STATISTICAL ANALYSIS PLAN FOR PROTOCOL EIP19-NFD-501

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DATE OF PLAN:

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STUDY DRUG:

Neflamapimod

PROTOCOL NUMBER:

EIP19-NFD-501

STUDY TITLE:

A DOUBLE-BLIND, PLACEBO-CONTROLLED 16-WEEK STUDY OF THE COGNITIVE EFFECTS OF THE ORAL P38 ALPHA KINASE INHIBITOR NEFLAMAPIMOD IN DEMENTIA WITH LEWY BODIES (DLB)

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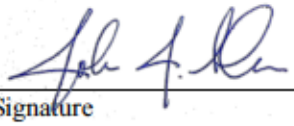
John J. Alam		6-30-2020
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List of Abbreviations

Abbreviation	Definition
AD	Alzheimer's disease
ADR	Adverse drug reaction
ANCOVA	Analysis of covariance
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	bis in die (twice a day)
CDR-GS	Clinical Dementia Rating Scale-Global Score
CDR-SB	Clinical Dementia Rating Scale-Sum of Boxes
CFT	Category Fluency Test
CP	Completer population
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
DET	Cogstate Detection test
DLB	Dementia with lewy bodies
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEG	Electroencephalography
EEP	Evaluable efficacy population
ET	Early Termination
FDA	Food and Drug Administration
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDN	Cogstate Identification Test
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio

ISLT	International Shopping List Test
ISRL	International Shopping List Test – Delayed Recall
ISRN	International Shopping List Test – Recognition
LFT	Letter fluency test
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
NPI-10	10-item Neuropsychiatric Inventory
NTB	Neuropsychological Test Battery
OCL	Cogstate One Card Learning test
ONB	Cogstate One Back Test
PACC	Preclinical Alzheimer Cognitive Composite
PK	Pharmacokinetic
PSG	Polysomnography
qEEG	Quantitative electroencephalograph
RBD	REM sleep behavioral disorder
SAE	Serious adverse event
SAP	Statistical analysis plan
TID	Three times daily
TUG	Timed Up and Go Test
ULN	Upper limit of normal

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1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol EIP19-NFD-501, Version 1.0, 12 April 2019.

This SAP is a more detailed companion to the Statistical Methods section of the study protocol and provides a comprehensive description of the analysis data sets, efficacy endpoints, assumptions, how missing data will be handled, as well as details on statistical methods will be used to analyze the safety and efficacy data. When differences exist in descriptions or explanations provided in the protocol and this analysis plan, the SAP prevails. The document may evolve over time; for example, to reflect the requirements of protocol amendments or regulatory requests. The final SAP will be finalized, approved by the Sponsor, and placed on file before database is locked. Deviations from the final approved plan will be noted in the clinical study report.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to evaluate the effect of neflamapimod on cognitive function as assessed in a study-specific Neuropsychological Test Battery (NTB) comprised of:

- Cogstate Detection test (DET)
- Cogstate Identification test (IDN)
- Cogstate One Card Learning test (OCL)
- Cogstate One Back test (ONB)
- Letter Fluency Test (LFT)
- Category Fluency Test (CFT)

2.2. Secondary Objectives

- Evaluate the effects of neflamapimod on informant/caretaker evaluation of cognition and function, as assessed by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB).
- Assess the effects of neflamapimod on general cognition, as assessed by the Mini Mental State Examination (MMSE).
- Assess the effects of neflamapimod on episodic memory, as assessed by the International Shopping List Test (ISLT).
- Assess the effects of neflamapimod on select domains of the 10-item Neuropsychiatric Inventory (NPI-10), including depression (dysphoria), anxiety, hallucinations, and agitation/aggression.
- Evaluate the effects of neflamapimod on motor function as assessed by the Timed Up and Go Test (TUG).
- Evaluate the effects of neflamapimod on quantitative electroencephalography (EEG) parameters.

2.3. Exploratory Efficacy and Safety Objectives

In addition, exploratory analyses of the full set of parameters in the NTB and associated composite scores will be conducted and exposure to safety relationship will be investigated if data allow.

3. STUDY DESIGN

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, proof-of- principle study of neflamapimod versus matching placebo (randomized 1:1) administered with food for 16 weeks in subjects with dementia with lewy bodies (DLB). Subjects weighing <80 kg will receive 2 capsules per day (in divided doses) and those weighing ≥80 kg will receive 3 capsules per day (in divided doses). Subjects receiving two capsules per day will be administered 1 capsule, twice daily (BID) with food (i.e., with the morning and evening meals), either neflamapimod 40 mg or placebo. Subjects receiving 3 capsules per day will be administered 1 capsule three times daily (TID) with food (i.e., with the morning, mid-day, and evening meals), either neflamapimod 40 mg or placebo. Doses should be administered at least 3 hours apart.

Following completion of informed consent procedures, subjects will enter the Screening phase of the study.

One to two Screening visits are planned, during which safety screening measures will be undertaken, a practice NTB will be performed, and the required diagnosis and cognitive impairment will be confirmed. Screening will be conducted within 21 days before Baseline (Day 1). If a DaTscan™ is required to determine study eligibility, Screening may be extended to 35 days.

Once eligibility is confirmed and before the first dose of study drug, subjects will be randomly assigned on a 1:1 basis to placebo or neflamapimod for the 16-week treatment period. Investigators and subjects will be blinded to the treatment assignment. Randomized subjects will be stratified by International Shopping List Test (ISLT) Total Recall score at Baseline (< 21 vs. >21), i.e. by whether patients have an episodic memory defect at baseline or not.

Subjects will receive study drug for 16 weeks. Dosing will start on Day 1 following completion of all baseline procedures. During the 16-week treatment period, subjects will return to the clinic every 2 weeks for the first month and then every 4 weeks thereafter. A Final Study Visit (i.e. Follow-Up Visit) will be conducted 2 weeks (+/-3 days) after completion of study drug or after the Early Termination (ET) visit.

The NTB, ISLT, and NPI-10 will be conducted at Screening, Baseline (Day 1), Week 4 (Day 28), Week 8 (Day 56), and Week 16 (Day 112) or ET if early termination. The CDR-SB and TUG will be conducted at Baseline (Day 1), Week 8 (Day 56), and Week 16 (Day 112) or ET. The MMSE will be conducted at Screening, Baseline (Day 1), Week 8 (Day 56), and Week 16 (Day 112) or ET. EEGs will be conducted at Baseline (Day 1) and Week 16 (Day 112) or ET. Samples for plasma biomarkers will be obtained at Screening, Baseline (Day 1) and Week 16 (Day 112) or ET.

3.1. Sample Size Justification

A total of approximately 80 subjects are planned to be enrolled, of whom 40 are planned to receive neflamapimod and 40 are planned to receive placebo.

As there is no prior experience with neflamapimod in patients with DLB upon which to base assumptions of treatment effect, no formal sample size calculation has been performed. However, based on prior experience with NTB in clinical studies, 40 subjects per treatment arm

should provide a reasonably robust first assessment of whether neflamapimod improves cognitive function in patients with DLB.

3.2. Study duration and visit schedule

Screening window of 21 days (unless DaTscan is required, in which case Screening window may be extended to 35 days), 16 weeks of treatment, a 2-week follow-up visit for a total of 21 weeks study duration. Complete descriptions of the assessments to be performed at each visit are listed in Table 1.

3.3. Randomization

After subjects have completed the Screening Visit and are deemed eligible, they will be 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 stratified by ISLT Total Recall score at Baseline (≤ 21 vs. > 21). Randomization and stratification will be administered via Interactive Response Technology (IRT). Subjects will follow the BID regimen if weighing <80 kg or the TID regimen if weighing ≥80 kg.

Table 1: Schedule of Assessments

	Study Period / Week / Study Day								
	Screening[p]	Treatment Period						Early Termination	Follow-Up
	Screening Visit[p]	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	ET Visit[c]	Follow-Up Visit[p]
Assessment	Within 21-35 days of D1	D1[b]	D14 (±3)	D28 (±3)	D56 (±5)	D84 (±5)	D112 (±5)	Within 3 days after last dose	Within 14 days (±3) of last dose
Informed Consent	X[e]								
Medical history review	X								
Pregnancy testing	X[f]								
Physical examination[g]	X						X	X	X
Vital signs[h]	X	X	X	X	X	X	X	X	X
Hematology and chemistry[i]	X	X		X	X	X	X	X	
Coagulation studies[i]	X				X				X
12-lead electrocardiogram[j]	X								
DaTscan™, if needed	X[k]								
CT/MRI	X[l]								
C-SSRS	X	X		X	X	X	X	X	
MMSE[m]	X	X			X		X	X	
NTB[m], International Shopping List Test (ISLT)	X	X		X	X		X	X	
CDR-SB		X			X		X	X	
NPI-10	X	X		X	X		X	X	
Timed Up and Go (TUG)		X			X		X	X	
EEG[n]		X					X	X	
Dispense study drug		X	X	X	X	X			
Pharmacokinetic sampling[o]			X	X	X				
Plasma sample for protein biomarker testing[p]	X[q]	X					X	X	

	Study Period / Week / Study Day								
	Screening[a]	Treatment Period						Early Termination	Follow-Up
	Screening Visit[b]	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	ET Visit[c]	Follow-Up Visit[d]
Assessment	Within 21-35 days of D1	D1[b]	D14 (±3)	D28 (±3)	D56 (±5)	D84 (±5)	D112 (±5)	Within 3 days after last dose	Within 14 days (±3) of last dose
Prior/concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event recording	X	X	X	X	X	X	X	X	X
Final study drug reconciliation							X	X	

CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; C-SSRS: Columbia-Suicide Rating Scale; CT: Computed tomography; D=day; MMSE: Mini-Mental State Examination; MRI: Magnetic resonance imaging; NPI-10: 10-item Neuropsychiatric Inventory; NTB: Neuropsychological Test Battery.

a. One to two Screening visits are planned during which safety screening procedures are to be completed and reviewed, including a practice NTB and the required diagnostic and cognitive impairment procedures. Screening will be conducted within 21 days before Baseline (Day 1); if a DaTscan and/or MRI or CT scan is required to determine study eligibility, Screening may be extended to 35 days. (If necessary, a second visit may be conducted on a different day to allow for scheduling purposes.) All screening assessments should be conducted within 21-35 days of Day 1 and can be condensed to one visit.
b. On Day 1, all procedures should be conducted prior to first dose of study drug.
c. Subjects who prematurely discontinue study drug for any reason will be asked to return to the study center for an Early Termination visit within 3 days following the last study drug dose; if it is determined that the subject will discontinue study drug while at the study center for a scheduled visit, then the Early Termination visit should be conducted at that time.
d. The Follow-up Visit should be conducted within 14 (±3) days of the last dose of study drug for subjects who complete the study or discontinue early.
e. Informed consent procedures, including signing of informed consent, must be completed before any study-specific procedures are performed.
f. Female subjects who have reached menopause in the previous year must have a serum or urine pregnancy test performed during Screening; subjects with positive results are not eligible for study participation.
g. Refer to Section 6.2.8 of Protocol for details regarding physical examination.
h. Vital signs include blood pressure, pulse, respiratory rate, and body temperature. Vital signs should be measured after the subject has been in sitting position for 5 minutes.
i. Details of clinical laboratory sampling for chemistry, hematology, and coagulation studies are discussed in Section 6.2.10 of Protocol.
j. Details of 12-lead ECG assessment are discussed in Section 6.2.9 of Protocol.
k. Subjects are required to have a prior DaTscan. If a DaTscan has not been performed within the previous 2 years, it is to be performed during Screening **only after** subject has been deemed eligible based on all other inclusion/exclusion criteria (e.g., medical history, laboratory testing) and prior to randomization. Note that if

DaTscan results are negative (i.e., no evidence of

reduced uptake in the basal ganglia), the subject is required to have historical PSG-verified RBD to be eligible for study participation.

l. If MRI or CT has not been performed within 3 years before Screening and/or results are not available, MRI or CT scan must be performed to exclude other disease as part of Screening **only after** subject has been deemed eligible based on all other inclusion/exclusion criteria (e.g., medical history, laboratory testing) and prior to randomization (see Section 6.2.2 of Protocol).

m. Refer to Section 6.2.4 of Protocol for details regarding cognitive function tests.

n. EEG need not performed at the ET visit for subjects who discontinue prior to Week 4 (Day 28).

o. Refer to Section 6.2.11 of Protocol for details regarding PK sampling.

p. Refer to Section 6.2.12 of Protocol for details regarding plasma biomarker sampling.

q. Only plasma Aβ42/40 ratio is required at Screening.

4. CLINICAL ASSESSMENTS

All clinical assessments will be conducted by the Investigator or designee at the time points specified in Table 1.

4.1. Baseline and Disease Characteristics

Details regarding DLB history, including method(s) of diagnosis will be collected during Screening, as specified in the eCRF. Subjects without documentation of prior diagnostic DLB tests (DaTscan and/or known amyloid biomarker status) are to have such tests performed during Screening.

4.2. Efficacy/Cognitive Assessments

Cognitive function tests include a Neuropsychological Test Battery (NTB) as well as the Letter Fluency Test and Category Fluency Test (CFT), which are all components of the primary objective/endpoint to assess attention, executive function, and visuospatial function.

Cognitive function tests to be performed as components of the secondary objective include the CDR-SB, MMSE, NPI-10, Timed Up and Go (TUG), and International Shopping List Test (ISLT).

At Baseline and on any visits at which both NTB and other cognitive tests are conducted, the NTB should be performed prior to the other tests.

4.2.1. Neuropsychological Test Battery (NTB)

The NTB includes:

- Cogstate Detection test (DET; Psychomotor Function)

  The Detection test is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli. In this test, the playing cards all depict the same joker. The subject is asked to press the Yes key as soon as the card in the center of the screen turns face up. The software records the mean reaction time (log10 ms). Duration of Test: 2 minutes

- Cogstate Identification test (IDN; Attention)

  The Identification test is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli. In this test, the playing cards are all either red or black jokers. The subject is asked whether the card displayed in the center of the screen is red. The subject responds by pressing the Yes key when the joker card is red and No when it is black. The software records the mean reaction time (log10 ms). Duration of Test: 2 minutes

- Cogstate One Card Learning test (OCL; Visual Learning)

  The One Card Learning test is a measure of visual learning and uses a well-validated pattern separation paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards).

The subject is asked whether the card displayed in the center of the screen was seen previously in this test. The subject responds by pressing the Yes or No key. The software measures the accuracy across all responses (arcsine sqrt % correct). Duration of Test: 5 minutes

- Cogstate One Back test (ONB; Working Memory)

  The One Back test is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously. The subject responds by pressing the Yes or No key. Because no card has been presented yet on the first trial, a correct first response is always No. The software records the mean reaction time (log10 ms) and the accuracy across all responses (arcsine sqrt % correct). Duration of Test: 3 minutes

- Letter Fluency Test: The Letter Fluency Test is a measure of phonemic fluency and is a subtest of the Multilingual Aphasia Examination (Benton et al, 1994). The LFT uses the 3- letter set of F, A, and S or C, F, and L to assess phonemic fluency. Individuals are given 1 minute to name as many words as possible beginning with one of the letters. The procedure is then repeated for the remaining two letters. The administration of phonemic and semantic fluency takes approximately 5 minutes. Admissible responses are summed and compared to a normative sample.
- Category Fluency Test (CFT): The CFT is a measure of verbal fluency and is sometimes called semantic fluency. In the standard version of the task, participants are given 1 minute to produce as many unique words as possible within a category. The subject's score is the number of unique correct words.

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

The Clinical Dementia Rating Scale (CDR) (Hughes, 1982) is a semi-structured interview resulting in a semi-quantitative scoring of cognitive impairment in milder and more progressed forms of dementia. It is sensitive in both AD dementia and Mild Cognitive Impairment, and is an approved regulatory endpoint recognized by the FDA. The CDR yields both a global score (CDR-GS) and Sum of Boxes score (CDR- SB). While the CDR-GS is typically utilized for staging purposes, the CDR-SB score is a more detailed quantitative general index than the CDR-GS and it provides more information than the CDR total score in cases of mild dementia (O'Bryant, et al, 2010).

4.2.3. Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al, 1975) consists of 11 tests of orientation, memory (recent and immediate), concentration, language, and praxis. Scores range from 0 to 30, with lower scores indicating greater cognitive impairment. It is based on the performance of the subject and takes approximately 5 to 10 minutes to administer.

4.2.4. International Shopping List Test (ISLT)

Word learning tests have been commonly utilized to assess episodic memory. In DLB, the recognition component is considered to be of particular utility (Wesnes et al, 2015). The ISLT is one such word learning test that has been utilized in a number of proof-of-concept clinical studies with novel therapeutics (Nathan et al, 2013; Maher-Edwards et al, 2015). Immediate and Delayed Recall (ISRL), as well as Recognition (ISRN), will be assessed. The software measures the number of correct responses as recorded by the test supervisor. Duration of Test: 5 minutes.

4.2.5. 10-item Neuro-Psychiatric Inventory (NPI-10)

The NPI-10 is designed to assess psychopathology in the person with dementia and to help distinguish between the different causes of dementia. The NPI-10 examines 10 sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor activity. For this study, the following domains are of specific interest: depression (dysphoria), anxiety, hallucinations, and agitation/aggression. The NPI-10 is administrated to caregivers of dementia subjects. A screening question is asked about each included sub- domain. If the responses to these questions indicate that the subject has problems with a particular sub- domain of behavior, the caregiver is only then asked all the questions about that domain, rating the frequency of the symptoms on a 4-point scale, their severity on a 3-point scale, and the distress the symptom causes them on a 5-point scale (Cummings, 1997).The NPI-10 takes approximately 10 minutes to complete.

4.2.6. Timed Up and Go Test (TUG)

The Timed Up and Go Test is designed to assess mobility. It measures the time in seconds for a person to rise from sitting from a standard armchair, walk 3 meters, turn, walk back to the chair, and sit down. The subject wears regular footwear and uses his/her customary walking aid. A score of >15 seconds indicates client has increased risk of falls. The test takes 1 to 2 minutes to complete.

4.3. Other Clinical Assessments

4.3.1. Columbia-Suicide Severity Rating Scale

The C-SSRS is a clinician-administered instrument that assesses suicidal ideation and behavior (Posner et al, 2011). The "Baseline" version of the instrument will be administered to subjects during Screening and before beginning the second treatment period, and the "Since Last Visit" version will be used at all other time points specified in Table 1.

4.3.2. Electroencephalography (EEG)

Quantitative electroencephalography (qEEG) will be performed with the subject awake in accordance with the 10-20 International System of Electrode placement at the time points specified in Table 6-1 according to a standard protocol that will be provided in a separate EEG manual. Slowing of the dominant frequency band by qEEG over posterior aspects of the brain has been recognized to be prominent in DLB (Olde Dubbelink et al 2013; Peraza et al, 2018), and various patterns have been identified to differentiate DLB from AD. EEG has also been recognized to be potential biomarker for DLB in the most recent consensus report of the DLB consortium (McKeith et al, 2017).

4.4. Physical Examination and Vital Signs

Physical examination will include a review of all body systems and measurement of weight, per each Investigators standard practice. Physical examination findings will be documented in the subject's source documents.

Vital signs include measurement of blood pressure, pulse, respiratory rate, and body temperature.

Any physical examination finding or vital sign measurement that represents a worsening from Baseline condition and is considered by the Investigator to be clinically significant will be recorded as an AE. The timing of assessments can be found in the schedule of assessments in Table 1.

4.5. 12-Lead Electrocardiogram

A 12-lead ECG will be performed during Screening using validated machinery available locally to each clinical site. ECG parameters to be captured include heart rate (bpm), PR interval, QRS duration, QT interval, corrected QT interval (using Fridericia's formula), and RR interval Each report will be reviewed by the Investigator or qualified sub-investigator and assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant. Abnormal, clinically significant findings are to be reported as part of the subject's medical history.

4.6. Clinical Laboratory Assessment

Blood samples will be collected at the time points specified in Table 1 for assessment of routine chemistry and hematology analytes. Additional blood samples will be collected for coagulation studies at the time points specified in Table 1. Clinical laboratory findings that represent a worsening from Baseline value and are considered by the investigator to be clinically significant will be recorded as an adverse event. Table 2 lists the analytes from routine chemistry,

hematology and coagulation studies. Clinical laboratory findings that represent a worsening from Baseline value and are considered by the investigator to be clinically significant will be recorded as an adverse event.

Table 2: Clinical Laboratory Analytes

Serum Chemistry	**Hematology**
Albumin	Differential (absolute and percent):
Alkaline Phosphatase	Basophils
Alanine Aminotransferase (ALT)	Eosinophils
Aspartate Aminotransferase (AST)	Lymphocytes
Bilirubin (total and direct)	Monocytes
Glucose	Neutrophils
Blood Urea Nitrogen	Erythrocytes:
Calcium	Mean corpuscular hemoglobin (MCH)
Bicarbonate	Mean corpuscular hemoglobin concentration (MCHC)
Chloride	Mean corpuscular volume (MCV)
Total cholesterol	Hemoglobin
Triglycerides	Leukocytes
Creatinine	Platelets
Gamma-Glutamyl Transferase (GGT)	**Coagulation Studies**
Lactate dehydrogenase (LDH)	
Phosphate	Prothrombin time
Potassium	Partial thromboplastin time
Sodium	INR
Total protein	
Uric acid	

4.7. Pharmacokinetics (PK)

Blood samples for PK are to be collected at the timepoints specified in Table 1. The actual sample collection time on the designated visit days is per study center / subject convenience. The actual sample collection date and time relative to the most recent study drug dose is to be documented.

4.8. Biomarker Testing

Plasma samples for protein biomarker assessment are to be collected at the timepoints specified in Table 1. Samples will be stored for future protein biomarker testing once applicable assays are identified or developed; note that such samples will be not be used for genetic testing.

For purposes of use during analysis of the clinical results, biomarker status (positive/negative) will be determined by historical amyloid PET, if available. If prior amyloid PET is not available, then biomarker status is to be determined by historical biomarker testing in CSF. If prior CSF is not available, then biomarker status is to be determined by Screening Aβ42/40 plasma ratio.

5. DEFINITIONS, CONVENTIONS AND DERIVED VARIABLES

5.1. Definitions and conventions

Age

The subject age (years) is calculated based on informed consent date and birth date.

Baseline

Baseline is defined as the measurement prior to first dose of study medication at study Day 1 of each period. If for any parameter the study Day 1 pre-dose value is not done or missing, then the value obtained at a Screening visit is used as Baseline. MMSE Baseline is defined as the average value of the Screening and Day 1 visits.

Concomitant medication

Concomitant medications are defined as any medications ongoing at the start of treatment or with a start date and time on or after the date of first study medication dose at study Day 1 through the end of study. A single medication may be prior, concomitant and post-treatment. (See also prior medication and post-treatment medication in this section.)

Informed consent date

Informed consent date is determined by the corresponding field in the database.

Missing Medication Dates

Medications with missing or partial start dates will be classified to any medication assignment that the available information allows. Should a stop date exist, the stop date will be taken into account. For example, if a medication has a missing start date, but the stop date is prior to first dose date, the medication will only be classified as prior. However, if a medication has a missing start date and the stop date occurs on the last day of treatment, the medication will be classified as prior and concomitant. Similarly, partial starts will use the available data to aid in the classification.

If the stop date is missing or ongoing, the medication will be classified based on the start date and then to all subsequent assignments. If there is partial stop date information, the available data will be used to aid in the classification.

Post-treatment medication

A post-treatment medication is defined as any medication ongoing or with a start date and time after the last day of treatment. A single medication may be prior, concomitant and post-treatment. (See also prior medication and concomitant medication in this section)

Prior medication

Prior medications are defined as any medications taken prior to first dose of study medication at the beginning of the study. A single medication may be prior, concomitant, and post-treatment.

5.2. Derived Variables

5.2.1. Change from Baseline

Change from baseline is defined as the post-baseline value minus the baseline value.

5.2.2. Standardized Scores Relative to Baseline Score

Due to the various scales among different tests and the need to have equal weights for deriving composite score metrics. Performance on each Cogstate test will be standardized relative to baseline data from all randomized subjects (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 z-score will be calculated as follows:

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

Where:

t = is the Cogstate test indicator

i = indexes subject i

j = indexes the jth assessment (visit)

x = cognitive score

$\bar{x}_{.1t}$ = mean performance score of the study sample's baseline for test t

$\sigma_{.1t}$ = Standard Deviation of the study sample's baseline for test t

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

5.2.3. Composite Outcome Measures Derived from the Individual Tests

The study primary outcome is an Attentional/Executive/Visuospatial Composite (NTB) score which will consist of the DET, IDN, OCL, ONB accuracy, Category Fluency (CFT) and Letter Fluency (LFT). The calculation Composite score is the average of Z-scores from the component of the composite tests.

In addition to this NTB composite score, a series of endpoints (exploratory composite scores) will be computed in order to facilitate understanding of the effects of the study drug on different aspects of cognition when combined.

These primary and exploratory composite scores are as defined in Table 3.

Table 3: Neuropsychological Test Composites

Cognitive Composite Name	Tests Included	Number of Tests with Data to Composite	Theoretical rationale for composite
Primary	DET, IDN, OCL, LFT, CFT, ONB (accuracy)	4 out of 6	Primary endpoint for the study
Attention	DET, IDN	2 out of 2	Allows understanding of the effect of the drug on attentional functions specifically
Executive Function	LFT, CFT, ONB (accuracy)	3 out of 3	Allows understanding of the effect of the drug on executive functions specifically
Learning and Memory	OCL, ISLT, ISRL	3 out of 3	Allows understanding of the effect of the drug on memory functions specifically
General Neuropsychological	DET, IDN, LFT, CFT, ONB (accuracy), OCL, ISLT, ISRL	6 out of 8	Can provide an index of the extent to which any experimental effects observed on the primary outcome, would be improved by the simultaneous consideration of memory
General Overall	DET, IDN, LFT, CFT, ONB (accuracy), OCL, ISLT, ISRL, MMSE	6 out of 9 and must include the MMSE	Allows an understanding of the extent to simultaneous consideration of general cognitive function measured using the MMSE will either improve or reduce any experimental effects observed

DLB-PACC	DET, ONB (accuracy), LFT, MMSE	3 out of 4	The PACC score has received some approval for use in Alzheimer's disease clinical trial. The PACC score developed for AD includes two measures of memory, one of executive function and MMSE. Hence this exploration is aimed at asking whether a similar approach to DLB, where the assessment of general cognition (MMSE) is combined with measures of attention and executive function, given their centrality to neuropsychological models of DLB.

PACC: Preclinical Alzheimer Cognitive Composite

6. ANALYSIS POPULATIONS

6.1. Safety Population

The safety population is defined as all randomized subjects who receive at least 1 dose of study drug.

6.2. Evaluable Efficacy Population (EEP) Population

The Evaluable Efficacy Population (EEP) population will be all subjects who have a baseline and at least one on-study assessment of the efficacy parameter.

6.3. Completer Population (CP)

The Completer Population will be subjects who have completed 16 weeks of treatment.

6.4. Pharmacokinetics (PK) Population

The Pharmacokinetics (PK) Population includes all randomized subjects who received at least one dose of study drug in neflamapimod treatment group and had at least one measurable post-dose PK data assessment.

7. DATA MANGEMENT, REVIEW AND PREESENTATION

7.1. Data Management and Quality Assurance Considerations

7.1.1. General Considerations

This study will employ electronic case report forms (eCRFs). The site will be trained on specific forms and procedures for source documentation and maintenance of an audit trail of the data that is entered on the eCRF prior to study initiation.

Study personnel at each site will enter data from source documents corresponding to a subject's visit onto the protocol-specific eCRF when the information corresponding to that visit is available.

The Investigators will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

Subjects and site personnel associated with study conduct will be blinded to treatment assignment. Treatment codes will be provided in sealed envelopes to the site and will be stored by the pharmacist or designee.

During the conduct of the study, the blind should be broken on an individual subject basis in the event of an emergency where it is necessary for the Investigator to know which treatment the subject is receiving before the subject can be treated. The code may also be broken if someone not in the study uses study drug (e.g., if a child in the participant's household takes study drug, the blind may be broken to determine treatment for the child.)

Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties.

Database lock will occur once quality assurance procedures have been completed.

All AEs will be coded using the latest version of the Medical Dictionary for Regulated Activities (MedDRA). Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting United States Food and Drug Administration (FDA), European Medicines Agency, and ICH guidelines for the handling and analysis of data for clinical studies. Data management details will be outlined in a separate data management plan.

7.1.2. Quality Assurance for Cogstate Computerized Tests

Data from the Cogstate Battery will be collected on computers at site(s) and uploaded to the Cogstate database for processing. Cogstate data management staff will query any data discrepancies. Queries will be confirmed and resolved with the sponsor.

For each of the Cogstate tests, subjects must provide sufficient responses to allow computation of reliable performance measures. For the majority of Cogstate tests, the term "sufficient" has been defined as a Test Completion criterion. The number of trials required for Test Completion is unique to each test. They do not vary for different patient groups or study samples.

Test Completion Criteria

The completion criteria set forth a priori for each test were as follows:

- DET: The subject provided 100% of the correct responses required for the test to complete
- IDN: The subject provided 100% of the correct responses required for the test to complete
- OCL: The subject performed 100% of the trials
- ONB: The subject provided 100% of the correct responses required for the test to complete
- ISLT: All words were presented to the subject on each of the learning trials and the subject attempted to recall the words on the shopping list
- ISRL: The subject attempted to recall the words on the shopping list presented to them previously AND met completion criteria on the ISLT
- ISRN: The subject attempted responses to the words presented to them during the recognition trial AND met completion criteria on the ISLT

Test performance criteria

Test performance criteria reflects the extent to which performance on a test suggests that the subject was responding in accordance with the test requirements. In other words, when a particular test administration does not meet criteria for test performance it suggests that the observed score may not be representative of the study population or the effect of a compound under investigation.

The criteria for test performance are derived by the Cogstate Science Team such that when trained and supervised appropriately, subjects from the relevant study population should typically achieve the criteria.

The performance criteria set forth a priori for each test were as follows:

- DET: The subject provided > 30% of the correct responses
- IDN: The subject provided > 30% of the correct responses
- OCL: The subject provided > 30% of the correct responses
- ONB: The subject provided > 30% of the correct responses

7.2. Data Presentation

The data will be presented in standard individual subject data listings. The listings will include subject identification number, demographics, and treatment. Selected listings will be included in the Clinical Study Report. In data summaries, descriptive statistics (n, arithmetic mean, standard deviation [SD], median, lower and upper quartiles, minimum and maximum values) will be presented for continuous variables. Counts and percentages will be presented for categorical variables.

7.3. Interim Data Review

An interim safety and efficacy analysis is not planned. After all patients have completed their treatment and their data are entered, an unblinded administrative analysis of the primary efficacy parameters as well as CDR-SB, ISLT and MMSE will be performed for planning purposes.

8. STATISTSICAL METHODOLOGY

All statistical analyses will be performed using S-PLUS (Version 8.2), R (Version 3.6.3 or higher) or SAS (Version 9.3 or higher). The version employed at the study start will be maintained throughout the project.

8.1. General Statistical Methodology

Data will be tabulated by treatment group by study period, with data listings provided for all data captured in the eCRF including laboratory data. On-treatment data will be assessed descriptively as both observed values and as changes from baseline. When tabulated, data will be presented using descriptive statistics. Most continuous data will be summarized with the following descriptive statistics unless otherwise noted: number of observations, mean, standard deviation, median, minimum, and maximum; interquartile ranges will be provided as appropriate. Categorical data will be summarized with frequencies and percentages.

Missing data will not be imputed unless otherwise documented in this SAP. Unless stated otherwise, statistical tests conducted will be two-sided at a level of 0.05. No adjustment for multiplicity will be made.

Two-sample t-test will be used to test the difference between treatments if the target metric is normally distributed (symmetrical distributed at the minimal), otherwise, the nonparametric approach -Wilcoxon signed rank test will be used.

Some exploratory endpoints may also be analyzed using analysis of covariance, t-test, Wilcoxon sign rank test or as descriptive summaries. There will be no correction to be made for multiple comparisons because of the exploratory nature of the data. Analysis of categorical exploratory endpoints may be performed using chi-square tests.

Additional exploratory analyses may be performed to further study the effects of the treatment, as data warranted. Subgroup analyses will be performed if data permit. Subgroup can be defined by disease severity, sex (male/female), age (dichotomized at pretreatment median age), race (White vs. non-White, Hispanic vs. non-Hispanic), and/or other grouping covariates.

For many variables, both absolute and percent change from pre-treatment assessments might be performed if data permitted. All data collected and captured in the eCRF will be included in data listings sorted by treatment, patient, study period and time point, or as appropriate.

8.2. Presentation of Efficacy Measures

Graphical presentation:

The time-course of efficacy measures will be plotted for each subject for both periods. The change from baseline of efficacy measures by period (treatment) will be plotted via boxplot. The distribution of difference of change from baseline by treatment (neflamapimod – placebo) will be plotted either via scatter plot or boxplot.

Tabular presentation:

The individual values and descriptive statistics for efficacy measures will be summarized by period/treatment and by visit.

8.3. Subject Disposition

A tabulation of subject disposition will be presented by treatment and overall, including the number in each analysis population, the number that completed the study, the number lost to follow-up, the number that withdrew prior to completing the study, and reason(s) for withdrawal.

8.4. Protocol Deviations

Protocol deviations and violations noted during clinical monitoring are entered into a trial management database. Important protocol deviations that could potentially influence study outcomes will be listed. These may include deviations from inclusion and exclusion criteria, recreational drug use, prohibited concomitant medications, incorrect treatment dosing, visit windowing deviations. Specifically, windowing deviations beyond +/- 7 days from the scheduled (target) study day will be listed in the protocol deviation data listing.

8.5. Missing Values

Subjects with incomplete data will be included in analyses, contributing as much as is available for any given endpoint. For AE, missing dates will not be imputed; however, if partial dates are available, they will be used to assess whether the AE occurred during the treatment period. Missing severities of AEs will be considered in any tabulations of AE severity.

Due to the impact of COVID-19 pandemic on data collection, there are some subjects who had week 8 efficacy assessment but no week 16 assessments while completing study treatment. Imputation strategy for this situation is detailed in the efficacy analysis section.

8.6. Subgroups

Subgroups may be defined by baseline disease severity, gender (male/female), age (dichotomized at pre-treatment median age), and race (White vs Non-White, Hispanic versus non-Hispanic). Some exploratory outcome analyses might be assessed by post-hoc subgroups as dictated by data.

8.7. Compliance

Study drug compliance will be assessed via tablet counts. A tabulation of percent compliance will be provided, where percent compliance will be derived as:

- Total number of tablets dispensed minus total number tablets returned, divided by the EXPECTED number of tablets (based on the number of days from first dose to last dose).
- Patients who do not have the last dose date or have missing capsule counts of study medication will not be included in this calculation of compliance.
- Patients with a compliance that is calculated to be over 100% will have their compliance set to 100%.

The number (%) of patients with compliance within each of the following intervals will be derived:

- 95-100%
- 90-<95%
- 85-<90%
- 80-<85%
- 75-<80%
- 70-<75%
- <70%

8.8. Baseline Subject Data and Disease Characteristics Analyses

For those patients missing a pre-treatment value (Day 1) for a particular parameter, the screening value may be used as the baseline value for that parameter.

Screening data, demographic characteristics, and baseline cognitive assessments will be presented using summary statistics by treatment.

Baseline categorical variables will be inferentially assessed via a chi square test, while baseline continuous outcomes will be inferentially assessed via Wilcoxon rank sum test between placebo and active treatments. Medical history data will be tabulated and listed.

8.9. Efficacy Analyses

8.9.1. Primary Efficacy Analysis

The primary endpoint is the study-specific NTB (Attentional/Executive/Visuospatial Composite) score which will consist of the DET, IDN, OCL, ONB accuracy, Category Fluency (CFT) and Letter Fluency (details in Section 5.2.3). The primary efficacy analysis will be using Mixed Model for Repeated Measures (MMRM) analysis method with change from baseline of Attentional/Executive/Visuospatial Composite as the dependent variable. There is a fixed effect on treatment and may be extended to other covariates (i.e. baseline composite score, study visit, patient characteristics). The interaction term (i.e. scheduled visit by treatment) will be considered. The random effect factor is subject.

Due to the impact of COVID-19 pandemic on data collection, there are some subjects who had week 8 assessment but no week 16 assessments while completing study treatment. In order to evaluate the impact of patients who completed treatment but did not have a week 16 NTB assessment, imputation technique will be use in Completer Population to accommodate deviations occurring due to COVID-19 illness and/or COVID-19 control measures. The first will be an ANCOVA analysis at week 16 and the second will be a trend analysis at week 16 for placebo vs. BID patients vs. TID patients using the Jonckere-Terpstra test. Single and multiple

imputation approaches will be used (i.e. the last observation will be carried forward (LOCF) and multiple imputed values using values derived from MMRM model).

The analyses results following the imputation approaches will be summarized to assess sensitivity of the estimates of treatment effect.

Descriptive statistics of the observed values and change from baseline will be presented by treatment group and visit.

8.9.2. Analysis of the Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- Change in CDR-SB in neflamapimod-treated subjects compared to placebo-recipients.
- Change in MMSE in neflamapimod-treated subjects compared to placebo-recipients.
- Change in NPI-10 domains in neflamapimod-treated subjects compared to placebo- recipients.
- Change in ISLT in neflamapimod-treated subjects compared to placebo-recipients.
- Change in Timed Up and Go Test.
- Change in EEG parameters.

The ANCOVA analysis will be applied for the analyses of the change in the secondary efficacy endpoints if the target endpoint has at least 2 post-dose measurements. For any endpoint that has only one post-dose measurements (Week 16), then two-sample t-test will be used to test the mean difference between treatment if the target metric is symmetrical at minimal. Otherwise, the nonparametric approach -Wilcoxon signed rank test will be used to test the median difference between treatment.

Data will be tabulated by visit and by treatment. Additional exploratory analyses, as stated in Section 8.1, may be performed to further study the effects of the treatment given data warranted.

8.9.3. Analysis of the exploratory Efficacy Endpoints

The exploratory efficacy composite measures are listed in Table 3. 2-sample t-test will be used to test the mean difference of each exploratory efficacy composite metric between treatment at each visit if the target metric is symmetrical at minimal. Otherwise, the nonparametric approach -Wilcoxon signed rank test will be used to test the median difference.

Descriptive analyses will be performed to describe the full set of exploratory efficacy composite measures.

Additional exploratory and subgroup analyses, as stated in Section 8.1, may be performed to further study the effects of the treatment as dictated by data.

8.9.4. Analysis of Plasma Biomarkers

There is no biomarker analysis planned.

8.9.5. Summary of Reasons for Efficacy Non-evaluability/Exclusion from Efficacy Analyses

All non-evaluable or exclusion values from efficacy analyses will be listed and tabulated by study visit and by treatment.

8.10. Pharmacokinetic Analysis

Concentration data will be tabulated by visit and by dosing regimen (TID or BID).

8.11. Safety and Tolerability Analyses

8.11.1. General Safety Analysis Methods

Safety and tolerability will be evaluated using descriptive statistics and listings of adverse events, clinical safety laboratory test values, vital signs, weight, body temperature, ECGs and other safety parameters. Safety outcomes will be presented for the safety population.

Analyses of AEs will be performed for those events that are considered treatment emergent, where treatment emergent is defined as any AE with onset (or worsening of a pre-existing condition) after the first dose of treatment. Adverse events with partial dates will be assessed using the available date information to determine treatment-emergent status. Adverse events with completely missing dates will be assumed to be treatment emergent.

Adverse events will be summarized by visit and treatment, using subject incidence rates; therefore, in any tabulation, a subject contributes only once to the count for a given AE (preferred term) per treatment. Separate tabulations will be produced for all TEAEs, treatment-related AEs (those considered by the investigator as possibly study drug related), SAEs, and discontinuations due to AEs. By subject listings will be provided for any deaths, SAEs, and AEs leading to discontinuation of treatment.

No formal hypothesis testing of AE incidence rates will be performed.

8.11.2. Routine Laboratory Data

For placebo and neflamapimod treatment groups, the actual value and change from baseline to each on-study evaluation will be summarized for each clinical laboratory parameter. Clinically significant laboratory values may be presented in a separate data listing.

8.11.3. Vital Signs and Physical Examination

Actual values and changes from baseline to each on-study evaluation will be summarized by visit and treatment for vital signs. Physical examination findings will be tabulated and summarized

by visit and treatment. The number of subjects with potentially clinically significant (PCS) changes in vital signs will be tabulated. Potentially clinically significant thresholds will be defined prior to breaking the study blind.

8.11.4. Electrocardiogram Evaluations

Electrocardiogram outcomes will be summarized descriptively by visit and by treatment. Corrected QT will be calculated using Fridericia's correction. The number of subjects with PCS changes in ECG intervals will be tabulated. The PCS thresholds will be defined prior to breaking the study blind.

8.11.5. Concomitant Medications

Concomitant medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical classification and preferred term. Concomitant medications information will be tabulated and summarized by visit and by treatment.

8.11.6. Study Termination Status

Study termination status will be tabulated and summarized by visit and by treatment.

9. REFERENCE

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10. APPENDIX

10.1. Table of Contents for Data Display Specifications

The numbering of tables, data listings, and figures will be consistent with the ICH E3 guidance.

10.1.1. List of Tables

Tables are divided into 4 sections: Study characteristics, efficacy, safety, and pharmacokinetic presentations.

- Tables in the 14.1.X series are study characteristics, i.e., patient disposition and baseline characteristics tabulations.
- Tables in the 14.2.X series are efficacy-based data.
- Tables in the 14.3.X series are safety-based data.

Title		Population
14.1 Study Population Section		
14.1.1	Summary of Subject Disposition	Randomized
14.1.2	Summary of Analysis Populations	Safety; EEP
14.1.3	Demographics and Baseline Characteristics	Safety; EEP
14.1.3.1	Summary of Demographic Characteristics	Safety; EEP
14.1.3.2	Summary of Baseline/Physical Examinations Characteristics	Safety; EEP
14.1.4	Medical History and Prior Medications	Safety
14.1.5	Major Deviations	Randomized
14.2 Efficacy Section		
14.2.1 Primary Efficacy Endpoint		
14.2.1.1	Summary of NTB by Visit and by Treatment	EEP
14.2.1.2	Summary of Change in NTB by Visit and by Treatment	EEP
14.2.2 Secondary Efficacy Endpoints		

14.2.2.1	Summary of CDR-SB by Visit and by Treatment	EEP
14.2.2.2	Summary of Change in CDR-SB by Visit and by Treatment	EEP
14.2.2.3	Summary of MMSE by Visit and by Treatment	EEP
14.2.2.4	Summary of Change in MMSE by Visit and by Treatment	EEP
14.2.2.5	Summary of NPI-10 by Visit and by Treatment	EEP
14.2.2.6	Summary of Change in NPI-10 by Visit and by Treatment	EEP
14.2.2.7	Summary of ISLT by Visit and by Treatment	EEP
14.2.2.8	Summary of Change in ISLT by Visit and by Treatment	EEP
14.2.2.9	Summary of TUG by Visit and by Treatment	EEP
14.2.2.10	Summary of Change in TUG by Visit and by Treatment	EEP
14.2.2.11	Summary of EEG by Visit and by Treatment	EEP
14.2.2.12	Summary of Change in EEG by Visit and by Treatment	EEP
14.2.3 Exploratory Efficacy Endpoints		
14.2.3.1	Summary of Attention Composite by Visit and by Treatment	EEP
14.2.3.2	Summary of Change in Attention Composite by Visit and by Treatment	EEP
14.2.3.3	Summary of Executive Function Composite by Visit and by Treatment	EEP
14.2.3.4	Summary of Change in Executive Function Composite by Visit and by Treatment	EEP
14.2.3.5	Summary of Learning and Memory Composite by Visit and by Treatment	EEP
14.2.3.6	Summary of Change in Learning and Memory Composite by Visit and by Treatment	EEP
14.2.3.7	Summary of General Neuropsychological Composite by Visit and by Treatment	EEP
14.2.3.8	Summary of Change in General Neuropsychological Composite by Visit and by Treatment	EEP
14.2.3.9	Summary of General Overall Composite by Visit and by Treatment	EEP
14.2.3.10	Summary of Change in General Overall Composite by Visit and by Treatment	EEP

14.3 Safety Data		
14.3.1	Summary of Exposure to neflamapimod by Treatment and by Visit	Safety
14.3.2.1	Summary of Adverse Events by Treatment and by Visit	Safety
14.3.2.2	Summary of Death and Serious Adverse Events by Treatment and by Visit	Safety
14.3.2.3	Summary of Drug-Related Adverse Events by Treatment Group	Safety
14.3.3	Listing of Subjects Who Became Pregnant During the Study	Safety
14.3.4	Summary of Actual Values and Changes from Baseline in Clinical Chemistry Data by Treatment Group and by Visit	Safety
14.3.5	Summary of Actual Values and Changes from Baseline in Hematology Data by Treatment Group and by Visit	Safety
14.3.6	Summary of Actual Values and Changes from Baseline in Vital Signs by Treatment Group and by Visit	Safety
14.3.7	Summary of ECG Data	Safety
14.3.8	Summary of Concomitant Medication	Safety
14.4 Pharmacokinetic Section		
14.4.1	Summary of neflamapimod plasma concentration by Visit and by Treatment	PK

10.1.2. List of Figures

	Title	Population
14.2 Figure for Efficacy Data		
14.2.1	***Figure Primary Efficacy Endpoint***	
14.2.1.1	NTB Time Profile Plot by individual and by Treatment	EEP
14.2.1.2	Mean Change (±SD) of NTB from Baselines by Treatment and by Visit	EEP

14.2.1.3	Boxplot of NTB Change from Baselines by Treatment and by Visit	EEP
14.2.2	***Figure for Secondary Efficacy Endpoint***	
14.2.2.1	CDR-SB Time Profile Plot by individual and by Treatment	EEP
14.2.2.2	Mean Change (±SD) of CDR-SB from Baselines by Treatment and by Visit	EEP
14.2.2.3	Boxplot of CDR-SB Change from Baselines by Treatment and by Visit	EEP
14.2.2.4	MMSE Time Profile Plot by individual and by Treatment	EEP
14.2.2.5	Mean Change (±SD) of MMSE from Baselines by Treatment and by Visit	EEP
14.2.2.6	Boxplot of MMSE Change from Baselines by Treatment and by Visit	EEP
14.2.2.7	NPI-10 Time Profile Plot by individual and by Treatment	EEP
14.2.2.8	Mean Change (±SD) of NPI-10 from Baselines by Treatment and by Visit	EEP
14.2.2.9	Boxplot of NPI-10 Change from Baselines by Treatment and by Visit	EEP
14.2.2.10	ISLT Time Profile Plot by individual and by Treatment	EEP
14.2.2.11	Mean Change (±SD) of ISLT from Baselines by Treatment and by Visit	EEP
14.2.2.12	Boxplot of ISLT Change from Baselines by Treatment and by Visit	EEP
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14.2.2.15	Boxplot of TUG Change from Baselines by Treatment and by Visit	EEP
14.2.2.16	EEG Time Profile Plot by individual and by Treatment	EEP
14.2.2.17	Mean Change (±SD) of EEG from Baselines by Treatment and by Visit	EEP
14.2.2.18	Boxplot of EEG Change from Baselines by Treatment and by Visit	EEP
14.2.3	***Figure for Exploratory Efficacy Endpoint***	
14.2.3.1	Attention Composite Time Profile Plot by individual and by Treatment	EEP
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14.2.3.3	Boxplot of Attention Composite Change from Baselines by Treatment and by Visit	EEP
14.2.3.4	Executive Function Composite Time Profile Plot by individual and by Treatment	EEP
14.2.3.5	Mean Change (±SD) of Executive Function Composite from Baselines by Treatment and by Visit	EEP
14.2.3.6	Boxplot of Executive Function Composite Change from Baselines by Treatment and by Visit	EEP
14.2.3.7	Learning and Memory Composite Time Profile Plot by individual and by Treatment	EEP
14.2.3.8	Mean Change (±SD) of Learning and Memory Composite from Baselines by Treatment and by Visit	EEP
14.2.3.9	Boxplot of Learning and Memory Composite Change from Baselines by Treatment and by Visit	EEP
14.2.3.10	General Neuropsychological Composite Time Profile Plot by individual and by Treatment	EEP
14.2.3.11	Mean Change (±SD) of General Neuropsychological Composite from Baselines by Treatment and by Visit	EEP

14.2.3.12	Boxplot of General Neuropsychological Composite Change from Baselines by Treatment and by Visit	EEP
14.2.3.13	General Overall Composite Time Profile Plot by individual and by Treatment	EEP
14.2.3.14	Mean Change (±SD) of General Overall Composite from Baselines by Treatment and by Visit	EEP
14.2.3.15	Boxplot of General Overall Composite Change from Baselines by Treatment and by Visit	EEP

10.1.3. **Listings**

Title		Population	Comment
16.2.1.1	Subject Enrollment Information	Enrolled	
16.2.1.2	Subject Disposition	Safety	
16.2.2.1	Subjects who did not Satisfy Inclusion/Exclusion Criteria (if applicable)	Screening Failure	
16.2.2.2	Protocol Deviations	Safety	
16.2.4.1	Subject Demographic and Baseline Characteristics	Safety	
16.2.4.2	Listing of Medical History	Safety	
16.2.4.3	Listing of Physical Exam	Safety	
16.2.4.4	Listing of Concomitant Medications	Safety	
16.2.5.1	Listing of Drug Administration	Safety	
16.2.6.1	NTB Listing	EEP	
16.2.6.2	CDR-SB Listing	EEP	
16.2.6.3	MMSE Listing	EEP	
16.2.6.4	NPI-10 Listing	EEP	
16.2.6.5	ISLT Listing	EEP	

16.2.6.6	TUG Listing	EEP	
16.2.6.7	EEG Listing	EEP	
16.2.6.8	Attention Composite Listing	EEP	
16.2.6.9	Executive Function Composite Listing	EEP	
16.2.6.10	Learning and Memory Composite Listing	EEP	
16.2.6.11	General Neuropsychological Composite Listing	EEP	
16.2.6.12	General Overall Composite Listing	EEP	
16.2.7.1	Listing of Relationship of Adverse Event Body Systems, Group Terms, and Verbatim Text	Safety	
16.2.7.2	Listing of All Adverse Events	Safety	
16.2.7.3	Listing of Subjects Withdrawn Due to AEs	Safety	
16.2.7.4	Listing of Deaths or SAEs (if any)	Safety	
16.2.8.1	Listing of Hematology Data	Safety	
16.2.8.2	Listing of Clinical Chemistry Data	Safety	
16.2.8.3	Listing of Urinalysis	Safety	if applicable
16.2.9	Listing of Vital Sign Data	Safety	
16.2.10	Listing of ECG Data	Safety	

10.2. Sample Table Template

10.2.1. Sample Template for Count Data

Table 14.x.x.x: Summary of Counts by visit and by Treatment

Population	n	Treatment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Randomized (N=x)	x (x%)	Placebo	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
	x (x%)	40 mg	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Safety (N=x)	x (x%)	Placebo	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
	x (x%)	40 mg	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
EEP (N=x)	x (x%)	Placebo	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
	x (x%)	40 mg	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Completer (N=x)	x (x%)	Placebo	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
	x (x%)	40 mg	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)

Note: Percentages are based on the total number of subjects in each treatment group of the same population

Table 14.x.x.x: Summary of Efficacy/Safety/Lab Count Data by visit and by Treatment

			For Example: Difference of Efficacy Score from Baseline					
Visit	**n**	**Treatment**	**≤-2**	**-1**	**±0**	**+1**	**+2**	**≥ 3**
Visit 1 (N=x)	x (x%)	Placebo	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
	x (x%)	40 mg	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Visit 2 (N=x)	x (x%)	Placebo	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
	x (x%)	40 mg	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Visit 3 (N=x)	x (x%)	Placebo	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
	x (x%)	40 mg	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Visit 4 (N=x)	x (x%)	Placebo	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
	x (x%)	40 mg	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Follow-up (N=x)	x (x%)	Placebo	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
	x (x%)	40 mg	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)

Note: Percentages are based on the total number of subjects in each treatment group of the same visit

10.2.2. Sample Template for Continuous Data (Efficacy/Safety/Lab)

Table 14.x.x.x: Summary of Endpoint by Visit and by Treatment

Visit	Treatment	Min.	Q1	Median	Mean	Q3	Max.	N	sd
Screening	Placebo								
	40 mg								
Visit 1	Placebo								
	40 mg								
Visit 2	Placebo								
	40 mg								