From Mechanisms to Medicines: Advancing Drug Development in Dementia With Lewy Bodies (DLB)

AD/PD 2026 Conference Symposium
March 20, 2026

Forward-looking statements

This presentation includes express and implied forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, regarding the intentions, plans, beliefs, expectations or forecasts for the future of the CervoMed Inc. (Company), including, but not limited to: the therapeutic potential of neflamapimod, including the degree of sustainability of any therapeutic effects and the meaningfulness of any correlation between any biomarker and clinical effects; the anticipated timing and achievement of clinical and development milestones, including the Company's announcement of additional data or any meeting or correspondence between the Company and any regulatory body; any other expected or implied benefits or results, including that any initial clinical results observed with respect to neflamapimod in the RewinD-LB trial will be replicated in later trials, including the Company's planned Phase 3 clinical trial of neflamapimod in patients with dementia with Lewy bodies (DLB); the timing of the initiation and readout of, and the design and endpoints of, any potential future trials, including the Company's planned Phase 3 clinical trial of neflamapimod in patients with DLB; the Company's need to acquire sufficient funding for any Phase 3 trial of neflamapimod in DLB and to otherwise fund its operations in the future; the timing of the Company's potential submission of a new drug application (NDA) or any other regulatory submission, if any, or any potential approval thereof; and the potential market for any DLB treatment that may be approved in the future. Terms such as "believes," "estimates," "anticipates," "expects," "plans," "aims," "seeks," "intends," "may," "might," "could," "might," "will," "should," "approximately," "potential," "target," "project," "contemplate," "predict," "forecast," "continue," or other words that convey uncertainty of future events or outcomes (including the negative of these terms) may identify these forward-looking statements. Although there is believed to be reasonable basis for each forward-looking statement contained herein, forward-looking statements by their nature involve risks and uncertainties, known and unknown, many of which are beyond the Company's control and, as a result, actual results could differ materially from those expressed or implied in any forward-looking statement. Particular risks and uncertainties include, among other things, those related to: the Company's available cash resources, the availability of additional funds on acceptable terms, and the Company's ability to continue as a going concern; the results of the Company's clinical trials; the likelihood and timing of any regulatory approval of neflamapimod or the nature of any feedback the Company may receive from any regulatory body; the ability to implement business plans, forecasts, and other expectations in the future; general economic, political, business, industry, and market conditions, inflationary pressures, and geopolitical conflicts; and the other factors discussed under the heading "Risk Factors" in the Company's Annual Report on Form 10-K for the year ended December 31, 2024 filed with the U.S. Securities and Exchange Commission (SEC) on March 17, 2025, and other filings that the Company may file from time to time with the SEC. Any forward-looking statements in this presentation speak only as of February 17, 2026 (or such earlier date as may be identified). The Company does not undertake any obligation to update such forward-looking statements to reflect events or circumstances after the date of this presentation, except to the extent required by law. Certain analyses reported herein are exploratory in nature; p-values and indications of statistical significance, along with 95% confidence intervals, are being reported to provide a measure of the probability that any differences identified between the samples are due to chance.

Disclaimers

- This activity is not accredited for CME
- The content is for informational purposes and may include discussion of investigational uses
- It is not intended to promote any specific product

Disclosures

- Neflamapimod is an investigational drug
- J. Alam is an employee of CervoMed Inc., the company developing neflamapimod
- N. Prins is a consultant for CervoMed Inc.

Our speakers

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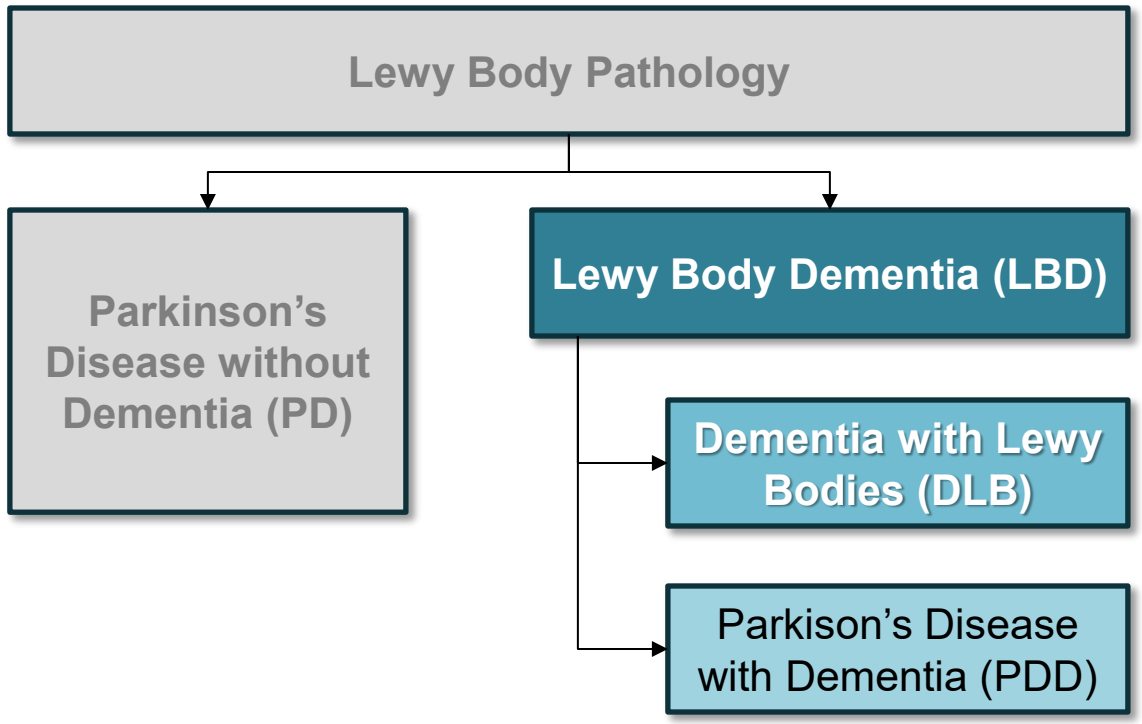
Role of The Basal Forebrain in the Pathology and Progression of Dementia with Lewy Bodies

Niels D. Prins, MD, PhD

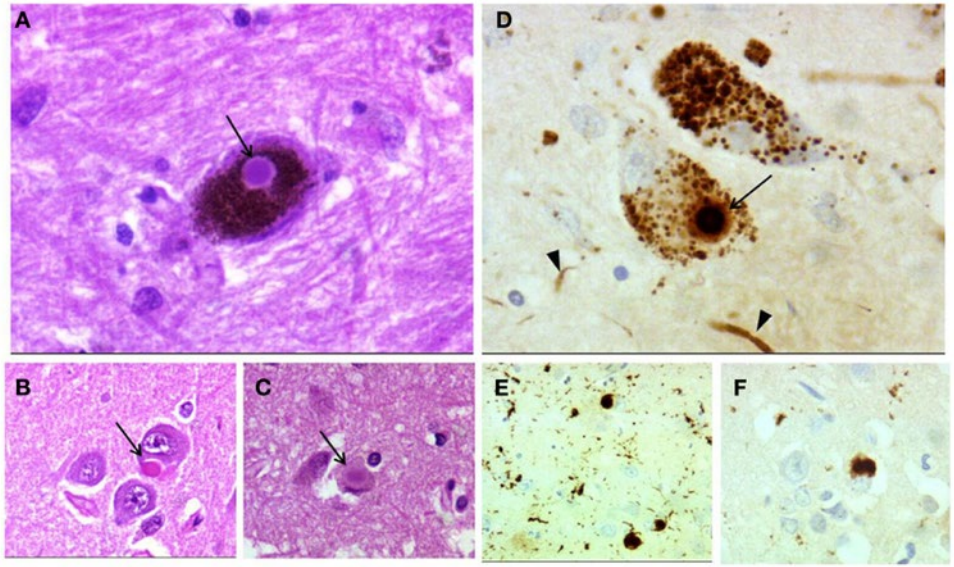
Lewy body dementia (LBD) is an umbrella term that covers 2 closely related diagnoses, dementia with Lewy bodies and Parkinson's disease dementia



Prevalence estimates of DLB range from 0% to 5% in the general population and from 0% to 30% of all dementia cases

Mol Neurodegener. 2025 Nov 3;20:117; Lancet Neurol. 2020 Feb;19(2):157-169. doi: 10.1016/S1474-4422(19)30153-X. Psychol Med. 2014 Mar;44(4):673-83; Can J Neurol Sci. 2016 Apr;43 Suppl 1:S83-95; Age Ageing. 2005 Nov;34(6):561-6; Zaccai J, McCracken C, Brayne C. A systematic review of prevalence and incidence studies of dementia with Lewy bodies. Age Ageing. 2005;34(6):561-566.

What is Dementia with Lewy bodies?



Dementia with Lewy bodies neuropathology

- Second most common neurodegenerative dementia after Alzheimer's disease (AD), affecting millions worldwide
- Characterized by presence of widespread cortical and subcortical Lewy bodies, which are made up of abnormal aggregates of misfolded α-synuclein
  - AD co-pathology is common in up to ~50% of patients
- Clinical diagnostic criteria are highly specific (>90%)
  - Biomarker confirmation typically not required
- High unmet clinical need
  - Significant impact on quality of life and caregiver burden
  - Progresses more rapidly than AD; average time from diagnosis to requiring nursing home care being 2 years

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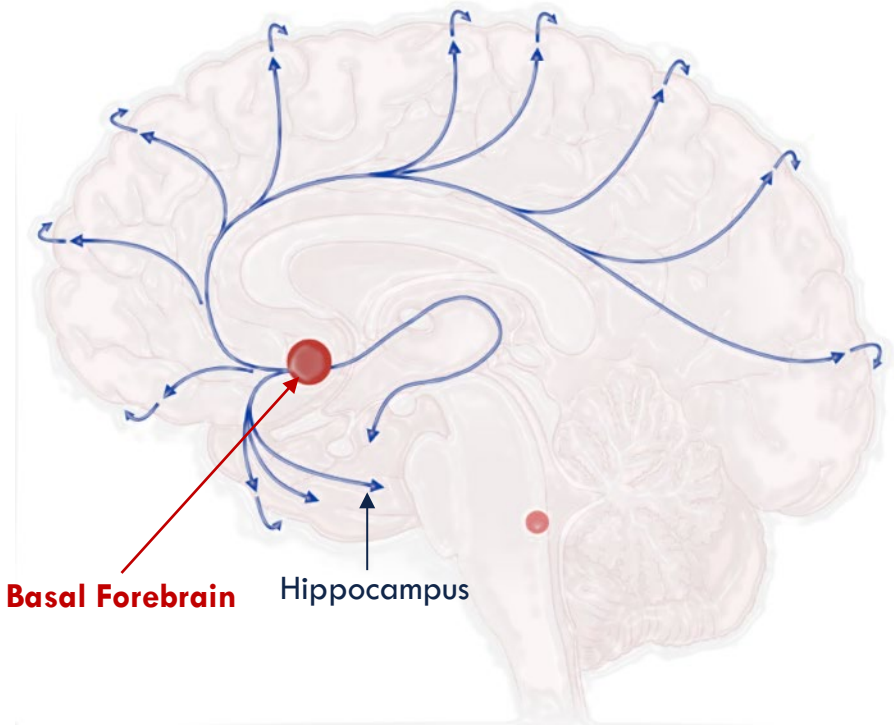
Clinically, DLB and AD differ in age of onset, symptomatology, and disease progression

	Demographics	Symptomology	Disease Progression
Dementia with Lewy Bodies	• Symptom onset 60s to mid-70s • Higher prevalence in males	• Deficits in executive function • Fluctuations in attention • Visual hallucinations • Parkinsonism • REM sleep behavior disorder	• Relative preservation of hippocampal volume and basal forebrain atrophy • Faster decline, higher mortality (avg, life expectancy of 3 to 5yrs)
Alzheimer's Disease	• Symptom onset as early as mid-60s but progressively increasing into 90s • Higher prevalence in females	• Profound impairment in episodic memory • Insomnia or fragmented sleep • Hallucinations and parkinsonism rare in early stages	• Prominent hippocampal atrophy • Slower, more consistent progression (avg. life expectancy of 4 to 10 yrs)

Neurology. 2017 Jul 4;89(1):88-100; Neurology. 2000 Mar 14;54(5):1050-8. Int. J. Geriatr. Psychiatry 24 1405–1412.; Alzheimer's Res. Ther. 10:19. 10.1186/s13195-018-0350-6; Lifelong Learning in Neurology. 2016;22(2 Dementia):435

In early stages of DLB, a major driver of disease expression and progression is dysfunction and degeneration of basal forebrain cholinergic neurons

Basal Forebrain Cholinergic Complex



- **Central hub for cognition and behavior**, providing cholinergic input to cortex and hippocampus that drives memory, executive function, mobility, and attention
- **Highly vulnerable to degeneration**, with progressive basal forebrain cholinergic loss documented across multiple neurological disorders
- **Mechanistically validated therapeutic target**, where restoring cholinergic function offers broad clinical impact in high-unmet-need indications

Disease processes in basal forebrain can be reversible

Adapted from Alam & Nixon, *Molecular Neurodegeneration*, 2023.

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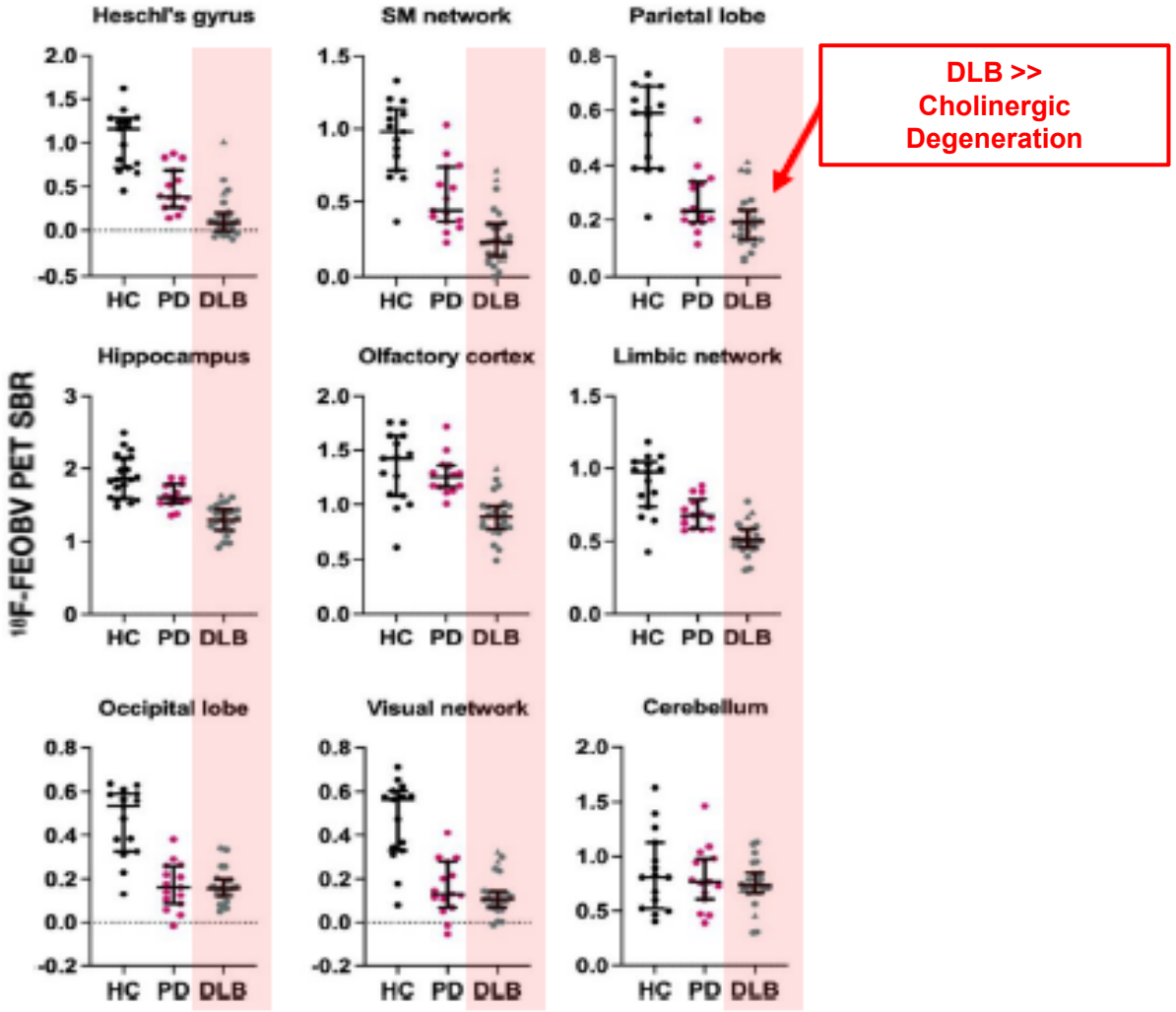
Patients with DLB have profound cholinergic degeneration

- Cholinergic degeneration is more widespread in DLB than PD
  - Aligns with earlier onset and more severe cognitive impairment
- Basal forebrain cholinergic degeneration correlates strongly with cognitive decline and attentional dysfunction in DLB
- Cholinergic dysfunction/degeneration and Lewy bodies are closely associated



Brain, Volume 146, Issue 9, September 2023, Pages 3690–3704. Adapted from Cantor Fitzgerald Research

DLB=dementia with Lewy bodies; PD= Parkinson's Disease; HC=health control

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The 2017 DLB clinical criteria are the widely accepted standard for clinical diagnosis and strongly correlate with autopsy-confirmed Lewy body pathology

- Specificity of the consensus clinical criteria against autopsy findings is high (≥90%)
- Clinical diagnosis of probable DLB based on presence of progressive dementia with ≥2 of the following core clinical features:
  - Fluctuating cognition
  - Visual hallucinations
  - Rapid Eye Movement (REM) sleep disorder
  - Parkinsonism, (i.e., certain movement problems seen in PD)
- Additional use of biomarkers/imaging can further support diagnosis

DLB remains underdiagnosed, with studies suggesting ~50% of cases are missed, often confused with Alzheimer's disease

Neurology. 2017 Jul 4;89(1):88-100; Neurology. 2000 Mar 14;54(5):1050-8. Int. J. Geriatr. Psychiatry 24 1405–1412.; Alzheimer's Res. Ther. 10:19. 10.1186/s13195-018-0350-6; Lifelong Learning in Neurology. 2016;22(2 Dementia):435

The Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) is a valid, sensitive tool that captures both cognitive and functional decline in patients with DLB

- "Gold standard" for evaluating severity & progression of dementia that evaluates both cognition and function
  - Established as the primary endpoint of choice for Phase 3 clinical trials in Early AD
- Clinical endpoint of choice in DLB:
  - Recent published studies have established CDR-SB as the clinical endpoint that most effectively captures clinical progression in DLB
  - Cognitive tests (e.g., MMSE, verbal list recall) impacted by cognitive fluctuations, while CDR-SB is not
  - Global measures such as CDR-SB inherently perform better than domain specific measures in DLB

Clinical Dementia Rating Sum of Boxes (CDR-SB, Total Score = 0-18)

Cognitive Domains:

- Memory (0-3)
- Orientation (0-3)
- Judgement and Reasoning (0-3)

Functional Domains:

- Community Affairs (0-3)
- Home & Hobbies (0-3)
- Personal Care (0-3)

Neurol Ther. 2025 Sep 19;14(6):2327–2344; Alzheimer's Res Ther. 2024 Dec 20;16(1):270; Neurol Ther 12, 177–195 (2023)

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There are no therapies that slow or stop the target the underlying causes of DLB; current strategies focus on treating symptoms

Current Treatment Landscape

- No approved DLB therapies in the US or EU; current treatment focuses on managing symptoms
- Acetylcholinesterase inhibitors are the mainstay of treatment
  - Provide transient improvement in cognition, but no improvement in motor function
- Carbidopa-levodopa may help with parkinsonism symptoms and slowness, though may worsen hallucinations
- Other treatments, including supportive care, physical therapy, and behavioral interventions, may also be used

There are no treatments that slow or stop the target the underlying causes of DLB; current strategies focus on reducing helping symptoms

Company	Drug	MoA	Category	Indication	Stage	Clinicatrials.gov	Primary Outcome
CervoMed	Neflamapimod	P38α inhibitor	Small molecule	DLB without AD co-pathology	P3	NCT05869669	Change in CDR-SB
AriBio (pvt)	AR1005	Voltage-gated sodium channel inhibitor	Small molecule	Lewy body dementia (incl DLB or PD)	P2	NCT06537076 (South Korea only)	Change in CDR- SB
Cognition Tx	Zervimesine	Sigma-2-receptor agonist	Small molecule	DLB Psychosis	P2	NCT05225415	Safety/ tolerability
Acadia	ACP-204	5HT2A inverse agonist	Small molecule	Lewy body dementia psychosis (incl. DLB or PD)	P2	NCT07029581	Change in SAPS-LBDP
Eli Lily	Donanemab	Anti amyloid	Monoclonal Antibody	DLB with AD co-pathology	P2	Not Listed	Change in CDR-SB

Lewy body pathology can co-exist with AD pathology (Aβ & tau), influencing clinical symptoms and progression of DLB

DLB without AD Co-Pathology (~50% of All DLB Patients)

Without biomarker evidence of AD (e.g., negative amyloid or tau PET scan, no elevation of phosphorylated tau in CSF or blood)

Disease primarily of synaptic dysfunction in basal forebrain, with no to limited neuronal loss in hippocampus

Have a reversible component of disease

DLB with AD Co-Pathology (~50% of All DLB Patients)

Have biomarker evidence of AD (e.g., positive amyloid or tau PET scan, elevated phosphorylated tau in CSF or blood)

More advanced disease with significant neuronal loss in hippocampus

Have primarily irreversible deficits

Effectively treating synaptic dysfunction can rapidly lead to significant clinical effects in DLB without AD co-pathology

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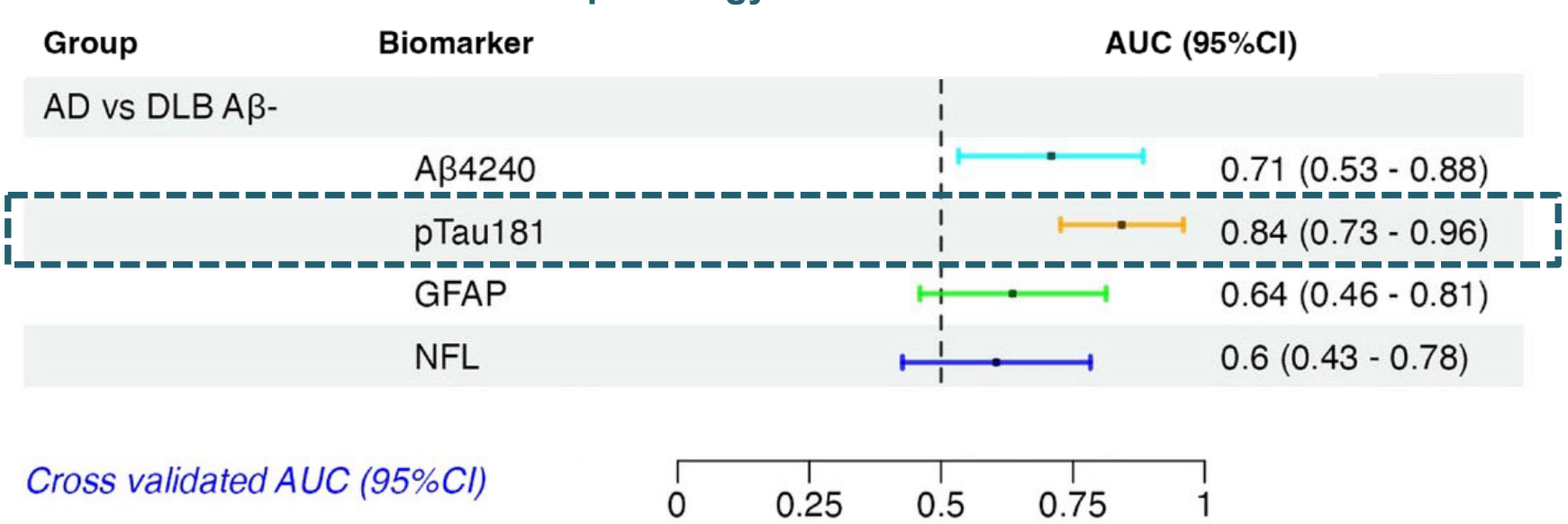
Plasma levels of phosphorylated Tau (pTau) can identify DLB patients with and without AD co-pathology; an important biomarker for clinical trials

- In a 2025 study (N = ~1,300 patients), plasma pTau181 levels were shown to differentiate patients with AD from those with DLB w/o AD co-pathology
  - DLB patients w/o AD co-pathology demonstrate minimal plasma pTau181 signal
  - Plasma pTau181 demonstrates strong ability (AUC 0.84) to discriminate AD from the DLB w dementia

Internal cross-validation AUC (95% CI) values for the DLB w/o AD co-pathology vs. AD controls



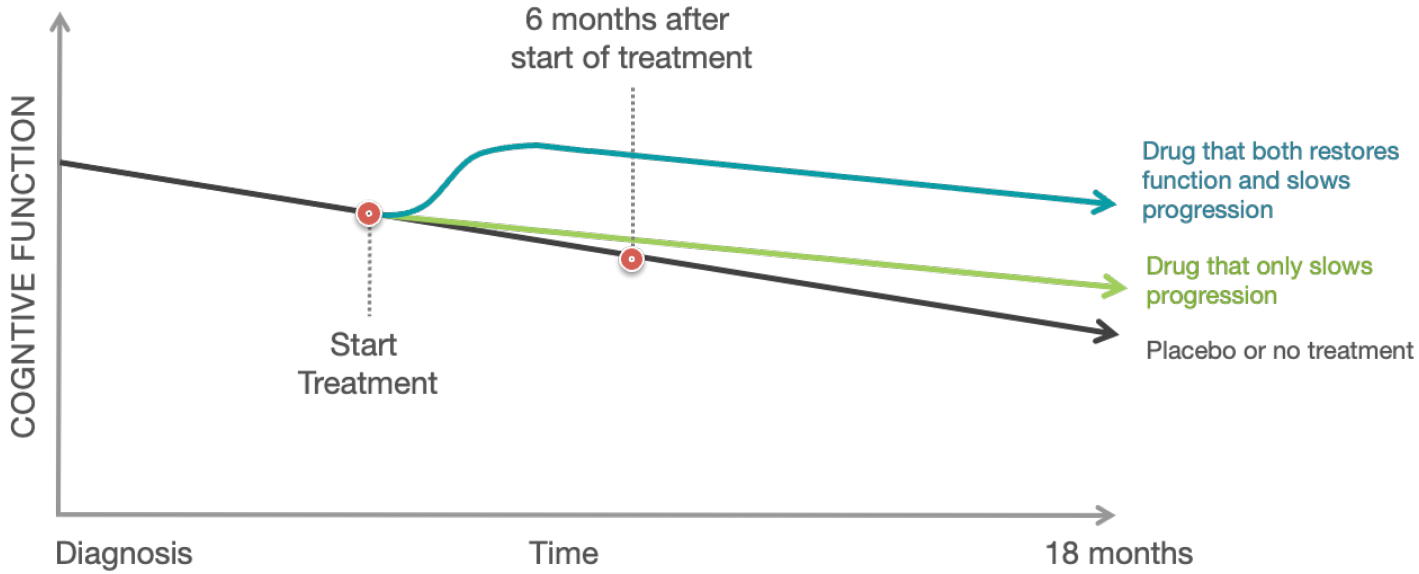
Separation between AD and DLB w/o AD co-pathology patients using plasma pTau181

Alzheimers Dement. 2025 Jun;21(6):e14573.

Why target synaptic dysfunction and the basal forebrain in neurodegenerative diseases?

- In DLB, synaptic dysfunction in the cholinergic system is a driver of clinical symptoms and disease progression
- As symptoms are due to synaptic dysfunction, and not frank neuronal loss, the neurodegenerative process in the basal forebrain is reversible through the earlier stages of disease

Reversing Synaptic Dysfunction Provides Ability to Demonstrate Efficacy in a 6-9 Month Clinical Study Duration



Nature Medicine, 15(3), 331–337; Journal of Comparative Neurology, 439(2), 221–234; Expert Review of Neurotherapeutics, 3(1), 95–105

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Involvement of p38 MAP Kinase in Basal Forebrain Cholinergic Dysfunction & Degeneration and Neflamapimod Development

John J. Alam, MD

Agenda

- Provide scientific rationale for targeting BFCN dysfunction & degeneration with a p38α kinase inhibitor
- Review data demonstrating preclinical proof-of-concept for neflamapimod to treat BFCN dysfunction & degeneration
- Review the results of mechanistic studies conducted in the clinic
- Ask two questions regarding the clinical trial results in DLB:

1. Are the clinical data when stratified by plasma pTau181 (measure of presence or absence AD co-pathology) consistent neflamapimod with acting on BFCN dysfunction and degeneration?
2. Are the PK-PD relationships (concentration-effect relationships) for clinical and biomarker effects consistent with the presumed mechanism of action?

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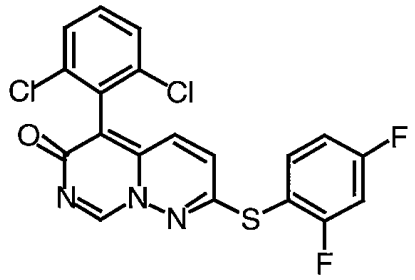
Neflamapimod is an oral, small molecule drug that selectively inhibits p38α, a key driver of neuroinflammation and synaptic dysfunction in the basal forebrain



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-1β 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 dementia.

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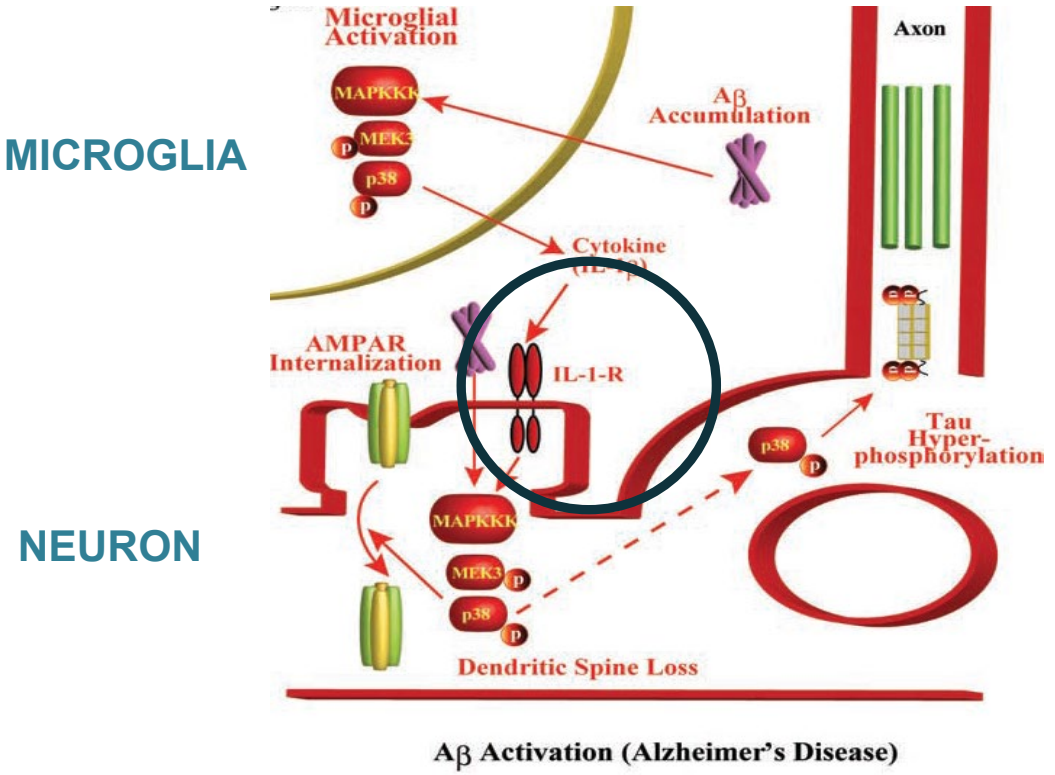
Scientific Rationale

Molecular target of neflamapimod: Alpha isoform of p38 MAP (p38α) kinase

- An intracellular enzyme that plays critical player in modulating cellular response to cellular injury, infection, and other environmental stress
- In immune cells in both periphery and in the brain, p38α upregulates cytokine production (i.e., it is pro-inflammatory)
- In neurons, there is distinct biology, where p38α plays dominant role (over p38β) in regulating stress response, and is only turned on during disease or other stress to neurons



Aβ Activation (Alzheimer's Disease)

Yasuda et al 2011

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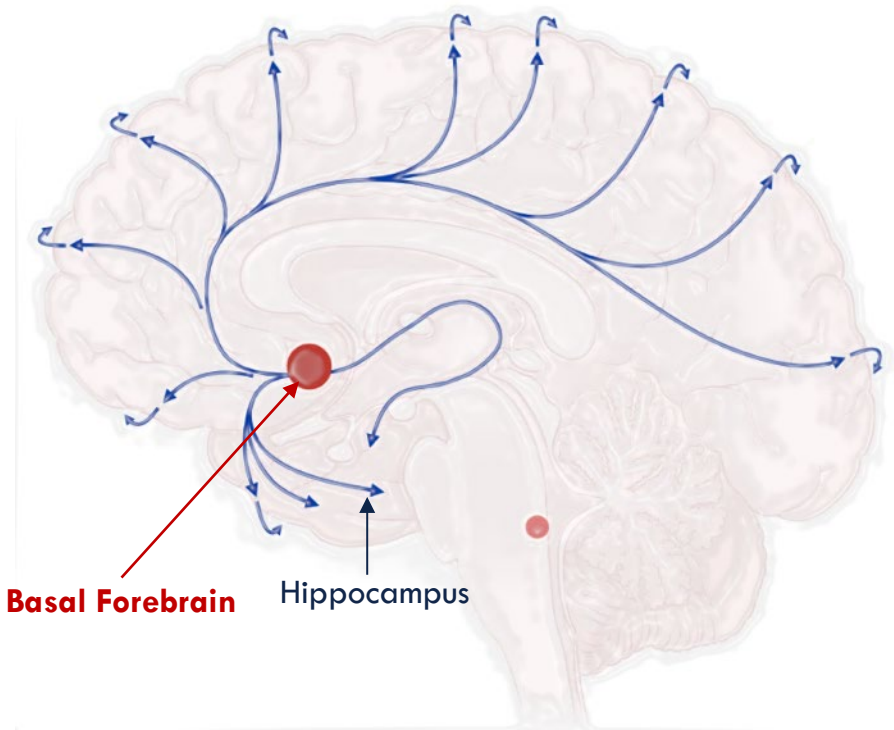
Dysfunction and degeneration of BFCNs is a major driver of disease expression and progression in DLB

Basal Forebrain Cholinergic Complex



Targets for drug development

- **Neuroinflammation/IL-1β**
  - LPS & other inflammatory stimuli reduce BFCN function via IL-1b
  - Pro-inflammatory IL-1β signaling induces synaptic dysfunction
  - IL-6 overexpression in vivo leads to loss of BFCNs
- **Lewy bodies/α-synclein**
  - In multiple clinical translational studies Lewy body pathology or synclein seed amplification (SAA) positivity is associated with basal forebrain atrophy
- **APP/amyloid pathology**
  - Down syndrome (DS) mice develop basal forebrain cholinergic neuron loss, which is prevented by targeting APP
  - Optogenetic stimulation of cholinergic neurons in basal forebrain reverses behavioral deficits in APP/PS1 mice
  - Earliest pathology in FAD/PSEN carriers/patients
  - Additive to Lewy body pathology for basal forebrain atrophy by MRI in AD

Disease processes in basal forebrain can be reversible

Adapted from Alam & Nixon, *Molecular Neurodegeneration*, 2023.

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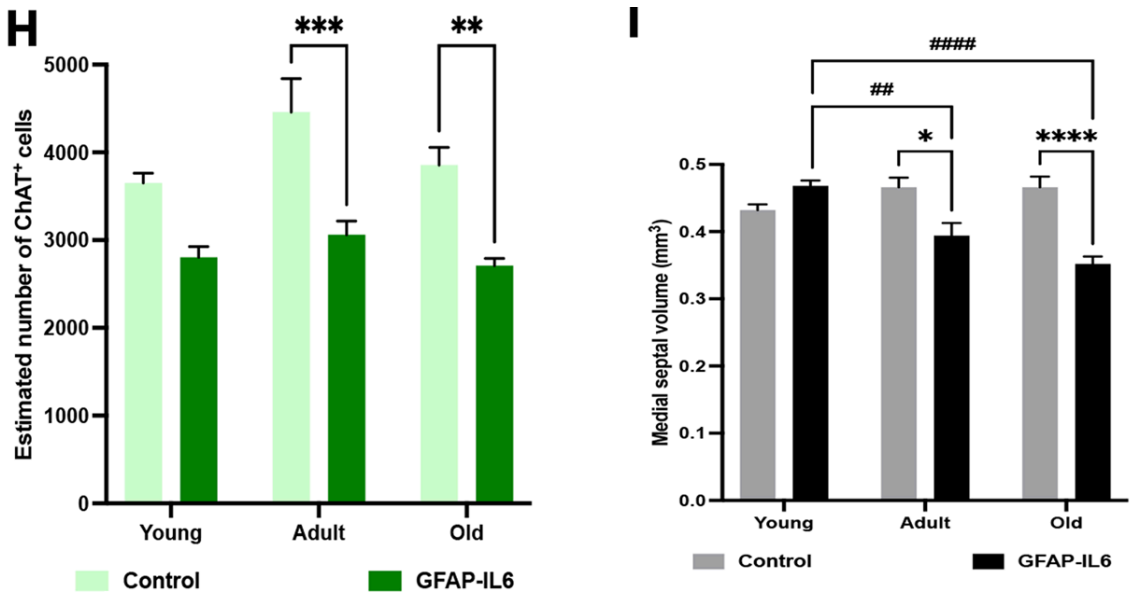
RESEARCH Open Access

Chronic neuroinflammation during aging leads to cholinergic neurodegeneration in the mouse medial septum

Rashmi Gamage[1†], Ilaria Rossetti[1†], Garry Niedermayer[2], Gerald Münch[1], Yossi Buskila[1†] and Erika Gyengesi[1*†]



Neuropathologic features associated with basal forebrain atrophy in Alzheimer disease

Stefan J. Teipel, MD, H.-Christian Fritz, BSc, and Michel J. Grothe, PhD, for the Alzheimer's Disease Neuroimaging Initiative

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Neurology® 2020;95:e1301-e1311. doi:10.1212/WNL.0000000000010192

Schumacher *et al. Alzheimer's Research & Therapy* (2025) 17:28
https://doi.org/10.1186/s13195-025-01678-x

Alzheimer's Research & Therapy

RESEARCH Open Access

Association of Alzheimer's and Lewy body disease pathology with basal forebrain volume and cognitive impairment

Julia Schumacher[1,2*], Stefan Teipel[2,3] and Alexander Storch[1,2]

JAMA Neurology | Original Investigation

MRI Signature of α-Synuclein Pathology in Asymptomatic Stages and a Memory Clinic Population

Laura E. M. Wisse, PhD; Nicola Spotorno, PhD; Marcello Rossi, PhD; Michel J. Grothe, PhD; Angela Mammana, PhD; Pontus Tideman, MSc; Simone Baiardi, MD, PhD; Olof Strandberg, PhD; Alice Ticca, MSc; Danielle van Westen, MD, PhD; Niklas Mattsson-Carlgren, MD, PhD; Sebastian Palmqvist, MD, PhD; Erik Stomrud, MD; Piero Parchi, MD, PhD; Oskar Hansson, MD, PhD; for the Alzheimer's Disease Neuroimaging Initiative

"In this cohort study, SAA α-syn+ was consistently associated with NBM atrophy already during asymptomatic stages. Further, in memory clinic populations, SAA α-syn+ was associated with NBM atrophy, which partially mediated α-syn–induced attention/executive impairment."

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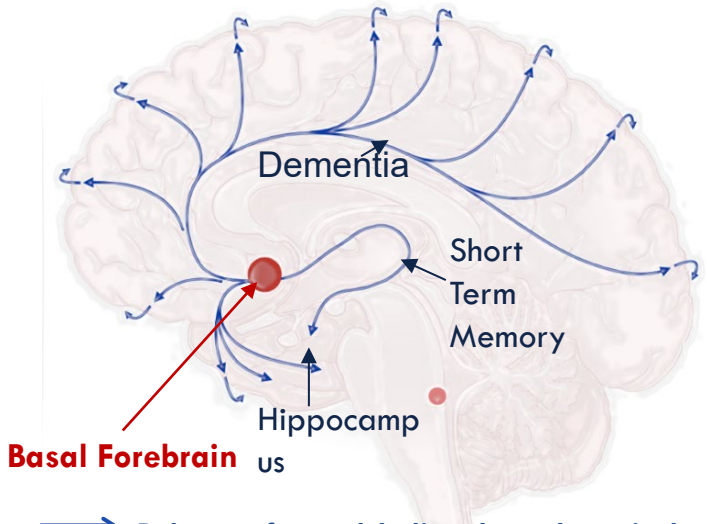
Neflamapimod mechanism of action

Basal Forebrain Cholinergic Complex

A major site of pathology in DLB



→ **Release of acetylcholine through cortical connections modulate cognitive and motor tasks**

Neuroinflammation (IL-1β),
Aggregated Proteins (*e.g.*, Aβ, α-synuclein, TDP-43)

↓

p38α ⊣ (-) **Neflamapimod**

↓

↑Rab5

↓

Endolysosmal Dysfunction, Tau Aggregation

↓

Defects in Axonal Transport, impaired NGF Signaling

↓

Cholinergic Dysfunction & Degeneration

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. Adapted from Alam & Nixon, *Molecular Neurodegeneration, 2023*. NGF: Nerve Growth Factor.

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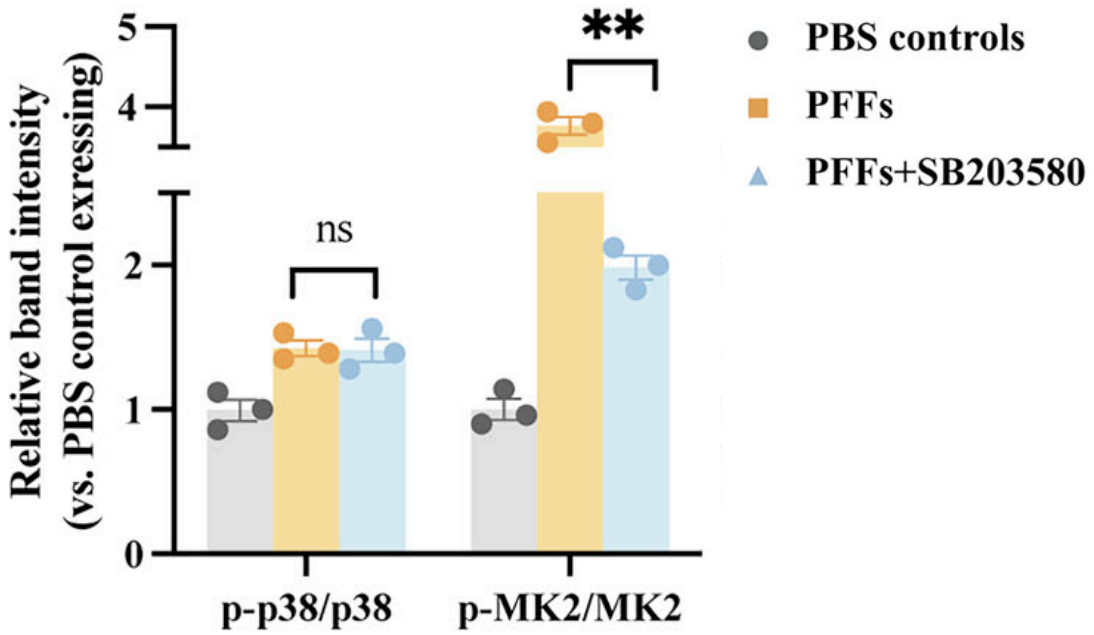
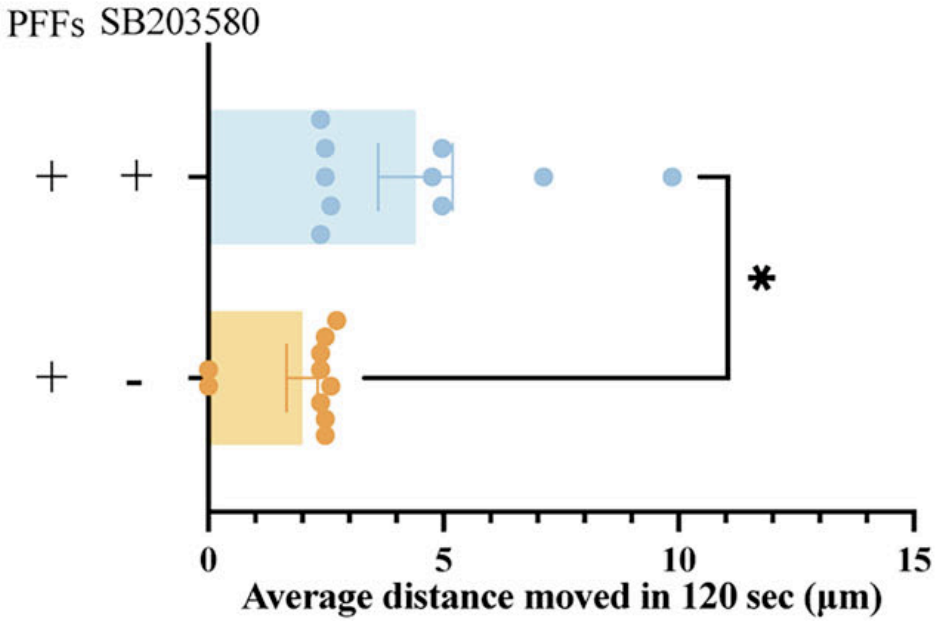
p38 MAPK inhibition ameliorates axonal transport defects induced by α-synuclein

Target engagement in rat cortical neuron axons



Antegrade mitochondrial transport in rat cortical neuron axons



PFF – pre-formed fibrils ; SB203850 – tool p38 MAPK inhibitor

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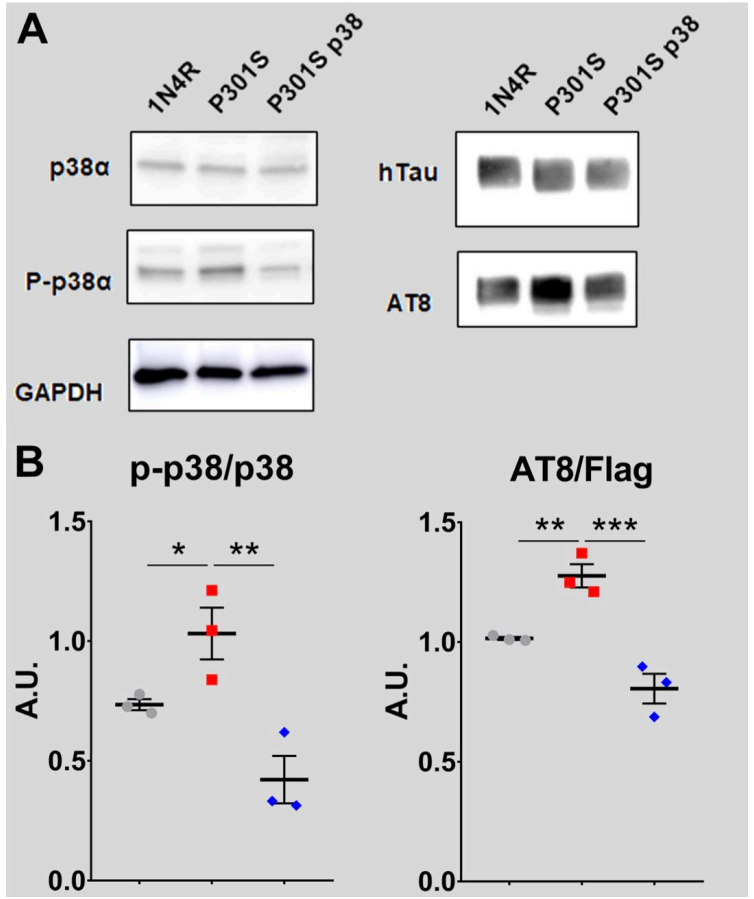
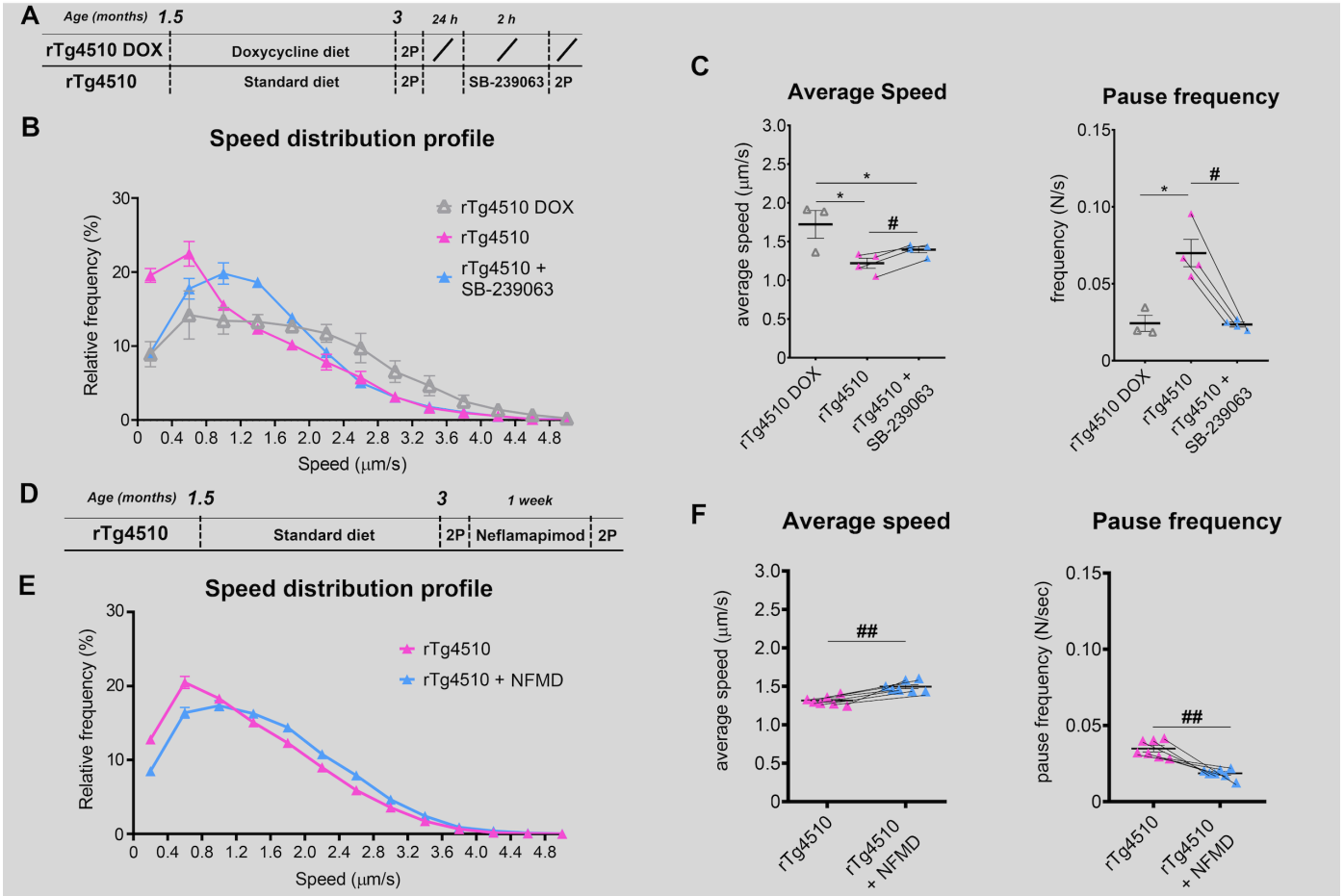
P38α has a role in the development of axonal transport defects induced by mutant tau in mouse tauopathy model

P301S tau is hyperphosphorylated and sensitive to p38α inhibition



In vivo axonal transport of BDNF secretory granules is impaired in rTg4510 mice and enhanced by treatment with p38α inhibitors



Moretto et al, Abstract #2438, AD-PD Conference 2024

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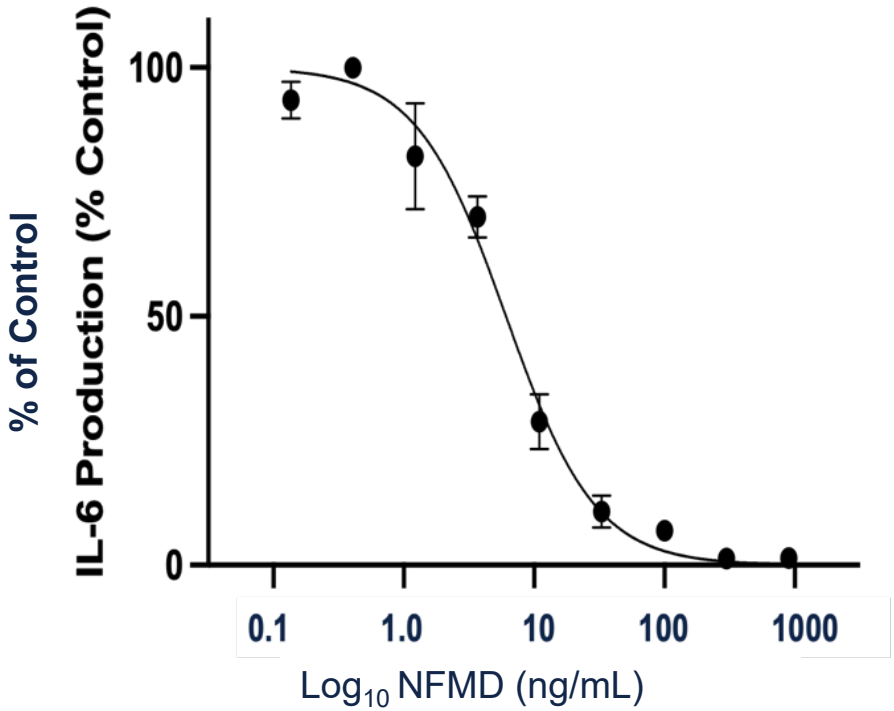
Demonstration of Pre-Clinical Proof-of-Concept

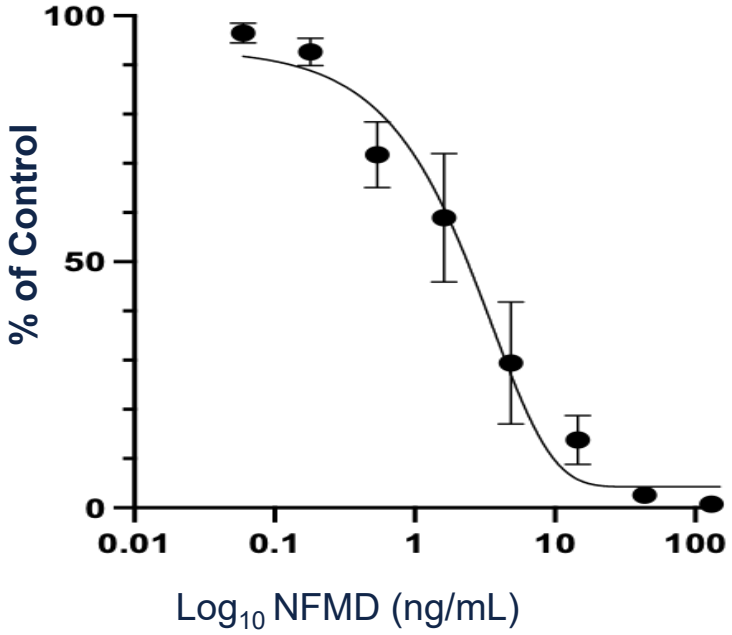
Neflamapimod potently inhibits pro-inflammatory Interleukin-1 beta (IL-1β) signaling

In Vitro: IL-1β stimulated IL-6 Production from human PBMCs



In vitro EC50 (n=5) = 2.7 ± 0.6 ng/mL

In Vitro: IL-1β stimulated IL-8 Production from human PBMCs



In vitro EC50 (n=5) = 3.1 ±1.4 ng/mL

CervoMed, Inc Data on File; PBMCs – peripheral blood mononuclear cells

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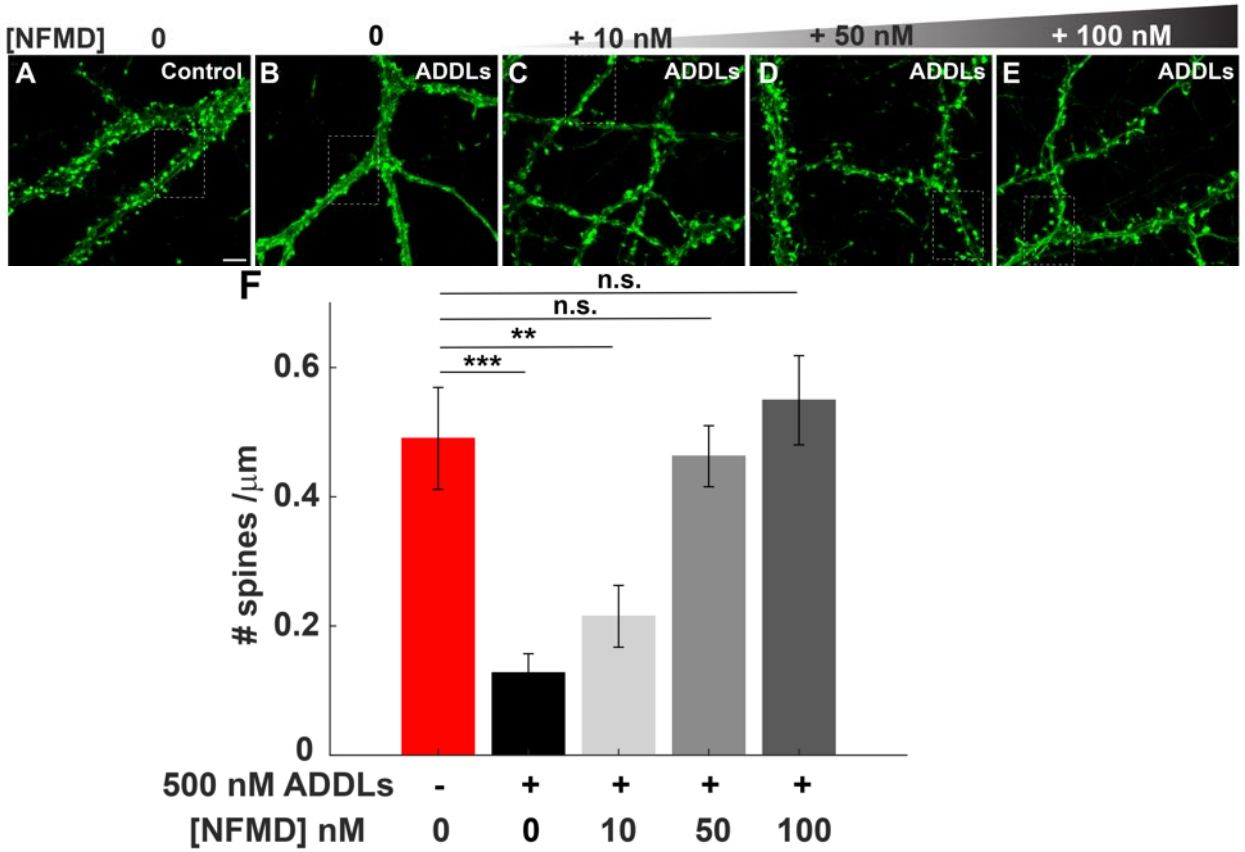
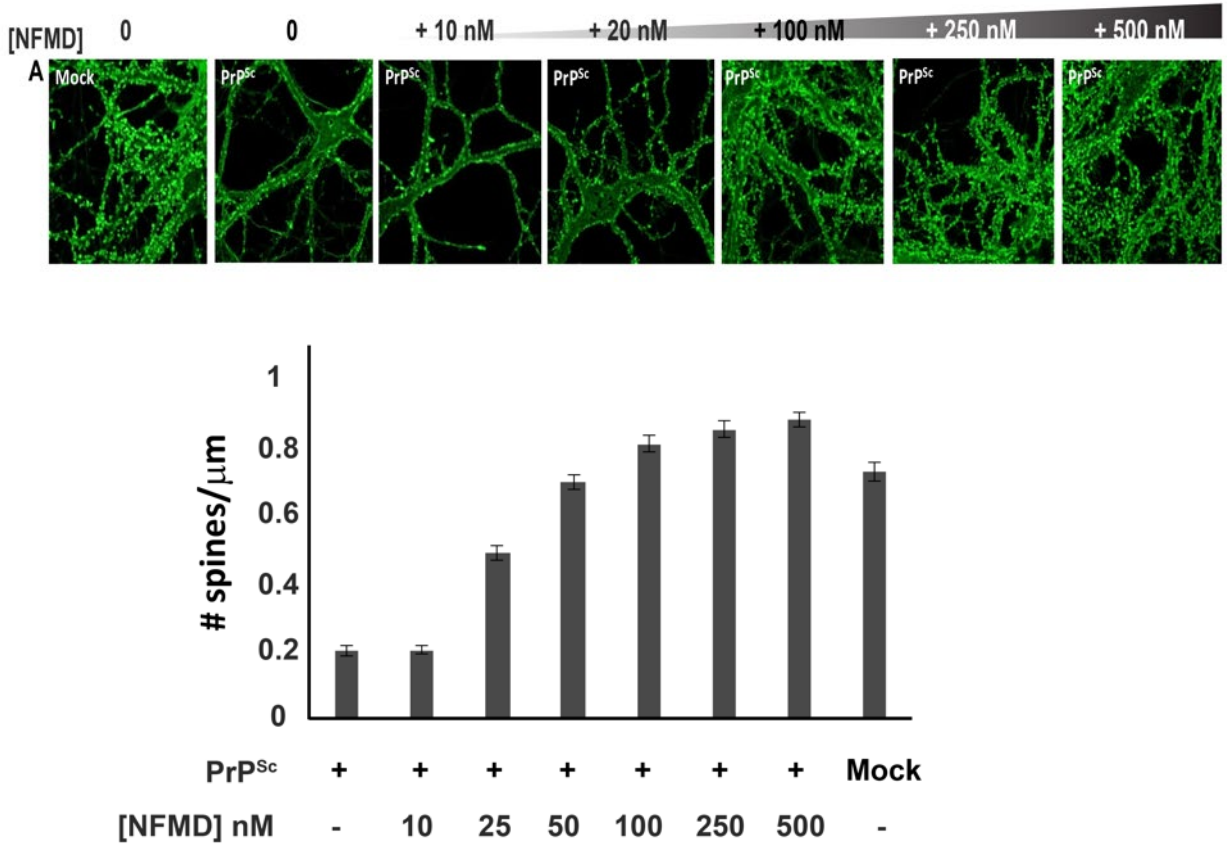
Neflamapimod potently inhibits dendritic spine retraction in mouse hippocampal neurons induced by aggregated proteins

Amyloid-β Derived Diffusible Ligand (ADDL)



PrP^{Sc} (Infectious form of prion protein)

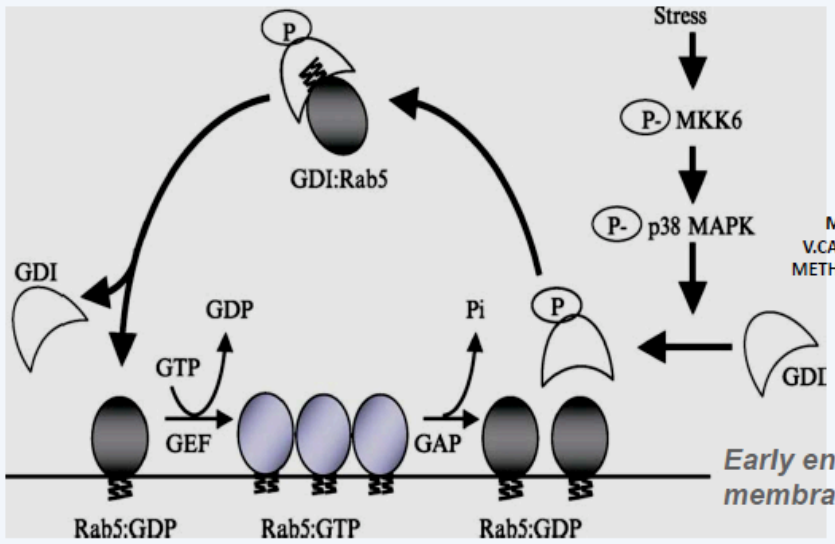


Amin L, Le NTT, Mercer RCC, German U, Alam J, Harris DA, AAIC, 2019

CERVOMED

Neflamapimod reverses Rab5 associated endosomal abnormalities

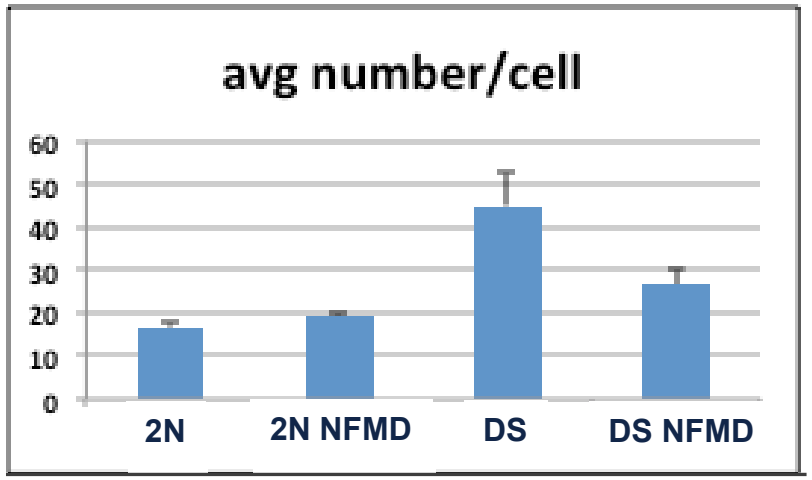
P38α is a Key Regulator of Rab5 Activity

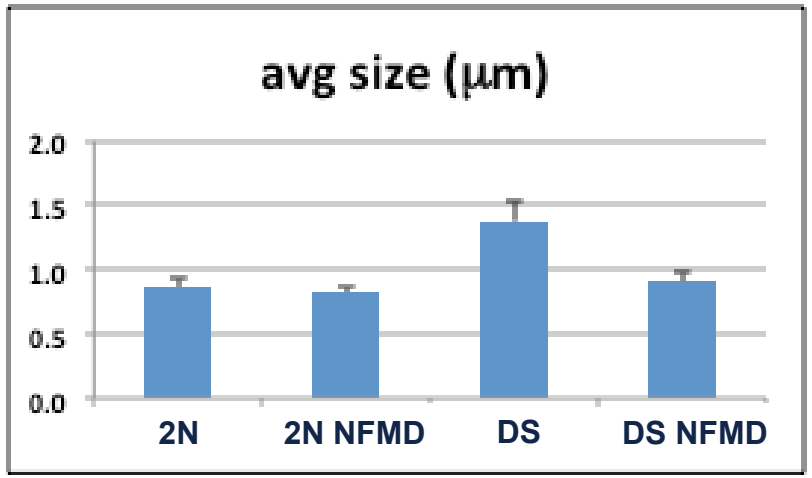


M. FELBERBAUM-CORTI, V.CAVALLI, and J. GRUENBERG METHODS IN ENZYMOLOGY, VOL. 403

P-p38 phosphorylates Ser^{121} of GDI, promoting removal of Rab5-GDP on endosomes and increasing re-activation of Rab5 by recruitment of cytosolic Rab5-GDP to endosomes resulting in increased endocytosis. (Cavalli *et al.*, 2001)

EAA1 positive Endosomes in Human Wild-Type (2N) or Down Syndrome (DS) Fibroblasts





CERVOMED

Neflamapimod reverses pathology and restores function in mice that develop basal forebrain cholinergic degeneration

Down Syndrome (DS) mice

- Ts2 transgenic mice that have both DS-like defects during early development and adult-onset basal forebrain cholinergic degeneration
- Treated with vehicle or 3 mg/kg neflamapimod (NFMD) BID x 28 days, starting at month 6

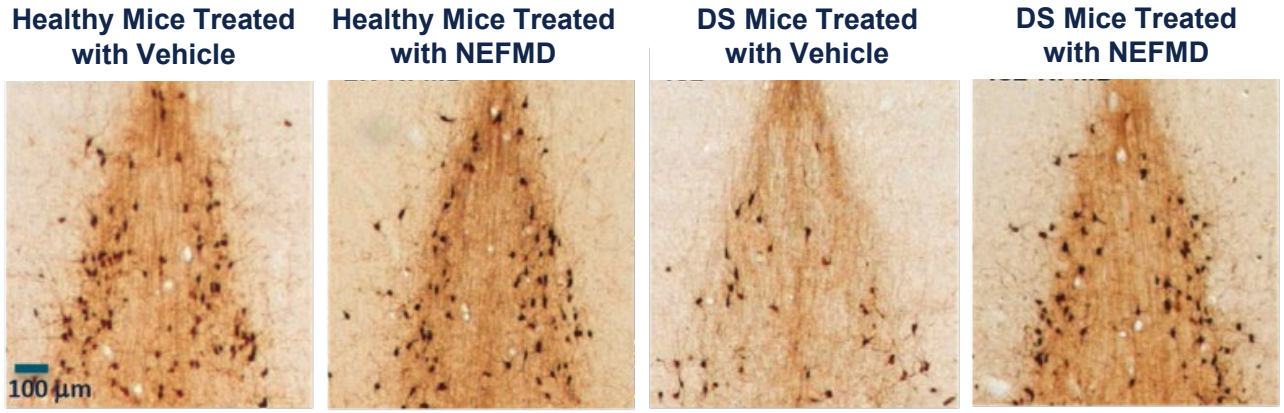
Reversed basal forebrain cholinergic neuron loss and restored cholinergic function

- Significantly increased number of cholinergic neurons in basal forebrain
- Normalized performance in Open field and NOR behavioral tests

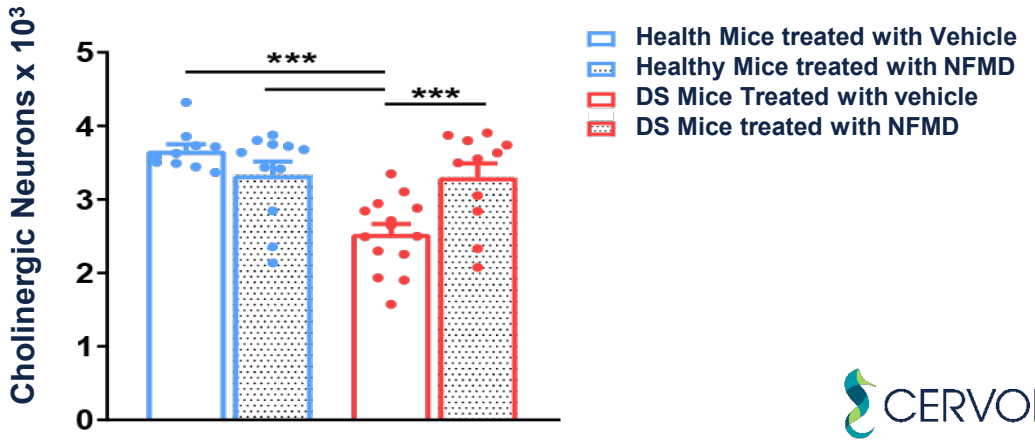
Mechanism of action well defined

- Significantly reduced Rab5 activity and BACE1 / b-CTF protein level
- Reversed Rab5+ endosomal pathology
- Normalized level of phosphorylated p38a and reduced levels of its downstream substrates MK2 and MNK1

Cholinergic (ChaT expressing) neurons in basal forebrain



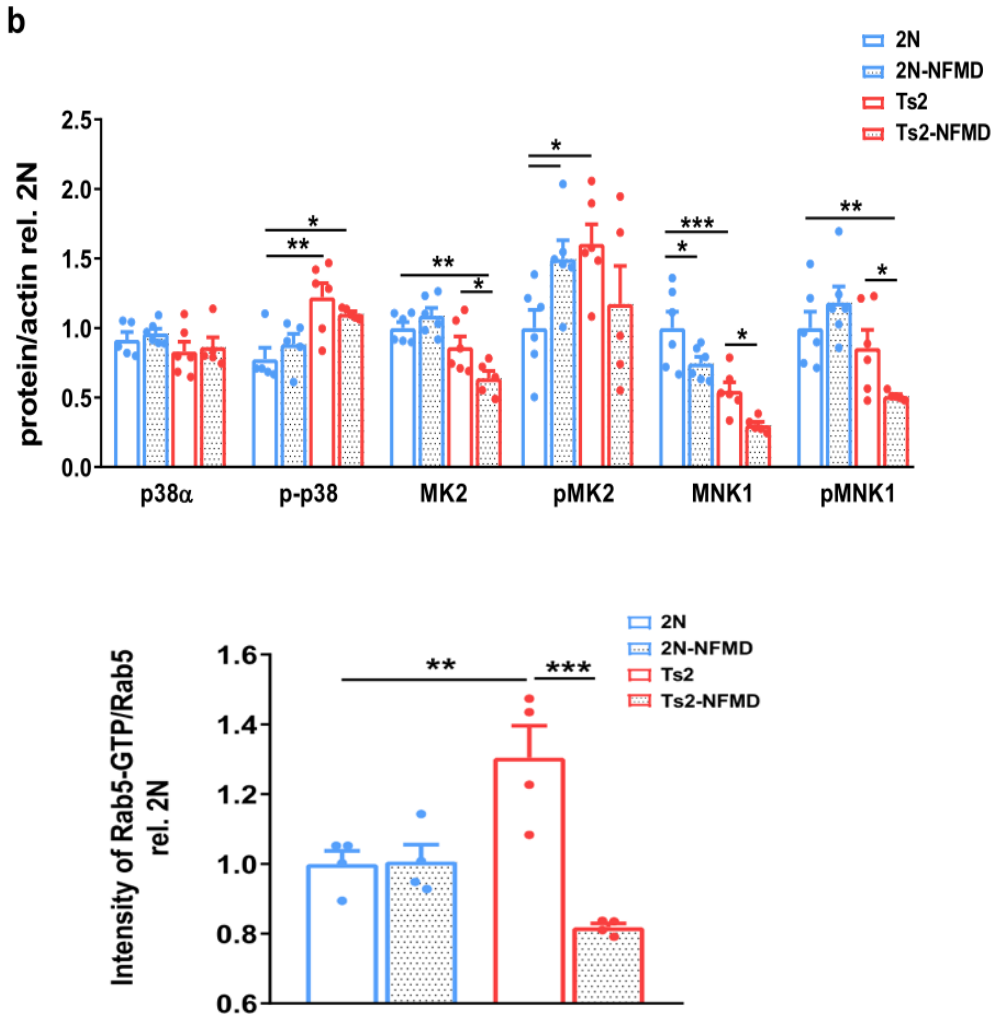
NFMD-treated DS mice show >30% increase in cholinergic neurons compared to vehicle-treated DS mice (*p<0.001)**

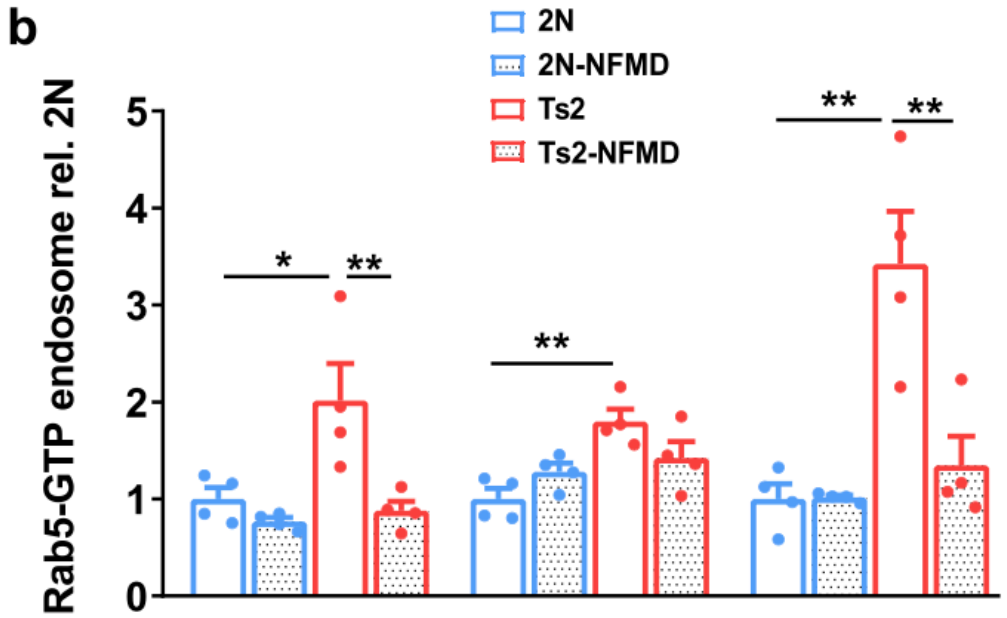


Jiang, Alam et al, Nature Communications volume 13, Article number: 5308 (2022)

CERVOMED

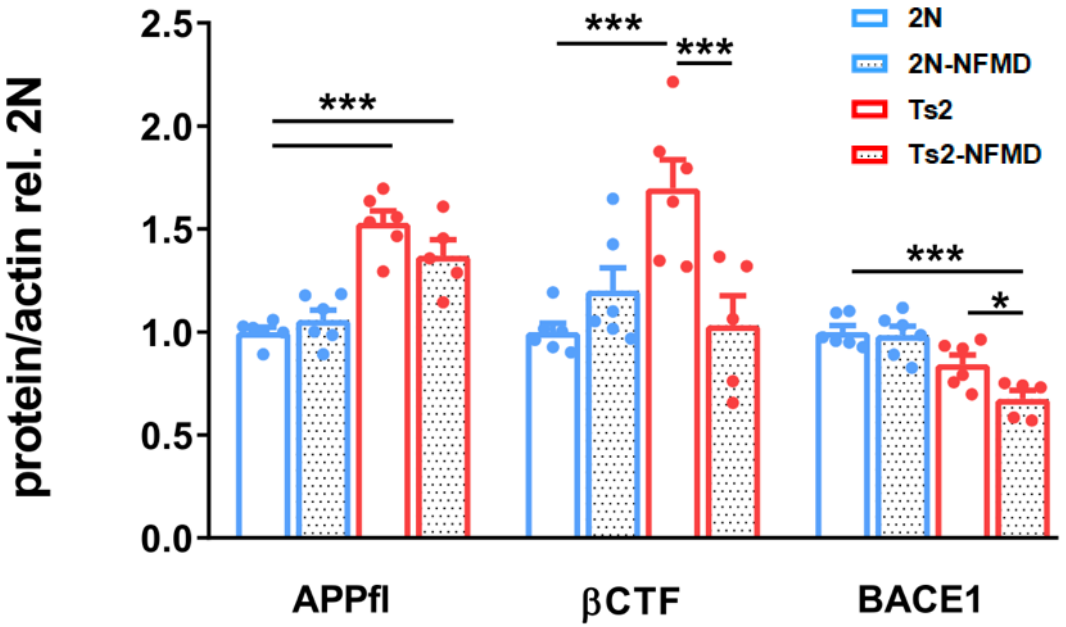
Neflamapimod demonstrates target engagement and reverses endosomal abnormality in preclinical model

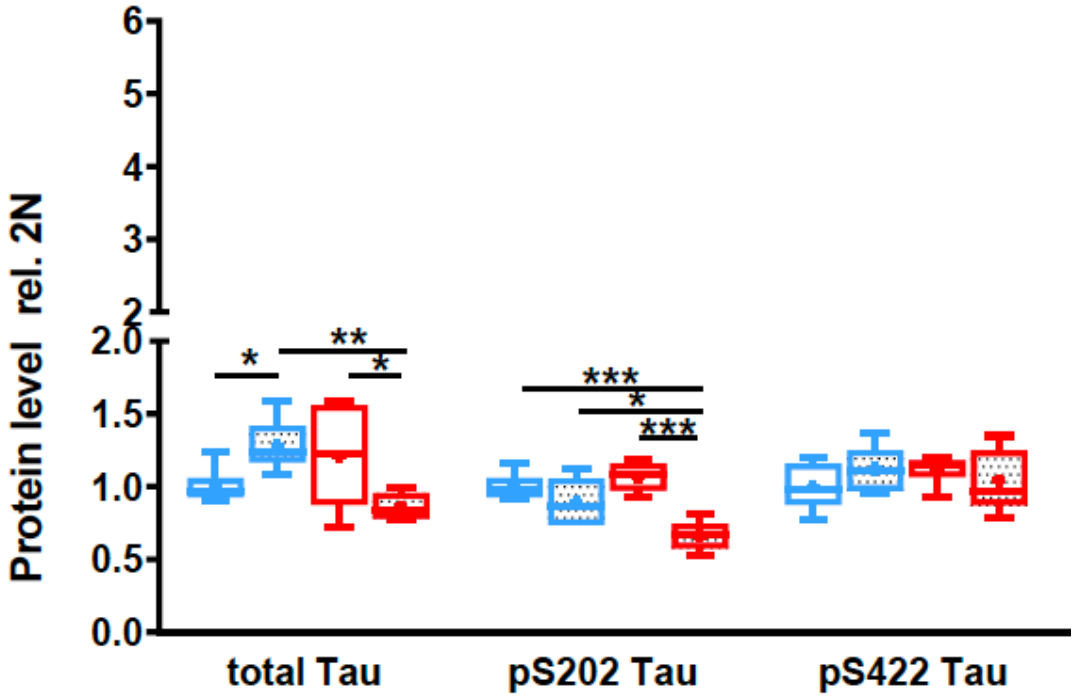




Jiang, Alam et al, Nature Communications volume 13, Article number: 5308 (2022)

Neflamapimod demonstrates impact on key pathogenic targets in preclinical model

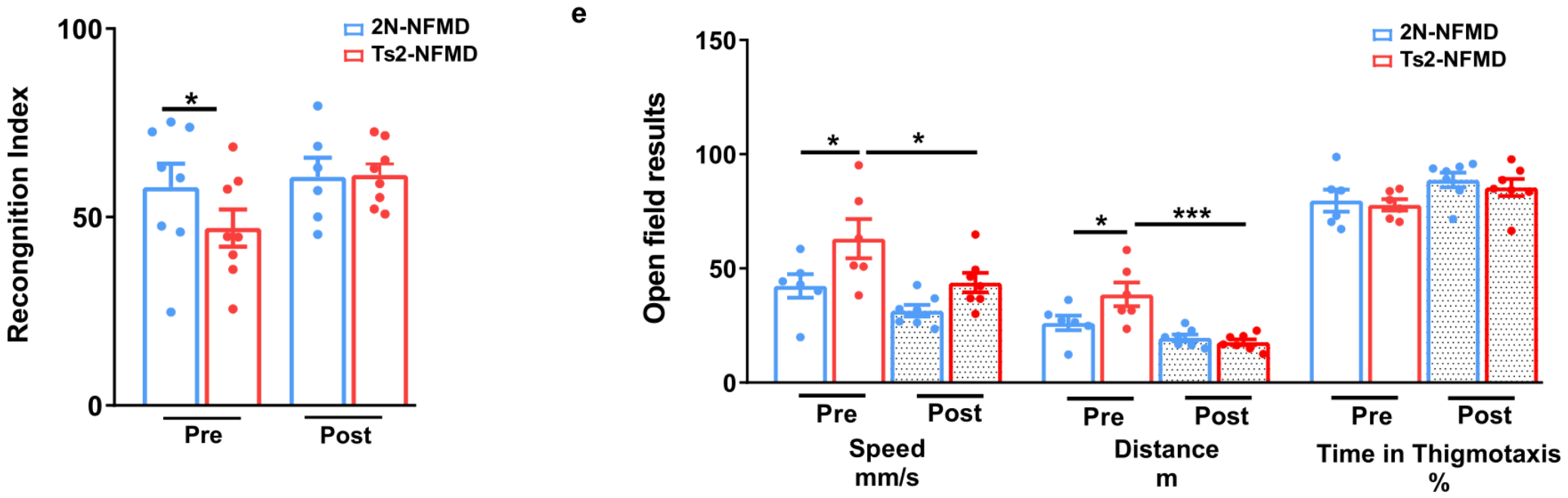




Jiang, Alam et al, Nature Communications volume 13, Article number: 5308 (2022)

CERVOMED

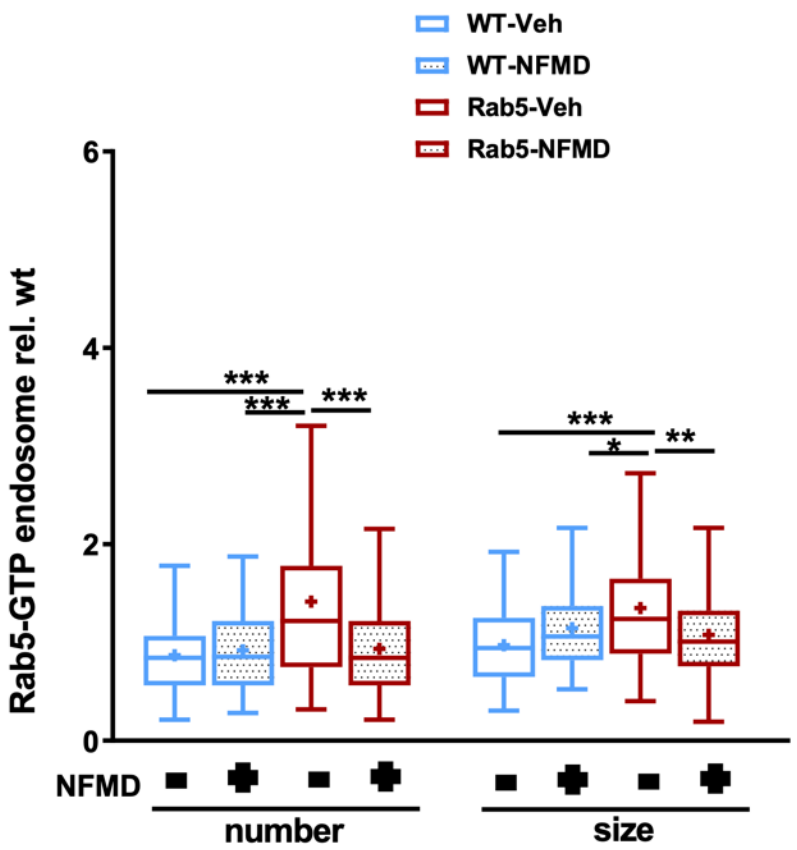
Neflamapimod normalized scores in behavioral tests associated with cholinergic function

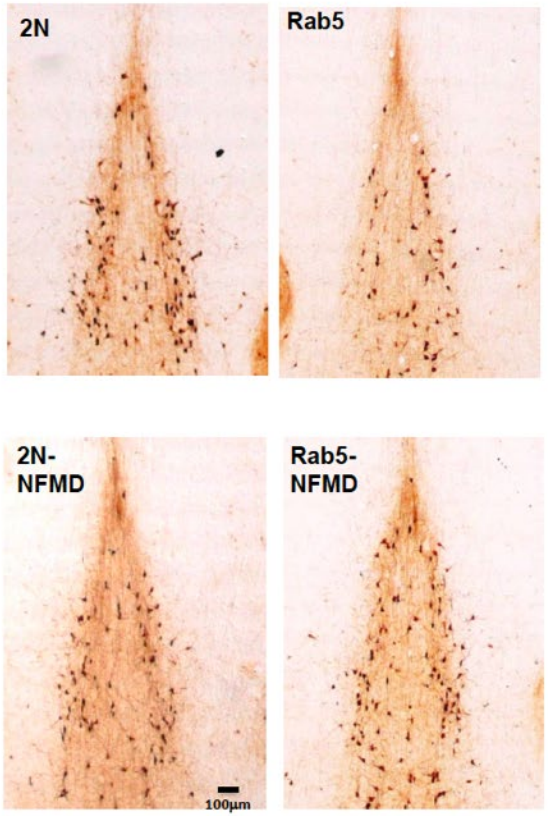


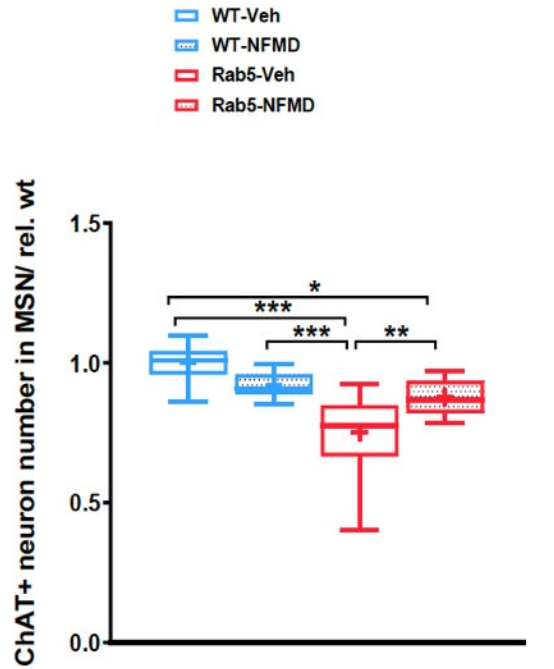
Jiang, Alam et al, Nature Communications volume 13, Article number: 5308 (2022)

CERVOMED

Neflamapimod effects in Rab5 overexpressing transgenic mice







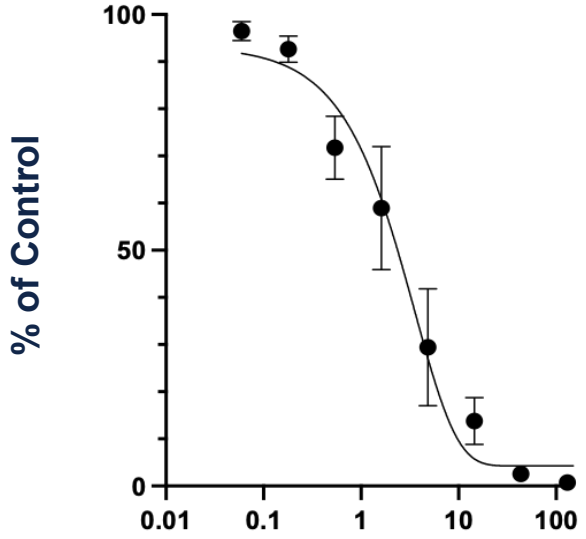
Combined with Anna's mouse ChAT data

CERVOMED

Mechanistic Studies in the Clinic

Concentration-pharmacodynamic relationship effect *in vitro* and in patients with early PD

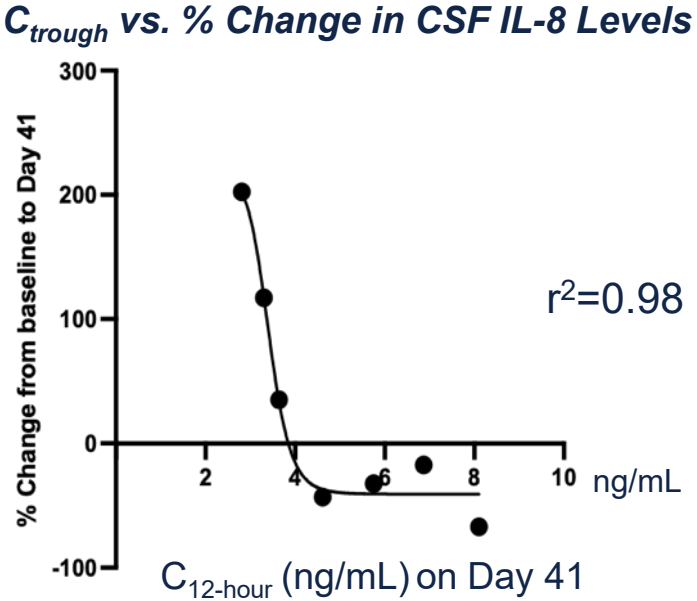
In Vitro: IL-1b stimulated IL-8 Production from PBMCs



Log_{10} NFMD (ng/mL)

In vitro EC50 (n=5) = 3.1 ±1.4 ng/mL

In Patients with Early Alzheimer's Disease: Change in CSF IL-8 After 6 Weeks of Neflamapimod Treatment



$C_{12\text{-hour}}$ (ng/mL) on Day 41

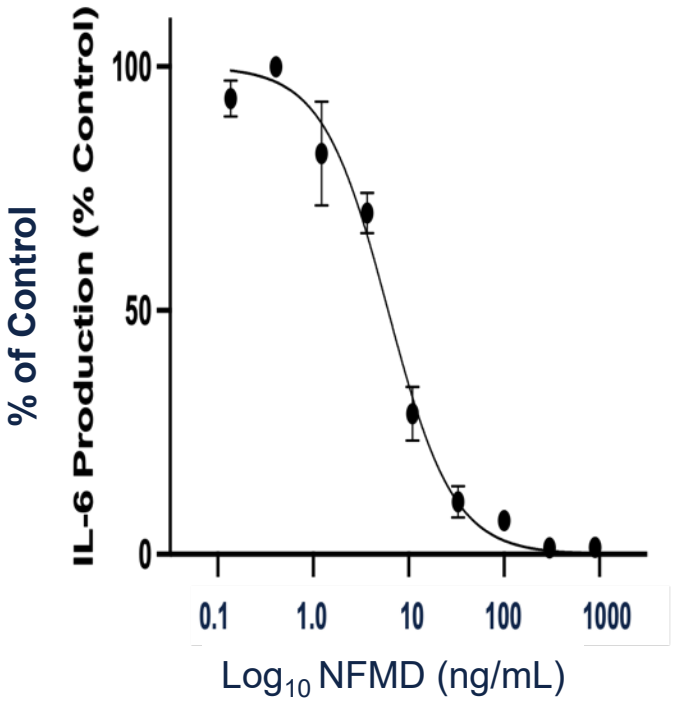
In Vivo EC_{50} = 3.4 ng/mL

Maximal pharmacodynamic effect in patients achieved at ~4 ng/mL, i.e. when EC50 is exceeded in plasma (2X EC50 in brain)

CERVOMED

In both *in vitro* and in patient studies, neflamapimod's pharmacodynamic (PD) effect is associated with a steep concentration-response curve

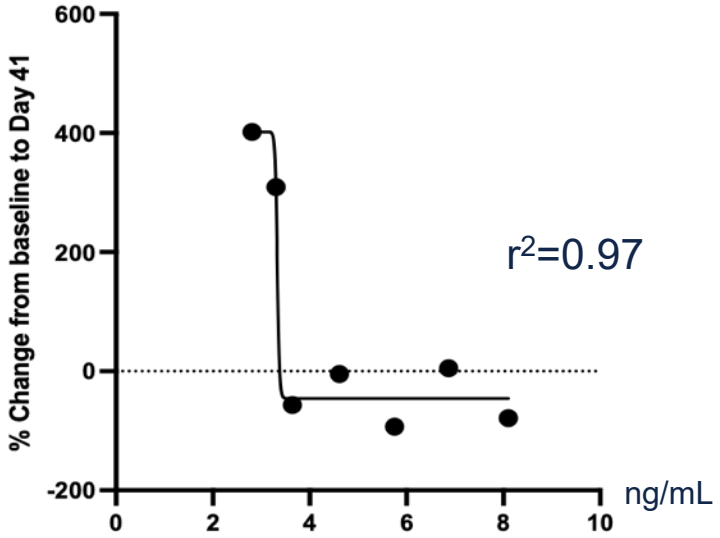
In Vitro: IL-1β stimulated IL-6 Production from PBMCs



In vitro EC50 (n=5) = 2.7 ± 0.6 ng/mL

In Patients with Early Alzheimer's Disease: Change in CSF IL-6 After 6 Weeks of Neflamapimod Treatment

C_{trough} vs. % Change in CSF IL-6 Levels



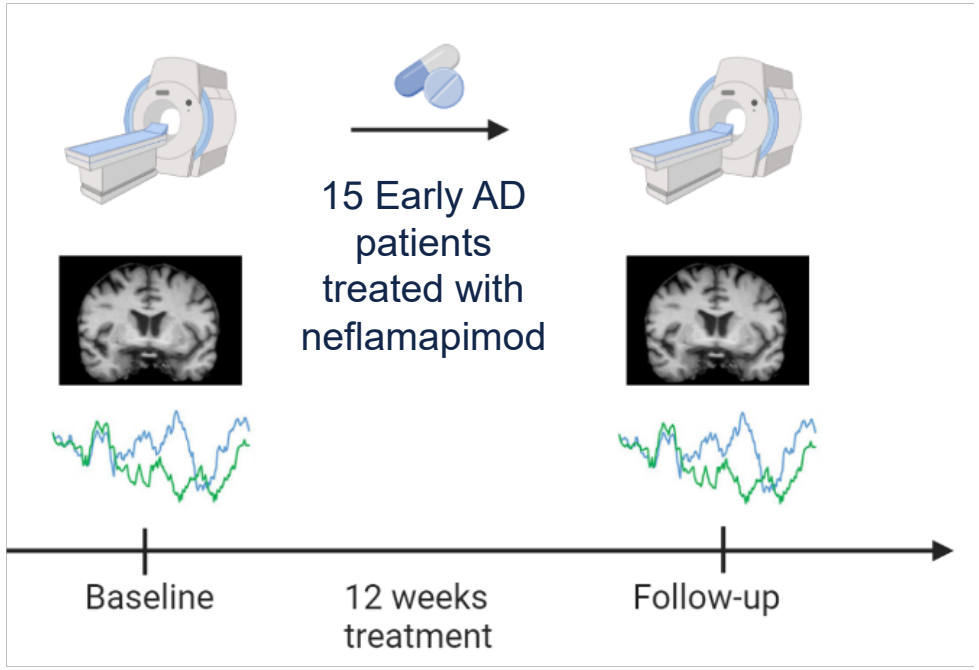
$C_{12\text{-hour}}$ (ng/mL) on Day 41

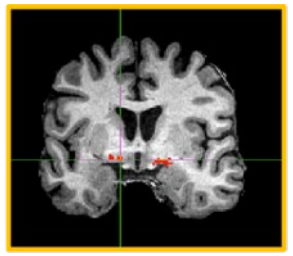
In Vivo EC_{50} = 3.3 ng/mL

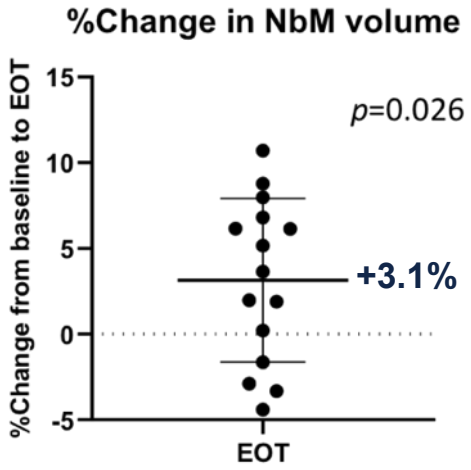
Maximal pharmacodynamic effect in patients achieved at ~4 ng/mL, i.e. when EC50 is exceeded in plasma (2X EC50 in brain)

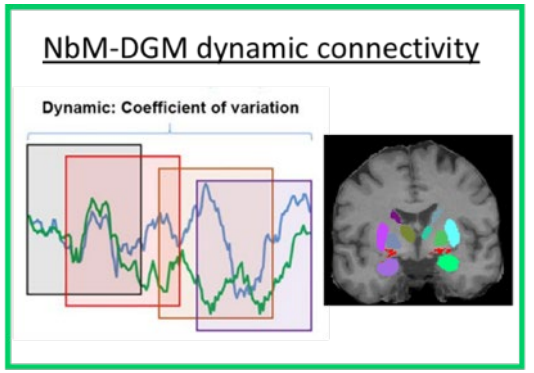
CERVOMED

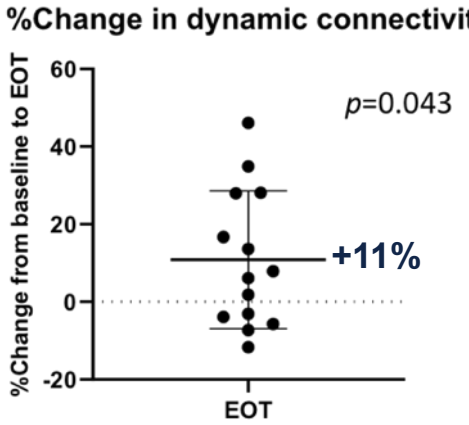
Neflamapimod treatment is associated with increased basal forebrain volume and functional connectivity in patients with early AD (Phase 2 Study)









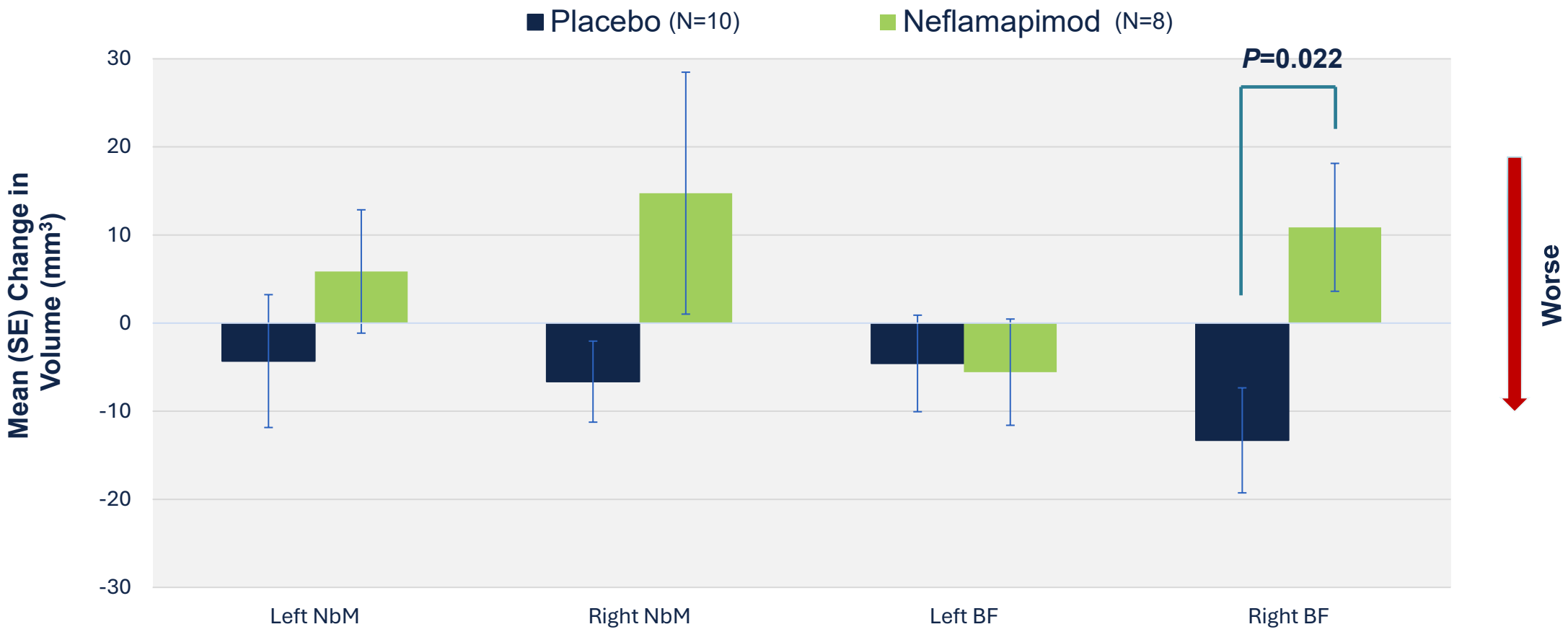


NbM – Nucleus basalis of Meynert; DGM – Deep Grey Matter

Lin C-P, Noteboom S, Bet M, Alam J, Prins N, Barkhof F, Jonkman L, Schoonheim M, Oral Presentation at AD/PD™ 2023, Gothenburg, Sweden, 1 April 2023; Prins et al, *JPAD*, 2023

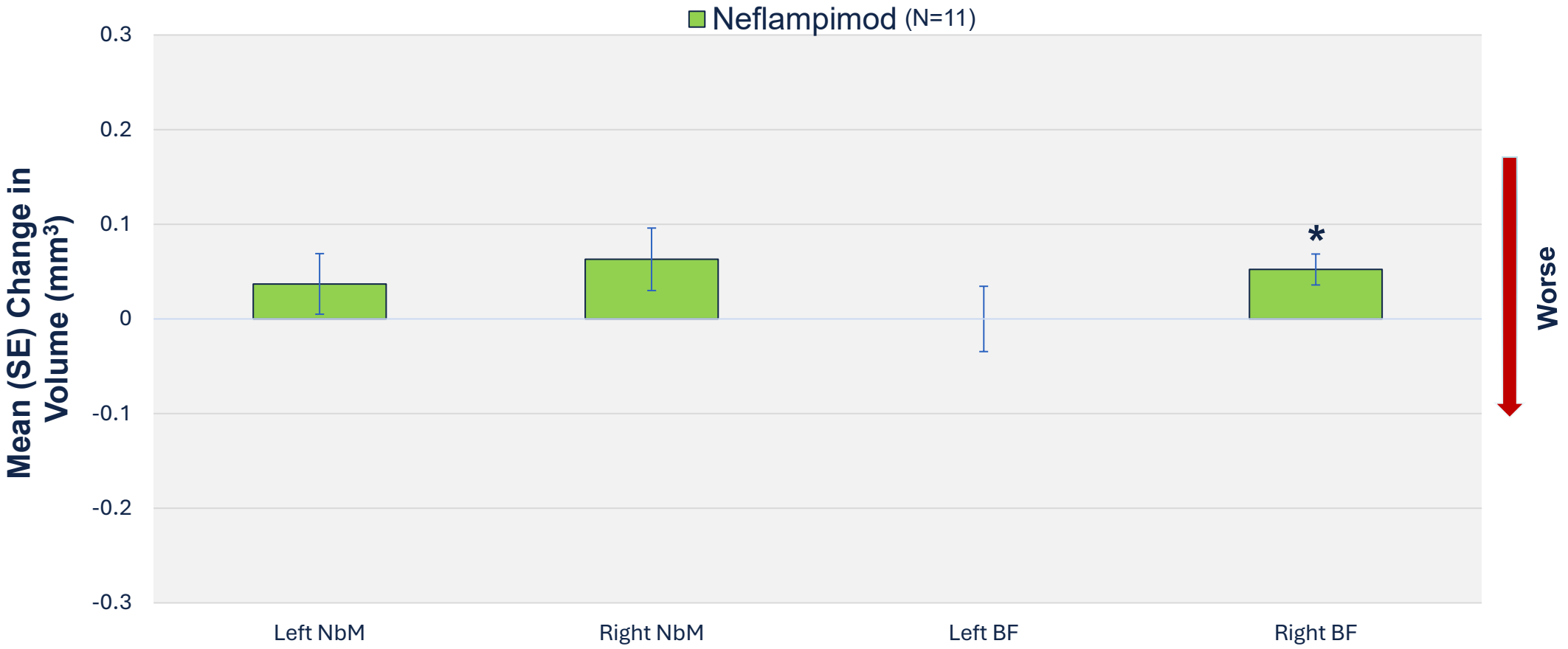
CERVOMED

Change from baseline in NbM or basal forebrain volume baseline during the 16-Week duration Placebo-Controlled Phase of RewinD-LB (Phase 2b in DLB)



Alam J, Koubyir I, Schoonheim MM, AAN, April 18-22, 2026, Chicago ILNbM – nucleus basalis of Meynert BF – Basal Forebrain..

Change in static functional connectivity to default mode network (DMN) from start to end of 32-Week neflamapimod only extension (Phase 2b in DLB)



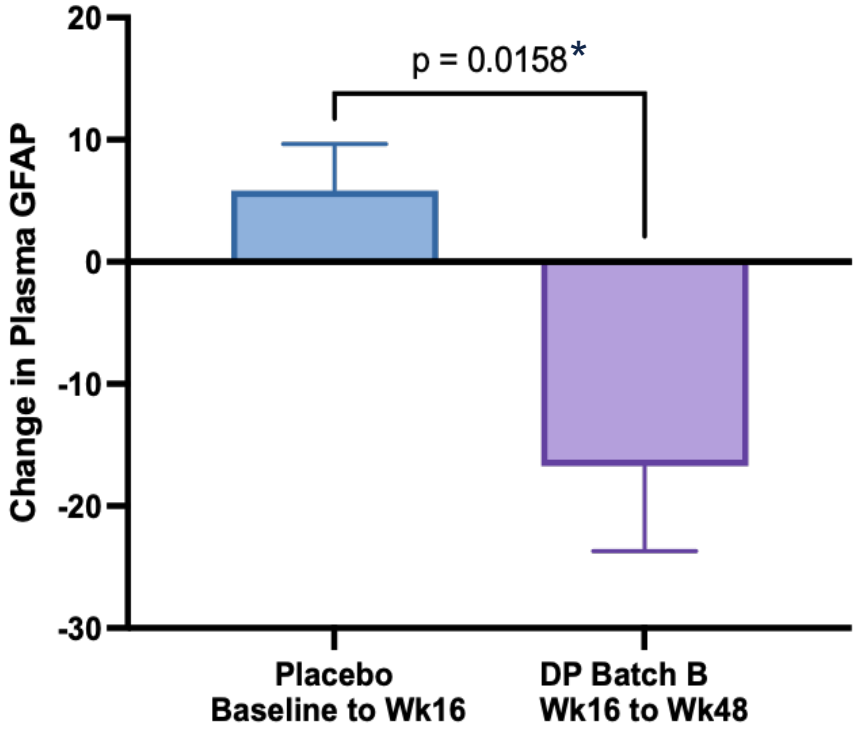
***P*=0.019 for change from baseline**

Alam J, Koubyir I, Schoonheim MM, AAN, April 18-22, 2026 Chicago ILNbM – nucleus basalis of Meynert BF – Basal Forebrain..

CERVOMED

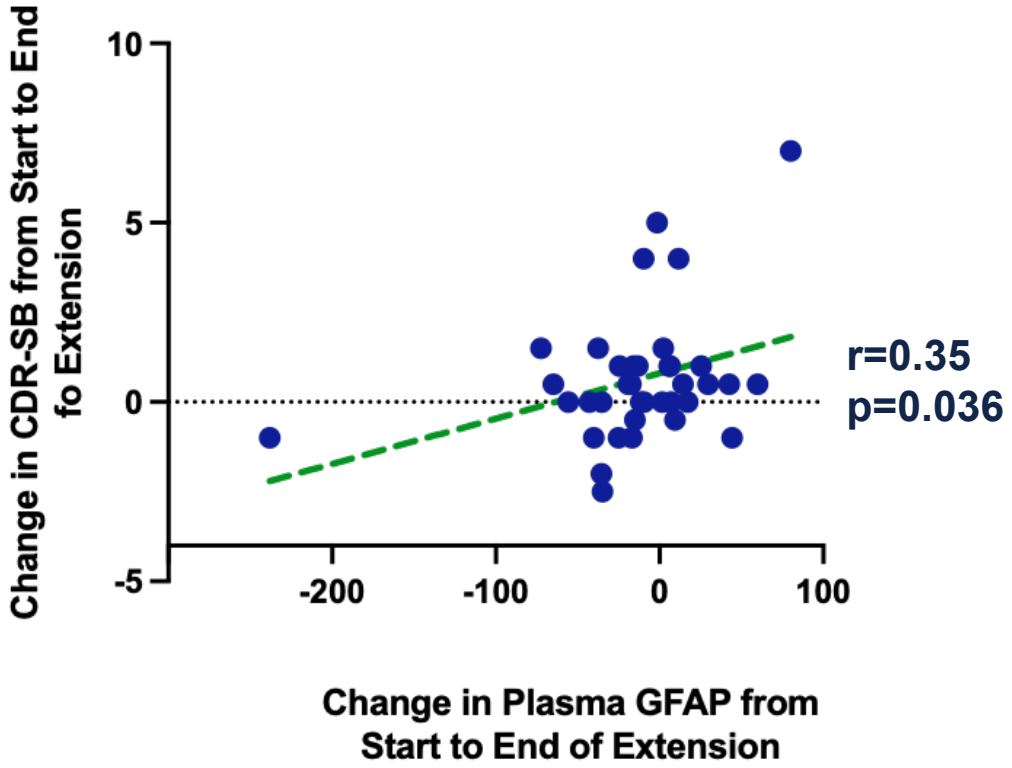
Neflamapimod significantly lowered plasma GFAP compared to placebo in Phase 2b study in DLB, an effect that was correlated to treatment response

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



Median Difference between Neflamapimod and placebo: -23.1 pg/mL (~50% of disease-specific elevation)

During the Extension, Change in Plasma GFAP is Correlated to Treatment Response Assessed by Change in CDR-SB



*Wilcoxon Rank Sum Test
Correlation analysis conducted in participants with low likelihood of AD co-pathology (screening ptau181<21 pg/mL)

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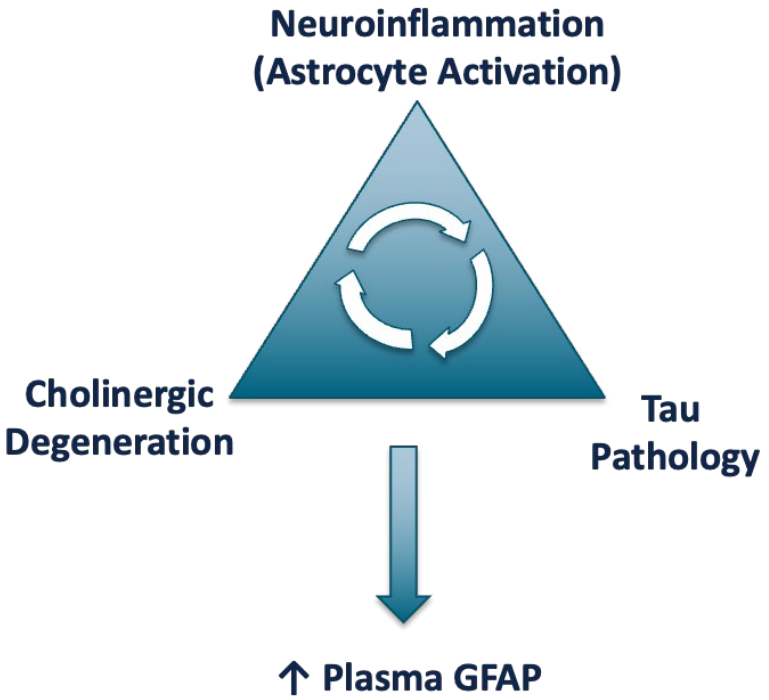
Plasma GFAP as a potential marker of neuroinflammation and Tau-associated neurodegeneration

- Neuroinflammation generally associated with basal forebrain cholinergic degeneration[1,2,3]
- Astrocyte activation connects neuroinflammation with tau pathology[4], which is linked to cholinergic degeneration[5]
- Plasma GFAP correlates with tau pathology at autopsy[4] or by tau-PET[6]
- GFAP-IL6 transgenic mice develop basal forebrain cholinergic degeneration[7]
- Astrocyte reactivity associated with synaptic dysfunction preclinically[8] and clinically[9].
- Plasma GFAP correlated to damage to cholinergic pathways by MRI (DTI)[10]
- In PD, plasma GFAP correlated to gait dysfunction[11] and cognitive impairment[12], both which are also correlated to basal forebrain atrophy



1 Willard et al, 1999 2 Quail et al, 2011 3 Liu et al, 2024 4 Peretti et al, 2024 5 Mesulam et al, 2013 6 Msulam et al, 2013 7 Gamage et al, 2024 8 Portal et al, 2023 9 Pascoal et al, 2024 10 Bettcher et al, 2024, Che et al, 2024, Tang et al, 2023

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1. Are the clinical data when stratified by plasma pTau181 (measure of presence or absence AD co-pathology) consistent neflamapimod with acting on BFCN dysfunction and degeneration?

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

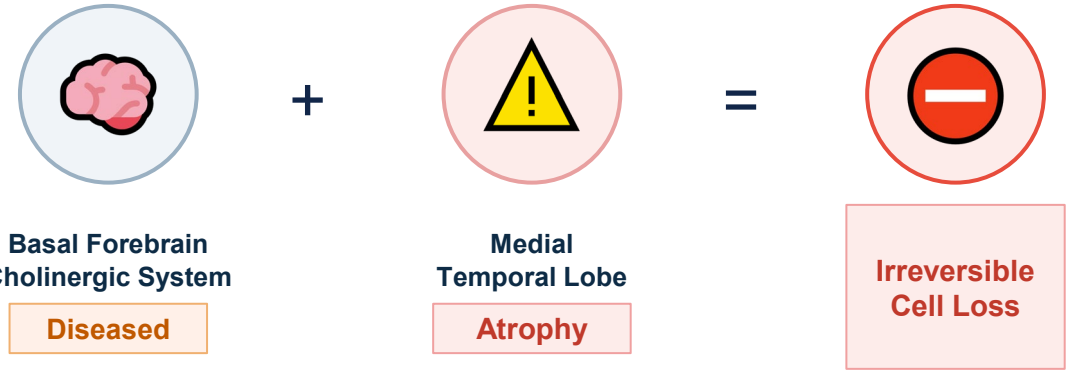
Reversible Function Deficient

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

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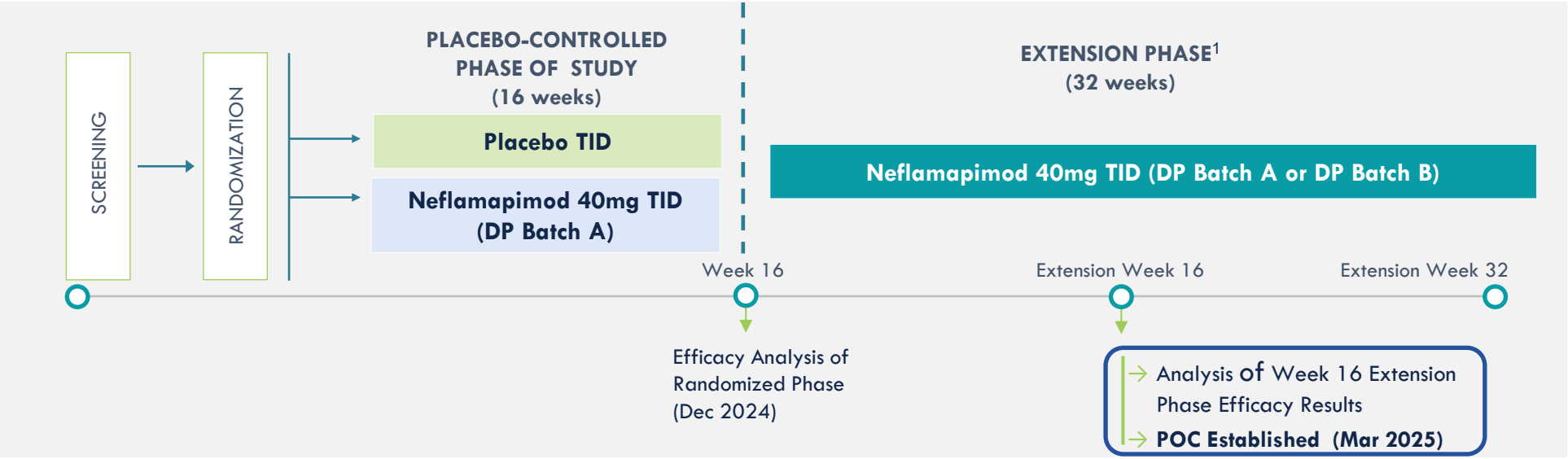
RewinD-LB Phase 2b Study in DLB: Design and Conduct

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)



Drug Product (DP) Batch A Results:

- Lower than expected plasma drug exposure
- No significant difference to placebo during Part A of study
- No significant effect on plasma GFAP in Part A nor in Part B

DP Batch B Results:

- Achieved expected plasma drug exposure
- Significant improvement compared to Batch A on mean change in CDR-SB
- Significant reduction in plasma glial fibrillary acidic protein (GFAP), compared to baseline and DP Batch A

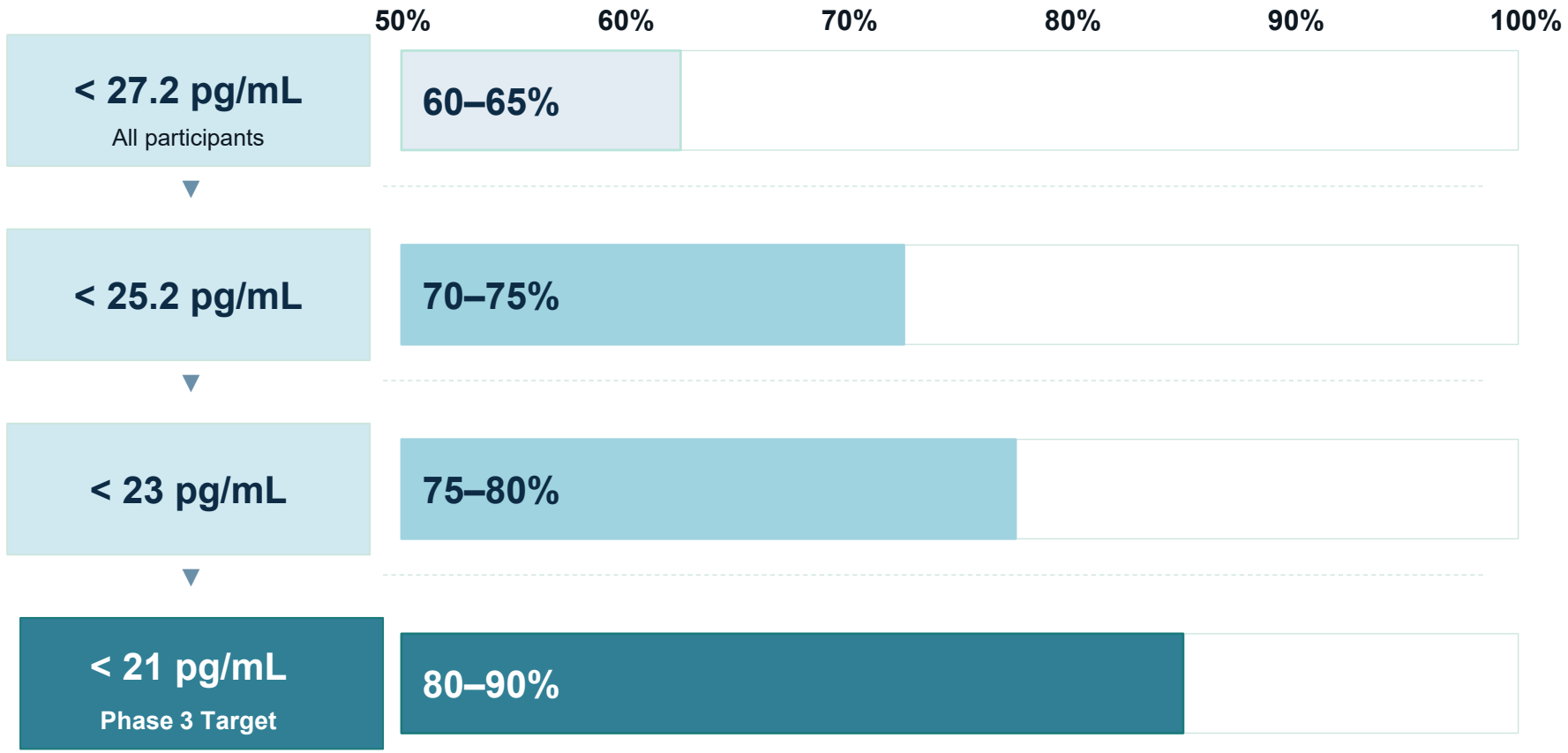
EMERGING THERAPIES ACROSS AD, PD, LBD: Dr. John-Paul Taylor, Auditorium 10, Sat., 14:10pm (ID 2617)

Participants were all aware that they were receiving neflamapimod in the Extension phase, but neither they nor study site personnel were aware if they were receiving DP Batch A or DP Batch B capsules

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

Estimated % of Participants Without AD Co-Pathology by pTau181 Cut-off

Stricter cut-off → purer DLB population



Participants in Efficacy Analysis (N)

< 27.2 pg/mL	Placebo=79 NFMD=79
< 25.2 pg/mL	Placebo=70 NFMD=66
< 23 pg/mL	Placebo=57 NFMD=56
< 21 pg/mL	Placebo=46 NFMD=48

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.

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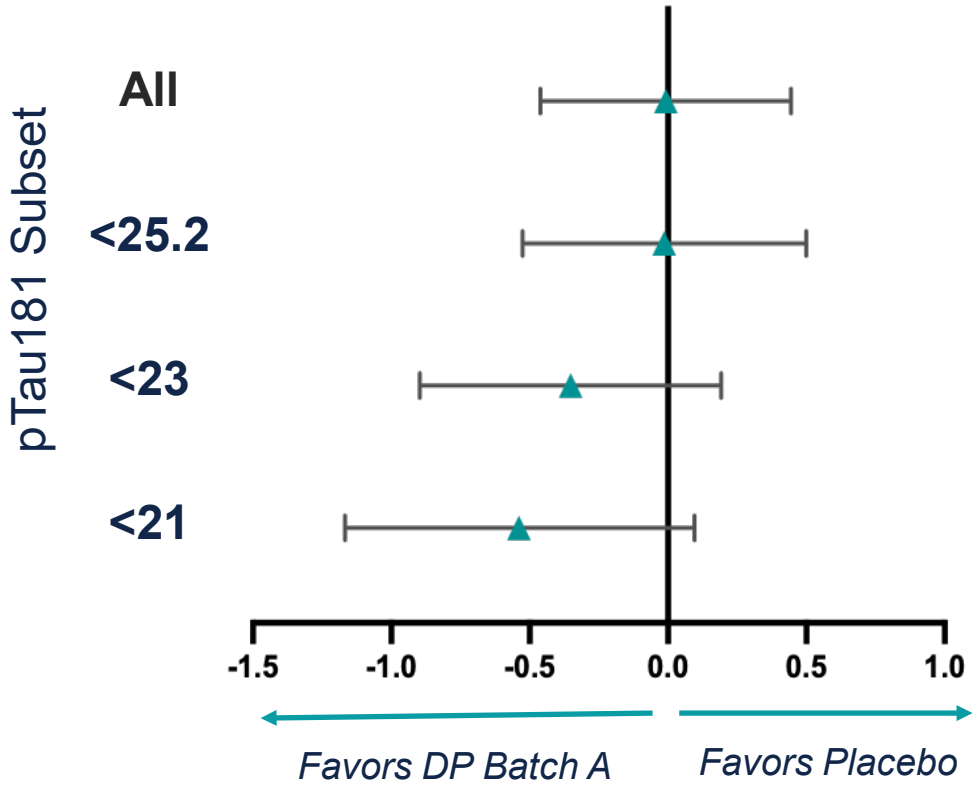
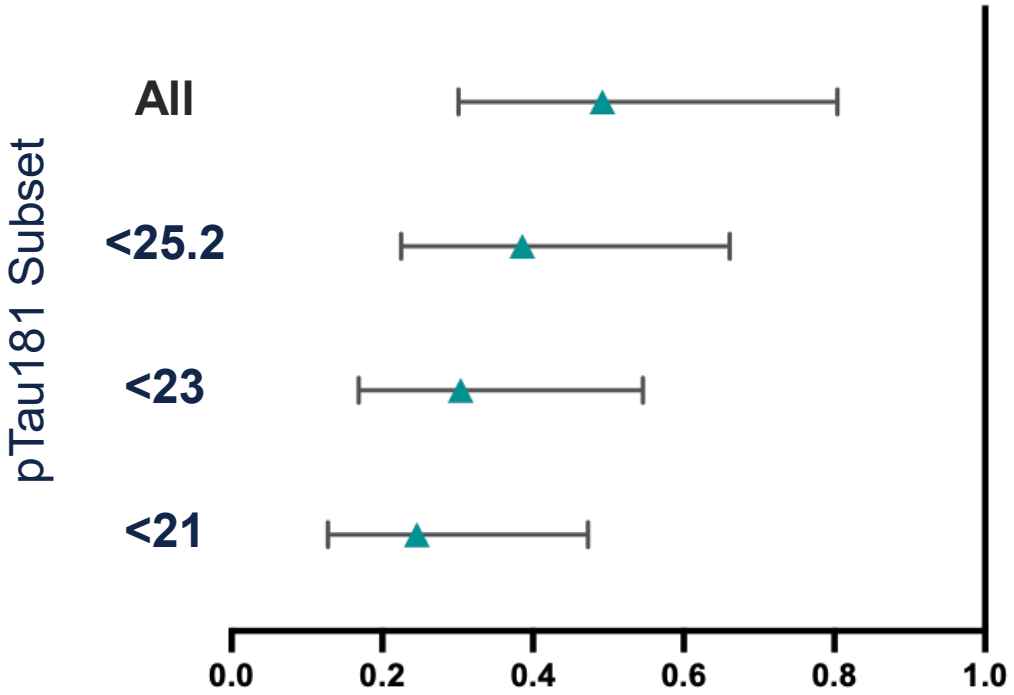
CDR-SB outcomes vs. placebo in RewinD-LB by plasma pTau181 subset

Difference (95% CI) in Change in CDR-SB Between DP Batch A vs. Placebo



Hazard Ratio For Progression (≥ 1.5-point increase in CDR-SB), DP Batch B vs. Placebo



Risk of Progression (≥ 1.5 increase in CDR-SB)
For DP Batch B Compared to Placebo

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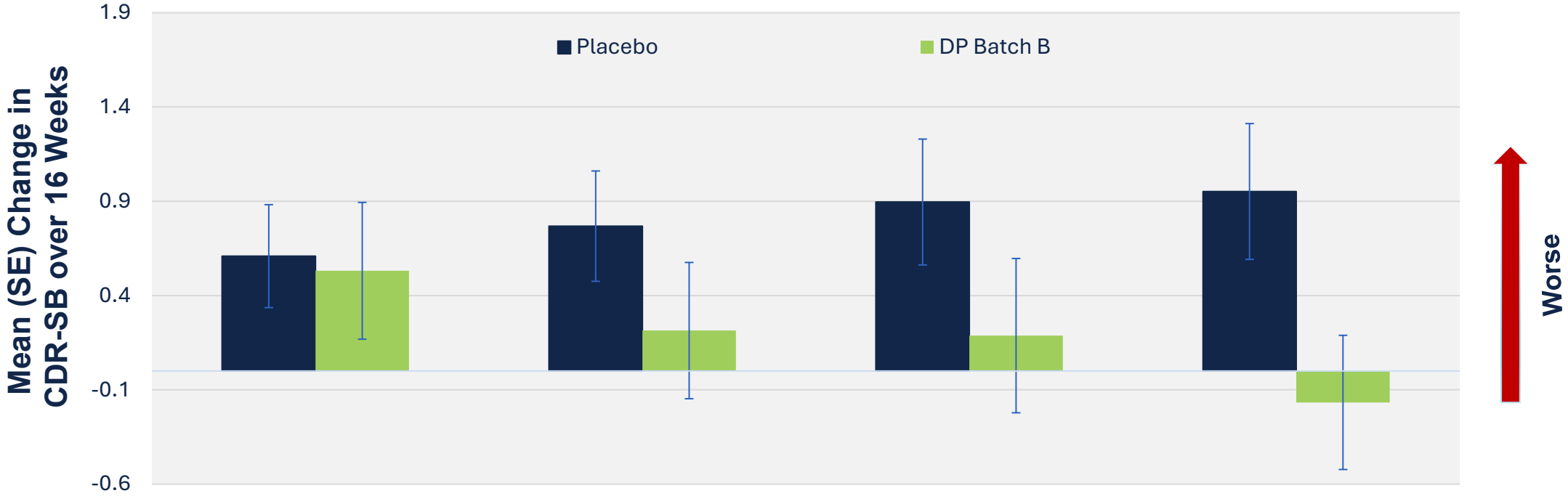
Within subject analysis by pTau181 subset of mean change in CDR-SB in participants who received placebo and then DP Batch B during Extension Phase[1]



	<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

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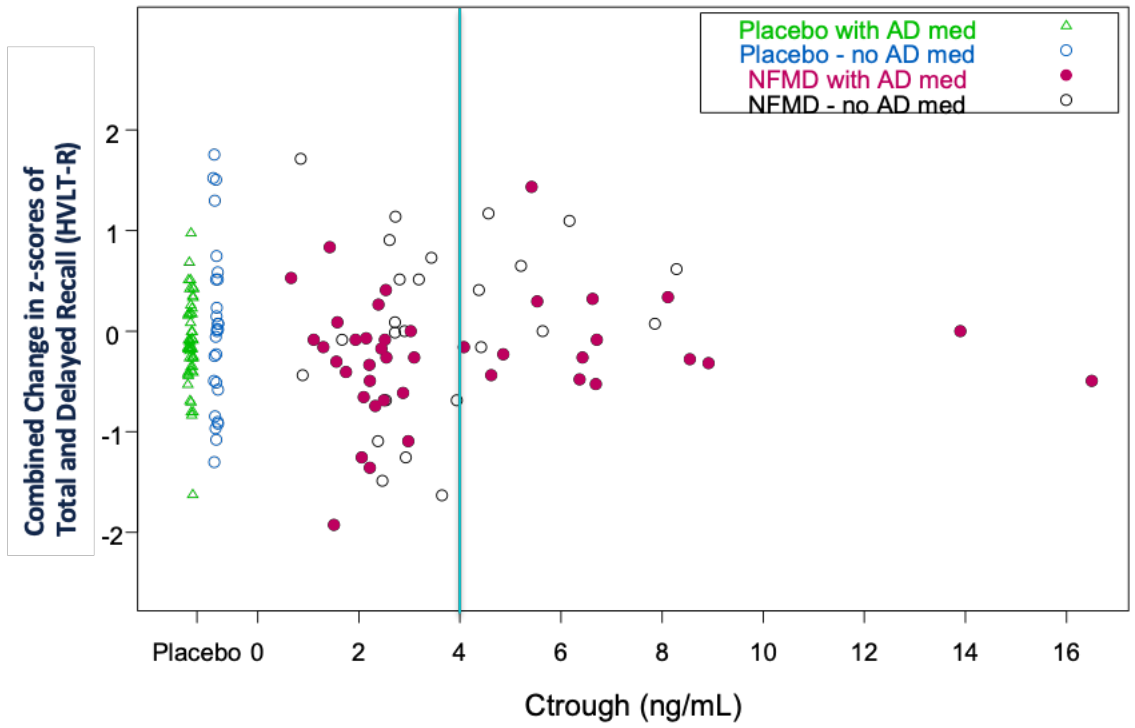
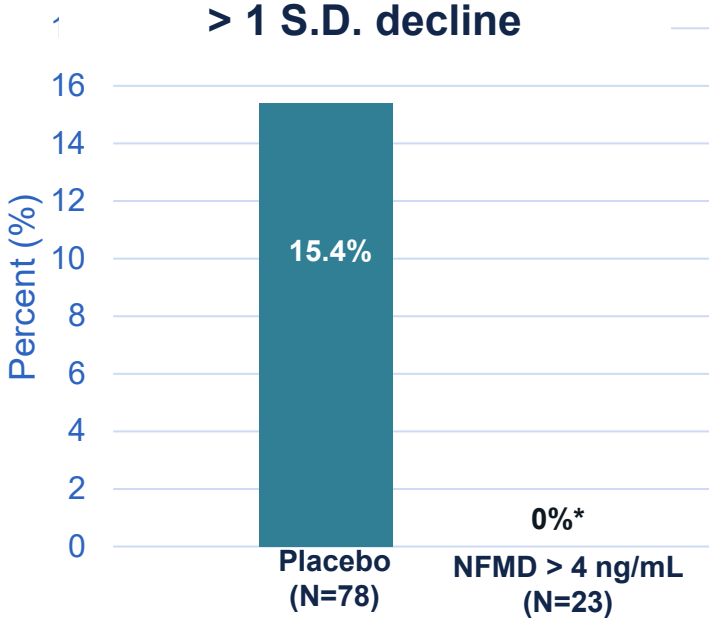
2. Are the PK-PD relationships (concentration-effect relationships) for clinical and biomarker effects consistent with the presumed mechanism of action?

C_{trough} threshold of 4 ng/mL for clinical activity PK-PD analysis of 24-Week placebo-controlled study in early AD (Reverse-SD Study)

Change from baseline to week 24 in primary endpoint



Percentage of patients with > 1 S.D. decline

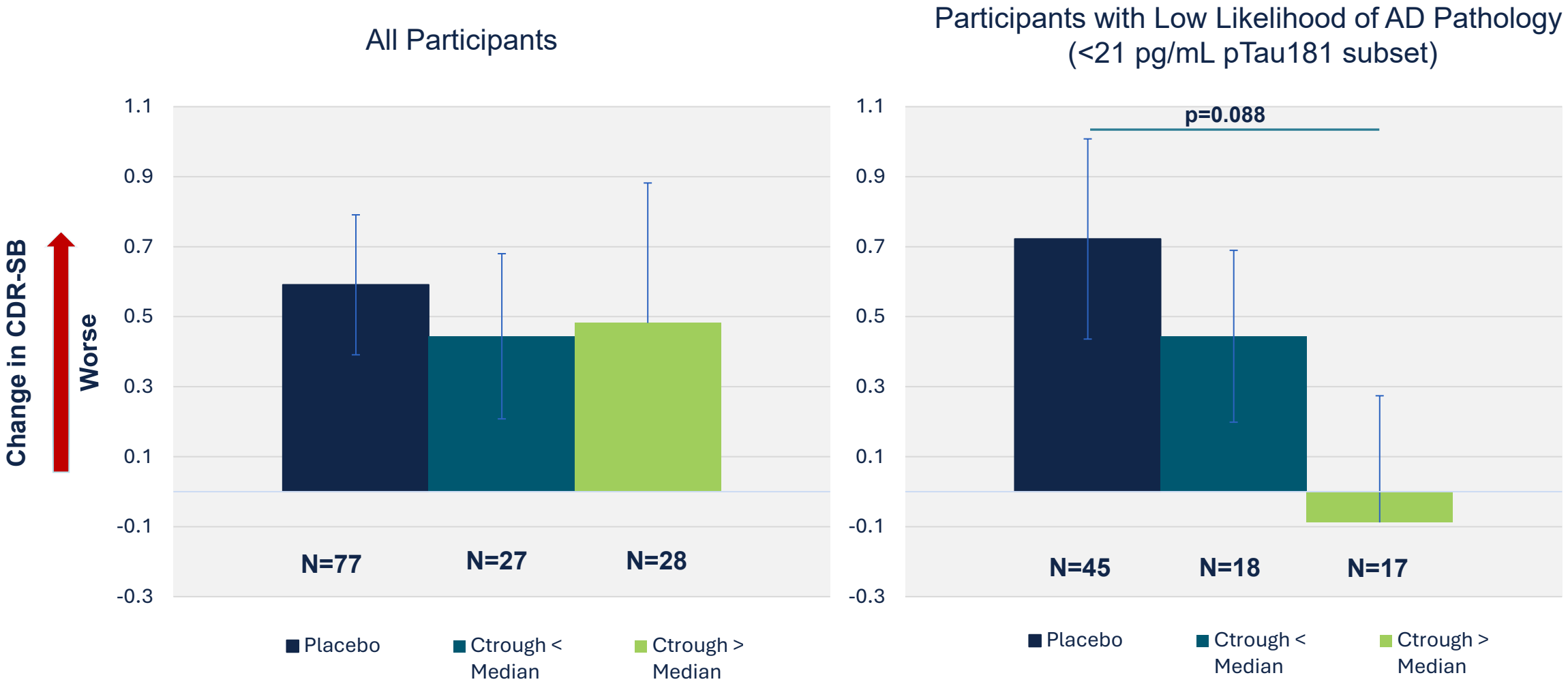


*p=0.06 vs. placebo, two-sided Fisher's exact test

Primary endpoint: Combined z-score of total and delayed recal in HVLT-R (word recall test)

CERVOMED

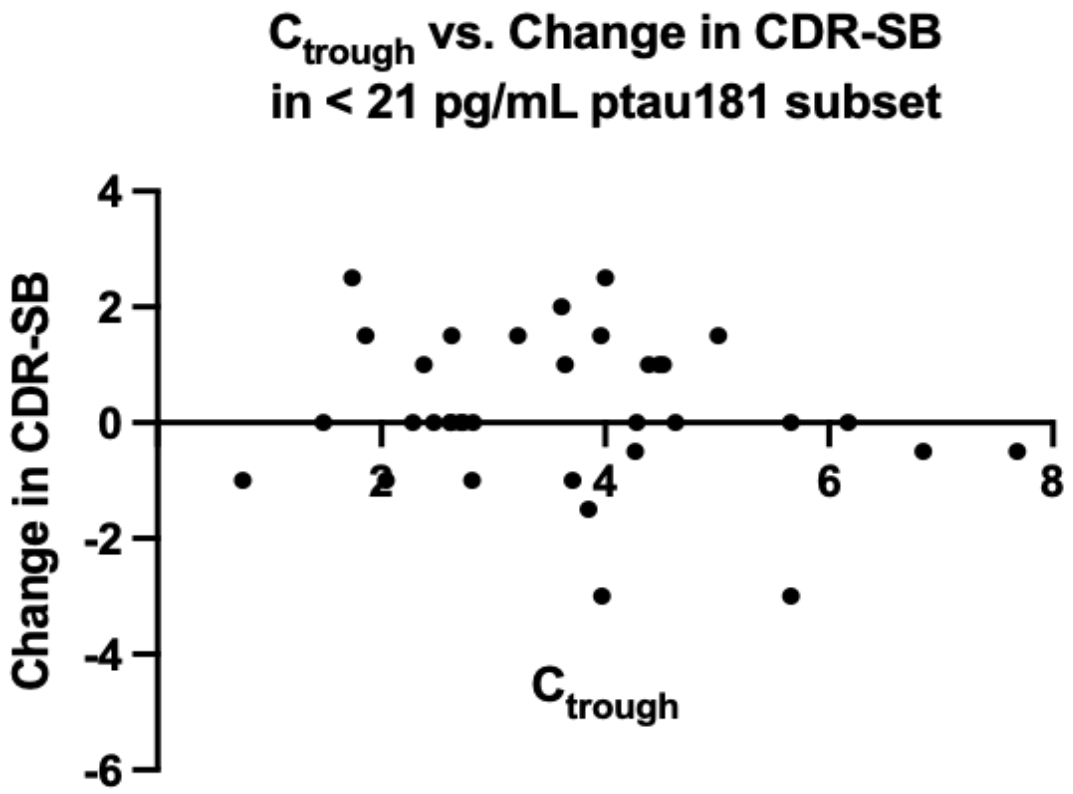
Change in CDR-SB By neflamapimod C_{trough} during Randomized Phase of RewinD-LB

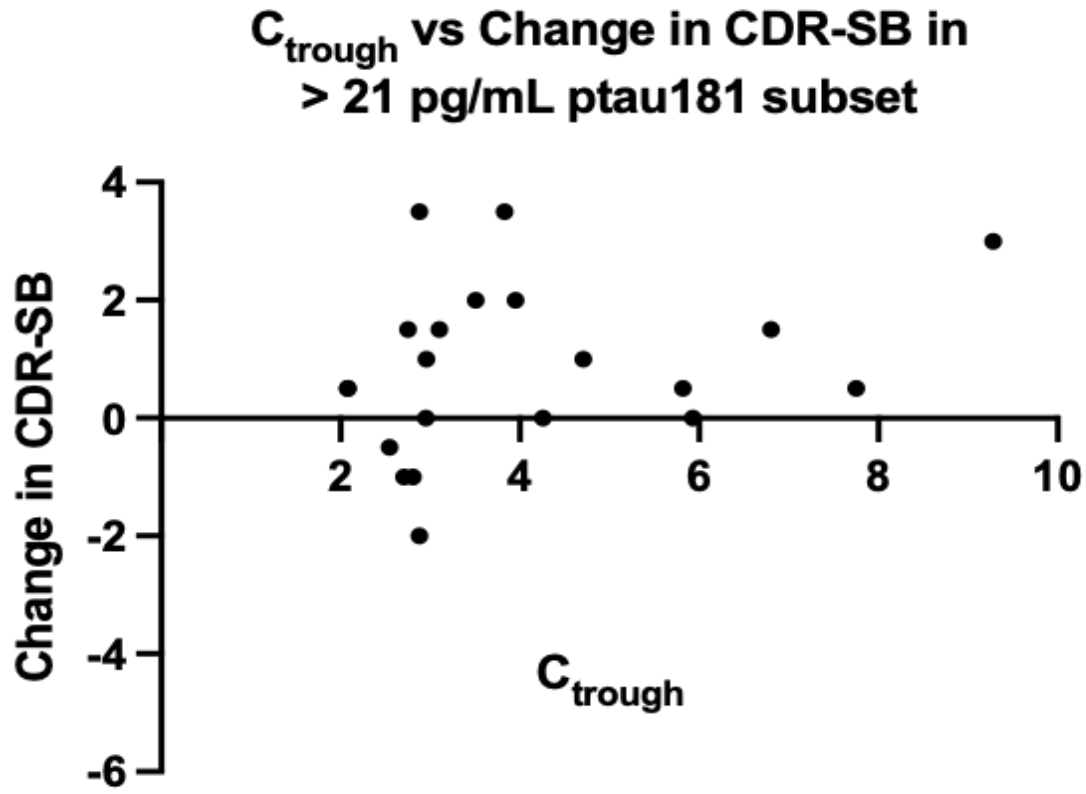


Median Observed C_{trough} = 3.6 ng/mL; calculated 12-hour post dose concentration, C_{12} = 4 ng/mL. Only patients that received a Ctrough concentration are included in the analysis.

CERVOMED

PK-PD relationship by plasma pTau181 subset with DP Batch A during the Randomized Phase of RewinD-LB

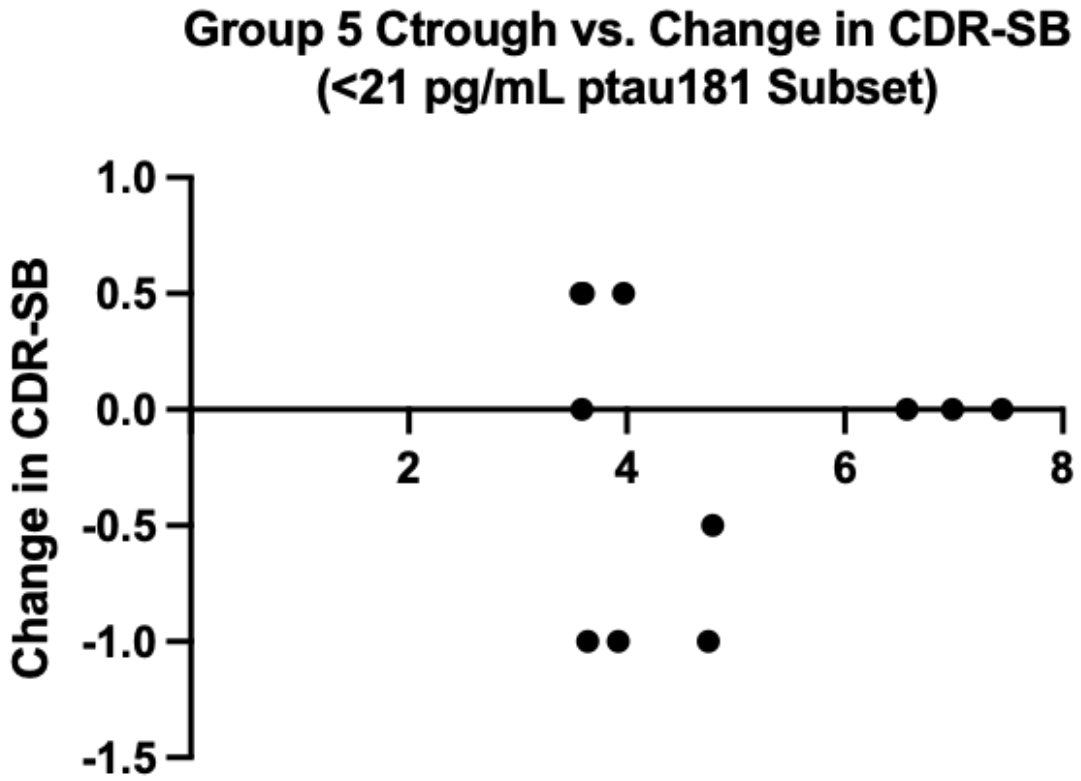


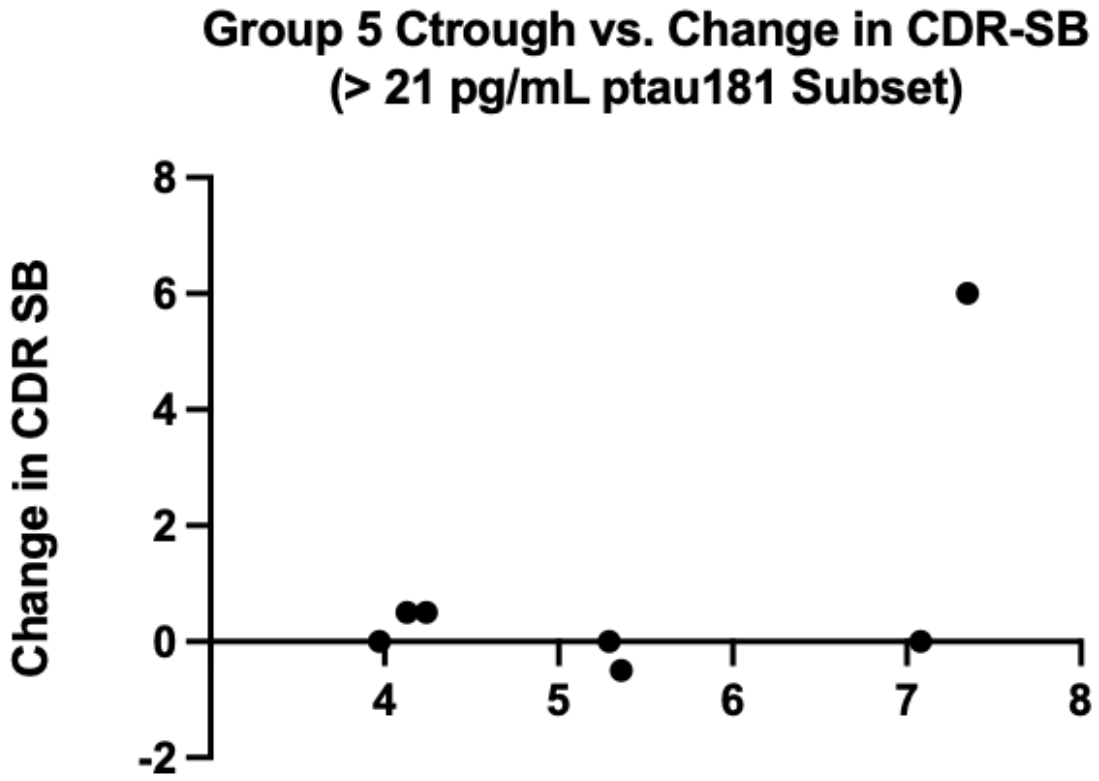


Ctrough = as measured, regardless of time post-dose, in ng/mL; change in CDR-SB from baseline to week 16 of Randomized Phase is shown

CERVOMED

PK-PD relationship by plasma pTau181 subset With DP Batch B during 1st 16 weeks of the Extension Phase of RewinD-LB

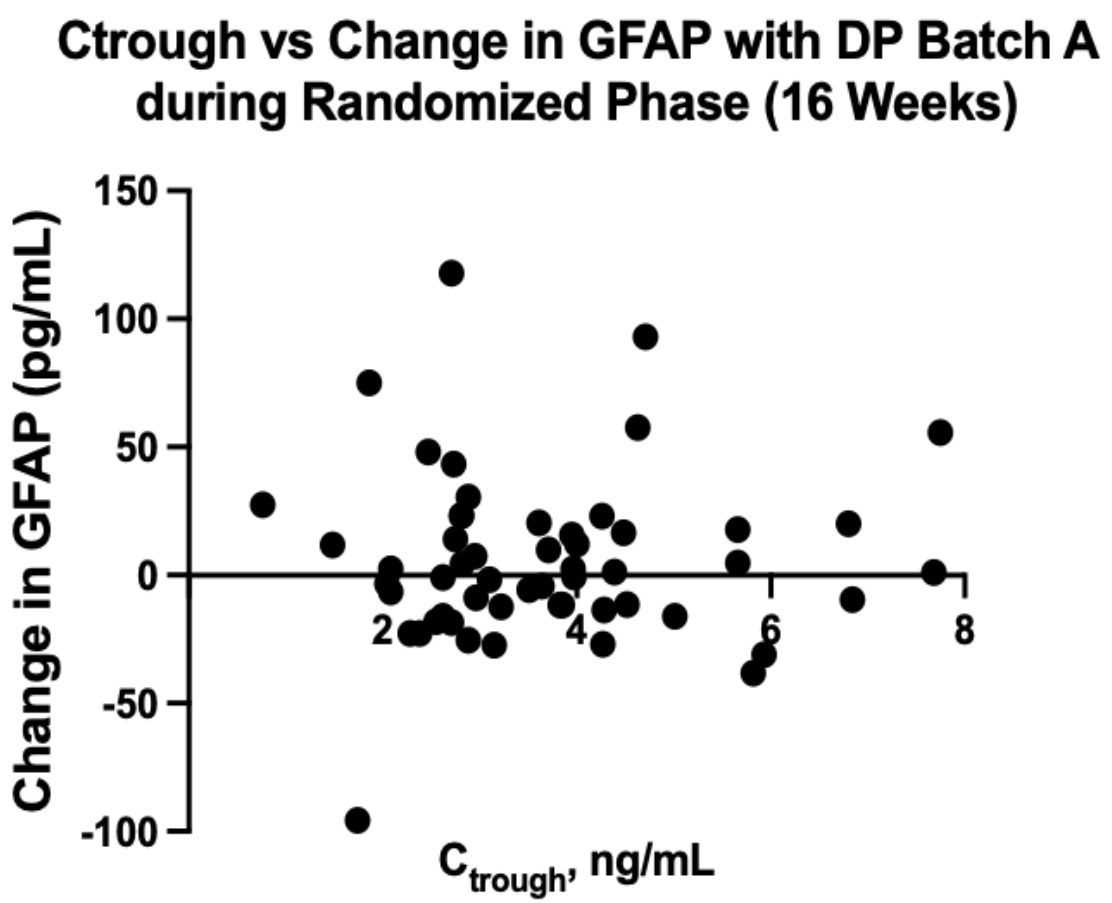


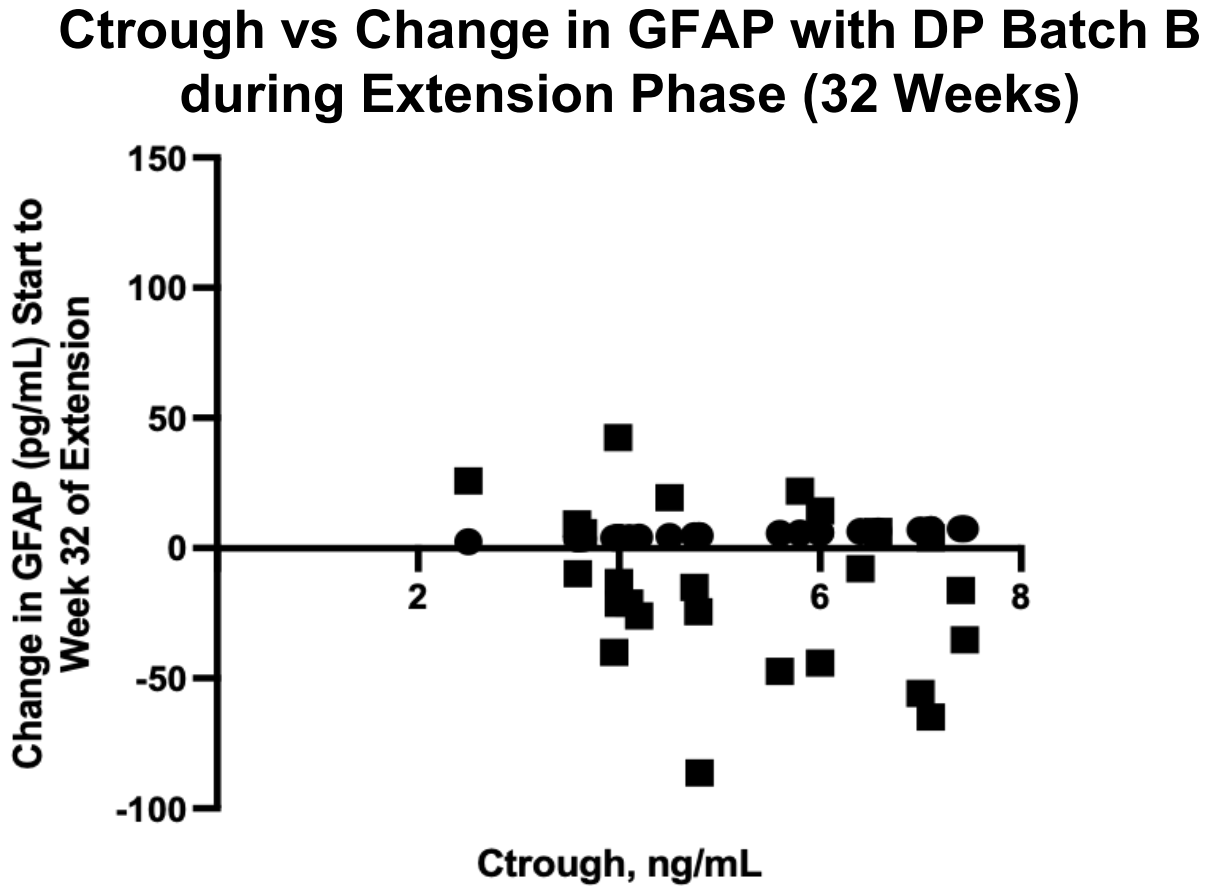


C_{trough} = 12-hour post-dose concentration from regression model

CERVOMED

PK-PD relationship for Change in Plasma GFAP with DP Batch A during Randomized Phase or DP Batch B During The Extension





Data from all participants, regardless of screening ptau181 level. For DP Batch B, C_{trough} = 12-hour post-dose concentration from regression model.

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PK-PD correlations for clinical activity are consistent with the potency and concentration relationship for primary pharmacology

	Percent of patients who achieve $C_{trough} \geq 4$ ng/ML	Clinical Activity
40 mg BID (Phase 2a only)	25%	No discernible activity
40 mg TID Batch A (Phase 2b)	50%	Marginal clinical activity, except potentially in those who achieve C_{trough} target
40mg TID Batch B (Phase 2b)	75%	Demonstrated improvement on CDR-SB, CGIC and plasma GFAP
Phase 3 formulation and dose (50mg TID)	80-90%[1]	TBD

[1] Estimated

Targeting basal forebrain cholinergic neuron BFCN) dysfunction & degeneration with the p38α kinase inhibitor neflamapimod: Summary

- Through transducing inflammatory signals p38α kinase dysregulates Rab5 activity and tau phosphorylation, leading to impaired axonal transport and defects in NGF signaling
- The p38α kinase inhibitor neflamapimod blocks IL-1β signaling and the synaptoxicity of aggregated proteins
- In preclinical mouse models, neflamapimod reverses basal forebrain cholinergic pathology and ameliorates behavioral deficits associated with cholinergic dysfunction
  - Mechanistic studies indicate preclinical activity is via inhibition of p38α kinase and through reducing Rab5 activity and tau phosphorylation
- In the clinic neflamapimod has demonstrated clinical and biological activity in patients with DLB that is consistent with an effect on the basal forebrain cholinergic system
  - pTau181 stratified (i.e., with or without AD co-pathology) analysis is inline with a preferential effect on the basal forebrain cholinergic system
  - PK-PD relationships (concentration-effect relationships) for clinical and biomarker effects are consistent with the potency and concentration-relationship of the primary pharmacology (i.e., presumed mechanism of action)

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Conclusion

Evaluation of mechanistic data and clinical data are consistent with neflamapimod having the intended effect on basal forebrain cholinergic dysfunction and degeneration via its presumed mechanism of action

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Audience Q&A