Statistical Analysis Plan

Title: A Phase 2b Clinical Study of the P38 Alpha Kinase Inhibitor Neflamapimod in Patients with Dementia with Lewy Bodies (DLB)

Protocol Number: EIP21-NFD-504

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Protocol Version: Version 2.0 / 15-DEC-2023
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Previous SAP Versions

Version 1.0, 10-JUL-2024

Version 2.0, 21-AUG-2024

SAP Amendments before database lock

Version	Issue Date	Section	Revision / Addition	Rationale
2.0	21-Aug-2024	5.11	Added note regarding Glial Fibrillary Acidic Protein (GFAP) and Neurofilament light (NfL) level measurements; however, analysis is still defined separately and will not be part of this SAP.	To clarify the timing of collection and analysis of GFAP and NfL.
3.0	24-Oct-2024	2.3, 5.10.2.1, 5.10.2.2	Analysis approach section updated to remove MMSE baseline score covariate and add baseline value of the endpoint being evaluated as a covariate.	Error in the SAP version 2.0 corrected.
		2.3, 5.10.2.1, 5.10.2.2	Updated strata covariate to use dichotomous strata by combining 'cholinesterase inhibitor therapy alone' and 'memantine therapy [with or without cholinesterase inhibitor therapy]' strata into one.	To clarify use of dichotomous strata for statistical analysis.
		5.1.1	Enrolled Set is renamed as Screened Set.	The name 'Enrolled Set' updated to clearly indicate the subjects to be included.
		5.1.3	Specified the cognitive assessments applicable for the mITT analysis set definition	To clarify the tests to be considered for identifying subjects in mITT analysis set.
		5.2.3	Baseline definition for CDR-SB score is updated to Day 1 assessment instead of average of screening and Day 1 assessment.	To clarify the assessment to be used for baseline.
		5.2.23	Updated to clarify for analysis randomization strata will be dichotomized as: 'cholinesterase inhibitor therapy' vs. 'no cholinesterase use'	To clarify use of dichotomous strata for statistical analysis.

		5.10.2.3, 5.10.3.1, 5.10.3.2, 5,10.3.3, 5.10.4.3.1	Subgroup analysis for cholinesterase inhibitor therapy subgroup (Yes/No) is added	To further explore the data based on cholinesterase inhibitor therapy
		5.10.4.3.1	Text added to clarify analysis approach for NIP.	Text inadvertently omitted in previous version of SAP.
		5.12.2	A table for Abnormal liver function test results is added	For additional safety reporting
		10	Text changes and new tables are included	To align with changes to SAP text.

REVIEW / APPROVAL SIGNATURES

Plan Author	Plan Reviewer, Worldwide
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Plan Approver, Sponsor Clinician	**Plan Approver, Sponsor Statistician**
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
AE	Adverse Event
ATC	Anatomic Therapeutic Chemical
CDR-SB	Clinical Dementia Rating Scale-Sum of Boxes
CI	Confidence Interval
CFT	Category Fluency Test
CS	Clinical Significance
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed Tomography
DCFS	Dementia Cognitive Fluctuations Scale
DLB	Dementia with Lewy Bodies
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEG	Electroencephalography
ET	Early Termination
FAS	Full Analysis Set
IRT	Interactive Response Technology
LFT	Letter Fluency Test
MAR	Missing at Random
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MI	Multiple Imputation
mITT	Modified Intent to Treat
MMRM	Mixed Model for Repeated Measures
MMSE	Mini Mental State Examination
MNAR	Missing Not at Random

Abbreviation	Definition
MRI	Magnetic Resonance Imaging
NCS	Not Clinically Significant
NPI-12	12-item Neuropsychiatric Inventory
NTB	Neuropsychological Test Battery
PSG	Polysomnography
pTau	Phospho-tau
RBD	REM sleep behavioral disorder
SAP	Statistical Analysis Plan
SE	Standard Error
TEAE	Treatment-emergent Adverse Event
TFL	Table, Figure, Listing
TID	Three times daily
TUG	Timed Up and Go Test

1 INTRODUCTION

This document details the planned statistical analyses for EIP Pharma, Inc, Protocol "EIP21-NFD-504" study titled "A Phase 2b Clinical Study of the P38 Alpha Kinase Inhibitor Neflamapimod in Patients with Dementia with Lewy Bodies (DLB)".

The proposed analyses are based on the contents of protocol version 2.0 (dated 15-Dec-2023 (US) / 20-Jun-2023 (Ex-US)).

This is a Phase 2b, multi-center, randomized, double-blind, placebo-controlled 16-week confirmatory (Phase 2b) treatment study of neflamapimod 40 mg vs matching placebo (randomized 1:1) administered with food for 16 weeks in subjects with Dementia with Lewy Bodies (DLB). All subjects will be administered 1 capsule of neflamapimod 40 mg capsules or matching placebo, orally TID with food (i.e., with the morning, mid-day, and evening meals) for 16 weeks. Doses should be administered at least 3 hours apart. The primary objective of this study is to assess the efficacy of neflamapimod, compared to placebo, as a treatment for DLB, as assessed by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB).

2 STUDY OBJECTIVES, ENDPOINTS, AND ESTIMANDS

2.1 Objectives

2.1.1 Primary Objective

The primary objective is to compare the efficacy of neflamapimod with placebo, as a treatment for DLB, as assessed by the CDR-SB.

2.1.2 Secondary Objectives

The secondary objectives are to:

- Demonstrate that neflamapimod improves motor function, compared to placebo, as assessed by the Timed Up and Go Test (TUG).
- Demonstrate that neflamapimod improves cognition, compared to placebo, as assessed by a DLB-specific Neuropsychological Test Battery (NTB). The NTB is comprised of:
    - Cogstate Detection test (DET)
    - Cogstate Identification test (IDN)
    - Cogstate One Card Learning test (OCL)
    - Cogstate One Back test (ONB)
- Demonstrate that neflamapimod improves global (cognition, function and behavior) disease status as evaluated by a clinician with caregiver input, compared to placebo, as

assessed by the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC).

2.1.3 Exploratory Objectives

- Evaluate the effect of neflamapimod on attention, as assessed by Cogstate Detection and Identification tests
- Evaluate effect of neflamapimod on cognitive fluctuations, as assessed by the Dementia Cognitive Fluctuations Scale (DCFS).
- Evaluate the effect of neflamapimod on select domains of the 12-item Neuropsychiatric Inventory (NPI-12), including depression (dysphoria), apathy, hallucinations, and agitation/aggression.
- Evaluate the effect of neflamapimod on visual hallucinations, as assessed by hallucinations frequency x severity score within the NPI-12 in subjects who report hallucinations at baseline.
- Evaluate the effect of neflamapimod on sleep and night-time behavior scores within the NPI-12.
- Evaluate the effect of neflamapimod on MDS-UPDRS3 motor examination (Part III) score.
- Evaluate the effect of neflamapimod on quantitative EEG parameters associated with cholinergic function, specifically, change in beta functional connectivity and in alpha reactivity.
- Evaluate the effect of neflamapimod on basal forebrain atrophy, as assessed by Nucleus of basalis of Meynert (NbM) volumetry by structural MRI.

2.2 Endpoints

2.2.1 Primary Endpoint

- Change from Baseline in CDR-SB during the double-blind treatment phase

2.2.2 Secondary Endpoints

- Change from Baseline in TUG during the double-blind treatment phase
- Change from Baseline in the composite score of the NTB, including tests of attention and visual learning, during the double-blind treatment phase
- ADCS-CGIC score at Week 16 at the end of the double-blind treatment phase

2.2.3 Exploratory Endpoints

- Change from Baseline in Attention composite score, including two tests within the NTB that evaluates attention (Detection and Identification)
- Change from Baseline in Dementia Cognitive Fluctuations Scale (DCFS)
- Change from Baseline to the end of the double-blind treatment period (average of Week 12 and Week 16) in select domains of the 12-item Neuropsychiatric Inventory (NPI-12), including depression (dysphoria), apathy, hallucinations, and agitation/aggression.
- For subjects who report hallucinations at Baseline, change from baseline to the end of the double-blind treatment period (average of Week 12 and Week 16) in hallucinations frequency x severity score within the NPI-12.
- Change from Baseline to the end of the double-blind treatment period (average of Week 12 and Week 16) in sleep and night-time behavior change within the NPI-12.
- Change from Baseline during the double-blind treatment period in MDS-UPDRS3 motor examination (Part III) score.
- Change from Baseline to Week 16 in beta functional connectivity and in alpha reactivity on quantitative EEG.
- Basal forebrain atrophy by structural MRI (Ex-US only)

2.3 Estimand

The following estimand attributes are defined with regards to the primary efficacy endpoint analysis:

Objective: The primary objective is to compare the efficacy of neflamapimod with placebo, as a treatment for DLB, as assessed by the CDR-SB	
Estimand: What is the effect of neflamapimod in the treatment of DLB, as assessed by the CDR-SB.	
Treatment: Neflamapimod 40mg vs placebo	
ESTIMAND	ANALYSIS
Target population	**Analysis set**
'Patients with DLB as defined by the study eligibility criteria	Modified Intent-To-Treat (mITT) Analysis Set, which consists of subjects who are randomized receive at least one dose of study drug and at least one post-dose cognitive assessment.
Variable	**Outcome measure**
CDR-SB Score	*Change from baseline in the CDR-SB Score*
Handling of intercurrent events	**Handling of missing data**

• Use of prohibited concomitant medication • Non-compliance to protocol (e.g., poor treatment adherence, use of prohibited medication and other protocol deviations) All these intercurrent events (ICEs) are assumed to be well-balanced events across both randomized arms and should not affect the estimation of the treatment effects. Therefore, all observed data will be used regardless of the occurrence of these intercurrent events (Treatment-policy strategy).	**Primary Analysis**: Only observed data will be used in the linear effects model. Missing data will NOT be imputed. **Sensitivity Analysis:** All missing data will be handled by Multiple Imputation (MI) under an assumption of missing not at random (MNAR) using pattern mixture model such as control-based imputation (i.e., placebo arm reference).
Population-level summary measure	**Analysis approach**
The difference between treatment arms in the average change from Baseline of the CDR-SB during the double-blind treatment phase.	The difference between treatment arms in the average change from Baseline of the CDR-SB score will be estimated from a linear mixed effects model, including treatment group, time in weeks, and treatment by time interaction as fixed effects; stratification factors (with and without cholinesterase inhibitor therapy), sex and baseline value as covariates. The random effect is on the subject term. A sensitivity analysis will be performed based on MNAR imputed data, the model will be fit across all imputed datasets and results will be pooled using Rubin's rules to obtain a single treatment effect estimate.

3 SAMPLE SIZE

The primary hypothesis for the study is that neflamapimod will significantly improve outcome vs. placebo on the CDR-SB. To demonstrate this effect, a total of approximately 160 subjects are planned to be enrolled, of whom 80 are planned to receive neflamapimod and 80 are planned to receive placebo. Sample size was determined by power analysis via simulations, conducted by utilizing outcomes in the CDR-SB in neflamapimod 40mg TID and placebo groups in the Phase 2a clinical study in DLB (Study 501), to generate for each patient a change from baseline in the CDR-SB score at individual visits over the course of the simulated clinical study, and then analyzing the result of each clinical study utilizing the linear mixed effects model for repeated measures that will

be utilized to analyze the current study. Based on the simulation of 100 clinical studies with 80 patients per treatment group, and assuming a 10% dropout rate, there is greater than 90% power (US: 95% confidence interval 80 to 90%; Ex-US: 95% confidence interval 90 to 99%) to detect a treatment effect at a two-sided alpha level of 0.05.

Note: In the phase 2a study, when the analysis was restricted to patients without Alzheimer's Disease co-pathology at study entry, the difference in change in CDR-SB between 40mg TID and placebo from the MMRM analysis was -0.56 (95% confidence interval -0.96, -0.16), and the Cohen's d effect size was 0.70. Additional 200 simulations conducted utilizing outcomes in phase 2a in these patients (i.e., 40mg TID and placebo in phase 2a who did not have AD co-pathology at study entry) indicated that the statistical power is greater than 95% to detect a treatment effect in the current study.

4 RANDOMIZATION

Subjects will be stratified by background dementia therapy (one of three strata: no cholinesterase inhibitor therapy, cholinesterase inhibitor therapy alone, or memantine therapy [with or without cholinesterase inhibitor therapy]), and then randomized on a 1:1 basis in a blinded manner to receive either placebo or 40 mg neflamapimod utilizing an automatically generated random code. Randomization will be administered via Interactive Response Technology (IRT).

5 PLANNED ANALYSES

The Statistical Analysis Plan (SAP) and Table, Figure, Listing (TFL) Shells (and any amendments) must be approved prior to breaking of the blind for the primary and secondary analysis. If post database lock, additional statistical analyses or changes to the statistical analysis are required, then those will be documented in a Post Database Lock Statistical Analysis Plan Addendum.

5.1 Analysis Sets

5.1.1 Screened Set

The Screened Set includes all subjects who gave informed consent.

5.1.2 Full Analysis Set

The Full Analysis (FAS) Set includes all subjects who were randomized into any treatment group. Subjects will be analyzed according to the study treatment arm to which they were randomly allocated. The FAS will be used for analysis of accountability and demographics.

5.1.3 Modified Intent-To-Treat Analysis Sets

The Modified Intent-To-Treat (mITT) Analysis Set for the double-blind treatment phase includes all subjects who are randomized and received at least one dose of study drug and who have at least one post-dose cognitive assessment (CDR-SB and/or NTB).

The mITT Analysis Set for the open-label extension phase will include all subjects included in the mITT Analysis Set for the double-blind treatment phase who completed the double-blind treatment phase and continued into the open-label extension phase.

Subjects will be analyzed according to the study treatment arm to which they were randomized. The mITT Analysis Set will be used for efficacy analysis. For outputs corresponding to each treatment phase, the analysis set defined for that corresponding phase will be used.

5.1.4 Safety Analysis Sets

The Safety Analysis Set for the double-blind treatment phase will include all subjects who receive at least one dose of study drug.

The Safety Analysis Set for the open-label extension phase will include all subjects who received at least one dose of study drug, completed the double-blind treatment phase, and continued into the open-label extension phase. These subjects will be analyzed according to the actual study treatment received. The Safety Analysis Set will be used for analysis of safety endpoints. For outputs corresponding to each treatment phase, the analysis set defined for that corresponding phase will be used.

5.1.5 Completer Analysis Set

The Completer Analysis Set for double-blind treatment phase will include all subjects in Safety Analysis Set who have Week 16 CDR-SB score.

The Completer Analysis Set for the open-label extension phase will include all subjects in double-blind treatment phase completer analysis set, who completed the double-blind treatment phase, and continued into the open-label extension phase. These subjects will be analyzed according to the actual study treatment received. The Completer Analysis Set will be used for summarizing treatment exposure and compliance.

5.1.6 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set will include all subjects who received at least one dose of study drug, for whom PK samples were obtained, and for whom sufficient plasma concentrations are available.

5.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

5.2.1 Age

Age (years) at informed consent will be reported as calculated in the electronic data case report form.

5.2.2 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labelled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

5.2.3 Baseline

For all study endpoints other than the TUG, baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug. Specifically, and for example, for the CDR-SB, the Day 1 value will be utilized for the Baseline value. If the Day 1 value is missing, screening (or repeat screening, if performed) value will be utilized. For the TUG, the mean of screening and Day 1 value will be taken as the Baseline value for analysis purposes.

For re-screened subjects, if assessments are not completed at re-screening, the results from original screening should be used.

If an assessment is scheduled to be made prior to dosing on First study day (SD1) and either time of assessment or time of first dose is missing, then such assessment is considered as prior to the first dose. The exceptions for this rule are AEs, which will be considered as treatment-emergent.

Change from baseline = Result at Visit – Result at baseline.

5.2.4 Early Withdrawal Assessments

For the analysis, assessments performed at early withdrawal visits will be mapped to the nearest missed visit, using midpoints between visits to window the early withdrawal. If the early withdrawal assessment is mapped to a visit where a scheduled assessment is already present, the scheduled assessment will take precedence, and the early withdrawal assessment will be disregarded (and listed only).

Table 1: Early withdrawal mapping for scheduled visits of Double-Blind Treatment Phase

Assessment(s)	Timing of Early Withdrawal Assessment	Mapped Visit

Physical Examination	Day 2 to Day 117	Week 16
	Day 118 to (Last dose+14 days)	Follow-Up
Vital Signs	Day 2 to Day 17	Week 2
	Day 18 to Day 33	Week 4
	Day 34 to Day 61	Week 8
	Day 62 to Day 89	Week 12
	Day 90 to Day 117	Week 16
	Day 118 to (Last dose+14 days)	Follow-Up
Hematology, Chemistry, C-SSRS, NTB, DCFS	Day 2 to Day 33	Week 4
	Day 34 to Day 61	Week 8
	Day 62 to Day 89	Week 12
	Day 90 to Day 117	Week 16
Coagulation, EEG	Day 2 to Day 117	Week 16
CDR-SB, TUG	Day 2 to Day 61	Week 8
	Day 62 to Day 89	Week 12
	Day 90 to Day 117	Week 16
NPI-12	Day 2 to Day 89	Week 12
	Day 90 to Day 117	Week 16
ADCS-CGIC	Day 2 to Day 117	Week 16
MDS-UPDRS	Day 2 to Day 61	Week 12
	Day 62 to Day 117	Week 16

Table 2: Early withdrawal mapping for scheduled visits of Open-Label Extension Phase

Assessment(s)	**Timing of Early Withdrawal Assessment**	**Mapped Visit**
Physical Examination	Day 2 to Day 229	Week 32
	Day 230 to (Last dose+14 days)	Follow-Up
Vital Signs	Day 2 to Day 33	Week 4
	Day 34 to Day 61	Week 8
	Day 62 to Day 117	Week 16
	Day 118 to Day 229	Week 32
	Day 230 to (Last dose+14 days)	Follow-Up
Hematology, Chemistry	Day 2 to Day 33	Week 4
	Day 34 to Day 61	Week 8
	Day 62 to Day 117	Week 16
	Day 118 to Day 229	Week 32
Coagulation	Day 2 to Day 229	Week 32
C-SSRS, CDR-SB, NTB, TUG, ADCS-CGIC, DCFS, NPI-12, MDS-UPDRS	Day 2 to Day 61	Week 8
	Day 62 to Day 117	Week 16
	Day 118 to Day 229	Week 32

5.2.5 Duration / Study Day / Time

First study day (SD1) is defined as the date of first administration of study drug. Study day will be calculated as the number of days from first administration of study drug.

- date of event – SD1 + 1, for events on or after first administration of study drug
- date of event – SD1, for events before first dose.

5.2.6 Conversion of Days, Height, and Weight

The following conversion factors will be used to convert days into months or years, or vice versa if needed:

1 week = 7 days,

1 month = 30.4375 days, and

1 year = 365.25 days.

The following conversion factors will be used for height and weight:

1 cm = 0.39370 in, and

1 kg = 2.20462 lb.

5.2.7 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates for events occurring during study conduct. Historical dates such as dates of medical history or prior medications may be missing or partial. Dates (historical or during study conduct) will only be imputed if a full date is needed for a calculation or to support a definition.

All dates presented in the individual subject listings will be as recorded on the Electronic Case Report Form (eCRF).

5.2.7.1 Missing / Partial Start / Stop Date of Adverse Events and Concomitant Medications

Missing and partial start and stop date will be imputed for analysis purposes as follows.

Partial or missing stop date will be imputed as follows:

- If the stop date is completely missing and the event has resolved, or the subject has stopped taking the concomitant medication, the stop date will be imputed as the date of the subject's last clinic visit in the study.
- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the subject's last clinic visit in the study if in the same year.

- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the subject's last clinic visit in which case the date of subject's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the subject's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed the date of the first dose of study drug. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

If the start time is missing it will be imputed only in the case where the start date of the concomitant medication / event corresponds to the date of the first dose of study drug. The time will be imputed as the same time as the first dose of study drug. In all other cases the time will not be imputed.

5.2.8 Missing Task(s) in Questionnaire

If the subject is unable to complete a task within the questionnaire for any cognitive reasons, the worse score for that task should be assigned. If the subject is unable to complete a task due to any of the other non-cognitive opt-out reasons, the score for the respective task should be considered as Missing at Random (MAR). A composite (i.e., total) score can be derived if at least 80% of tasks are not missing with the following formula.

(Sum of Observed Task Scores / Sum of Observed Max Task Scores) * Sum of All Max Task Scores

If more than 20% tasks are missing, then the total score is set to be missing.

5.2.9 Exposure to Study Drug

The exposure calculation will take into account interruptions in therapy. The duration of interruption will be subtracted from the total exposure. The exposure to study drug will be calculated as:

(Date of last dose – date of first dose + 1) – (Sum of Interruption durations), where each interruption duration will be calculated as:

End date of treatment interruption – Start date of treatment interruption + 1.

5.2.10 Treatment Compliance

Treatment compliance will be calculated per visit as follows:

$$\frac{Total\ number\ of\ capsules\ dispensed\ at\ Visit\ X - Total\ number\ of\ capsules\ returned\ at\ Visit\ Y}{[Date\ returned\ (Visit\ Y) - Date\ dispensed(Visit\ X)] \times 3} \times 100$$

Period	Visit Interval	Visit X	Visit Y
Double-Blind Treatment Phase	Baseline to Week 2	Baseline	Week 2
	Week 2 to Week 4	Week 2	Week 4
	Week 4 to Week 8	Week 4	Week 8
	Week 8 to Week 12	Week 8	Week 12
	Week 12 to Week 16	Week 12	Week 16
Open-Label Extension Phase	Week 4 to Week 8	Week 4	Week 8
	Week 8 to Week 16	Week 8	Week 16
	Week 16 to Week 32	Week 16	Week 32

Overall compliance will be calculated as:

$$\frac{Total\ number\ of\ capsules\ dispensed - Total\ number\ of\ capsules\ returned}{[Date\ of\ last\ dose - Date\ of\ first\ dose] \times 3} \times 100$$

Any kits that are not returned will be considered missing data and corresponding treatment compliance will not be calculated.

5.2.11 Adverse Events

A treatment-emergent Adverse Event (TEAE) is defined as one that started, or worsened in severity or seriousness, following the first dose of study drug. An AE with onset prior to the start of administration of the first dose of study drug, or when the stop date is before the start of the administration of the first dose of study drug, or when the study drug was not started, will be considered as pre study. In case the onset date is on the same day as the first dose of study drug

and either the time of first dose or time of AE onset is missing, then AE is considered treatment-emergent.

TEAEs starting after first dose of study drug in the double-blind treatment phase and before the first dose of study drug in the open-label extension phase will be summarized under the Double-Blind summary. TEAEs starting after first dose of study drug in open-label extension phase will be summarized under the open-label extension phase.

Maximum severity (Severe) will be assumed for an AE with missing severity.

A treatment-related AE is defined as an AE as being possibly related or related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

5.2.12 Vital Signs

Temperatures reported in Fahrenheit will be converted to Celsius for reporting using the following formula:

Celsius = (Fahrenheit – 32)/1.8

The converted values will be set to one decimal.

5.2.13 Physical Examination

If the CRF field 'Were there any abnormalities in the physical examination' in the physical examination form is answered 'No' in a given visit, then all the body systems will be reported as 'Normal' for that visit for the summary purpose.

5.2.14 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes, unless specified otherwise. In the listing, data will be reported as collected.

For example, for lab values that are entered as "<0.3" or ">1476", this rule means that for summary tables, 0.3 or 1476 will be used. In the lab listings the original values ("<0.3" or ">1476") will be displayed.

5.2.15 Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB)

The CDR-SB is a tool that measures the severity of cognitive impairment and dementia in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR-SB score is calculated by adding up the scores of each domain, which range from 0 (normal) to 3 (severe impairment). The total CDR-SB score can range from 0 to 18, with higher scores indicating more severe dementia.

5.2.16 Neuropsychological Test Battery Composite Scores

To compute each of the composite scores defined below, it is necessary first to standardize the performance scores from each of the component cognitive tests at each of the post-baseline visits using data from the study baseline.

For each subject, for each visit the composite score is obtained by averaging the standardized change from baseline scores for the relevant cognitive tests. The details of cognitive tests are provided in Appendix A.

Table 3: Composite Scores of the Neuropsychological Test Battery Used in the Study

Composite score	Tests included in composite
NTB	DET, IDN, OCL, ONB (accuracy only)
Attention	DET, IDN

The NTB composite score is a secondary endpoint, while the Attention composite is an exploratory endpoint.

A comparison of individual scores to baseline data will be conducted. The process will be as follows:

- Performance on each Cogstate test will be standardized relative to baseline data (i.e., the score will be converted to a z-score by subtracting the study sample's mean at baseline from the score and dividing by the standard deviation (SD) of the study sample's baseline).

- The multiplicand equals 1 for tests for which a higher score is indicative of better cognitive performance (i.e., OCL, ONB (Accuracy)) and -1 for tests where a lower score is indicative of better cognitive performance (i.e., DET, IDN).

The z-score will be calculated as follows:

$$z - Score(z_{ijt}) = \frac{(x_{ijt} - \bar{x}_{1t})}{\sigma_{1t}} \times Multiplicand$$

Where:

t = is the test indicator
i = indexes subject i
j = indexes the assessment at the j^{th} visit for subject i (j = 1 means baseline)
x = cognitive score
$\bar{x}_{1t}$ = mean performance score of the study sample for test t at baseline

σ_{1t} = Standard Deviation of the study sample for test *t* at baseline

Each of the composite scores described above will be calculated as follows:

1. For a given subject at a given assessment, determine if as many valid test scores are available as specified in table above.
2. If the condition in Step 1 is not satisfied, set the composite to missing for that assessment. If the condition in Step 1 is satisfied, proceed with the following steps:
3. Compute z-scores (based on the formula provided above) using the score for the primary outcome measure listed in Appendix A (Section 11) for each available test included in the corresponding Composite (listed in *Table 3*).
4. Calculate the mean of the z-scores to compute the Composite score for a given subject at a given assessment.

5.2.17 Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC)

The ADCS-CGIC rating is made on a 7-point scale similar to other global change scales, where a lower score indicated marked improvement. No imputation of missing scores will be done.

0	Not Assessed
1	Marked Improvement
2	Moderate Improvement
3	Minimal Improvement
4	No Change
5	Minimal Worsening
6	Moderate Worsening
7	Marked Worsening

5.2.18 Dementia Cognitive Fluctuations Scale (DCFS)

The DCFS consists of 4 items with each item based on 5-point Likert Scale. The total score (ranging from 4 to 20) is calculated as sum of each item score (ranging from 1 to 5) with higher score indicating more severe CFs. No imputation of missing scores will be done.

Difference in function	5	A very large difference (a very severe impact on daily functioning)
	4	A large difference (a severe impact on daily functioning
	3	A moderate difference (a clear impact on daily functioning)
	2	A slight difference (only a mild impact on daily functioning)
	1	No difference (no impact on daily functioning)

Daytime sleep	5	3 hours or more
	4	2 hours to 3 hours
	3	1 hour to 2 hours
	2	Less than 1 hour
	1	Not at all
Daytime drowsiness	5	3hours or more
	4	2 hours to 3 hours
	3	1 hour to 2 hours
	2	Less than 1 hour
	1	Not at all
Level of consciousness	5	Mostly asleep
	4	Drowsy, but difficult to arouse
	3	Drowsy, but moderately easy to arouse
	2	Drowsy, but easy to arouse
	1	Mostly alert

5.2.19 Neuropsychiatric Inventory (NPI-12)

The Neuropsychiatric Inventory (NPI-12) assesses twelve behavioral domains common in dementia and is administered to the caregiver. Ten behavioral domains and 2 neurovegetative items are included in the NPI-12. The domains are as follows: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep, and appetite and eating change. Each domain is rated in 3 scores as below:

- Frequency with 4 response options ranging from 1 (Occasionally) to 4 (Very Frequently)
- Severity with 3 response options ranging from 1 (Mild) to 3 (Severe)
- Distress with 5 response options ranging from 0 (No distress) to 5 (Very Severe or Extreme)

Frequency	
1	Occasionally - less than once per week
2	Often - about once per week
3	Frequently - several times per week but less than every day
4	Very frequently - daily or essentially continuously present
Severity	
1	Mild - produces little distress in the patient
2	Moderate - more disturbing to the patient but can be redirected by the caregiver
3	Severe - very disturbing to the patient and difficult to redirect
Distress	
0	No distress

1	Minimal
2	Mild
3	Moderate
4	Severe
5	Very severe or extreme

NPI-12 Score of each domain = (Frequency × severity) of the domain

Total NPI-12 Score = Sum of all 12 domain scores (frequency × severity)

- P_n = Frequency × Severity where n = 1 to 12 and P_n = Total NPI-12 Score of each domain
- Total NPI-12 Score = $P_1 + P_2 + \ldots\ldots\ldots\ldots P_{11} + P_{12}$

NPI-10 Score = Sum of 10 domain scores (excluding sleep, and appetite and eating change domains)

NPI-4 Score = Sum of 4 domain scores (Depression (dysphoria), Apathy, Hallucination, Agitation/aggression)

Missing data will be handled as defined in section 5.2.8.

5.2.20 Movement Disorder Society – Unified Parkinson's Disease Rating Scale – Part III (MDS-UPDRS3)

The motor examination (Part III) assesses motor symptoms and signs. The total score is the sum of 33 items with scores ranging from 0-132, with higher scores meaning more severe symptoms. All items have 5 response options ranging from 0 (Normal) to 4 (Severe). Missing data will be handled as defined in section 5.2.8.

5.2.21 Columbia-Suicide Severity Rating Scale (C-SSRS)

The following outcomes are C-SSRS categories and have binary responses (yes / no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints:

Category 1	Wish to be Dead
Category 2	Non-specific Active Suicidal Thoughts
Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent

Category 6	Preparatory Acts or Behaviour
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non-fatal)
Category 10	Suicide

Suicidal Ideation since baseline – A "yes" answer at any time during double-blind treatment phase to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS.

Suicidal Behaviour since baseline – A "yes" answer at any time during double-blind treatment phase to any one of the 5 suicidal behaviour questions (categories 6-10) on the C-SSRS.

There will be no imputation of missing data for C-SSRS.

5.2.22 Unscheduled Visits

Visit data will be presented using nominal times as collected in the eCRF. Both scheduled and unscheduled post-baseline visits will be tabulated. Unscheduled visits will be presented as 'Visit x.xx' (e.g., Visit 3.01).

5.2.23 Randomization Strata

The subjects are stratified by background dementia therapy as follows:

- No cholinesterase inhibitor therapy
- Cholinesterase inhibitor therapy alone
- Memantine therapy (with or without cholinesterase inhibitor therapy)

The stratification group used in the randomization (including mis-stratification) will be used for the analysis. For analysis purpose, dichotomous stratification as cholinesterase inhibitor therapy (Yes / No) will be used. Cholinesterase inhibitor therapy alone and memantine therapy (with or without cholinesterase inhibitor therapy) strata will be combined into single strata and will be considered as 'with cholinesterase inhibitor therapy' (cholinesterase inhibitor therapy=YES) while No cholinesterase inhibitor therapy strata will be considered as 'without cholinesterase inhibitor therapy' (cholinesterase inhibitor therapy=NO).

The randomization list was generated under protocol v1.0. Hence, the randomization strata text in Protocol v2.0 and SAP will not match the randomization list and IRT label. For reporting purposes, text from the SAP will be used to be consistent with the latest protocol.

5.3 Conventions

All data listings, summaries, figures and statistical analyses will be generated using SAS version 9.4 or higher[1].

Summaries will be presented by treatment group or overall. Subjects will be summarized under same treatment group in both double-blind and open-label extension phase. Treatment group labels will be displayed as follows:

Neflamapimod (40mg TID) (N=XX)	Placebo (N=XX)

Listings will be sorted in the following order treatment group, subject, parameter, and visit unless otherwise stated. All data will be listed, subjects who were not randomized will be displayed after the randomized treatment / sequence groups. Any safety/efficacy data collected during screening for the subjects who failed screening will not be included in the TLFs.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of subjects in the column header unless otherwise specified in the footnote. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. If the reported/derived data contains more than 3 decimals, they will be rounded off to three decimal places before calculating the summaries. Percentages will be displayed with one decimal place.

Estimates and confidence intervals will be displayed to one more decimal place than the data, if estimate values are very small (i.e., <0.005) then estimates will be presented with decimals up to 2 significant digits; standard error will be displayed to two more decimal places than the data.

P- Values will be quoted to 4 decimal places consistent with SAS PVALUE*w.d* format set to PVALUE6.4. P-values < 0.0001 will be presented as p<0.0001.

5.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects who entered the study, were randomized, and who are in each analysis set will be summarized by treatment group and overall. Separate summaries will be provided for the double-blind treatment phase and open-label extension phase.
- The number and percentage of subjects who completed the double-blind treatment phase, the open-label extension phase, overall study and who terminated early, along with reasons for early termination (ET), will be presented for the Full Analysis Set. Summaries will be presented separately for the double-blind treatment phase and the open-label extension phase.
- The number of subjects who failed screening and the reasons for failure will be tabulated for the Screened Set.
- The number and percentage of subjects failing each eligibility criteria will be tabulated for the Screened Set.
- The initial recruitment to double-blind treatment phase will be summarized by country and site for the double-blind treatment phase and open-label extension phase for the Full Analysis Set.
- The number of subjects present at each scheduled visit will be summarized by treatment group for the double-blind treatment phase and open-label extension phase for Full Analysis Set.

All subject disposition data and screen failures will be listed.

5.5 Protocol Deviations

Protocol deviations will be summarized for the double-blind treatment phase and open-label extension phase separately for the Full Analysis Set. The summary will be provided by classification (Major, Minor) and description listed under 'Protocol deviation description' in the latest version of Protocol Deviation Handling Plan. A listing of protocol deviations will be provided within Appendix 16.2 of the CSR.

5.6 Demographics and Baseline Comparability

The comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Standard continuous or categorical variable summaries will be presented by randomized treatment group for the following variables based on the Safety Analysis Set and Full Analysis Set separately for double-blind treatment phase.

- Demographic data
    - Age at informed consent (years)
    - Sex

- Fertility status
- Ethnicity
- Race
- Weight at screening (kg)

- Baseline characteristics
  - Background dementia therapy (Randomization Strata)
  - MMSE Total Score
  - Subject's DLB diagnosis confirmed with the presence of dementia plus 2 or more core clinical features
  - DaTscan result (in case of missing historic DaTscan, screening DaTscan will be used)
  - Presence of historical diagnosis
  - Core clinical features
  - Presence of evidence of other neurodegenerative disease

5.7 Medical History

Separate tabulations of previous and ongoing conditions will be presented by randomized treatment group and overall, for the Safety Analysis Set. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA) primary system organ class and preferred term. MedDRA version 26.1 or higher will be used for coding purposes.

5.8 Prior and Concomitant Medications

Separate tabulations will be produced for prior and concomitant medications presented by randomized treatment group and overall, for the Safety Analysis Set. Prior medications are defined as medications that ended before the date of the first dose of study drug. Concomitant medications are defined as medications that ended or are ongoing on or after the date of the first dose of study drug.

The following rules will be used in the analysis of concomitant medications:

- Concomitant medications will be counted in the double-blind treatment phase if the end date is on or before the end of double-blind treatment phase (Follow-Up: Day 118 to Last dose+14 days).
- Concomitant medications starting after the end of the double-blind treatment phase will be counted in the open-label extension phase.
- Concomitant medications starting in or before the double-blind treatment phase and ongoing in the open-label extension phase will be counted in both treatment phases for period-wise summaries and will be counted once for the overall study summary.

All the above summaries will be presented using Anatomic Therapeutic Chemical (ATC) Level 2 and preferred term coded using the WHO Drug (B3 Global) dictionary, version September 2023 or higher.

All prior and concomitant medications will be listed. A separate listing will be provided for cholinesterase inhibitors and memantine therapy.

5.9 Exposure to Study Drug and Treatment Compliance

Extent of exposure (number of days of exposure to study drug), treatment compliance between each scheduled visits and overall compliance will be presented by actual treatment group for the Completer Analysis Set.

Additionally, treatment compliance will be summarized by the following categories:

- <80%
- Within 80-120%
- >120%

All data will be listed.

5.10 Efficacy Analyses

5.10.1 General Statistical Methodology

Efficacy data will be tabulated by treatment group and by visit for double-blind treatment and open-label extension phase separately. When tabulated, data will be presented using descriptive statistics for both observed values and as change from baseline. Continuous data will be summarized with the following descriptive statistics unless otherwise noted: number of observations, mean, standard deviation, median, minimum, and maximum; and 95% CI, as appropriate. Categorical data will be summarized with frequencies and percentages.

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. All comparisons between treatments will be reported with 95% confidence intervals for the difference.

5.10.2 Primary Efficacy Endpoint (CDR-SB)

The primary efficacy endpoint is the change in CDR-SB in neflamapimod-treated subjects compared to placebo-recipients. The analysis for the primary endpoint will be performed using the mITT Analysis Set.

5.10.2.1 Primary Analysis

The difference between neflamapimod and placebo in the average change from baseline in CDR-SB score during the double-blind treatment phase (i.e., utilizing data from week 8, 12 and 16 in the model) will be estimated using a linear mixed effects model including treatment, time (in weeks), treatment-by-time interaction as fixed effects, cholinesterase inhibitor therapy (Yes/No), age, sex and baseline value as covariates. The random effect is on the subject term. An unstructured covariance structure will be used to model the within-subject error and an adjustment to the degrees of freedom will be made using the Kenward-Roger's approximation. If this model does not converge then the following covariance matrices will be used in order until the model converges: Toeplitz, first-order autoregressive, compound symmetry.

The estimate of the difference between neflamapimod versus placebo and standard error (SE) for the average change from baseline in CDR-SB will be derived from this LME model. The LS means, corresponding SEs, and 2-sided 95% CI for each treatment group, the treatment difference of LS means, corresponding SEs, 2-sided 95% CI and 2-sided p-value will be presented.

Example SAS code:

```
proc mixed data= <input>  method = REML alpha=0.05;
  class <subject> <treatment> <cholinesterase inhibitor therapy> <sex>;
  model <change from baseline> = <treatment> < cholinesterase inhibitor therapy> <sex> <age>
< baseline value> <time in weeks><treatment>*<time in weeks> / ddfm=kr s;
  random <time in weeks> / subject=<subject> type=un;
  lsmeans <treatment> / cl diff;
run;
```

5.10.2.2 Sensitivity Analysis

A sensitivity analysis will be performed to assess the robustness of the primary analysis to deviations from the assumptions around missing data.

The change from Baseline in CDR-SB will be repeated based on the mITT Analysis Set. All missing data will be handled by Multiple Imputation (MI) under an assumption of missing not at random (MNAR). Details of MI and SAS codes are provided below.

The monotone and non-monotone missing data will be imputed using a pattern mixture model such as control-based imputation (i.e., placebo arm reference) with the following SAS code. This statistical model uses fully conditional specification (FCS) with a predictive mean matching method where missing values will be imputed with random value from set of k=5 (default in SAS) closest estimated value and MNAR statement in the below code indicates that imputation will be control-based i.e., placebo value will be used to impute missing data points in both treatment arms.

```
proc mi data = <input> nimpute = 5 seed = 134 out = <dataset_mnar>
```

```
minimum = . 1 1 56 0 0 0 0 maximum = . 2 2 X 18 18 18 18 round = .1;
 class <treatment> ; /*X=Max age in the data; Min and Max should be updated for each
endpoint*/
 var <cholinesterase inhibitor therapy> <sex> <age> < baseline value> Week_8 Week_12
Week_16;
 fcs nbiter = 1000 regpmm(Week_8 Week_12 Week_16);
 mnar model(Week_8 Week_12 Week_16/ modelobs = (<treatment> = 'Placebo'));
run;
```

where *<treatment> = Treatment groups (Neflamapimod(40mg TID)/Placebo)*

Change from baseline will be calculated for the imputed values. A Linear mixed effect model will then be fit for each imputed dataset as described in the previous section and following sample SAS code will be used to fit the model.

```
ods output lsmeans=lsm diffs = diff solutionF = solution;
proc mixed data= <input>  method = REML alpha=0.05;

 by _imputation_;
 class <subject> <treatment> <cholinesterase inhibitor therapy><sex>;
 model <change from baseline> = <treatment> < cholinesterase inhibitor therapy> <sex> <age>
<baseline value> <time in weeks><treatment>*<time in weeks> / ddfm=kr s;
 random <time in weeks> / subject=<subject> type=un;
 lsmeans <treatment> / cl diff;
run;
```

The results of the model from each imputed dataset will be pooled using Rubin's rule to obtain single treatment effect estimates. The difference between the neflamapimod treatment group and placebo with corresponding SE and the 2-sided 95% CI, p-value (2-sided) will be presented. The sample SAS code given below will be used:

```
proc mianalyze data = <input>;
 by trt01pn;
 modeleffects Estimate;
 stderr StdErr;
 ods output parameterestimates = <output>;
run;
```

5.10.2.3 Subgroup Analysis

The change from baseline in CDR-SB will be analyzed in for each subgroup of cholinesterase inhibitor therapy (Yes / No) separately, using similar methods as described in Section 5.10.2.1 except cholinesterase inhibitor therapy covariate will be removed from the model.

5.10.3 Secondary Endpoints

5.10.3.1 Change in TUG in neflamapimod-treated subjects compared to placebo-recipients

Change in TUG will be analyzed in a manner similar to that of the primary endpoint as described in Section 5.10.2.1. The dependent variable is change from baseline in TUG. The analysis will be repeated for each subgroup of cholinesterase inhibitor therapy (Yes/No) separately, as described in Section 5.10.2.1 except cholinesterase inhibitor therapy covariate will be removed from the model.

5.10.3.2 Change in the composite score of the Neuropsychological Test Battery (NTB)

Change in NTB composite score defined in *Table 3* will be analyzed in a manner similar to that used for the primary endpoint as described in section 5.10.2.1. Change from baseline will be the dependent variable. The analysis will be repeated for each subgroup of cholinesterase inhibitor therapy (Yes/No) separately, as described in Section 5.10.2.1 except cholinesterase inhibitor therapy covariate will be removed from the model.

5.10.3.3 ADCS-CGIC at Week 16 in neflamapimod-treated subjects compared to placebo-recipients

ADCS-CGIC at Week 16 in neflamapimod vs. placebo will be compared utilizing a two-sided Mann Whitney U test (Wilcoxon Rank Sum Test).

The number of observations in each group, sum of ranks, mean, standard deviation, z-score and corresponding 2-sided p-value will be presented.

```
proc npar1way data=<input> wilcoxon;
   class <treatment>;
   var < ADCS-CGIC at Week 16>;
   ods output WilcoxonScores=scores WilcoxonTest=Wilcoxon;
run;
```

The analysis will be repeated for each subgroup of cholinesterase inhibitor therapy (Yes/No) separately.

5.10.4 Exploratory Endpoints

Exploratory endpoints will not be tested for significance, but presented with treatment effect vs. placebo, with 95% confidence intervals.

5.10.4.1 Change in the attention composite score

Change in attention composite score defined in *Table 3* will be analyzed in a manner similar to that used for the primary endpoint as described in section 5.10.2.1.. Change from baseline will be the dependent variable.

5.10.4.2 Change in Dementia Cognitive Fluctuations Scale (DCFS)

Change in DCFS will be analyzed similar to primary endpoint as described in Section 5.10.2.1. Observed results will be the dependent variable. Difference between the neflamapimod treatment group and placebo with corresponding SE and 2-sided 95% CI will be presented.

All DCFS data will be listed.

5.10.4.3 12-item Neuropsychiatric Inventory (NPI-12)

5.10.4.3.1 Select domains of the 12-item Neuropsychiatric Inventory (NPI-12), including depression (dysphoria), apathy, hallucinations, and agitation/aggression.

Each selected domain score will be analyzed similar to primary endpoint as described in Section 5.10.2.1. Change from baseline will be the dependent variable. Difference in the change from baseline to the end of double-blind treatment period (average of the week 12 and week 16 score) between the neflamapimod treatment group and placebo with corresponding SE and 2-sided 95% CI will be presented.

The domains include:

- Depression (dysphoria)
- Apathy
- Hallucination
- Agitation/aggression

In addition, NPI-12 total score, NPI-4 total score and NPI-10 total score will be analyzed similar to primary endpoint as described in Section 5.10.2.1. NPI-10 total score will also be analyzed for each subgroup of cholinesterase inhibitor therapy (Yes/No) separately, as described in Section 5.10.2.1 except cholinesterase inhibitor therapy covariate will be removed from the model.

5.10.4.3.2 Change in hallucinations frequency x severity score within the NPI-12 in subjects who report hallucinations at baseline.

Hallucination domain score in subjects who reported hallucination at baseline will be analyzed similar to primary endpoint as described in Section 5.10.2.1. Change from baseline will be the dependent variable. The average change from baseline to the end of the double-blind treatment period (average of the week 12 and week 16 score) between the neflamapimod treatment group and placebo with corresponding SE and 2-sided 95% CI will be presented.

5.10.4.3.3 Change in sleep and night-time behavior change within the NPI-12.

Sleep and night-time behavior will be analyzed similar to primary endpoint as described in Section 5.10.2.1. Change from baseline will be the dependent variable. The average change from baseline to the end of the double-blind treatment period (average of week 12 and week 16) between the neflamapimod treatment group and placebo with corresponding SE and 2-sided 95% CI will be presented.

5.10.4.4 Change in MDS-UPDRS3 motor examination (Part III) score

MDS-UPDRS3 score will be analyzed similar to primary endpoint as described in Section 5.10.2.1. Change from baseline will be the dependent variable. The difference in the change from baseline during the double-blind treatment period between the neflamapimod treatment group and placebo with corresponding SE and 2-sided 95% CI will be presented.

5.10.4.5 Change in beta functional connectivity and in alpha reactivity on quantitative EEG and Basal forebrain atrophy by structural MRI

The EEG data will be analysed independently by CortiCare and the report will be provided to EIP. No analysis of EEG data will be included as part of this SAP. Similarly, MRI analysis will be defined separately, and it will not be a part of this SAP.

5.10.5 Multiplicity

Secondary endpoints will be evaluated in a hierarchical manner. If the two-sided p-value for the comparison of neflamapimod and placebo for the primary endpoint (average change from baseline in CDR-SB during the double-blind treatment period) is ≥ 0.05, the secondary endpoints will not be evaluated for statistical significance. If, on the other hand, the two-sided p-value for the primary endpoint is < 0.05, the difference between neflamapimod and placebo on the TUG will be evaluated utilizing a statistical threshold of p=0.05 (i.e., neflamapimod will have demonstrated an effect on the TUG test if $p<0.05$). If the two-sided p-value for the difference between neflamapimod and placebo in average change from baseline in the TUG test is < 0.05, then treatment effects on the NTB and the ADCS-CGIC will be independently evaluated using a local significance threshold of 0.025 (i.e. utilizing Bonferroni correction), such that neflamapimod will have demonstrated an effect for any of these two endpoints if the associated two-sided p-value is < 0.025 for the comparison between neflamapimod and placebo for the respective endpoint.

5.11 Pharmacokinetic and Biomarker Analyses

A listing of plasma trough concentrations will be presented for the PK Analysis Set. Plasma biomarker analysis will be defined separately and will not be part of this SAP.

Note: Glial Fibrillary Acidic Protein (GFAP) and Neurofilament light (NfL) levels will be measured in pre-treatment, week 12 and week 16 and the results analyzed for treatment effects concurrently with the primary efficacy analysis.

5.12 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Analysis Set for each treatment phase.

5.12.1 Adverse Events

The following tables will be presented for AEs. Incidence and/or number of events will be reported as appropriate:

- Overall summary of TEAEs
- TEAEs by system organ class and preferred term
- Treatment related TEAE by system organ class and preferred term
- Serious TEAE by system organ class and preferred term
- TEAE by system organ class, preferred term and maximum severity
- TEAE by system organ class, preferred term and closest relationship
- TEAEs leading to early withdrawal by system organ class and preferred term
- Listing of Serious TEAEs (presented in the Table section of the appendices).
- Listing of Deaths (presented in the Table section of the appendices).

AE incidence is counted only once per system organ class and once per preferred term. The number and percent of subjects experiencing events are reported. Outputs reported at maximum severity show the highest severity reported by a subject per system organ class and preferred term. MedDRA version 26.1 or higher will be used for coding purposes.

All AEs will be listed.

5.12.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, chemistry, and coagulation parameter. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

Further, number (%) of patients that meet the following cut-off points at baseline and each post-baseline visit will be presented:

- ALT >3 x ULN

- ALT >5 x ULN
- ALT >8 x ULN
- AST >3 x ULN
- AST >5 x ULN
- AST >8 x ULN
- ALT or AST >3 x ULN
- ALT or AST >5 x ULN
- ALT or AST >8 x ULN
- Total Bilirubin >1.5 x ULN
- Total Bilirubin >2 x ULN
- (ALT or AST >3 x ULN) and (Total Bilirubin > 2 x ULN or INR >1.5)*

*For multi-parameter categories, parameter values must be from the same sample (e.g., have same sample date).

All laboratory data will be listed.

5.12.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath / min)
- Temperature (degrees Celsius)

5.12.4 Electrocardiogram Data

All ECG data collected at screening for variables listed below including details of any abnormalities, will be listed.

- Heart rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS complex (ms)
- QT interval (ms)
- QTc interval (ms) [Fridericia's formula - QTcF]

5.12.5 Physical Examination

The body systems within the physical examination data at the end of the study will be summarized by treatment (Normal; Abnormal NCS, Abnormal CS). A continuous summary of weight (kg) will be provided. Shift from baseline in body system results will also be tabulated.

All physical examination data will be listed.

5.12.6 Columbia-Suicide Severity Rating Scale

A shift summary of C-SSRS by treatment and visit will be provided. All C-SSRS data will be listed.

6 INTERIM ANALYSIS

No interim analysis is planned. The primary analyses will be performed after the blinded treatment phase of 16 weeks. Subjects may go on to a long term open-label extension and a final analysis will be performed with the additional long-term data.

7 DATA SAFETY MONITORING BOARD ANALYSIS

Data safety monitoring board (DSMB) analyses are described in the DSMB analysis plan.

8 CHANGES TO PLANNED PROTOCOL ANALYSIS

- A few changes made to the US protocol in v2.0 have not been made in Ex-US protocol v2.0. Hence there are few differences between the US and Ex-US protocols. In such cases, the SAP has followed details as in US protocol. E.g., Letter Fluency Test is not part of NTB as per US protocol v2.0.
- The exploratory objectives are reframed to provide more clarity on the objective of each endpoint being assessed as the statements in protocol only specified the scales of measurement and not the intent for assessing them.
- All endpoints are reframed to specify the analysis will be performed for the double-blind treatment period data.
- Primary objective wording has been changed from “to demonstrate the efficacy of neflamapimod, compared to placebo” to “to compare the efficacy of neflamapimod, with placebo”.
- Attention composite is added as exploratory endpoint instead of secondary endpoint.
- Exploratory endpoints for NPI-12 are reframed to specify average of Week 12 and Week 16 will be analyzed.
- The error in protocol regarding directionality of ADCS-CGIC score was corrected from “higher score indicates improvement” to “lower score indicates improvement”.

- Efficacy analysis set was renamed as mITT Analysis Set.
- PK Analysis Set and completer analysis set was added.
- mITT Analysis Set, Safety Analysis Set were defined separately for double-blind treatment phase and open-label extension phase.

9 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA.
2. McKeith IG. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88-100.
3. Ratitch, B., and O'Kelly, M. (2011). "Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures." In Proceedings of PharmaSUG 2011 (Pharmaceutical Industry SAS Users Group). Paper SP04. Nashville.
4. Mainland BJ, Herrmann N, Mallya S, et al. Cognitive Fluctuations and Cognitive Test Performance Among Institutionalized Persons with Dementia. American Journal of Alzheimer's Disease & Other Dementias®. 2017;32(7):393-400.

10 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods may be used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Table Number	Table Title	Validation Method	Shell Number (if repeat)	Topline
Items in bold are not table titles but references to the section headings within eCTD.				
14.1	**Demographics Data**			
14.1.1	**Disposition**			
14.1.1.1a	Subject Disposition – Double-Blind Treatment Phase - Screened Set	IP		Topline
14.1.1.1b	Subject Disposition – Open-Label Extension Phase - Full Analysis Set	IP		
14.1.1.2	Screen Failures - Screened Set	IP		
14.1.1.3	Inclusion / Exclusion Criteria Violation - Screened Set	IP		
14.1.1.4a	Recruitment by Site - Double-Blind Treatment Phase - Full Analysis Set	IP		
14.1.1.4b	Recruitment by Site - Open-Label Extension Phase - Full Analysis Set	IP	14.1.1.4a	
14.1.1.5	Visit Attendance - Full Analysis Set	IP		
14.1.1.6a	Protocol Deviations – Double-Blind Treatment Phase - Full Analysis Set	IP		
14.1.1.6b	Protocol Deviations – Open-Label Extension Phase - Full Analysis Set	IP	14.1.1.6a	
14.1.2	**Demographics**			
14.1.2.1	Demographics - Safety Analysis Set	IP		
14.1.2.2	Demographics - Full Analysis Set	IP	14.1.2.1	Topline
14.1.3	**Baseline Characteristics**			
14.1.3.1	Baseline Characteristics - Safety Analysis Set	IP		
14.1.3.2	Baseline Characteristics - Full Analysis Set	IP	14.1.3.1	Topline
14.1.3.3	Previous Medical History - Safety Analysis Set	IP		
14.1.3.4	Medical History Ongoing at Screening - Safety Analysis Set	IP	14.1.3.2	

Table Number	Table Title	Validation Method	Shell Number (if repeat)	Topline
14.1.3.5	Prior Medications - Safety Analysis Set	IP		
14.2	**Efficacy Data**			
14.2.1	**Primary Efficacy Endpoint**			
14.2.1.1a	Primary Endpoint, Clinical Dementia Rating Scale-Sum of Boxes (Descriptive statistics) – Double-Blind Treatment Phase - mITT Analysis Set	IP		Topline
14.2.1.1b	Primary Endpoint, Clinical Dementia Rating Scale-Sum of Boxes (Descriptive statistics) – Open-Label Extension Phase - mITT Analysis Set	IP	14.2.1.1a	
14.2.1.2	Primary Endpoint, Clinical Dementia Rating Scale-Sum of Boxes (Linear Mixed Effects Model) – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP		Topline
14.2.1.3	Primary Endpoint, Clinical Dementia Rating Scale-Sum of Boxes (Sensitivity Analysis, MI, MNAR) – Double-Blind Treatment Phase – mITT Analysis Set	Stat IP		Topline
14.2.1.4	Primary Endpoint, Clinical Dementia Rating Scale-Sum of Boxes (Linear Mixed Effects Model), Subgroup Analysis – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP		
14.2.2	**Secondary Efficacy Endpoints**			
14.2.2.1.1a	Secondary Endpoint, Change in Timed Up and Go Test (Descriptive Statistics) – Double-Blind Treatment Phase - mITT Analysis Set	IP	14.2.1.1a	Topline
14.2.2.1.1b	Secondary Endpoint, Change in Timed Up and Go Test (Descriptive Statistics) – Open-Label Extension Phase - mITT Analysis Set	IP	14.2.1.1a	
14.2.2.1.2	Secondary Endpoint, Change in Timed Up and Go Test (Linear Mixed Effects Model) – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.1.2	Topline
14.2.2.1.3	Secondary Endpoint, Change in Timed Up and Go Test (Linear Mixed Effects Model), Subgroup Analysis – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.1.4	
14.2.2.2.1a	Secondary Endpoint, Neuropsychological Test Battery (Descriptive Statistic) – Double-Blind Treatment Phase - mITT Analysis Set	IP		Topline

Table Number	Table Title	Validation Method	Shell Number (if repeat)	Topline
14.2.2.2.1b	Secondary Endpoint, Neuropsychological Test Battery (Descriptive Statistic) – Open-Label Extension Phase - mITT Analysis Set	IP	14.2.2.2.1a	
14.2.2.2.2a	Secondary Endpoint, Composite Score of Neuropsychological Test Battery (Descriptive Statistic) – Double-Blind Treatment Phase - mITT Analysis Set	IP	14.2.2.2.1a	Topline
14.2.2.2.2b	Secondary Endpoint, Composite Score of Neuropsychological Test Battery (Descriptive Statistic) – Open-Label Extension Phase - mITT Analysis Set	IP	14.2.2.2.1a	
14.2.2.2.3	Secondary Endpoint, Composite Score of Neuropsychological Test Battery (Linear Mixed Effects Model) – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.1.2	Topline
14.2.2.2.4	Secondary Endpoint, Composite Score of Neuropsychological Test Battery (Linear Mixed Effects Model), Subgroup Analysis – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.1.4	
14.2.2.3.1a	Secondary Endpoint, Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (Descriptive Statistics) – Double-Blind Treatment Phase - mITT Analysis Set	IP		Topline
14.2.2.3.1b	Secondary Endpoint, Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (Descriptive Statistics) – Open-Label Extension Phase - mITT Analysis Set	IP	14.2.2.3.1a	
14.2.2.3.2	Secondary Endpoint, Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (Mann Whitney U Test) – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP		Topline
14.2.2.3.3	Secondary Endpoint, Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (Mann Whitney U Test), Subgroup Analysis – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.2.3.2	
14.2.3	**Exploratory Endpoints**			
14.2.3.1.1a	Exploratory Endpoint, Dementia Cognitive Fluctuations Scale (Descriptive Statistics) – Double-Blind Treatment Phase - mITT Analysis Set	IP	14.2.1.1a	

Table Number	Table Title	Validation Method	Shell Number (if repeat)	Topline
14.2.3.1.1b	Exploratory Endpoint, Dementia Cognitive Fluctuations Scale (Descriptive Statistics) – Open-Label Extension Phase - mITT Analysis Set	IP	14.2.1.1a	
14.2.3.1.2	Exploratory Endpoint, Dementia Cognitive Fluctuations Scale (Linear Mixed Effects Model) – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP		
14.2.3.2.1.1a	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Total Score (Descriptive Statistics) – Double-Blind Treatment Phase - mITT Analysis Set	IP	14.2.3.2.1a	Topline
14.2.3.2.1.1b	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Total Score (Descriptive Statistics) – Open-Label Extension Phase - mITT Analysis Set	IP		
14.2.3.2.1.2	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Total Score (Linear Mixed Effects Model) – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.3.2.2a	Topline
14.2.3.2.1.3	Exploratory Endpoint, NPI-10 Total Score (Linear Mixed Effects Model), Subgroup Analysis – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.1.4	
14.2.3.2.2.1a	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Domain Score (Descriptive Statistics) – Double-Blind Treatment Phase - mITT Analysis Set	IP		
14.2.3.2.2.1b	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Domain Score (Descriptive Statistics) – Open-Label Extension Phase - mITT Analysis Set	IP	14.2.3.2.3a	
14.2.3.2.2.2	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Domain Score (Linear Mixed Effects Model) – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP		
14.2.3.2.3.1a	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Hallucination Score Within Subjects with Hallucination at Baseline (Descriptive Statistics) – Double-Blind Treatment Phase - mITT Analysis Set	IP	14.2.3.2.4a	
14.2.3.2.3.1b	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Hallucination Score Within Subjects with Hallucination at Baseline (Descriptive	IP		

Table Number	Table Title	Validation Method	Shell Number (if repeat)	Topline
	Statistics) – Open-Label Extension Phase - mITT Analysis Set			
14.2.3.2.3.2	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Hallucination Score Within Subjects with Hallucination at Baseline (Linear Mixed Effects Model) – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.1.1a	
14.2.3.2.4.1a	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Sleep Domain Score (Descriptive Statistics) – Double-Blind Treatment Phase - mITT Analysis Set	IP		
14.2.3.2.4.1b	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Total Score (Descriptive Statistics) – Open-Label Extension Phase - mITT Analysis Set	IP		
14.2.3.2.4.2	Exploratory Endpoint, 12-Item Neuropsychiatric Inventory Sleep Domain Score (Linear Mixed Effects Model) – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP		
14.2.3.3.1a	Exploratory Endpoint, Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III (Descriptive Statistics) – Double-Blind Treatment Phase - mITT Analysis Set	IP		Topline
14.2.3.3.1b	Exploratory Endpoint, Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III (Descriptive Statistics) – Open-Label Extension Phase - mITT Analysis Set	IP		
14.2.3.3.2	Exploratory Endpoint, Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III (Linear Mixed Effects Model) – Double-Blind Treatment Phase - mITT Analysis Set	Stat IP		Topline
14.2.3.4.1a	Exploratory Endpoint, Attention Composite Score of Neuropsychological Test Battery (Descriptive Statistic) – Double-Blind Treatment Phase - mITT Analysis Set	IP		
14.2.3.4.1b	Exploratory Endpoint, Attention Composite Score of Neuropsychological Test Battery (Descriptive Statistic) – Open-Label Extension Phase - mITT Analysis Set	IP		
14.2.3.4.2	Exploratory Endpoint, Attention Composite Score of Neuropsychological Test Battery (Linear Mixed	Stat IP		

Table Number	Table Title	Validation Method	Shell Number (if repeat)	Topline
	Effects Model) – Double-Blind Treatment Phase - mITT Analysis Set			
14.3	**Safety Data**			
14.3.1	**Displays of Adverse Events**			
14.3.1.1a	Overall Summary of Adverse Events, Double-Blind Treatment Phase - Safety Analysis Set	IP		Topline
14.3.1.1b	Overall Summary of Adverse Events, Open-Label Extension Phase - Safety Analysis Set	IP	14.3.1.1a	
14.3.1.2a	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Double-Blind Treatment Phase - Safety Analysis Set	IP		Topline
14.3.1.2b	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Open-Label Extension Phase - Safety Analysis Set	IP	14.3.1.2a	
14.3.1.3a	Treatment-Emergent Related Adverse Events by System Organ Class, Preferred Term, Double-Blind Treatment Phase - Safety Analysis Set	IP	14.3.1.2a	
14.3.1.3b	Treatment-Emergent Related Adverse Events by System Organ Class, Preferred Term, Open-Label Extension Phase - Safety Analysis Set	IP	14.3.1.2a	
14.3.1.4a	Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term, Double-Blind Treatment Phase - Safety Analysis Set	IP	14.3.1.2a	Topline
14.3.1.4b	Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term, Open-Label Extension Phase - Safety Analysis Set	IP	14.3.1.2a	
14.3.1.5a	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity, Double-Blind Treatment Phase - Safety Analysis Set	IP		
14.3.1.5b	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity, Open-Label Extension Phase - Safety Analysis Set	IP	14.3.1.5a	
14.3.1.6a	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Closest Relationship, Double-Blind Treatment Phase - Safety Analysis Set	IP		
14.3.1.6b	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Closest	IP	14.3.1.6a	

Table Number	Table Title	Validation Method	Shell Number (if repeat)	Topline
	Relationship, Open-Label Extension Phase - Safety Analysis Set			
14.3.1.7a	Treatment-Emergent Adverse Events Leading to Early Withdrawal by System Organ Class, Preferred Term, Double-Blind Treatment Phase - Safety Analysis Set	IP		
14.3.1.7b	Treatment-Emergent Adverse Events Leading to Early Withdrawal by System Organ Class, Preferred Term, Open-Label Extension Phase - Safety Analysis Set	IP	14.3.1.7a	
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**			
14.3.2.1	Serious Treatment Emergent Adverse Events - Safety Analysis Set	IP		Topline
14.3.2.2	Deaths - Safety Analysis Set	IP		
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**			
14.3.4	**Abnormal Laboratory Values**			
14.3.4.1	Abnormal Laboratory Values – Safety Analysis Set	IP		
14.3.5	**Extent of Exposure, Dosage Information, And Compliance**			
14.3.5.1a	Exposure to Study Drug and Treatment Compliance, Double-Blind Treatment Phase - Completer Analysis Set	IP		
14.3.5.1b	Exposure to Study Drug and Treatment Compliance, Open-Label Extension Phase - Completer Analysis Set	IP	14.3.5.1a	
14.3.6	**Vital Signs and Physical Examination**			
14.3.6.1a	Vital Signs – Double-Blind Treatment Phase - Safety Analysis Set	IP		
14.3.6.1b	Vital Signs – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.6.1a	
14.3.6.2a	Physical Examination – Double-Blind Treatment Phase - Safety Analysis Set	IP		
14.3.6.2b	Physical Examination – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.6.2a	
14.3.6.3a	Shift Table of Physical Examination – Double-Blind Treatment Phase - Safety Analysis Set	IP		

Table Number	Table Title	Validation Method	Shell Number (if repeat)	Topline
14.3.6.3b	Shift Table of Physical Examination – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.6.3a	
14.3.7	**Other Safety**			
14.3.7.1a	Hematology – Double-Blind Treatment Phase - Safety Analysis Set	IP	14.3.6.1a	
14.3.7.1b	Hematology – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.6.1a	
14.3.7.2a	Chemistry – Double-Blind Treatment Phase - Safety Analysis Set	IP	14.3.6.1a	
14.3.7.2b	Chemistry – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.6.1a	
14.3.7.3a	Coagulation – Double-Blind Treatment Phase - Safety Analysis Set	IP	14.3.6.1a	
14.3.7.3b	Coagulation – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.6.1a	
14.3.7.4a	Shift Table of Hematology – Double-Blind Treatment Phase - Safety Analysis Set	IP		
14.3.7.4b	Shift Table of Hematology – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.7.4a	
14.3.7.5a	Shift Table of Chemistry – Double-Blind Treatment Phase - Safety Analysis Set	IP	14.3.7.4a	
14.3.7.5b	Shift Table of Chemistry – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.7.4a	
14.3.7.6a	Shift Table of Coagulation – Double-Blind Treatment Phase - Safety Analysis Set	IP	14.3.7.4a	
14.3.7.6b	Shift Table of Coagulation – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.7.4a	
14.3.7.7a	Abnormal Liver Function Test Results – Double-Blind Treatment Phase – Safety Analysis Set	IP		
14.3.7.7b	Abnormal Liver Function Test Results – Open-Label Extension Phase – Safety Analysis Set	IP	14.3.7.7a	
14.3.7.8a	Shift Table of C-SSRS, by Visit – Double-Blind Treatment Phase - Safety Analysis Set	IP		
14.3.7.8b	Shift Table of C-SSRS, by Visit – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.7.8a	
14.3.8	**Concomitant Medication**			
14.3.8.1a	Concomitant Medications – Double-Blind Treatment Phase - Safety Analysis Set	IP		
14.3.8.1b	Concomitant Medications – Open-Label Extension Phase - Safety Analysis Set	IP	14.3.8.1a	

Table Number	Table Title	Validation Method	Shell Number (if repeat)	Topline
14.4	**PK Tables**			
14.5	**PD Tables**			
14.6	**Other Data**			

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)	Topline
14.2.1.4	Primary Endpoint, Line Plot of Mean ± SE of Clinical Dementia Rating Scale-Sum of Boxes - mITT Analysis Set	IP		
14.2.1.5	Primary Endpoint, Line Plot of Mean ± SE of Change from Baseline in Clinical Dementia Rating Scale-Sum of Boxes - mITT Analysis Set	IP		
14.2.1.6	Primary Endpoint, Box Plot of Change from Baseline in Clinical Dementia Rating Scale-Sum of Boxes - mITT Analysis Set	IP		
14.2.2.1.3	Secondary Endpoint, Line Plot of Mean ± SE of Timed Up and Go Test - mITT Analysis Set	IP	14.2.1.4	
14.2.2.1.4	Secondary Endpoint Line Plot of Mean ± SE of Change from Baseline in Timed Up and Go Test – mITT Analysis Set	IP	14.2.1.5	
14.2.2.1.5	Secondary Endpoint, Box Plot of Change from Baseline in Timed Up and Go Test - mITT Analysis Set	IP	14.2.1.6	
14.2.2.2.3	Secondary Endpoint, Line Plot of Mean ± SE of Composite Score of Neuropsychological Test Battery - mITT Analysis Set	IP	14.2.1.4	
14.2.2.2.4	Secondary Endpoint, Line Plot of Mean ± SE of Change from Baseline in Composite Score of Neuropsychological Test Battery - mITT Analysis Set	IP	14.2.1.5	
14.2.2.2.5	Secondary Endpoint, Box Plot of Change from Baseline in Composite Score of Neuropsychological Test Battery - mITT Analysis Set	IP	14.2.1.6	
14.2.2.3.3	Secondary Endpoint, Line Plot of Mean ± SE of Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change - mITT Analysis Set	IP	14.2.1.4	
14.2.3.1.3	Exploratory Endpoint, Line Plot of Mean ± SE of Dementia Cognitive Fluctuations Scale - mITT Analysis Set	IP	14.2.1.4	
14.2.3.1.4	Exploratory Endpoint, Line Plot of Mean ± SE of Change from Baseline in Dementia Cognitive Fluctuations Scale - mITT Analysis Set	IP	14.2.1.5	
14.2.3.1.5	Exploratory Endpoint, Box Plot of Change from Baseline in Dementia Cognitive Fluctuations Scale - mITT Analysis Set	IP	14.2.1.6	
14.2.3.2.5	Exploratory Endpoint, Line Plot of Mean ± SE of 12-Item Neuropsychiatric Inventory - mITT Analysis Set	IP	14.2.1.4	

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)	Topline
14.2.3.2.6	Exploratory Endpoint, Line Plot of Mean ± SE of Change from Baseline in 12-Item Neuropsychiatric Inventory - mITT Analysis Set	IP	14.2.1.5	
14.2.3.2.7	Exploratory Endpoint, Box Plot of Change from Baseline in 12-Item Neuropsychiatric Inventory - mITT Analysis Set	IP	14.2.1.6	
14.2.3.3.3	Exploratory Endpoint, Line Plot of Mean ± SE of Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III - mITT Analysis Set	IP	14.2.1.4	
14.2.3.3.4	Exploratory Endpoint, Line Plot of Mean ± SE of Change from Baseline in Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III - mITT Analysis Set	IP	14.2.1.5	
14.2.3.3.5	Exploratory Endpoint, Box Plot of Change from Baseline in Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III - mITT Analysis Set	IP	14.2.1.6	
14.2.3.4.3	Exploratory Endpoint, Line Plot of Mean ± SE of Attention Composite Score - mITT Analysis Set	IP	14.2.1.4	
14.2.3.4.4	Exploratory Endpoint, Line Plot of Mean ± SE of Change from Baseline in Attention Composite Score - mITT Analysis Set	IP	14.2.1.5	
14.2.3.4.5	Exploratory Endpoint, Box Plot of Change from Baseline in Attention Composite Score mITT Analysis Set	IP	14.2.1.6	
14.3.7.8	Laboratory Data, Box Plot of Change from Baseline in Hematology - Safety Analysis Set	IP	14.2.1.6	
14.3.7.9	Laboratory Data, Box Plot of Change from Baseline in Chemistry - Safety Analysis Set	IP	14.2.1.6	
14.3.7.10	Laboratory Data, Box Plot of Change from Baseline in Coagulation - Safety Analysis Set	IP	14.2.1.6	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)	Topline
16.2	**Subject Data Listings**			
16.2.1	**Discontinued Subjects**			
16.2.1.1	Subject Disposition - Screened Set	IP		
16.2.1.2	Screen Failures - Screened Set	IP		
16.2.1.3	Inclusion/Exclusion Criteria - Screened Set	IP		
16.2.2	**Protocol Deviations**			
16.2.2.1	Protocol Deviations - Full Analysis Set	IP		
16.2.3	**Subjects Excluded from The Efficacy Analyses**			
16.2.3.1	Analysis Sets - Full Analysis Set	IP		
16.2.4	**Demographic Data**			
16.2.4.1	Demographics - Full Analysis Set	IP		
16.2.4.2	Baseline Characteristics - Full Analysis Set	IP		
16.2.4.3	Medical History - Safety Analysis Set	IP		
16.2.4.4	Prior and Concomitant Medications - Safety Analysis Set	IP		
16.2.4.5	Cholinesterase Inhibitors and Memantine Therapy – Safety Analysis Set	IP	16.2.4.4	
16.2.5	**Compliance and / or Drug Concentration Data**			
16.2.5.1	Extent of Exposure - Completer Analysis Set	IP		
16.2.5.2	Drug Accountability - Completer Analysis Set	IP		
16.2.5.3	Plasma Trough PK Concentration Data – PK Analysis Set	IP		
16.2.5.4	Plasma Trough pTau Analysis Data – PK Analysis Set	IP		
16.2.6	**Individual Efficacy Response Data**			
16.2.6.1	Clinical Dementia Rating Scale-Sum of Boxes - mITT Analysis Set	IP		Topline
16.2.6.2	Timed Up and Go Test - mITT Analysis Set	IP		Topline
16.2.6.3	Primary Parameters of the Neuropsychological Test Battery - mITT Analysis Set	IP		Topline
16.2.6.4	Composite Score of the Neuropsychological Test Battery - mITT Analysis Set	IP		Topline
16.2.6.5	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change - mITT Analysis Set	IP		Topline
16.2.6.6	Dementia Cognitive Fluctuations Scale - mITT Analysis Set	IP		
16.2.6.7	12-item Neuropsychiatric Inventory – Domain Scores - mITT Analysis Set	IP		
16.2.6.8	12-Item Neuropsychiatric Inventory – Overall Scores - mITT Analysis Set	IP		

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)	Topline
16.2.6.9	Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III - mITT Analysis Set	IP		
16.2.7	**Adverse Event Listings**			
16.2.7.1	Adverse Events - Safety Analysis Set	IP		Topline
16.2.7.2	Adverse Events Leading to Early Withdrawal - Safety Analysis Set	IP	16.2.7.1	Topline
16.2.8	**Individual Laboratory Measurements and Other Safety**			
16.2.8.1	Hematology - Safety Analysis Set	IP		
16.2.8.2	Chemistry - Safety Analysis Set	IP		
16.2.8.3	Coagulation - Safety Analysis Set	IP		
16.2.8.4	Vital Signs - Safety Analysis Set	IP		
16.2.8.5	12-Lead Electrocardiogram at Screening - Safety Analysis Set	IP		
16.2.8.6	Physical Examination - Safety Analysis Set	IP		
16.2.8.7	Columbia-Suicide Severity Rating Scale - Safety Analysis Set	IP		
16.2.8.8	Pregnancy Test Data – Safety Analysis Set	IP		

11 APPENDIX A: TEST INFORMATION AND COGNITIVE DOMAIN ASSESSED

Endpoint	Cognitive Domain	Primary Outcome (Variable)	Interpretation	Range Values
Detection Test (DET)	Psychomotor Function	Speed of performance; mean of the log10 transformed reaction times for correct responses	Lower score = better performance	2.001 to 6
Identification Test (IDN)	Attention	Speed of performance; mean of the log10 transformed reaction times for correct responses	Lower score = better performance	2.001 to 6
One Card Learning Test (OCL)	Visual Learning	Accuracy of performance; arcsine square root proportion correct	Higher score = better performance	0 to 1.5708
One Back Test (ONB)	Working Memory	Speed of performance; mean of the log10 transformed reaction times for correct responses	Lower score = better performance	2.001 to 6
	Working Memory	Accuracy of performance; arcsine square root proportion correct (Additional outcome)	Higher score = better performance	0 to 1.5708
International Shopping List Test (ISLT)	Verbal Learning Tell me the items on the shopping list.	Number of correct responses remembering the word list on three consecutive trials	Higher score = better performance	0 to 999

Statistical Analysis Plan
Post Database Lock Addendum

Title: A Phase 2b Clinical Study of the P38 Alpha Kinase Inhibitor Neflamapimod in Patients with Dementia with Lewy Bodies (DLB)

Protocol Number: EIP21-NFD-504

Protocol Version: Version 2.0 / 15-DEC-2023

Version 2.0 Ex-US / 20-JUN-2023

SAP Version: 3.0 / 24-OCT-2024

Addendum Version: 1.0

Addendum Issue Date: 17-OCT-2025

Previous Addenda

Not Applicable

POST DATABASE LOCK STATISTICAL ANALYSIS PLAN ADDENDUM

1. BACKGROUND

This document details changes and / or additions to the planned statistical analyses for EIP Pharma, Inc, Protocol "EIP21-NFD-504" study previously described in V3.0 of the Statistical Analysis Plan (SAP) dated 24-OCT-2024.

These amendments were made post database lock and after the study was unblinded.

Rationale for Addendum:

1) Removal of treatment*time interaction term from the efficacy analysis model.
2) Definition added for missing last dose date.
3) Additional tables generated to report the efficacy analysis for subjects with pTau181 <21 pg/mL at Screening.

2. CHANGES TO EXISTING SAP

2.1 Change 1

2.1.1 Original Text

Section 2.3 Estimand

Analysis Approach:

> The difference between treatment arms in the average change from Baseline of the CDR-SB score will be estimated from a linear mixed effects model, including treatment group, **time in weeks, and treatment by time interaction as fixed effects**; stratification factors (with and without cholinesterase inhibitor therapy), sex and baseline value as covariates. The random effect is on the subject term.

2.1.2 New Text

Section 2.3 Estimand

Analysis Approach:

> The difference between treatment arms in the average change from Baseline of the CDR-SB score will be estimated from a linear mixed effects model, including treatment group, **and time in weeks as fixed effects**; stratification factors (with and without cholinesterase inhibitor therapy), sex and baseline value as covariates. The random effect is on the subject term.

2.2 Change 2

2.2.1 Original Text

Section 5.10.2.1 Primary Analysis

> The difference between neflamapimod and placebo in the average change from baseline in CDR-SB score during the double-blind treatment phase (i.e., utilizing data from week 8, 12 and 16 in the model) will be estimated using a linear mixed effects model including treatment, time (in weeks**), treatment-by-time interaction** as fixed effects, cholinesterase inhibitor therapy (Yes/No), age, sex and baseline value as covariates.

2.2.2 New Text

Section 5.10.2.1 Primary Analysis

> The difference between neflamapimod and placebo in the average change from baseline in CDR-SB score during the double-blind treatment phase (i.e., utilizing data from week 8, 12 and 16 in the model) will be estimated using a linear mixed effects model including treatment, time (in weeks) as fixed effects, cholinesterase inhibitor therapy (Yes/No), age, sex and baseline value as covariates.

2.3 Change 3

2.3.1 Original Text

Section 5.10.2.1 Primary Analysis

Example SAS code:

```
proc mixed data= <input>  method = REML alpha=0.05;
  class <subject> <treatment> <cholinesterase inhibitor therapy> <sex>;
  model <change from baseline> = <treatment> < cholinesterase inhibitor therapy> <sex> <age> <
baseline value> <time in weeks><treatment>*<time in weeks> / ddfm=kr s;
  random <time in weeks> / subject=<subject> type=un;
  lsmeans <treatment> / cl diff;
run;
```

2.3.1 New Text

Section 5.10.2.1 Primary Analysis

Example SAS code:

```
proc mixed data= <input>  method = REML alpha=0.05;
  class <subject> <treatment> <cholinesterase inhibitor therapy> <sex>;
  model <change from baseline> = <treatment> < cholinesterase inhibitor therapy> <sex> <age> <
baseline value> <time in weeks> / ddfm=kr s;
  random <time in weeks> / subject=<subject> type=un;
  lsmeans <treatment> / cl diff;
run;
```

2.4 Change 4

2.4.1 Original Text

Section 5.10.2.2 Sensitivity Analysis

Example SAS code:

```
proc mixed data= <input>  method = REML alpha=0.05;
  class <subject> <treatment> <cholinesterase inhibitor therapy> <sex>;
  model <change from baseline> = <treatment> < cholinesterase inhibitor therapy> <sex> <age> <
baseline value> <time in weeks><treatment>*<time in weeks> / ddfm=kr s;
  random <time in weeks> / subject=<subject> type=un;
```

```
  lsmeans <treatment> / cl diff;
run;
```

2.4.2 New Text

Section 5.10.2.2 Sensitivity Analysis

Example SAS code:

```
proc mixed data= <input>  method = REML alpha=0.05;
  class <subject> <treatment> <cholinesterase inhibitor therapy> <sex>;
  model <change from baseline> = <treatment> < cholinesterase inhibitor therapy> <sex> <age> <
baseline value> <time in weeks> / ddfm=kr s;
  random <time in weeks> / subject=<subject> type=un;
  lsmeans <treatment> / cl diff;
run;
```

3. ADDITIONS TO EXISTING SAP

3.1 Addition 1

3.1.1 New Text

5.2.9.1 Missing Date of Last Dose of Study Drug

In case the last dose date is missing for a subject, the date of last scheduled visit completed will be used as last dose date.

3.2 Addition 2

Following additional tables are added to the analysis

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.1.1c	Primary Endpoint, Clinical Dementia Rating Scale-Sum of Boxes (Descriptive statistics), pTau181 <21 at Screening - Double-Blind Treatment Phase - mITT Analysis Set	Stat IPS	14.2.1.1a
14.2.1.2b	Primary Endpoint, Clinical Dementia Rating Scale-Sum of Boxes (Linear Mixed Effects	Stat IP	14.2.1.2

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	Model), pTau181 <21 at Screening - Double-Blind Treatment Phase – mITT Analysis Set		
14.2.2	**Secondary Efficacy Endpoints**		
14.2.2.1.1c	Secondary Endpoint, Change in Timed Up and Go Test (Descriptive Statistics), pTau181 <21 at Screening - Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.2.1.1a
14.2.2.1.2b	Secondary Endpoint, Change in Timed Up and Go Test (Linear Mixed Effects Model), pTau181 <21 at Screening - Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.2.1.2
14.2.2.2.2c	Secondary Endpoint, Composite Score of Neuropsychological Test Battery (Descriptive Statistic), pTau181 <21 at Screening - Double-Blind Treatment Phase – mITT Analysis Set	Stat IP	14.2.2.2.2a
14.2.2.2.3b	Secondary Endpoint, Composite Score of Neuropsychological Test Battery (Linear Mixed Effects Model), pTau181 <21 at Screening - Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.2.2.3
14.2.2.3.1c	Secondary Endpoint, Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (Descriptive Statistics), pTau181 <21 at Screening - Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.2.3.1a
14.2.2.3.2b	Secondary Endpoint, Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (Mann Whitney U Test), pTau181 <21 at Screening - Double-Blind Treatment Phase - mITT Analysis Set	Stat IP	14.2.2.3.2

POST DATABASE LOCK STATISTICAL ANALYSIS PLAN ADDENDUM

Approval for Implementation of

Statistical Analysis Plan Post Database Lock Addendum

REVIEW / APPROVAL SIGNATURES

Plan Author	**Plan Reviewer, Worldwide**
Aparna Bhide, Senior Statistician, Biostatistics Signature:	*Robin White, Associate Director, Biostatistics* Signature:
Plan Approver, Sponsor Clinician	
John Alam, MD, CEO, CervoMed Inc. (parent company of EIP Pharma, Inc.) Signature:	

February 10th, 2025

Approach for OLE Analysis

Treatment groups:

There are five treatment groups in the OLE:

Group 1 = old batch for all of OLE (or through ET), N=20
Group 2 = started OLE on old batch, switched at W16 OLE, N=35
Group 3 = started OLE on old batch, switched at W8 OLE, N=26
Group 4 = started OLE on old batch, switched at W4 OLE, N=22
Group 5 = new batch for all of OLE (or through ET), N=46

Total=149, though not all the participants above will be in the mITT analysis, with some being excluded because they do not have at least one efficacy evaluation during the OLE.

In addition, three populations will be evaluated:

1. All participants in OLE
2. OLE participants with screening plasma ptau181 <25.2 pg/mL (2.2 pg/mL in prior version of assay)
3. OLE participants with screening plasma ptau181 < 21 pg/mL (1.8 pg/mL in prior version of assay)

For OLE week 8 data point, groups 1, 2 and 3 will be pooled under "old capsule treatment" and only group 5 will be included under "new capsule treatment" (i.e. only participants with ≥ 8 weeks of new capsules will be included).

For the week 16 OLE analysis, groups 1 and 2 will be pooled under the label of "Old Capsules Treatment", and groups 3, 4 and 5 will be pooled under the label of "New Capsule Treatment" (i.e. all participants with ≥ 8 weeks of new capsules will be included for the new capsule treatment group).

The baseline value for all change analyses will be the value at the end of the double-blind period, i.e. at week 16 of the main study (if no value, week 12 will be carried forward).

Analyses to be Conducted

The primary analyses to be conducted are a comparison of new capsule treatment with old capsule treatment:

- For CGIC, this comparison will be a static, unpaired comparison at f week 8 using a parametric test (Mann-Whitney U-test.

- For all other endpoints (CDR-SB, TUG, NPI-10, NTB composite, ISLT immediate, ISLT recognition, UPDRS Motor (Part III), the statistical analysis will be change from baseline using linear mixed effects model with baseline as a covariate, i.e. utilizing data from week 8 and 16 of the OLE. The recommendation would be to utilize the LME model from AscenD-LB (phase 2a), but the Worldwide model from RewinD-LB may also be utilized. In addition, descriptive data (i.e. mean, with sem, change from baseline) with p-values (parametric or non-parametric, as appropriate) for the comparison at each of week 8 and 16 will be provided.

A secondary analysis will be comparing the outcomes during the OLE with outcome during the double-blind period in participants who received placebo during the main study and received ≥ 8 weeks of new capsules in the OLE (i.e. received new capsules for either the entire 16 weeks or for 12 weeks starting at week 4):

- For CGIC, the comparison will be a paired comparison of the CGIC score at week 16 of the double-blind period with the CGIC score at week 8 of the OLE utilizing Mann-Whitney U-test.
- For all other endpoints, it will be paired comparison (parametric or non-parametric, as appropriate) of the change from baseline to week 8, and from baseline to week 16. If LME model allows for a within-subject comparison, this would be the preferred method.

Finally, comparison of proportions of progressors (early treatment discontinuation or increase from baseline in CDR-SB of ≥ 1.5) during the OLE with new capsule treatment vs. old capsule treatment will be conducted. Along with proportion of progressors anytime during the OLE, a Kaplan-Meier analysis of the time to progression may be conducted.

All analyses will be conducted with the observed data at each time point. That is, missing data will **not** be imputed (e.g., week 8 results being carried forward for missing week 16 data).

Plasma Biomarkers

Plasma for biomarker (GFAP, NfL) were obtained at week 8 during the OLE, and will be analyzed as change from baseline (result at week 16 of the double-blind period) for participants treated with new capsules (Group 4 and Group 5 combined) vs. old capsules (Groups 1, 2 and 3; the latter because they received old capsules through to week 8).

In addition, for participants treated with placebo, a within-subject comparison will be made for change from baseline (average of screening and baseline value) to week 12 during placebo treatment compared to change from baseline for OLE (average of week 12 and week 16 of double-blind phase) to week 8 during treatment with either old or new capsules during OLE (the participants who received old vs. new capsules being analyzed separately.

The plasma biomarker data should also be the best opportunity to establish a PK-PD relationship within the participants who received the new capsules at any time within the first eight weeks (for either 4 or 8 weeks).