Statistical Analysis Plan

NCT02615002

Document Type:	Template	Document ID:	03.007A.02
Issue Date:	01 SEP 2015	Effective Date:	29 SEP 2015

Sponsor Name:	Neurim Pharmaceuticals
Protocol Number and Title:	NEUP11-AD2 Randomized, double-blind, parallel-group, placebo controlled, dose-ranging study of piromelatine in patients with mild dementia due to Alzheimer's Disease
Protocol Version and Date:	V7.0 (10th April 2017)
Protocol Amendment numbers and dates	V6.0 (14th August 2016) V5.0 (25th May 2016) V4.0 (16th February 2016) V3.0 (13th November 2015) V2.0 (11th September, 2015) V1.0 (23rd July 2015)
INC Research Project Code:	1006401
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SAP Version:	Final 1.0
SAP Version Date:	20 May 2019

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Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
Draft Version 0.1	22 Dec 2017	David White	Initial Release Version – Draft Version 0.1
Draft Version 0.2	01 Oct 2018	Philippa Rook	Updated Draft Version 0.2
Draft Version 0.3	17 Jan 2019	Philippa Rook	Updated Draft Version 0.3
Draft Version 0.4	26 Mar 2019	Philippa Rook	Updated Draft Version 0.4
Final Version 1.0	20 May 2019	Philippa Rook	Final Version 1.0

I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AD	Alzheimer's Disease
ADAS-cog14	Alzheimer's Disease Assessment Scale cognitive subscale
ADCS-MCI-ADL	Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients
AE	Adverse Event
ALAT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ASAT	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BDRM	Blinded Data Review Meeting
BMI	Body Mass Index
CDR	Clinical Dementia Rating
CFT	Category Fluency Test
CGIC	Clinical Global Impression of Change
CI	Confidence Interval
cNTB	computerized Neuropsychological Test Battery
COWAT	Controlled Oral Word Association Test
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBL	Data Base Lock
DET	Detection
DMC	Data Monitoring Committee
DMP	Data Management Plan
ECG	Electrocardiogram
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Description
GGT	Gamma-Glutamyltransferase
ICH	International Council on Harmonization
IDN	Identification
ISLT	International Shopping List Test
IVRS	Interactive Voice Randomization System
IWRS	Interactive Web Randomization System
LOTE	Lack of Therapeutic Efficacy
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCI	Mild Cognitive Impairment
MCMC	Markov Chain Monte Carlo
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed-effects Maximum likelihood Repeated Measures
MMSE	Mini Mental State Examination
N/A	Not Applicable
NA	Not Applicable
NCI	National Cancer Institute
NPI	Neuropsychiatric Inventory
OBK	One Back Card
OCL	One Card Learning
PPS	Per Protocol Set
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Description
SD	Standard Deviation
SHBG	Sex Hormone Binding Globulin
Sheehan-STS	Sheehan Suicidality Tracking Scale
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Analysis Set
STS	Suicidality Tracking Scale
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
VAS	Visual Analogue Scale
WHO	World Health Organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

INC Research will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

2.2. TIMINGS OF ANALYSES

The primary analysis of safety and efficacy and/or pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study, and database is locked after all data related edits and queries are resolved.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of the study is to compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in the change from baseline in global composite score of the computerized Neuropsychological Test Battery (cNTB) after 26 weeks of double-blind treatment.

The global composite score includes the computerized International Shopping List Test (ISLT; immediate and delayed recall), One Card Learning (OCL), Identification (IDN), Detection (DET), One Back Card (OBK), and the paper-based Controlled Oral Word Association Test (COWAT) and Category Fluency Test (CFT).

3.2. SECONDARY OBJECTIVES

The key secondary objectives are:

1. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on global impression assessed by the Clinical Global Impression of Change (CGIC) after 26 weeks of double-blind treatment.

2. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in the Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients (ADCS-MCI-ADL) at Weeks 13 and 26 and over 26 weeks of double-blind treatment.

The other secondary objectives are:

1. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-cog14) at Weeks 13 and 26 and over 26 weeks of double-blind treatment.

2. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in the change from baseline in global composite score of the cNTB at Weeks 4 and 13 and over 26 weeks of double-blind treatment.

3.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

1. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the episodic memory domain* composite score of the cNTB at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment.

   * episodic domain tests: ISLT (immediate and delayed recall) and OCL

2. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the attention domain* composite score of the cNTB at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment.

   * Attention domain tests: IDN and DET

3. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the executive function* composite score of the cNTB at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment.

   * Executive function domain tests: OBK, COWAT and CFT.

4. To compare the safety and tolerability of piromelatine (5, 20, and 50 mg) to that of placebo.

5. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on cognitive aspects of mental function assessed by the Mini Mental State Examination (MMSE) after 2 weeks of run-in single-blind placebo and 26 weeks of double-blind treatment.

6. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in individual cNTB test scores (ISLT immediate and delayed recall, OCL, IDN, DET, OBK, COWAT, and CFT) at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment.

7. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the change from baseline in behavioral signs and symptoms assessed by the Neuropsychiatric Inventory (NPI) Scale after 26 weeks of double-blind treatment.

8. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on sleep variables derived from the Pittsburgh Sleep Quality Index (PSQI) at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment.

9. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in ADAS-cog13, ADAS-cog12, and ADAS-cog11 score at Weeks 13 and 26 and over 26 weeks of double-blind treatment.

3.4. BRIEF DESCRIPTION

This is a Phase 2, double-blind, parallel group, placebo-controlled, dose ranging safety and efficacy study of piromelatine in patients with mild dementia due to Alzheimer's disease (AD).

During the double-blind period, patients will be enrolled in a 1.2:1:1:1 randomization ratio to the 4 trial arms (placebo [1.2], and the equal piromelatine treatment arms 5,

20, and 50 mg [1:1:1]). Intermediate visits will be carried out at 4 weeks (Visit 3) and 13 weeks (Visit 4) after randomization.

Figure 1: Overall Study Design

Period	Screening	Single-blind Run-in		Double-blind Treatment			Follow-up Phone call
		Run-in	Randomization				
Week		-2	0	4	13	26	28
Visit	1		2	3	4	5	
Treatment		Placebo		Piromelatine 5, 20, or 50 mg or Placebo			N/A

Each patient will undergo a 2-week, single blind run-in period and a 26-week, randomized, double-blind treatment period, for a total of 28 weeks. Two weeks after last dosing of study medication, the patient will receive a follow-up phone call. The duration of the study is expected to be approximately 40 months from first patient screened to final patient completing the randomized treatment.

3.5. SUBJECT SELECTION

Male and female patients between the ages of 60 and 85 (inclusive) with mild AD.

3.5.1. Inclusion Criteria

The inclusion criteria are defined in Section 11.1.2 of the protocol.

3.5.2. Exclusion Criteria

The exclusion criteria are defined in Section 11.1.3 of the protocol.

3.6. DETERMINATION OF SAMPLE SIZE

Eligible patients will be enrolled equally in a 1.2:1:1:1 randomization ratio to the 4 trial arms (placebo [1.2] and the equal piromelatine treatment arms 5 mg, 20 mg, and 50 mg [1:1:1]). Assuming an effect size between treatment dose and placebo of 0.35 over 26 weeks, a significant level (α) of 0.05 for one-sided test, and power of 80%, a sample size

of 115 patients for the placebo arm and 95 for each of the 3 piromelatine arms is calculated. Assuming a 50% screen failure rate and allowing for 15% patient withdrawal, 920 patients should be screened in order to randomly assign 460 patients, of whom it is expected 400 will complete the study. Enrollment will end on November 30th 2018.

3.7. TREATMENT ASSIGNMENT AND BLINDING

Patients will be assigned a patient number once written informed consent has been obtained. The randomization list will be generated using a computer-based system and randomization will be performed using an interactive web response system (IWRS). Patients will be randomized, with a ratio of 1.2:1:1:1:1 to each treatment group after successful completion of the single-blind run-in period.

The lead statistician will create a dummy randomization and will be used to provide the dry run of Table, Figure and Listing (TFL) outputs before database lock. An independent unblinded statistician, who will not communicate with the sponsor or other interested party, will create the actual randomization. This will be stored in a restricted folder where only the unblinded statistician will have access to.

Unblinding will occur after database lock. The lead statistician will receive the unblinded randomization list from the unblinded team and rerun all the TFL outputs using this list.

3.8. ADMINISTRATION OF STUDY MEDICATION

Piromelatine will be administered orally, once daily, after a meal, before habitual bedtime, preferably between 2100h and 2300h.

3.9. STUDY PROCEDURES AND FLOWCHART

The schedule of assessments can be found in table 10.1 of the protocol.

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the cNTB global composite score (ISLT immediate and delayed recall, OCL, IDN, DET, OBK, COWAT and CFT) over 26 weeks of double blind treatment.

4.2. SECONDARY EFFICACY ENDPOINTS

Efficacy will be further assessed based on the following secondary variables:

- CGIC at Weeks 13 and 26 and over 26 weeks of double-blind treatment;
- ADCS-MCI-ADL at Weeks 13 and 26 and over 26 weeks of double blind treatment;
- ADAS-cog14 at Weeks 13 and 26 and over 26 weeks of double-blind treatment;
- cNTB global composite score (ISLT, ISLT-delayed, OCL, IDN, DET, OBK, COWAT, and CFT) over 4 and 13 weeks of double blind treatment.

4.3. EXPLORATORY EFFICACY ENDPOINTS

Efficacy will be further assessed based on the following exploratory variables:

- cNTB episodic memory domain composite score (ISLT, ISLT-delayed, and OCL) at Weeks 4, 13 and 26 and over 26 weeks of double blind treatment;
- cNTB attention domain composite score (IDN and DET) at Weeks 4, 13 and 26 and over 26 weeks of double blind treatment;
- cNTB executive function composite score (OBK, COWAT and CFT) at Weeks 4, 13 and 26 and over 26 weeks of double blind treatment.
- MMSE after 2 weeks of run-in single-blind placebo and 26 weeks of double-blind treatment;
- Individual cNTB test scores at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment;
- NPI scale after 26 weeks of double-blind treatment;
- PSQI (global score and individual components) at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment;

- ADAS-cog13, ADAS-cog12, and ADAS-cog11 scores at Weeks 13 and 26 and over 26 weeks of double-blind treatment;
- All of the above primary and secondary cNTB composite global score analyses, without the paper-based CFT and COWAT in the executive function domain;
- All of the above primary and secondary analyses comparing placebo with the combined 20 mg and 50 mg piromelatine treatment group;
- All the above primary and secondary efficacy endpoints separated for ApoE4 carriers and non-carriers (see Section 6.6);
- All the above primary and secondary efficacy endpoints separated for insomnia and non-insomnia patients (see Section 6.6);
- All the above primary and secondary efficacy endpoints separated for naïve patients and patients taking AD medications at baseline (see Section 6.6).

4.4. SAFETY ENDPOINTS

The following variables will be collected for assessment of safety:

- Adverse events (including Serious Adverse Events [SAEs]);
- Physical examination;
- Vital signs;
- Concomitant medications;
- Laboratory parameters (hematology, biochemistry [including sex hormones], and urinalysis);
- Electrocardiograms (ECG);
- Sheehan Suicidality Tracking Scale (Sheehan-STS).

5. ANALYSIS SETS

All the primary, secondary and exploratory efficacy endpoints will be analyzed using the full analysis set. The per protocol set will also be used for the analysis of the primary and secondary efficacy endpoints. Safety and tolerability will be analyzed using the safety analysis set.

5.1. SCREENED SET

The screened set will include all patients screened who have given written informed consent. Unless specified otherwise, this set will be used for the listing and summarization of subject disposition, and for the listing of patient eligibility.

5.2. SAFETY ANALYSIS SET

The safety analysis set (SS) will include all randomized patients who were administered at least one dose of study medication. Patients will be analyzed according to treatment received. The SS will be used for all analyses of safety endpoints and for the presentation of patients in all subject listings, with the exception of disposition and eligibility.

5.3. FULL ANALYSIS SET

The full analysis set (FAS) will include all patients in the safety analysis set who have efficacy data for the primary parameter recorded for baseline and at least 1 post baseline assessment. Patients will be analyzed according to randomized treatment. The FAS will be used for all analyses of primary, secondary and exploratory efficacy endpoints (including the primary and secondary endpoints analysis of the combined 20 mg and 50 mg arm versus placebo) and for the summarization of demographics and baseline characteristics data.

5.4. PER PROTOCOL SET

The per protocol set (PPS) will include all patients in the full analysis set who have no major protocol violations to be determined at the Blinded Data Review Meeting (BDRM). Patients will be analyzed according to randomized treatment. The PPS will be used for all analyses of primary and secondary efficacy endpoints.

5.5. PROTOCOL DEVIATIONS AND VIOLATIONS

A protocol deviation is any change or alteration from the procedures stated in the study protocol, consent document, recruitment process, or study materials (e.g., questionnaires).

A major protocol violation is a deviation that has an impact on subject safety, may

substantially alter risks to subjects, may have an effect on the integrity of the study data, or may affect the subject's willingness to participate in the study. Major protocol violations include (but are not limited to): deviation from inclusion/exclusion criteria, withdrawal criteria met during the study but subject was not withdrawn, prohibited concomitant medications, substantial deviations from the dosing schedule.

A minor protocol violation is a deviation that does not impact subject safety, compromise the integrity of the study data, or affect the subject's willingness to participate in the study.

Protocol deviations will be documented during the study period using the IMPACT monitoring database and will be assigned into one of the following categories:

- Visit schedule;
- Concomitant medication;
- Dosing;
- Laboratory;
- Non-compliance;
- Visit/procedures requirements;
- Other.

This data will be exported from IMPACT and a listing will be generated with the date of occurrence, the category (as above), type of violation, and the reason for the deviation. The listing will be reviewed prior to database lock.

All protocol deviation/violation data will be listed and summarized on the safety analysis set.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

This section describes analytical analysis issues that relate to all or some of the analytic analysis sections that follow. It describes general guidelines for analysis as well as the following items:

- SAS version 9.4 or higher will be used.
- INC Research will be responsible for reporting the demographic, safety, and efficacy data including listings of the administration information for collection of samples.
- Unless otherwise specified, summaries will be presented for each treatment group and dose level and overall.
- The total number of patients in the treatment group and dose level will be used as the denominator for percentage calculations, unless stated otherwise in the table shell.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, 25th and 75th percentile, 5th percentile and 95th percentile, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of patients.
- All safety data will be entered in to the patient data listings. All patients entered into the database, including screen failures, will be included in the disposition listings. Patients who are screened only (who have given signed written informed consent) will be presented as a separate group at the end of the appropriate listings.
- All patients who provide informed consent will be accounted for in this study.
- In general, the listings will be sorted by dose level (treatment group), patient number, and assessment date (and time) if applicable.
- The summary tables will include the total column and columns as follows:
    - Placebo, 5 mg piromelatine, 20 mg piromelatine, 50 mg piromelatine.
- Multiple assessments at a given time point (planned, repeat, and unscheduled) will not be included in summary tables unless specified otherwise, but will be included in the listings. For example if there are multiple laboratory results at a given visit/time point, the latest non-missing value within the visit/time point window will be used. See the specific sections of the SAP for further descriptions.
- See Section 12 for INC standard programming conventions.

6.2. KEY DEFINITIONS

For the purposes of this study, the term “study drug” refers to piromelatine or placebo.

The study day is the day relative to the date of first dose of study drug, where day -1 is the day before the first dose of study drug and day 1 is the day of first dose of study drug (Week 0 (Visit 2)).

The last dose date is defined as the last non-missing date where a nonzero dose of study drug was recorded.

Unless otherwise specified, baseline is the last non-missing observation before the start of the study treatment, which is expected to be the baseline visit at Week 0, or Screening (if existing) if the Week 0 data are not available.

6.3. MISSING DATA

In cases of missing baseline data for cNTB tests, the pre-baseline value will be taken for analysis. If the pre-baseline value is missing as well, values from Screening will be taken and used for analysis as baseline. In cases where the baseline value for COWAT, CFT and ADAS-cog14 are missing, values obtained at Screening will be taken and used for analysis.

Pattern mixture model imputation will be used to treat missing data for all analyses of covariance (ANCOVA) as described in Section 8.1. In the case of cNTB composite scores the imputation will be carried out at the level of the composite score, not at the level of individual tests.

Missing data for AEs where toxicity and relationship to study drug are missing will be treated as described in Section 9.3.

Missing or partial dates for concomitant medications and adverse events will be treated as described in Sections 7.6 and 9.3 respectively.

No other imputation of missing data shall be performed.

6.4. POOLING OF CENTERS

For all mixed-effects maximum likelihood repeated measures (MMRM) and ANCOVA models for the efficacy endpoints, data collected from investigators who enrolled fewer than 3 patients in any 1 treatment group will be combined prior to analysis. If this combination still results in a treatment group having fewer than 3 patients in any 1 treatment group, then this group of patients will be combined with the next fewest-enrolling investigator. In the event that there is a tie for fewest-enrolling investigator, one of these will be chosen at random by a random-number generator.

6.5. STATISTICAL ASSUMPTIONS

The inherent assumption of normally distributed data will be evaluated by generating output for the residuals from the full MMRM and ANCOVA models, which include the interaction term, and by testing for normality using the Shapiro-Wilk test. In the event that the data are predominantly non-normally distributed, analyses will also be conducted on the ranked data. This rank transformation will be applied by ranking all the data for a particular variable, across all investigators and treatments, from lowest to highest. Integer ranks will be assigned starting at 1; mean ranks will be assigned when ties occur.

6.6. SUBGROUPS

For the piromelatine treatment, the 20 mg and 50 mg arms will be combined to create an active arm subgroup. The active subgroup versus placebo analyses will be applied to all primary and secondary endpoints for the FAS using the MMRM.

Additional subgroups will be determined according to ApoE4 carrier status (the presence of ApoE4 allele), baseline insomnia severity (patients being below or above the PSQI cutoff score of ≥5) and naïve patients and those taking AD medication (acetylcholinesterase inhibitors and/or memantine) at baseline. These evaluations will be applied to all primary and secondary efficacy endpoints for the FAS using the MMRM model and will include also the calculation of effect size (Cohen's d).

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

The overall number of screened patients who have given written informed consent will be summarized for the screened set.

Patient disposition will be summarized for the screened set.

The study discontinuation along with the reasons for discontinuation as recorded on the eCRF, and the study day of discontinuation will be listed.

The study disposition summary tables will include the number and percentage of patients in each of the analysis sets and the reason for study discontinuation. Patients who are screen failures will be included in the all patients column. Flowcharts, similar to CONSORT study diagrams, will be created for each analysis set.

Subject disposition data will be listed on the screened set.

7.2. PROTOCOL DEVIATIONS AND VIOLATIONS

Protocol deviations will be captured by the clinical monitoring team on an ongoing basis throughout the study. These deviations will be discussed in a case-by-case process and classified into major and minor violations before the data base lock at the BDRM.

All protocol deviations will be summarized by major/minor violations (defined within the BDRM) and classification for each treatment group for the safety analysis set.

All protocol deviation/violation data will be listed on the safety analysis set.

7.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Age (years) will be calculated as the number of years between the date of birth and the date informed consent was recorded on the eCRF.

Age at Screening = (informed consent date - date of birth + 1) / 365.25 and truncated to complete years.

Age (years) and body mass index (BMI) will be summarized using summary statistics for continuous variables. Demography (sex, race, ethnicity, age, and child-bearing potential) will be summarized by treatment group for patients in the full analysis set.

Sex, race, ethnicity and child bearing potential will be summarized using the summary statistics for categorical variables.

Education status will be summarized using summary statistics for years of education achieved. Highest level of education achieved will be summarized using the summary statistics for categorical variables. Education status will be summarized by treatment group for patients in the full analysis set.

All demography and education status data will be listed on the safety analysis set.

7.4. MEDICAL/SURGICAL HISTORY

Medical/surgical history as recorded at Screening (Visit 1) will be summarized using the full analysis set by treatment group using the number and percentage of patients reporting each system organ class (SOC) and preferred term (PT). Medical/surgical history will be sorted by descending overall total by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 17.1 or later in the summary table.

Medical/surgical history data will be listed on the safety analysis set and sorted by treatment group, patient number, onset date, SOC, and PT.

7.5. OTHER BASELINE CHARACTERISTICS

Duration of AD and severity of insomnia as expressed by PSQI score at baseline will be summarized by treatment group using the full analysis set.

Duration of AD will be calculated as:

(Date of informed consent – onset date of AD) / 365.25 and displayed to 1 decimal place.

For the calculation 01JAN will be imputed as only onset year of AD is recorded. Duration of AD and severity of disease will be summarized using summary statistics for continuous variables.

Duration of AD and severity of insomnia will be summarized using the full analysis set.

Optional ApoE4 genotyping will be summarized using the full analysis set. Subjects will be classified as ApoE4 carriers if they will have one or more copies of the ApoE4 allele. That is, subjects of the genotypes e4/e4, e4/e3 and e4/e2. Subjects without the ApoE e4 allele will be classified as Non-carriers (i.e., e3/e3, e3/e2, and e2/e2). This definition will be used for the subgroup exploratory analysis (Section 8.3.11).

Severity of insomnia will be determined using a score cutoff of ≥5 in PSQI global score for insomnia at baseline. This definition will be used for the subgroup analysis (Section 8.3.12).

Alzheimer disease medications at baseline will be summarized using the full analysis set. Subjects will be classified as naïve if they do not take acetylcholinesterase inhibitors and/or memantine at baseline. This definition will be used for the subgroup exploratory analysis (Section 8.3.13).

This will be summarized post data base lock (DBL) once the data is analyzed.

All data will be listed on the safety analysis set.

7.6. PRIOR AND CONCOMITANT MEDICATIONS

A summary of medications taken during the course of the study will be presented in tabular form using Anatomical Therapeutic Chemical (ATC) classification level 2 and PT via the World Health Organization Drug classification Dictionary (WHO-DD) version March 2012 or later. All medications will be summarized using the full analysis set by treatment group and sorted alphabetically by ATC level 2 class and PT.

Prior medications are those medications taken before the start of treatment in the single-blind run-in phase, not including medications ongoing at the start of the run-in. A medication is considered concomitant in the single-blind run-in phase if ongoing at or taken on or after the start date of treatment in the run-in. A medication is considered concomitant in the double-blind treatment phase if ongoing at or taken on or after the start date of study treatment. A medication can be concomitant in both the single-blind run-in and double-blind treatment phases. Concomitant medications will be summarized by the number and percentage of patients taking a particular medication using the coding described above by phase. If a patient has taken a medication more than once, the patient will be counted only once in the total. Prior medications will be listed only.

See Section 12.9 of the protocol for more details on the time frame allowed for medications.

All prior and concomitant medications will be listed on the safety analysis set by treatment group.

Medications with incomplete end dates will be considered concomitant, unless an incomplete date (e.g. month and year) clearly indicates that the medication started and stopped prior to the start of treatment:

- Day and month are missing and the year is equal to or after the year of the start of treatment in the run-in;

- Day is missing and the year is after the year of the start of treatment in the run-in;
- Day is missing and the year is equal to the year of the start of treatment in the run-in and the month is equal to or after the month of the start of the run-in;
- Year is missing; or
- Complete date is missing.

7.7. SCANS

CT/MRI scans results and PET/CSF results will be recorded at Screening (Visit 1). This data will be listed only on the safety analysis set.

8. EFFICACY

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy endpoint is the change from baseline over 26 weeks of cNTB global composite score.

The global composite score of the cNTB is a composite score of the ISLT (immediate and delayed recall), OCL, IDN, DET, OBK and paper-based COWAT and CFT tests.

Calculation of scores: for each test listed above a z-score relative to study baseline will be calculated.

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

Where:
t = is the test indicator (ISLT, ISLT delayed, OCL, IDN, DET, OBK, COWAT or CFT)
i = indexes subject i
j = indexes the jth assessment for subject i (j = 1 means baseline)
x = cognitive score
x_{ijt} = subject's score for test t at the current assessment
$\bar{x}_{1t}$ = mean performance score of the study sample for test t at baseline
σ_{1t} = standard deviation of the study sample for test t at baseline
Multiplicand equals 1 for tests for which a higher score is indicative of better cognitive performance (i.e., ISLT, ISLTR, OCL, COWAT, CFT) and -1 for tests where a lower score is indicative of better cognitive performance (i.e., IDN, DET, OBK)

Calculation of composite global score: A z-score for each test will be calculated as described above. A mean of all available z-scores for given patient in a given assessment will be calculated as the composite global score. For a given patient at a given assessment a minimum of 5 valid test scores of the tests listed above will be determined, of which at least 1 test are included from each of the domain composites as described in Section 3.2.

cNTB global composite scores and changes from baseline will be summarized (by treatment) at Visits 2, 3, 4 and 5. Change in cNTB global composite scores from baseline over 26 weeks (Visit 5) will be analyzed using a MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model will include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score, age, gender and ApoE4 as covariates, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2 or before. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed by using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

An effect size calculation will be performed, where Cohen's d effect size will be calculated on the adjusted mean difference of change from baseline of treatment versus placebo. The effect size will be derived as the adjusted mean difference divided by the pooled standard deviation. The pooled within group variance (standard deviation squared) of two treatments is defined as:

$$\text{Pooled Variance} = [(n1 - 1)*\text{Var1} + (n2 - 1)*\text{Var2}]/ (n1 + n2 - 2)$$

Where:
n1 = number of subjects with non-missing data for Placebo at Week 26
Var1 = variance for Placebo
n2 = number of subjects with non-missing data for active treatment at Week 26
Var2 = variance for active treatment

These analyses will be performed on the full analysis set and additionally on the per protocol set as a supportive analysis.

A supportive efficacy analysis will be carried out using an ANCOVA method where the change in cNTB global composite scores from baseline to Week 26 will be the outcome variable and treatment group and study site will be main effects. cNTB global composite scores at baseline, age, gender, and ApoE4 will be included as covariates. The standard error of the change from baseline will also be included. Missing data (at the level of the composite score, not at the level of the individual tests) will be imputed using a pattern mixture model approach. Four patterns of missing data will be considered and imputed independently as follows:

- Pattern 1: will include patients who completed treatment on study drug (any missing data here is considered missing at random);
- Pattern 2: will include patients who discontinue treatment early due to adverse events (AEs);
- Pattern 3: will include patients who discontinue treatment early due to lack of therapeutic efficacy (LOTE);
- Pattern 4: will include patients who discontinue treatment early due to reasons other than AE event or LOTE.

The pattern mixture model methodology will be implemented using SAS procedures MI and MIANALYZE. Specifically, the following steps will be followed:

- Intermittent missing data will first be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.

- Data for patients who discontinue early will be multiply imputed as follows:

    - If the patient discontinues due to an AE (Pattern 2) or LOTE (Pattern 3), then missing data will be assumed to follow a distribution similar to the baseline values observed in the placebo arm of the study;

    - If the patient discontinues due to reasons other than an AE or LOTE (Pattern 4), at each time point, missing data will be assumed to follow a distribution similar to scores for patients that are still in the study and randomized to the same treatment group.

- Results of the ANCOVA on the multiply imputed data will be summarized using the SAS procedure MIANALYZE.

These analyses will be performed on the full analysis set and additionally on the per protocol set as a supportive analysis.

8.2. SECONDARY EFFICACY ENDPOINTS AND ANALYSES

8.2.1. Clinical Global Impression of Change

The CGIC is a single score with ordered values of 1 to 7 for “marked improvement” to “marked worsening”. A negative change from baseline indicates an improvement.

Since the result for CGIC is one of a set of ordered scores, the number and percentage of patients with each score at each visit (Week 13 and Week 26) will be provided. The difference between groups will be evaluated by means of the van Elteren version of the Cochran-Mantel-Haenszel test and *P* values will be presented.

8.2.2. Alzheimer’s Disease Cooperative Study/Activities of Daily Living Scale Adapted for MCI Patients

The Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory (ADCS-ADL) score is the total of scores from 18 (questions 19-24 shall not be analyzed for this endpoint) multiple-choice questions. Higher total scores mean better performance; a positive change from baseline indicates an improvement. Many of the questions begin with a selection of yes, no or don’t know, with no or don’t know given scores of 0 and yes leading to the multiple choices. Scores including many don’t know responses could be less reliable than scores with fewer such responses.

The ADCS-ADL global scores and changes from baseline will be summarized (by treatment) at each visit. Change in ADCS-ADL scores from baseline to Week 26 (Visit 5) will be analyzed using a MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model will include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score, age, gender and ApoE4 as covariates, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

An effect size calculation will be performed, where Cohen’s d effect size will be calculated on the adjusted mean difference of change from baseline of treatment versus placebo. The effect size will be derived as the adjusted mean difference divided by the pooled standard deviation.

These analyses will be performed on the full analysis set and additionally on the per protocol set as a supportive analysis.

A supportive efficacy analysis will be carried out using an ANCOVA method where the change in ADCS-ADL scores from baseline to Week 13 (Visit 4) and Week 26 (Visit 5) will be the outcome variable and treatment group and study site will be main effects. The ADCS-ADL scores at baseline, age, gender and ApoE4 will be included as covariates. Multiple imputation for missing values will take place using the pattern mixture model approach, as described in Section 8.1. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed on the full analysis set and additionally on the per protocol set as a supportive analysis.

8.2.3. Alzheimer's Disease Assessment Scale Cognitive 14 Subscale

The ADAS-cog consists of 11 tasks measuring the disturbances of memory, language, praxis, attention, and other cognitive abilities that are often referred to as the core symptoms of AD. The test comprises 11 items summed to a total score ranging from 0 to 70, with lower scores indicating less severe impairment. A negative change indicates an improvement from baseline. The addition of delayed recall, number cancellation, and maze tasks – and thus turning ADAS-cog into a 12-, 13-, and 14-item scale, respectively – has increased the ability to detect changes in patients in the early stages of the disease.

The ADAS-cog14 global scores and changes from baseline will be summarized (by treatment) at each visit. Change in ADAS-cog14 scores from baseline over Week 26 (Visit 5) will be will be analyzed using a MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model will include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score, age, gender and ApoE4 as covariates, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2 or before. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

An effect size calculation will be performed, where Cohen's d effect size will be calculated on the adjusted mean difference of change from baseline of treatment versus placebo. The effect size will be derived as the adjusted mean difference divided by the pooled standard deviation.

A supportive analysis will be carried out using an ANCOVA method where the change in ADAS-cog14 scores from baseline to Week 13 (Visit 4) and Week 26 (Visit 5) will be the outcome variable and treatment group and study site will be main effects. The ADAS-cog14 scores at baseline, age, gender and ApoE4 will be included as covariates. Baseline will be the last non-missing observation at Visit 2 or before. Multiple imputations for

missing values will take place using the pattern mixture model approach, as described in Section 8.1. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed on the full analysis set and additionally on the per protocol set as a supportive analysis.

8.2.4. Computerized Neuropsychological Test Battery Global Composite Score

Change in cNTB global composite scores from baseline to Week 4 (Visit 3) and from baseline to Week 13 (Visit 4) will be analyzed using a MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model will include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score, age, gender and ApoE4 as covariates, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2 or before. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

An effect size calculation will be performed, where Cohen's d effect size will be calculated on the adjusted mean difference of change from baseline of treatment versus placebo. The effect size will be derived as the adjusted mean difference divided by the pooled standard deviation.

These analyses will be performed on the full analysis set and additionally on the per protocol set as a supportive analysis.A supportive efficacy analysis will be carried out using an ANCOVA method where the change in cNTB global composite scores from baseline to Week 4 (Visit 3) and Week 13 (Visit 4) will be the outcome variable and treatment group and study site will be main effects. cNTB global composite scores at baseline, age, gender and ApoE4 will be included as covariates. The standard error of the change from baseline will also be included. Multiple imputation for missing values (at the level of the composite score, not at the level of the individual tests) will take place using the pattern mixture model approach, as described in Section 8.1. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval. Global composite scores will be calculated as described in Section 8.1.

These analyses will be performed on the full analysis set and additionally on the per protocol set as a supportive analysis.

8.3. EXPLORATORY EFFICACY ENDPOINTS AND ANALYSES

8.3.1. Computerized Neuropsychological Test Battery Episodic Memory Domain Composite Score

The episodic memory domain of the cNTB is a composite score of the ISLT (immediate and delayed recall) and OCL tests. Calculation of the episodic memory domain composite score will be carried out by calculating for each given patient at each given assessment the z score as described in Section 8.1. A minimum of 2 out of 3 valid test scores are required for the calculation of the mean of the available z-scores composing the domain composite score.

The cNTB episodic memory domain global scores and changes from baseline will be summarized (by treatment) at each visit. Change in cNTB episodic memory domain composite scores from baseline to Week 26 (Visit 5) will be analyzed using an MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model will include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score, age, gender and ApoE4 as covariates, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2 or before. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

A supportive efficacy analysis will be carried out using an ANCOVA method where the change in cNTB episodic memory domain scores from baseline to Week 4 (Visit 3), Week 13 (Visit 4) Week 26 (Visit 5) will be the outcome variable and treatment group and study site will be main effects. The cNTB episodic memory domain composite scores at baseline, age, gender and ApoE4 will be included as covariates. Multiple imputations for missing values (at the level of the composite score, not at the level of the individual tests) will take place using the pattern mixture model approach, as described in Section 8.1. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

8.3.2. Computerized Neuropsychological Test Battery Attention Domain Composite Score

The attention domain of the cNTB is a composite score of the IDN and DET tests. Calculation of the attention domain composite score will be carried out by calculating for each given patient at each given assessment the z score as described in Section 8.1. Two valid test scores are required for the calculation of the mean of the available z-scores composing the domain composite score.

The cNTB attention domain global scores and changes from baseline will be summarized (by treatment) at each visit. Change in cNTB attention domain scores from baseline over Week 26 will be analyzed using a MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model will include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score, age, gender and ApoE4 as covariates, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2 or before. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

A supportive efficacy analysis will be carried out using an ANCOVA method where the change in cNTB attention domain composite scores from baseline to Week 4 (Visit 3), Week 13 (Visit 4) and Week 26 (Visit 5) will be the outcome variable and treatment group and study site will be main effects. cNTB attention domain composite scores at baseline, age, gender and ApoE4 will be included as covariates. Multiple imputations for missing values (at the level of the composite score, not at the level of the individual tests) will take place using the pattern mixture model approach, as described in Section 8.1. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

8.3.3. Executive Function Domain Composite Score

The executive function domain is a composite score of the OBK, COWAT and CFT tests. Calculation of the executive function domain composite score will be carried out by calculating for each given patient at each given assessment the z score as described in Section 8.1. A minimum of 2 out of 3 valid test scores are required for the calculation of the mean of the available z-scores composing the domain composite score.

The cNTB executive function domain global scores and changes from baseline will be summarized (by treatment) at each visit. Change in cNTB executive function domain scores from baseline over Week 26 will be analyzed using a MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model will include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score, age, gender and ApoE4 as covariates, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2 or before. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

A supportive efficacy analysis will be carried out using an ANCOVA method where the change in cNTB executive function domain scores from baseline to Week 4 (Visit 3), Week 13 (Visit 4) and Week 26 (Visit 5) will be the outcome variable and treatment group and study site will be main effects. The cNTB executive function domain scores at baseline, age, gender and ApoE4 will be included as covariates. Multiple imputations for missing values (at the level of the composite score, not at the level of the individual tests) will take place using the pattern mixture model approach, as described in Section 8.1. The standard error of the change from baseline will also be included. No imputation for missing values at Week 26 will take place. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

8.3.4. Mini Mental State Examination

The MMSE is a brief assessment instrument used to assess cognitive function in elderly patients. The instrument is divided into 2 sections. The first section measures orientation, memory, and attention; the maximum score is 21. The second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures: the maximum score is 9. The scoring range for the MMSE is 0-30.

Change in MMSE global scores from baseline to Week 26 (Visit 5) will be analyzed using an ANCOVA method where the change in MMSE scores from baseline to Week 26 will be the outcome variable and treatment group and study site will be main effects. MMSE scores at baseline, age, gender and ApoE4 will be included as covariates. Baseline will be the last non-missing observation at Screening (Visit 1). The standard error of the change from baseline will also be included. Multiple imputations for missing values will take place using the pattern mixture model approach, as described in Section 8.1. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

8.3.5. Individual Computerized and Paper-Based Neuropsychological Test Battery Score

The individual z-scores of the cNTB include ISLT (immediate and delayed recall), OCL, IDN, DET, OBK, and paper-based COWAT and CFT.

Change in the individual NTB scores from baseline to Week 26 (Visit 5) will be analyzed using a MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score, age, gender and ApoE4 as covariates, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and

P values. Baseline will be the last non-missing observation at Visit 2 or before. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

As supportive analysis for the change in the individual NTB scores from baseline to Week 4 (Visit 3), Week 13 (Visit 4) and Week 26 (Visit 5) will be analyzed using an ANCOVA method, where the change in individual NTB scores from baseline (Visit 2) to Week 26 (Visit 5) will be the outcome variable and treatment group and study site will be main effects. The individual NTB scores at baseline, age, gender and ApoE4 will be included as covariates. The standard error of the change from baseline will also be included. Multiple imputations for missing values will take place using the pattern mixture model approach, as described in Section 8.1. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

8.3.6. Neuropsychiatric Inventory

The NPI scale consists of 12 domains that are rated for both frequency (range 1-4) and severity (range 1-3). A composite score for each domain is calculated (frequency × severity), which ranges from 1 to 12. There is a leading question for each item. If the symptom is not present, then the frequency, severity, and distress scores are not completed. In this case the score is 0 for the item. The sum of the composite scores yields the NPI-12 total score (range 0-144). A negative change in score indicates an improvement from baseline (symptom reduction).

Change in the NPI individual items and global scores from baseline to Week 26 (Visit 5) will be analyzed using an ANCOVA method, where the change in the NPI scores from baseline to Week 26 will be the outcome variable and treatment group and study site will be main effects. The NPI scores at baseline, age, gender, and ApoE4 will be included as covariates. Baseline will be the last non-missing observation at Visit 2. The standard error of the change from baseline will also be included. Multiple imputations for missing values will take place using the pattern mixture model approach, as described in Section 8.1. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

The NPI-10 total score (range 0-120) will also be calculated by removing the sleep and appetite and eating domains. This will be summarized and analyzed as per the NPI-12 score. The distress score shall be listed only.

8.3.7. Pittsburgh Sleep Quality Index

The PSQI is an effective instrument used to measure the quality and patterns of sleep in older adults. It differentiates “poor” from “good” sleep by measuring 7 areas

(components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. The patient self-rates each of these 7 areas of sleep. Scoring of answers is based on a 0 to 3 scale, where a score of 3 reflects the negative extreme on the Likert Scale. A global sum of 5 or greater indicates a "poor" sleeper.

Change in the PSQI, for each of the 7 individual components, questions 2 and 4, and the global scores from baseline will be summarized (by treatment) at each visit. Change in PSQI scores from baseline to Week 26 will be analyzed using a MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model will include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score, age, gender and ApoE4 as covariates, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

As supportive analysis for the change in PSQI scores (individual components and global) from baseline to Week 4 (Visit 3), Week 13 (Visit 4) and Week 26 (Visit 5) will be analyzed using an ANCOVA method where the change in the PSQI scores from baseline to Week 4, Week 13, or Week 26 will be the outcome variable and treatment group and study site will be main effects. The PSQI scores at baseline, age, gender, and ApoE4 will be included as covariates. Multiple imputations for missing values will take place using the pattern mixture model approach, as described in Section 8.1. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

8.3.8. Alzheimer's Disease Assessment Scale Cognitive 13, 12 and 11 Subscale

The ADAS-cog13, ADAS-cog12 and ADAS-cog11 scores and changes from baseline will be summarized (by treatment) separately at each visit. Change in ADAS-cog13, ADAS-cog12 and ADAS-cog11 scores from baseline to Week 26 (Visit 5) will be analyzed separately using a MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model will include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score as a covariate, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

As supportive analysis for the change in ADAS-cog 11, 12 and 13 scores from baseline to Week 13 (Visit 4) and Week 26 (Visit 5) will be analyzed using an ANCOVA method, where the change in ADAS-cog 11, 12 and 13 scores from baseline to Week 26 will be the outcome variable and treatment group and study site will be main effects. The ADAS-cog 11, 12 and 13 scores at baseline, age, gender, and ApoE4 will be included as covariates. Multiple imputations for missing values will take place using the pattern mixture model approach, as described in Section 8.1. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

8.3.9. Computerized Neuropsychological Test Battery Global Composite Score without Paper-Based Components

The cNTB global composite score contains both computerized and paper-based (CFT and COWAT) scores. As an exploratory analysis, the analyses on the cNTB global composite score shall be repeated with the paper-based components removed.

Change in cNTB global composite scores from baseline to Week 4 (Visit 3), from baseline to Week 13 (Visit 4), and from baseline to Week 26 (Visit 5) will be analyzed using a MMRM model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model will include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score, age, gender and ApoE4 as covariates, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2 or before. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

A supportive efficacy analysis will be carried out using an ANCOVA method where the change in cNTB global composite scores from baseline to Week 4 (Visit 3), Week 13 (Visit 4), and Week 26 (Visit 5) will be the outcome variable and treatment group and study site will be main effects. cNTB global composite scores at baseline, age, gender, and ApoE4 will be included as covariates. The standard error of the change from baseline will also be included. Multiple imputation for missing values (at the level of the composite score, not at the level of the individual tests) will take place using the pattern mixture model approach, as described in Section 8.1. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval. Global composite scores will be

calculated as described in Section 8.1, but with the removal of the paper-based CFT and COWAT components.

8.3.10. Combined Piromelatine Treatment Group 20 mg + 50 mg vs Placebo

An additional exploratory efficacy analysis will be carried out for the primary and secondary efficacy endpoints (as detailed in Sections 4.1 and 4.2) comparing placebo with a combined treatment group of 20 mg + 50 mg.

These analyses will be performed on the full analysis set using the MMRM model and will include calculation of an effect size. See Section 8.1 and 8.2 for the individual analyses.

8.3.11. ApoE4 Carrier Status

An additional exploratory efficacy analysis will be carried out for all primary and secondary efficacy endpoints (as detailed in Sections 4.1 and 4.2) separately for ApoE4 carriers and non-carriers (as described in Section 7.5).

These analyses will be performed on the full analysis set using the MMRM model and will include calculation of an effect size. See Sections 8.1 and 8.2 for the individual analyses.

These analyses will be performed only for patients who have provided their consent to use their genetic material for the analysis of the ApoE gene.

8.3.12. Insomnia at Baseline

An additional exploratory efficacy analysis will be carried out for all primary and secondary efficacy endpoints (as detailed in Sections 4.1 and 4.2) separately for patients with and without insomnia as determined by the PSQI score obtained at baseline (as described in Section 7.5).

These analyses will be performed on the full analysis set using the MMRM model and will include calculation of an effect size. See Sections 8.1 and 8.2 for the individual analyses.

8.3.13. Alzheimer's Disease Medications at Baseline

An additional exploratory efficacy analysis will be carried out for all primary and secondary efficacy endpoints (as detailed in Sections 4.1 and 4.2) separately for patients receiving Alzheimer's disease medications (acetylcholinesterase inhibitors and/or memantine) and naïve patients (as described in Section 7.5).

These analyses will be performed on the full analysis set using the MMRM model and will include calculation of an effect size. See Sections 8.1 and 8.2 for the individual analyses.

8.3.14 Clinical Dementia Rating

The Clinical Dementia Rating (CDR) data will be listed only.

9. SAFETY

The safety analysis set will be used for the listing of safety data and for all safety analyses. Safety will be assessed on the basis of adverse event (AE) reports, clinical laboratory data (including sex hormones), ECG parameters, physical examinations, vital signs and suicidal ideation (Sheehan-STS).

9.1. EXTENT OF EXPOSURE

The duration of exposure (in days) to study medication will be summarized using summary statistics for continuous variables. This will be calculated using the safety analysis set.

Duration of exposure will be calculated by:

Date of last dose – date of first dose + 1

The study medication accountability will be listed along with the duration of exposure.

9.2. TREATMENT COMPLIANCE

Treatment compliance will be calculated at each visit by the investigator. Compliance to study medication will be summarized using summary statistics for continuous variables for each visit and overall. This will be calculated using the full analysis set.

Compliance (%) for each visit will be calculated as:

(Number of tablets actually taken / number of days since last visit) * 100

Compliance will also be listed.

For Screening (Visit 1), compliance will be calculated as:

(Number of tablets actually taken / number of days since beginning of run-in) * 100

9.3. ADVERSE EVENTS

Adverse events will be collected throughout the study, from informed consent until the end of the treatment period.

Adverse events will be summarized by the SOC and PT based on the MedDRA dictionary version 17.1 or later.

Treatment emergent adverse events (TEAEs) are defined as any adverse events (AEs) that occur after the start of administration of the first dose of study drug and through

14 days after the last dose of study drug, or any event that is present at baseline and continues after the first dose of study drug but worsens in intensity.

See Section 14.1 of the protocol for definition of serious adverse events (SAEs).

Treatment emergent AEs will be characterized based on the onset date relative to each patient's participation in the study.

Adverse events with incomplete start dates will be considered a TEAE if:

- Day and month are missing and the year is equal to or after the year of the first dose date;
- Day is missing and the year is after the year of the first dose;
- Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;
- Year is missing; or
- Complete date is missing.

If the relationship to study treatment is missing then related will be used for the summaries. Similarly, events with missing intensity or severity will be counted as severe (Grade 3).

The summary tables will include the number of subjects and the number of events. Percentages will be based on the number of subjects. For summaries by SOC and PT, a patient will be counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT, and maximum severity, a patient will be counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level.

The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following AE tables will be provided:

- An overall summary of the number and percentage of patients reporting AEs, TEAEs, treatment-related TEAEs, severe TEAEs, serious TEAEs, treatment-related serious TEAEs, and TEAEs leading to withdrawal of study medication;
- TEAEs, overall and by SOC and PT;

- Serious TEAEs, overall and by SOC and PT;
- TEAEs related to study medication, overall and by SOC and PT;
- TEAEs, overall and by SOC, PT and maximum severity;
- TEAEs leading to withdrawal of study medication, overall and by SOC and PT;
- TEAEs, overall and by PT;
- All AEs, overall and by SOC and PT;
- All AEs, overall and by SOC, PT and maximum severity.

With the exception of the all AEs table, only the TEAEs will be included in the summary tables; however, all AEs will be included in the listings. Any AE occurring during the single-blind run-in, before the first dose of study medication in the double-blind treatment phase, will be included in the summaries of all AEs only. Any AE occurring before the single-blind run-in will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within the defined 14 day follow-up period after discontinuation of study medication will be included in the AE summaries.

With the exception of the all AEs tables, the summaries of TEAEs will present frequency of AEs by SOC and PT, will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

An additional listing will be provided for SAEs leading to withdrawal from the study. TEAEs will be flagged in the listings.

9.4. LABORATORY EVALUATIONS

All blood and urine samples will be analyzed using a local laboratory. The sampling will be performed at the site at Screening (Visit 1), Visit 4 (Week 13), and Visit 5 (Week 26) and as soon as possible following the premature discontinuation visit (if applicable).

The following parameters will be measured:

- Hematology: hemoglobin, hematocrit, red blood cells, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration, large unstained cells, white blood cells, lymphocytes, monocytes, neutrophils, eosinophils, basophils and platelets.
- Chemistry: creatinine, uric acid, urea, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), albumin, gamma-glutamyltransferase (GGT),

total protein, sodium, potassium, chloride, calcium, phosphorus, glucose, alkaline phosphatase, total bilirubin, total testosterone, free testosterone, Sex Hormone Binding Globulin (SHBG) and prolactin.

- Urinalysis: bilirubin, blood, clarity, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity and urobilinogen.

All summaries of hematology, chemistry and urinalysis will be based on results in standard international (SI) system of units, conversion will be performed according to the data management plan (DMP) prior to the transfer to INC Research. The high and low classifications will be derived relative to the result and normal range in SI units.

Summary tables for hematology, chemistry and urinalysis laboratory variables will include the following: descriptive statistics for SI values and change from baseline for all continuous variables by assessment for each module and dose level. In general, any quantitative assessments for urinalysis will be summarized using the number and percentage of subjects with the given result. Percentages will be calculated out of the number of subjects with non-missing data. Shift tables showing the number of patients having values below, within and above the normal range at each assessment at Screening and each post baseline visit will be presented.

All laboratory results in original and SI units will be included in data listings. Tests will be listed in alphabetical order. Urine drug screen will be listed.

Optional blood sampling for ApoE4 genotyping (e4/e4, e4/e3, e4/e2, e3/e3, e3/e2, e2/e2) will be listed. This data will be collected and reported after DBL.

9.5. VITAL SIGNS

Vital sign measurements will include measurements of heart rate (beats/min) and systolic and diastolic blood pressure (mmHg). Height (cm) and weight (kg) will also be recorded at Screening (Visit 1) and at Visit 5 (Week 26) for weight only. BMI (kg/m2) will be calculated at Screening also and summarized with the demography data (see Section 7.3).

Vital signs will be taken before administration of study drug.

Summary tables by visit and time point and change from baseline to visit and time point for each vital sign parameter will be provided.

All vital signs measurement data will be listed.

9.6. ECG

Resting 12-lead ECGs will be recorded at Screening (Visit 1), Visit 4 (Week 13), Visit 5 (Week 26), and early termination visit.

Summary tables by visit and time point and change from baseline to visit and time point for each ECG parameter (heart rate (bpm), PR interval (msec)), QRS interval (msec), QT interval (msec), RR interval (msec) and QTcF interval (msec) will be provided.

The overall results of the ECGs recorded as "normal", "abnormal, not clinically significant (NCS)" or "abnormal, clinically significant (CS)" will be summarized by treatment group at each time point.

12-lead ECG data will be listed.

9.7. PHYSICAL EXAMINATION

Physical examination will be performed at Screening (Visit 1), Visit 4 (Week 13), Visit 5 (Week 26), and early termination visit.

At all visits, the assessment of clinically significance abnormal finding will be reported as either medical history or an AE as applicable.

The overall physical examination results recorded as "normal" or "abnormal" will be summarized by treatment group at each visit.

Physical examination data will also be listed.

9.8. OTHER SAFETY

Suicidal ideation will be rated at Screening (Visit 1), Visit 4 (Week 13), and Visit 5 (Week 26) using the Sheehan-STS.

A summary table by visit and change from baseline to visit will be provided for the total score. A summary table of the individual Sheehan-STS scores will also be provided by visit showing the number and percentage of subjects with each response for each individual question.

10. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Sample size and statistical power: In order to meet piromelatine drug development program timelines it has been decided to reduce the sample size for the ReCOGNITION study from 500 to 400 evaluable subjects. This reduction results from changing the originally highly powered study at 88% to 80%, while keeping the effect size (0.35) based on which the sample size was calculated. This is still an acceptable power in clinical trials which Neurim believes is appropriate to confirm the potential efficacy of piromelatine.

Primary endpoint: Version 7 of the protocol included the addition of COWAT and CFT to executive function domain of the cNTB. These two tests should have been included also in the global composite score. The rules for a valid global composite score will include now over 8 tests (ISLT immediate and delayed, OCL, IDN, DET, OBK, COWAT and CFT) instead of 6, of which the executive function domain will include 3 tests (OBK, COWAT and CFT).

Primary and secondary statistical analysis: For all endpoints the order was reversed; MMRM will be used as the primary endpoint, while ANCOVA will be used as the secondary analysis.

Secondary and exploratory analysis: cNTB attention, cNTB episodic and executive function domains have been moved from secondary to exploratory efficacy endpoints.

Co-variates: Age, gender, and ApoE4 will be used as co-variates for the MMRM and ANCOVA.

Imputations: The pattern mixture model approach will be used for the ANCOVA in cases of missing values as described in Section 8.1.

Analysis of the CGIC endpoint: The protocol states that the ANCOVA method will be used to analyze the change from baseline between the treatment groups. As there is no baseline result recorded in the CRF, this method is not appropriate for this endpoint. The difference between the treatment groups will instead be evaluated by means of the van Elteren version of the Cochran-Mantel-Haenszel test.

MMSE: Section 17.3.4 of the protocol states that MMSE will be analyzed using an ANCOVA. This analysis will be performed on the global scores.

NPI: Section 17.3.4 of the protocol states that NPI will be analyzed using an ANCOVA. This analysis will be performed on individual items and the global score of 10 and 12 items.

Additional analyses: For the purpose of increasing the statistical power the 20 mg and 50 mg arms will be combined to create an active arm with larger sample size for an analysis as compared to placebo. This active versus placebo analysis will be applied to all endpoints for the FAS using the MMRM.

As the paper-based CFT/COWAT and computerized OBK of the cNTB executive function domain are collected differently, an exploratory analysis shall be performed, where the analyses on the cNTB global composite score shall be repeated with the paper-based components removed as detailed in Section 8.3.9.

Additional subgroup exploratory analyses will be performed, as detailed in Sections 8.3.11 – 8.3.13, to explore the subgroup effects for ApoE4 carriers, insomnia at baseline and AD concomitant medications.

Prior medications: Section 17.3.1 of the protocol states that prior medications will be summarized by treatment group, but prior medications will be listed only.

11. REFERENCE LIST

12. PROGRAMMING CONSIDERATIONS

All TLFs and statistical analyses will be generated using SAS® 9.3 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated TLF output will adhere to the following specifications.

12.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs. Or a separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word rtf and Excel CSV format.
- Numbering of TFLs will follow International Council on Harmonization (ICH) E3 guidance

12.2. TABLE, LISTING, AND FIGURE FORMAT

12.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

12.2.2. Headers

- All output should have the following header at the top left of each page:
  Neurim ReCOGNITION Protocol NEUP11-AD2 (INC Research study number 1006401)

Draft/Final Run <date>

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
Safety Analysis Set

12.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

12.2.5. Body of the Data Display

12.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

12.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Effect size Cohen’s d value should be rounded to 2 decimal places.
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as “-”.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

12.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

12.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

13. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analysis. INC Research SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

INC Research SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

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Listing 16.2.4.1	Demographic Characteristics and Education Status	Safety Analysis Set
Listing 16.2.4.2	Medical/Surgical History	Safety Analysis Set
Listing 16.2.4.3	Baseline Characteristics - Alzheimer's Disease	Safety Analysis Set
Listing 16.2.4.4	Prior and Concomitant Medications	Safety Analysis Set
Listing 16.2.4.5	CT/MRI Scan	Safety Analysis Set
Listing 16.2.4.6	PET/CSF Scan	Safety Analysis Set
Listing 16.2.5.1	Study Medication Accountability	Safety Analysis Set
Listing 16.2.5.2	Patient Compliance	Safety Analysis Set
Listing 16.2.5.3	Caregiver Telephone Call	Safety Analysis Set
Listing 16.2.6.1.1	Individual Computerized and Paper-Based Neuropsychological Test Battery Scores	Safety Analysis Set
Listing 16.2.6.1.2	Neuropsychological Test Composite Scores	Safety Analysis Set
Listing 16.2.6.2	Clinical Global Impression of Change	Safety Analysis Set
Listing 16.2.6.3	Alzheimer's Disease Cooperative Study/Activities of Daily living Scale Adapted for MCI Patients	Safety Analysis Set
Listing 16.2.6.4.1	Alzheimer's Disease Assessment Scale Cognitive Subscale-14 Results Part 1	Safety Analysis Set
Listing 16.2.6.4.2	Alzheimer's Disease Assessment Scale Cognitive Subscale-14 Results Part 2	Safety Analysis Set
Listing 16.2.6.4.3	Alzheimer's Disease Assessment Scale Cognitive Subscale-14 Results Part 3	Safety Analysis Set
Listing 16.2.6.4.4	Alzheimer's Disease Assessment Scale Cognitive Subscale-14 Results Part 4	Safety Analysis Set
Listing 16.2.6.4.5	Alzheimer's Disease Assessment Scale Cognitive Subscales Scores	Safety Analysis Set
Listing 16.2.6.5.1	Executive Function Domain - Controlled Oral Word Association Test	Safety Analysis Set
Listing 16.2.6.5.2	Executive Function Domain – Category Fluency Test	Safety Analysis Set
Listing 16.2.6.6	Mini Mental State Examination	Safety Analysis Set
Listing 16.2.6.7	Neuropsychiatric Inventory	Safety Analysis Set
Listing 16.2.6.8.1	Pittsburgh Sleep Quality Index Part 1	Safety Analysis Set
Listing 16.2.6.8.2	Pittsburgh Sleep Quality Index Part 2	Safety Analysis Set
Listing 16.2.6.9	Clinical Dementia Rating	Safety Analysis Set
Listing 16.2.7.1	All Adverse Events	Safety Analysis Set

Listing 16.2.8.1.1	Laboratory Results: Hematology	Safety Analysis Set
Listing 16.2.8.1.2	Laboratory Results: Chemistry	Safety Analysis Set
Listing 16.2.8.1.3	Laboratory Results: Hormones (Testosterone, SHBG, Prolactin)	Safety Analysis Set
Listing 16.2.8.1.4	Laboratory Results: Urinalysis	Safety Analysis Set
Listing 16.2.8.1.5	Laboratory Results: Urine Drug Screen	Safety Analysis Set
Listing 16.2.8.1.6	Optional Blood Sample for ApoE4 Genotyping	Safety Analysis Set
Listing 16.2.8.2.1	Vital Signs	Safety Analysis Set
Listing 16.2.8.2.2	12-Lead ECG	Safety Analysis Set
Listing 16.2.8.2.3	Physical Examination	Safety Analysis Set
Listing 16.2.8.2.4.1	Sheehan-STS - Part 1	Safety Analysis Set
Listing 16.2.8.2.4.2	Sheehan-STS - Part 2	Safety Analysis Set
Listing 16.2.8.2.4.3	Sheehan-STS - Part 3	Safety Analysis Set

16. APPENDICES

- NEUP11-AD2_Table and Figure Shells_Final Version 1.0
- NEUP11-AD2_Listing Shells_Final Version 1.0

17. MOCK-UPS

Attachments:

- NEUP11-AD2_Listing Shells_Final Version 1.0
- NEUP11-AD2_Table and Figure Shells_Final Version 1.0