LB25 - Plasma biomarker data indicates clinical activity of neflamapimod in dementia with Lewy bodies (DLB) is mediated through effects on the basal forebrain cholinergic system

John Alam[1] , Charlotte Teunissen [2]

[1]CervoMed Inc. – Boston (United States), [2]Amsterdam UMC, Vrije Universiteit – Amsterdam (Netherlands)

cerveau (sair-voh), noun, in French for *brain* or *mind*

Disclosures

- Neflamapimod is an investigational drug
- J. Alam is an employee of CervoMed, Inc., which is developing neflamapimod and the sponsor of the clinical trial
- C. Teunissen has a collaboration contract with Quanterix Corporation, the company that provides and markets the ptau181 assay utilized in the current study

Acknowledgements

- Patients, caregivers, study investigators and clinical site staff involved with the AscenD-LB study
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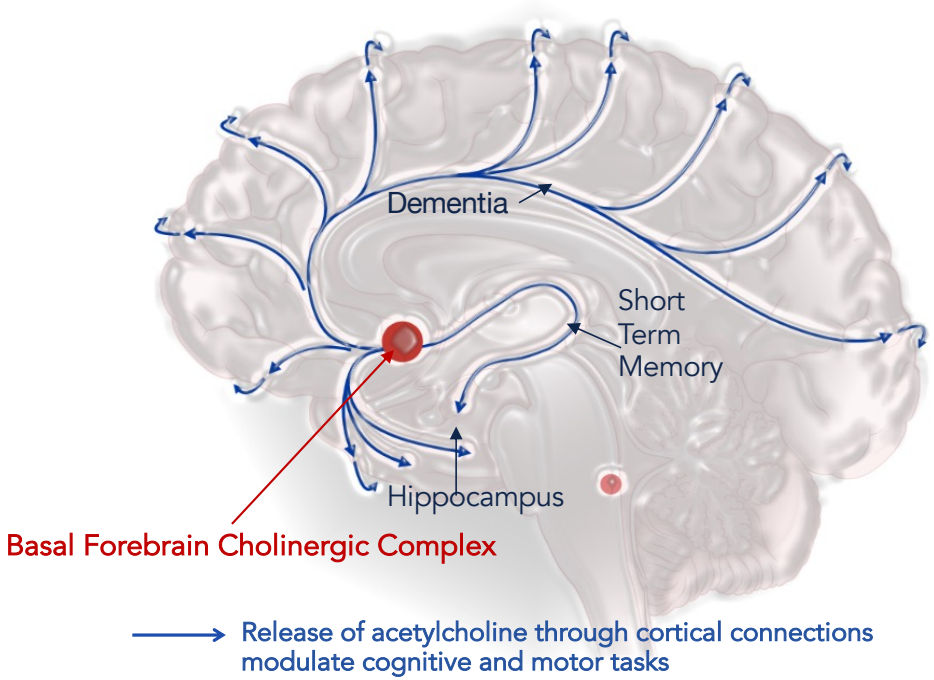
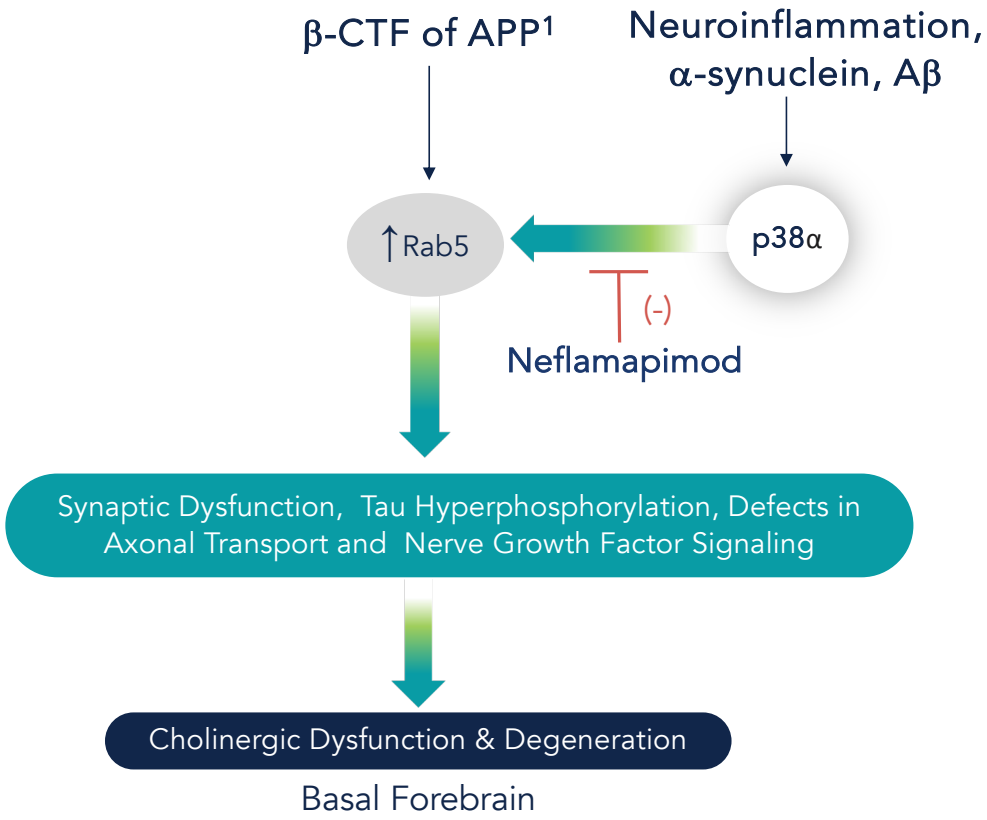
- Amanda Gardner, Jennifer Conway, and Kelly Blackburn in the Clinical Development group at CervoMed, Inc.

Neflamapimod: Oral p38α Kinase Inhibitor that Targets Cholinergic Dysfunction and Degeneration



Disease processes in basal forebrain are reversible



NGF: Nerve Growth Factor

Adapted from Alam & Nixon, *Molecular Neurodegeneration, 2023.* 1. APP: Amyloid Precursor Protein

CERVOMED

Neflamapimod Background

Pre-Clinical

Through inhibiting p38α, protein kinase mediating cellular response to neuroinflammation, acts on molecular mechanisms underlying cholinergic degeneration:

- Rab5
- Tau

In mice that develop basal forebrain cholinergic degeneration:

- ✓ ↓ Rab5 activity and ↓ tau phosphorylation
- ✓ Reverses reversed loss of cholinergic (ChaT+) neurons in the basal forebrain
- ✓ Normalized performance in behavioral tests of cholinergic function

Studies in Early AD

Two pilot Phase 2a studies (n=25, total):

- ✓ Reached target concentration in CSF
- ✓ ↑ in basal forebrain volume and its functional connectivity by MRI

161-patient 24-week placebo-controlled study:

- ✓ ↓ CSF levels of total tau and phospho-tau
- ✓ Evidence of slowing of disease progression in PK/PD analysis

AscenD-LB

Phase 2a Study in DLB

16-week placebo-controlled study in patients with DLB

Placebo (N=45) vs. Neflamapimod 40 mg (N=46)), BID or TID

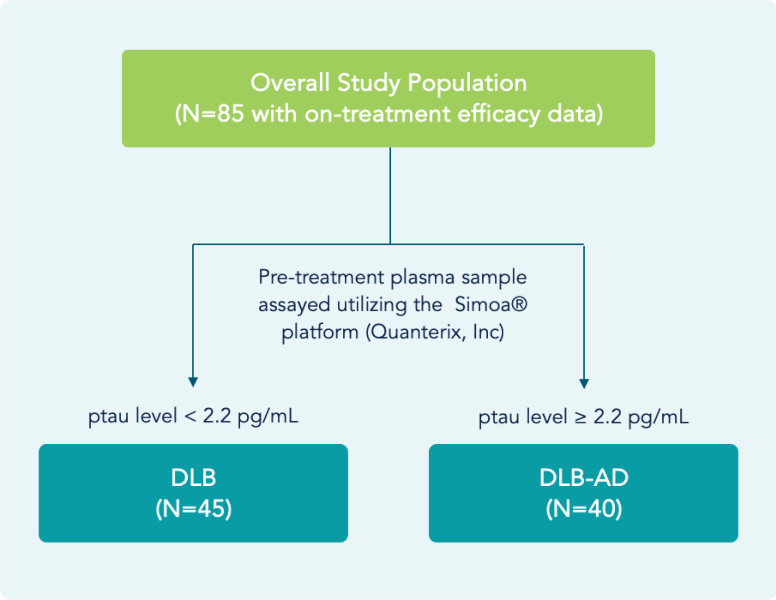
Results vs. placebo:

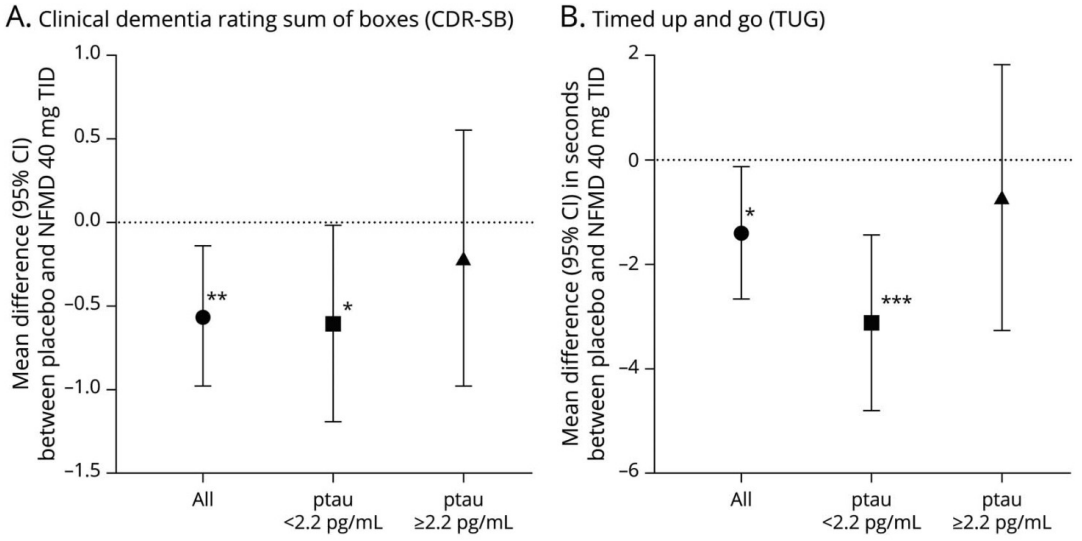
- ✓ Significant improvement on dementia severity (CDR-SB) and mobility (TUG) in full efficacy population analysis (i.e. including BID dose)
- ✓ Significant improvement on cognitive testing at 40mg TID vs. placebo, particularly with respect to attention
- ✓ Results most prominent in patients without elevated plasma ptau181

Abbreviations. CDR-SB: Clinical Dementia Rating Sum of Boxes; TUG: Timed Up and Go test

References: Prins et al, 2021; Jiang et al, 2022; Alam et al, 2023; Prins et al, JPAD, 2024

Phase 2a AscenD-LB Results Stratified by Plasma ptau181 Levels



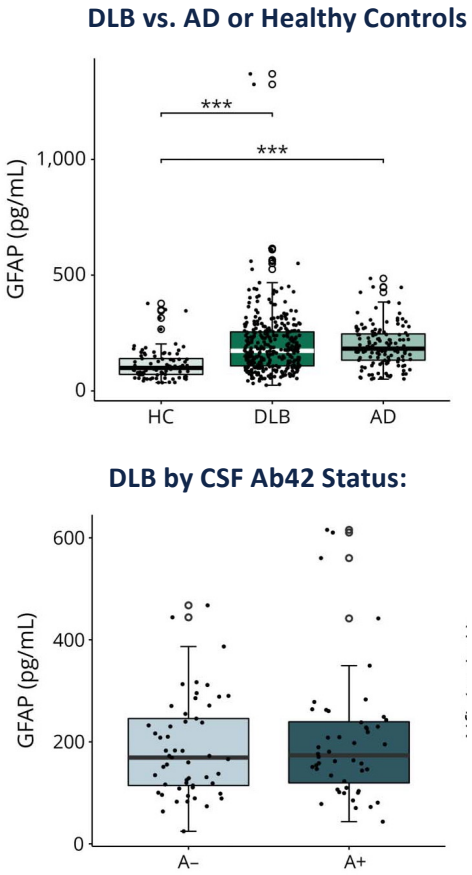


*$P<0.05$, **$P<0.01$, ***$P<0.001$

Alam et al, *Neurology*, 2023

Blood Glial Fibrillary Acidic Protein (GFAP) as a Biomarker of the Neurodegenerative Process in DLB

- A marker of astrocyte activation, as well neurodegeneration[1,2]
  - Correlated to cognitive decline, as well to tau (and not amyloid) pathology by autopsy[3] and PET scan[4]
- In Parkinson's disease, associated with cognitive impairment[5], motor subtype[6] and predicts dementia conversion[7]
- Elevated in MCI-DLB (aka prodromal DLB), while other plasma biomarkers (NfL, ptau) are not.[8]
- In DLB[9,10], associated with rate of cognitive decline, but not with CSF Aβ42 status, suggesting that GFAP elevation has potential to evaluate DLB-specific disease processes



Bolsweig et al, *Neurology,* 2024

[1] Abdelhak et al, 2022 [2]Want et al, 2024 [3] Sanchez-Juan et al, 2024 [4] Peretti et al, 2024[5] Lin et al, 2023
[6] Che et al, 2024 [7] Tang et al, 2023 [8] Diaz-Galvan et al, 2024 [9] Bolweig et al, 2024 [10] Vrillon et al, 2024

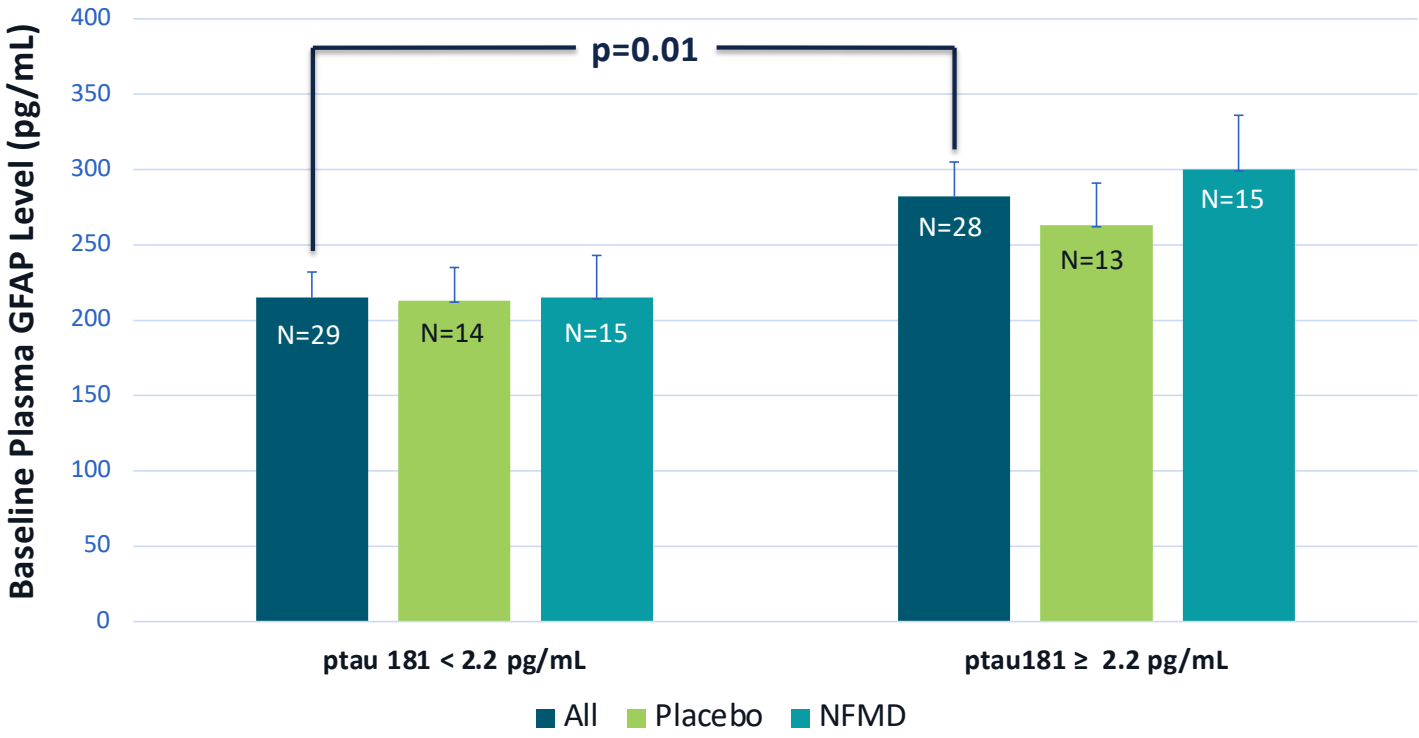
Objectives

- To report on the effects of neflamapimod on plasma GFAP in AscenD-LB and correlate the results to emerging understanding of DLB pathogenesis.

Methods

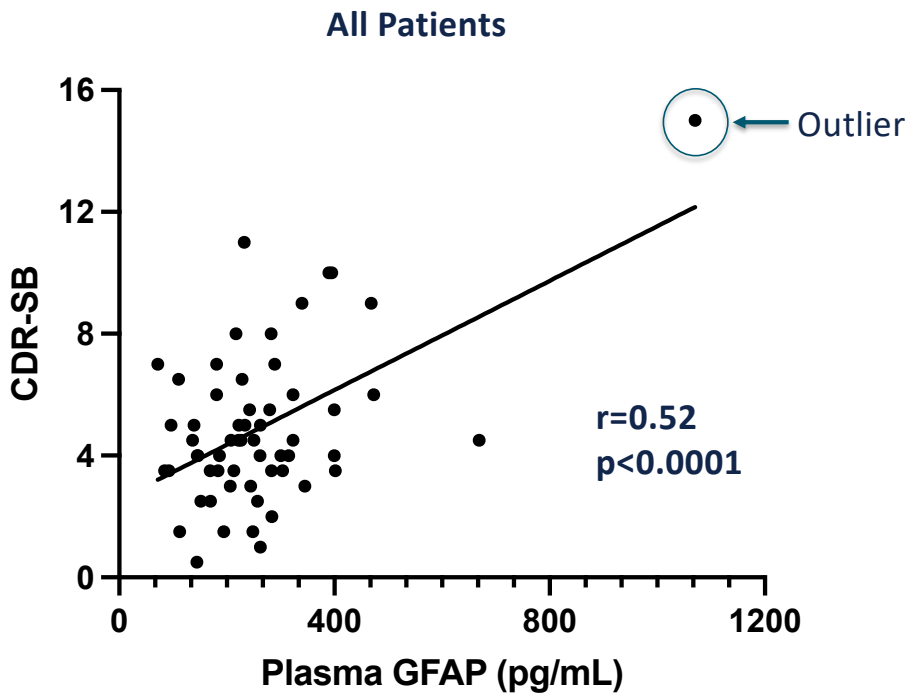
- Stored pre-treatment and Week 16 plasma samples available for 57 patients (28 placebo, 29 neflamapimod)
- GFAP levels (pg/mL) determined in these samples using Simoa® platform
- Analysis stratified by pre-treatment plasma ptau181 < or ≥ 2.2 pg/mL (as per Alam et al, *Neurology*, 2023)

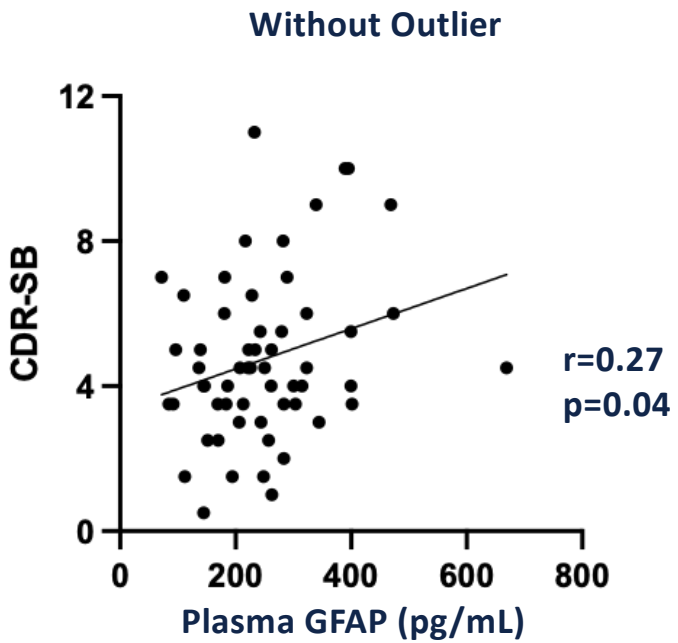
Baseline GFAP Levels (pg/mL) by Baseline ptau181 Strata and Treatment Group



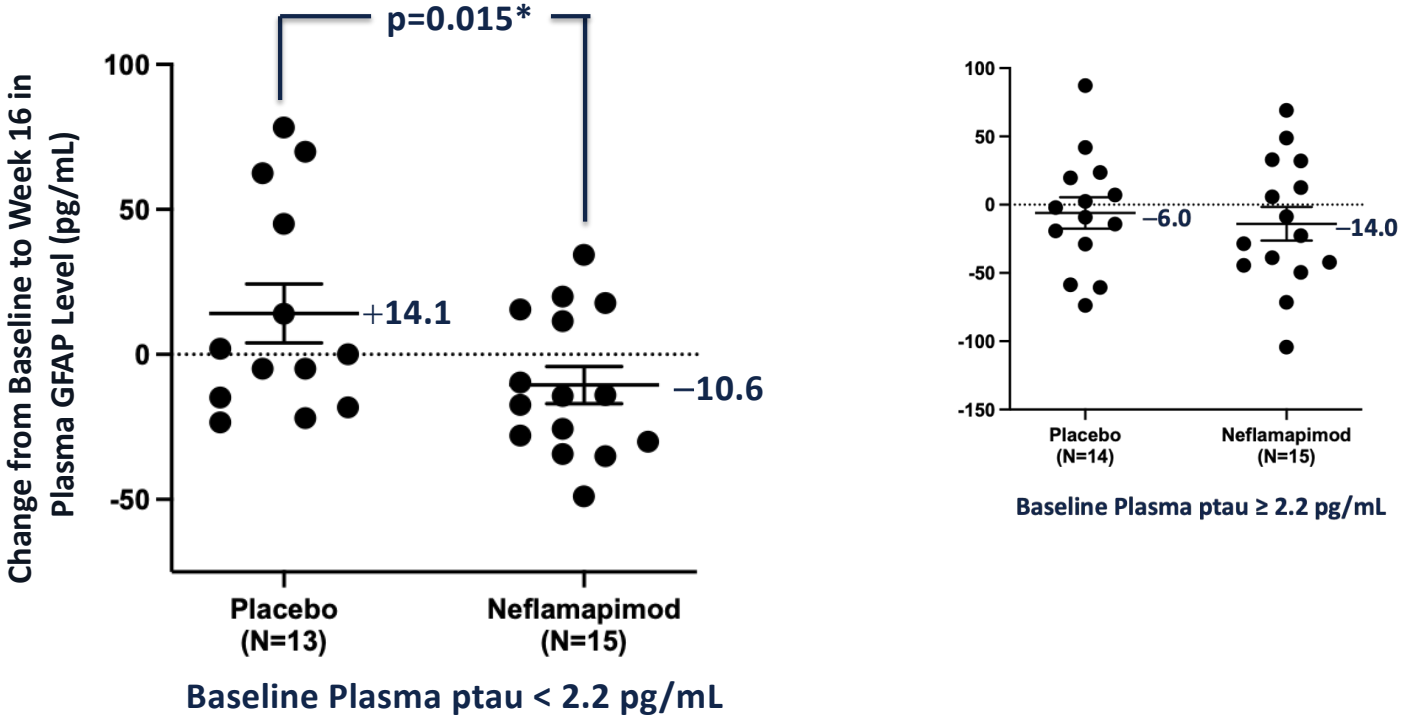
Both strata significantly elevated compared to healthy controls from the literature (Hamilton et al, *Psychol Med*, 2023

Baseline level of GFAP is correlated to baseline CDR-SB score



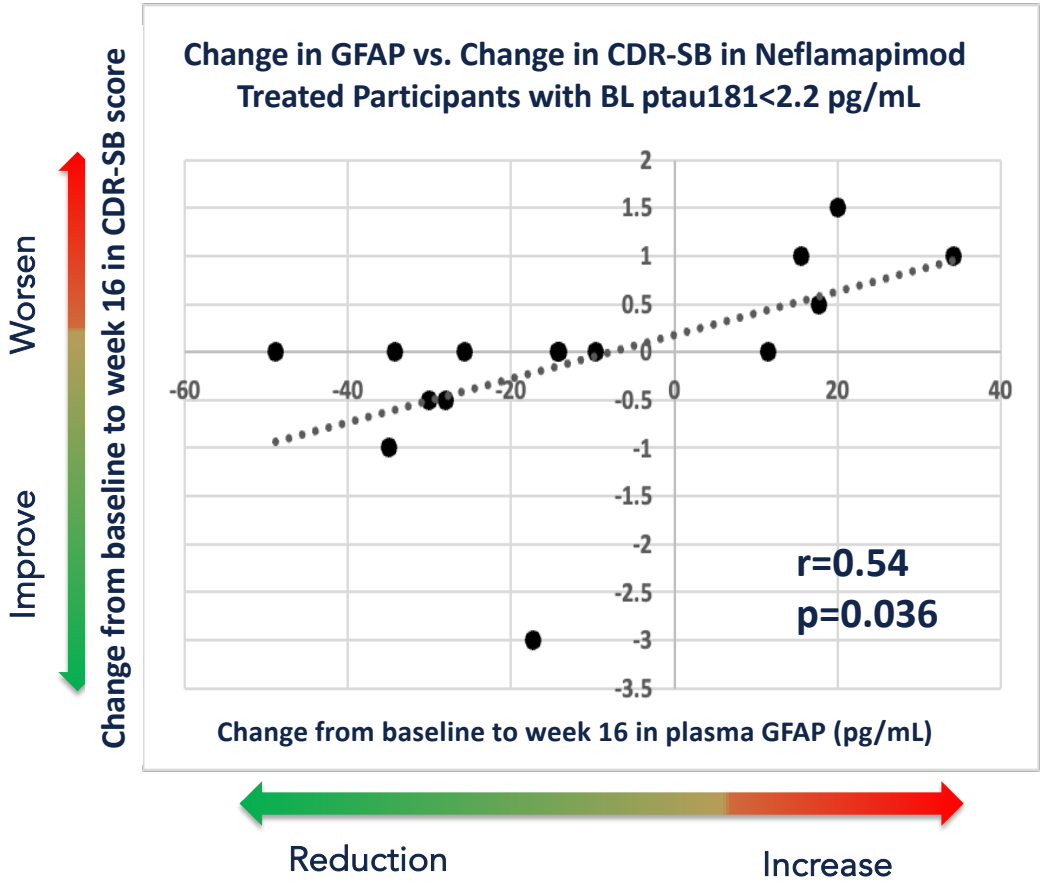


On Treatment, Neflamapimod Reduced GFAP Levels in Patients with pre-treatment ptau181< 2.2 pg/mL

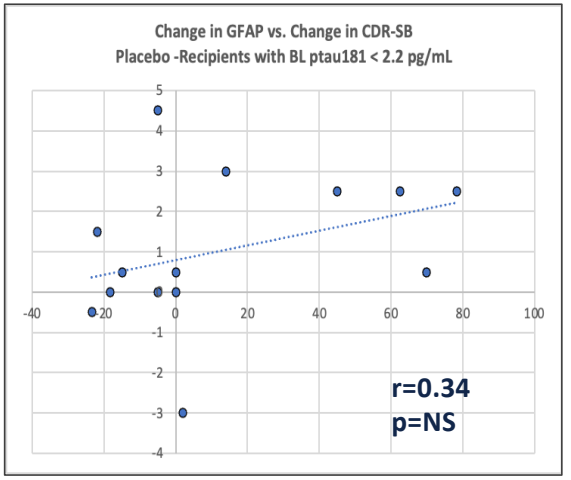


*ANCOVA with baseline as a covariate

On-treatment change in GFAP is correlated to clinical outcome, as assessed by change in CDR-SB



Correlation not seen in placebo-recipients



Discussion: Plasma ptau181 and underlying pathology in dementia with Lewy bodies

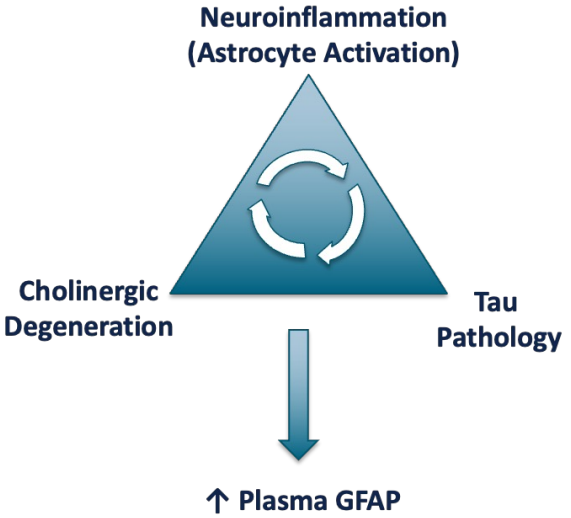
- 2.2 pg/mL cut-off is based on published report that indicates that value was optimal cut-off for CSF biomarker positive (A+T+) confirmed AD dementia[1]
- In DLB, plasma ptau181 associated with:
  - PET amyloid status, but more strongly associated with tau PET status (positive "AD signature tau signal"; AUC=0.82) status[2], with optimal cut-off for tau PET status being 2.3 pg/mL
  - CSF ptau181/Aβ42 ratio, with optimal cut-off of 2.5 pg/mL[3]; also correlated to A+T+ by CSF (AUC=0.85)[4]
  - Medial temporal lobe atrophy by MRI, with optimal cutoff of 2.4 pg/mL (unpublished data from Charlotte Teunissen, Amsterdam Medical Center)

DLB Patients with elevated plasma ptau181 represent those with temporal lobe neurodegeneration, while those without plasma ptau181 are those in whom temporal lobe is spared; while all patients with DLB have significant cholinergic dysfunction and degeneration[5]

[1] Bayoumy et al, 2021 [2] Diaz-Galvan et al, 2024 [3] Abdelnour et al, 2024 [4] Vrillon et al, 2024 [5] Okkels et al, 2024

Discussion

- Selective effect on plasma GFAP of a cholinergic degeneration directed therapy in patients DLB (i.e., those with pure cholinergic deficit), and not in DLB-AD, further supports that GFAP elevation is associated with disease in the basal forebrain cholinergic system
- The association between plasma GFAP and CDR-SB, both at baseline and on-treatment, is consistent with astrocyte activation being a major contributor to the cholinergic degenerative process
  - 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]
  - GFAP-IL6 transgenic mice develop basal forebrain cholinergic degeneration[6]
  - Astrocyte reactivity associated with synaptic dysfunction preclinically[7] and clinically[8].
  - Plasma GFAP associated with abnormalities of cholinergic pathways by MRI (diffusion-tensor imaging) in humans[9]

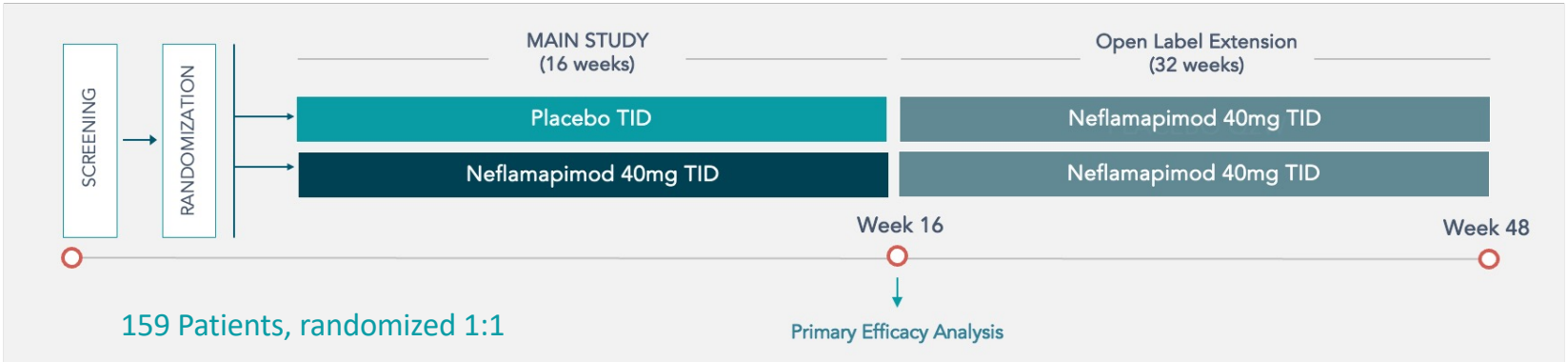


[1] Willard et al, 1999 [2] Quail et al, 2011 [3] Liu et al, 2024 [4] Peretti et al, 2024 [5] Mesulam et al, 2013 [6] Gamage et al, 2024 [7] Portal et al, 2023 [8] Pascoal et al, 2024 [9] Bettcher et al, 2024 [10] Pontecorvo et al, 2024

Conclusions

- Plasma GFAP appears to be a robust, and treatment responsive biomarker of the underlying disease process in the basal forebrain cholinergic system
- Neflamapimod has a significant beneficial pharmacological effect on the basal forebrain cholinergic system and its clinical activity in DLB appears to be mediated by this effect
- The results also provide further support that basal forebrain cholinergic degeneration is the primary driver of disease expression in patients with DLB who do not have evidence of tau pathology and associated temporal lobe atrophy.

RewinD-LB Phase 2b Clinical Trial Ongoing



- Topline results from the double-blind portion of the study to be announced in Dec'24
- Oral presentation at ILBDC conference in in Jan'25