

#4007 – Initial Biomarker Results from A Phase 2a Clinical Trial of Neflamapimod in Patients with Nonfluent Variant Primary Progressive Aphasia

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Sunday, October 11, 8:45 a.m. ET



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Disclosures

- Neflamapimod is an investigational drug
- DJ. Irwin, IM. Grant, H. Botha, LS. Honig, DW. Scharre, M. Lad, and A. Murley were site PIs on the study
- JJ. Alam, A. Gardner, and K. Blackburn are employees of CervoMed Inc, the company developing neflamapimod
- The other co-authors have no disclosures to declare

Background: Neflamapimod

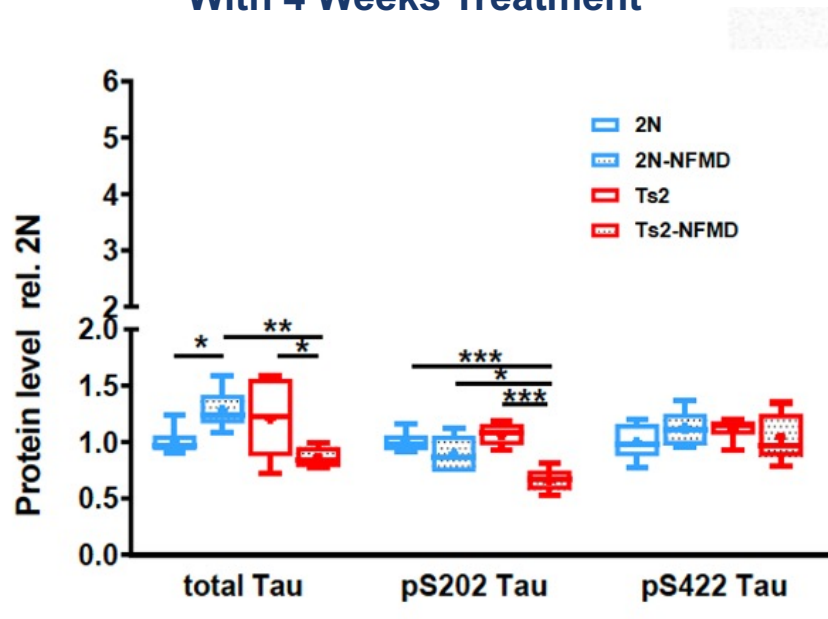
- **Brain-penetrant p38 α inhibitor.** Oral small molecule in development as a potential disease-modifying treatment for dementia with Lewy bodies (DLB).
- **Targets inflammatory signaling.** Inhibits p38 α -dependent interleukin-1 β signaling and its downstream effects (Alam et al, *Cells*, 2026).
- **Preclinical evidence of neuronal rescue.** Reverses basal forebrain cholinergic pathology and improves associated behavioral outcomes (Jiang et al, *Nat Comm*, 2022).
- **Clinical evidence in DLB.** Phase 2 studies show signals on CDR-SB and plasma GFAP, with supportive basal forebrain MRI findings (Jiang et al, *Nat Comm*, 2022; Alam et al, *Neurology*, 2023; Taylor et al, CTAD conference, 2025; Taylor et al, AD-PD meeting 2026; AAIC 2026).

Scientific Rationale for Neflamapimod in FTLD

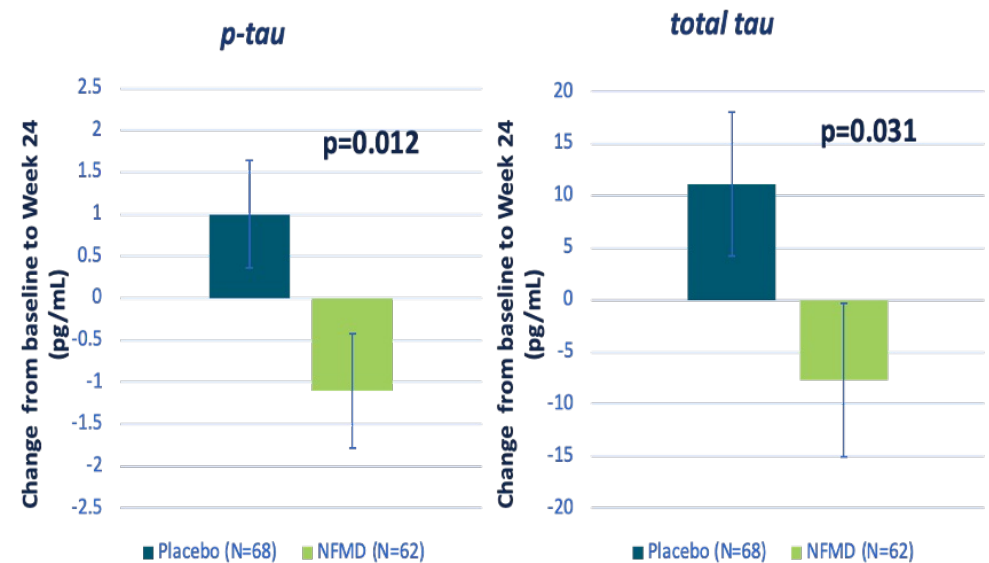
- **p38 α links inflammation to tau pathology.** Contributes to pathological tau phosphorylation and aggregation (Stefanowska, 2022; Chen, 2023; Yeganeh, 2025).
- **Genetic inhibition supports the target.** Neuronal p38 α deficiency reduces tau pathology and improves spatial navigation in P301S tau-transgenic mice (Schnöder et al., 2020).
- **Pharmacological evidence supports neflamapimod.** Studies in FTD-tau models implicate p38 α in mutant tau toxicity and support its inhibition (Moretto, 2026).
- **Evidence extends to human disease models.** Neflamapimod reduces tau phosphorylation at clinically relevant concentrations in cerebral organoids carrying the FTD-associated P301L mutation.
- **Emerging evidence linking p38 α with toxicity of TDP-43.** Potential role in pathological phosphorylation, aggregation, cytoplasmic mislocalisation, and neurotoxicity of TDP-43 (Aikio, 2025; Dong, 2024)

Neflamapimod Reduces Total Tau and Phosphorylated Tau Levels in Preclinical and Clinical Studies

**In the Basal Forebrain in Ts2 Mice
With 4 Weeks Treatment**



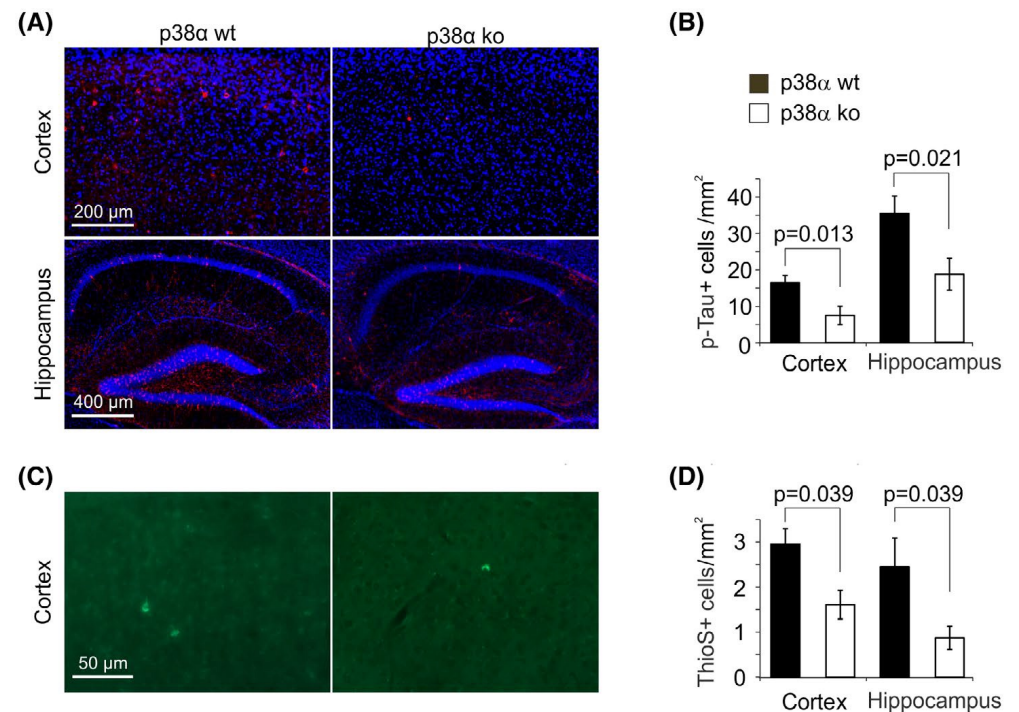
**In CSF in Patients with Early AD
After 24 weeks of Treatment**



Prins et al, *Alz Res Ther* 2021

Neuronal p38 α Deficiency Reduces Tau Pathology and Improves Cognitive Performance in FTD-Tau Mouse Model (P301S Tau Transgenic Mice)

- Crossed neuronal p38 α deficient mice with P301S tauopathy mouse model
- p38 α activity increased in P301S mice, and reduced to WT levels in neuronally p38 α deficient P301S mice
- Neuronal deficiency of p38 α led to reduced pTau levels and neurofibrillary tangles, enhanced autophagy
- P301S mice have impaired cognitive function in Morris-Water-Maze, which was improved with neuronal deficiency of p38 α



p38 α As a Drug Target and Neflamapimod Validated in FTD-Tau Mice

nature neuroscience



Article

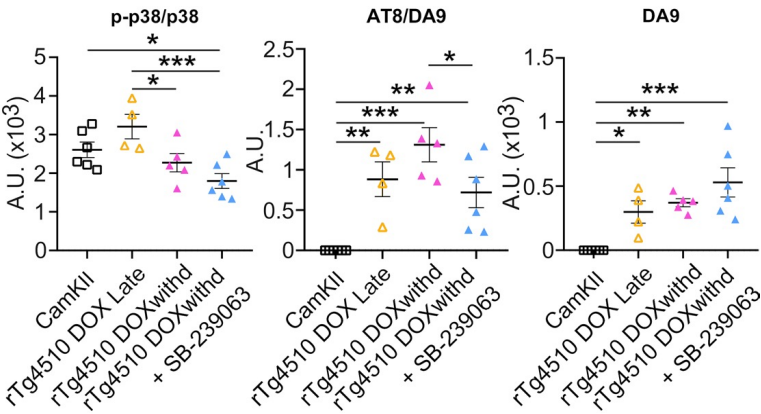
<https://doi.org/10.1038/s41593-026-02266-4>

Aberrant tau accumulation caused by *MAPT* mutations induces early pathological changes in axonal transport that are rescued by p38 α inhibition

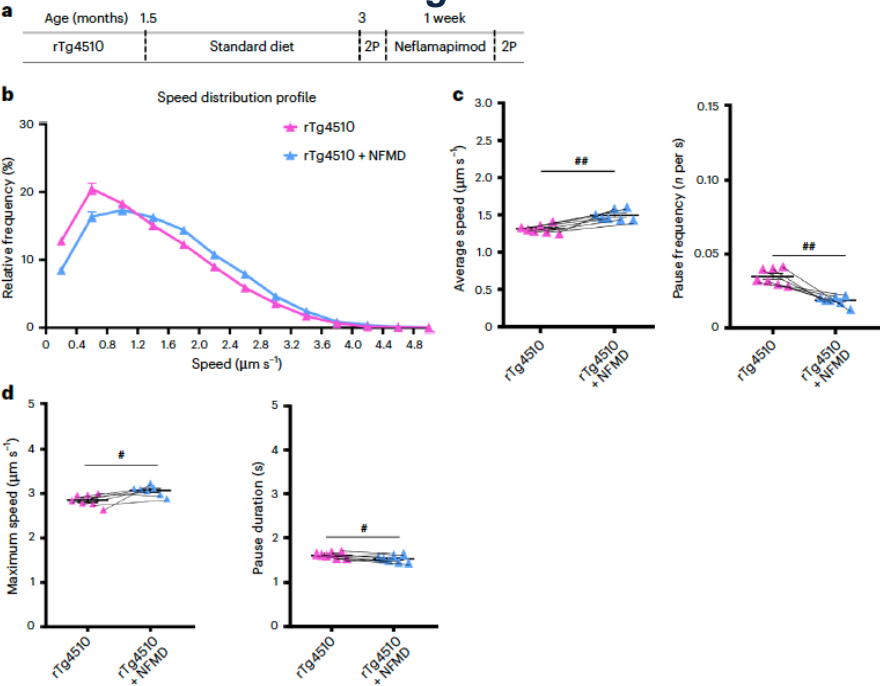
Received: 7 January 2024

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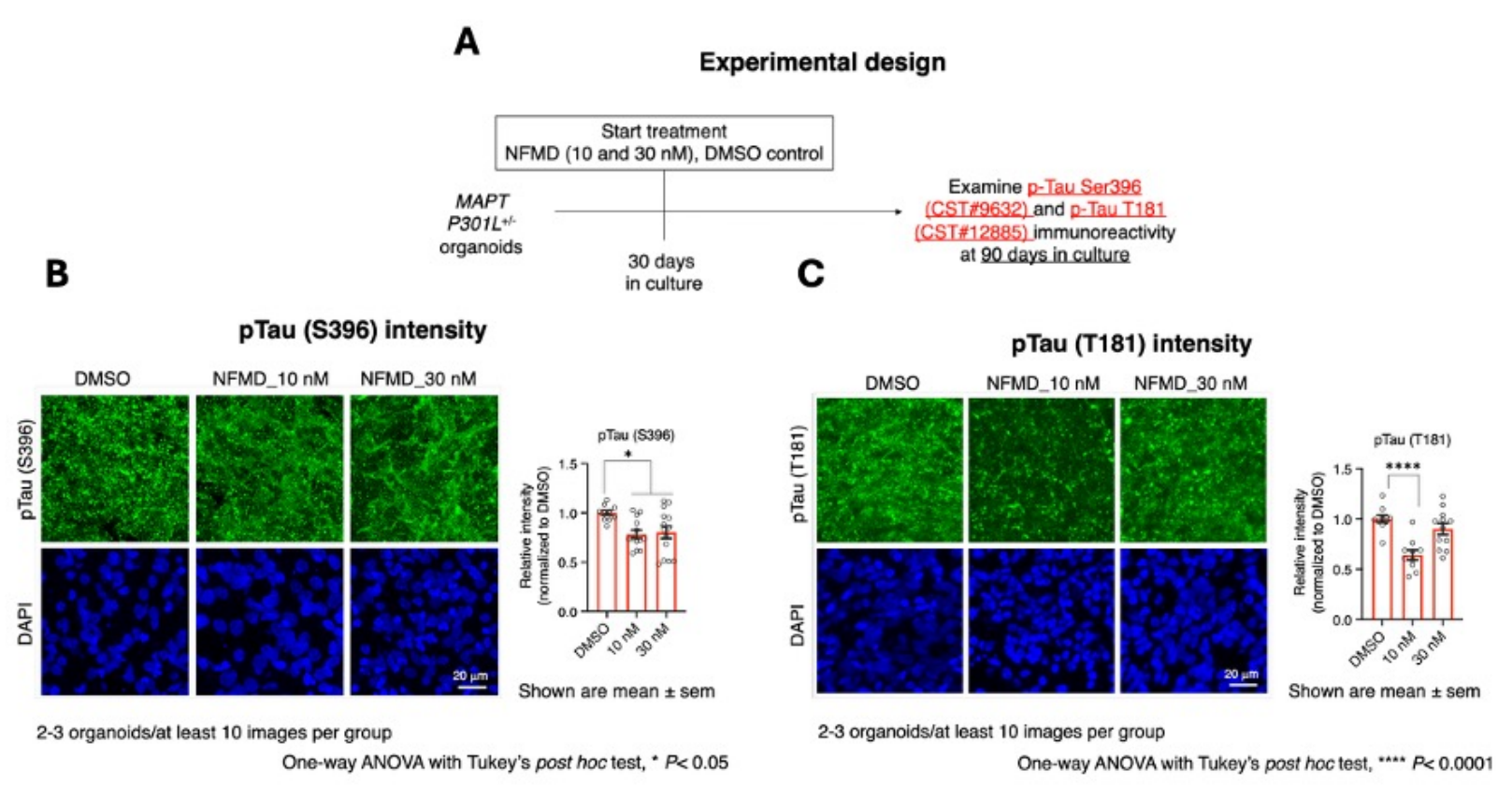
Accepted: 10 March 2026



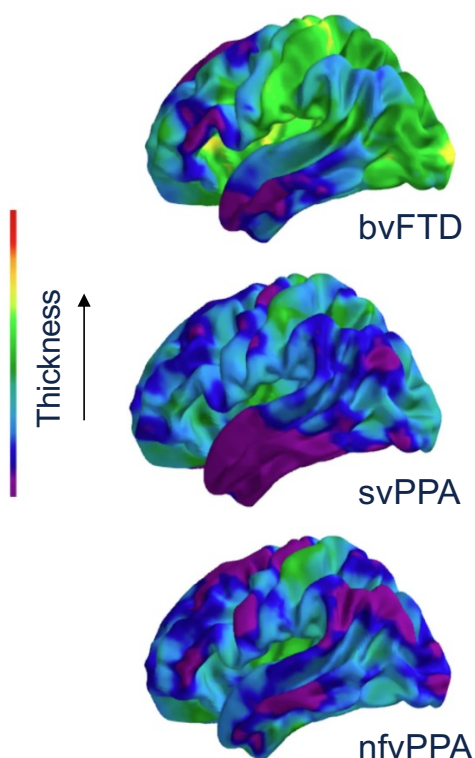
Neflamapimod enhances axonal transport *in vivo* in rTg4510 mice



Neflamapimod at Clinically Relevant Concentrations Reduces Tau Phosphorylation in Cerebral Organoids from FTD Tau P301L Patients



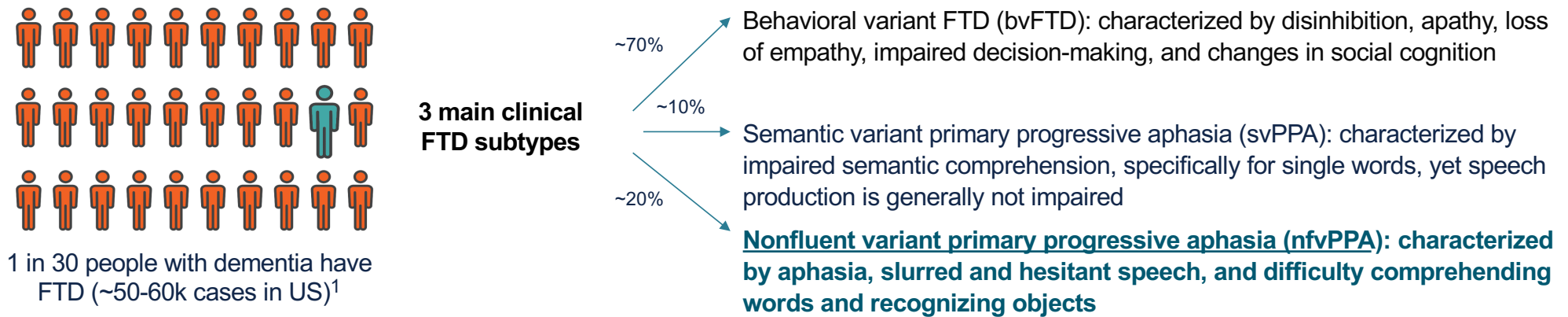
Neflamapimod Targets the Effect of Tau Pathology, the Key Driver of Disease in Non-Fluent Variant Primary Progressive Aphasia (nfvPPA)



- Pathologically, PPA is characterized by significant neuronal loss in the frontal and temporal cortex
- nfvPPA is strongly linked to tau protein aggregation (up to 88% of nfvPPA cases at exhibited FTLD-tau pathology at autopsy)¹
 - svPPA is more closely associated with TDP-43 pathology ^{2,3,4}
- Patients with FTD-tau pathology have also been shown to have significant atrophy in the basal forebrain, the major site of cholinergic neurons within the brain^{5,6}
 - In patients with FTD, the smallest MRI volumes of the basal forebrain were seen in those with tau pathology at autopsy

Progressive changes in cortical thickness over a 12-month period, demonstrating differential regional changes for each variant, with the greatest atrophy in the purple and blue colors. Modified from <https://imaging.cro.biospective.com/resources/neuroimaging-ftd-clinical-trials>. 1. Spinelli, E.G., et al., Typical and atypical pathology in primary progressive aphasia variants. Ann Neurol, 2017. 81(3): p. 430-443; 2. Josephs, K.A., et al., Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain, 2006. 129(Pt 6): p. 1385-98; 3. Mesulam, M., et al., Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. Ann Neurol, 2008. 63(6): p. 709-19; 4. Knibb, J.A., et al., Clinical and pathological characterization of progressive aphasia. Ann Neurol, 2006. 59(1): p. 156-65; 5. Convery, R.S., et al., Basal forebrain atrophy in frontotemporal dementia. Neuroimage Clin, 2020. 26: p. 102210; 6. Lagarde, J., et al., Combined in vivo MRI assessment of locus coeruleus and nucleus basalis of Meynert integrity in amnesic Alzheimer's disease, suspected-LATE and frontotemporal dementia. Alzheimers Res Ther, 2024. 16(1):p. 97.

Overview of Non-Fluent Variant Primary Progressive Aphasia



Patients with nfvPPA experience significant morbidity and mortality



Median age of onset is 62 years (range 49 to 73 years) with median survival from symptom onset of ~7 years²

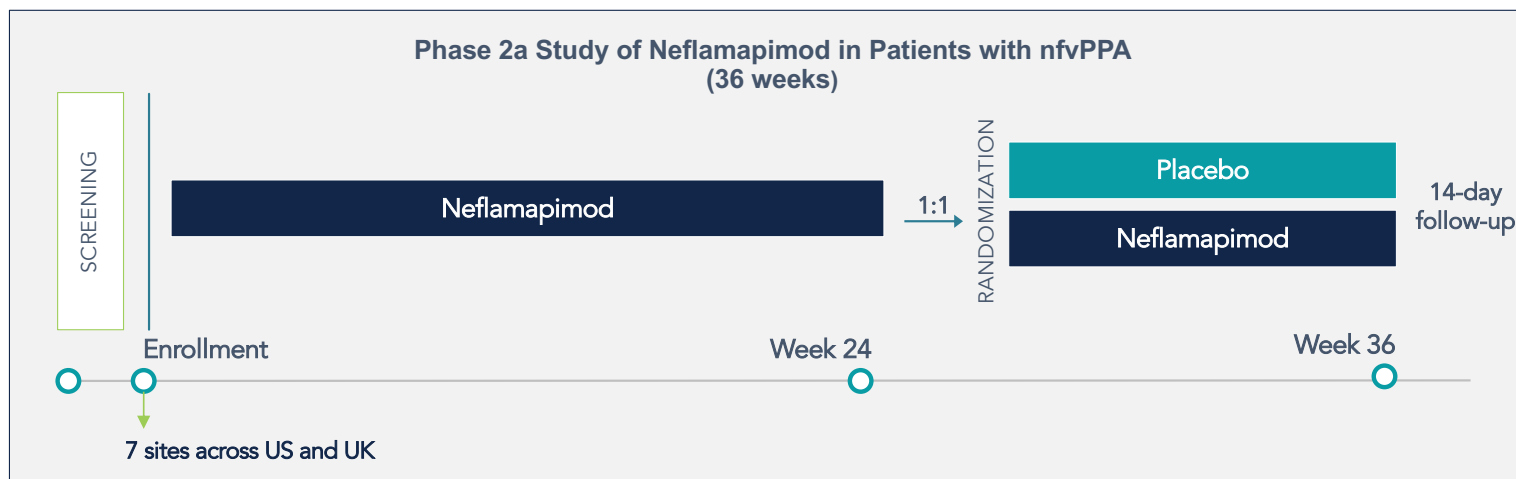


Cognitive impairment, behavioral disturbances, and/or motor deficits can occur as disease progresses^{3,4,5}



No approved treatments for nfvPPA in US; language impairments are managed by speech pathologists^{6,7}

Phase 2a Clinical Trial Design



Patients

- 40 to 85 years
- Clinical diagnosis of nvfPPA by consensus criteria¹
- Global CDR® plus NACC FTLD score of 0.5 or 1
- CDR® plus NACC FTLD language domain score of 0.5, 1 or 2

- The objectives of this exploratory study are to evaluate in patients with nvfPPA:
 - The effect of neflamapimod on clinical measures of aphasia
 - The effect of neflamapimod plasma biomarkers of neurodegeneration (Neurofilament light chain, glial fibrillary acidic protein)
 - The safety and pharmacokinetics of neflamapimod
- Dosing:
 - 40mg TID in the US (5 centers, 19 participants)
 - 80mg BID in the UK (2 centers, 6 participants)

Baseline Characteristics

	Neflamapimod (N=25)
Male: Female	14:11
Age (mean, SD)	69.5 (8.1)
CDR + NACC FTLD-SB (Mean, SD)	3.2 (2.0)
CDR + NACC FTLD-SB Language Domain, 0.5/1.0/2.0	8/10/7
CDR-SB (Mean, SD)	2.0 (1.4)
Western Aphasia Battery (WAB) Aphasia Quotient (Mean, SD)	85.5 (9.2)
WAB Language (Mean, SD)	82.2 (12.1)
WAB Cortical Quotient (Mean, SD)	85.5 (9.2)
Progressive Aphasia Severity Scale (PASS) (Mean, SD)	6.6 (2.6)
Category Fluency Test (words correct) (Mean, SD)	10.9 (6.9)
Letter Fluency Test (words correct) (Mean, SD)	16.2 (8.9)

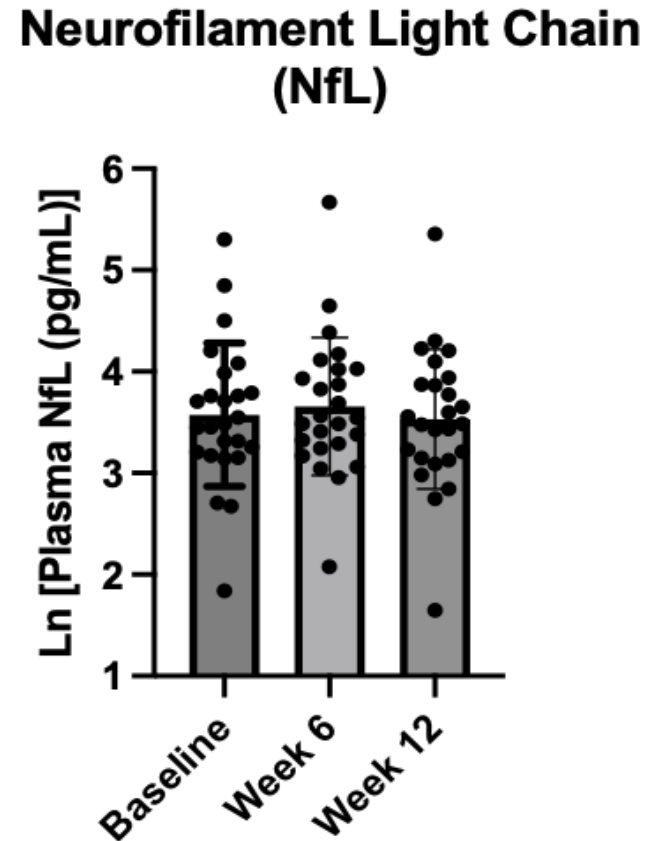
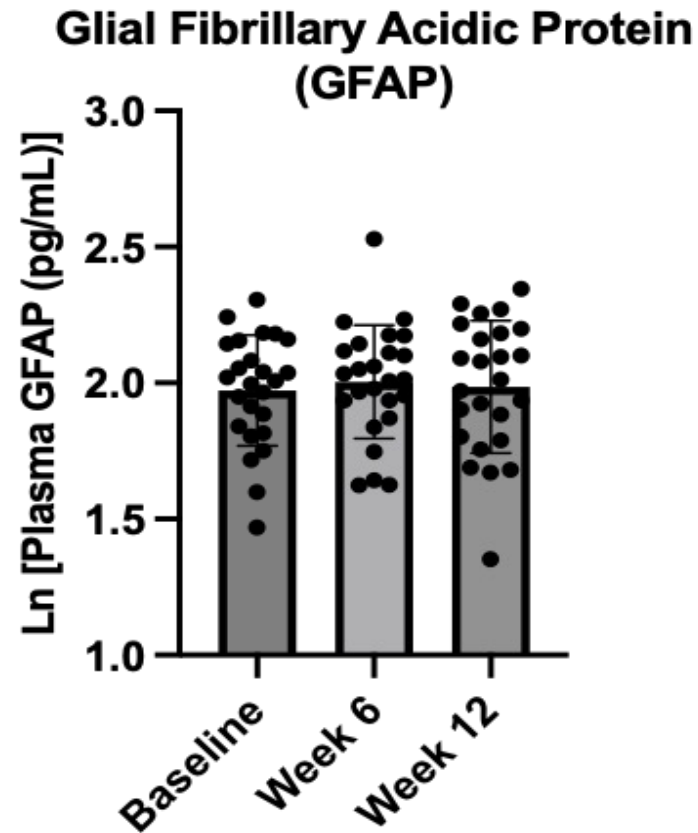
Safety

- Generally well tolerated, with no new safety signals identified and no serious adverse events reported
- Most common treatment emergent adverse events were falls and diarrhea, each reported in 4 (16%) of 25 participants. All events of falls and diarrhea were reported as being mild in severity
- One participant with ALT/AST elevation, treated with 80mg BID, met protocol-defined criteria for treatment discontinuation. Participant was asymptomatic, with no associated bilirubin elevation, and elevations resolved with treatment discontinuation. Two other events of ALT/AST elevation were transient and resolved without treatment interruption

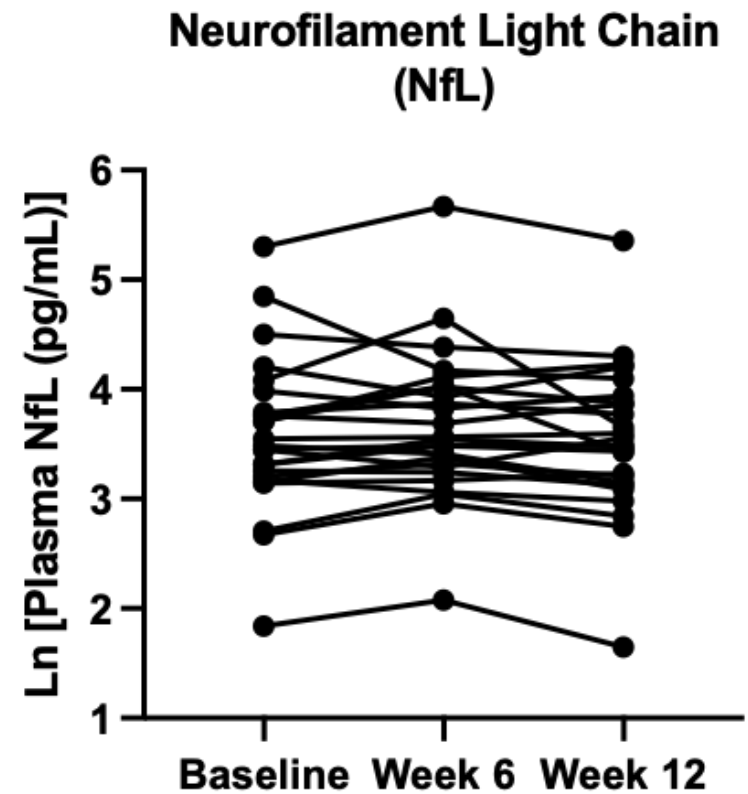
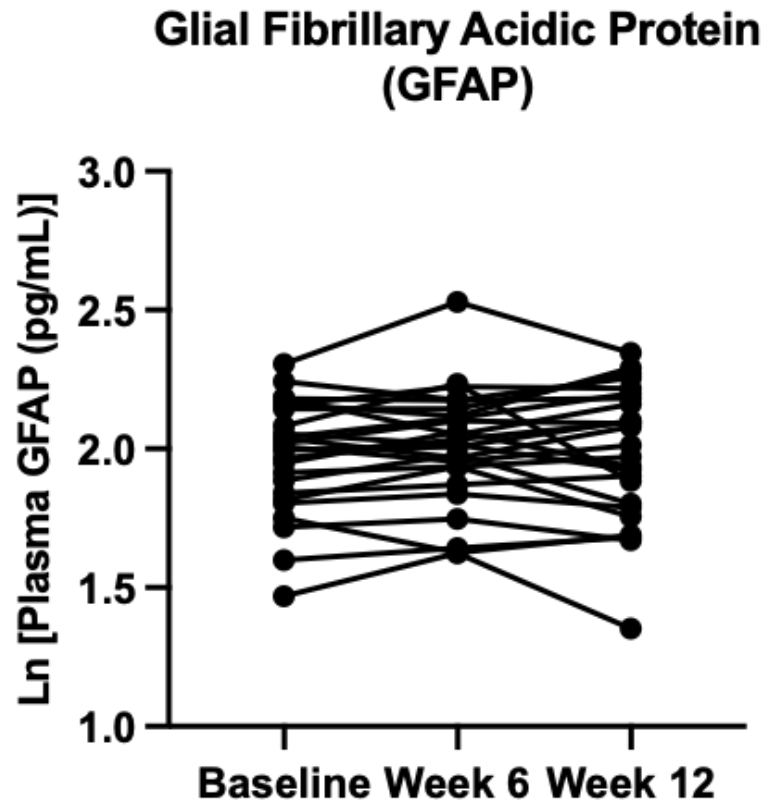
Baseline Levels of Neurofilament Light Chain (NfL) and Glial Fibrillary Acidic Protein (GFAP) in Plasma

	NfL	Plasma GFAP
Mean (SD)	45.7 (39.6)	103.4 (43.2)
Number (%) > 1 SD above healthy control mean	18 of 25 (72%)	4 of 25 (16%)

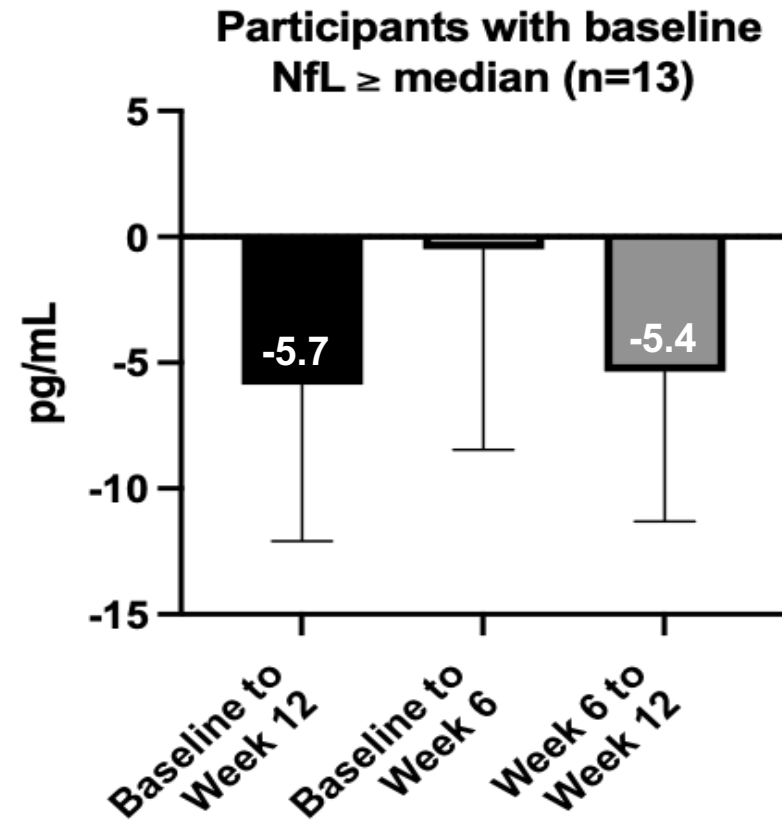
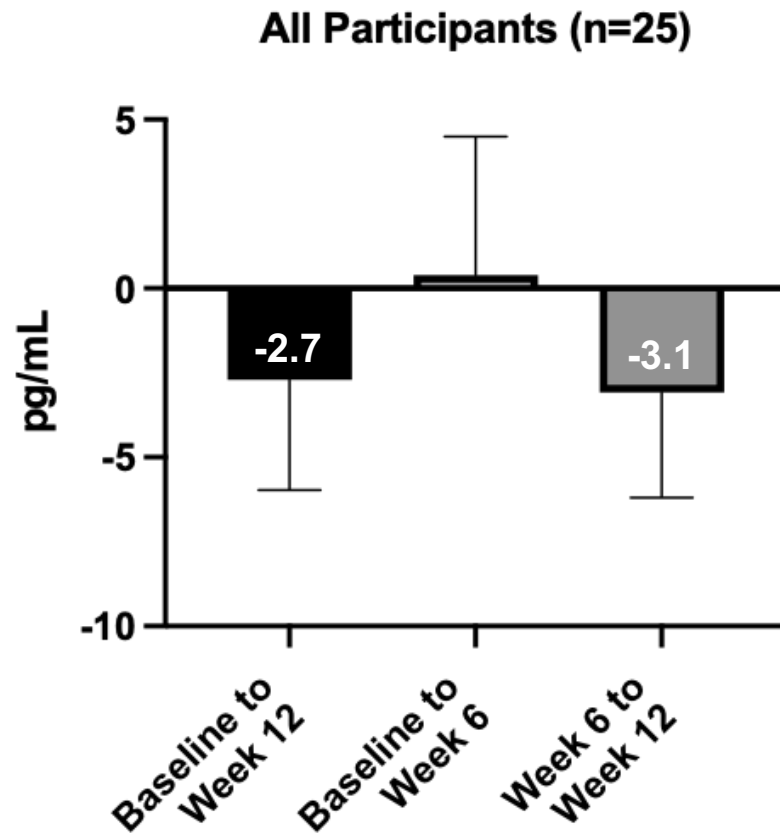
Plasma GFAP and NfL Results Over 1st 12 Weeks of nfvPPA Phase 2a Study



Plasma GFAP and NfL Results Over 1st 12 Weeks of nfvPPA Phase 2a Study



Plasma NfL Over 1st 12 Weeks of nfvPPA Phase 2a Study



Neurofilament Light Chain to Evaluate Drug Effects in Frontotemporal Disorders

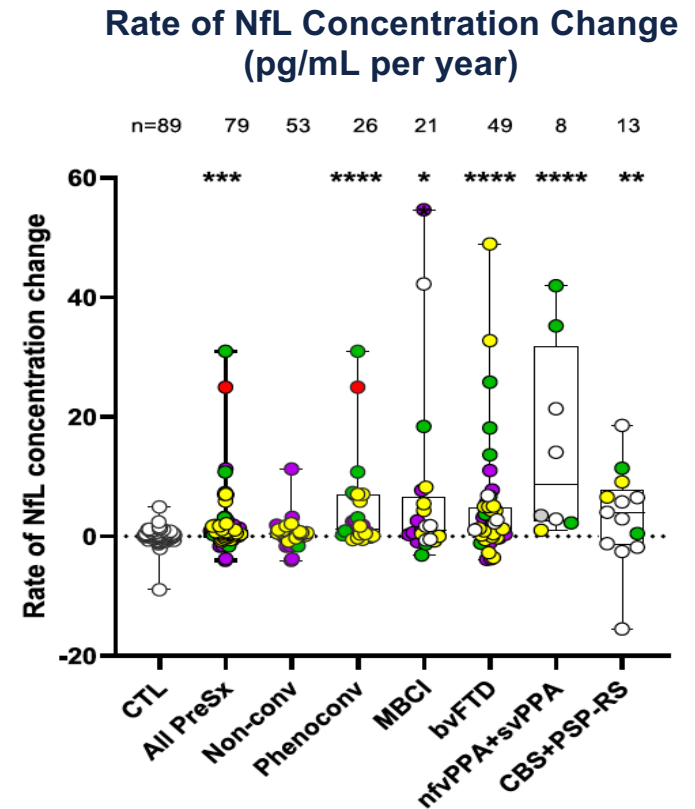
Opportunity

Elevated in majority of patients and in longitudinal studies invariable increases over time

Risks

High intra-subject variability relative to disease-specific elevation (i.e., poor signal-to-noise ratio)

“Extremely slow turnover” in brain with CSF half-life > 3 months (Leckey et al, *Brain Communications*, 2025: fcaf468)



Sheth et al. *Molecular Neurodegeneration* (2025) 20:30

Conclusions

- **Strong mechanistic rationale.** Preclinical evidence supports p38 α inhibition to reduce tau pathology and associated neuronal dysfunction, providing a basis to evaluate neflamapimod in nvPPA.
- **NfL is the more relevant plasma biomarker.** Baseline levels exceeded 1 SD above the healthy-control mean in 72% of participants for NfL, compared with 16% for GFAP.
- **Early NfL findings warrant follow-up.** Decreased by 3.7 pg/mL over 12 weeks in overall population, with a 5.7 pg/mL decrease among participants with baseline NfL at or above the median (n=13) and the decline occurring between weeks 6 and 12. GFAP showed no clear change.
- **Longer follow-up will clarify the signal.** 24-week biomarker results to be presented at CTAD conference in Nov'26 and 24-week clinical data to be presented at AD-PD conference in Mar'27. Final analysis, including placebo-controlled randomized withdrawal phase, in Q2'27.

Acknowledgements

- Patients and caregivers
- Clinical project teams at CervoMed, Inc.
- Neurochemistry laboratory at Amsterdam Medical Center
- Study investigators and clinical site staff at clinical sites:

University of Pennsylvania Site PI: David J. Irwin, MD

Mayo Clinic Site PI: Hugo Botha, M.B.Ch.B.

Northwestern University Site PI: Ian M. Grant, MD

Columbia University Site PI: Lawrence S. Honig, MD, PhD

Ohio State University Site PI: Douglas W. Scharre, MD

Newcastle University (United Kingdom) Site PI: Dr Meher Lad

Cambridge University (United Kingdom) Site PI: Dr Alexander G Murley