LB32 – Participants enrolled in the RewinD-LB clinical trial: a large cohort of patients with dementia with Lewy bodies (DLB) without temporal lobe neurodegeneration, as defined by absence of elevation in plasma ptau181

Stephen Gomperts[1] , John-Paul Taylor[2] , Paul Maruff[3], Amanda Gardner[4], Kelly Blackburn[4], John Alam[4], James Galvin[5],

1Massachusetts General Hospital – Charlestown (United States), 2Newcastle University – Newcastle Upon Tyne (United Kingdom), 3Cosgate Ltd – London (United Kingdom), 4CervoMed Inc. – Boston (United States),5U.of Miami Miller School of Medicine – Boca Raton (United States)

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

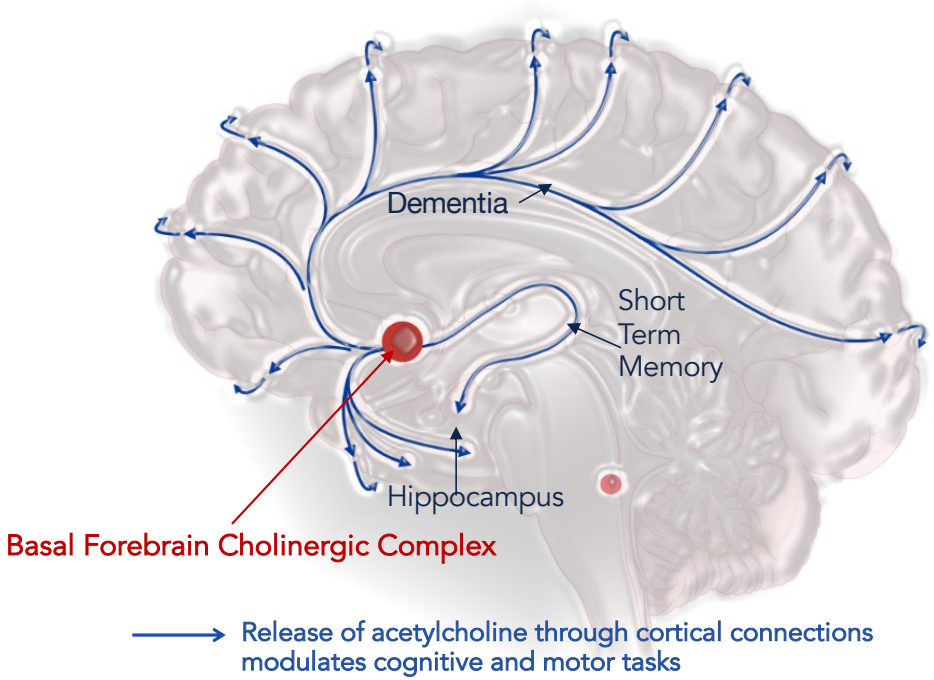
Disclosures

- Neflamapimod is an investigational drug
- J. Alam, A. Gardner, K. Blackburn are employees of CervoMed Inc, the company developing neflamapimod and the parent company of the study sponsor (EIP Pharma)
- P. Maruff is an employee of Cogstate, Ltd
- S.N. Gomperts has acted as a consultant for EIP Pharma

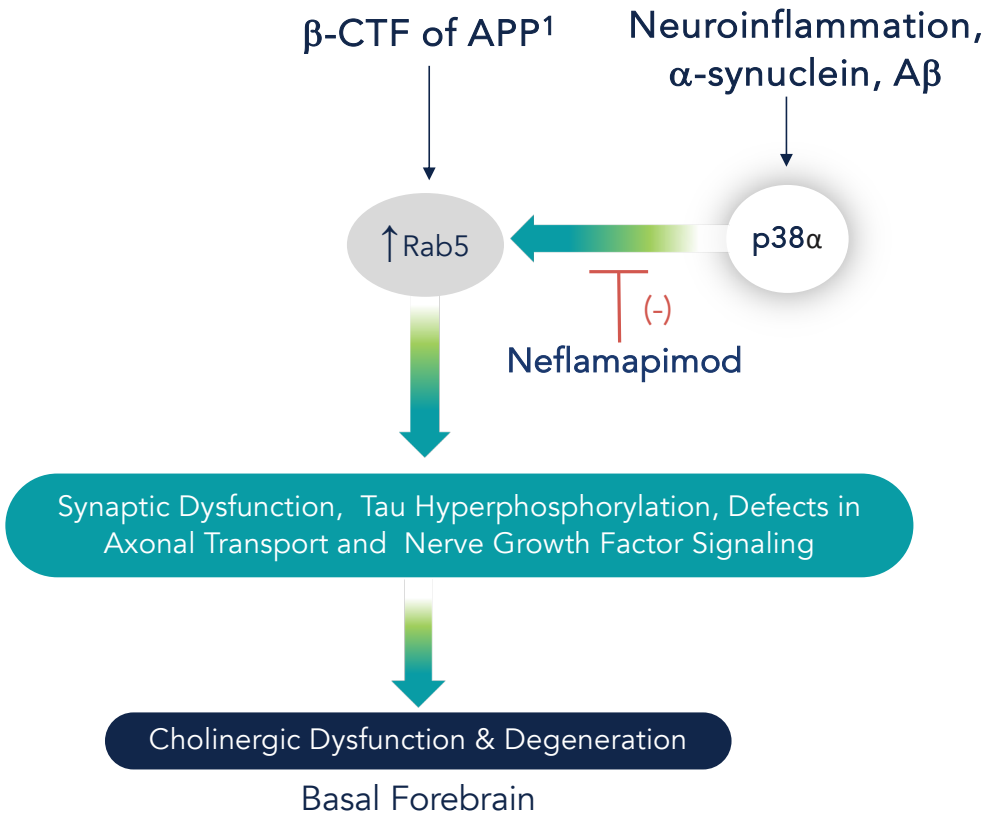
Acknowledgements

- Patients, caregivers, study investigators and clinical site staff involved with both the AscenD-LB and RewinD-LB studies
- Clinical project teams at Worldwide Clinical Trials and CervoMed, Inc.
- Members of the Data Safety Monitoring Board (DSMB) for the RewinD-LB study: Kenneth Rockwood MD, FRCPC, FRCP, FCAHS (Chair), Jennifer Goldman MD MS, Janet Wittes, PhD
- Primary funding source for the clinical trial: US National Institute on Aging (NIA) Grant #R01AG080536.

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

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 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

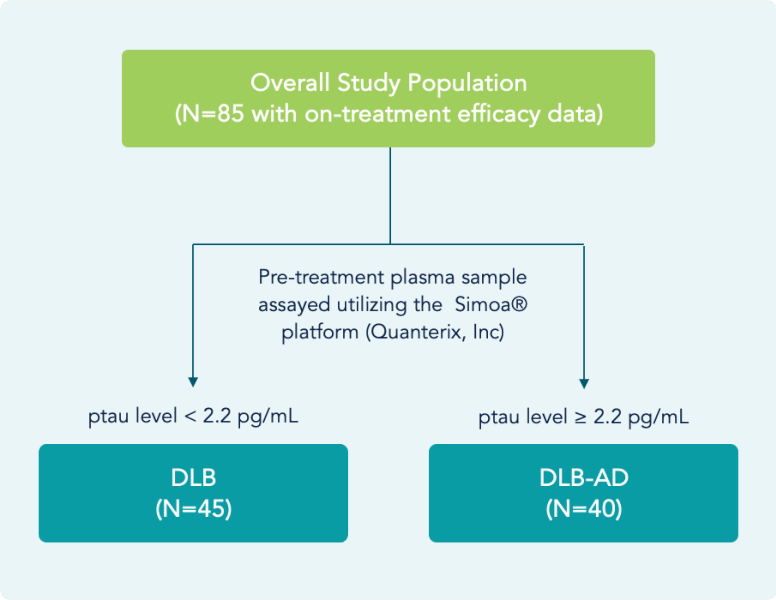
Results vs. placebo:

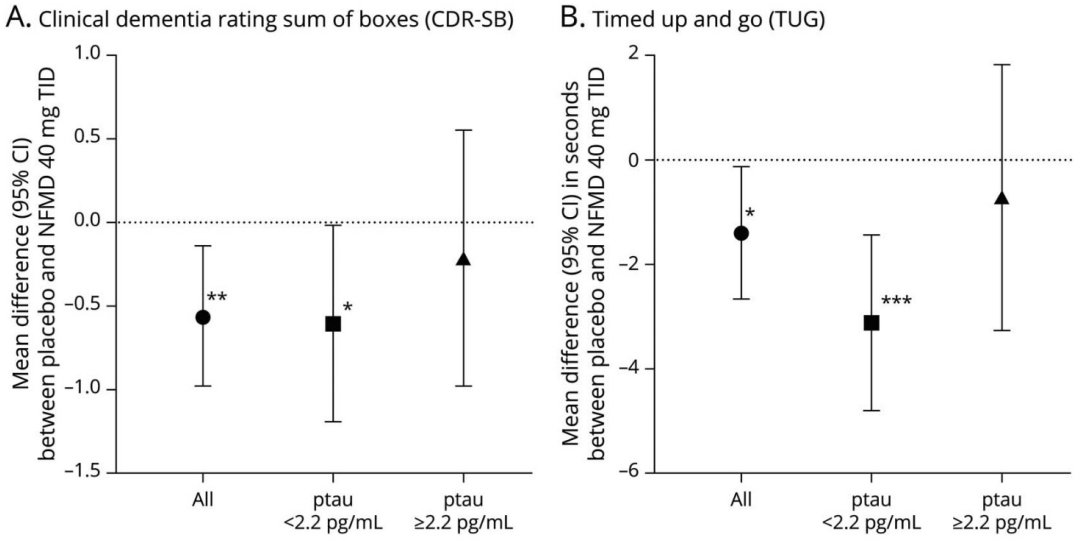
- ✓ Significant improvement on dementia severity (CDR-SB) and mobility (TUG) in full efficacy population analysis (i.e. including BID dose)
- ✓ Significant improvement on cognitive testing at 40mg TID vs. placebo, particularly with respect to attention
- ✓ Results most prominent in patients without elevated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

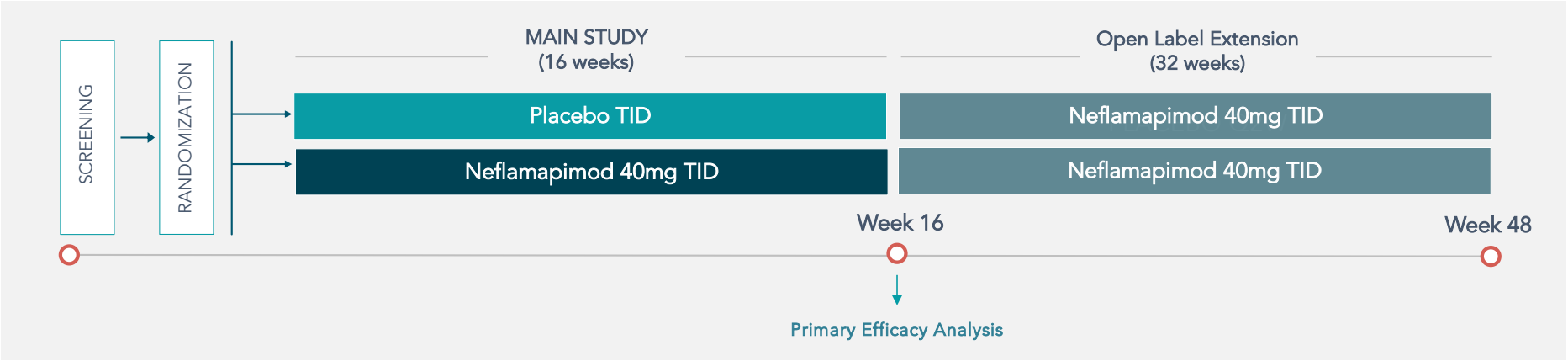
Plasma ptau181 and underlying pathology in dementia with Lewy bodies

- 2.2 pg/mL cut-off is based on published report that indicates that value was optimal cut-off in the assay utilized for CSF biomarker positive (A+T+) confirmed AD dementia
- In DLB, plasma ptau181 associated with:
  - Tau PET status (positive "AD signature tau signal") AUC=0.82, with optimal cut-off for tau PET status being 2.3 pg/mL (Diaz-Galvan et al, 2024)
  - CSF ptau181/Aβ42 ratio, with optimal cut-off of 2.5 pg/mL (Abdelnour et al, 2024
  - CSF A+T+status (AUC=0.85; Vrillon et al, 2024)
  - 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 elevated plasma ptau181 are those in whom temporal lobe is spared.

All patients with DLB have significant cholinergic dysfunction and degeneration (Okkels et al, *Brain*, 2024)

RewinD-LB Phase 2b Clinical Trial



PARTICIPANTS

DLB by consensus criteria; Global CDR=0.5 or 1.0

Pre-treatment plasma ptau181 <2.4 pg/ml (i.e., **excluding patients with temporal lobe neurodegeneration)**

INTERVENTION

159 participants randomized on a blinded basis 1:1 to neflamapimod 40mg capsules or matching placebo capsules, TID for 16 weeks, followed by 32-week open-label neflamapimod treatment extension

OUTCOME MEASURES

Primary: Clinical Dementia Rating Sum of Boxes (CDR-SB): >95% (approaching 100%) statistical power to detect treatment effect on CDR-SB

Secondary: Timed Up and Go (TUG) test, Neuropsychological Test Battery (NTB), Clinical Global Impression of Change (CGIC)

EEG: beta functional connectivity (primary), eyes-closed to eyes-open alpha reactivity

MRI: atrophy of basal forebrain, and its functional connectivity

Plasma biomarker: GFAP

RewinD-LB Investigator Sites

USA

A. Burke, Barrow Neurological Institute, Phoenix AZ
D. Sprecher, Banner Sun Health Research Institute, Sun City AZ
K. Bradley, Banner Alzheimer's Institute, Tucson AZ
R. Hess, UCSD, La Jolla, CA
A. Ritter, Hoag Memorial Hospital Presbyterian, Newport Beach CA
M.L. Purino, SC3 Research Group, Pasadena CA
S. Sha, Stanford Neuroscience Health Center, Palo Alto CA
S. Holden, U. of Colorado, Aurora, CO
Y. Torres-Yaghi, Georgetown University, Washington DC
M. Tolea, J. Galvin, U. Of Miami Miller School of Medicine, Boca Raton FL
L. Pau, JEM Research Institute, Lake Worth FL
R. Laird, ClinCloud, Viera FL
A. Ahmed, AdventHealth Neuroscience, Orlando FL
J. Cahill, Panhandle Research, Pensacola FL
J.E. Fleisher,Rush University Medical Center, Chicago IL
R. Pahwa, U. of Kansas Medical Center, Kansas City, KS
A. Traylor, Tandem Clinical Research, Marrero LA
L.S. Rosenthal, Johns Hopkins, Baltimore MD
S.N. Gomperts, MGH, Charlestown, MA
B. Boeve, Mayo Clinic, Rochester MN
D.L. Murman, U. Of Nebraska Medical Center, Omaha, NE

USA, continued

C., Bernick, Cleveland Clinic Foundation, Las Vegas
L. Honig, Columbia, New York NY
A. Bozoki, U. of North Carolina, Chapel Hill NC
R. Drake, Neuroscience Research Center, Canton OH
B. Tousi, Cleveland Clinic, Cleveland OH
D. Scharre. The Ohio State University, Columbus OH
M. Mega, Center for Cognitive Health, Portland OR
J. Toledo Atucha, Houston Methodist Hospital, Houston TX
S. Czander, Sana Research, Arlington VA
R.S. Turner, ReCognition Health, Fairfax, VA
M.J. Barrett, Virginia Commonwealth University, Richmond VA

Netherlands

EGB Vijverberg, N. Prins, Brain Research Center, Amsterdam
P. Dautzenberg, Brain Research Center, Den Bosch
L. Exalto, Brain Research Center, Zwolle

United Kingdom

J. Kane, Queen's University Belfast
L. Chouliaras, U. Of Cambridge
D. Aarsland, King's College London
E. MacSweeny, ReCognition Health, London
R. Weil, University College London, London
A. Byrne, J-P Taylor, U. Of Newcastle, Newcastle upon Tyne
C. Ballard, U. Of Exeter, Exeter
S. Sharif, Southern Health NHS Trust, MARC, Southampton

Study Progress

- 335 screened, and 159 patients enrolled (randomized) between August 2023 and June 2024
  - 66.7% (94 of 142) of CDR=0.5 patients and 75.2% (103 of 137) of CDR=1.0 patients had plasma ptau181 level < 2.4 pg/mL at screening
- 96% of enrolled patients completed the DB treatment period, of which 98% continued into the open label extension phase
- Topline efficacy (primary and secondary clinical endpoints) and safety results for the DB phase of the study expected in December 2024; full results expected in January 2025

RewinD-LB Study: Baseline Characteristics

Age	71.4 (6.1)
Male	85%
MMSE	23.5 (4.4)
CDR-SB	4.4 (2.0)
Core Clinical Criteria:	
Cognitive fluctuations	67%
Visual Hallucinations	50%
REM sleep behavioral disorder	69%
Parkinsonism	77%
Background Therapy	
AChEI alone	65%
AChEI + Memantine	11%
Memantine alone	3%
No background therapy	22%

Includes all participants randomized; mean (sd)

AChEI = acetylcholinesterase inhibitor therpay

RewinD-LB Study: Baseline Neuropsychological Characteristics

Cognitive domain	Cogstate® test	Magnitude of impairment* (mean, SD)
Psychomotor function	Identification Test	-0.78 (1.69)
Attention	Detection Test	-0.83 (1.82)
Working memory	One Back Test	-2.34 (1.90)
Visual learning	One Card Learning Test	-2.56 (1.33)
Verbal learning	Internation Shopping List Test (ISLT) immediate	-2.28.(1.26)
Verbal memory	ISLT delayed	-1.68 (1.11)

Includes all participants randomized

* Relative to age marched normative data

Dementia Severity in DLB without Temporal Lobe Neurodegeneration is higher than in Early AD

	Baseline MMSE Score	Baseline CDR-SB Score
Rewind-LB (Current Study)	23.5 (4.4)	4.4 (2.0)
AscenD-LB (Neflamapimod phase 2a in DLB)		
All patients	23.0 (3.3)	5.0 (2.5)
Participants with ptau181 < 2.2 pg/mL))	24.0 (3.4)	4.5 (2.1)
Clarity AD (Lecanemab Phase 3 in Early AD)	25.5 (2.2)	3.2 (1.3)
TRAILBLAZER-ALZ 2[1] (Donanemab Phase 3 in Early AD)	22.9 (2.1)	3.7 (2.1)

[1] Primary efficacy population, i.e., low/medium tau population

Statistical Power in RewinD-LB Clinical Trial Increased Through Excluding Patients with Elevated Plasma pTau181 at Baseline

Preliminary Study Design

Plasma ptau181 Inclusion/Exclusion Criteria

- No exclusion for plasma ptau181, randomization stratified by baseline plasma ptau181 status

Sample Size

- 80 participants per arm provided ***85% power*** to detect an effect on change in CDR-SB assuming the treatment effect size vs. placebo of 0.35 that was seen in the overall patient population in phase 2a (i.e. including patients with and without elevated plasma ptau181 status)

Final Study Design[1]

Plasma ptau181 Inclusion/Exclusion Criteria

- Potential participants excluded if plasma ptau181 ≥ 2.4 pg/mL at screening

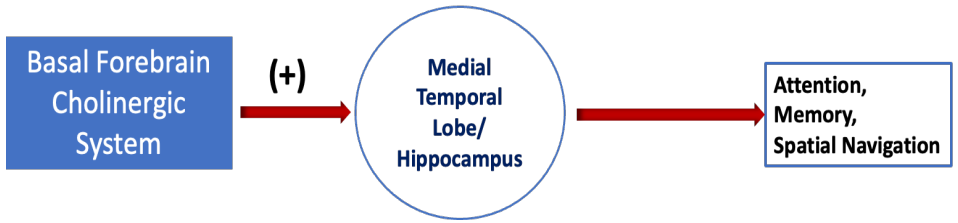
Sample Size

- Maintained at 80 participants per arm
- Assuming treatment effect size=0.70 (i.e., effect size vs. placebo seen in phase 2a in patients without plasma ptau181 elevation), provides ***greater than 95%, approaching 100%, statistical power*** to detect an effect on change in CDR-SB

[1] Implemented after NIH grant review recommended enrolling a more homogenous patient population, and before final sign-off of the protocol

Drug Development Opportunity in Enrolling Participants with DLB Who Do Not Have Advanced Disease

	Basal Forebrain Cholinergic System	Temporal (Hippocampus) Lobe	Response to Cholinergic Directed Therapy	Prevalence
DLB ptau181 - normal	Diseased	Spared	High	Approximately 50% of all patients with DLB[1]
Advanced DLB ("DLB-AD") ptau181 - elevated	Diseased	Atrophy	Limited by Temporal Lobe Atrophy	Approximately 50% of all patients with DLB[1]

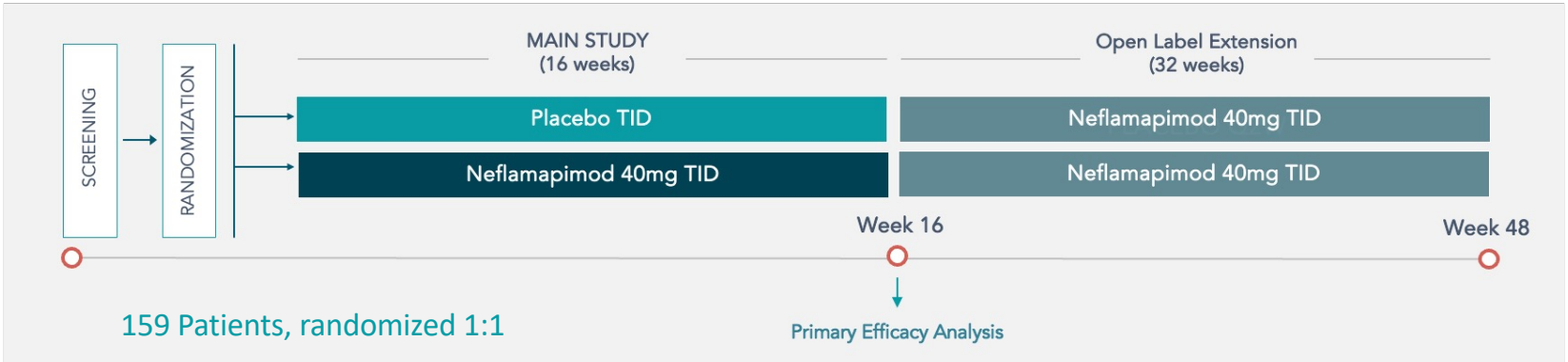


[1] Jain et al, 2024; Bolseweig et al, 2024

Conclusions

- Approximately 70% of patients with very mild or mild dementia with Lewy bodies screened for inclusion into the RewinD-LB clinical trial did not have temporal lobe neurodegeneration, as defined by absence of elevation in plasma ptau181
- The clinical burden in patients with DLB without temporal lobe neurodegeneration, despite treatment with acetylcholinesterase inhibitor therapy, is substantial
- The combination (limited neurodegeneration, accessible, sufficient clinical signal) makes DLB without temporal lobe neurodegeneration an attractive patient population for drug development, particularly for treatments targeting the cholinergic system

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 Jan'25