Neflamapimod Treatment Effects in Patients with Dementia with Lewy Bodies without Concomitant AD Pathology in the RewinD-LB Clinical Study (NCT05869669)

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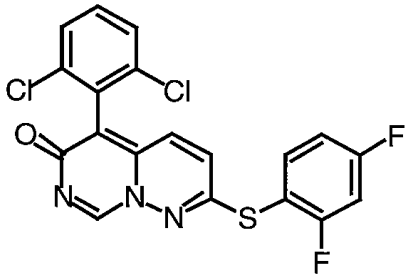
Disclosures

- 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

Neflamapimod is an oral, small molecule drug that selectively inhibits p38α, a key synaptic dysfunction in the basal forebrain cholinergic system



Preclinical proof-of-concept achieved

1

- Potent (<10nM IC50), highly selective inhibitor of p38α
- Blood-brain-barrier penetrant with brain to plasma ratio of ~2
- Reversed neurodegenerative process in basal forebrain in relevant animal disease models
- Improves both histological and behavioral outcomes in preclinical pharmacology studies

Target engagement demonstrated in clinical studies

2

- Highly selective
- Reduction in CSF levels of IL-8 (marker of IL-1b signaling)
- Reduction in CSF levels of phosphorylated tau and total tau
- Increase in volume of basal forebrain and its functional connectivity by MRI

Safety profile well defined

3

- Clinical safety data in >700 volunteers and patients, with up to 48 weeks treatment duration
- Chronic, repeat dose toxicology studies completed
- Human 40mg TID dose has 10-fold safety margin to NOAEL in long-term toxicology studies

Clinical proof-of-concept achieved in DLB*

4

- Positive Phase 2a and 2b results
- Phase 3 ready

Neflamapimod is an investigational product currently in clinical development for the treatment of DLB, recovery after ischemic stroke, and frontotemporal disorders (nfvPPA).

Today's objectives

1. **To review the primary analyses of the RewinD-LB study**

2. **Present new secondary analyses that inform on an optimal plasma pTau181 cutoff point to enrich for DLB patients without AD co-pathology**

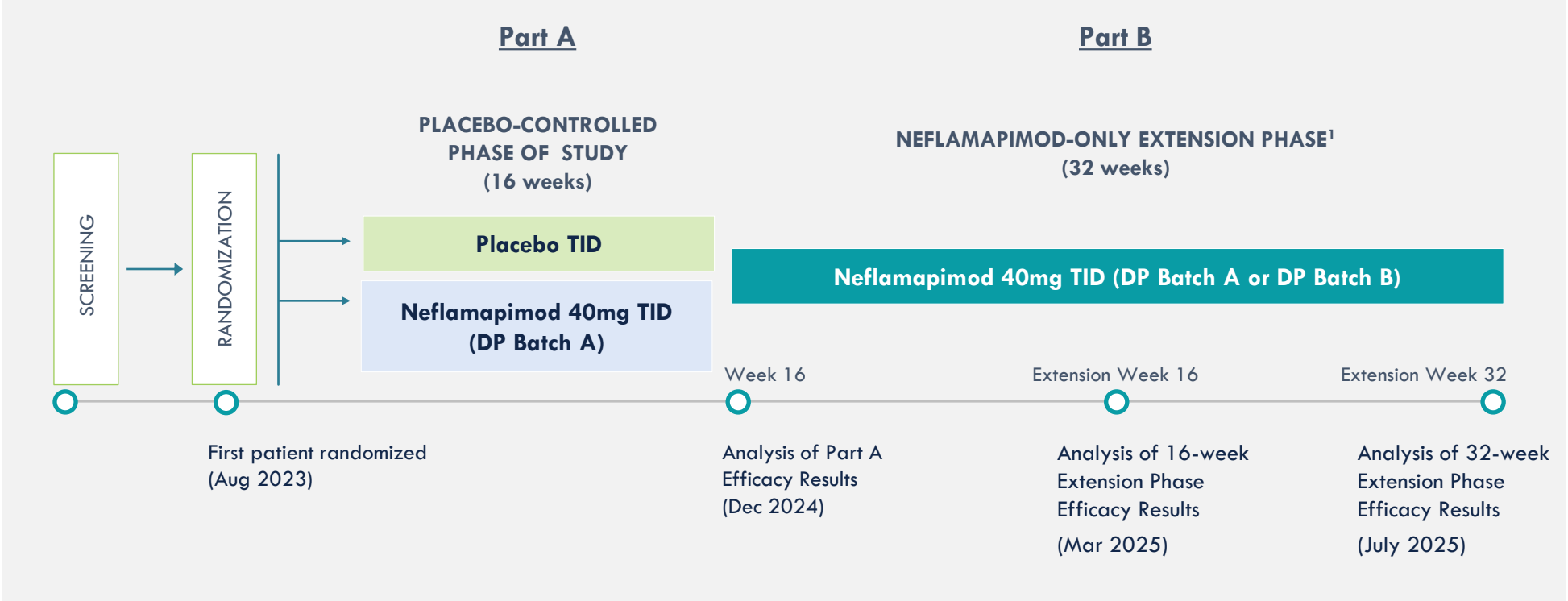
RewinD-LB Phase 2b study in DLB: A two-part study design

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

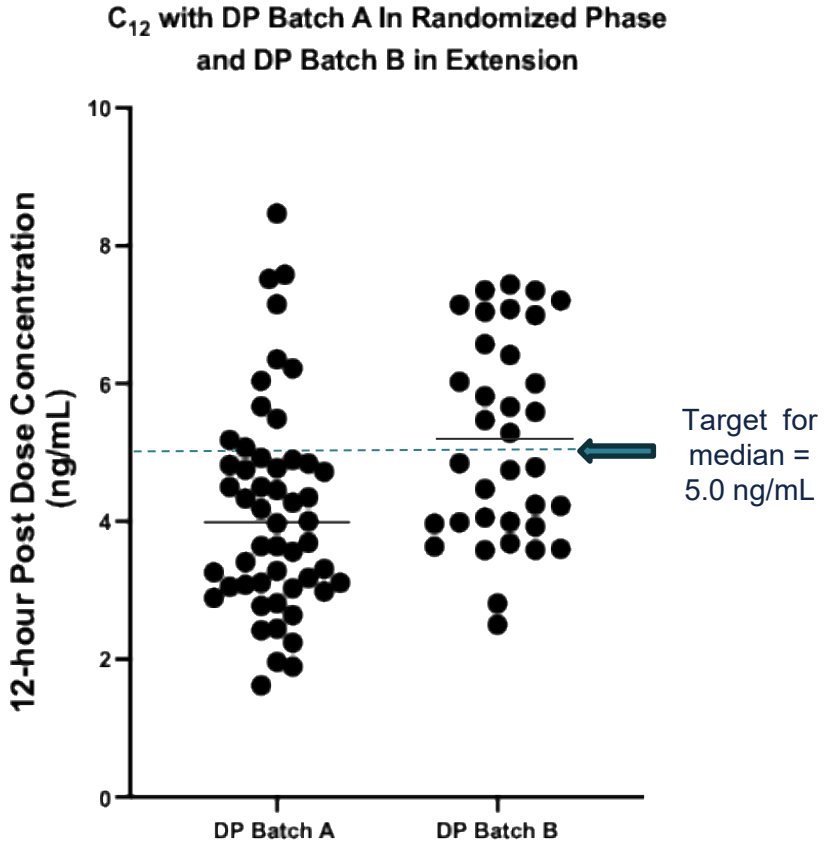


Note: Last patient, last visit, June 2025.

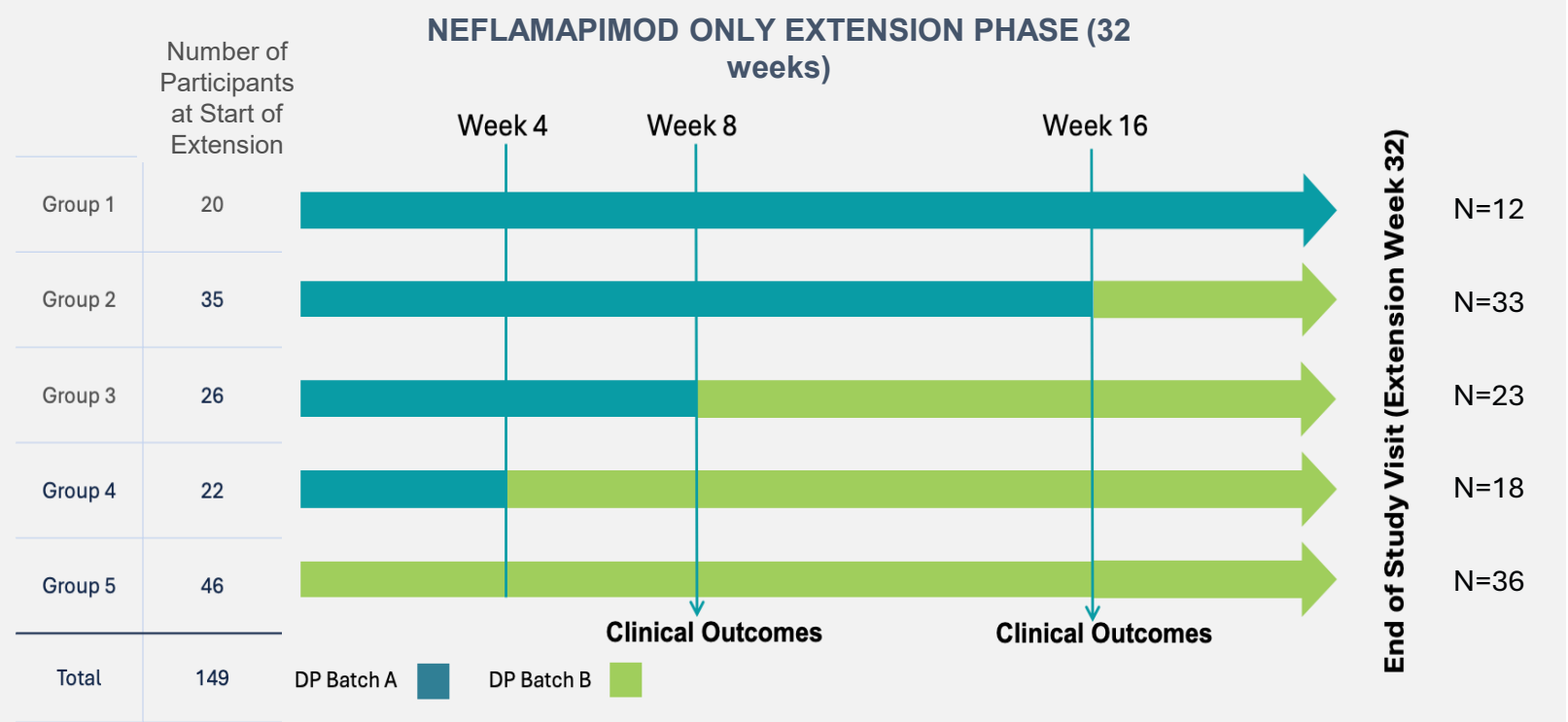
DP Batch A failed to achieve target plasma drug concentrations, effectively underdosing participants; in contrast, DP Batch B achieved 5.0 ng/mL target

	DP Batch A	DP Batch B
Use in RewinD-LB	Randomized Phase (Part A) and Extension Phase (Part B)	Extension Phase (Part B) only
Date of Production	October 2020 (~3-4 yrs old during utilization in RewinD-LB)	March 2023 (~2 yrs old during utilization in RewinD-LB)
Median trough plasma drug concentrations	4.0 ng/mL; lower than expected plasma drug concentrations, with only 50% reaching individual target concentration	5.0 ng/mL; expected plasma drug concentrations, with 75% reaching individual target concentration

DP Batch A and DP Batch B manufacturing processes were identical



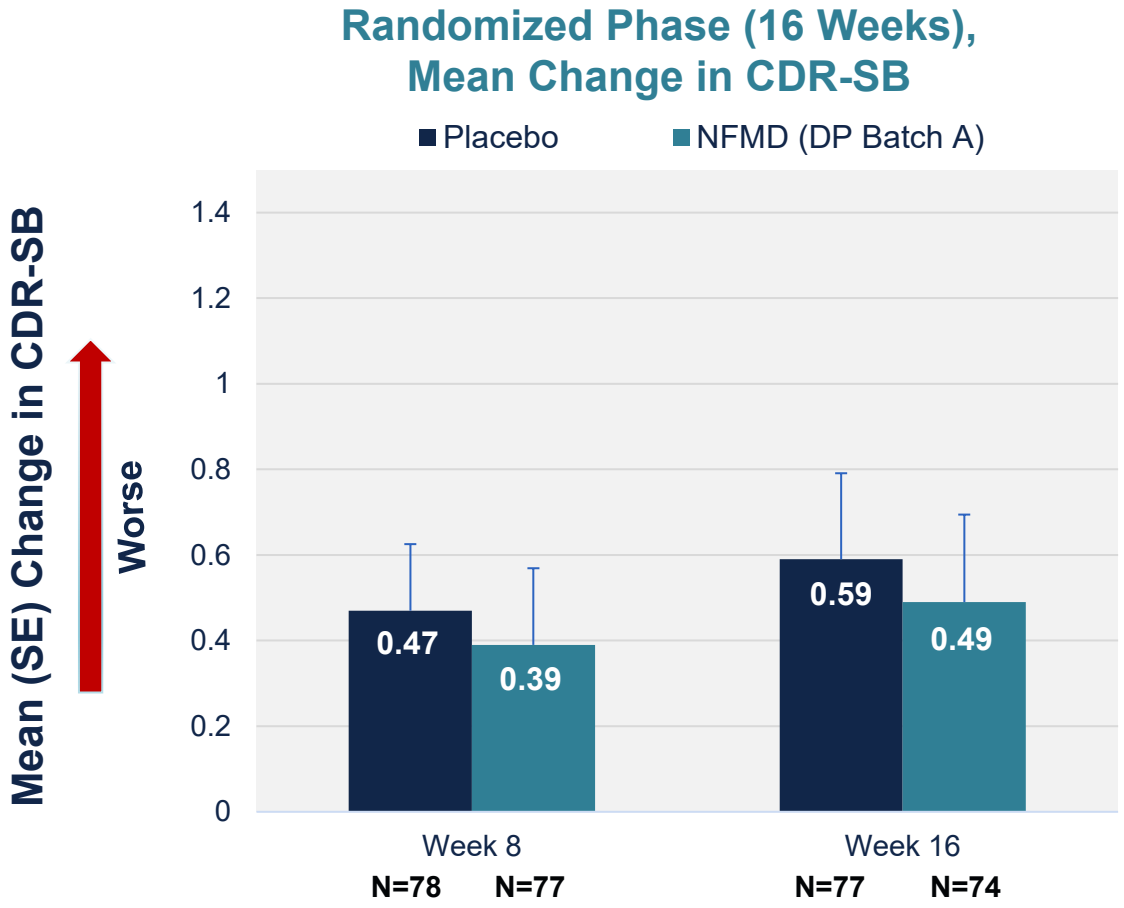
Pre-planned introduction of DP Batch B, which achieved target plasma drug concentrations enabled a robust Extension Phase analyses

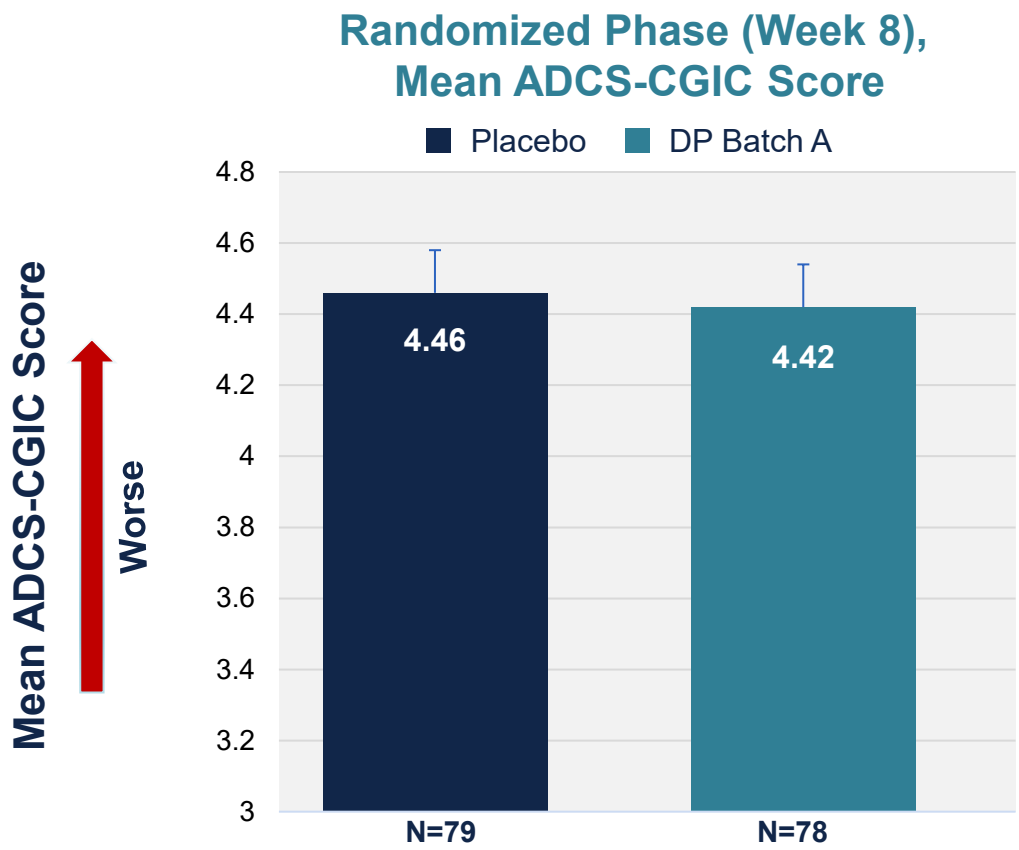


Treatment in Extension Phase was open-label; capsule batch identity (DP Batch A vs. DP Batch B) remained blinded to participants and site personnel

All analyses were pre-specified in either original statistical analysis plan (SAP) or in an addendum to the SAP implemented after analysis of Part A, but before Part B data were available

No significant differences between placebo and neflamapimod (DP Batch A) in mean change in CDR-SB or ADCS-CGIC during Randomized Phase

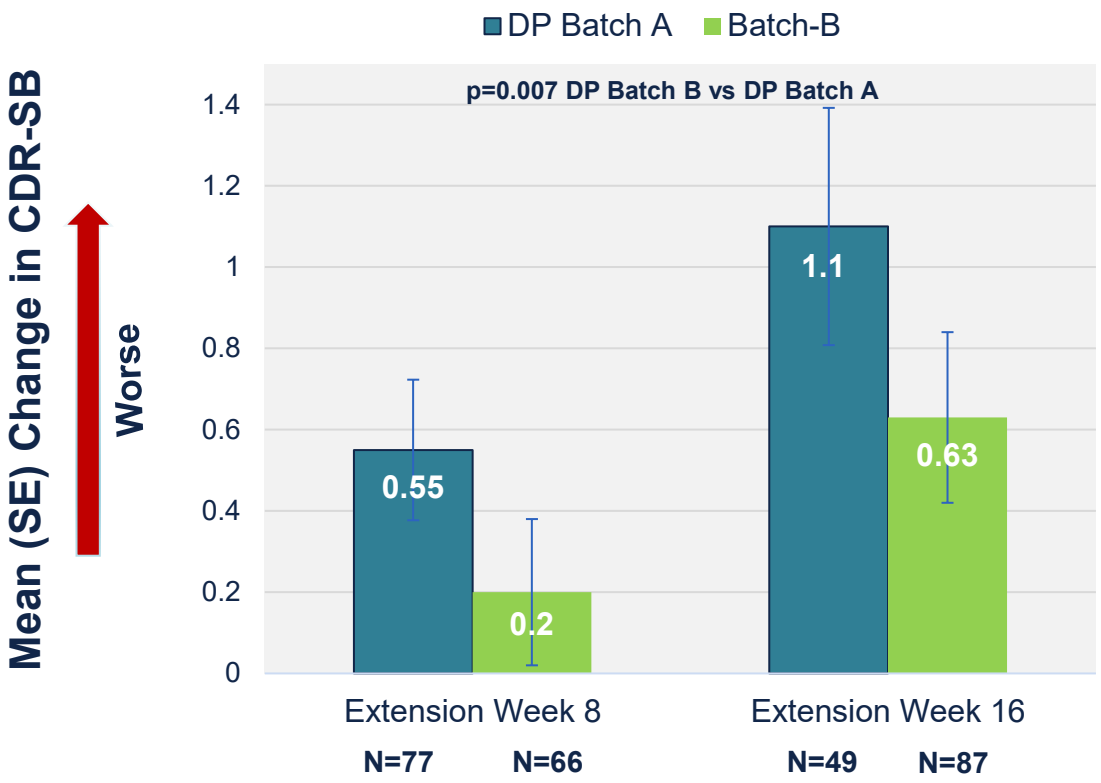




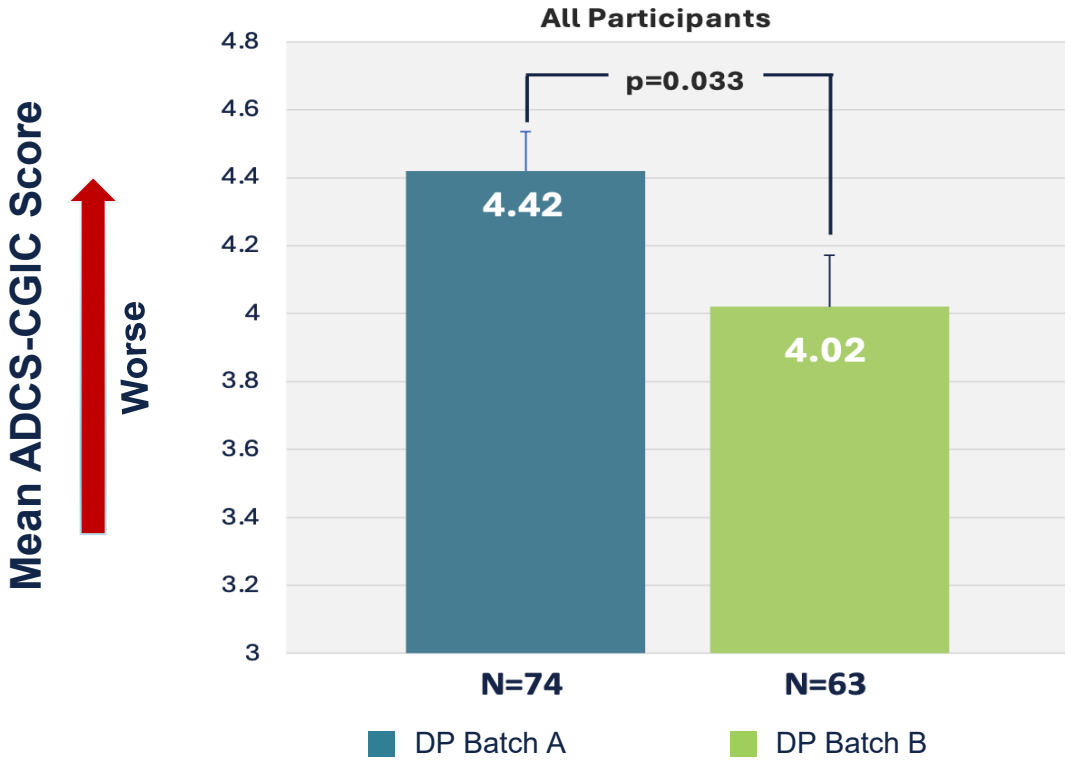
Linear Mixed-Effects Model for Repeated Measures (MMRM) with baseline CDR-SB, Sex, Age and Mini-Mental State Examination (MMSE) as covariates. DP Batch A data includes participants in Groups 1, 2, and 3 at Week 8 and in Groups 1 and 2 at Week 16. DP Batch B data includes participants in Groups 4 and 5 at Week 8 and Groups 3, 4, and 5 at Week 16. See Slide 16 for additional details.

Significant improvement demonstrated on mean change in CDR-SB and ADCS-CGIC, during first 16 weeks of the Extension Phase with DP Batch B

Extension Phase (Week 8 and Week 16), Mean Change in CDR-SB



Extension Phase (Week 8), Mean ADCS-CGIC Score



Linear Mixed-Effects Model for Repeated Measures (MMRM) with baseline CDR-SB, Sex, Age and Mini-Mental State Examination (MMSE) as covariates. DP Batch A data includes participants in Groups 1, 2, and 3 at Week 8 and in Groups 1 and 2 at Week 16. DP Batch B data includes participants in Groups 4 and 5 at Week 8 and Groups 3, 4, and 5 at Week 16. See Slide 16 for additional details.

Summary of other key results from the Phase 2b RewinD-LB study (full results presented at CTAD 2025)

- The effects on CDR-SB were durable out 32 weeks of treatment as assessed by both mean change in CDR-SB or risk of significant progression (≥ 1.5-point increase in CDR-SB)

- Neflamapimod significantly reduced plasma GFAP levels, a key marker of the neurogenerative disease activity, when target plasma drug concentrations were achieved

    - Treatment with the DP Batch B neflamapimod reduced disease-associated elevation of GFAP by ~50%, as compared to placebo

- Neflamapimod exhibited a favorable safety profile, including a very low rate (<1%) of discontinuation due to liver enzyme elevation

AD co-pathology determines severity of disease and whether targeting the basal forebrain cholinergic system can slow clinical progression in DLB

DLB Without AD Co-Pathology = Low Levels of Plasma pTau181

Basal Forebrain Cholinergic System
Diseased

Medial Temporal Lobe
No Atrophy

Reversible Function Deficient

Clinical Effect of Basal Forebrain-Directed Treatment

With cholinergic dysfunction as the primary driver of disease progression and the medial temporal lobe structurally intact, targeting the basal forebrain can slow clinical decline

VS

DLB With AD Co-Pathology = Elevated Levels of Plasma pTau181

Basal Forebrain Cholinergic System
Diseased

Medial Temporal Lobe
Atrophy

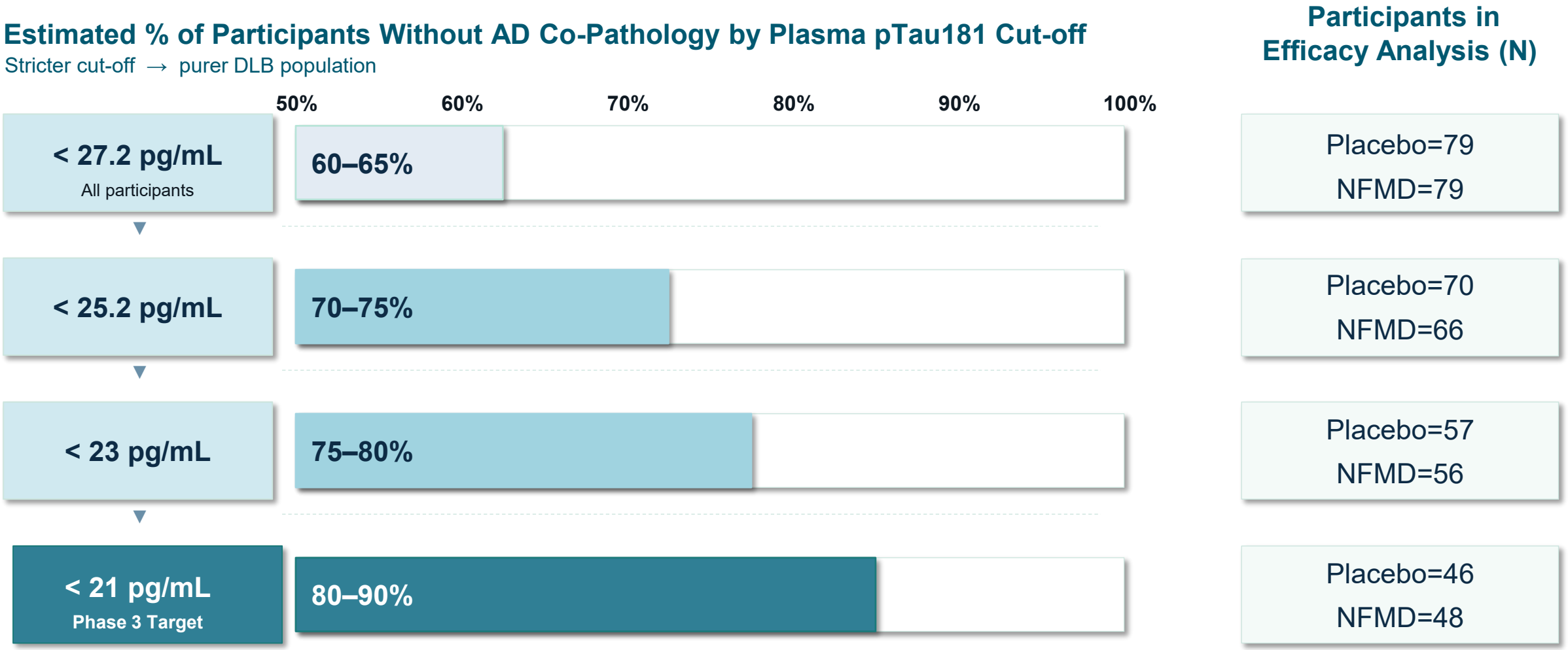
Irreversible Cell Loss

Clinical Effect of Basal Forebrain-Directed Treatment

More advanced disease with significant **hippocampal atrophy from AD co-pathology which becomes the primary driver of disease progression** and results in irreversible deficits

Schumacher et al, *Brain* (2022) 145:1773–1784; Alam et al, *Neurology*, (2023) 101 (17) e1708-e1717; Schumacher et al. Alz Res & Ther (2025) 17:28

Lowering plasma pTau181 cut-off progressively enriches for patients without AD co-pathology

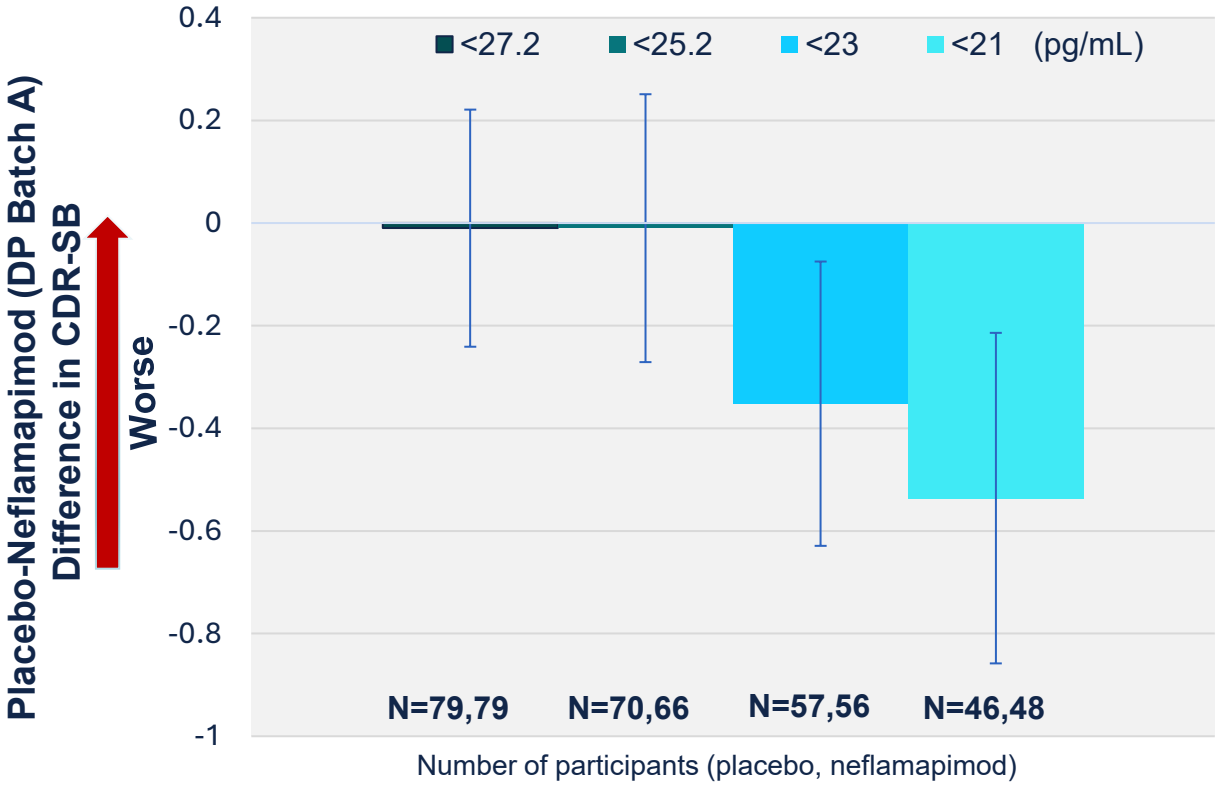


Optimal pTau181 cut-off of <21pg/ml validated externally in large (N=1,298) third party validation study published in February 2025[1]

NFMD = neflamapimod. 1. Doecke et al. 2025, Alzheimer's & Dementia, 2025;21:e14573.

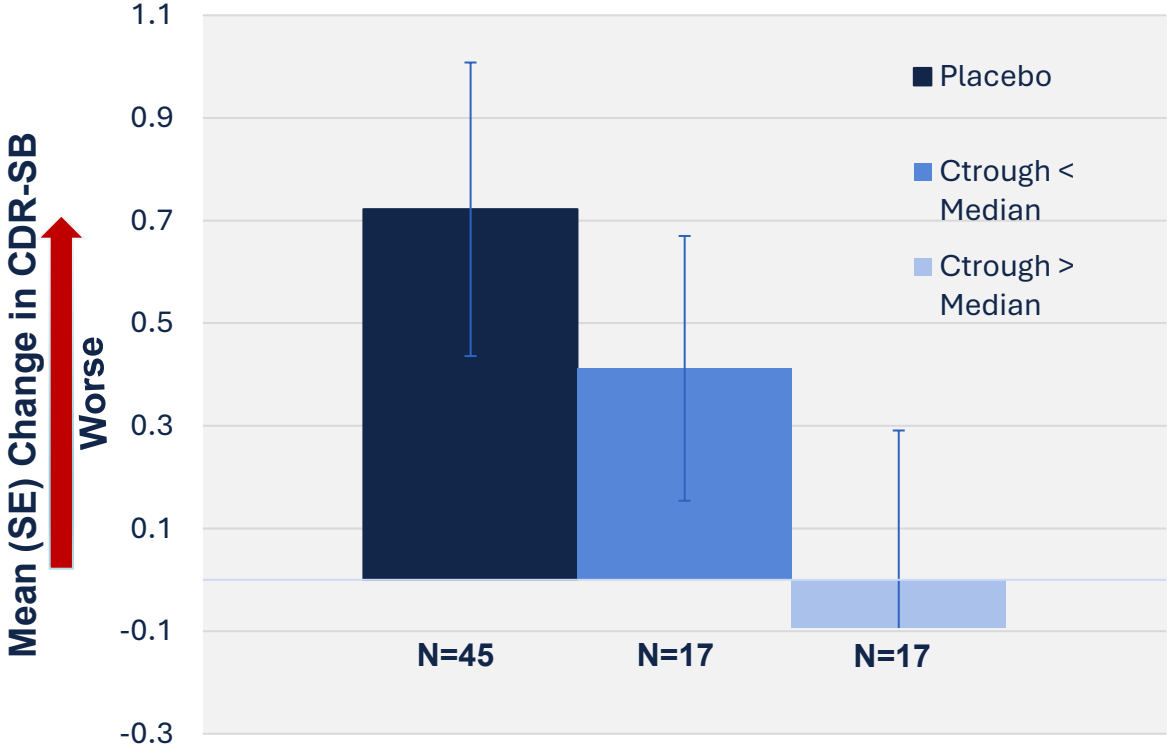
Primary outcome results in patients treated with DP Batch A during Randomized Phase by plasma pTau181 cutoff

Neflamapimod (DP Batch A) Effect on Change in CDR-SB by Plasma pTau181 Cutoff



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

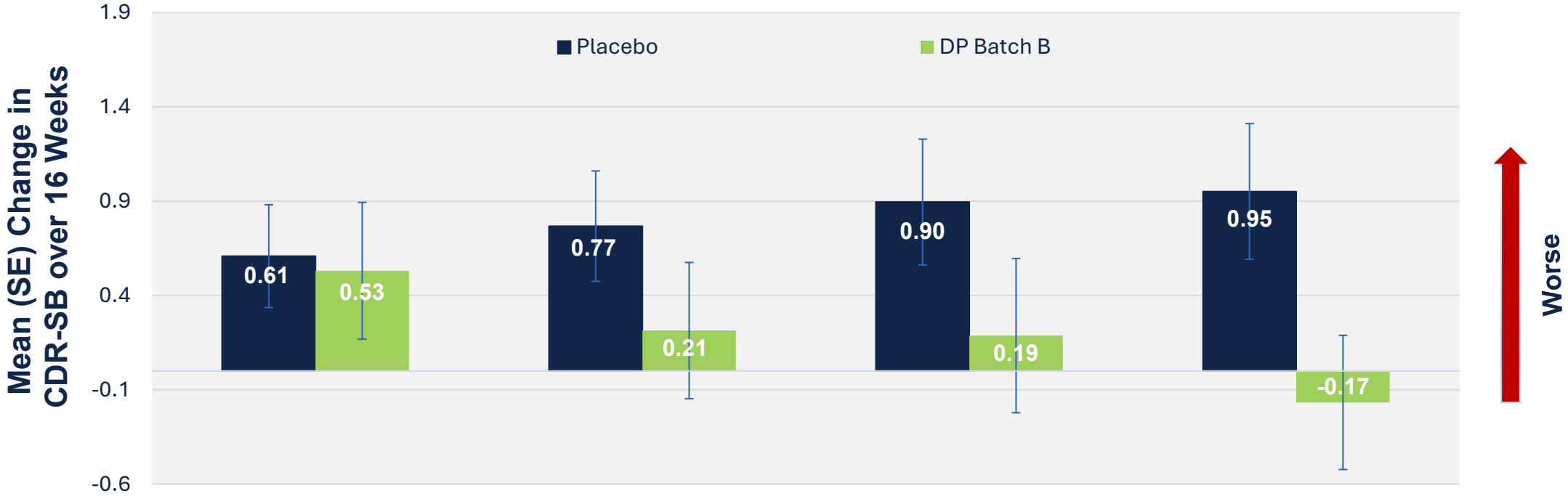
Change in CDR-SB During Placebo Controlled Phase by Trough Plasma Drug Concentration in <21 pTau181 Subset



Median Observed C_{trough} = 3.64 in < 21 pg/mL subset

Note: ctrough>median = effective dose

Within subject analysis by pTau181 subset of mean change in CDR-SB in participants who received placebo and then DP Batch B during Extension Phase[1]

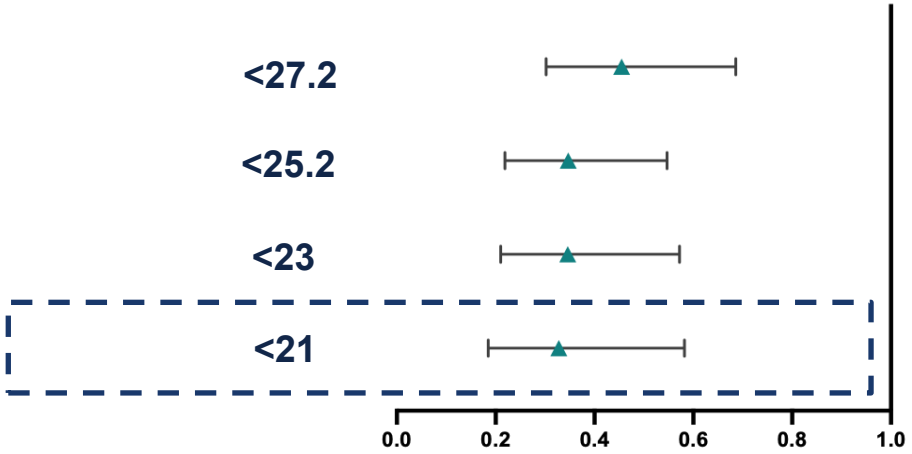


	<27.2	<25.2	<23	<21
Number of Participants	32	28	24	21
NFMD-Placebo Difference	**-0.08**	**-0.55**	**-0.71**	**-1.11**
P-value NFMD vs. Placebo	p=0.9	p=0.044	p=0.034	p=0.005

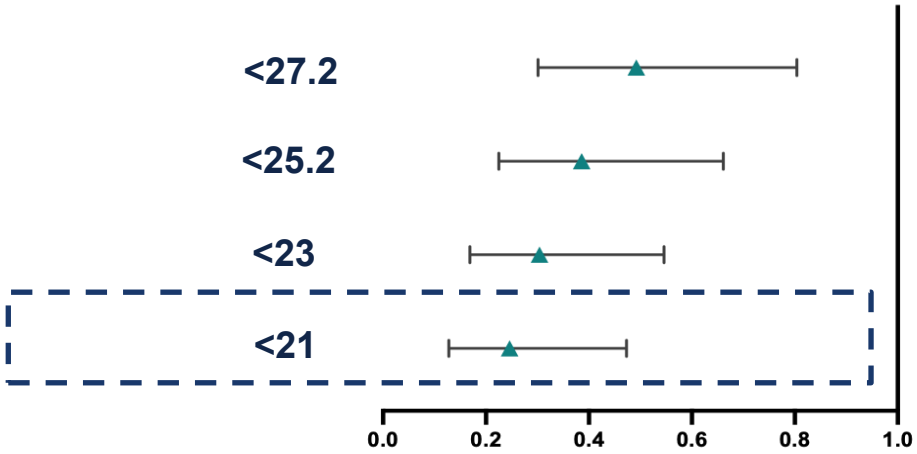
1. Group 4 and Group 5 Patients, i.e. ≥12 weeks DP Batch B Treatment During 1st 16 weeks of Extension

Risk of clinically meaningful progression (≥ 1.5-point increase in CDR-SB) by pTau181 subset

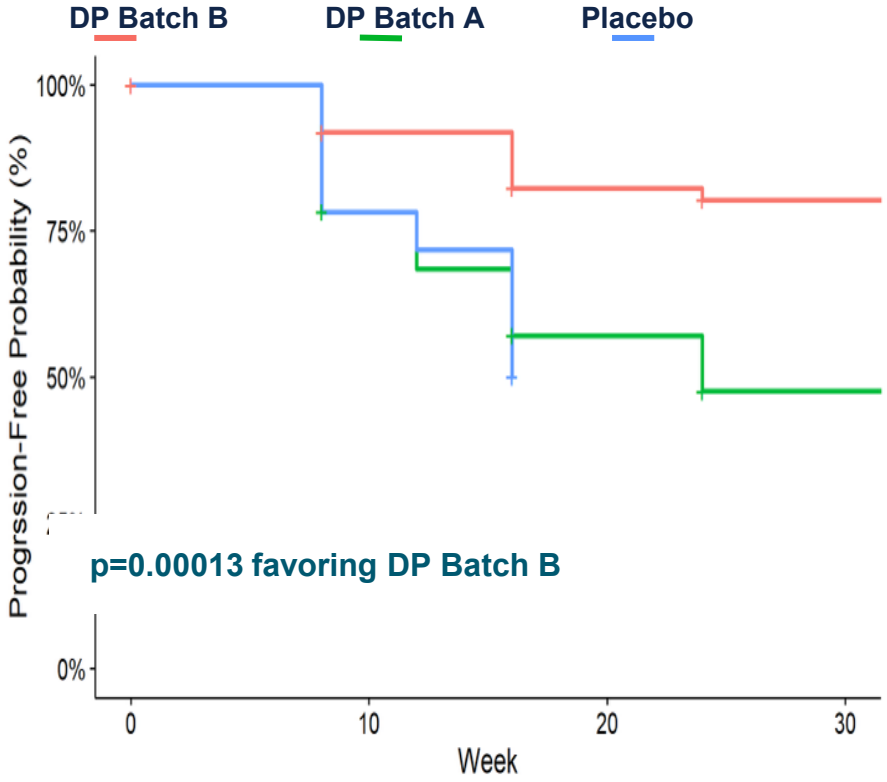
Hazard Ratio DP Batch B vs. DP Batch A



Hazard Ratio DP Batch B vs. Placebo



Participants with Screening Plasma pTau181 < 21 pg/mL



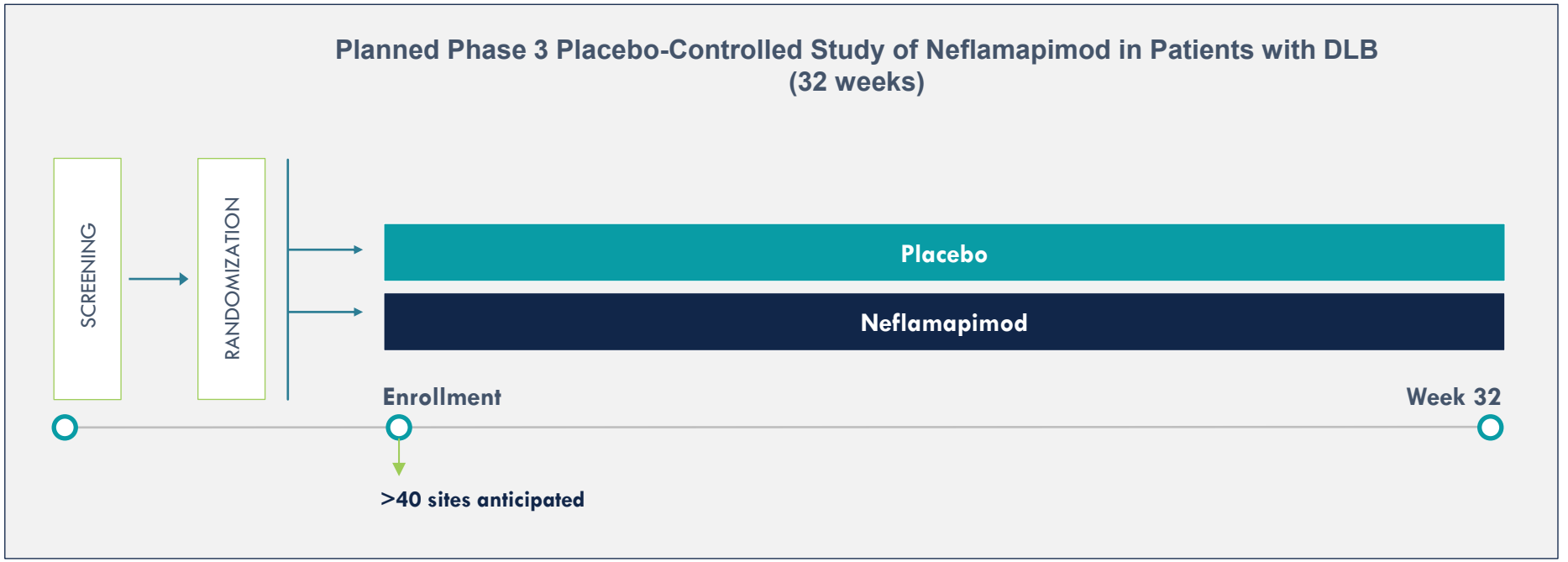
p=0.00013 favoring DP Batch B

Number at Risk

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

Kaplan-Meier survival curve analysis utilizing data from both placebo-controlled and extension phase. DP Batch B, DP Batch A, and placebo data include all participants on such treatment at the time of measurement (i.e., participants may change groups over time).

Reached alignment with the FDA on registration path for potential approval in dementia with Lewy bodies



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
- 50 mg TID Dose

- Single Phase 3 clinical trial of 32 weeks duration, with change in CDR-SB as primary endpoint
- Plan to initiate the trial in 2H 2026

Summary and conclusions

Findings From Randomized Phase Consistent with Inadequate Drug Exposure

In contrast, analysis by plasma pTau181 subset and plasma trough drug concentrations demonstrate clinical effect in patients with pure DLB who reach target drug concentrations in Randomized Phase

Patient Enrichment Enhances Treatment Effect

In line with neflamapimod's mechanism of action and current understanding of DLB pathogenesis, enrichment for patients without AD co-pathology results in a greater magnitude of treatment effect

Consistent pTau181 Cutoffs Strengthen Efficacy Conclusions

The consistency of the impact of plasma pTau181 cutoffs across both study phases, corroborated by multiple endpoints*, further strengthens the overall efficacy conclusions of the study

*CDR-SB and ADCS-CGIG (data on file)

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