OC5 - Effects of the oral p38α kinase inhibitor neflamapimod on motor function (gait) in patients with mild-to-moderate dementia with Lewy bodies (DLB)

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Disclosure

- John J. Alam and Kelly Blackburn are employees of EIP Pharma, Inc., a private company developing the investigational drug neflamapimod as a treatment for dementia with Lewy bodies

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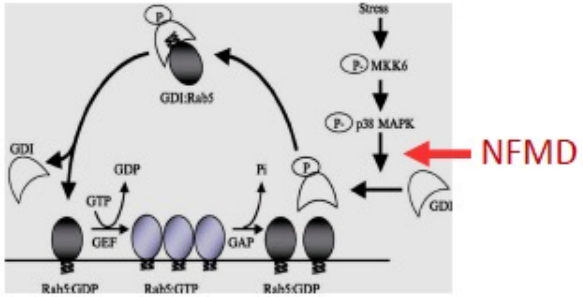
Background

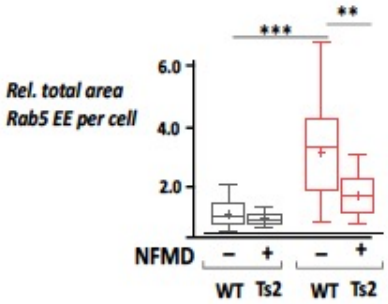
- Neflamapimod is an oral p38α kinase inhibitor that targets pathogenic mechanisms involved in cholinergic degeneration.
  - Reverses deficits in Morris-water-maze performance in aged rats (21-day treatment)
  - Restores the number of cholinergic neurons in medial septal nucleus in Ts2 transgenic mice (4-week treatment), that develop adult-onset basal forebrain cholinergic degeneration
- At last year's CTAD, initial results of a 91-patient, 16-week treatment placebo-controlled study ("*AscenD-LB Study*") in mild-to-moderate dementia with Lewy bodies were reported:
  - 40mg TID neflamapimod significantly ($p<0.05$) improved cognition relative to placebo, as assessed by a 6-test Neuropsychological Test Battery designed to evaluate attention and executive function
  - 40mg TID also significantly improved relative to placebo results on Timed Up and Go test, an effect attributed at the time to the positive effect on cognition

Neflamapimod blocks Rab5 over-activation and neuroprotects DS mice (Ts2)

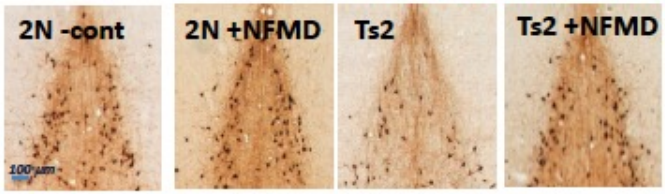
NFMD: a specific p38a inhibitor

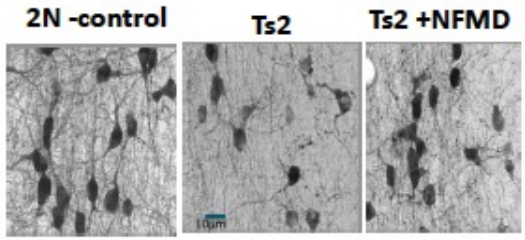


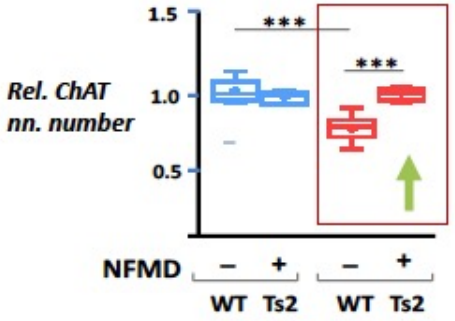
Blocks rab5 EE enlargement



Rescues cholinergic neurodegeneration

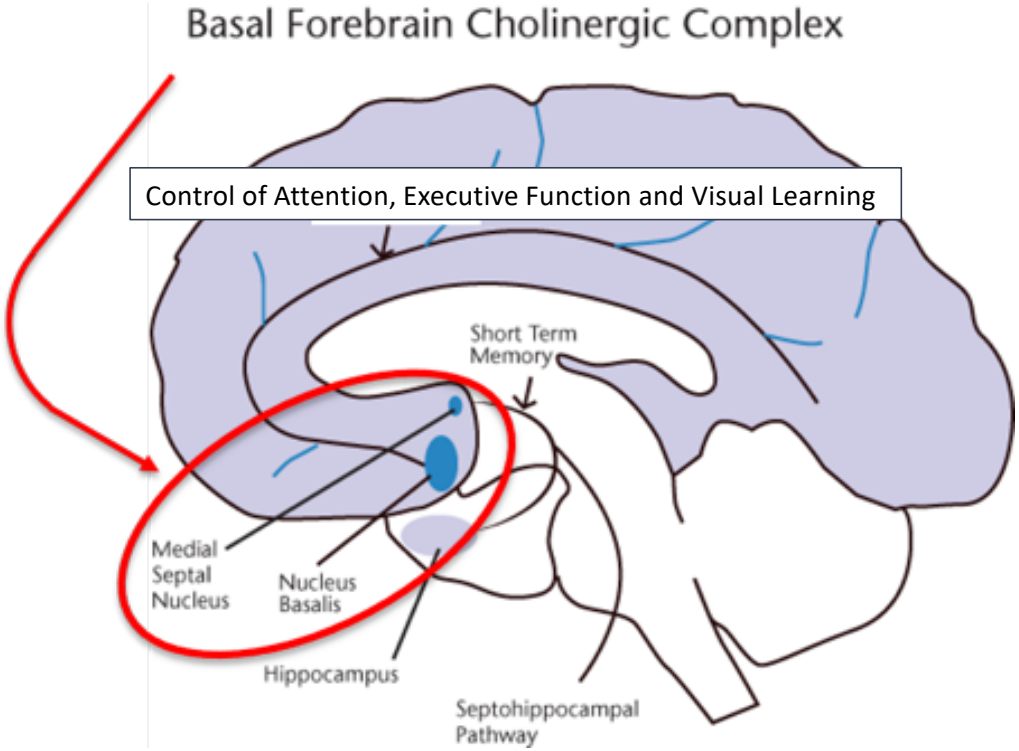






Nixon RA, Digital Symposia RS3, CTAD 2021, Presentation #2: Mechanisms of, and Preclinical Results with Novel Approaches to Treating, BFCN Dysfunction and Degeneration

Rationale for Primary Endpoint in AscenD-LB Clinical Study



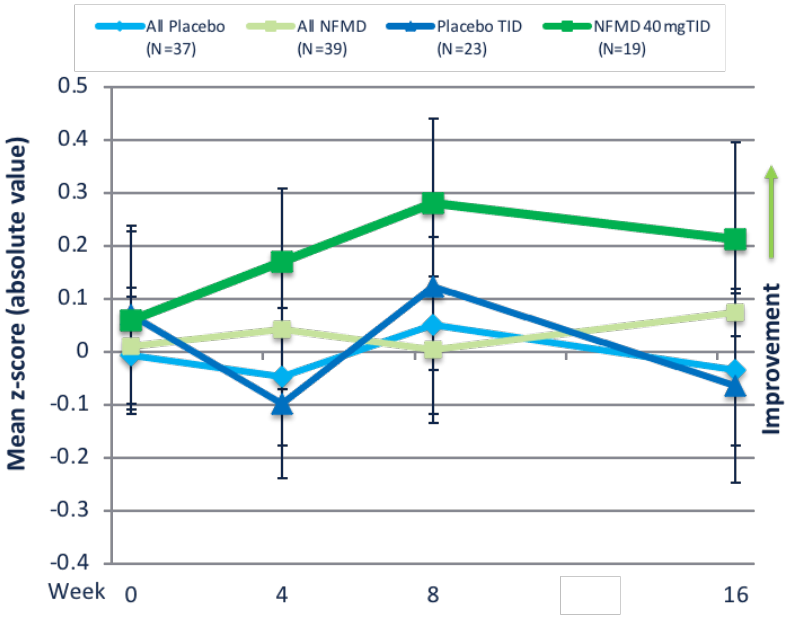
Neuropsychological Test Battery (NTB):

- Detection (computerized)
- Identification (computerized)
- One Card Learning (computerized)
- One Back (computerized)
- Letter Fluency Test (recorded on paper)
- Category Fluency Test (recorded on paper)

AscenD-LB Results: Neflamapimod Improves Cognition in DLB

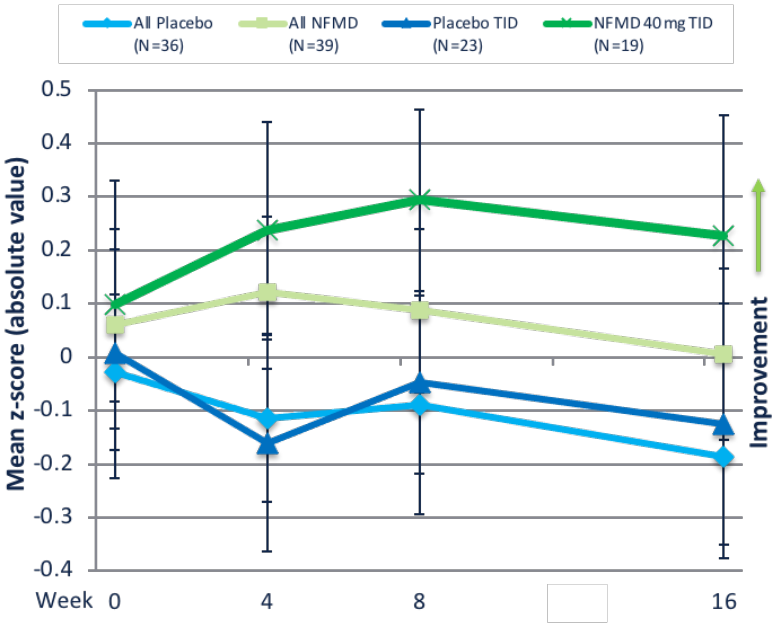
Neuropsychological Test (NTB*) Composite

p=0.049 (effect size=0.47) for NFMD 40mg TID vs. placebo



Attention Composite

p=0.023 (effect size=0.41) for NFMD 40 mg TID vs. Placebo



*6-test cognitive test battery designed to assess attention and executive function

Oral Presentation at CTAD 2020

Effect on TUG Reflects Distinct Role of the Cholinergic System in Control of Gait

RESEARCH ARTICLE

CME **Cholinergic Basal Forebrain Volumes Predict Gait Decline in Parkinson's Disease**

Joanna Wilson, MRes,[1] Alison J. Yarnall, FRCP, PhD,[1,2] Chesney E. Craig, PhD,[3] Brook Galna, PhD,[1,4] Sue Lord, PhD,[5] Rosie Morris, PhD,[6] Rachael A. Lawson, PhD,[1] Lisa Alcock, PhD,[1] Gordon W. Duncan, FRCP, PhD,[7,8] Tien K. Khoo, FRCP, PhD,[9,10] John T. O'Brien, DM, FMedSci,[11] David J. Burn, FRCP, MD,[12] John-Paul Taylor, MBBS(hons), PhD, MRCPscyh,[1] Nicola J. Ray, PhD,[3†] and Lynn Rochester, PhD[1†*]

"In conclusion, nucleus of basalis of Meynert (NBM) atrophy measured in PD can predict future disease-specific gait changes. Findings reinforce the notion that gait control in PD involves the cortical cholinergic system, and that acetyl choline should, therefore, be considered as a therapeutic target to mitigate gait dysfunction.

Wilson et al, Movement Disorders 2021 36:611-621

doi:10.1093/brain/awaa411 BRAIN 2021: 144: 781–788 | 781

BRAIN
A JOURNAL OF NEUROLOGY

REPORT

Cortical connectivity of the nucleus basalis of Meynert in Parkinson's disease and Lewy body dementias

Ashwini Oswal,[1,2,3,†] James Gratwicke,[4,†] Harith Akram,[4] Marjan Jahanshahi,[4] Laszlo Zaborszky,[5] Peter Brown,[1,2] Marwan Hariz,[4,6] Ludvic Zrinzo,[4] Tom Foltynie[4] and Vladimir Litvak[3]

We observe that NBM-cortical structural and functional connectivity correlate within spatially and spectrally segregated networks including a beta band network to supplementary motor area….

Gait variability is linked to the atrophy of the Nucleus Basalis of Meynert and is resistant to STN DBS in Parkinson's disease

Kevin B. Wilkins[a], Jordan E. Parker[a], Helen M. Bronte-Stewart[a,b,*]

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Objective of Today's Presentation

To evaluate the effects of neflamapimod on motor function in the *AscenD-LB* clinical study

Phase 2 Proof-of-Concept Study p38α kinase inhibition in Dementia with Lewy Bodies (DLB)

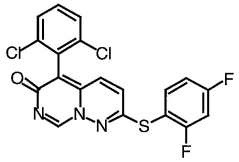
AscenD-LB

Patients

- Mild-to-Moderate DLB by consensus criteria (McKeith, *Neurology*, 2017)
- Abnormal dopamine uptake by DaTscan™
- **On background cholinesterase inhibitor therapy**
- 91 patients

16-WEEK TREATMENT, DOUBLE-BLIND
NFMD 40 mg or placebo, twice or thrice daily

Neflamapimod (NFMD): Oral p38α kinase inhibitor



Objectives

- 1º: Evaluate cognition, assessed by DLB-specific Neuropsychological Test Battery (NTB)
- 2º: Cognition and Function, assessed by CDR-SB; Motor Function, assessed by Timed Up and Go (TUG) test

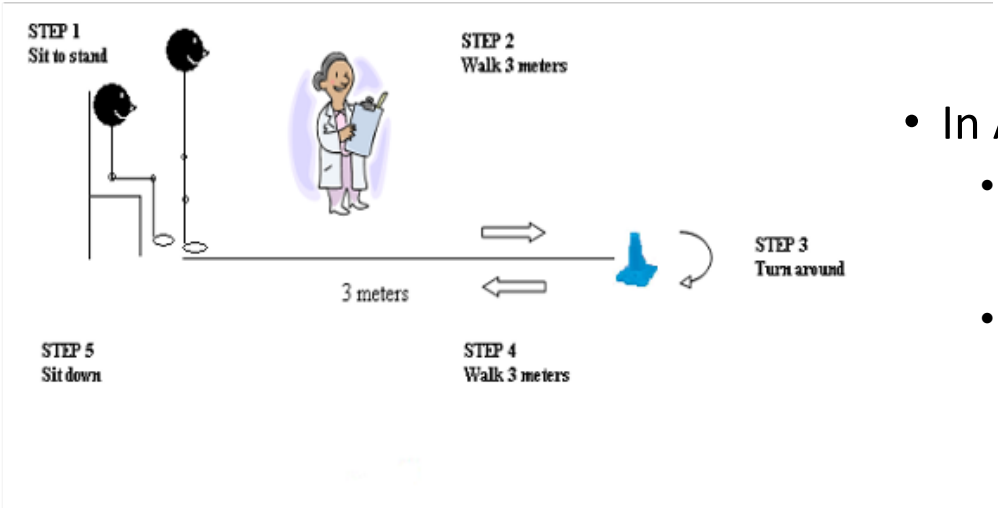
AscenD-LB Weight-Based Dosing Regimen

- With the objective of uniformly achieving a target average plasma drug concentration of 20nM patients, dosing regimen after randomization to neflamapimod or placebo was based on weight:
  - Weight < 80kg: 40mg neflamapimod capsule or matching placebo capsule BID
  - Weight ≥ 80kg: 40mg neflamapimod capsule or matching placebo capsule TID
- However, in the study, 40mg TID achieved target plasma drug concentration; but 40mg BID did not, missing by approximately 30-40%
  - Trough plasma drug concentrations 50% lower with 40mg BID vs. 40mg TID
- As a result, efficacy analyses compared compared (1) all neflamapimod (i.e., including 40mg BID and 40mg TID) vs. placebo; (2) 40mg TID (dose group that achieved target concentration) vs. placebo

Baseline Disease Characteristics

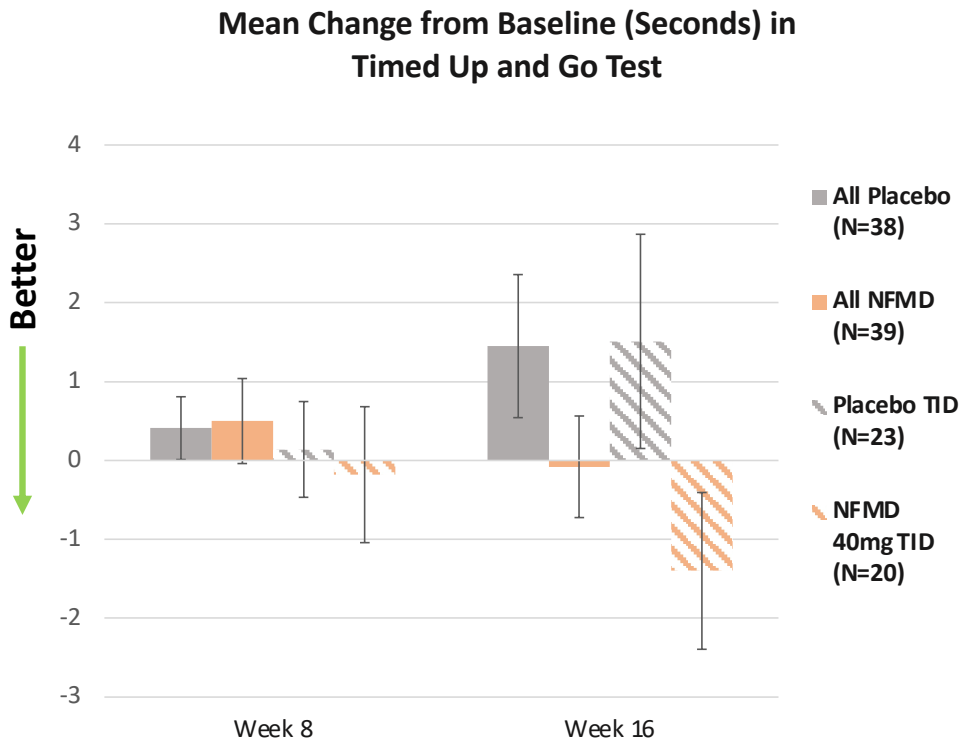
	Placebo (N=45)	NFMD ALL (N=46)	Placebo TID (N=27)	NFMD 40mg TID (N=20)
Age (years)	72.1 (6.9)	73.5 (6.9)	70.4 (5.7)	72.2 (6.6)
Male	87%	85%	96%	95%
CDR Sum of Boxes	5.1 (3.2)	4.9 (1.8)	4.3 (2.3)	4.7 (1.8)
MMSE	23.0 (3.3)	23.1 (3.9)	23.6 (3.3)	23.4 (3.3)
Timed Up and Go (seconds)	13.5 (6.4)	12.7 (3.7)	13.3 (5.2)	13.3 (3.8)

Timed Up and Go (TUG) Test



- Validated test of functional mobility
  - High test-retest reliability(ICC ≥ 0.80)
  - In PD, time required to complete > 11.5 seconds associated with increased risk of falls, with every one second increase associated with 5.4% increased in risk (Nocera et al, 2013)
- In AscenD-LB at baseline:
  - Mean time required to complete 13.5 seconds in placebo, 12.7 in combined neflamapimod, and 13.3 sec in neflamapimod 40 mg TID
  - 12 of 45 (27%) placebo participants and 13 of 46 (28%) of neflamapimod participants were receiving carbidopa-levodopa
    - One neflamapimod and three placebo participants started carbidopa-levodopa during the study

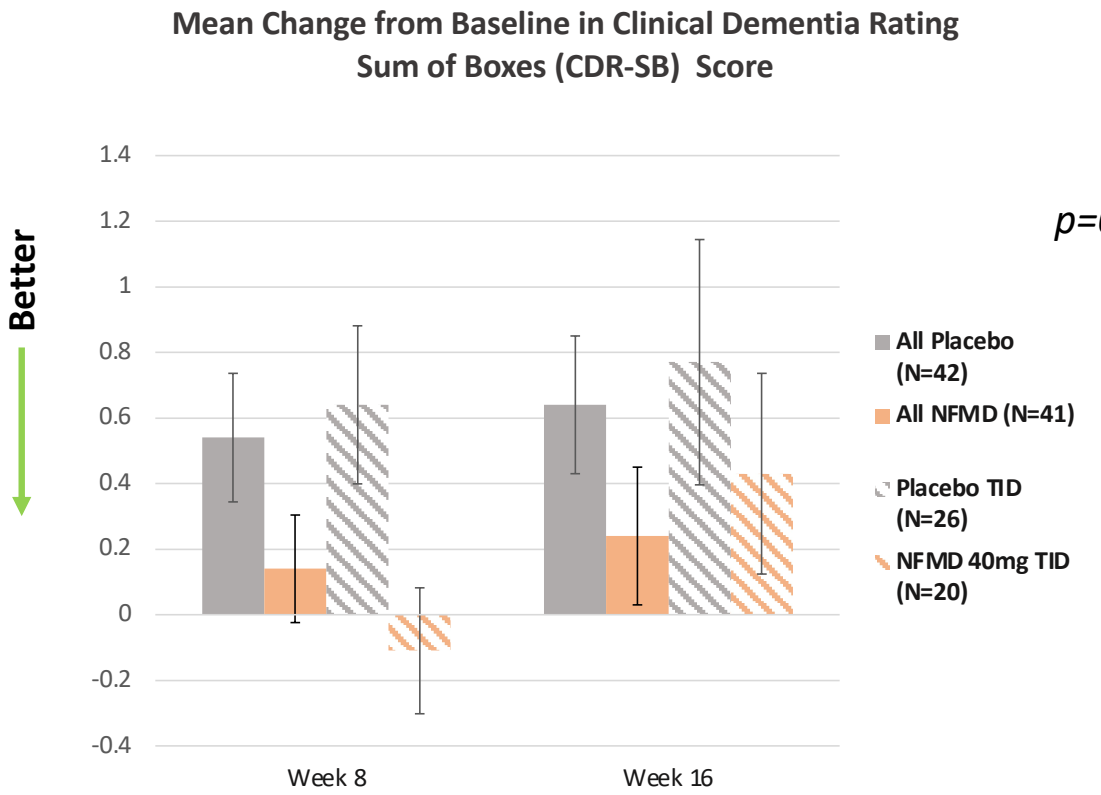
AscenD-LB Results: Neflamapimod is First Drug to Show Significant Beneficial Effect on Functional Mobility in DLB



p=0.044 all neflamapimod vs. all placebo, p=0.024 neflamapimod 40mg TID vs. all placebo, (Linear Mixed Model for Repeated Measures)

Mean difference of 1.4 seconds for each comparison

AscenD-LB Results: Significant Reduction in Worsening of Global Cognition and Function (Dementia Progression)



p=0.024 for all neflamapimod vs. all placebo
p=0.007 for all neflamapimod 40mg TID vs. all placebo
(Linear Mixed Model for Repeated Measures)

Compared to placebo, neflamapimod treatment led to 65% reduction in worsening from baseline to week 16

Late-Breaking Poster (LP14)

Impact of Alzheimer's disease (AD) related co-pathology on treatment effects of the oral p38α kinase inhibitor neflamapimod in mild-to-moderate dementia with Lewy bodies (DLB)

John Alam 1, Stephen Gomperts 2, 3, Afina Lemstra 4, 5, Inge Verberk 4, Sherif Bayoumi 4, Hui-May Chu 6, Amanda Gardner 1, Kelly Blackburn 1, Niels Prins 4, 5, Charlotte Teunissen 4

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Hypothesis:

If the beneficial activity of neflamapimod is through improving basal forebrain cholinergic degeneration, it should be more effective in patients with DLB without co-pathology (where primary disease pathology is in the basal forebrain) than in patients with DLB with co-pathology (where there is significant pathology in other regions of the brain)

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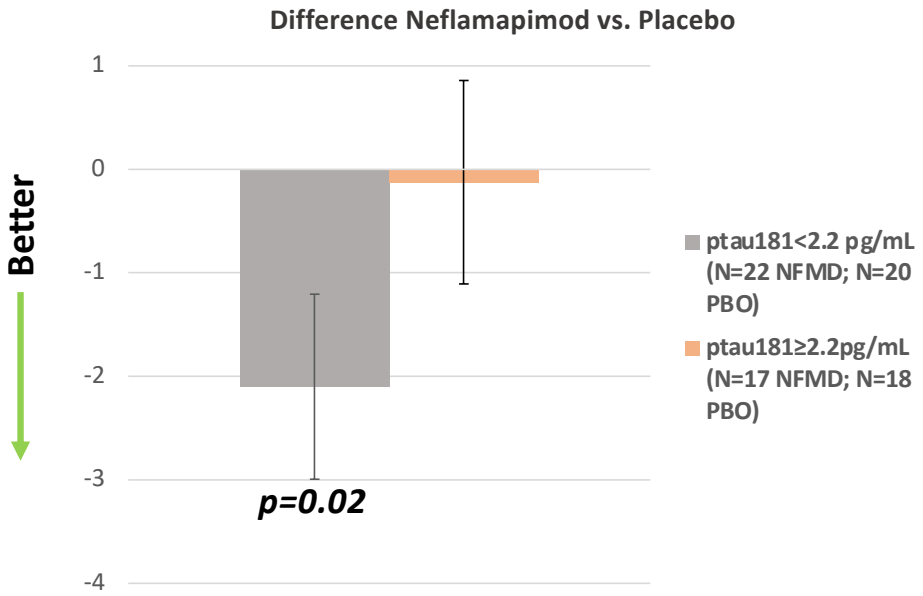
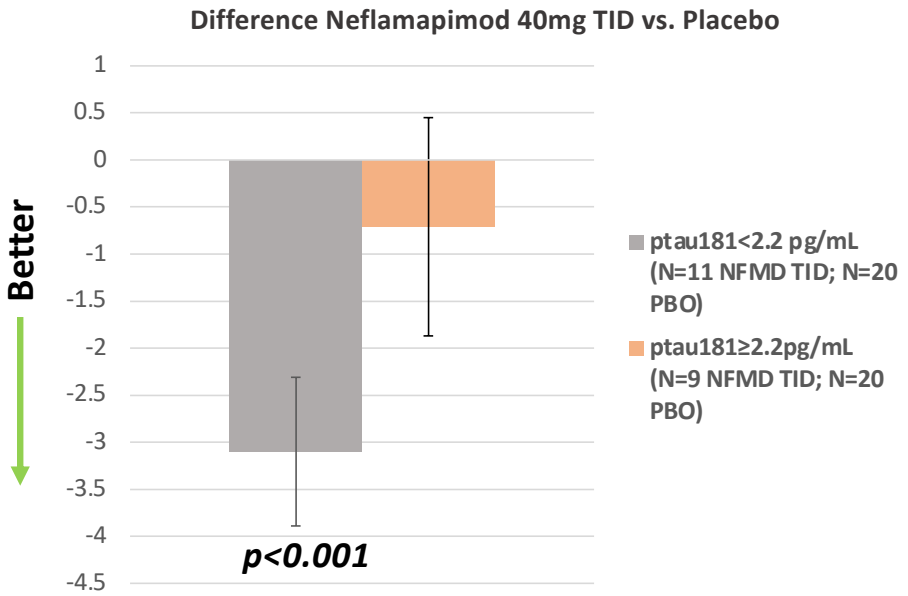
Summary:

- Baseline samples from AscenD-LB assayed at VUMc in Amsterdam for plasma p-tau181, a biomarker that is predictive of AD co-pathology (particularly cortical tau pathology) in patients with DLB (Hall et al, 2021)
  - 53% of patients had baseline plasma ptau181 < 2.2 pg/mL (cut-off for AD pathology set at VUMc, based on internal dataset), indicating absence of co-pathology
- Analysis of efficacy stratified by plasma ptau181 status shows patients without co-pathology demonstrated demonstrated better efficacy, with effect size ranging from 0.56 to 0.78 for the major efficacy endpoints for the comparison of 40mg TID vs. placebo

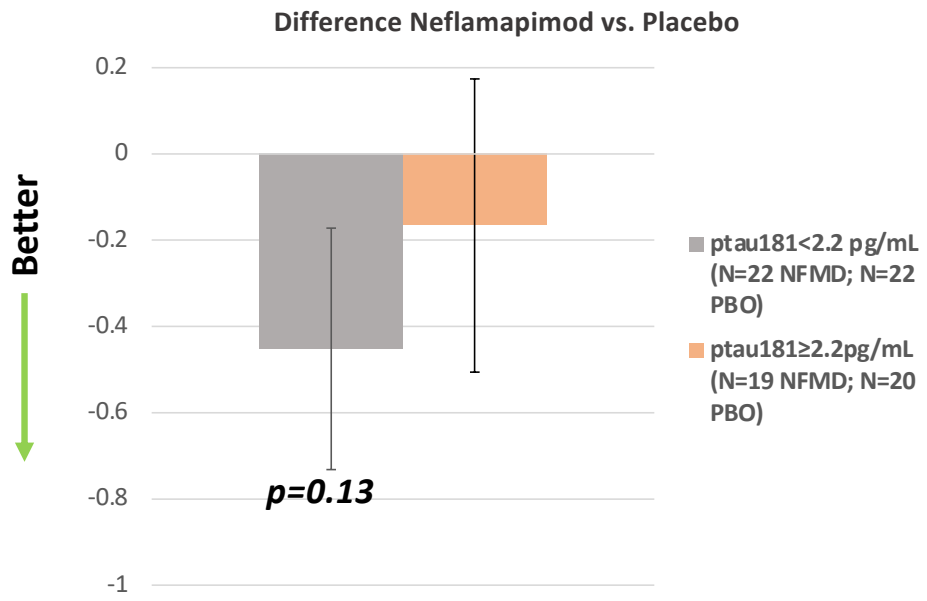
Timed Up and Go (TUG) results by baseline plasma ptau181 status

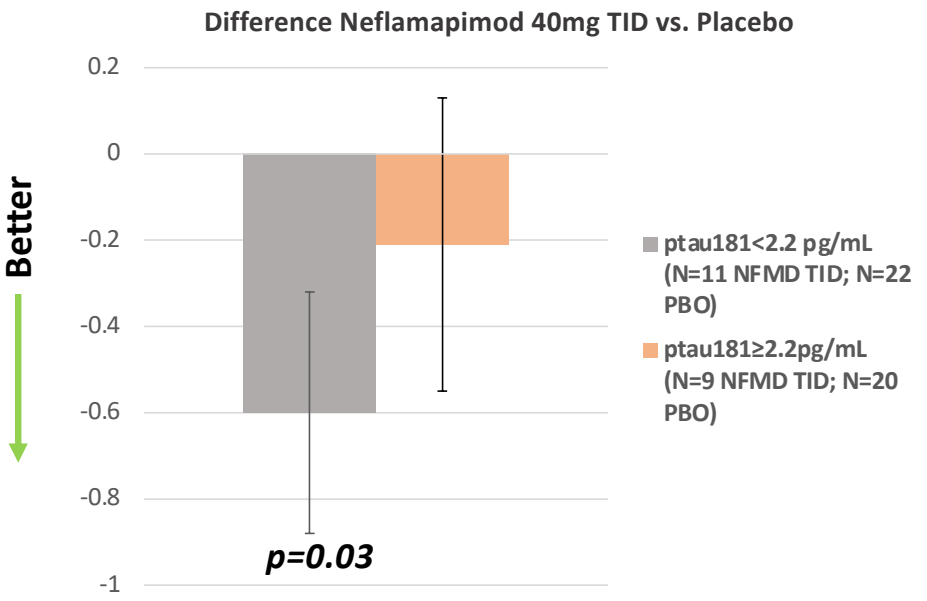




Baseline plasma ptau181 < 2.2 pg/mL predicted to not have co-pathology, ≥ 2.2 pg/mL predicted to have co-pathology

CDR-SB by baseline plasma ptau181 status





Baseline plasma ptau181 < 2.2 pg/mL predicted to not have co-pathology, ≥ 2.2 pg/mL predicted to have co-pathology

Summary of Final AscenD-LB Results

- Neflamapimod treatment led to significant, dose-dependent improvement vs. placebo on multiple major clinical aspects of dementia with Lewy bodies:
  - ✓Cognition: Neuropsychological Test Battery, Attention Composite
  - ✓Functional Mobility (motor function): Timed Up and Go Test
  - ✓Cognition and Function (Dementia Progression): Clinical Dementia Rating sum of boxes (CDR-SB)
    - Particularly robust effects on CDR-SB may reflect the test being able to capture the combined effect on cognitive and motor aspects of DLB.
- Clinical effects, including better effects in patients without co-pathology, are consistent with substantial improvement in basal forebrain cholinergic function

Conclusions

- Relative to placebo, neflamapimod improves cognition, motor function, and cognition & function (dementia progression) in mild-to-moderate dementia with Lewy bodies, consistent with a disease-modifying effect on basal forebrain cholinergic degeneration
- The positive effects on functional mobility (TUG test) provides further evidence of the role of the cholinergic system in the development of gait dysfunction in Lewy body disorders
- From DLB clinical trial standpoint:
  - The TUG test appears to be a robust clinical trial endpoint to evaluate cholinergic function and dysfunction
  - The CDR-SB has potential as a primary endpoint to evaluate dementia progression