Statistical Analysis Plan

A Double-Blind, Placebo-Controlled Proof-of-Concept Study of a Selective p38 MAP Kinase Alpha Inhibitor, Neflamapimod, Administered for 24 Weeks in Subjects with Mild Alzheimer's Disease

Protocol Number: EIP-VX17-745-304

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
APP	Amyloid-Precursor-Protein
AST	Aspartate aminotransferase
AUC	Area under the time concentration curve
BID	bis in die (twice a day)
CDR	Clinical Dementia Rating Scale
CR_{max}	Maximum concentration
CNS	Central Nervous System
CT	Computed tomography
CR_{Trough}	Trough concentration
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
ES	Effect sizes
FDA	Food and Drug Administration
HVLT-R	Hopkins Verbal Learning Test – Revised
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IL-1beta	Interleukin-1 beta
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LFT	Liver function test
LM	Logical Memory
MAP	Mitogen activated protein
MCI	Mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NFT	Neurofibrillary Tangle
p38 alpha	p38 mitogen activated protein kinase alpha
PD	Pharmacodynamic
PET	Positron emission tomography
PK	Pharmacokinetic
PT	Prothrombin time
PTT	Partial thromboplastin time
RA	Rheumatoid arthritis
SAE	Serious adverse event
ULN	Upper limit of normal
VPA	Verbal Paired Associates
VR	Visual Reproduction
WMS	Wechsler Memory Scale

SAP Amendments before database lock

Version	Issue Date	Section	Revision/Addition	Rationale
Final 1.2	17-Jul-2019	6.2.2	Add following wordings: Visit 3 (Day 1) date is definded as the date of the first dose.	Agreed by sponsor
Final 1.2	17-Jul-2019	6.10.2	Remove log transformaion	Required by sponsor
Final 1.2	17-Jul-2019	6.10.3	Revises as follow: Original … baseline sum of total recall and delayed recall on the HVLT-R as the covariate ... Change to … baseline z-score as the covariate …	Required by sponsor
Final 1.2	26-Jul-2019	6.10.5	The main change is to the subgroup analyses which should include disease severity (CDR 0.5 vs 1.0) as this was sponsor stratification along with AD background therapy. The analysis come out of exploratory	Required by sposnor
Final 1.2	26-Jul-2019	6.10.6	Add additional subgroup analyses for primary and secondary endpoints as below: baseline body weight <80kg and those baseline body weight ≥80k disease severity (CDR 0.5 vs 1.0)	Required by sposnor
Final 1.2	17-Jul-2019	6.12	Revision of PK parameters. Original Additional PK-PD exploratory analyses may be performed to further study the effects of the treatment via PK parameters (i.e. PPK model derived C_{Trough} and	Required by sposnor

			C_{max},, AUC, etc.) on HVLT-R, WMS, CDR, and/or CSF biomarkers, as warranted by data. Change to Additional PK-PD exploratory analyses may be performed to further study the effects of the treatment via PK parameters (i.e. C_{Trough} and C_{max}) on HVLT-R, WMS, CDR, and/or CSF biomarkers, as warranted by data. Nominal CTrough and Cmax will be summarized based on concentration values by nominal hour at Day 21 (i.e. 2.5 hour for C_{max} and 0 hour for C_{Trough}).	
Final 1.2	17-Jul-2019	11	Revised TOC of Tables, Figures and Listings	Required by sposnor

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1 INTRODUCTION

This document details the planned statistical analyses for the EIP Pharma, LLC, protocol "EIP-VX17-745-304" study titled "A Double-Blind, Placebo-Controlled Proof-of-Concept Study of a Selective p38 MAP Kinase Alpha Inhibitor, Neflamapimod, Administered for 24 Weeks in Subjects with Mild Alzheimer's Disease".

The proposed analyses are based on the contents of the final version 3.0 of the protocol (dated27-AUG-2018).

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept study of neflamapimod 40 mg or matching placebo administered twice daily for 24 weeks in subjects aged 55 to 85 years with CSF biomarker-confirmed AD; with CDR-Global score of 0.5 or 1.0, with CDR memory subscore of at least 0.5, and MMSE scores between 20 and 28, inclusive.

All screening assessments should be conducted within 42 days of Day 1 (first dose of study drug). Once eligibility is confirmed and before the first dose of study drug, subjects are randomly assigned (1:1 basis) to receive placebo or neflamapimod treatment. Randomization is stratified by 1) background AD-specific therapy (cholinesterase inhibitor or memantine versus no cholinesterase inhibitor or memantine); and 2) CDR 0.5 versus 1.0. Dosing will start on Day 1 following completion of all Baseline procedures.

Subjects will return to the clinic on Days 21, 42, 84, 126, and 168.

A Follow-up Visit will be conducted 14 (±3) days following the last dose of study drug.

Trough and maximum concentrations for PK analysis will be collected for each patient and summarized. An integrated population PK analysis including other study PK parameters will be completed and reported on outside of the standard reporting.

2 STUDY OBJECTIVES

Primary Objective

- To evaluate the effect of administration of neflamapimod (VX-745) for 24-weeks on immediate and delayed recall aspects of episodic memory, as assessed by the Hopkins Verbal Learning Test – Revised (HVLT-R) in subjects with mild Alzheimer's disease (AD).

Secondary Objectives

- To evaluate effects of neflamapimod on immediate and delayed recall of Logical Memory (LM), Verbal Paired Associates (VPA) and Visual Reproduction (VR) components of the Wechsler Memory Scale® (WMS).
- To evaluate effects of neflamapimod on the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) and (Mini-Mental State Examination) MMSE.
- To evaluate the effects of neflamapimod on AD-related cerebrospinal fluid (CSF) biomarkers (total tau, phospho-tau, amyloid-beta peptides, neurogranin, and neurofilament light chain).

3 ENDPOINTS

3.1 Primary Endpoint

The primary efficacy variable is:

- Combined change in z-scores of total recall and delayed recall on the HVLT-R in neflamapimod-treated subjects compared to placebo-recipients at Week 24.

The detailed calculation of combined change in z-scores is described in section 6.2.12.

3.2 Secondary Endpoints

The secondary efficacy variables at Week 24 and follow-up when applicable are:

- Change in WMS immediate and delayed recall composites in neflamapimod-treated subjects compared to placebo-recipients.
- 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 CSF biomarkers [total tau (T-tau), P-tau$_{181}$, Aβ_{1-40}, Aβ_{1-42}, neurogranin, neurofilament light chain] in neflamapimod-treated subjects compared to placebo-recipients at the end of treatment.

4 SAMPLE SIZE

Up to 76 subjects per treatment arm (152 total) provides 90% power to detect ES of 0.53 and 80% power to detect ES of 0.46. This level of ES is the minimum treatment effect amount considered clinically relevant and is less than the effect size seen in the Phase 2a studies.

5 RANDOMIZATION

Randomization was stratified by 1) background AD-specific therapy (cholinesterase inhibitor or memantine versus no cholinesterase inhibitor or memantine); and 2) CDR-Global Score of 0.5 versus 1.0.

Eligible subjects were randomized 1:1 to two treatment arms: Neflamapimod 40mg or placebo utilizing a central Interactive Web Response System (IWRS).

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final clinical study report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Populations

6.1.1 Safety Population

The Safety Population is defined as all randomized subjects who receive at least one dose of study drug (neflamapimod or placebo).

6.1.2 Evaluable Efficacy Population

The Efficacy Population used for efficacy analyses, consistent with the intent-to-treat (ITT) principles includes all subjects who received at least one dose of study drug and had at least one post-dose efficacy assessment.

6.1.3 Per-Protocol Population

The Per-Protocol Population (PP) will be a subset of the Efficacy Population.

All protocol deviations will be assessed and documented on a case-by-case basis before the database lock, and deviations considered to have a significant impact on the efficacy results will lead to the relevant subject being excluded from the PP. Before database lock, potential subject exclusions from the PP will be reviewed by the Sponsor and documented in a subject evaluability document (WCT-TP-ST-016).

6.1.4 Pharmacokinetics (PK) Population

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

6.2 Derived Data and Clinical Assessments

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

6.2.1 Screening

For each variable where a subject is re-screened, his/her latest non-missing value from the original or re-screening assessment will be taken for tabulation purposes.

6.2.2 Baseline and Change from Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives first dose of study drug (Day 1). Visit 3 (Day 1) date is definded as the date of the first dose.

Baseline score of MMSE for each subject is calculated using the average of Screen and Day 1 measurements.

Change from baseline CHG=AVAL-BASE where AVAL is the post-baseline value, BASE is the baseline value.

Baseline z-score will be used as a covariate in the MMRM and ANCOVA analysis. It will be calculated as below:

For baseline total recall, a z-score for each subject is defined by z=(x-m)/s where **x** is the subject's total recall at baseline, and **m** and **s** are the overall mean and overall standard deviation of total recall at baseline across all subjects. Similarly, a baseline z-score for each subject for delayed recall can be calculated.

A composite baseline z-score for each subject is calculated using equal weighting in the following way:

Z=0.5*z-score for total recall at baseline + 0.5*z-score for delayed recall at baseline.

The calculation method can be referenced to Section 6.2.12.

6.2.3 Duration/Study Day/Time

Study day will be calculated as the number of days from first dose of study drug.

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

- Duration (e.g., event duration/medication usage) = stop date-start date +1.

6.2.4 Conventions for Missing and Partial Dates

All rules explained below for partial/missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual subject listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

6.2.5 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 as "01-Jan" of the same year or the date of the first dose of study drug

whichever is latest. 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.

Missing start/stop time of adverse events:

- If the start time of the adverse event (AE) is missing, it will imputed only in the case where the start date of the AE 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.
- If the stop time of the adverse event is missing, it will be imputed as 23:59 for stop time.

6.2.6 Missing Last Dates of Study Drug Dosing

If the date of last dose of study drug is completely missing then the date of last dose of study drug will be taken for analysis purposes as the date when the subject would have run out of study drug assuming full compliance from the date the study drug was last dispensed or the date of subject's last clinic visit in the study or early withdrawal or death whichever the earlier

If only the month and year of the last dose was recorded, then the date of last dosing will be taken for analysis purposes as the date the subject would have run out of study drug assuming full compliance from the date the study drug was last dispensed, the last day of the month of the recorded last dose or the date of subject's last clinic visit in the study or early withdrawal or death whichever the earlier.

6.2.7 Missing Diagnosis Dates

If the month and year are present but the day is missing, the diagnosis date will be set to the first day of the relevant month. If only the year is recorded the diagnosis date will be set as "01-Jan" for that year.

6.2.8 Exposure to Study Drug

Exposure to study drug will be calculated as follows from the date of last dosing minus the first day of dosing + 1. The exposure calculation will not take into account breaks in therapy.

6.2.9 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, Where a range of values is quoted the midpoint of the range will be taken.

6.2.10 Electrocardiogram Data

For 12-lead ECG data recorded on continuous scales, if more than one value is recorded at a visit, the mean value rounded to the integer will be presented. For overall interpretation if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

6.2.11 HVLT-R and WMS

The HVLT-R is a verbal learning and memory test, with 6 validated alternate forms. Each form contains 12 nouns, 4 words each from 1 of 3 semantic categories (e.g., precious gems, articles of clothing, vegetables), to be learned, and repeated back to the evaluator over the course of 3 learning trials. Approximately 20–25 minutes later, a delayed recall trial and a recognition trial are completed. The delayed recall requires free recall of any words remembered. The recognition trial is composed of 24 words, including the 12 target words and 12 false-positives, 6 semantically related, and 6 semantically unrelated. The 3 learning trials are combined to calculate a total recall score; the delayed recall trial creates the delayed recall score.

For WMS, LM I & II & II-(Recognition), VPA I & II & II-(Recognition), and VR I & II & II-(Recognition) will be applied.

There are following tests in WMS: Logical Memory test, in which subject is read a story; Verbal-Paired Associates, in which subject is given pairs of words and asked remember which words go together; and Visual Reproduction, in which subject is given drawings of specific shapes. Subjects were then asked to recall the information within each test both in an immediate (WMS-Immediate Recall composite) and delayed (WMS-Delayed Recall composite) basis.

The WMS immediate recall composite score is the total of all of the immediate recall tasks combined and the delayed recall composite is the delayed recall tasks combined.

The HVLT-R and WMS tests must be performed sequentially within the day; with the HVLT-R to be conducted first and completed (including delayed recall component), prior to commencing WMS test.

6.2.12 Z-Score

For post-baseline total recall, a z-score for each subject at a specific visit is defined by z=(x-m)/s where **x** is the subject's total recall at that visit, and **m** and **s** are the overall mean and overall standard deviation of total recall from baseline visit across all subjects. Similarly, a z-score for each subject for delayed recall can be calculated.

A post-baseline composite z-score for each subject on the HVLT-R at that visit is calculated using equal weighting in the following way: Z = 0.5*z-score for total recall + 0.5*z-score for delayed recall.

Combined change in z-scores = Z(post-baseline) – Z(baseline).

Z(baseline) is described in Section 6.2.2.

6.2.13 CDR

The 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. The overall CDR rating, along with the memory box score, will be used to determine a subject's eligibility for inclusion. The CDR score - SB will also be used in calculating treatment group means for change from baseline calculation. Standardized CDR will be conducted by the Investigator or designee.

CDR score (sum of boxes) is the sum of each domain score.

6.2.14 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. Standardized MMSE (Version 2.0) will be conducted by the Investigator or designee. The MMSE score is used for eligibility as well as calculating treatment group means for change from baseline.

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

The C-SSRS is a clinician-administered instrument that assesses suicidal ideation and behavior (38TPosner, 201138T).

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 Behavior
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non fatal)
Category 10	Completed Suicide

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

Suicidal Behavior since baseline – A “yes” answer at any time during double blind treatment to any one of the 5 suicidal behavior questions (categories 6-10) on the C-SSRS.

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

6.2.16 Early Termination Efficacy Assessments

For analysis purposes, efficacy data collected from early termination (ET) visit will be assigned to the next scheduled visit.

6.2.17 Unscheduled Visits

In general, only scheduled post-baseline laboratory, ECG, and vital signs values will be tabulated. Post-baseline repeat/unscheduled assessments will be disregarded from table, although these post-baseline assessments will be listed in the relevant appendices to the CSR.

6.2.18 Follow-Up Visit

A follow-up visit should be scheduled 14 (+/- 3) days after the last dose of study drug for all subjects that complete or are withdrawn from the study.

6.3 Conventions

All data listings, summaries, figures and statistical analyses will be generated using SAS version 9.3 or higher[1].

Summaries will be presented by treatment group or overall. Treatment group labels will be displayed as follows:

Neflamapimod (40 mg)	Placebo

Overall columns are to be included within the table shells as follows:

Demography	*Treatment and overall*
Baseline	*Treatment and overall*
Disposition	*Treatment and overall*
Efficacy	*Treatment*
PD	*Treatment*
PK	*Treatment*
AEs	*Treatment*
Other safety	*Treatment*

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 groups.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum. For all tabulations of changes from baseline data, the lower and upper 95% confidence limits for the mean for the individual treatments will be given.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

6.3.1 Decimal Places

Decimal places for derived data described in section 6.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer for example *day, month, year, number of days and total scores (for rating scales)* will be presented with zero decimal places.

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. Percentages will be displayed with one decimal place.

P- Values will be quoted to 3 decimal places. P-values < 0.001 will be presented as p<0.001. Where this value is less than 0.05, 0.01 or 0.001, attention will be drawn to this fact using the conventional “*”, “**” or “***” annotation, respectively.

6.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects, who entered in the study, were randomized and are in each population will be summarized by treatment group and overall for Enrolled Subjects.
- The number of subjects who failed screening and the reasons for failure will be tabulated for Enrolled Subjects.
- The number of study completers, early withdrawals and the reasons for withdrawals will be tabulated by treatment group and overall for the Safety and Efficacy Analysis Population.

6.5 Protocol Deviations

Separate tabulations of previous and ongoing conditions at screening will be presented by treatment group and overall for the Safety Population. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA version 21.0) primary system organ class and preferred term.

6.8 Prior and Concomitant Medications

Separate tabulations will be produced for prior and concomitant medications presented by treatment group and overall for the Safety Population. Prior medications are defined as all medications starting before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug. Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 and Preferred Name using the World Health Organization (WHO) dictionary (Version WHODrug Global B3 March 2018). In addition, CNS medications will be summarized similarly.

6.9 Exposure to Study Drug and Treatment Compliance

Extent of exposure will be presented by randomized treatment group for the Safety Population (see Section 6.1.1).

Overall compliance (%) will be calculated as: [Total number of capsules dispensed minus total number capsules returned, divided by the expected number of tablets (based on the number of days from first dose to last dose)] multiplied by 100, as a percentage.

Number and percentage of subjects who had at least 80% of the (cumulative) planned dose will be summarized by treatment group. In addition, the number (%) of subjects with compliance within each of the following intervals will be provided:

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

6.10 Efficacy Analyses

All efficacy analyses will be based on the Evaluable Efficacy Population by randomized treatment regardless of the treatment actually received. Descriptive statistics by treatment group

and visit will be reported for all efficacy endpoints. 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.

There will be no imputation of missing efficacy data.

6.10.1 Primary Endpoint

The primary efficacy endpoint is:
Combined change in z-scores of total recall and delayed recall on the HVLT-R in neflamapimod-treated subjects compared to placebo-recipients at Week 24.

Neflamapimod 40 mg group will be compared to the placebo group.

The hypothesis test is as follows:

Ho: $\mu_{neflamapimod} = \mu_{placebo}$

H1: $\mu_{neflamapimod} \neq \mu_{placebo}$

The null hypothesis will be rejected at a significance level of α (two-sided) = 0.05. There will be no p-value adjustment for multiplicity.

6.10.2 Primary Efficacy Analysis

The primary endpoint will be analyzed using Mixed Model for Repeated Measures (MMRM) with fixed effects for treatment, background AD-specific therapy (cholinesterase inhibitor or memantine versus no cholinesterase inhibitor or memantine), CDR-Global Score of 0.5 versus 1.0, scheduled visit (nominal) and scheduled visit by treatment interaction, random effect for subject and baseline z-score as a covariate. Least-square means (LSM) and 2-sided 95% confidence intervals (CI) will be provided for treatment group differences and estimated endpoint values by visit.

The normally-distributed assumption for the combined change in z-scores of total recall and delayed recall on the HVLT-R will be examined (at 0.05 alpha level). In case the assumption is violated, rank transformed data will be applied to the MMRM model. Ranks will be determined separately within each time point, based on observed data only.

In addition, Scale plot will be provided for combined change in z-scores of total recall and delayed recall on the HVLT-R at each post-baseline visit by treatment group.

6.10.3 Sensitivity Analyses

- Repeat the primary efficacy analysis with the Per Protocol Population
- Use an analysis of covariance (ANCOVA) with treatment group, background AD-specific therapy, CDR-Global Score as main effects and the baseline z-score as the covariate to compare Z-scores of total recall and delayed recall on the HVLT-R at Week 24 in the neflamapimod and placebo groups

The results of the ANCOVA will be summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value.

6.10.4 Secondary Analyses

The secondary efficacy endpoints at Week 24 and follow-up when applicable are:

- Change in WMS immediate and delayed recall composites in neflamapimod-treated subjects compared to placebo-recipients.
- 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 CSF biomarkers (T-tau, P-tau$_{181}$, Aβ_{1-40}, Aβ_{1-42}, neurogranin, neurofilament light chain) in neflamapimod-treated subjects compared to placebo-recipients at the end of treatment.

The same method used for the primary efficacy analysis will be applied for the analyses of the change in WMS and change in CDR-SB.

Changes in MMSE and CSF biomarkers will be compared using an analysis of covariance (ANCOVA) with treatment group, background AD-specific therapy, CDR-Global Score as main effects and the baseline assessment as the covariate. The results of the ANCOVA will be summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value. Scale Plots of Mini-Mental State Examination (MMSE) Score by Visit and by Treatment; and Baseline and Change from Baseline to Day 84 MMSE Score.

6.10.5 Exploratory Analyses

Additional exploratory analyses may be performed to further study the effects of treatment as data warranted. Numerical exploratory endpoints will be analyzed using analysis of covariance, t-tests, or Wilcoxon sign rank test. Analysis of categorical exploratory endpoints will be performed using chi-square test. Exploratory endpoints include

- Change of total recall on the HVLT-R
- Change of delayed recall on the HVLT-R
- Change of retention (%) on the HVLT-R
- Change of recognition on the HVLT-R
- Change of recognition on the WMS
- Subgroups analyses by , sex (male/female), age (dichotomized at pretreatment median age), race (white vs. non-white, Hispanic vs. non-Hispanic), CYP2C19 genotype status and/or other grouping covariates, if data permit.
- Outlier analyses to identify the impact of any extreme values on the analysis results.
- Categorical exploratory endpoints (i.e. responder analysis), if data permit, will be performed using Pearson's chi-square test

6.10.6 Subgroup Analyses

The results for the primary and secondary endpoints will be further analyzed on the patients with a background AD-specific therapy, and those not on a background AD-specific therapy as well as for disease severity (patients who have a CDR score of 0.5 versus 1.0). Another subgroup analysis will be performed base on patient baseline body weight (<80 kg and ≥80kg).

6.10.7 Multiplicity

All secondary endpoints and the supportive analyses will be considered as descriptive evidence of efficacy and will be analyzed without any procedures to account for multiple comparisons.

6.11 Pharmacokinetic Analysis

Neflamapimod concentration values will be reported for the PK population. All PK data collected will be included in data listings sorted by treatment, patient and time point, as appropriate.

Individual values and descriptive statistics for the plasma concentrations of neflamapimod will be summarized by neflamapimod treatment and by visit. Boxplots of the distributions of neflamapimod concentrations by visit will be used to present graphical summaries of neflamapimod concentration data.

Trough and maximum concentrations (C_{Trough} and C_{max}, respectively) will be obtained on Day 21 (i.e., at steady-state) for each subject by observation and descriptive statistics for the neflamapimod treatment group will be presented.

In addition, the effect of CYP2C19 genotype status on PK parameters will be investigated.

The robust PK parameters (i.e. PPK model derived C_{Trough} and C_{max}, AUC and etc.) will be derived by an integrated population pharmacokinetic (PPK) analysis. PPK analysis plan will be detailed in a separate Pharmacometrics Analysis Plan and reported separately from the study results.

6.12 Pharmacokinetic-Pharmacodynamic Analyses

Analyses of CSF biomarkers (T-tau, P-tau_{181}, $A\beta_{1-40}$, $A\beta_{1-42}$, neurogranin, neurofilament light chain) will use observational Trough and maximum concentrations (C_{Trough} and C_{max}, respectively) on Day 21 as exposure parameters in the initial PK-PD analysis. For numerical PD endpoints, both absolute and percent change from pre-treatment assessments will be performed, as appropriate. Number and percent will be provided for categorical PD parameters (e.g. CYP2C19). Overall, summary statistics and for each treatment group for biomarkers will be presented and a by-subject listing of plasma biomarker results will be provided as an appendix.

Additional PK-PD exploratory analyses may be performed to further study the effects of the treatment via PK parameters (i.e. C_{Trough} and C_{max}) on HVLT-R, WMS, CDR, and/or CSF biomarkers, as warranted by data. Nominal C_{Trough} and C_{max} will be summarized based on concentration values by nominal hour at Day 21 (i.e. 2.5 hour for C_{max} and 0 hour for C_{Trough}).

For many endpoints, both absolute and percent change from pre-treatment assessments will be performed. All data collected and captured in the CRF will be included in data listings sorted by treatment, patient and time point, as appropriate.

6.13 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Population.

6.13.1 Adverse Events

A treatment emergent adverse event (TEAE) is defined as:

- Any AE with an onset on or after the first dose of study drug and through 30 days after the last dose of study drug in the double blind treatment period.
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug and through 30 days after the last dose of study drug in the double blind treatment period.

A treatment-related AE is defined as an AE as being possibly related to the study drug. If an AE has a missing relationship, it is assumed to be related to the study drug for analysis purposes. Maximum severity will be assumed for an AE with missing severity.

The following tables will be presented for AEs:

- Overall incidence and the number of AEs, SAEs, Treatment related TEAEs, TEAEs leading to withdrawal of study/study drug
- TEAE by system organ class and preferred term, incidence and number of events
- Treatment related TEAE by system organ class and preferred term, incidence and number of events
- Serious TEAE by system organ class and preferred term, incidence and number of events
- TEAEs leading to withdrawal of study drug by system organ class and preferred term, incidence and number of events
- TEAE by system organ class, preferred term and maximum severity, incidence
- Listing of serious TEAEs (presented in the Table section of the appendices)
- Listing of deaths (presented in the Table section of the appendices)

Adverse events will be coded using MedDRA version 21.0.

A complete subject listing of all AEs will be provided. This listing will include treatment, AE verbatim term, primary system organ class and preferred term, the time of onset and cessation of event relative to the first dose of study drug, duration of AE (for ongoing AEs, no duration will be calculated), whether serious, severity, relationship to study drug, action taken and outcome.

In counting the number of AEs reported, a continuous event (i.e. reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same subject will be counted as multiple events.

6.13.2 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, serum 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.

A listing of any clinically significant laboratory measurements recorded throughout the study will be presented.

Liver Function Parameter

The number and percentage of subjects meeting certain liver function abnormality categories will be summarized by visit:

- Alanine Aminotransferase (ALT) assessment > 3 times upper limit of normal (ULN),

- Aspartate aminotransferase (AST) > 3xULN,
- ALT or AST: > 3xULN; > 10xULN; > 20xULN
- Total Bilirubin: > 1.5xULN; > 2xULN
- Alkaline Phosphatase: > 1.5xULN; >2xULN
- (ALT or AST > 3xULN) and total bilirubin>2xULN
- (ALT or AST>3xULN) and total bilirubin>2xULN and alkaline phosphatase<2xULN

Coagulation Parameter Abnormalities

- International Normalized Ratio (INR) >1.5

6.13.3 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)
- Body temperature (degrees Celsius)
- Body weight (kg)

Box plots for the above vital signs will be provided for changes from Baseline by visit and maximal change.

6.13.4 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following 12-lead ECG variables will be tabulated at each follow-up visit:

- Heart rate (beats/min)
- PR interval (msec)
- RR interval (msec)
- QRS complex (msec)
- QT interval (msec)
- QTc interval (msec)
- QTcF interval (msec) [Fridericia's formula - QTcF]

ECG Result Interpretation (Normal, Abnormal Not Clinically Significant [NCS], and Abnormal Clinically Significant [CS]) will be summarized by treatment group and visit.

The incidence of ECG abnormalities for subjects with any abnormal CS ECG result will be presented by treatment group and visit.

Additionally, the number and percentage of subjects in each treatment group who meet any of the following criteria for QT or QTcF will be tabulated by treatment group and visit.

- Maximum value >450 to 480 msec
- Maximum value >480 to 500 msec
- Maximum value >500 msec
- Maximum increase from baseline >30 to 60 msec
- Maximum increase from baseline >60 msec

Shift tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS) from baseline to each follow-up visit will be presented.

Box plots for ECG data will be provided for changes from baseline by visit and maximal change.

6.13.5 Physical Examination

The body systems within the physical examination data will be summarized by treatment group and visit (Abnormal NCS and Abnormal CS). Changes from baseline will also be tabulated. Details of clinically significant findings will be listed.

Descriptive statistics for observed values and changes from baseline in weight will be presented by treatment group and visit.

7 INTERIM ANALYSIS

No formal interim analyses are planned.

8 DATA SAFETY MONITORING BOARD ANALYSIS

No data safety monitoring board (DSMB) analyses are planned.

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

Not applicable.

10 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA

11 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 maybe 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)
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1	Subject Disposition, Analysis Population	IP	
14.1.1.2	Subject Disposition, Screen Failures Enrolled Subjects	IP	
14.1.1.3	Inclusion/Exclusion Criteria Not Met Enrolled Subjects	IP	
14.1.1.4.1	Subject Disposition, Early Withdrawals Safety Population	IP	
14.1.1.4.2	Subject Disposition, Early Withdrawals Efficacy Population	IP	14.1.1.4.1
14.1.1.5.1	Number of Subject by Site Safety Population	IP	
14.1.1.5.2	Number of Subject by Site Efficacy Population	IP	14.1.1.5.1
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14.1.2.1.2	Demographics Efficacy Population	IP	14.1.2.1.1
14.1.2.2.1	Baseline Characteristics Safety Population	IP	
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14.2.2.3.1	Mixed Models for Repeated Measures Analysis of Change from Baseline in Wechsler Memory Scale (WMS) Immediate Composite Score (0-136) Efficacy Population	IP	
14.2.2.3.2	Mixed Models for Repeated Measures Analysis of Change from Baseline in Wechsler Memory	Stat IP	14.2.1.3

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14.2.2.6	Mini-Mental State Examination (MMSE) Efficacy Population	IP	
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14.2.2.8.1	CSF Biomarkers (T-tau, P-tau181, Aβ1-40, Aβ1-42, Neurogranin, Neurofilament Light Chain, pTau/Aβ1-42 Ratio) Efficacy Population	IP	
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14.2.4.3	Analysis of Covariance of Change from Baseline in Retention (%) on the Hopkins Verbal Learning Test – Revised (HVLT-R) Efficacy Population	IP	14.2.4.1
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14.2.4.6.x	Subgroup Analysis of Covariance of Combined Change from Baseline in Z-score of Total Recall and Delayed Recall on the HVLT-R Efficacy Population	IP	
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14.2.5.2.1	Combined Change from Baseline in Z-score of Total Recall and Delayed Recall on the Hopkins Verbal Learning Test – Revised (HVLT-R), Cholinesterase Inhibitor or Memantine Efficacy Population	IP	
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14.2.5.3	Mixed Models for Repeated Measures Analysis of Combined Change from Baseline in Z-score of Total Recall and Delayed Recall on the Hopkins Verbal Learning Test – Revised (HVLT-R) by Background AD-specific Therapy Efficacy Population	IP	
14.2.6.1.1	Wechsler Memory Scale (WMS) Subscore, Cholinesterase Inhibitor or Memantine Efficacy Population	IP	
14.2.6.1.2	Wechsler Memory Scale (WMS) Subscore, No Cholinesterase Inhibitor or Memantine Efficacy Population	IP	

14.2.6.2.1	Wechsler Memory Scale (WMS) Composite and Overall Score, Cholinesterase Inhibitor or Memantine Efficacy Population	IP	
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14.2.6.3	Mixed Models for Repeated Measures Analysis of Change from Baseline in Wechsler Memory Scale (WMS) Immediate and Delayed Recall Composite Score (0-228) by Background AD-specific Therapy Efficacy Population	IP	14.2.5.3
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14.2.6.8.1	CSF Biomarkers (T-tau, P-tau181, Aβ1-40, Aβ1-42, Neurogranin, Neurofilament Light Chain,	IP	

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14.3.5.1	Study Drug Exposure and Compliance Safety Population	IP	
14.3.6	**Vital Signs And Physical Examination**		
14.3.6.1	Vital Signs Safety Population	IP	

14.3.6.2	Physical Examinations at Post-baseline Visits Safety Population	IP	
14.3.6.3	Body Weight Safety Population	IP	
14.3.7	**Other Safety**		
14.3.7.1	12-lead ECG Safety Population	IP	
14.3.7.2	12-lead ECG Result Interpretations Safety Population	IP	
14.3.7.3	12-lead ECG Abnormalities for Subjects with Any Abnormal Clinically Significant ECG Interpretation Safety Population	IP	
14.3.7.4	12-lead ECG – QT, QTc, and QTcF Categories QTcF Categories Safety Population	IP	
14.3.8	**Concomitant Medication**		
14.3.8.1	Concomitant Medications Safety Population	IP	
14.4	**PK Data**		
14.4.1.1	Neflamapimod Concentrations by Visit PK Population	IP	
14.4.1.2	Pharmacokinetic Parameters of Neflamapimod PK Population	IP	
14.4.1.3.x	Pharmacokinetic Parameters of Neflamapimod by CYP2C19 Genotype Status PK Population	IP	
14.4.2	Correlation Analysis of PK Parameters and Efficacy Data (Combined Change in Z-score, Change in WMS, CDR-SB) Efficacy Population	IP	
14.4.3	Correlation Analysis of PK Parameters and Change from Baseline in CSF Biomarkers Efficacy Population	IP	

Figure Number	**Figure Title**	**Validation Method**	**Shell Number (If Repeat)**
14.2 Figure	**Figure for Efficacy Data**		
14.2.1.1	Mean (±SE) Combined Change from Baseline in Z-score of Total Recall and Delayed Recall on the HVLT-R by Visit and by Treatment Efficacy Population	IP	

14.2.1.2	Mean (±SE) Change from Baseline in Total Recall on the HVLT-R by Visit and by Treatment Efficacy Population	IP	14.2.1.1
14.2.1.3	Mean (±SE) Change from Baseline in Delayed Recall on the HVLT-R by Visit and by Treatment Efficacy Population	IP	14.2.1.1
14.2.2	Mean (±SE) Change from Baseline in Wechsler Memory Scale (WMS) Immediate and Delayed Recall Composite Score by Visit and by Treatment Efficacy Population	IP	14.2.1.1
14.2.3	Mean (±SE) Change from Baseline Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) by Visit and by Treatment Efficacy Population	IP	14.2.1.1
14.2.4	Mean (±SE) Change from Baseline in Mini-Mental State Examination (MMSE) Score by Visit and by Treatment Efficacy Population	IP	14.2.1.1
14.2.5.1	Box Plot of CSF Biomarker (T-tau) Efficacy Population	IP	
14.2.5.2	Box Plot of CSF Biomarker (P-tau181) Efficacy Population	IP	14.2.5.1
14.2.5.3	Box Plot of CSF Biomarker (Aβ1-40) Efficacy Population	IP	14.2.5.1
14.2.5.4	Box Plot of CSF Biomarker (Aβ1-42) Efficacy Population	IP	14.2.5.1
14.2.5.5	Box Plot of CSF Biomarker (Neurofilament Light Chain) Efficacy Population	IP	14.2.5.1
14.2.5.6	Box Plot of CSF Biomarker (pTau/Aβ1-42 Ratio) Efficacy Population	IP	14.2.5.1
14.2.5.7	Box Plot of CSF Biomarker (Brain derived neurotrophic factor (BDNF)) Efficacy Population	IP	
14.3 Figure	**Figure for Safety Data**		
14.3.1.1	Box Plot of Change from Baseline in Heart Rate (beats/min) Safety Population	IP	
14.3.1.2	Box Plot of Change from Baseline in PR (msec) Safety Population	IP	14.3.1.1

14.3.1.3	Box Plot of Change from Baseline in RR (msec) Safety Population	IP	14.3.1.1
14.3.1.4	Box Plot of Change from Baseline in QT (msec) Safety Population	IP	14.3.1.1
14.3.1.5	Box Plot of Change from Baseline in QRS (msec) Safety Population	IP	14.3.1.1
14.3.1.6	Box Plot of Change from Baseline in QTcF (msec) Safety Population	IP	14.3.1.1
14.3.1.7	Box Plot of Change from Baseline in QTc (msec) Safety Population	IP	14.3.1.1
14.3.2.1	Box Plot of Change from Baseline in Systolic Blood Pressure (mmHg) Safety Population	IP	
14.3.2.2	Box Plot of Change from Baseline in Diastolic Blood Pressure (mmHg) Safety Population	IP	14.3.2.1
14.3.2.3	Box Plot of Change from Baseline in Pulse Rate (beats/min) Safety Population	IP	14.3.2.1
14.3.2.4	Box Plot of Change from Baseline in Respiration (breaths/min) Safety Population	IP	14.3.2.1
14.3.2.5	Box Plot of Change from Baseline in Weight (kg) Safety Population	IP	14.3.2.1
14.3.2.6	Box Plot of Change from Baseline in in Temperature (C) Safety Population	IP	14.3.2.1
14.4 Figure	**Figure for PK and PD Data**		
14.4.1	Box Plot of Neflamapimod Concentrations by Visit Safety Population	IP	
14.4.2.1.1	Scatter Plot: CTrough vs. Change from Baseline in CSF Biomarker (T-tau) Efficacy Population	IP	
14.4.2.1.2	Scatter Plot: CTrough vs. Change from Baseline in CSF Biomarker (P-tau181) Efficacy Population	IP	14.4.2.1.1
14.4.2.1.3	Scatter Plot: CTrough vs. Change from Baseline in CSF Biomarker (Aβ1-40) Efficacy Population	IP	14.4.2.1.1
14.4.2.1.4	Scatter Plot: CTrough vs. Change from Baseline in CSF Biomarker (Aβ1-42) Efficacy Population	IP	14.4.2.1.1
14.4.2.1.5	Scatter Plot: CTrough vs. Change from Baseline in CSF Biomarker (Neurofilament light chain) Efficacy Population	IP	14.4.2.1.1

14.4.2.1.6	Scatter Plot: CTrough vs. Change from Baseline in CSF Biomarker (pTau/Aβ1-42 Ratio) Efficacy Population	IP	14.4.2.1.1
14.4.2.1.7	Scatter Plot: CTrough vs. Change from Baseline in CSF Biomarker (Brain derived neurotrophic factor (BDNF)) Efficacy Population	IP	14.4.2.1.1
14.4.2.2.1	Scatter Plot: CTrough vs. Combined Change from Baseline in Z-score of Total Recall and Delayed Recall on the HVLT-R Efficacy Population	IP	14.4.2.1.1
14.4.2.2.2	Scatter Plot: CTrough vs. Change from Baseline in Wechsler Memory Scale (WMS) Immediate and Delayed Recall Composite Score Efficacy Population	IP	14.4.2.1.1
14.4.2.2.3	Scatter Plot: CTrough vs. Change from Baseline in Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) Efficacy Population	IP	14.4.2.1.1
14.4.2.2.4	Scatter Plot: CTrough vs. Change from Baseline in Mini-Mental State Examination (MMSE) Score Efficacy Population	IP	14.4.2.1.1
14.4.3.1.1	Scatter Plot: Cmax vs. Change from Baseline in CSF Biomarker (T-tau) Efficacy Population	IP	14.4.2.1.1
14.4.3.1.2	Scatter Plot: Cmax vs. Change from Baseline in CSF Biomarker (P-tau181) Efficacy Population	IP	14.4.2.1.1
14.4.3.1.3	Scatter Plot: Cmas vs. Change from Baseline in CSF Biomarker (Aβ1-40) Efficacy Population	IP	14.4.2.1.1
14.4.3.1.4	Scatter Plot: Cmax vs. Change from Baseline in CSF Biomarker (Aβ1-42) Efficacy Population	IP	14.4.2.1.1
14.4.3.1.5	Scatter Plot: Cmax vs. Change from Baseline in CSF Biomarker (Neurofilament light chain) Efficacy Population	IP	14.4.2.1.1
14.4.3.1.6	Scatter Plot: Cmax vs. Change from Baseline in CSF Biomarker (pTau/Aβ1-42 Ratio) Efficacy Population	IP	14.4.2.1.1
14.4.3.1.7	Scatter Plot: Cmax vs. Change from Baseline in CSF Biomarker (Brain derived neurotrophic factor (BDNF)) Efficacy Population	IP	14.4.2.1.1

14.4.3.2.1	Scatter Plot: Cmax vs. Combined Change from Baseline in Z-score of Total Recall and Delayed Recall on the HVLT-R Efficacy Population	IP	14.4.2.1.1
14.4.3.2.2	Scatter Plot: Cmax vs. Change from Baseline in Wechsler Memory Scale (WMS) Immediate and Delayed Recall Composite Score Efficacy Population	IP	14.4.2.1.1
14.4.3.2.3	Scatter Plot: Cmax vs. Change from Baseline in Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) Efficacy Population	IP	14.4.2.1.1
14.4.3.2.4	Scatter Plot: Cmax vs. Change from Baseline in Mini-Mental State Examination (MMSE) Score Efficacy Population	IP	14.4.2.1.1

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition (Enrolled Subjects)	IP	
16.2.1.2	Screen Failures	IP	
16.2.1.3	Early Withdrawals (Enrolled Subjects)	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations (Protocol Deviations)	IP	
16.2.3	**Subjects Excluded From The Efficacy Analyses**		
16.2.3.1	Analysis Sets (Enrolled Subjects)	IP	
16.2.4	**Demographic Data, Medical History and Medications**		
16.2.4.1	Subject Randomization (Randomized Subjects)	IP	
16.2.4.2	Demographic Data (Enrolled Subjects)	IP	
16.2.4.3	Computed tomography (CT)/Magnetic Resonance Imaging (MRI) Data (Enrolled Subjects)	IP	
16.2.4.4.1	Prior Medical History (Enrolled Subjects)	IP	
16.2.4.4.2	Ongoing Medical History (Enrolled Subjects)	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.4.4.3	Medical History-Probable Alzheimer's Diagnosis (Enrolled Subjects)	IP	
16.2.4.5.1	Inclusion Criteria Not Met (Enrolled Subjects)	IP	
16.2.4.5.2	Exclusion Criteria Met (Enrolled Subjects)	IP	
16.2.4.6.1	Prior and Concomitant Medications (Enrolled Subjects)	IP	
16.2.4.6.2	Prior and Concomitant Alzheimer's Medications (Enrolled Subjects)	IP	
16.2.5	**Compliance And/Or Drug Concentration Data**	IP	
16.2.5.1	Study Drug Exposure and Compliance (Enrolled Subjects)	IP	
16.2.5.2	Plasma Pharmacokinetic Parameters of Neflamapimod Concentrations Over Time (Enrolled Subjects)	IP	
16.2.5.3	Individual Pharmacokinetic Parameters of Neflamapimod (Enrolled Subjects)	IP	
16.2.6	**Individual Efficacy Response Data and PD data**		
16.2.6.1.1	Hopkins Verbal Learning Test – Revised (HVLT-R) (Enrolled Subjects)	IP	
16.2.6.1.2	Combined Change from Baseline in Z-score of Total Recall and Delayed Recall on the HVLT-R (Enrolled Subjects)	IP	
16.2.6.2	Wechsler Memory Scale (WMS) (Enrolled Subjects)	IP	
16.2.6.3	Clinical Dementia Rating (CDR) (Enrolled Subjects)	IP	
16.2.6.4	Mini-Mental State Examination (MMSE) (Enrolled Subjects)	IP	
16.2.6.5	Cerebrospinal Fluid (CSF) Biomarkers (Enrolled Subjects)	IP	
16.2.7	**Adverse Event Listings**	IP	
16.2.7.1	Adverse Events (Enrolled Subjects)	IP	
16.2.7.2	All Serious Adverse Events (Enrolled Subjects)	IP	
16.2.8	**Individual Laboratory Measurements And Other Safety and PD data**		
16.2.8.1.1	Hematology Results (Enrolled Subjects)	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.8.1.2	Chemistry Results (Enrolled Subjects)	IP	
16.2.8.1.3	Coagulation Results (Enrolled Subjects)	IP	
16.2.8.1.4	Clinically Significant Laboratory Results (Enrolled Subjects)	IP	
16.2.8.1.5	Laboratory Liver Function and Coagulation Parameter Abnormalities (Enrolled Subjects)	IP	
16.2.8.2	Vital Signs (Enrolled Subjects)	IP	
16.2.8.3	12-lead ECG Parameters (Enrolled Subjects)	IP	
16.2.8.4	Physical Examination, Abnormal Results (Enrolled Subjects)	IP	
16.2.8.5	Columbia Suicide Severity Rating Scale (C-SSRS) Questionnaire (Enrolled Subjects)	IP	

Approval for implementation of Statistical Analysis Plan

Title:	A Double-Blind, Placebo-Controlled Proof-of-Concept Study of a Selective p38 MAP Kinase Alpha Inhibitor, Neflamapimod, Administered for 24 Weeks in Subjects with Mild Alzheimer's Disease
Protocol Reference:	EIP-VX17-745-304 Protocol V1.0 Final 17-NOV-2017
Sponsor:	EIP Pharma, LLC.
Author:	Shuhua Qi: Senior Biostatistician
WCT reviewer:	Jonathan White: Director, Biostatistics

Author's signature: **Date:**

Reviewer's signature: **Date:**

The above Statistical Analysis Plan has been reviewed and approved by the Sponsor:

Name of Approver: Kelly Blackburn, MHA, MeD
Position: Head of Clinical Development, EIP Pharma

Signature: Date:

Name of Approver: Hui-May Chu, PhD, MBA
Position: Senior Director of Statistics, Anoixis Corporation

Signature: Date:

Name of Approver: John Alam, MD
Position: CEO, EIP Pharma

Signature: Date: