16.1.9 Documentation of Statistical Methods

Listed below are all versions of the Statistical Analysis Plan for this study. The corresponding documents are provided on the following pages.

Statistical Analysis Plan	Version	Date
Revised original	2.0	03 Jul 2024
Original	1.0	18 Jan 2023

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2006-J082-204
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Assess the Pharmacodynamics of Lemborexant in Korean Subjects with Insomnia Disorder
Date:	3/ Jul/ 2024
Version:	Version.2.0

Major Revisions to Version 2.0

Date of Revisions: 3 Jul 2024

Change	Rationale	Affected Sections
Added a word of "randomized" to "study drug" in the definition of Safety Analysis Set.	To clarify the definition of Safety Analysis Set.	Section 5.2.1
Added the LPS analysis based on non-log transformed data.	To evaluate original unit for LPS as a sensitivity analysis.	Section 5.4.1
Deleted the summary of urinalysis parameters.	Provide only data listings to make consistent with the approach in the precedent studies.	Section 5.6.3
Defined the exploratory analyses for polysomnography parameters.	To clarify the exploratory analyses for other polysomnography parameters.	Section 5.8

Major Revisions to Version 1.0

Date of Revisions: 12 JAN 2023

Change	Rationale	Affected Sections
Deleted a word of "major" from "a major protocol deviation" in the definition of Per Protocol Analysis Set.	Protocol deviation that is likely to affect the LPS data of PSG is not limited to major protocol deviation.	Section 5.2.1

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
AR	autoregressive covariance matrix
ATC	anatomical therapeutic class
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory - II
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
EOS	end of study
FAS	full analysis set
IRLS	International Restless Legs Scale
ISI	Insomnia Severity Index
LEM5	lemborexant 5 mg
LEM10	lemborexant 10 mg
LLOQ	Lower Limit of Quantification
LPS	latency to persistent sleep
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
PBO	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetic
PSG	Polysomnography
QTcF	corrected QT interval by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SE	sleep efficiency

Abbreviation	Term
SI	Système International
SDSB	Sleep Disorder Screening Battery
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TIB	time in bed
TST	total sleep time
WASO	wake after sleep onset
WHO DD	World Health Organization Drug Dictionary

3 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-J082-204.

SAP is based on protocol (V4.0) (14-Sep-2023).

3.1 Study Objectives

3.1.1 Primary Objective

To evaluate, using polysomnography (PSG), the treatment difference between lemborexant 5 mg (LEM5) and placebo (PBO) on latency to persistent sleep (LPS) on Day 30.

3.1.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate, using PSG, the treatment difference between lemborexant 10 mg (LEM10) and PBO on LPS on Day 30
- To evaluate, using PSG, the treatment difference between LEM5 and PBO on sleep efficiency (SE) on Day 30
- To evaluate, using PSG, the treatment difference between LEM10 and PBO on SE on Day 30
- To evaluate safety and tolerability of lemborexant following multiple doses
- To evaluate the pharmacokinetics of lemborexant

3.1.3 Exploratory Objectives

CCI

[redacted]

3.2 Overall Study Design and Plan

This study is a multicenter, multiple dose, randomized, double-blind, placebo-controlled, parallel-group study in Korean subjects with insomnia disorder. Subjects will be randomized to LEM5, LEM10 or PBO in a ratio of 2:2:1 and will receive study drug for 30 days.

The study will consist of 2 phases: Prerandomization Phase and Randomization Phase.

The Prerandomization Phase will comprise 3 periods that will last up to a maximum of 35 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase

will comprise a Treatment Period during which subjects will be treated for 30 nights, and a minimum 28-day Follow-up Period before an End of Study (EOS) Visit.

The estimated study duration for each subject on study is anticipated to be a maximum of 93 days consisting of the Screening Period plus Run-in Period plus Baseline Period maximum of 35 days plus Treatment Period plus Follow-up Period and EOS Visit maximum of 58 days. A subject who completes the Treatment Period (assessments through discharge from the clinic on Day 31) will be considered to have completed the study.

An overview of the study design is presented in Figure 1.

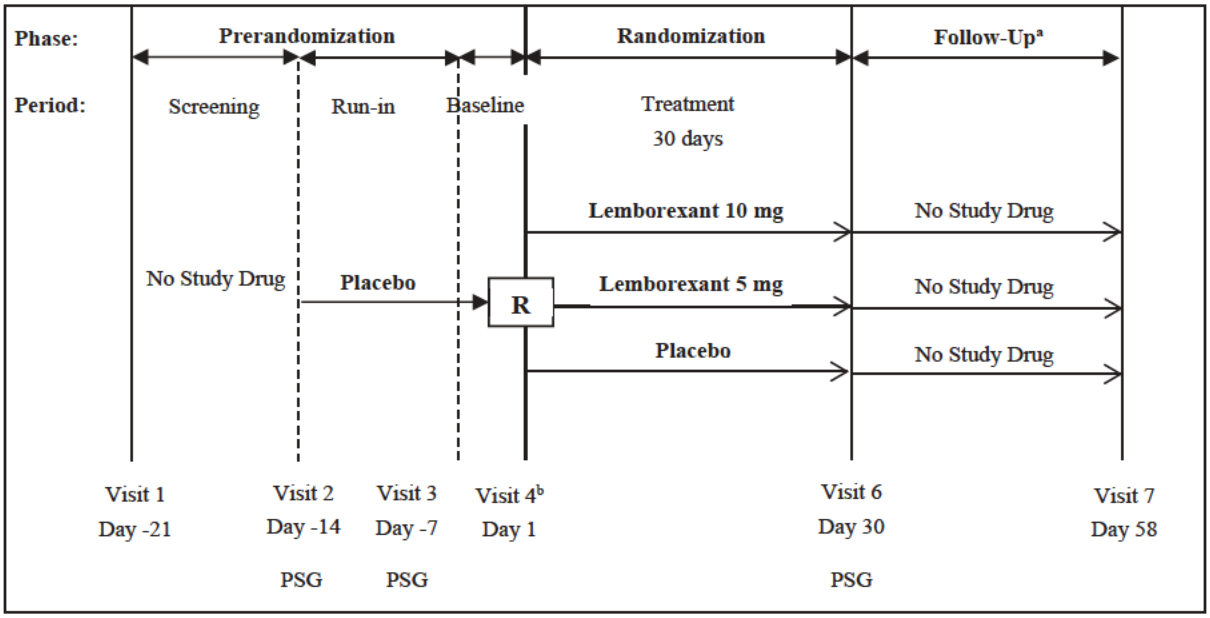

Figure 1 Schematic Diagram of E2006-J082-204 Study Design

PSG = polysomnography, R = randomization

a: a minimum 28-day Follow-up

b: On Day 1 (at Visit 4), the Run-in Period will end and the Baseline Period will begin. The Treatment Period will begin on Day 1 immediately after the Baseline Period as study drug will be administered before bedtime

4 DETERMINATION OF SAMPLE SIZE

The sample size was calculated with re-sampling simulation using Study 201 (E2006-G000-201) data in order to power the study to detect point estimate of mean difference below a certain threshold with sufficient probability. The certain threshold is defined as –0.44 as derived from the upper limit of 95% CI of pairwise difference between LEM5 and PBO for log(LPS) from Study 201. Using the mean difference to PBO of log(LPS) in LEM5 from the baseline to Days 14/15 from each simulation (10,000 times) that using a grid search and assuming a 2:1 ratio (LEM5: PBO), demonstrated the difference < –0.44 could be achieved with more than 85% power. It is assumed that the mean difference to PBO of log(LPS) in lemborexant groups from baseline to Day 30 in this study will be similar with those from baseline to Days 14/15 in Study 201. When the number of subjects randomized to LEM5 and PBO are 24 and 12, respectively, the number of subjects who complete with evaluable efficacy data will be 22 and 11, respectively. Based on this evaluation, this study will provide power at 88.64% for comparing LEM5 and PBO. Since LEM10 is set as a reference arm, therefore the sample size for LEM10 will be 24 as the same of LEM5 above.

5 STATISTICAL METHODS

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All descriptive statistics for continuous variables will be reported using number of observations (n), mean (arithmetic unless otherwise specified), standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum. Categorical variables will be summarized as number and percentage of subjects.

Treatment groups will be defined as PBO, LEM5, LEM10, and LEM total. Treatment arms will be defined as PBO, LEM5, and LEM10.

All statistical tests will be based on the 5% level of significance (two-sided).

5.1 Study Endpoints

5.1.1 Primary Endpoint

The primary endpoint will be change from baseline of LPS on Day 30 of LEM5 compared to PBO.

5.1.2 Secondary Endpoints

Efficacy Endpoints

- Change from baseline of LPS on Day 30 of LEM10 compared to PBO
- Change from baseline of SE on Day 30 of LEM5 compared to PBO

- Change from baseline of SE on Day 30 of LEM10 compared to PBO

Safety Endpoints

- Safety and tolerability of lemborexant

Other Endpoint

- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10

5.1.3 Exploratory Endpoints

Efficacy Endpoints

cci

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 dose of randomized study drug and had at least 1 postdose safety assessment.

Full Analysis Set (FAS): The FAS is the group of randomized subjects who received at least 1 dose of randomized study drug and had LPS data from the PSG on Day 30.

Per Protocol (PP) Analysis Set: The PP Analysis Set is the FAS who received protocol-assigned study drug and did not have a protocol deviation that is likely to affect the LPS data of PSG as follows.

- Incorrect study drug kit dispensed
- Protocol-assigned study drug not administered
- Prohibited concomitant medication
- Primary efficacy assessment out of window
- Missing primary efficacy assessment
- Duplicate randomization
- Violated inclusion/exclusion criteria

PK Analysis Set: The PK analysis set is the group of subjects who had at least 1 quantifiable plasma concentration of lemborexant or its metabolites, with adequately documented dosing history.

The number of subjects randomized, the number and the percentage of subjects included in each analysis set will be presented by each treatment group. The reasons for exclusion from each analysis set will be summarized by each treatment group. Subject listing of analysis set and reasons for exclusion from FAS, PP Analysis Set, PK Analysis Set and Safety Analysis Set will be provided.

5.2.2 Subject Disposition

The number of subjects screened and the number failing screening (overall and by reason for failure) will be summarized for all enrolled subjects (subjects who signed informed consent). Screen failure data will be listed.

The number of subjects completing the study will be presented. Subjects who prematurely terminated their participation in the study will be summarized by their primary reason for study termination. Subjects who prematurely discontinued from study treatment will also be presented and summarized by primary reason for premature treatment discontinuation. Other reasons for study treatment and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by each treatment group.

5.2.3 Protocol Deviations

Protocol deviations will be identified, reviewed and documented by the clinical team prior to database lock/treatment unblinding. All protocol deviations will be categorized according to important/minor and standard classifications including but not limited to the following:

- GCP-related deviations
  - Failure to obtain informed consent / ICF absent
  - Study-specific procedures / data captured before subject signed ICF
- Eligibility criteria
  - Subject was enrolled while all inclusion criteria were not met.
  - Subject was enrolled while an exclusion criteria was met.
- IMP deviations
  - Subject received less than 80% or more than 120% of the total number of doses that should have been administered in study period.
- Prohibited concomitant medications / procedure
  - Subjects who received prohibited concomitant therapies and/or drugs in study protocol 9.4.7.2 during the study by the last dose of study drug.

Important protocol deviations will be summarized for category by each treatment group. In addition, COVID-19 related deviations will also be summarized by each treatment group. Subject listing of important protocol deviation and COVID-19 related deviation will be provided.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height, weight, and body mass index (BMI); categorical variables include sex (male and female), age group (< 65 years, ≥ 65 years), BMI group (< 18.5, 18.5 ≤ 25.0, 25.0 ≤ 30.0, ≥ 30.0), and race.

Characteristics of insomnia at Study Baseline will be summarized using LPS, SE, WASO, TST from PSG, ISI (items 1 to 7, 4 to 7), BDI-II, BAI, STOP Bang, and IRLS.

5.2.4.1 Medical History

All medical histories as documented by the Medical History and Current Medical Conditions CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA [Version 27.0]).

The number and percent of subjects with medical history will be summarized by System Organ Class (SOC), preferred term for each treatment group based on Safety Analysis Set.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (WHO DD MAR24B3G).

The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by each treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term (PT). If a subject takes the same medications for the same class level or drug name, the subject will be counted only once for that class level or drug name. A separate summary will be provided for subjects who take concomitant medications during Run-in and Treatment Periods. All prior and concomitant medications and non-pharmacologic medications will be presented in subject data listings. If the Safety Analysis Set and FAS differ substantially, then the prior and concomitant medication summaries will be repeated on the FAS.

Prior medications will be defined as medications that stopped before the first dose of study drug where study drug includes PBO during the Run-in Period.

Concomitant medications will be defined as medications that (1) started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose.

5.2.6 Treatment Compliance

Treatment compliance (in %) is defined as follows:

$$\frac{100 \times (\text{total number of tablets dispensed - total number of tablets returned or lost})}{\text{number of tablets expected to be taken}}$$

Compliance during the Run-in and Treatment Periods will be summarized separately using descriptive statistics based on Safety Analysis Set Summaries will provide descriptive summary statistics and number (percentage) of subjects <80%, ≥80% to ≤100%, >100% to ≤120%, and >120%by each treatment group. Subject listing of study drug compliance will be provided.

5.3 Data Analysis General Considerations

The main analysis group for the primary endpoint is the FAS. The efficacy analyses will be performed on the FAS except per protocol analysis which will be performed on the PP analysis set. The values of each variable and the difference from baseline will be used for summary statistics by each visit and each treatment arm.

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

In the statistical models, baseline (log-transformation) of the efficacy variables will be applied as adjustment factor.

5.3.3 Multiple Comparisons/Multiplicity

No multiplicity adjustment is planned for primary endpoint.

5.3.4 Examination of Subgroups

No subgroup analysis will be performed.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

No imputation will be performed for missing data.

5.3.6 Other Considerations

Not Applicable.

5.4 Efficacy Analyses

5.4.1 Primary Efficacy Analyses

The LPS change from baseline to Day 30 after log-transformed will be analyzed using analysis of covariance (ANCOVA), with treatment arms (PBO, LEM5, and LEM10) and baseline LPS (log-transformation) as fixed effects on the FAS. Since LPS is known to be non-normally distributed, a log-transformation will be used in the analysis.

The pairwise comparison of LEM5 compared to PBO will be applied in this analysis. The least square (LS) means between LEM5 and PBO of change from baseline to Day 30 of LPS after log-transformed will be performed. The 95% confidence interval (CI) and *P* value of the treatment differences will be provided. This is not confirmation study so that *P* value will be only a reference value.

5.4.1.1 Sensitivity Analysis

The same primary efficacy analysis described in Section 5.4.1 will be repeated based on non-log transformed data as a sensitivity analysis.

5.4.1.2 Supplemental Analysis

PP analysis will be performed the same primary efficacy analysis described in Section 5.4.1 based on PP analysis set.

5.4.2 Secondary Efficacy Analyses

The pairwise comparison of LEM10 compared to PBO for LPS with log-transformed will be applied within the same model of primary efficacy analysis. The same analyses as the sensitivity and supplemental analyses for the primary efficacy analysis will also be conducted.

The SE change from baseline to Day 30 of each active arm (LEM5 and LEM10) compared to PBO will be analyzed using ANCOVA, with treatment arms (PBO, LEM5, and LEM10) and baseline SE as fixed effects on the FAS. The LS means between each active arm (LEM5 and LEM10) and PBO of change from baseline to Day 30. The 95% CI and *P* value of the treatment differences will be provided.

The SE described above will be repeated based on PP analysis set.

Longitudinal plot for LPS and SE of median and LS geometric means or LS means for the changes from baseline will be presented by each treatment arm.

Subject listing of individual visit results and averaged analysis results for PSG parameters (LPS and SE) will be provided.

5.4.3 Other Efficacy Analyses

Other efficacy analysis will be defined in 5.8 Exploratory Analyses.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual lemborexant and its metabolites M4, M9, and M10 plasma concentration listings. The PK Analysis Set will be used for summaries of plasma concentrations of lemborexant and its metabolites M4, M9, and M10 by nominal sampling time and dose.

5.5.1.1 Plasma Concentration Analysis

Plasma concentrations for lemborexant and its metabolites M4, M9, and M10 will be summarized using summary statistics (n, mean, SD, median, minimum, and maximum) by dose group, and nominal sampling time.

Plasma concentrations of lemborexant and its metabolites M4, M9, and M10 will be listed for each subject by dose group and actual sampling time.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment 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. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

5.6.1 Extent of Exposure

The extent of exposure (mean daily dose, cumulative dose, duration of exposure) to study drug will be summarized using descriptive statistics by treatment group. Duration of exposure of study drug will be defined as the number of days between the date the subject received the first dose of study drug during Treatment Period and the date the subject received the last dose of study drug during Treatment Period, inclusive. Subject listing of dosing and extent of exposure will be provided.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the

MedDRA (Version 27.0) lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and SOC are also captured in the database.

A TEAE is defined as an AE that emerges during treatment (on or after the first dose of study drug up to 28 days after the subject's last dose), having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (before the Run-in Period) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized for Run-in Period and Treatment Period by treatment group separately. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. TEAEs by PT during Treatment Period will also be summarized by decreasing frequency. A subject will be counted only once within a 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 subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

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

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

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

5.6.3 Laboratory Values

Laboratory results except urinalysis parameters will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4.3 in protocol, the actual value for each visit (Screening, Day 1, Day 31, the end of

treatment and the end of study) and the change from baseline to Day 31, each postbaseline visit, the end of treatment and the end of study will be summarized by visit and treatment group using descriptive statistics.

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 for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit, the end of treatment and the end of study. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the Treatment period. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Appendix 1 in protocol (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Subject listing of laboratory results for hematology, chemistry, urinalysis, urine drug test and pregnancy test will be provided.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group. Analysis of changes from baseline will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

In addition, clinically notable vital sign values will be identified using the criteria in Table 1. The clinically notable vital sign values will be summarized using frequency count at each visit by treatment group. Subject listing of vital signs will be provided.

Table 1 Vital Sign Criteria

	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

Table 1 Vital Sign Criteria

	Criterion value[a]	Change relative to baseline[a]	Clinically notable range
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L
Weight	--	Increase of ≥7%	H
	--	Decrease of ≥7%	L
Respiratory Rate	>20 bpm	--	H
	< 10 bpm	--	L

BP = blood pressure, H = high, L = low.

a. Clinically notable means that a value must meet the criterion value and must attain the specified magnitude of change relative to baseline.

5.6.5 Electrocardiograms

ECG assessments will be performed as designated in the Schedule of Procedures/Assessments (Table 3 in protocol). Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia (QTcF) during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

Subject listing of ECG will be provided.

5.6.6 Other Safety Analyses

Not applicable.

5.7 Other Analyses

Not applicable.

5.8 Exploratory Analyses

CCI

[redacted]

CCI

[redacted]

5.9 Extension Phase Analyses

Not Applicable

6 INTERIM ANALYSES

No interim analysis is planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

Major changes of analysis plan between SAP version 1.0 to version 2.0 are listed in revision history.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Visit Window

Study Day 1 is defined as the date of the first dose of study drug during the Treatment Period. The nominal visit (ie, study visit captured on the CRF) will be used as the analysis visits in all by-visit summaries. The Early Term visit will be considered as unscheduled visit and will not be included in the by-visit summary. Where applicable, the Early Term visit will be used along with the Day 31 visit for completers as the End of Treatment visit for the safety analyses.

8.2 Baseline Assessment

Unless otherwise specified, baseline measurement is the last observed measurement, including unscheduled assessments, prior to the first dose of study medication of treatment period for a given assessment.

- ISI: Last available ISI measurement at Visit 1
- BDI-II and BAI : Last available measurement at Visit 1
- SDSB (STOPBang and IRLS) : Last available measurement at Visit 1

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

9.1 Pharmacokinetic Data Handling

9.1.1 Lower Limit of Quantification of Lemborexant and its metabolites M4, M9, and M10 Plasma Concentration

The LLOQ of lemborexant and its metabolites M4, M9, and M10 are 0.0500 ng/mL.

9.1.2 Below Limit of Quantification Handling for Calculating Summary Statistics of Lemborexant and its metabolites M4, M9, and M10 Plasma Concentration

When calculating the mean (or median) value for the concentration at a given time point, all

BLQ values are assigned as zero.

9.1.3 Handling of Anomalous Concentration Values

Anomalous values are those that are inconsistent with known or expected PK behavior of the drug, but are not defined on the basis of statistical tests for outliers. Individual concentrations deemed to be anomalous can be excluded from the summary statistics of Lemborexant and its metabolites M4, M9, and M10 Plasma Concentration. Anomalous values are identified in the clinical study report (CSR). Clear justification must be provided in the CSR for exclusion of any data.

9.1.4 General Rules for Presentation of Drug Concentrations

When presenting individual/raw values and summary statistics, the following rule will be applied: for drug concentrations, all summary statistics (mean, median, and SD) will have 3 significant digits.

Typical variable	Standard Unit	N	Digit rule	Raw Minimum Maximum	Mean Median	SD
E2006 and its metabolites M4, M9, and M10 concentration	ng/mL	X	Significant digits	3	3	3

10 STATISTICAL SOFTWARE

Analysis will be performed using SAS (release 9.4 or newer) and Microsoft Excel (2010 or newer).

11 MOCK TABLES, LISTINGS, AND GRAPHS

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

12 REFERENCES

Not applicable.

SIGNATURE PAGE

Author:

[electronic approval in eDMS] Date

PPD

Eisai Co., Ltd.

Approval:

[electronic approval in eDMS] Date

PPD

PPD Biostatistics PPD

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Clinical Pharmacology,

PPD

Eisai Co., Ltd.

[electronic approval in eDMS] Date

PPD

Study Director

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Eisai Co., Ltd.

Audit Trail Entries

Report for document "e2006-j082-204--statistical-methods-interim-analysis-plan"

11-Jul-2024 01:04 EST

Basic Object Properties:

Object Name	e2006-j082-204--statistical-methods-interim-analysis-plan
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Version Creation Date	08-Jul-2024 21:08 EST
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Document Type	Clinical
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User Acknowledgements

Version Number	Outcome	Event Name	Activity	Meaning	User Name	Server Date and Time
1.3	Approved	Acknowledgement	Approval	Biostatistics Approval	PPD	08-Jul-2024 21:08 EST
1.3	Approved	Acknowledgement	Approval	Clinical Pharmacology Approval		08-Jul-2024 20:05 EST
1.3	Approved	Acknowledgement	Approval	Clinical Approval		08-Jul-2024 20:00 EST
1.3	Approved	Acknowledgement	Approval	Biostatistics Approval		08-Jul-2024 17:05 EST
0.4	Approved	Acknowledgement	Approval	Clinical Pharmacology Approval		24-Jan-2023 01:26 EST
0.4	Approved	Acknowledgement	Approval	Clinical Approval		24-Jan-2023 00:33 EST
0.4	Approved	Acknowledgement	Approval	Biostatistics Approval		24-Jan-2023 00:20 EST
0.4	Approved	Acknowledgement	Approval	Biostatistics Approval		24-Jan-2023 00:02 EST
0.2	Approved	Acknowledgement	Approval	Clinical Approval		16-Jan-2023 00:19 EST
0.2	Approved	Acknowledgement	Approval	Biostatistics Approval		15-Jan-2023 23:37 EST
0.2	Approved	Acknowledgement	Approval	Clinical Pharmacology Approval		15-Jan-2023 23:36 EST

Relationships Manager

None

Change Status

Original Status	New Status	Original Version	New Version	Server Date and Time	User Name
For Approval	Approved	1.3	2.0	08-Jul-2024 21:08 EST	edge
Approved	Superseded	1.0	1.0	08-Jul-2024 21:08 EST	edge
Draft	For Approval	1.3	1.3	08-Jul-2024 17:00 EST	PPD
For Approval	Draft	1.3	1.3	08-Jul-2024 10:20 EST	
Draft	For Approval	1.3	1.3	08-Jul-2024 08:55 EST	
Approved	Draft	1.0	1.1	02-Jul-2024 01:02 EST	
For Approval	Approved	0.4	1.0	24-Jan-2023 01:26 EST	edge
Draft	For Approval	0.4	0.4	23-Jan-2023 23:59 EST	PPD
For Approval	Draft	0.2	0.2	18-Jan-2023 00:37 EST	
Draft	For Approval	0.2	0.2	15-Jan-2023 23:33 EST	
	Draft	0.1	0.1	12-Jan-2023 21:53 EST	

Retention Actions

None

Task Signoff Failure

None

Restricted Property Update

None

Property Modification - Generic Audit Trail Entries

None

Reassign Work

None

Periodic Review

None

Forced Task Completion

None

Terminate Workflow

Event Name	Numeric version label	Server Date and Time	User Name
Terminate Workflow	1.3	08-Jul-2024 10:20 EST	PPD
Terminate Workflow	0.2	18-Jan-2023 00:37 EST	PPD

Repeat Task

None

Print

None

Print Status Change

None

Reclassify

None

Bulk Property Update

None

System Generated Audit Trails

Event Name	String 1	String 2	String 3	String 4	String 5	Server Date and Time	User Name	Version Label
dm_checkin						08-Jul-2024 21:08 EST	dmadmin	2.0
dm_checkin						03-Jul-2024 02:52 EST	PPD	1.3
dm_checkin						03-Jul-2024 01:44 EST	PPD	1.2
dm_checkin						02-Jul-2024 01:02 EST	dmadmin	1.1
dm_checkin						24-Jan-2023 01:26 EST	dmadmin	1.0
dm_checkin						18-Jan-2023	PPD	0.4

						03:18 EST		
dm_checkin						18-Jan-2023 02:44 EST	PPD [redacted]	0.3
dm_checkin						12-Jan-2023 22:04 EST	PPD [redacted]	0.2

Application Number Change

None

Other

Event Name	String 1	String 2	String 3	String 4	String 5	Server Date and Time	User Name	Version Label
Export Document						05-Jul-2024 03:21 EST	PPD [redacted]	1.3
Export Document						03-Jul-2024 08:56 EST		1.3
Export Document						03-Jul-2024 02:52 EST		1.2
Export Document						03-Jul-2024 01:42 EST		1.1
Export Document						03-Jul-2024 01:28 EST		1.1
Export Document						03-Jul-2024 00:41 EST		1.1
Export Document						13-Jan-2023 08:23 EST		0.2

11-Jul-2024 01:04 EST

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2006-J082-204
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Assess the Pharmacodynamics of Lemborexant in Korean Subjects with Insomnia Disorder
Date:	18 / Jan / 2023
Version:	Version 1.0

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
AR	autoregressive covariance matrix
ATC	anatomical therapeutic class
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory - II
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
EOS	end of study
FAS	full analysis set
LEM5	lemborexant 5 mg
LEM10	lemborexant 10mg
IRLS	International Restless Legs Scale
ISI	Insomnia Severity Index
LPS	latency to persistent sleep
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
PBO	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetic
QTcB	corrected QT interval by Bazett's formula
QTcF	corrected QT interval by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SE	sleep efficiency

Abbreviation	Term
SI	Système International
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TIB	time in bed
TST	total sleep time
WASO	wake after sleep onset
WHO DD	World Health Organization Drug Dictionary

3 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-J082-204.

SAP is based on protocol (V3.0) (29-Sep-2022).

3.1 Study Objectives

3.1.1 Primary Objective

To evaluate, using polysomnography (PSG), the treatment difference between lemborexant 5 mg (LEM5) and placebo (PBO) on latency to persistent sleep (LPS) on Day 30.

3.1.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate, using PSG, the treatment difference between lemborexant 10 mg (LEM10) and PBO on LPS on Day 30
- To evaluate, using PSG, the treatment difference between LEM5 and PBO on sleep efficiency (SE) on Day 30
- To evaluate, using PSG, the treatment difference between LEM10 and PBO on SE on Day 30
- To evaluate safety and tolerability of lemborexant following multiple doses
- To evaluate the pharmacokinetics of lemborexant

3.1.3 Exploratory Objectives

CCI

[redacted]

3.2 Overall Study Design and Plan

This study is a multicenter, multiple dose, randomized, double-blind, placebo-controlled, parallel-group study in Korean subjects with insomnia disorder. Subjects will be randomized to LEM5, LEM10 or PBO in a ratio of 2:2:1 and will receive study drug for 30 days.

The study will consist of 2 phases: Prerandomization Phase and Randomization Phase.

The Prerandomization Phase will comprise 3 periods that will last up to a maximum of 35 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase

will comprise a Treatment Period during which subjects will be treated for 30 nights, and a minimum 28-day Follow-up Period before an End of Study (EOS) Visit.

The estimated study duration for each subject on study is anticipated to be a maximum of 93 days consisting of the Screening Period plus Run-in Period plus Baseline Period maximum of 35 days plus Treatment Period plus Follow-up Period and EOS Visit maximum of 58 days. A subject who completes the Treatment Period (assessments through discharge from the clinic on Day 31) will be considered to have completed the study.

An overview of the study design is presented in Figure 1.

Estimates for End of study are as follows:

- The end of the study will be the date of the last study visit for the last subject in the study.
- The estimated duration for each subject on study is anticipated to be a maximum of 93 days (12.7 weeks) consisting of the Screening Period plus Run-in Period plus Baseline Period maximum of 35 days plus Treatment Period plus Follow-Up Period and EOS Visit maximum of 58 days. A subject who completes the Treatment Period (assessments through discharge from clinic on the morning of Day 31) will be considered to have completed the study.

An overview of the study design is presented in Figure 1.

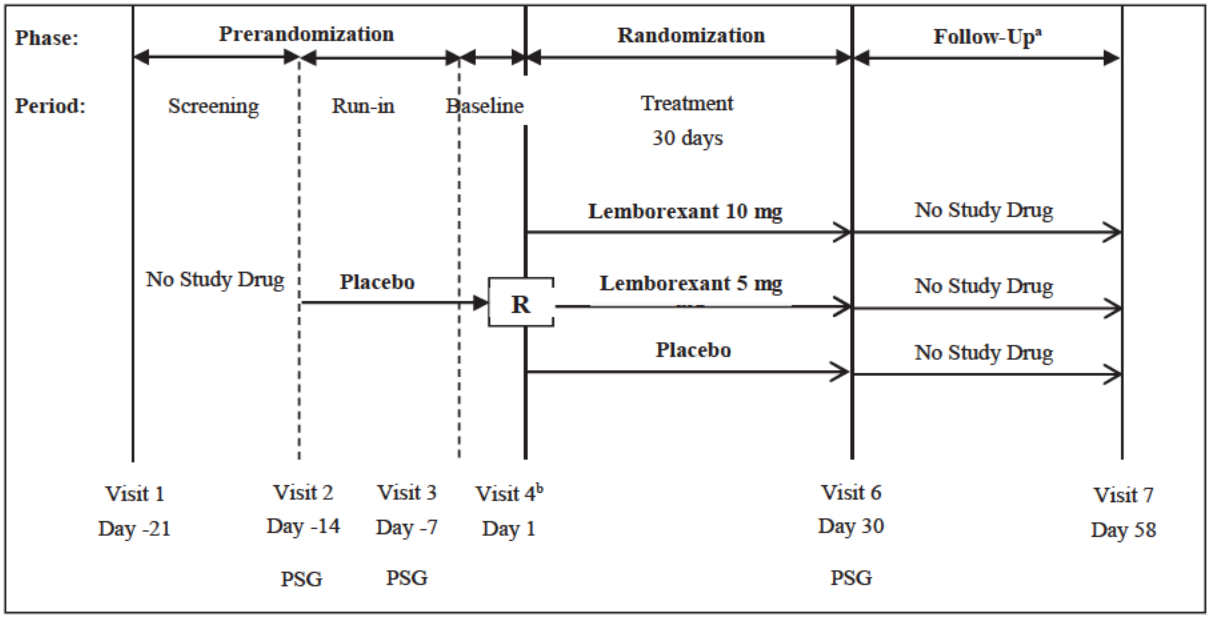

Figure 1 Schematic Diagram of E2006-J082-204 Study Design

PSG = polysomnography, R = randomization

a: a minimum 28-day Follow-up

b: On Day 1 (at Visit 4), the Run-in Period will end and the Baseline Period will begin. The Treatment Period will begin on Day 1 immediately after the Baseline Period as study drug will be administered before bedtime

4 DETERMINATION OF SAMPLE SIZE

Sample size was calculated with re-sampling simulation using Study E2006-G000-201 data in order to power the study to detect point estimate of mean difference below a certain threshold with sufficient probability. The certain threshold is defined as –0.44 as derived from the upper limit of 95% CI of pairwise difference between LEM5 and PBO for log(LPS) from Study 201. Using the mean difference to PBO of log(LPS) in LEM5 from the baseline to Days 14/15 from each simulation (10,000 times) that using a grid search and assuming a 2:1 ratio (LEM5:PBO), demonstrated the difference < –0.44 could be achieved with more than 85% power. It is assumed that the mean difference to PBO of log(LPS) in lemborexant groups from baseline to Day 30 in this study will be similar with those from baseline to Days 14/15 in Study 201. When the number of subjects randomized to LEM5 and PBO are 24 and 12, respectively, the number of subjects who complete with evaluable efficacy data will be 22 and 11, respectively. Based on this evaluation, this study will provide power at 88.64% for comparing LEM5 and PBO. Since LEM10 is set as a reference arm, therefore the sample size for LEM10 will be 24 as the same of LEM5 above.

5 STATISTICAL METHODS

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using SAS software or other validated statistical software as required.

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

All statistical tests will be based on the 5% level of significance (two-sided).

5.1 Study Endpoints

5.1.1 Primary Endpoint

The primary endpoint will be change from baseline of LPS on Day 30 of LEM5 compared to PBO.

5.1.2 Secondary Endpoints

Efficacy Endpoints

- Change from baseline of LPS on Day 30 of LEM10 compared to PBO
- Change from baseline of SE on Day 30 of LEM5 compared to PBO
- Change from baseline of SE on Day 30 of LEM10 compared to PBO

Safety Endpoints

- Safety and tolerability of lemborexant

Other Endpoint

- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10

5.1.3 Exploratory Endpoints

CCI

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

Full Analysis Set (FAS): The FAS is the group of randomized subjects who received at least 1 dose of randomized study drug and had LPS data from the PSG on Day 30.

Per Protocol (PP) Analysis Set: The PP Analysis Set is the FAS who received protocol-assigned study drug and did not have a protocol deviation that is likely to affect the LPS data of PSG as follows.

- Incorrect study drug kit dispensed
- Protocol-assigned study drug not administered
- Prohibited concomitant medication
- Primary efficacy assessment out of window
- Missing primary efficacy assessment
- Duplicate randomization
- Violated inclusion/exclusion criteria

More details of the evaluability criteria will be determined before database lock and will be specified in revised SAP.

PK Analysis Set: The PK analysis set is the group of subjects who had at least 1 quantifiable plasma concentration of lemborexant or its metabolites, with adequately documented dosing history.

The number of subjects randomized, the number and the percentage of subjects included in each analysis set will be presented by dose group and overall.

5.2.2 Subject Disposition

The number of subjects screened and the number failing screening (overall and by reason for failure) will be summarized. Screen failure data will be listed.

The number of subjects completing the study will be presented. Subjects who prematurely terminated their participation in the study will be summarized by their primary reason for study termination. Subjects who prematurely discontinued from study treatment will also be presented and summarized by primary reason for premature treatment discontinuation. Other reasons for study treatment and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by treatment group.

5.2.3 Protocol Deviations

Protocol deviations will be identified, reviewed and documented by the clinical team prior to database lock/treatment unblinding. All protocol deviations will be categorized according to important/minor and standard classifications including but not limited to the following:

- Failure to obtain informed consent / ICF absent
- Study-specific procedures / data captured before subject signed ICF
- Subject was enrolled while all inclusion criteria were not met.
- Subject was enrolled while an exclusion criteria was met.
- Subject received less than 80% or more than 120% of the total number of doses that should have been administered in study period.

Important protocol deviations will be summarized by category and treatment group.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height, weight, and body mass index (BMI); categorical variables include sex, age group, BMI group, and race.

Characteristics of insomnia at Study Baseline will be summarized using LPS, SE and WASO from PSG, ISI, BDI-II, BAI, Stop-BANG and IRLS.

5.2.4.1 Medical History

All medical histories as documented by the Medical History and Current Medical Conditions CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA [Version 23.0 or higher]).

The number and percent of subjects with medical history will be summarized by System Organ Class (SOC), preferred term for each treatment group based on Safety Analysis Set.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (WHO DDE/HD Mar 2018 or latest version). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term (PT). If the Safety Analysis Set and FAS differ substantially, then the prior and concomitant medication summaries will be repeated on the FAS.

Prior medications will be defined as medications that stopped before the first dose of study drug where study drug includes PBO during the Run-in Period.

Concomitant medications will be defined as medications that (1) started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Treatment compliance (in %) is defined as follows:

$$\frac{100 \times (\text{total number of tablets dispensed} - \text{total number of tablets returned or lost})}{\text{number of tablets expected to be taken}}$$

Compliance for each study drug will be calculated on the basis of number of tablets dispensed, lost and returned. Summaries will provide descriptive summary statistics and number (percentage) of subjects below 80%, between 80% and 120%, and greater than 120%.

5.3 Data Analysis General Considerations

The main analysis group for the primary endpoint is the FAS. The efficacy analyses will be performed on the FAS except per protocol analysis will be performed on the PP analysis set. The each variables and the difference from baseline will be used for summary statistics by each visit and treatments. Data will be plotted as appropriate.

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

In the statistical models, baseline (log-transformation) of the efficacy variables will be applied as adjustment factor.

5.3.3 Multiple Comparisons/Multiplicity

No multiplicity adjustment is planned for primary endpoint.

5.3.4 Examination of Subgroups

No subgroup analysis will be performed.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

No imputation will be performed for missing data.

5.3.6 Other Considerations

Not Applicable.

5.4 Efficacy Analyses

5.4.1 Primary Efficacy Analyses

The LPS change from baseline to Day30 after log-transformed will be analyzed using analysis of covariance (ANCOVA), with treatment and baseline (log-transformation) as fixed effects on the FAS. The analysis will be modeled pairwise by the relevant treatment groups for the comparison. Since LPS is known to be non-normally distributed, a log-transformation will be used in the analysis.

The pairwise comparison of LEM5 compared to PBO will be applied in this analysis. The least square (LS) means between LEM5 and PBO of change from baseline to Day30 of LPS after log-transformed will be performed. The 95% confidence interval (CI) and -p-value of the treatment differences will be provided. This is not confirmation study so that p-value will be only a reference value.

5.4.2 Secondary Efficacy Analyses

The pairwise comparison of LEM10 compared to PBO for LPS with log-transformed will be applied within the same model of primary efficacy analysis.

The SE change from baseline to Day30 of each active arm (LEM5 and LEM10) compared to PBO will be analyzed using ANCOVA, with treatment and baseline as fixed effects on the FAS. The analysis will be modeled pairwise by the relevant treatment groups for the

comparison. The LS means between each active arm (LEM5 and LEM10) and PBO of change from baseline to Day30. The 95% CI and -p value of the treatment differences will be provided.

The LPS with log-transformed and SE described above will be repeated based on PP analysis set.

5.4.3 Other Efficacy Analyses

Other efficacy analysis will be defined in 5.8 Exploratory Analyses.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual lemborexant and its metabolites M4, M9, and M10 plasma concentration listings. The PK Analysis Set will be used for summaries of plasma concentrations of lemborexant and its metabolites M4, M9, and M10 by nominal sampling time and dose.

5.5.1.1 Plasma Concentration Analysis

Plasma concentrations for lemborexant and its metabolites M4, M9, and M10 will be summarized using summary statistics (n, mean, SD, median, minimum, and maximum) by dose group, and nominal sampling time.

Plasma concentrations of lemborexant and its metabolites M4, M9, and M10 will be listed for each subject by dose group and actual sampling time.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment 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. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

5.6.1 Extent of Exposure

The extent of exposure (mean daily dose, cumulative dose, duration of exposure) to study drug will be summarized using descriptive statistics by treatment group. Duration of

exposure of study drug will be defined as the number of days between the date the subject received the first dose of study drug during Treatment Period and the date the subject received the last dose of study drug during Treatment Period, inclusive.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 23.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and SOC are also captured in the database.

A TEAE is defined as an AE that emerges during treatment (on or after the first dose of study drug up to 28 days after the subject's last dose), having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (before the Run-in Period) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. 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 a 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 subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

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

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

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4.3 in protocol, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.4.3 in protocol will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

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 for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 in protocol (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group. Analysis of changes from baseline will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

In addition, clinically notable vital sign values will be identified using the criteria in Table 1. The clinically notable vital sign values will be summarized using frequency count at each visit by treatment group.

Table 1 Vital Sign Criteria

	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

Table 1 Vital Sign Criteria

	Criterion value[a]	Change relative to baseline[a]	Clinically notable range
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
Weight	--	Increase of ≥7%	H
	--	Decrease of ≥7%	L
Respiratory Rate	>20 bpm	--	H
	< 10 bpm	--	L

BP = blood pressure, H = high, L = low.

a. Clinically notable means that a value must meet the criterion value and must attain the specified magnitude of change relative to baseline.

5.6.5 Electrocardiograms

ECG assessments will be performed as designated in the Schedule of Procedures/Assessments (Table 3 in protocol). Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia (QTcF) during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

5.6.6 Other Safety Analyses

Not applicable.

5.7 Other Analyses

Not applicable.

5.8 Exploratory Analyses

CCI

[redacted]

5.9 Extension Phase Analyses

Not Applicable

6 INTERIM ANALYSES

No interim analysis is planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

Not Applicable

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Visit Window

Study Day 1 is defined as the date of the first dose of study drug during the Treatment Period. The nominal visit (ie, study visit captured on the CRF) will be used as the analysis visits in all by-visit summaries. The Early Term visit will be considered as unscheduled visit and will not be included in the by-visit summary. Where applicable, the Early Term visit will be used along with the Day 31 visit for completers as the End of Treatment visit for the safety analyses.

8.2 Baseline Assessment

Unless otherwise specified, baseline measurement is the last observed measurement , including unscheduled assessments, prior to the first dose of study medication of treatment period for a given assessment.

- ISI: Last available ISI measurement at Visit 1
- BDI-II and BAI : Last available measurement at Visit 1
- SDSB (Stop-BANG and IRLS) : Last available measurement at Visit 1

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

9.1 Pharmacokinetic Data Handling

9.1.1 Lower Limit of Quantification of Lemborexant and its metabolites M4, M9, and M10 Plasma Concentration

The LLOQ of lemborexant and its metabolites M4, M9, and M10 are 0.0500 ng/mL.

9.1.2 General Rules for Presentation of Drug Concentrations

When presenting individual/raw values and summary statistics, the following rule will be applied: for drug concentrations, all summary statistics (mean, median, and SD) will have 3 significant digits.

Typical variable	Standard Unit	N	Digit rule	Raw Minimum Maximum	Mean Median	SD
E2006 and its metabolites M4, M9, and M10 concentration	ng/mL	X	Significant digits	3	3	3

10 STATISTICAL SOFTWARE

Analysis will be performed using SAS (release 9.4 or newer), Phoenix WinNonlin (version 6.4 or newer), and Microsoft Excel (2010 or newer).

11 MOCK TABLES, LISTINGS, AND GRAPHS

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

12 REFERENCES

Not applicable.

SIGNATURE PAGE

Authors:

[electronic signature in eDMS] Date

PPD
PPD
PPD
Eisai Co., Ltd.

Approval:

[electronic signature in eDMS] Date

PPD
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Biostatistics
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PPD
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Eisai Co., Ltd.

[electronic signature in eDMS] Date

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Clinical Pharmacology,
PPD
PPD
Eisai Co., Ltd.

[electronic signature in eDMS] Date

PPD
Study Director
PPD
Eisai Co., Ltd.

Audit Trail Entries

Report for document "E2006-J082-204--statistical-methods-interim-analysis-plan"

18-Jan-2023 01:06 EST

Basic Object Properties:

Object Name	E2006-J082-204--statistical-methods-interim-analysis-plan
Title	E2006-J082-204--statistical-methods-interim-analysis-plan
Version Creation Date	12-Jan-2023 22:04 EST
Last Modified Date	18-Jan-2023 00:43 EST
Version Labels	0.2, CURRENT, LATEST, Draft
Document Type	Clinical
Document Subtype	Study Report Appendix

Audit Trail Entries:

User Acknowledgements

Version Number	Outcome	Event Name	Activity	Meaning	User Name	Server Date and Time
0.2	Approved	Acknowledgement	Approval	Clinical Approval	PPD	16-Jan-2023 00:19 EST
0.2	Approved	Acknowledgement	Approval	Biostatistics Approval	PPD	15-Jan-2023 23:37 EST
0.2	Approved	Acknowledgement	Approval	Clinical Pharmocology Approval	PPD	15-Jan-2023 23:36 EST

Change Status

Original Status	New Status	Original Version	New Version	Server Date and Time	User Name
For Approval	Draft	0.2	0.2	18-Jan-2023 00:37 EST	PPD
Draft	For Approval	0.2	0.2	15-Jan-2023 23:33 EST	PPD
	Draft	0.1	0.1	12-Jan-2023 21:53 EST	PPD

Retention Actions

None

Task Signoff Failure

None

Restricted Property Update

None

Property Modification - Generic Audit Trail Entries

None

Reassign Work

None

Periodic Review

None

Forced Task Completion

None

Terminate Workflow

Event Name	Numeric version label	Server Date and Time	User Name
Terminate Workflow	0.2	18-Jan-2023 00:37 EST	PPD

Repeat Task

None

Print

None

Print Status Change

None

Reclassify

None

Bulk Property Update

None

System Generated Audit Trails

Event Name	String 1	String 2	String 3	String 4	String 5	Server Date and Time	User Name	Version Label
dm_checkin						12-Jan-2023 22:04 EST	PPD	0.2

Application Number Change

None

Other

Event Name	String 1	String 2	String 3	String 4	String 5	Server Date and Time	User Name	Version Label
Export Document						13-Jan-2023 08:23 EST	PPD	0.2

18-Jan-2023 01:06 EST