Efficacy and safety results of REVERSE-SD, phase-2b clinical study of the selective p38α kinase inhibitor neflamapimod in early-stage Alzheimer's disease (AD)

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Disclosures

- Philip Scheltens is a consultant to EIP Pharma, Vivoryon, Biogen, Toyama, Green Valley, Novartis,
- Niels Prins consultant to EIP Pharma, Boehringer Ingelheim, Vivoryon, and Fuji Film Toyama Chemical. He serves on the DSMB of Abbvie's M15-566 trial. He is CEO and co-owner of the Brain Research Center, The Netherlands.
- John Alam is founder and CEO of EIP Pharma, Inc., the study sponsor
- Kelly Blackburn is an employee of EIP Pharma, Inc.
- John Harrison consults for 23andMe, AC Immune, Alkahest, AlzeCure, Aptinyx, Athira Pharma, Axon, Axovant, Biogen, BlackthornRx, Boehringer Ingelheim, Cognition Therapeutics, Compass Pathways, Curasen, DeNDRoN, EIP Pharma, Eisai, Eli Lilly, FSV7, GfHEU, Heptares, Johnson & Johnson, Kaasa Health, Longeveron, Lundbeck, Lysosome Therapeutics, Merck, Neurocentria, Neurodyn, Neurotrack, Novartis, Nutricia, Regeneron, Rodin Therapeutics, Roivant, Samumed, Sanofi, Signant Health, Syndesi Therapeutics, Takeda, Vivoryon & WinterLight Labs. Patents and share options: MyCognition & Neurotrack.

Background

- Neflamapimod is a potent, oral selective small molecule inhibitor of the alpha isoform of the intracellular signal transduction enzyme p38 MAP kinase (p38α)
- p38α implicated in oligomeric Aβ and IL-1β impairment of synaptic plasticity
  - Also implicated in βCTF mediated induction of Rab5+ endosomal enlargement and associated endosomal/endocytic dysfunction
- Genetic knockout of neuronal p38α or selective inhibitors of p38α inhibitors improve behavioral abnormalities and synaptic transmission in animal models of AD
  - Neuronal p38α knockout in APP/PS1 mice also reduces amyloid-beta production and pathology; and selective p38α inhibitors reverse tau pathology in aged h-tau mice

Li et al, 2011; Correa et al, 2012; Koppensteimer et al, 2016; Prieto et al, 2015; Roy et al, 2015; Alam, 2015; Maphis et al, 2016; Colie et al, 2017; Jiang et al, 2019; Schnoder et al, 2016

Neflamapimod: Prior Experience

- Preclinical
  - Reversed spatial learning deficits, as assessed in Morris-Water-Maze test, in aged rats(1)
  - Prevents oligomeric Aβ-induced dendritic spine loss in mouse hippocampal neurons (2)
  - Rescues neurodegenerative phenotype in Ts2 Down Syndrome transgenic mice (3)
- Clinical
  - Safety experience in >175 patients and volunteers at doses up to 750 mg BID for one month, and 250 mg BID for three months
  - Phase 2a at doses of 40 mg or 125 mg BID in patients with MCI due to AD or mild AD demonstrated (4)
    - Well tolerated
    - Blood-brain-barrier penetration, achieving target CSF drug concentration; and evidence of target engagement (reduction in CSF IL-8 levels)
    - Evidence of improvement in episodic memory function, though no placebo control

1. JAD, 2015; 48:219-27; 2. Amin et al, AAIC, 2019; 3. Jiang et al, AAIC, 2019; 4. Scheltens et al. Ann Clin Trans Neurol, 2018

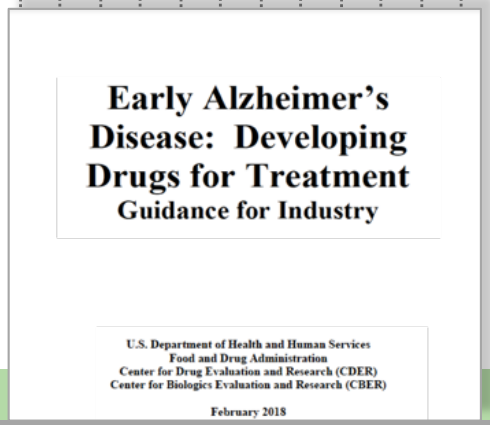
Overview of Phase 2b Trial in Early AD

REVERSE-SD

Patients

- MCI or mild AD
- Documented memory deficit
- MMSE 20 to 28
- CSF Ab_{42} < 1000 pg/mL and pTau/Ab_{42} > 0.024 Ratio by Roche Elecsys® assay
- 161 patients enrolled

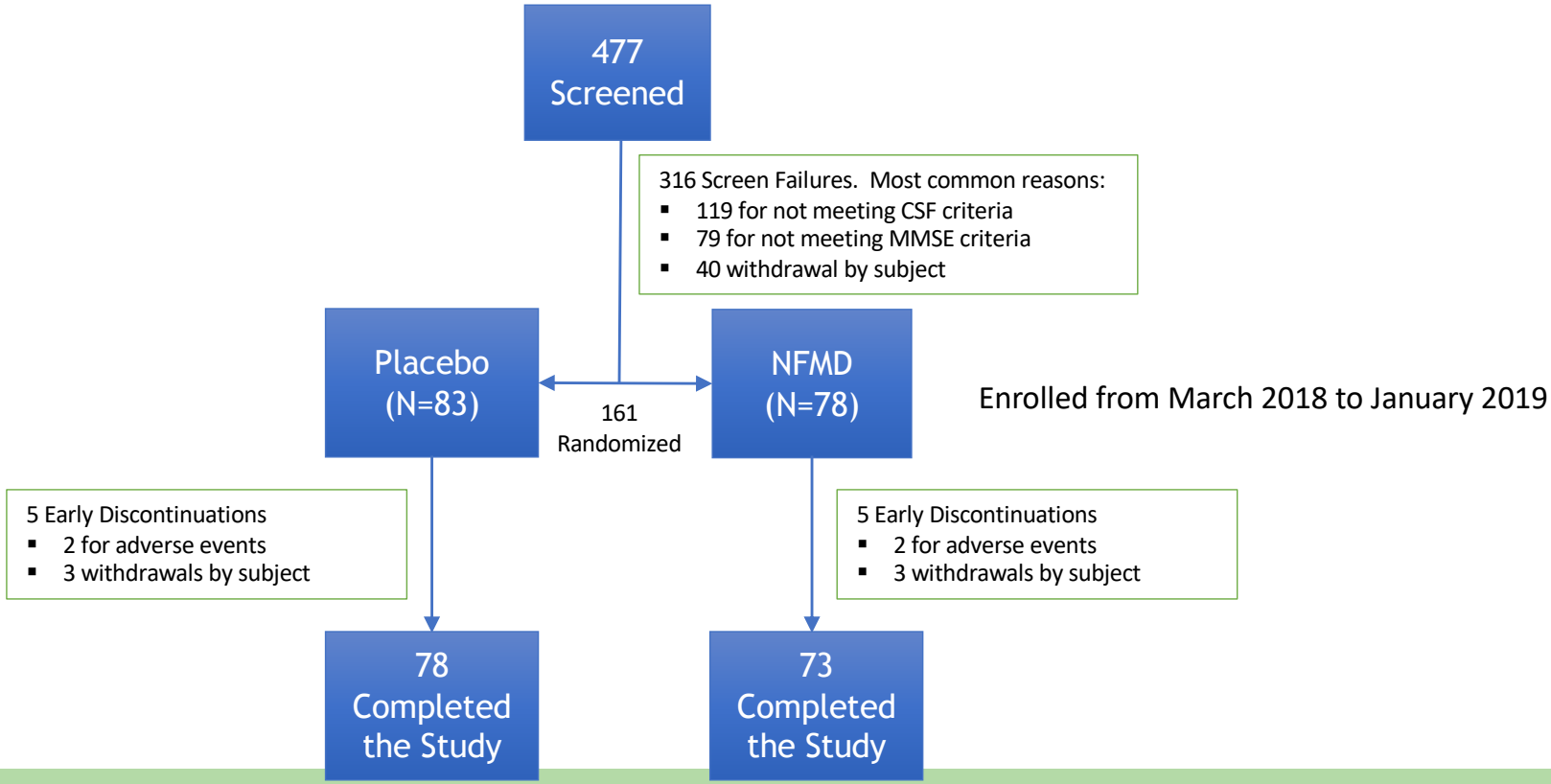
24 WEEK TREATMENT
40 mg or placebo twice daily



Endpoints

- 1º: episodic memory (Hopkins Verbal Learning Test)
- 2º: Wechsler Memory Scale (WMS), Clinical Dementia Rating Scale, MMSE, CSF biomarkers (p-tau, tau, neurogranin, NfL, Aβ40, Aβ42)

Patient Disposition



Enrollment By Country

Country	Number of Sites	Number of Subjects Enrolled	Number of Subjects (%) on Background AD Therapy
USA	16	73	44 (60%)
UK	11	52	30 (58%)
Netherlands	3	20	10 (50%)
Czech Republic	5	9	9 (100%)
Denmark	3	7	4 (57%)

Note: “Background Therapy” consists of cholinesterase inhibitor (85%) or memantine (15%); dual therapy not allowed

Reverse-SD Study
Baseline Characteristics

	Placebo (N=83)	Neflamapimod (N=78)
Age	72.6 (0.8)	70.8 (0.7)
Female	52%	47%
CDR 0.5/1.0	75%/25%	81%/19%
CDR Sum of Boxes	3.2 (0.18)	3.1 (0.15)
MMSE	23.6 (0.3)	23.7 (0.3)
HVLT Total Recall	15.3 (0.6)	16.4 (0.7)
% on Background AD Therapy	61%	59%
ApoE4+ (hetero- & homozygous)	69%	72%

Safety

- Neflamapimod well tolerated with only 2 discontinuations (vs. 2 in placebo) for adverse events, one for nausea and one for diagnosis of myeloma
- Two SAEs in neflamapimod patients (vs. three in placebo), hypokalemia and myeloma; both considered unrelated.
- Most common adverse events were upper respiratory tract infection (5% neflamapimod, 8% placebo), headache (5%, 6%) falls (6%, 4%), diarrhea (5%, 2%), post lumbar puncture syndrome (4%, 4%), vomiting (3%, 4%), depressed mood (3%, 4%), and fatigue (1%, 5%).
- One subject in neflamapimod arm (vs. none in placebo) with liver enzyme elevation to three times upper limit of normal. Elevation started resolving during one additional week of dosing, and then subject withdrew from the study.

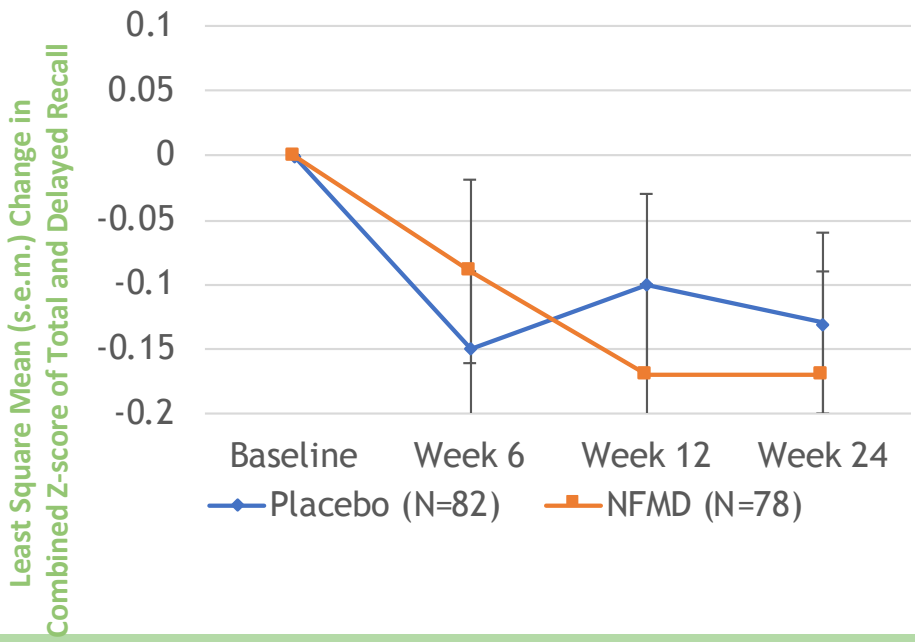
REVERSE-SD safety profile compares favorably with prior experience at higher dose

Incidence of Adverse Event By Study

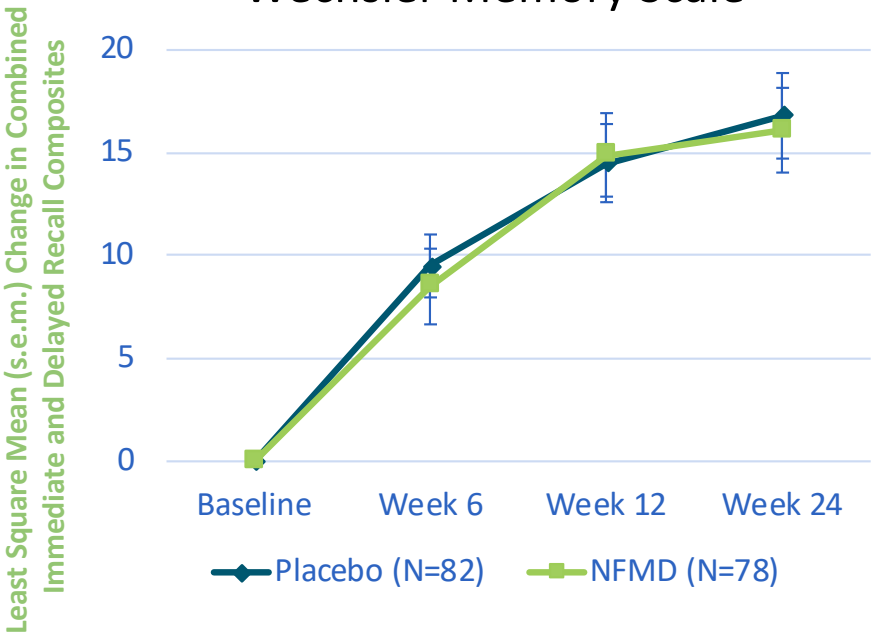
Adverse Events	Rheumatoid Arthritis Study (250 mg BID Twice Daily for 12 weeks)	REVERSE-SD (40 mg BID Twice Daily for 24 weeks)
Diarrhea, Abdominal Pain	20%	≤5%
ALT/AST elevation to ≥ 3X ULN	15%	<2%

Primary Objective: Improve Episodic Memory Function

Primary Endpoint:
Hopkins Verbal Learning Test



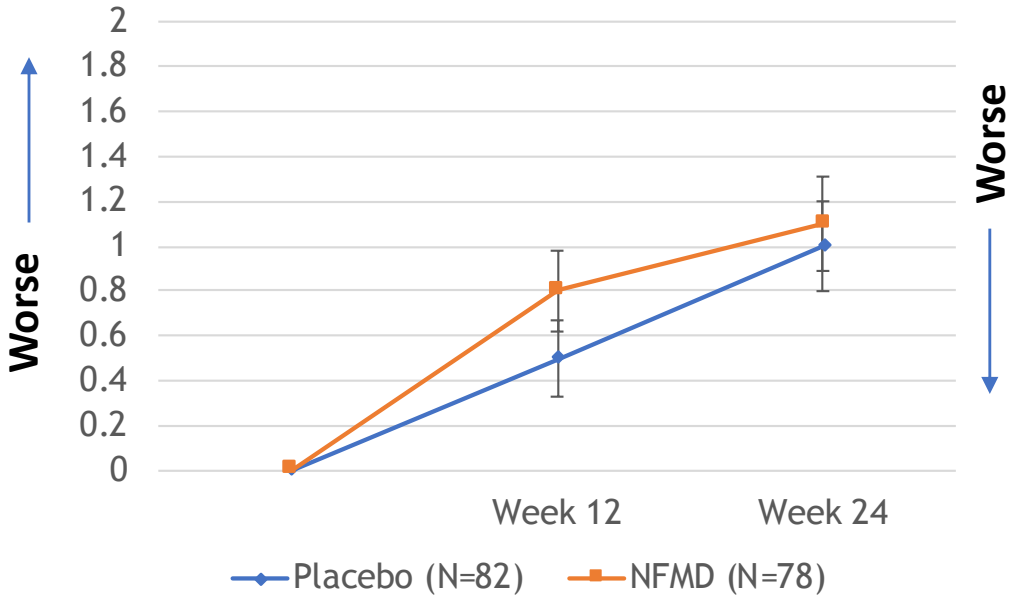
Secondary Endpoint:
Wechsler Memory Scale



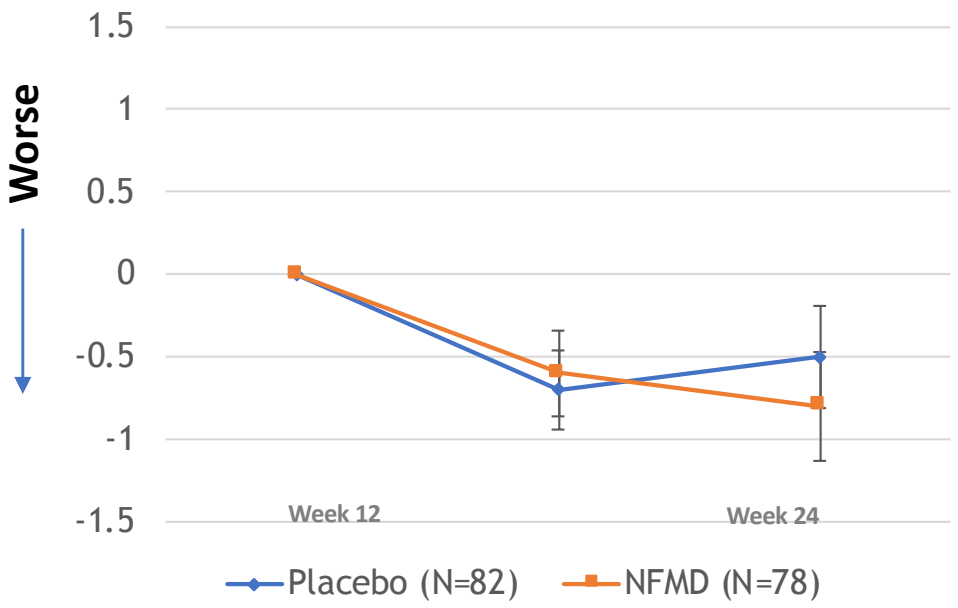
Mixed Effects Repeated Measures Model did not reveal any statistically significant difference between placebo and neflamapimod treatment arms

Mean Change from Baseline in 2º Clinical Endpoints: Full Efficacy Population

CDR Sum of Boxes



MMSE



Mixed Effects Repeated Measures Model did not reveal any statistically significant difference between placebo and neflamapimod treatment arms

CSF Biomarkers: Full Efficacy Population

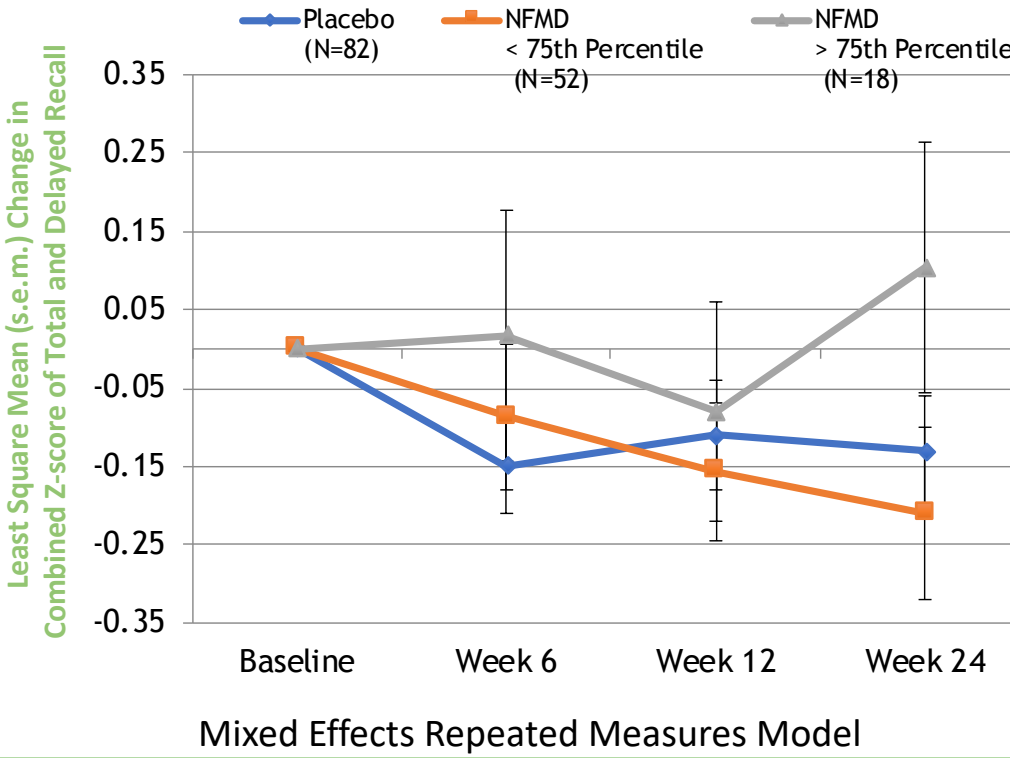
	LS mean (s.e.m.) absolute change (pg/mL) from baseline to week 24			
	Placebo (N=68)	Neflamapimod (N=62)	Difference in Change (95% CI)	P-value
Total tau	11.1 (6.91)	-7.7 (7.4)	-18.9 (-36.0, -1.8)	0.03
p-tau$_{181}$	1.0 (0.6)	-1.1 (0.7)	-2.0 (-3.6, -0.5)	0.012
Neurogranin	11.4 (9.3)	-9.4 (9.9)	-20.9 (-43.6, 1.9)	0.071
NfL	234.4 (61.8)	122.4 (67.0)	-111.9 (264.6,40.7)	0.15
Aβ$_{1-40}$	399.8 (251)	280.9 (269)	-118.9 (-740, 503)	0.7
Aβ$_{1-42}$	31.8 (12.8)	10.6 (13.8)	-21.2 (-53.0, 10.5)	0.19

Note: ANCOVA with fixed effect for treatment, background AD-specific therapy, CDR-Global Score as main effects, and baseline of the biomarker being analyzed as a covariate. LS – least square mean. NfL - neurofilament light chain

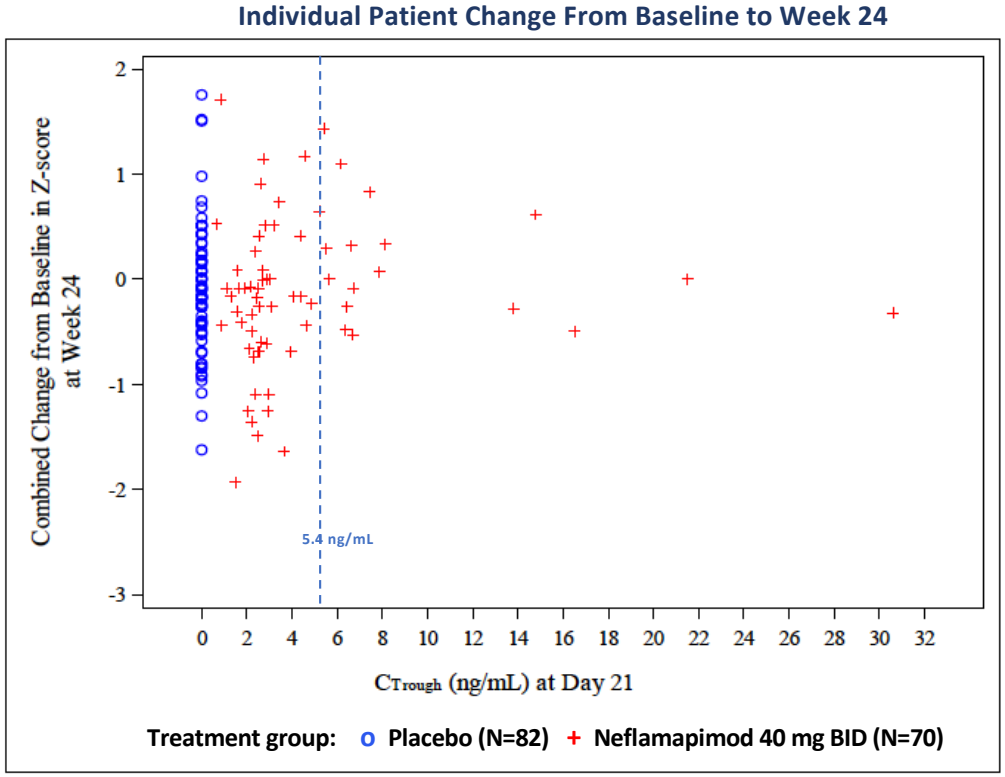
Pharmacokinetic-Pharmacodynamic (PK-PD) Analyses

- As only one dose level was utilized, PK-PD analyses included in Statistical Analysis Plan to evaluate the results for potential dose-dependency.
- Blood obtained immediately prior to first dose on Day 21 for determination of trough plasma drug concentration ("C_{trough}")
- 75th percentile of C_{trough} chosen prospectively as cut-off for PK-PD analyses because plasma drug exposures associated with that cut-off had shown greater biomarker and episodic memory effects in phase 2

Relationship Between Plasma Drug Concentration (C_{TROUGH}) and Primary Endpoint

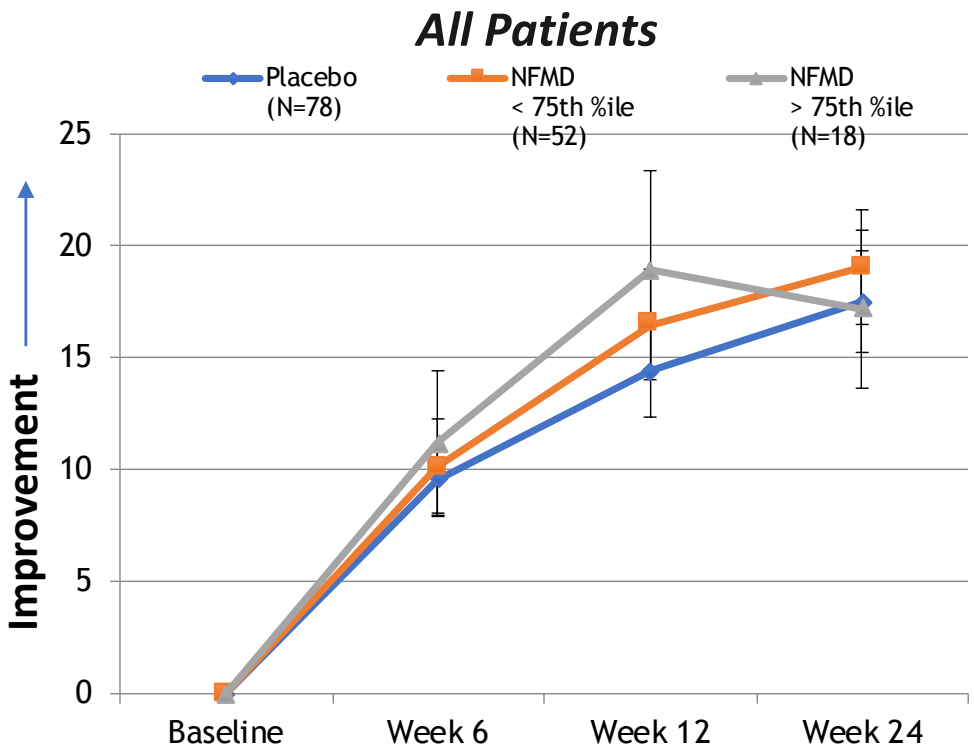


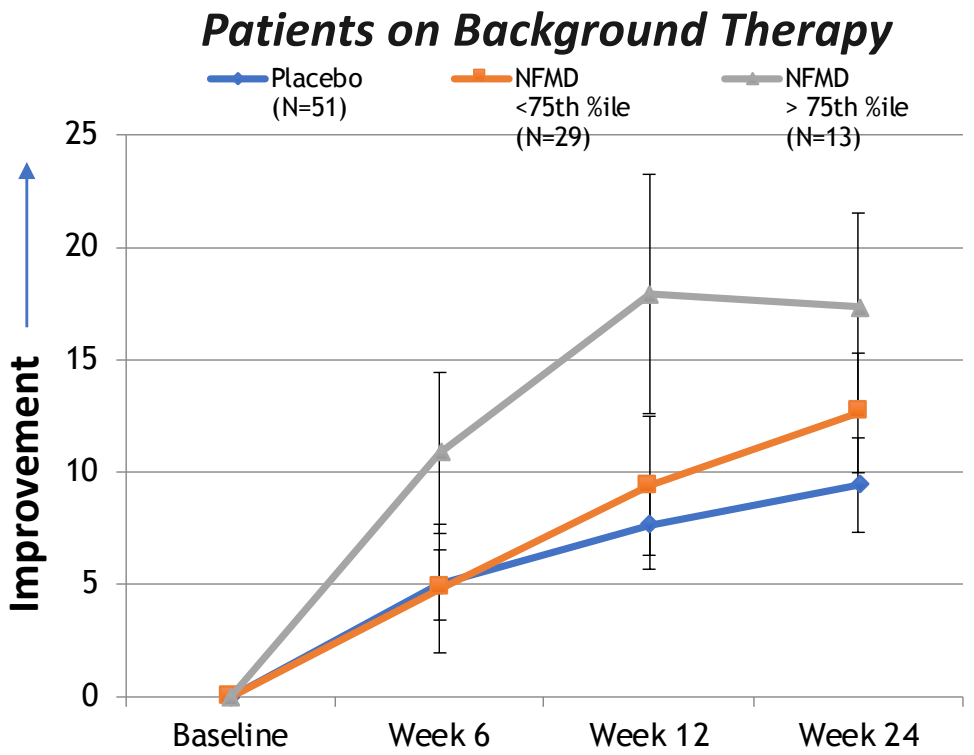
Mixed Effects Repeated Measures Model



"C_{TROUGH}" = Plasma drug concentration immediately prior to the morning dose on Day 21
75th percentile = 5.4 ng/mL

Change in Wechsler Memory Scale Combined Immediate and Delayed Recall Composite by Plasma Drug C_{TROUGH}





"C_{TROUGH}" = Plasma drug concentration immediately prior to the morning dose on Day 21. 75th percentile = 5.4 ng/mL

Summary

- No improvement in episodic memory in full efficacy patient population.
- Statistically significant effect of neflamapimod treatment relative to placebo on CSF ptau and total tau, and trend on CSF neurogranin, levels in full efficacy population.
- PK-PD analysis shows arent improvement in tests of episodic memory in patients with the highest (top quartile) plasma drug concentrations.
  - Positive effects on both Hopkins Verbal Learning Test and Wechsler Memory Scale
  - Results consistent with PK-PD for episodic memory and CSF IL-8 in phase 2a, and most recent potency and dose-response data from preclinical studies
  - Indicates need for 50-100% increase in dose for optimal outcome
  - Effect of background therapy needs further study
- Very good safety/tolerability profile that provides room for increasing dose.

Conclusions

- The CSF biomarker effects of neflamapimod demonstrate (1) target engagement and (2) p38α inhibition impacts the AD disease process (i.e. provides proof-of-mechanism).
- The CSF biomarker effects, combined with the episodic memory effects in patients with the highest blood concentrations of neflamapimod, indicate that a study of longer duration and at a higher dose of neflamapimod in patients with early-stage AD is merited and has the potential to demonstrate proof-of-concept.

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