Excerpts from “Behavioral Neurology and Dementia: Therapeutic Advances in Neurodegenerative Diseases” Presented by Dr. James Galvin at the 150th Annual American Neurology Association Conference

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Neflamapimod: Oral Investigational p38a Kinase Inhibitor Targeting Basal Forebrain Cholinergic Degeneration[1]

Preclinical — *Disease processes in basal forebrain reversed*

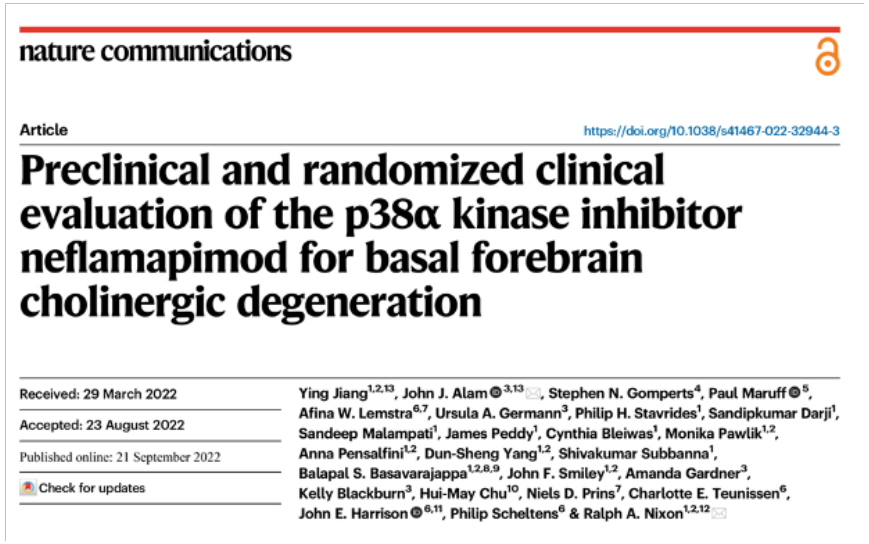
When administered in mice that develop basal forebrain cholinergic degeneration, neflamapimod:

- ✓ 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[2]

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))
- ✓ Results most prominent in patients without AD Co-Pathology (i.e., patients without elevation in plasma ptau181)[3]



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Preclinical and randomized clinical evaluation of the p38α kinase inhibitor neflamapimod for basal forebrain cholinergic degeneration

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Check for updates

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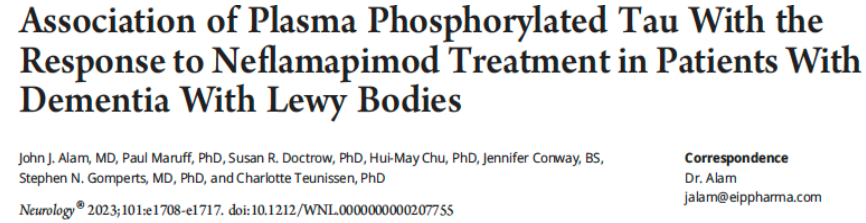

Association of Plasma Phosphorylated Tau With the Response to Neflamapimod Treatment in Patients With Dementia With Lewy Bodies

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

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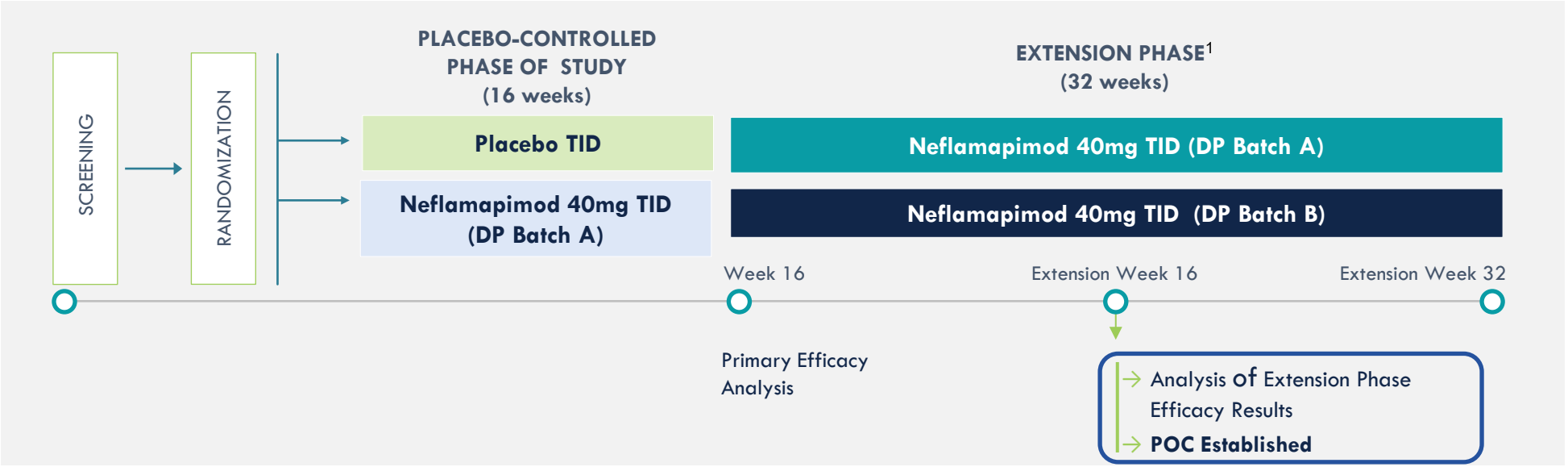
RewinD-LB Phase 2b Study in DLB: Design and Conduct

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, NTB,



Neflamapimod Dosing Groups and Comparisons

- **Drug Product (DP) Batch A:** Batch of capsules utilized in placebo-controlled phase and initially during the extension. Did not achieve expected and targeted plasma drug concentrations.
- **DP Batch B:** introduced 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

1. 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 old or new capsules

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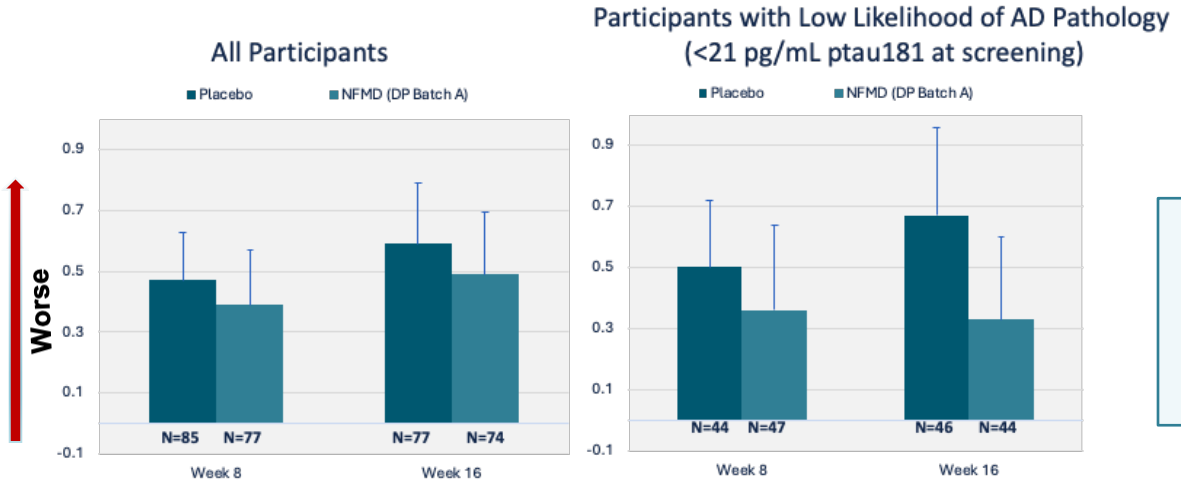
Primary Outcome Measure: Change in CDR-SB Over 16 Weeks

Placebo Controlled Phase

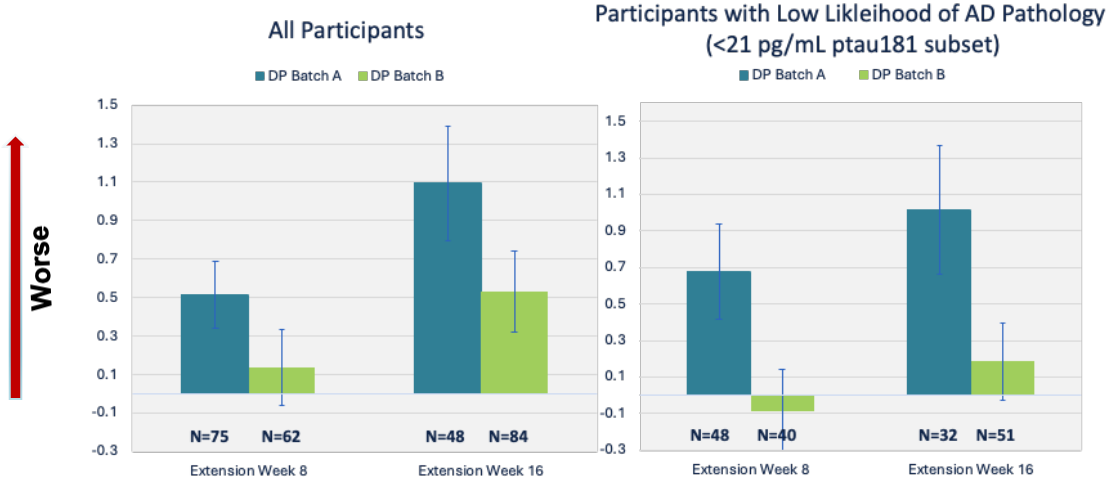


P=0.7 placebo vs. NFMD (DP Batch A)

P=0.10 placebo vs. NFMD (DP Batch A)

No significant differences between placebo and neflamapimod during placebo-controlled phase of study. Attributed to age of the batch of capsules utilized (DP Batch A) in this phase, which led to not achieving targeted plasma drug concentrations with this batch

Extension Phase



P=0.004 DP Batch B vs. DP Batch A\

p=0.045 DP Batch B vs. DP Batch A

Significant effect on clinical progression when target plasma concentrations were achieved, most prominently in patients with low likelihood of having AD co-pathology

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

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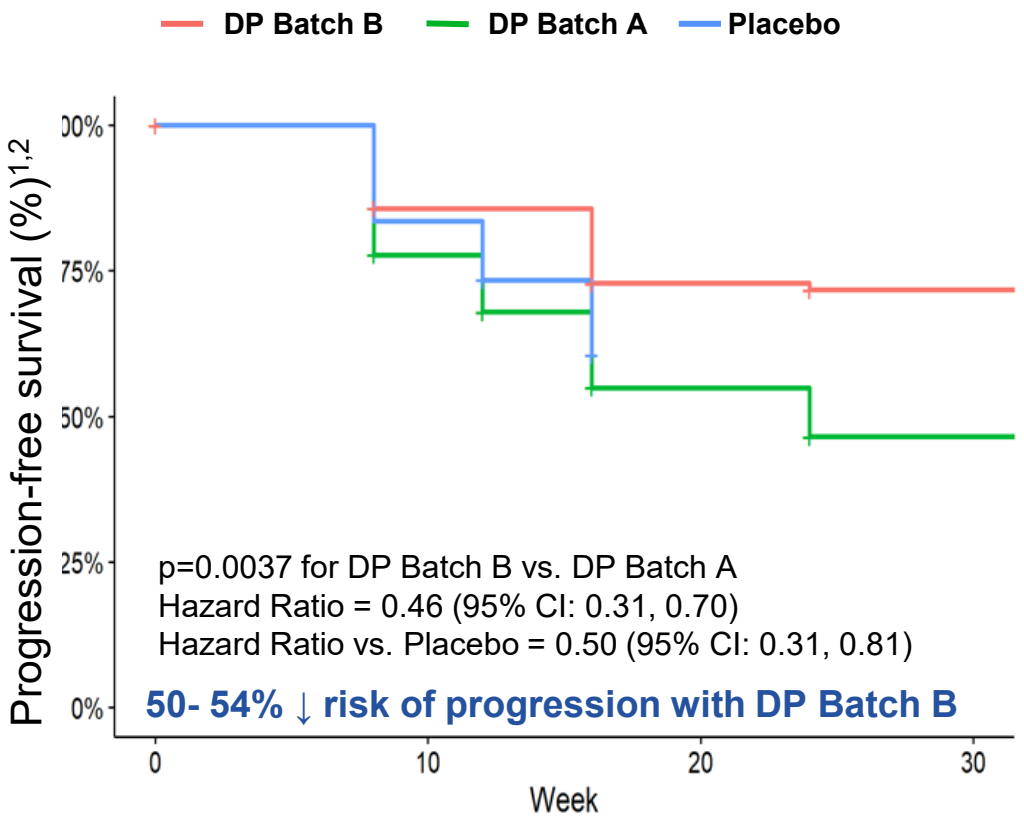
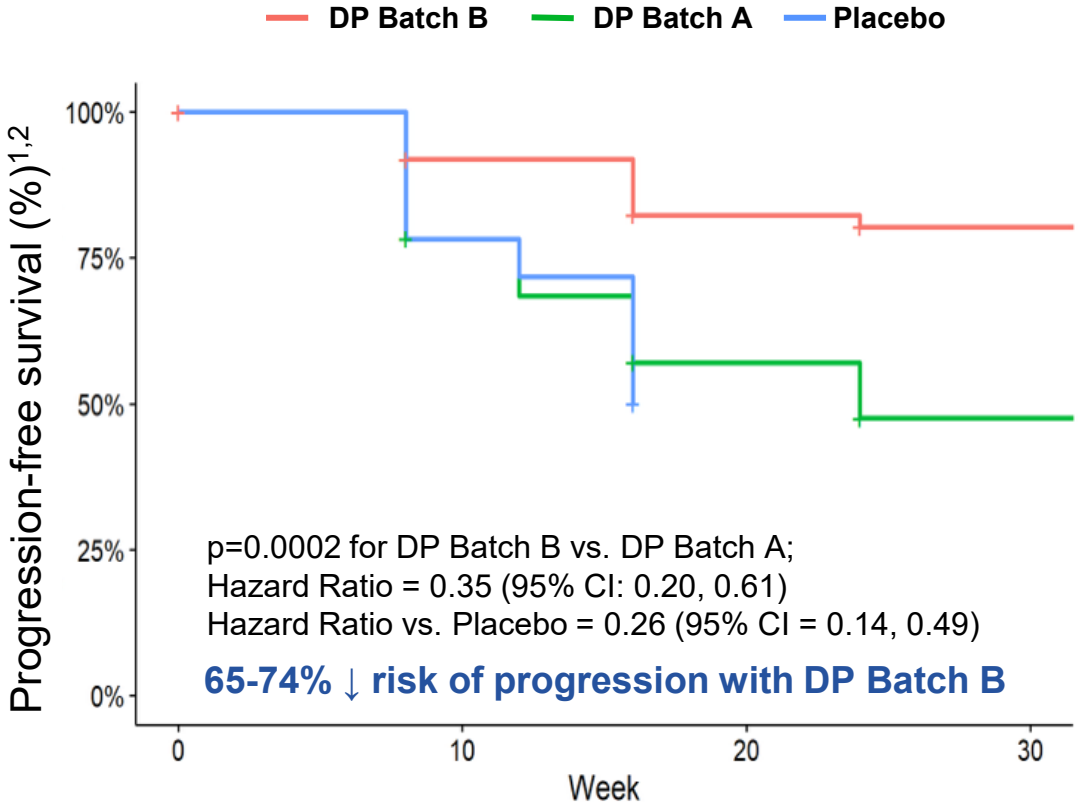
Risk of Clinically Meaningful Progression (≥ 1.5 Pt Increase in CDR-SB) Over 32 Weeks Reduced with Neflamapimod When Target Plasma Drug Concentrations are Achieved

All Participants



Number at Risk			
	Week 8	Week 16	Week 24
New	126	107	62
Old	117	68	26
Placebo	79	57	

Participants with Screening Plasma ptau181 < 21 pg/mL



Number at Risk			
	Week 8	Week 16	Week 24
New	74	67	41
Old	69	42	18
Placebo	46	33	

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.

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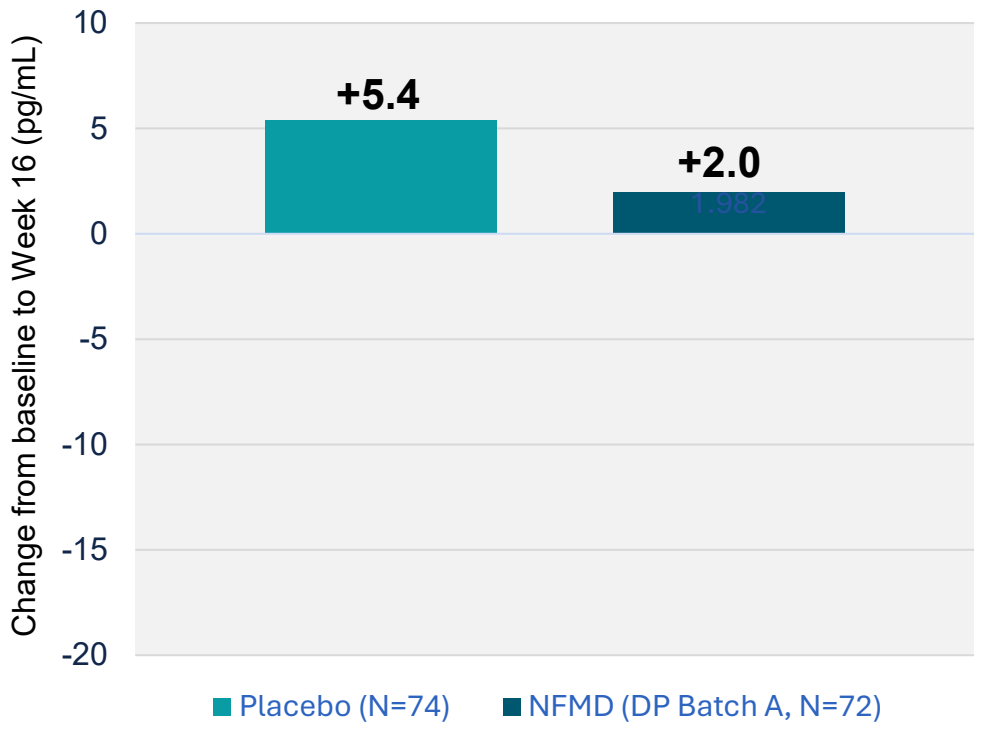
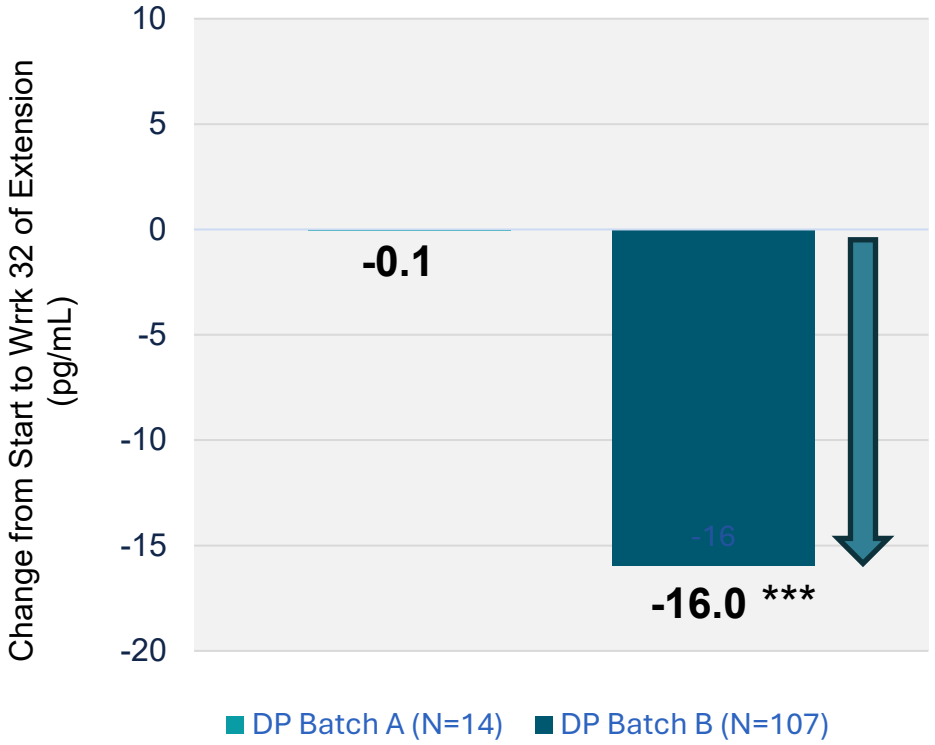
Significant Reduction in Plasma Glial Fibrillary Acidic Protein (GFAP) Levels When Targeted Plasma Drug Concentrations are Achieved

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



Median Change from Start to Week 32 of Extension



***P<0.0001 for change from start of extension to Week 32

Summary of RewinD-LB Results

- Neflamapimod treatment leads to slowing of clinical worsening, as assessed by CDR-SB, when target plasma drug concentrations were achieved.
  - Patients treated with neflamapimod showed 50-54% risk reduction in clinically significant worsening on the CDR-SB over up to 32 weeks of treatment, compared to controls
  - Risk reduction improved to 65-75% among patients who do not have biomarker evidence of AD co-pathology (ptau181 < 21 pg/mL at screening)
- Primary result supported by improvement on multiple other clinical endpoints at Week 16 when target plasma drug concentrations were achieved (not shown in today's presentation):
  - ADCS-CGIC
  - Dementia Cognitive Fluctuation Scale
  - International Shopping List Test Recognition (working memory)
  - Positive trends Timed Up and Go, and 12-item Neuropsychiatric Inventory
- The effects on clinical progression associated with a significant reduction in plasma levels of the neurodegenerative disease marker GFAP, which further support that neflamapimod has disease-modifying potential
- Neflamapimod was well tolerated with low rate of treatment discontinuation over up to 48 weeks of treatment

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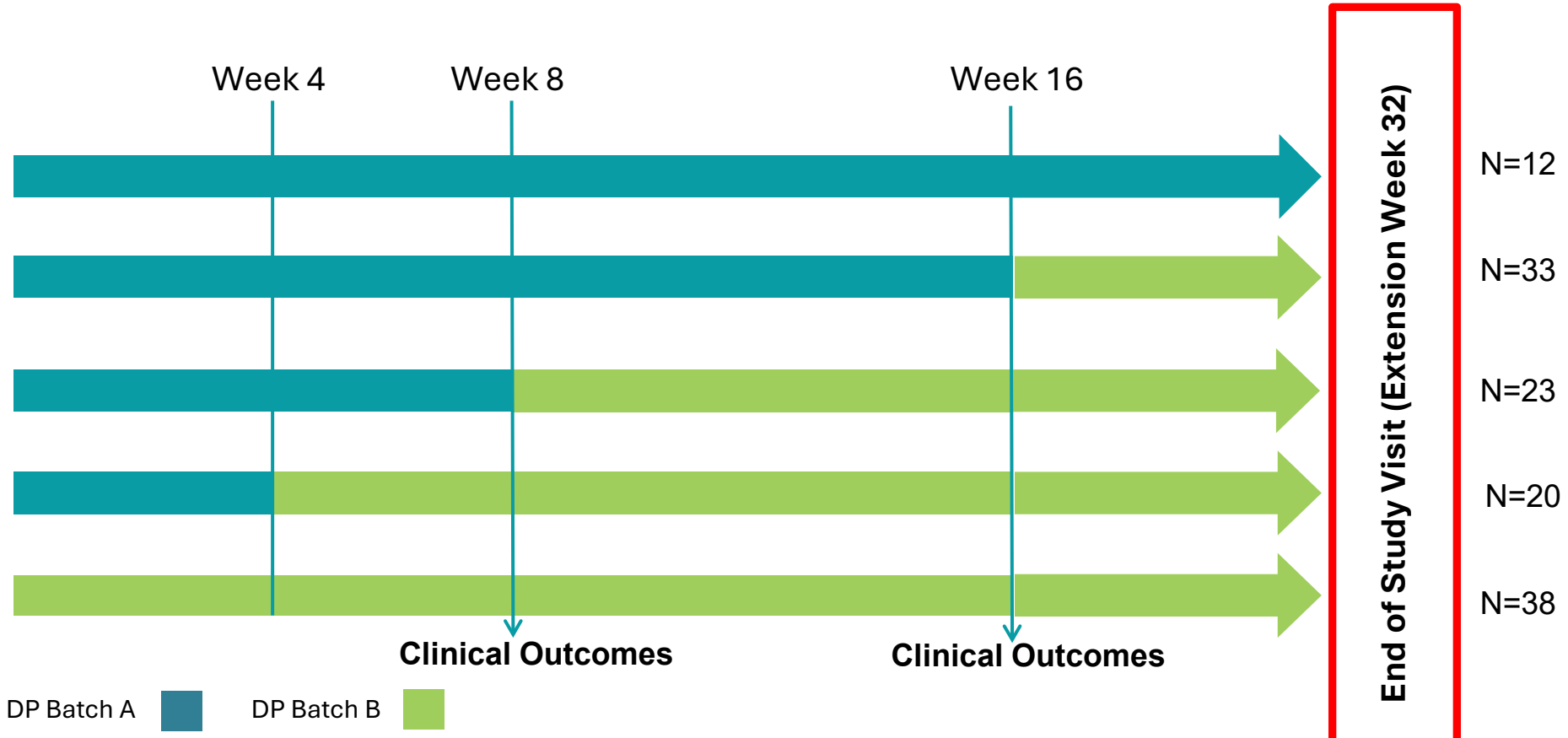
Appendix (Not Presented at Conference)

Neflamapimod Dosing Groups in Extension Phase of RewinD-LB Study

	Number of Participants
Group 1	20
Group 2	35
Group 3	26
Group 4	22
Group 5	46
Total	149

Study Visits During First 16 Weeks of Extension Phase



Note: 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

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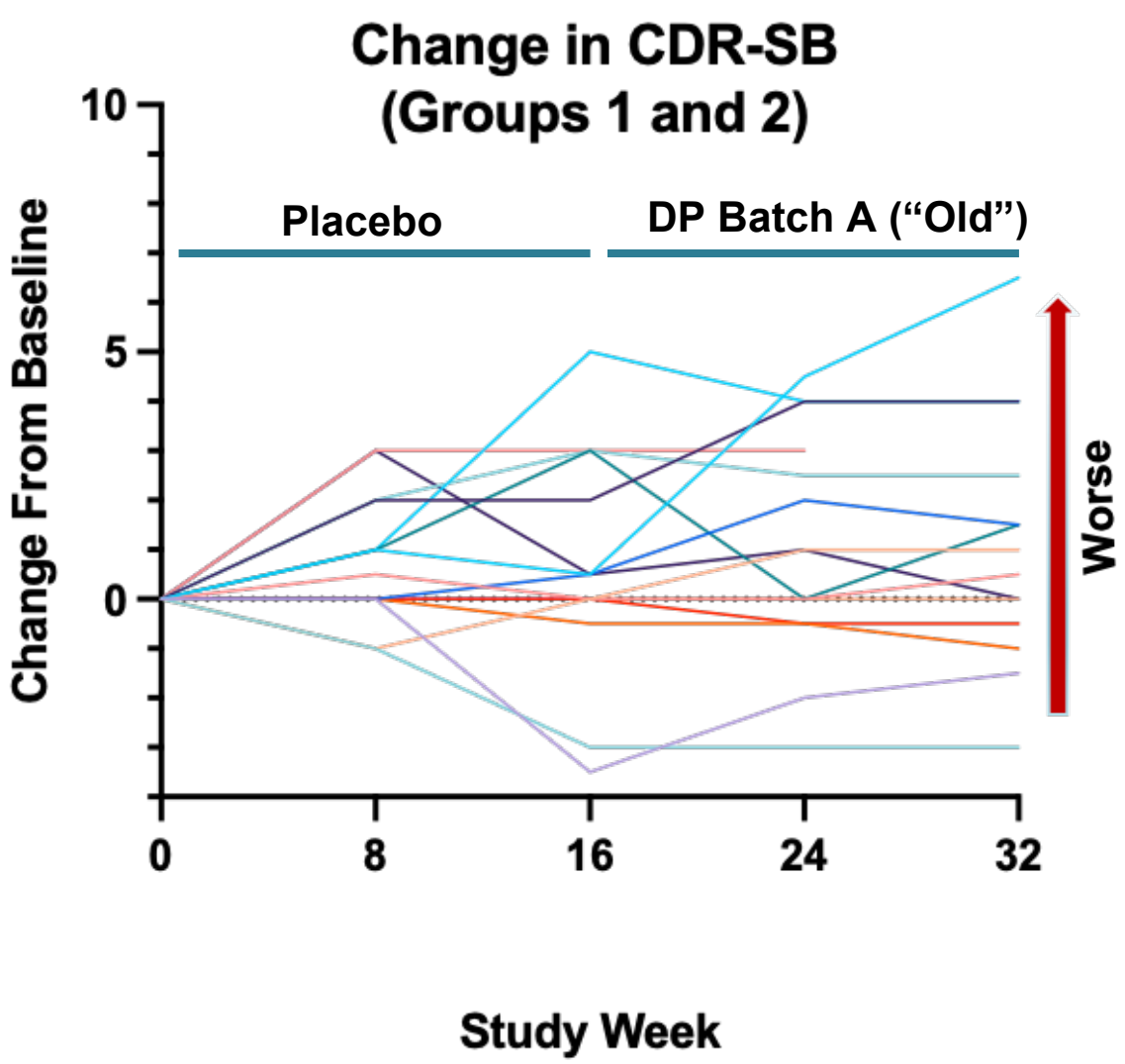
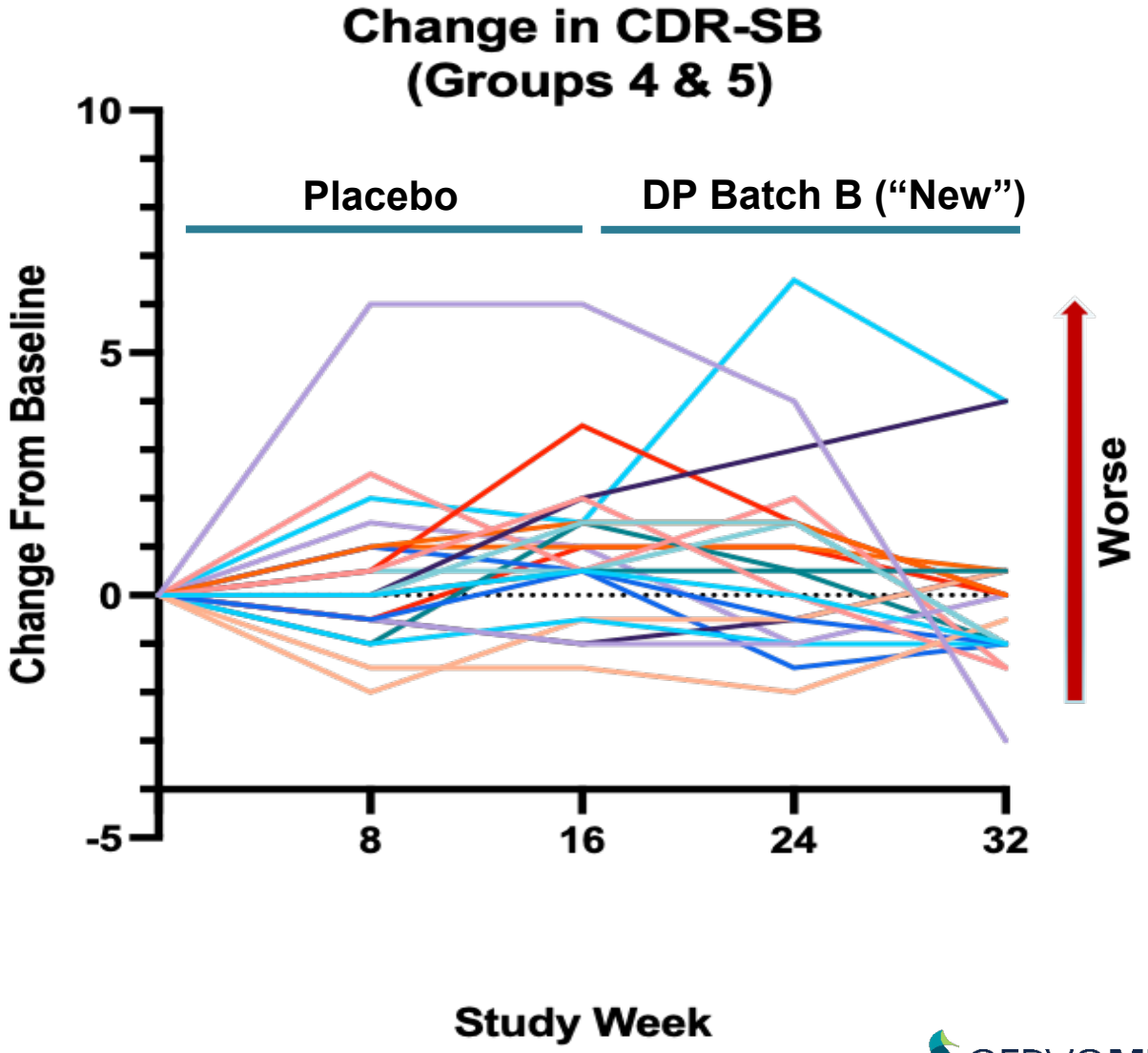
Optimal Ptau181 Cutoff for Phase 3

- Inclusion criteria in RewinD-LB was < 27.2 pg/mL (Quanterix v2.1 assay, which utilized different standard than prior version of assay, v.2.0)
  - Per 2023 data sheet of assay, corresponded to 2.4 pg/mL in v2.0, the cutoff specified in the protocol (vs. 2.2 pg/mL cutoff utilized to analyze phase 2a results), identified at the time as optimal cutoff for AD pathology for patients with DLB
- Large (N=1293) international multi-center validation study, published in June 2025[1], indicated that the ptau181 for having low likelihood of AD pathology in AD and non-AD dementia by CSF criteria is 21 pg/mL in v2.1 assay.
  - Sensitivity analysis of RewinD-LB efficacy in sub-set with ptau181< 21 pg/mL had been added to statistical analysis plan in February 2025
- Based on the validation study publication and the sub-set analysis, the ptau181 cutoff for phase 3 now planned to be 21 pg/mL
  - Target population (i.e. patients with DLB without AD pathology) remains at approximately 50% of overall DLB patient population (which is the % that are positive by CSF criteria for AD pathology)

[1]Doeke et al, *Alzheimer's & Dement*, 2025;21:e14573.

Individual Participant Change from Baseline in CDR SB in Those Who Received Placebo During Placebo-Controlled Phase of Study





1 Screening plasma ptau181 < 21 pg/mL (i.e., low likelihood of having AD pathology)

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