STATISTICAL ANALYSIS PLAN (Extension Phase)

Study Protocol Number:	E2006-G000-202
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of the Efficacy and Safety of Lemborexantin Subjects with Irregular Sleep-Wake Rhythm Disorder and Mild to Moderate Alzheimer's Disease Dementia
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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
AE	adverse event
AMP	Amplitude of the rest-activity rhythm
ANCOVA	analysis of covariance
aSE	Actigraphy sleep efficiency
ATC	anatomical therapeutic class
aWE	Actigaphy wake efficiency
BMI	body mass index
CGIC- ISWRD	Clinician's Global Impression of Change - Irregular Sleep-Wake Rhythm Disorder version
CI	confidence interval
CRF	case report form
CSR	clinical study report
E2006	lemborexant
EQ-5D-5L	EuroQOL version 5D-5L
FAS	full analysis set
IS	Interdaily Stability
ISWRD	Irregular Sleep-Wake Rhythm Disorder
IV	Intradaily Variability
LEM	lemborexant
LEM2.5	lemborexant 2.5 mg
LEM5	lemborexant 5 mg
LEM10	lemborexant 10 mg
LEM15	lemborexant 15 mg
LS	least squares
OLE	Open Label Extension
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
NPI-10	Neuropsychiatric Inventory

Abbreviation	Term
PBO	Placebo
PD	pharmacodynamic
PK	pharmacokinetic
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RA	Relative amplitude of the rest-activity rhythm
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SDI	Sleep Disorders Inventory
SE	Sleep efficiency (PSG)
SFI	Sleep Fragmentation Index
SI	Système International
TEAE	treatment-emergent adverse event
TIB	Time in bed
TLG	tables, listings, and graphs
WFI	Wake Fragmentation Index
WHO	World Health Organization
ZBI	Zarit Burden Interview – short form

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E2006-G000-202 open label extension (Extension Phase). Additional exploratory or post-hoc analyses not identified in this SAP may be performed to facilitate interpretation of study results and documented in the clinical study report. A separate SAP has already been finalized for the core study.

This document is prepared on the basis of the final study protocol version 10.0 (dated 20 Jun 2018). The reader is referred to the study protocol, the case report form (CRF), general CRF completion guidelines, and various data collection instruments employed in the study for details of study design, conduct, and data collection.

This SAP is to be reviewed and approved prior to study database lock. If any updates are made upon blinded review of study data or for any other reasons in the course of the study, such modifications and rationale are likewise to be documented and approved prior to unblinding of study database.

2.1 STUDY OBJECTIVES

The objective of the Extension Phase is to evaluate the long-term safety and tolerability of flexible doses of Lemborexant 5 mg (LEM5), Lemborexant 10 mg (LEM10) and Lemborexant 15 mg (LEM15) once per day over a period of 30 months in subjects with Alzheimer's disease dementia (AD-D) who have Irregular Sleep-Wake Rhythm Disorder (ISWRD).

2.2 Overall Study Design and Plan

2.2.1 Extension Phase

The Extension Phase comprises a 30-month Maintenance Period (Treatment Period) and a 14-day Follow-Up Period.

Subjects who complete the Core Study End of Study (EOS) Visit within 30 days prior to enrollment in the Extension Phase will be eligible for participation.

For subjects continuing directly from the Core Study to the Extension Phase, the End of Study (EOS) Visit of the Core Study will be the start of the Extension Phase.

Subjects who complete the Core Study, but who do not elect to immediately roll over to the Extension Phase will be required to return to the site within 30 days of completion of the Core Study and repeat selected assessments before being dispensed drug for the Extension Phase. If subjects return before 30 days of the last study visit, the tests that are required at that time are vital signs, weight, the Sleep Disorders Inventory (SDI), and the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). All other data will be carried over from Visit 6A. If subjects return on Day 30, all tests listed for Visit 6B will be performed. Details are as in (Figure 1).

During the Treatment Period, all subjects initially will receive lemborexant 10 mg per day (LEM10). At the discretion of the investigator, subjects will have the option of increasing the dose to lemborexant 15 mg per day (LEM15) or decreasing to lemborexant 5 mg per day (LEM5). All dose adjustments will be performed at an unscheduled visit or at the next scheduled visit.

All doses will be taken orally in tablet form each night for the duration of the Extension Phase immediately (ie, within 5 minutes) before the time the subject intends to sleep. The dose can be adjusted more than once during the Extension Phase. Subjects will receive 1 or 2 tablets as described below:

- LEM5: one lemborexant 5-mg tablet
- LEM10: one lemborexant 10-mg tablet
- LEM15: one lemborexant 5-mg tablet and one lemborexant 10-mg tablet

Study visits, either in person or by telephone, will be conducted according to the Schedule of Procedures and Assessments for the Extension Phase. If the phone visit indicates an ongoing adverse event (AE), the subject should be brought to the clinic for an Unscheduled Visit. Subjects may discontinue from study drug for any reason. A subject who prematurely discontinues taking study drug should return to the clinic within 2 weeks of discontinuation to complete an Early Termination (ET) Visit. The assessments of the ET Visit are the same as those for the EOS Visit for the Core Study.

If the subject discontinues from the study due to an AE, the subject must complete an ET Visit, and the AE must be followed to resolution for a period of 4 weeks, whichever comes sooner.

2.2.2 Follow-Up Period

The Follow-Up Period will be 14 to 18 days in duration and begins when subjects leave the clinic at the end of the Maintenance Period. Subjects and caregivers will return to the clinic at least 14 days but no more than 18 days after the end of the Maintenance Period for the End of Study Visit, including the recording of AEs and concomitant medications, and assessment of clinical laboratory tests, vital signs, and weight, and measurement of an electrocardiogram (ECG).

Treatment in the Extension Phase will last for a maximum duration of 30 months or until the lemborexant clinical development program for Irregular Sleep-Wake Rhythm Disorder (ISWRD) is discontinued. A study design that includes the Extension Phase is presented in Figure 1.

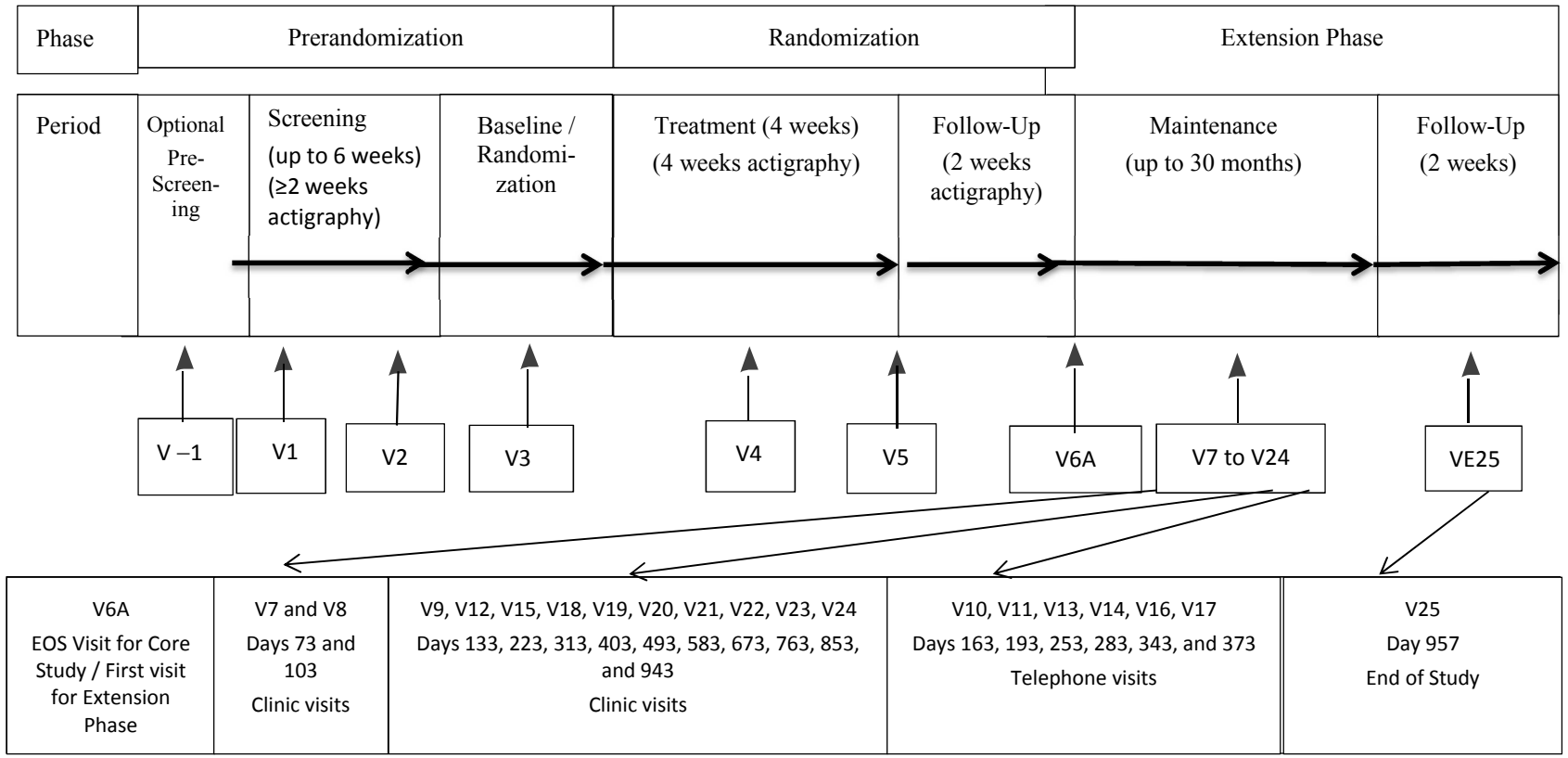

Figure 1 Study Design

Note: Visit –1 is an optional Prescreening Period for subjects and caregivers who are unsure whether the subject has Irregular Sleep-Wake Rhythm Disorder (ISWRD). Subjects will wear an activity tracker for approximately 4 days, then return to the site to have the data from the activity tracker downloaded and analyzed to determine whether they are candidates for the study. (revised per Amendment 05)
Note: Visit 2 is a caregiver visit for downloading actigraphy data to determine eligibility; Visit 3 is the baseline visit for both subject and caregiver; Visit 4 is a visit for both subject and caregiver to download actigraphy data and perform safety assessments; Visit 5 is the end-of-treatment assessments visit; and Visit 6A is for end-of-study assessments for the Core Study. For subjects continuing directly from the Core Study into the Extension Phase, Visit 6A will be the start of the Extension Phase. Subjects who complete the Core Study, but who do not elect to immediately continue into the Extension Phase have up to 30 days after Visit 6A to participate. These subjects will be required to repeat selected assessments (Visit 6B) before being dispensed drug for the Extension Phase. Some subjects will have fewer visits based on the availability of lemborexant commercially.
ISWRD = Irregular Sleep-Wake Rhythm Disorder, V = Visit.

2.2.1 END OF EXTENSION PHASE

The End of the Extension Phase will be the date of the last study visit for the last subject in the Extension Phase.

Duration of Treatment: Up to 30 months or until the lemborexant clinical development program for ISWRD is discontinued.

3 DETERMINATION OF SAMPLE SIZE

While approximately 60 subjects will enroll in the Core Study, any subject who completed the Core Study after the protocol was amended to include the the Extension Phase will be allowed to enroll in this Extension Phase, if eligible.

4 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

There will be no hypothesis testings, and data will be only be summarized by timepoint and by modal dose received by the subject.

Modal dose will be calculated as follows:

If subject has one dose start date and no dose end date, then subject has been on initial10 mg dose, model dose = 10 mg.

If a subject has start dose date and only one end date, and a second dose start date; then subject has been on 10 mg dose till first end dose date, the number of days on 10 mg is calculated as follows: first end date - first start date +1 , and number of days on the new dose is calculated as: database snapshot date- second start date +1. The modal dose is the most frequent of these two numbers, ... and so on.

4.1 Study Endpoints

4.1.1 Efficacy Endpoints

The SDI, completed by the caregiver as proxy for the subject, will be performed according to the Schedule of Procedures and Assessments.

4.1.2 Safety Endpoints

Subjects will have routine safety assessments during the Extension Phase, including monitoring, questioning and recording of AEs, measurements for ECGs, vital signs, and weight, and blood and urine collection for clinical hematology and chemistry analysis, urinalysis, and the eC-SSRS.

4.2 Study Subjects

4.2.1 Definitions of Analysis Sets

Safety Analysis Set: the group of Extension Phase subjects who received at least 1 dose of Treatment Phase study drug and had at least 1 postdose safety assessment

4.2.2 Subject Disposition

The number of subjects entered in the Extension Phase and the number of subjects completing the Extension Phase will be presented. Subjects who prematurely terminated their participation in this extension phase will be summarized by their primary reason for study termination. Other reasons for study drug and study terminations will also be summarized. These tabulations will be produced for all subjects by modal dose.

4.2.3 Protocol Deviations

Protocol deviations, as specified by the monitor, will be categorized into major and minor deviations prior to unblinding and will be listed. Major protocol deviations will be summarized by modal dose group.

4.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized by modal dose using descriptive statistics. Continuous demographic and baseline variables include age, height, and weight; body mass index (BMI); categorical variables include sex, age group (60 to <65, 65 to <75, 75 to <85, and 85 to 90), BMI group (<18.5, 18.5 to <25, 25 to ≤30, and >30 kg/m2, or other suitable categorization), race, ethnicity, and country.

4.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2016 or latest version). The number (percentage) of subjects who take prior and concomitant medications will be summarized on the Safety Analysis Set by modal dose group, Anatomical Therapeutic Chemical class (ATC), and WHO DD -preferred term (PT).

Prior medications are defined as medications that stopped before the first dose of Extension Phase study drug.

Concomitant medications are defined as medications that (1) started before the first Extension Phase dose of study drug and continued at the time of the first dose of study drug, or (2) started on or after the date of the first Extension Phase dose of study drug to the last dose day plus 14 days. All medications will be presented in subject data listings.

4.2.6 Treatment Compliance

Compliance will be summarized by visit as reported by investigators.

Compliance for lemborexant will also be calculated on the basis of the number of tablets dispensed, lost, and returned as (total number of tablets dispensed – total number of tablets returned – total number of tablets lost)/total of number of tablets should have been taken.

Summaries will provide descriptive summary statistics and number (percentage) of subjects below 80%, between 80% and 120%, and greater than 120%.

4.3 Efficacy Analyses

SDI will be summarized by visit and modal dose based on the Safety Analysis Set.

4.4 Safety Analyses

Safety analyses will be performed on the Safety Analysis Set. Safety data, presented by modal dose group, will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, eC-SSRS. Study Day 1 for all safety analyses is defined as the date of the first dose of study drug in the Core Study.

4.4.1 Extent of Exposure

The extent of exposure (mean daily dose, cumulative dose, duration of exposure) to study drug will be summarized descriptively for lemborexant by modal dose based on the Safety Analysis Set.

4.4.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE for Extension Phase is defined as an AE that emerges during Extension Phase treatment, having been absent during the interval between the end of the Core and before Extension Phase Baseline) or

- Reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings. AEs will be classified as TEAEs up to 14 days after the last study treatment.

An overview of the TEAEs will be summarized by modal dose group, including the number and percentage of subjects who experience TEAEs, treatment-related TEAEs, severe TEAEs, TEAEs leading to death and discontinuation from study/study drug.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of non-serious TEAEs with an incidence of greater than 5% will be summarized.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]). Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each modal dose. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each modal dose. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug, the number (percentage) of subjects with TEAEs leading to dose reduction, and The number (percentage) of subjects with TEAEs leading to dose interruption will be summarized by MedDRA SOC and PT and by modal dose. Subject data listings of all AEs leading to discontinuation, leading to dose reduction, and leading to dose interruption will be provided.

The number (percentage) of subjects with TEAEs of cataplexy that are characterized according to the customized MedDRA query PT as potential cataplexy-related events (Section 9.2.8 of the Protocol), or as seizure-related events will be summarized as deemed necessary. Adjudicated events may also be presented separately.

The following adverse event tables will be also summarized by dose at first AE onset: The number (percentage) of subjects with TEAE by MedDRA SOC and PT, the number (percentage) of subjects with TEAE summarized by PT sorted by decreasing frequency, and the summary of selected AEs. A flag for dose at first AE onset will be created, and this set of tables will be then produced accordingly by ONSET dosing group (5 mg, 10 mg, and 15 mg) within the modal dose.

4.4.3 Laboratory Values

Clinical laboratory values will be evaluated for each laboratory parameter by subject for Extension Phase.

Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the clinical study report for this study. Descriptive summary statistics (eg, mean, SD, median, minimum, maximum for continuous variables, and number and percentage for categorical variables) for the laboratory parameters and changes from baseline will be evaluated by modal dose and visit.

Laboratory test results will be assigned a low-normal-high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons will be based on 3 by 3 tables (shift tables) that, for a particular laboratory test, compare the Study Baseline LNH classification to the LNH classification at end of study/early termination, by modal dose.

Clinical laboratory results post-baseline will be evaluated for markedly abnormal values. A laboratory test will be considered markedly abnormal if the result worsens to meet Eisai grading criteria for laboratory values limit of Grade 2 or higher. If the Grade 2 limit is missing, the Grade 1 limit will be considered. Appendix 12.1 presents the Eisai grading criteria for laboratory values that were used to identify subjects with markedly abnormal laboratory values. For the incidence of markedly abnormal laboratory values, each subject may be counted once in the laboratory parameter value high and in the laboratory parameter low categories as applicable.

While this section covers laboratory data starting from Extension Phase baseline, laboratory data before Extension Phase might be presented if deemed appropriate.

4.4.4 Vital Signs

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, pulse, respiration rate, temperature) and weight, and changes from Baseline will be presented by visit and treatment group.

Vital sign values will be listed. Clinically notable vital sign values will be identified on the listings as those above (H) or below (L) a clinically notable range (Table 1). Categorical analyses of subjects (number and percent) who fall outside the below clinically notable vital sign ranges will also be presented by modal dose group and visit.

Table 1 Vital Sign and Weight

Variable	Criterion value[a]	Change relative to baseline[a]	Clinically notable range
Heart rate	>120 bpm	Increase of ≥ 15 bpm	H
	<50 bpm	Decrease of ≥15 bpm	L
Systolic BP	>180 mmHg	Increase of ≥20 mmHg	H
	<90 mmHg	Decrease of ≥20 mmHg	L
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L

BP = blood pressure, bpm = beats per minute, H = high, L = low.
Clinically notable means that a value must meet the criterion value and must attain the specified magnitude of change relative to baseline.

4.4.5 Electrocardiograms

Descriptive statistics for ECG parameters and changes from Baseline will be presented by modal dose group. Shift tables will present changes from Baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by visit. Later on, shift tables may be presented by post baseline year instead of visit as deemed appropriate.

For each subject, the maximum observed corrected QT interval calculated using Fridericia's formula (QTcF), and the maximum prolongation from baseline in QTcF will be compiled. Categorical analyses of subjects (number and percent) with maximum observed QTcF values >450 msec, >480 msec, and >500 msec and maximum prolongations (from Baseline) in QTcF >30 msec and >60 msec will be presented by modal dose group and by time point. Categorical analyses of subjects (number and percent) with maximum observed PR values >220 msec, and QRS values > 120 msec will be presented by modal dose group and by visit.

4.4.6 Other Safety Analyses

The results of eC-SSRS assessments will be listed for each subject. The incidence of treatment-emergent suicidal ideation or suicidal behavior will be summarized by modal dose group and visit using descriptive statistics as appropriate.

5 INTERIM ANALYSES

Interim analyses will be performed for this study to provide data for a synoptic report to support new drug applications.

6 CHANGES IN THE PLANNED ANALYSES

No efficacy analysis set has been defined for extension phase and safety set will be used for all analysis.

7 DATA ANALYSIS GENERAL CONSIDERATIONS

The Safety Set will be used for all analyses.

7.1.1 Examination of Subgroups

No subgroup analysis is planned for this Extension Phase.

7.1.2 Handling of Missing Data, Dropouts, and Outliers

Data will not be imputed, unless otherwise specified; i.e., all missing values will remain as missing in all statistical summaries and listings, unless otherwise specified.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

7.1.3 Other Considerations

Individual subject data in the database will be presented in data listings.

7.1.4 Visit Window

All efficacy and safety data will be presented using derived visits as follows.

Visit	Target Visit Day (in study days)	Visit Window (in study days)
Ext. Visit 6B		On or prior to the study day of first dose of Extension Phase
Ext. Visit 7	73	Post study day of first dose of Extension Phase - 88
Ext. Visit 8	103	89-118
Ext. Visit 9	133	119-148
Ext. Visit 10	163	149-178
Ext. Visit 11	193	179-208
Ext. Visit 12	223	209-238
Ext. Visit 13	253	239-268
Ext. Visit 14	283	269-298
Ext. Visit 15	**313**	299-328
..etc	X	(X -14, X+15)

8 PROGRAMMING SPECIFICATIONS

All efficacy and safety data will be presented using derived visit window described in this SAP. The rules for programming derivations and dataset specifications are provided in separate documents.

9 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS v 9.3 or later.

10 MOCK TABLES, LISTINGS, AND GRAPHS

The study table, listing, and graph (TLG) shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

11 REFERENCES

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12 APPENDICES

Appendix 12.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table of Sponsor's Grading for Laboratory Values is taken from the protocol.

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL	<55 – 40 mg/dL	<40 – 30 mg/dL	<30 mg/dL

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
	<LLN – 3.0 mmol/L	<3.0 – 2.2 mmol/L	<2.2 – 1.7 mmol/L	<1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: 28 May 2009 (v4.03: 14 Jun, 2010).
ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, , LLN = lower limit of normal, N/A = not applicable, ULN = upper limit of normal, WBC = white blood cell.

SIGNATURE PAGE

Author:

PPD

Date

Approval:

PPD

Date

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Date