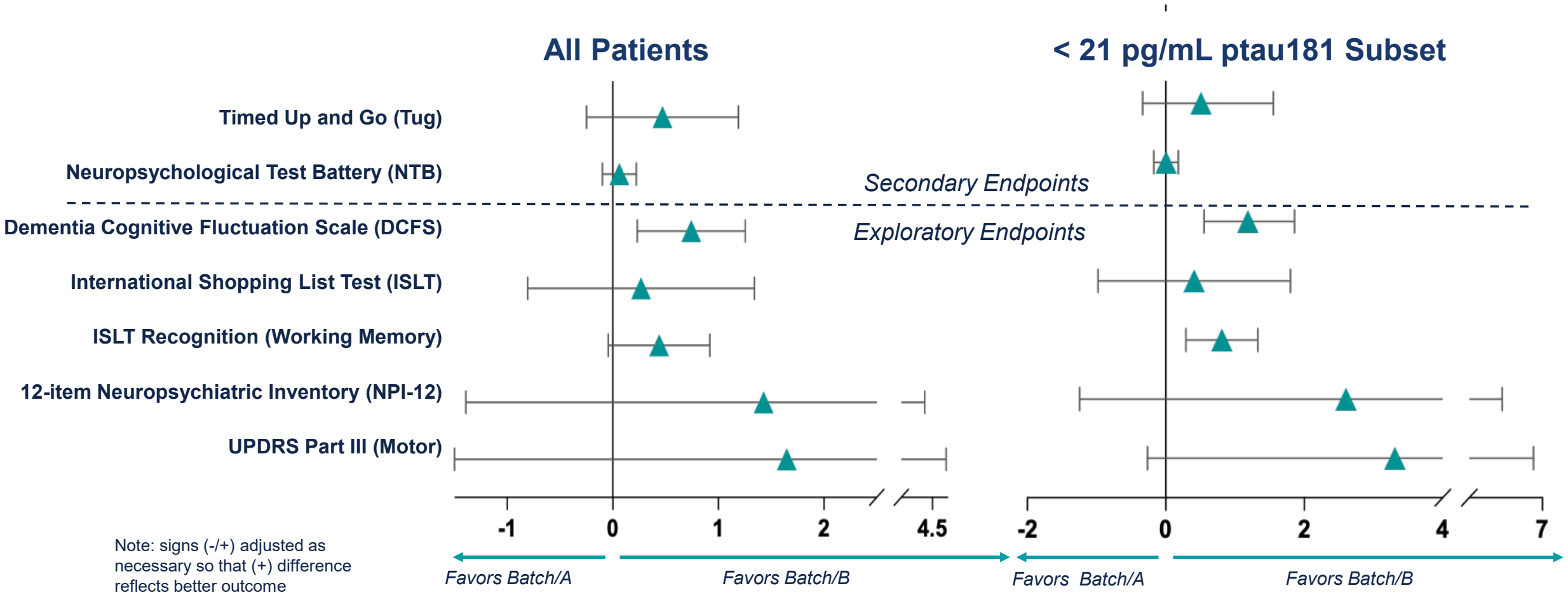


Difference = -0.82
95% CI: -1.33,-0.33
p=0.004

P-values from Wilcoxon Rank Sum Test

Treatment Effect Across Multiple Domain Specific Secondary and Exploratory Clinical Endpoints Favor Treatment with DP Batch B

Mean Difference (95% Confidence Interval) Between DP Batch A and DP Batch B in Change from Baseline to Week 16 of Extension



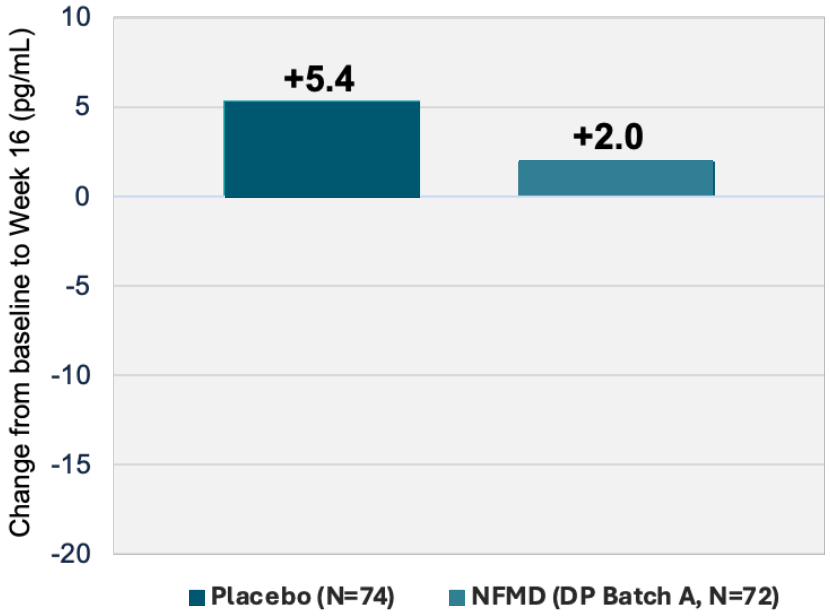
Note: signs (-/+) adjusted as necessary so that (+) difference reflects better outcome

Linear Mixed-Effects Model for Repeated Measures (MMRM) with baseline CDR-SB, Sex, Age and MMSE as covariates; green boxes highlight endpoints where 95% confidence interval does not cross zero

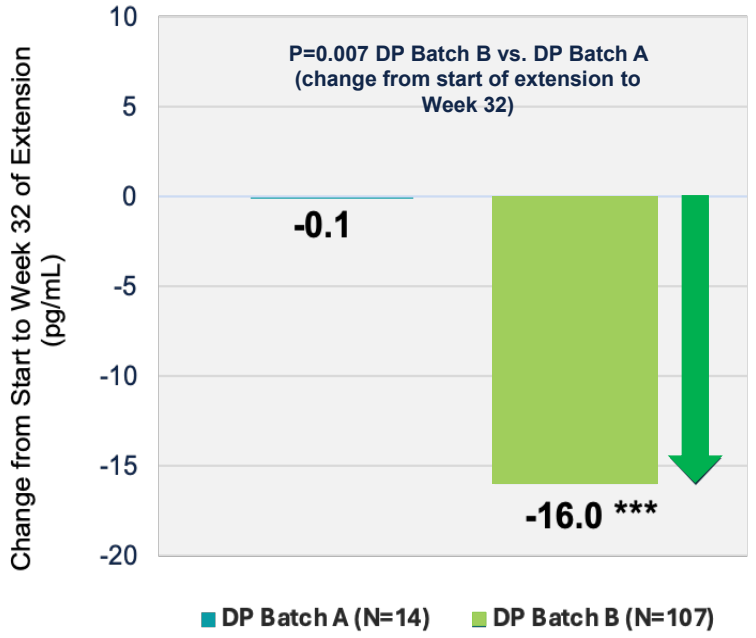
Neflamapimod Achieves Significant Reduction in Key Biomarker of Neurodegeneration

Poster 071

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

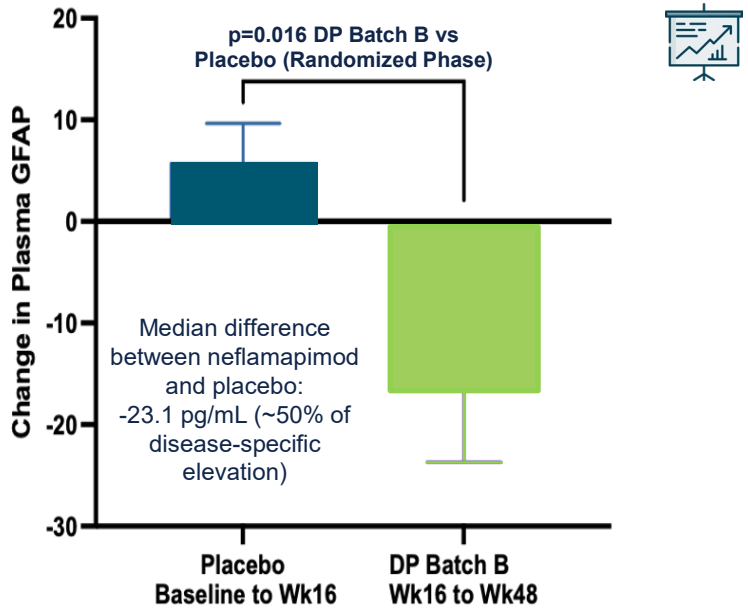


Median Change from Start to Week 32 of Extension



***p<0.001

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



Participants with Low Likelihood of AD Pathology (plasma pTau181 <21 pg/mL)

During the Extension Phase, change in plasma GFAP correlated with treatment response, as assessed by change in CDR-SB in participants with low likelihood of AD co-pathology

Poster P071 - Neflamapimod Significantly Lowers Plasma GFAP and Correlates with Clinical Benefit in Dementia with Lewy Bodies: Results from the RewinD-LB Trial. John J ALAM , Hui-May CHU, Amanda GARDNER, Kelly BLACKBURN, Charlotte E TEUNISSEN.

Neflamapimod Exhibited a Favorable Safety Profile

Neflamapimod Was Well-tolerated with No New Safety Signals Identified

The incidence of discontinuation due to adverse events was low

- 4% with neflamapimod and 1% with placebo during the placebo-controlled phase
- 4% with DP Batch A and 2% with DP Batch B through to Week 16 of the Extension Phase

All events of liver enzyme elevation were reversible; none were associated with bilirubin elevation

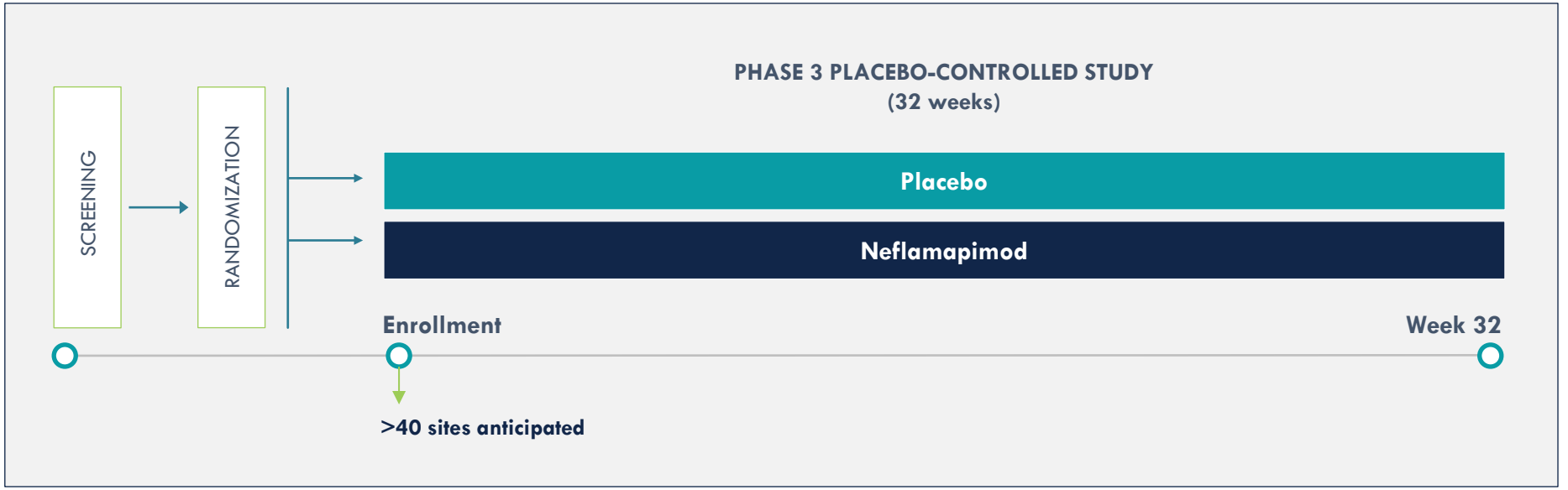
- 2 of 80 (2.5%) neflamapimod recipients discontinued for liver enzyme elevation during the placebo-controlled phase
- 2 of 149 (1.3%) neflamapimod recipients discontinued for liver enzyme elevation during the Extension Phase*

Only adverse event seen at greater than 10% incidence was falls

- 15% with neflamapimod and 19% with placebo during placebo-controlled phase
- 15% with DP Batch A and 7% DP Batch B through Week 16 of the Extension Phase

*DP Batches A and DP Batches B

Alignment Achieved with FDA on Global Phase 3 Clinical Trial Design and Path to Registration



KEY PARAMETERS

- DLB by consensus criteria
- Primary endpoint: Change in CDR-SB
- Approximately 300 patients

- CervoMed to initiate the trial in 2H26 after obtaining feedback from global regulatory authorities
- Participants will be randomized 1:1 to receive either oral neflamapimod or placebo for 32 weeks, followed by a neflamapimod only extension for 48 weeks
- Trial will focus on DLB patients with low likelihood of AD co-pathology (i.e., plasma pTau181 <21 pg/ml), which accounts for ~50% of DLB patients

Advancing Neflamapimod as A Potential First-in Class Therapy for the Treatment of DLB

Well documented scientific rationale and clinically validated mechanism of action

Durable, clinically significant effect and favorable safety profile of neflamapimod in patients with pure DLB[1]

“Pure” DLB represents an area of high unmet need with no currently approved therapies in US or EU

Alignment achieved with FDA on registration path in DLB

1. Pure DLB is defined as patients with DLB with a low likelihood of having AD co-pathology

Acknowledgements

- Patients, caregivers, study investigators, and clinical site staff involved with the RewinD-LB study
- 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 for the clinical trial: US National Institutes of Aging (NIA) Grant #R01AG080536