STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2006-J086-311
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of the Efficacy and Safety of Lemborexant in Chinese Subjects with Insomnia Disorder
Date:	02 Jun 2023
Version:	Version 3.0

REVISION HISTORY

Revisions to Version 3.0

Date: <02 Jun 2023>

Change	Rationale	Affected Sections
PP criteria added in detail.	PP criteria were defined at data review meeting. They were defined in detail in this section as SAP Ver. 1.0 declared.	Section 5.2.1
Protocol deviations added in detail.	Protocol deviation was defined based on important deviation concretely as SAP Ver. 1.0 declared.	Section 5.2.3
Site definition added.	Pooling sites was needed for the factor of primary analysis model as SAP Ver. 1.0 declared so this section defined the factor of site based on geographic regions.	Section 5.3.1
Subgroup definition added.	Subgroups and its category were defined in detail.	Section 5.3.4
Forest plot of subgroup analysis for LPS, SE, WASO and TST added.	To grasp efficacy characteristics by subgroup through visualization.	Section 5.3.4
Analysis type (sensitivity analysis or supplemental analysis) revised and added.	Analysis type (sensitivity analysis or supplemental analysis) were revised for each estimand correctly and added tipping point analysis in sensitivity analysis to evaluate missing data impact.	Section 5.3.6 Section 5.4.1.2 Section 5.4.1.3
LPS analysis and sSOL analysis based on non-log transformed data added.	To compare the results of log transformation.	Section 5.4.1.2 Section 5.4.2
Exploratory analyses described in detail.	Exploratory analyses were defined for other polysomnography parameter and electronic sleep diary.	Section 5.4.3
Analysis item of Adverse Event limited.	The analysis of number of events was deleted.	Section 5.6.2
Handling of central and local laboratory values described.	Pooling of central and local laboratory values were defined for analysis to clarify data handling from different source.	Section 5.6.3
PK data handling added.	This section was added to clarify PK data handling.	Section 8.4

Revisions to Version 2.0

Date: <16 Sep 2022>

Change	Rationale	Affected Sections
Handling rule for subjective parameter added	The analysis of subjective sleep parameter both with and without handling rule in secondary efficacy analysis was added. The handling rule was attached in Appendix 3. / It was detected irregular data in e-Diary like Study 304 that has refeed in sample size rationale. Hence the same analysis and same rule in study304 were added.	Section 5.4.2 Section 13 Appendix 3

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
LEM5	lemborexant 5 mg
LEM10	lemborexant 10mg
ISI	Insomnia Severity Index
LPS	latency to persistent sleep
LS	least squares
MAR	missing at random
MMRM	Mixed effect model with Repeated Measure
MedDRA	Medical Dictionary for Regulatory Activities
PBO	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetic
QTcF	corrected QT interval by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SE	sleep efficiency
SI	Système International

Abbreviation	Term
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
sSE	subjective sleep efficiency
sSOL	subjective sleep onset latency
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TIB	time in bed
TST	total sleep time
UN	unstructured covariance matrix
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-J086-311. As per Center for Drug Evaluation (CDE) requirements, a statistical analysis report will be produced after database lock.

SAP is based on Protocol Amendment 05 (28 Jun 2022).

3.1 Study Objectives

3.1.1 Primary Objective

To confirm using polysomnography (PSG) that lemborexant 10 mg (LEM10) is superior to placebo (PBO) on objective sleep onset as assessed by latency to persistent sleep (LPS) during the last 2 nights of 1 month of treatment in subjects with insomnia disorder

3.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate LEM10 compared to PBO on sleep efficiency as assessed by objective sleep efficiency (SE) during the last 2 nights of treatment
- To evaluate LEM10 compared to PBO on sleep maintenance as assessed by objective wake after sleep onset (WASO) during the last 2 nights of treatment
- To evaluate LEM10 compared to PBO on sleep maintenance as assessed by subjective sleep onset latency (sSOL), subjective sleep efficiency (sSE), subjective wake after sleep onset (sWASO) over the last 7 nights of 1 month of treatment
- To evaluate the efficacy of LEM10 compared to PBO on sleep (LPS, WASO, SE) as measured by PSG during the first 2 nights of treatment
- To evaluate the safety and tolerability of lemborexant
- To evaluate the effect of lemborexant compared to PBO on insomnia severity and daytime functioning, as assessed by the Insomnia Severity Index (ISI)
- To evaluate rebound insomnia following completion of treatment with lemborexant
- To evaluate morning residual sleepiness during treatment and following completion of treatment with lemborexant

3.1.3 Exploratory Objectives

The exploratory objectives are:

- To explore the effects of LEM10 and PBO on subjective quality of sleep
- To evaluate the effects of LEM10 and PBO on sleep architecture
- To explore the effects of LEM10 and PBO on Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI)

- To summarize plasma concentrations of lemborexant and its metabolites M4, M9, and M10

3.2 Overall Study Design and Plan

E2006-J086-311 is a multicenter, randomized, double-blind, PBO-controlled, parallel-group study of LEM10 for 30 nights in Chinese subjects (age 18 years or older, only in Taiwan age 20 years or older) who have insomnia disorder. (revised per Amendment 03)

The study will have 2 phases: the Prerandomization Phase and the 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 14-day Follow-Up Period before an End of Study (EOS) Visit.

Throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments at specified visits, including questioning regarding adverse events (AEs), 12-lead ECG, vital signs, weight, height (once at Visit 1), clinical hematology and chemistry analysis and urinalysis. At each visit from Screening to the EOS Visit, subjects will also undergo a urine drug screen.

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 89 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 54 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.

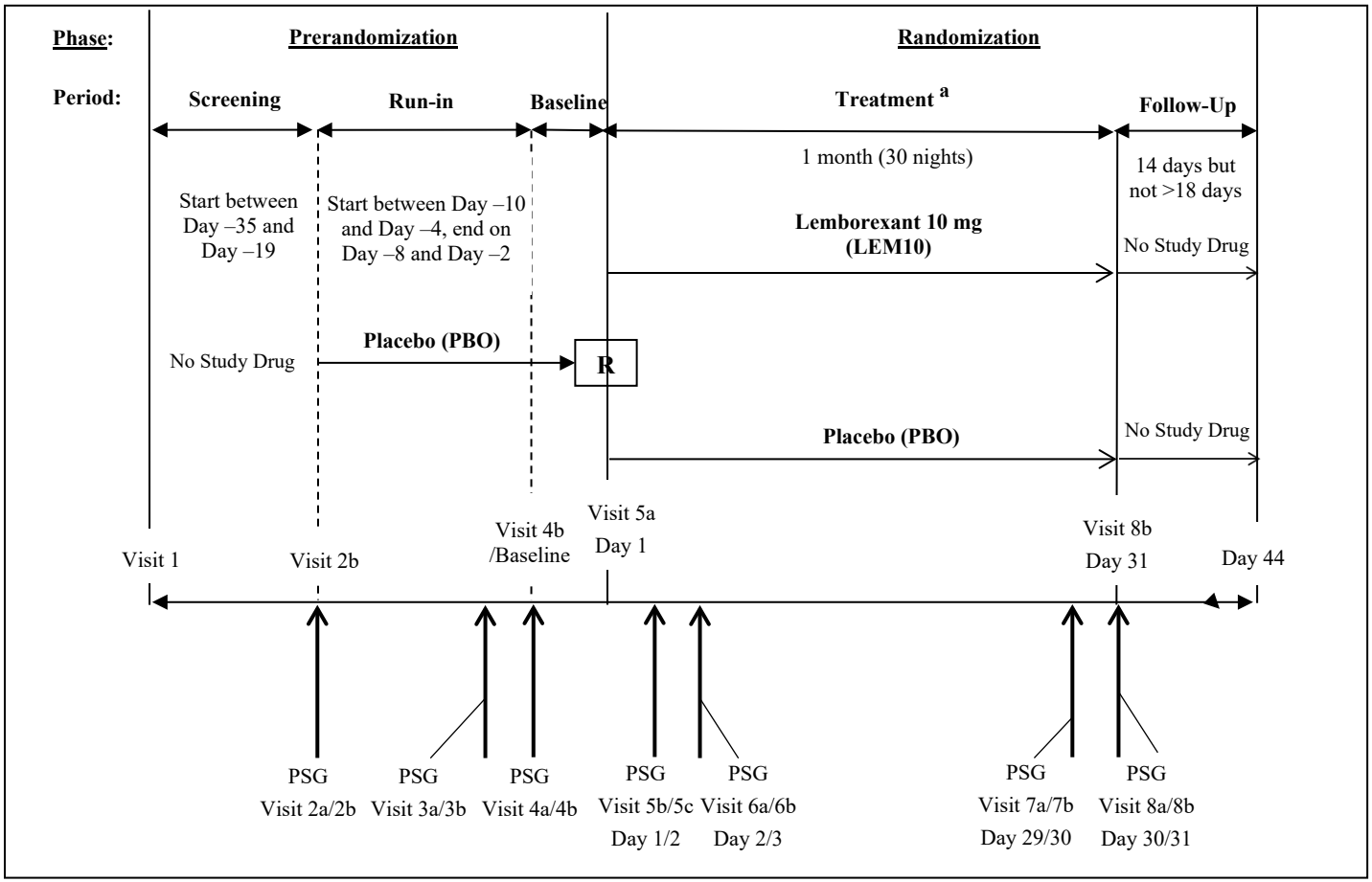

Figure 1 Schematic Diagram of E2006-J086-311 Study Design

PSG = polysomnography, R = randomization.

a: The first dose of active study drug will be administered at Visit 5b. The last dose of active study drug will be administered at Visit 8a.

4 DETERMINATION OF SAMPLE SIZE

The sample size was considered based on LPS for each comparison between Study 201 (E2006-G000-201) and Study 304 (E2006-G000-304). For LEM10 on Days 29 and 30, we assume the effect size that mean difference divided by common standard deviation as –0.411 under logarithm transformation. Therefore, to detect a difference in LPS comparing LEM10 with PBO, at least 94 subjects per group (total 188) will be needed for a 0.05 α-level, 2-sided test and more than 80% power based on above assumption.

5 STATISTICAL METHODS

All final statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

All descriptive statistics for continuous variables will be reported using number of observations (n), mean (arithmetic unless otherwise specified), standard deviation (SD), median, Q1, Q3, minimum and maximum. Categorical variables will be summarized as number and percentage of subjects. In summaries for safety the denominator for all percentages will be the number of subjects in a given treatment.

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 objective LPS during the last 2 nights of 1 month of treatment of LEM10 compared to PBO.

5.1.2 Secondary Endpoints

- Change from baseline of objective SE during the last 2 nights of 1 month of treatment of LEM10 compared to PBO
- Change from baseline of objective WASO during the last 2 nights of 1 month of treatment of LEM10 compared to PBO
- Change from baseline of sSOL during the last 7 nights of 1 month of treatment of LEM10 compared to PBO
- Change from baseline of sSE during the last 7 nights of treatment of LEM10 compared to PBO
- Change from baseline of sWASO during the last 7 nights of treatment of LEM10 compared to PBO
- Change from baseline of PSG parameters (LPS, SE, WASO) over the first 2 nights of 30 nights of LEM10 compared to PBO
- Safety and tolerability of lemborexant

- Change from Study Baseline in insomnia severity and daytime functioning, assessed as the ISI total number and total score from the 4 items related to daily function on the ISI after 1 month of treatment with LEM10 compared to PBO
- Rebound insomnia endpoints as assessed from the sleep diary during the Follow-Up Period
- Morning residual sleepiness during treatment and following completion of treatment

5.1.3 Exploratory Endpoints

- Subjective quality of sleep
- Sleep architecture
- Effects on BDI–II and BAI
- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

Safety Analysis Set: The Safety Analysis Set is the group of randomized 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 at least 1 postdose primary efficacy measurement.

Per Protocol (PP) Analysis Set: The PP Analysis Set is the group of all randomized subjects who received assigned randomized study drug and do not have a following protocol deviation that is likely to affect the primary endpoint:

Clinical Study Procedures

- 2-consecutive PSG (Visit 5/6 and/or Visit 7/8) data were missing/unscorable
- Study drug was taken more than 30 minutes before lights off
- Prohibited drug was taken at PSG assessment visit

IMP Deviations

- Lower compliance less than 80%
- PSG recording without taking study drug

Subjects who met any of the criteria listed above will be excluded from the PP Analysis Set due to possible introduction of bias.

PK Analysis Set: The PK Analysis Set is the group of subjects who received at least 1 dose of randomized study drug and had at least one 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, and the number, the percentage and the reason of subjects excluded from PP Analysis Set will be presented by treatment group and overall. Subject listing of analysis set and reason 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 randomized subjects by each site will also be summarized by treatment group.

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 discontinuation and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by treatment group. Subject listing of disposition and reasons for discontinuation from study treatment and study will be provided.

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
- Protocol Deviation
  - inclusion/exclusion criteria
- Withdrawal criteria
- Investigational medicinal products (IMPs) deviation
- Use of prohibited concomitant medication
- Clinical Study Procedure

Important protocol deviations will be summarized by category and treatment group. In addition, COVID-19 related deviations will also be summarized by 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 FAS, PP Analysis Set, PK Analysis Set and Safety Analysis Set will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height at screening visit (SCR), weight at SCR and Study Baseline, and BMI at SCR; categorical variables include sex (male and female), age group 1 (<55 years, 55-<65 years, ≥65 years), age group 2 (<65 years, ≥65 years), BMI group (<18.5, 18.5 -<25, 25 -<30, ≥30), race and ethnicity.

Characteristics of insomnia at Study Baseline will be summarized using LPS, SE, WASO, TST, sSOL, sSE, sWASO, sTST, sTIB, Quality of sleep, Morning Sleepiness, ISI Total Score (item 1 to 7), ISI Total Score (item 4 to 7) and its each item score. The Beck Depression Inventory II Total (BDI-II) and Beck Anxiety Inventory (BAI) Total scores will also be summarized at Study Baseline.

The above tables will be produced for the FAS, PP Analysis Set and Safety Analysis Set. Subject listing of demographics and baseline characteristics will be provided.

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 21.0 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. Subject listing of medical history and current medical conditions will be provided.

5.2.5 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 DDE/HD Mar 2018 or latest version).

Prior medications are defined as medications that stopped before the 1st dose of study drug, where study drug includes PBO during the Run In Period.

Concomitant medications are defined as medications that (1) started before the 1st dose of study drug (including the Run In Period) and are continuing at the time of the 1st dose of study drug, or (2) started on or after the date of the 1st dose of study drug (including the Run In Period) to the last dose day plus 14 days.

The number and percentage of subjects who take prior and concomitant medications will be summarized using the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class (ATC), 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 medication during Run-in and Treatment Periods. All prior and concomitant medications and no pharmacologic medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Treatment compliance (in %) is defined as follows:

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

Treatment compliance during the Run-in and Treatment Periods will be summarized separately using descriptive statistics based on Safety Analysis Set. Treatment compliance will also be summarized by treatment group using the categories <80%, ≥80% to ≤100%, >100% to ≤120%, and >120%. Subject listing of study drug compliance will be provided.

5.3 Data Analysis General Considerations

The FAS will be used as the primary population for all efficacy analyses. The PP analysis set will be used for sensitivity analyses to corroborate the primary efficacy analysis.

5.3.1 Pooling of Centers

This study was a multicenter study. Due to small expected number of subjects in each site, sites will be pooled within specific geographic regions for primary and secondary efficacy analyses. Other analyses will be performed with all sites pooled across the study unless stated otherwise.
Site is defined as the pooled sites geographically in Table 1. Category 1 means North China / Northeast China / Northwest China region (name “North”), category 2 means East China region (name “East”) and category 3 means Central China / South China region (name “South”). Site will be defined for sites with at least 1 randomized subject.

Table 1 Site definition

Site ID	Category	Province
1001	1	Beijing
1002	3	Henan
1003	3	Guangdong
1004	2	Shanghai
1006	1	Beijing
1007	2	Shanghai
1008	3	Hubei
1009	1	Hebei
1010	2	Shandong
1011	2	Jiangsu
1012	3	Guangdong
1013	1	Shaanxi
1014	2	Jiangxi
1015	1	Shanxi

1016	1	Tianjin
1017	2	Jiang Su
1018	3	Guangdong
1019	1	Hebei
1020	1	Beijng
1023	1	Jilin

5.3.2 Adjustments for Covariates

Site (North, East, South) and age groups (<65 years, ≥65 years) are used as covariates in the analyses model.

5.3.3 Multiple Comparisons/Multiplicity

No multiplicity adjustment is planned.

5.3.4 Examination of Subgroups

Subgroup analysis of LPS, SE WASO and TST will be performed using age group 2 (<65 years, ≥65 years), sex (male and female), site (North, East, South), and BMI group (<18.5, 18.5 -<25, 25 -< 30, ≥30) as detailed in the respective sections in Section 5.4. Forest plot of LS means difference in change from baseline between treatments and its 95% CI will be presented based on above subgroups.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

LPS, SE, WASO and TST will be analyzed using mixed effect model repeated measurement analysis (MMRM), the missing values will be imputed using pattern-mixture multiple imputation (MI) assuming the missing data is missing not at random (MNAR). As its supplemetal analysis, the primary efficacy endpoint will also be analyzed using MMRM assuming the missing data is missing at random (MAR).

Unless otherwise stated for other efficacy parameters, missing values of the continuous variables will be analyzed using MMRM assuming MAR. All safety analyses will be performed based on the observed data only.

5.3.6 Other Considerations

The following estimands in Table 2 are evaluated for the primary efficacy endpoint (change from baseline in mean LPS on Days 29 and 30) in this study (Mallinckrodt, et al., 2012, and ICH, E9(R1) Final Concept Paper, 2014). The details of the analysis method are discussed in Section 5.4.

Table 2 Estimand List

Estimand	Description	Population	Intervention Effect of Interest	Analysis Type
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - include data after dropout	FAS	missing values imputed using MI assuming MNAR (Assumes the probability of missing observations for any subject depends on the unobserved events. For the missing pattern, complete cases will be used in the imputation. ***Thus this method assumes dropouts or subjects with missing values have similar treatment effect as the completers within the respective treatment group****.)*	Primary
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - include data after dropout	FAS	missing values imputed using MI assuming MNAR utilizing CCMV-4 missing value pattern (all available up to 4 monotone missing patterns) (Assumes the probability of missing observations for any subject depends on the unobserved events. For the missing pattern, complete cases up to 4 monotone missing patterns will be used in the imputation – see 5.4.1.2 for details. ***Thus this method relaxes the assumption of the primary analysis of using only completers to impute the missing data.***	Sensitivity (CCMV-4)
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - include data after dropout	FAS	a range of shifts will be used in the multiple imputation of missing data assuming MNAR to identify the specific shift and treatment effect that will tip the results from statistically significant to nonsignificant	Sensitivity (tipping point)
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - include data after dropout	FAS	missing values will not be imputed; MMRM model is used on all available data assuming MAR (Assumes subjects with missing values behave the same as the observed data within that treatment group, i.e., the missingness is independent of unobserved data after accounting for the observed data in the model. ***Thus the dropouts or subjects with missing values may continue to benefit from the treatment as if they were still on treatment (just like completers.))***	Supplimental (MMRM analysis assuming MAR)
Difference in outcome improvement for all randomized subjects who complete treatment period	- all randomized subjects regardless of what treatment subjects actually received - subjects who complete the study without missing efficacy assessments	FAS	subjects who completed all efficacy assessments without missing values	Supplimental (completer analysis)
Difference in outcome improvement for those who adhere to treatment	- subjects without major protocol violations that would impact efficacy assessments - include data after dropout	PP	missing values imputed using MI assuming MNAR (Assumes the probability of missing observations for any subject depends on the unobserved events. For the missing pattern, complete cases will be used in the imputation. ***Thus this method assumes dropouts or subjects with missing values have similar treatment effect as the completers within the respective treatment group.)***	Supplemental (PP analysis)

FAS = full analysis set; MI = multiple imputation; MAR = missing at random; MMRM = mixed effect model with repeated measurement; MNAR = missing not at random; PP = per-protocol analysis set

5.4 Efficacy Analyses

5.4.1 Primary Efficacy Analyses

Null Hypothesis: For objective LPS, no difference exists in the mean change from Study Baseline to the last 2 nights of Month 1 of treatment with LEM10 compared with PBO.

Alternative Hypothesis: For objective LPS, a difference exists in the mean change from Study Baseline the last 2 nights of Month 1 for LEM10 compared with PBO.

The objective LPS change from Baseline (the mean of Days 1 and 2, and the mean of Day 29 and 30) will be analyzed using the MMRM on the FAS. The model will include all data and will be adjusted for the corresponding baseline value (the means from the 2 PSG recordings during the Run-in Period), site (North, East, South), age group (<65 years, ≥65 years), treatment, time (Days 1/2, and Days 29/30), and the interaction of treatment by time. Since LPS is known to be non-normally distributed, a log-transformation will be used in the analysis. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. The missing values will be imputed using a pattern mixture model utilizing MI assuming the missing values are MNAR utilizing the complete case missing value pattern (CCMV-subjects who completed primary efficacy assessments without missing values). The missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data. The *P*-value, least square (LS) means and the 95% confidence interval (CI) for the treatment difference will also be provided. Longitudinal plot of median and geometric mean for the changes from baseline will be presented by treatment groups.

5.4.1.1 Multiple Imputation

Step 1-1 (imputing non-monotone missing data): Thirty multiple imputed complete datasets were to be constructed using the imputation regression model of age, baseline BMI, baseline log(LPS), baseline ISI, baseline sSOL, and individual log(LPS) assessments on Days 1, 2, 29, and 30, with a predefined arbitrary seed number (seed=311). SAS PROC MI will be used to implement the imputation procedure using all available values. The dataset will be converted into monotone missing pattern by imputing arbitrary missing data as the first step.

Step 1-2 (imputing monotone missing data): Data develop at Step 1-1 were to be constructed using the imputation regression model of treatment, age, sex (male, female), site (North, East, South), baseline BMI, baseline log(LPS), baseline ISI, baseline sSOL, and individual log(LPS) assessments on Days 1, 2, 29, and 30, with a predefined arbitrary seed number (seed=311). SAS PROC MI will be used to implement the imputation procedure using all available values. The monotone data will then be imputed with monotone regression method and MNAR.

Step 2 (performing MMRM using each imputed dataset): The MMRM model with factors of age group (<65 years, ≥ 65 years), site (North, East, South), treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline log(LPS) as a covariate will be applied to each imputed dataset. SAS PROC MIXED will be used for the MMRM analysis.

Step 3 (combine results): Resulting treatment effect parameter estimators and standard errors from each of 30 multiple imputed datasets from Step 2 will be combined using SAS PROC MIANALYZE to obtain the pooled treatment effect and variance parameter estimators according to Rubin's rules (Rubin DB, 1987).

5.4.1.2 Sensitivity Analyses

The following analyses will be considered as sensitivity analysis for the primary endpoint:

- MI assuming MNAR utilizing CCMV-4: The same MMRM method used in the primary analysis will be applied utilizing CCMV-4 (ie, up to 4 monotone missing patterns will be used for missing value imputation as follows)

Study days where results are available	**1**	**2**	**29**	**30**
Pattern 1	X	X	X	X
Pattern 2	X	X	X	–
Pattern 3	X	X	–	–
Pattern 4	X	–	–	–

X: result present; – : result missing

- Tipping point analysis: A range of shifts will be used in the MI of missing data assuming MNAR to identify the specific shift and treatment effect that will tip the results from statistically significant to non-significant.

- The same primary efficacy analyses described in Section 5.4.1(MMRM analysis with MI for missing value imputation) will be repeated based on non-Log transformed data.

5.4.1.3 Supplemental Analyses

The following analyses will be considered as supplemental analysis for the primary endpoint:

- PP analysis: The same primary efficacy analyses described in Section 5.4.1 will be repeated based on PP analysis set.
- Completer analysis: The same primary efficacy analyses described in Section 5.4.1 will be repeated on subjects who completed all efficacy assessments and have no missing values.
- MMRM analysis assuming MAR: The same primary endpoint analysis described above will be analyzed using MMRM assuming the missing values are MAR.

5.4.2 Secondary Efficacy Analyses

The secondary efficacy endpoints (change from Baseline of the following for LEM10 compared to PBO; mean objective SE, mean objective WASO) will be analyzed same manner without log transformation and same model except tipping point analysis in

sensitivity analysis of 5.4.1 Primary Efficacy Analysis. Subgroup analyses will be applied like primary endpoint. Longitudinal plot of mean and LS mean (model mean) for the changes from baseline will be presented by treatment groups.

The other secondary efficacy endpoints (mean sSOL, mean sSE, mean sWASO, mean sTST at the first 7 nights and last 7 nights of treatment) will be analyzed using the MMRM, assuming the missing values are MAR. The sSOL will be implemented on both log-transformation and no log-transformation. The MMRM model will be same as the primary efficacy analysis with factors of age group (<65 years, ≥65 year), site (North, East, South), treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effect, and baseline of each parameter as covariates based on FAS. The unstructured covariance matrix will be used in the analysis. In case of non-convergence, the AR(1) will be used in the model. The treatment comparison will be performed using contrasts. The p-value, LS means and the 95% CI of the treatment differences will also be provided. Subgroup analyses will not be applied in these secondary endpoints. All analysis of subjective sleep parameter (sSOL, sSE, sWASO, sTST) will be conducted both without data handling rule and with data handling rule in Appendix 3.

The change from Baseline of ISI Daytime functioning (Item4 to 7) and ISI total Score (Item 1 to 7) for LEM10 compared to PBO will be analyzed using ANCOVA. The ANCOVA model will be included factors of age group (<65 years, ≥65 year), site (North, East, South) and treatment as fixed effect, and baseline of each parameter as covariates based on FAS. The *P*-value, LS means and the 95% CI of the treatment differences will also be provided.

Rebound insomnia is defined as worsened sleep relative to Screening after study drug treatment is completed. Sleep diary data from the Follow-Up Period will be compared to sleep diary data from the Screening Period to assess whether subjects experience rebound insomnia. To assess rebound insomnia, both categorical analysis at the subject level and continuous analysis at the group mean level will be performed. For each of the first 3 nights, the average of first 3 nights, the average of first 7 nights and the average of last 7 nightsof the Follow-Up Period the proportion of subjects whose corresponding value for sSOL or sWASO exceeds the corresponding Screening Period value by 5 minutes will be summarized by treatment group and compared to PBO. To assess statistical significance using the continuous data, the data will be analyzed using ANCOVA with factors age group(<65 years; and ≥65 year), site (North, East, South) and treatment. The LS mean of each of the first 3 nights, the average of first 3 nights, the average of first 7 nights and the average of last 7 nights of the Follow-Up Period will be compared to the Screening Period between LEM10 and PBO. If the lower bound of the 95% CI of sSOL or sWASO for each of the first 3 nights, the average of first 3 nights, the average of first 7 nights and the average of last 7 nights of the Follow-Up Period exceeds the upper bound of a 95% CI for the values during the Screening Period in the given treatment group, it will be considered strong evidence for rebound insomnia. If the LS means for sSOL and sWASO for the Follow-Up Period are all lower than for the Screening Period, then no rebound insomnia is suggested. Otherwise, the degree to which the parameters worsen, and the time point(s) at which they worsen will be considered to evaluate whether clinically meaningful rebound insomnia is present.

To evaluate morning residual sleepiness during study treatment and following completion of treatment, the change from baseline of the mean of morning sleepiness item on the sleep diary for the first 7 mornings of the Treatment Period, the last 7 mornings of the Treatment Period, as well as the means of the first 7 morning and last 7 morning of the Follow-Up Period will be analyzed using MMRM assuming MAR.

Subject listing of individual visit results and averaged analysis results for polysomnography parameter (LPS, SE and WASO), averaged analysis results for sleep diary parameters with/without handling rule, ISI, Stop-Bang, IRLS, MHB and will be provided.

5.4.3 Other Efficacy Analyses

The following endpoints are considered exploratory. Comparison of LEM10 will be made with PBO. Unless specified otherwise, for all other efficacy analyses endpoints, the change from baseline assessment will be analyzed using MMRM assuming MAR. No multiplicity adjustment will be made for all analyses.

POLYSOMNOGRAPHY

- Change from baseline of TST on Days 1/2 and Days 29/30
  - The change from Baseline of mean objective TST for LEM10 compared to PBO will be analyzed using MMRM analysis assuming MNAR with MI and MAR.
- Percentage of the change from baseline of total duration of sleep stage of non-REM (N1, N2, N3 separately and combined) and REM
  - per time in bed (TIB) on Days 1/2 and Days 29/30
  - per TST on Days 1/2 and Days 29/30
- Change from baseline of REM latency (defined as the first sleep epoch to first REM sleep epoch) on Days 1/2 and Days 29/30
  - The change from baseline of mean REM latency will be analyzed separately for Days 1/2 and for Days 29/30 using Wilcoxon rank sum test. The treatment difference will be estimated using Hodges-Lehmann estimation, and the asymptotic (Moses) 95% CI for the difference will be provided.
- Change from baseline in number of awakenings on Days 1/2 and Days 29/30
- Change from baseline in number of long awakenings (defined as awakenings of 5 minutes or longer) on Days 1/2 and Days 29/30

ELECTRONIC SLEEP DIARY

- Change from baseline of the mean rating on the Quality of Sleep question from the Sleep Morning Sleepiness Questionnaire
- Change from baseline of morning sleepiness ratings on Days2/3, and Days 30/31

The change from Baseline (at Screening) for BDI-II and BAI on Day31 will be analyzed using ANCOVA including age group (<65 years; and ≥65 year), site (North, East, South),

treatment and Baseline. Subject listing of individual visit results and averaged analysis results for polysomnography parameter (Other) and for morning sleepiness in clinic, BDI-II and BAI will be provided.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Lemborexant and its metabolites M4, M9, and M10 plasma concentrations were obtained from blood samples drawn at prespecified visit.

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual lemborexant and its metabolite (M4, M9, and M10) plasma concentration listings. The PK Analysis Set will be used for the summaries of lemborexant, M4, M9, and M10 plasma concentrations. Lemborexant, M4, M9, and M10 plasma concentrations will be summarized using summary statistics (n, mean, SD, median, minimum, and maximum).

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

5.6 Safety Analyses

All safety analyses will be performed based on observed data using the Safety Analysis Set. Safety data will be summarized on an "as treated" basis using descriptive statistics or frequency count only. No hypothesis testing will be performed for safety analyses.

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 Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 22.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment (including the Run-in Period), having been absent at pretreatment (before the Run-in Period) 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. AEs will be classified as TEAEs up to 14 days after the last study treatment.

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. 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 of events as TEAEs by SOC and PT will also be summarized.

The number of subjects (percentage) 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 of subjects(percentage) with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number of subjects (percentage) with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number of subjects (percentage) 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 of subjects (percentage) with treatment emergent SAEs and treatment-emergent non-serious adverse events (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 of subjects (percentage) 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 death, all serious AEs and 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. With the exception of urinalysis, all quantitative parameters listed in protocol Section 9.5.1.5 Laboratory Measurements, the actual value and the change from baseline will be summarized at each visit using descriptive statistics by treatment group. For urinalysis, the actual and the change from baseline of pH and specific gravity will be summarized at each visit by treatment group. Analysis of changes from baseline 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. Shifts from baseline (LNH) to the Day 31, End of Treatment and the EOS visit will be provided by treatment groups for each laboratory parameter.

The Sponsor's Grading for Laboratory Values (Appendix 1) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). 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 will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

All above analyses will be conducted by pooled data of central and local laboratory values. Subject listing of laboratory results for hematology, Chemistry, Urinalysis, Urine Drug Test and Pregnancy Test will be provided.

5.6.4 Vital Signs

For each vital signs parameters (ie, diastolic and systolic BP, pulse, respiration rate, temperature) and weight, the actual value and changes from Study Baseline will be summarized by treatment group at each visit using descriptive statistics. Analysis of changes from baseline will be based on the number of subjects with both non missing baseline and relevant postbaseline results.

In addition, clinically notable vital sign values will be identified using the criteria in Table 3. 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 3 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
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

For each ECG parameters (including PR interval, RR interval, QRS interval, QT interval, QTcF interval and heart rate) and actual value and changes from baseline will be summarized by treatment group at each visit using descriptive statistics. Shift tables from baseline to the Day 31, End of Treatment and the EOS visits will be presented by treatment group for ECG interpretation (categorized as normal and abnormal).

In addition, maximum postbaseline measurement will also be tabulated by treatment group as follows:

- Number and percentage of subjects with QTcF of >450 msec, and >500 msec during the treatment
- Number and percentage of subjects with a QTcF increment of >30 msec, and >60 msec from the baseline visit.
- Number and percentage of subjects with PR of >220 msec

Subject listing of ECG will be provided.

5.6.6 Other Safety Analyses

5.7 Subject listing of physical examination will be provided.Other Analyses

Not applicable.

5.8 Exploratory Analyses

Not applicable.

5.9 Extension Phase Analyses

Not Applicable

6 INTERIM ANALYSES

This is a fixed design. There is no interim analysis for efficacy and no alpha spending before final analysis. However a blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, may be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment.

7 CHANGES IN THE PLANNED ANALYSES

Major changes of analysis plan between SAP ver 2.0 to ver 3.0 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 Termination visit will be considered as unscheduled visit and will not be included in the by-visit summary. Where applicable, the Early Termination visit will be used along with the Day 31 visit for completers as the End of Treatment visit for the safety analyses.

For diary efficacy endpoints, the following visit window in Table 4 will be applied:

Table 4 Visit Window

Timepoint	Visit Window (in study days)
First 7 days of Treatment	2-8
Last 7 days of Treatment	22-36[a]

a: Last seven days within this window while on treatment

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. For the following endpoints, baseline measurement is defined as follows:

- PSG parameters: average of the two PSG recordings during the Run-in Period
- Sleep diary parameters:
  - For rebound insomnia: the mean of diary data entered on the last 7 mornings before the Screening PSG during the Screening Period
  - Other Sleep Diary-derived endpoints: the mean of diary data entered on the last 7 mornings before the first Baseline PSG during the Run-In Period
- ISI: Last available ISI measurement on or prior to Visit 5a
- BDI-II and BAI: Last available measurement during Prerandomization phase

8.3 Missing Data Handling

Unless stated otherwise, missing values will be analyzed using MMRM to handle the missing values assuming MAR in all other efficacy analyses. Details can be found in Section 5.4.

All safety analyses will be performed based on the observed data only.

8.3.1 Polysomnography, Cognitive Performance Assessment, Posture Stability, and Morning Sleepiness Questionnaire

Each PSG parameters will be derived by calculating the averages of pairs of values, i.e., the average of the two PSG recordings during the Run-in Period, Day 1 and Day 2, and Day 29 and Day 30. If one of each pair of values is missing, the other available value will be taken as the average of the pair; if both values are missing, then the parameter will be missing for the corresponding pair.

8.3.2 Sleep Diary

Each Sleep Diary parameter will be derived by calculating the average of weekly (7 days) diary parameter values. For the follow-up period, if the first 7 nights overlaps with the last 7 nights (eg, the follow-up period is less than 14 days in total), the last non-overlaps nights will be used in calculating the average value for the last 7 nights.

For each Sleep Diary parameter at baseline, if no more than 2 of the 7 nights' values are missing, the available values will be used to calculate the mean. If more than 2 values are missing, the parameter will be considered missing for baseline. For each Sleep Diary parameter during treatment period and follow-up period, if at least 4 of the 7 nights' values are available, the available values will be used to calculate the mean. If less than 4 values are available, the parameter will be considered missing for the corresponding time point.

8.4 Pharmacokinetic Data Handling

8.4.1 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.

8.4.2 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

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

Statistical analyses will be performed using SAS version 9.4 (or later versions), Phoenix WinNonlin (version 6.4 or newer), and Microsoft Excel (2010 or newer). In the event that certain features graphical analyses cannot be implemented by SAS, other statistical software such as Splus can be employed.

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

ICH Final Concept Paper E9(R1): Addendum to statistical principles for clinical trials on choosing appropriate estimands and defining sensitivity analyses in clinical trials dated 22October 2014.

Mallinckrodt CH, Lin Q, Lipkovich I, Molenberghs G. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharmaceutical Statistics 2012,11:456-461, 10 September 2012.

Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons; 1987.

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

Appendix 1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

	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 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/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 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/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 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/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 – 2.5×ULN if baseline was normal; 2.0 – 2.5×baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
ALT	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
AST	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN if baseline was normal; 1.0 – 1.5×baseline if baseline was abnormal	>1.5 – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 10.0×ULN if baseline was normal; 3.0 – 10.0×baseline if baseline was abnormal	>10.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal

	Grade 1	Grade 2	Grade 3	Grade 4
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium <LLN - 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	<6.0 mg/dL <1.5 mmol/L Ionized calcium <0.8 mmol/L; life-threatening consequences
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium >ULN - 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	>13.5 mg/dL >3.4 mmol/L Ionized calcium >1.8 mmol/L; life-threatening consequences
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×baseline; >1.5 – 3.0×ULN	>3.0×baseline; >3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 2.5×ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Glucose, serum-high (hyperglycemia)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	life-threatening consequences; urgent intervention indicated
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	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; intervention initiated	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences

	Grade 1	Grade 2	Grade 3	Grade 4
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	125-129 mmol/L and asymptomatic	<125 – 129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<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 without physiologic consequences	N/A	>ULN with physiologic consequences	life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 5.0. Published: January 5, 2018.

Appendix 2 Derivations of Efficacy Endpoints from Electronic Sleep Diary

The following 7 questions are captured in the electronic Sleep Diary:

Q1: What time did you try to go to sleep?

Q2: How long did it take you to fall asleep?

Q3: How many times did you wake up, not counting your final awakening?

Q4: In total, how long did these awakenings last?

Q5: What time was your final awakening?

Q6: After your last awakening, how much longer did you try to sleep?

Q7: What time did you get out of bed for the day?

The efficacy endpoints from electronic Sleep Diary are defined as follows:

- sSOL= Q2
- sWASO = Q4 + Q7 – Q5
- sTST = sTIB – time spent awake [where sTIB = Q7 – Q1; and time spent awake = Q2 + Q4 + Q7 – Q5]
- sSE = sTST/sTIB (as defined above)

Appendix 3 Data handling rule of e-Diary

Rule 1: AM PM error	1a	If Q1 (time you started trying to fall asleep) is before 6:00 PM or after 6:00 AM, then Q1 is considered illogical and set to missing, and that day's value for sSE is not included in endpoint average for relevant timepoint.
	1b	If Q7 (out of bed time) is before 12:00 AM (midnight) or later than 12:00 PM (noon), then Q7 is considered illogical and set to missing, and that day's value for sSE is not included in endpoint average for relevant timepoint.
	1c	If Q7 (out of bed time) is earlier than Q5 (time of final awakening) as a result of an AM/PM error in either parameter, set the question that is 12 hrs off to missing; if question = Q5, then that day's sWASO is not included in the endpoint average for relevant timepoint; if question = Q7, then that day's value for sSE and sWASO is not included in the endpoint average for relevant timepoint.
Rule 2: Inverting Hours and Minutes	2a	If time spent awake after sleep onset is greater than time spent in bed, i.e., sWASO > sTIB, then that day's value for sWASO is set to missing and is not included in the endpoint average for relevant timepoint.
	2b	If the estimated time to fall asleep is greater than time spent in bed, i.e., sSOL > sTIB, then that day's value for sSOL is set to missing and is not included in the endpoint average for relevant timepoint.
Rule 3: Final Awakening Later than Out of Bed	3	If the time of final awakening is later than the time the subject got out of bed for the day, i.e., Q5 > Q7 then:
	3a	If AM/PM error in either question, follow rule 1c.
	3b	Otherwise, set both Q5 and Q7 to missing, and that day's values for sSE and sWASO are not included in the endpoint average for relevant timepoint.

Note: For Rule 2 "Inverting Hours and Minutes", the parameter (sWASO) is set to missing instead of setting each individual question included in the derivation of the parameter to missing. This is because it is possible to have an illogical parameter value but logical values for some of the individual questions used in the derivation of the parameter.

Due to the subject data entry errors, apply the following rule for adjustment.

- Rule1
  - 1a: If 06:00 < Q1 < 18:00, then consider Q1 and sSE (sTST, sTIB) to be missing.
  - 1b: If 12:00 < Q7 < 24:00, then consider Q7 and sSE (sTST, sTIB)to be missing.
  - 1c: If Q5 > Q7 > missing, then consider Q5 ,Q7, sWASO and sSE (sTST, sTIB) to be missing
- Rule2
  - 2a: If sWASO > sTIB > missing, then set sWASO to be missing.
  - 2b: If sSOL > sTIB > missing, then set sSOL to be missing.
- Rule3
  - 3a: If Q5 > Q7 > missing, then consider Q5 ,Q7, sWASO and sSE (sTST, sTIB) to be missing
  - 3b: If (sSOL+sWASO) > sTIB > missing, then set both sTST and sSE to be missing.

SIGNATURE PAGE

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STATISTICAL ANALYSIS PLAN ADDENDUM

Study Protocol Number:	E2006-J086-311
Study Protocol Title:	A multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of the Efficacy and Safety of Lemborexant in Chinese Subjects with Insomnia Disorder
Version of Final SAP:	Version 3.0
Date of Final SAP:	02/Jun/23
Addendum Date:	29/Sep/23
Addendum Version:	Version 1.0

1 TABLE OF CONTENTS

2 INTRODUCTION

The purpose of this Addendum to the Statistical Analysis Plan (SAP) <Version 3.0, 02 Jun 2023> is to describe the analysis methods and rationale for unplanned analyses included in the Clinical Study Report following database lock and treatment unblinding for Eisai Protocol Amendment 05 (28 Jun 2022).

3 CHANGES ANALYSIS PLAN

3.1 Changes from Planned Analyses

The sTST analysis was added secondary efficacy analysis in SAP version 3.0. It will be treated as exploratory analysis in CSR.

3.2 Deletions from Planned Analyses

Subgroup analyses of BMI group (≥ 30kg/m) for LPS, SE, WASO and TST analysis were not conducted LS(G)M (95% CI) for Visit/Baseline and LS(G)M Difference (95% CI and p value) for Active-Placebo due to small sample size of this subgroup.

Analysis of change from baseline of morning sleepiness ratings on Days2/3, and Days 30/31 for electronic sleep diary was an error in writing.

3.3 Additions from Planned Analyses

Based on previous experience and published literature (Rosenberg, et al., 2019), LPS is expected to be non-normally distributed, hence the statistical analysis plan pre-specified a log-transformation of the data prior to analysis. However, LPS data from this study did not have a normal distribution, even after the LPS data was log transformed.

For this reason, we do not believe that using the pre-specified log transformed approach was appropriate for this study. Other statistical methods were required to correct the skewness of raw LPS data.

3.3.1 Analysis for LPS after Box-Cox Transformation

3.3.1.1 Normality Check on LPS

Normality of LPS, which is the primary endpoint, was checked. The following untransformed values (ie, original scale) and log transformed values in LPS parameter were presented using histogram and QQ plot. Furthermore, the same figures for the selected Box-Cox transformed values as described in 3.3.1.2 were also provided.

All untransformed LPS of each day
All log transformed LPS of each day
All Box-Cox transformed LPS of each day
Change from baseline of untransformed LPS representative value
Change from baseline of log transformed LPS representative value

Change from baseline of Box-Cox transformed LPS representative value

3.3.1.2 Box-Cox Transformed LPS

As a result, it was suggested that the log transformed LPS still did not fully follow the normal distribution. Therefore, Box-Cox transformation (Box and Cox, 1964) was implemented to explore the transformation for making the obtained LPS data conform more closely to the normality. Box-Cox transformation is defined as follows.

$$y^{(\lambda)} = \begin{cases} \frac{y^{\lambda} - 1}{\lambda}, \lambda \neq 0 \\ \log y, \lambda = 0 \end{cases}$$

where λ, y, and $y^{(\lambda)}$ shows transformation parameter, the value before transformation, and the value after transformation using λ, respectively. By selecting an appropriate λ, the Box-Cox transformation can derive the transformation formula that follows a normal distribution. In addition, this transformation formula can stand for the transformation family that includes the original scale, log transformation, and the other various transformations. By using the Kolmogorov-Smirnov test on the Box-Cox transformed values under the various λ values, the non-normality of the Box-Cox transformed LPS was statistically checked. The threshold of P value less than 0.05 was employed to determine the non-normality of Box-Cox transformed LPS.

The below table shows the P values of Kolmogorov-Smirnov test shifting transformation parameter λ from 0 to 1 by 0.01 unit. The most suitable λ was considered to be the value that was closest to the study-assumed log transformation (corresponding to λ=0) and the normality of Box-Cox transformed LPS was not rejected. As a result, λ=0.25 (quarter root transformation) was selected as the most suitable value based on the below table.

Table Grid search for suitable lambda through Kolmogorov-Smirnov test

Transformation Parameter: λ	P value
0.00 (log transformation)	0.0100
0.01	0.0100
0.02	0.0100
0.03	0.0100
0.04	0.0100
0.05	0.0100
0.06	0.0100
0.07	0.0100
0.08	0.0100
0.09	0.0100
0.10	0.0100
0.11	0.0100

0.12	0.0100
0.13	0.0100
0.14	0.0100
0.15	0.0100
0.16	0.0106
0.17	0.0190
0.18	0.0192
0.19	0.0342
0.20	0.0264
0.21	0.0176
0.22	0.0145
0.23	0.0199
0.24	0.0334
0.25	0.0532
0.26	0.0537
0.27	0.0840
0.28	0.0819
0.29	0.0518
0.30	0.0740
0.50	0.1234
1.00 (Original Scale)	0.0100

3.3.1.3 Analysis for Box-Cox Transformed LPS

The change from baseline of Box-Cox transformed LPS with transformation parameter of λ=0.25 was analyzed using same MMRM model of primary efficacy analyses. Missing values were imputed using MI assuming MNAR on FAS.

3.3.2 Analysis for LPS by Generalized Estimating Equations (GEE)

Feng, et al. (2014) suggested log-transformation widely used in biomedical research to deal with skewed data has serious problems. Despite the common belief that the log transformation can decrease the variability of data and make data conform more closely to the normal distribution, this is usual not the case. They recommended that in most circumstances researchers should abandon these traditional methods of dealing with skewed data and, instead, use newer analytic methods that are not dependent on the distribution the data, such as generalized estimating equations (GEE).
Based on the recommendation, the objective LPS (the mean of Days 1 and 2, and the mean of Day 29 and 30) was analyzed using the GEE analysis on the FAS. The model included

factors of baseline LPS, age group, site, treatment, visit (Days 1/2 and Days 29/30), and treatment by visit interaction. Link function was defined as identity. The unstructured covariance matrix was used in the analysis. Missing values were handled by two approaches: 1) imputed data with MI assuming MNAR on FAS and 2) not imputed data. In term of approach 1), the missing values was imputed using a pattern mixture model utilizing MI assuming the missing values are MNAR utilizing the complete case missing value pattern (CCMV-subjects who completed primary efficacy assessments without missing values). The multiple imputation was implemented same manner of 5.4.1.1 of SAP Version 3.
The following sample SAS statement provides the framework for the GEE analysis through MI.

```
PROC GEE data=<dataset1>;
    BY imputation_;
    CLASS subjid trtpn avisitn agegr2n sitegr1n;
    MODEL aval = bl_lpsa agegr2n sitegr1n trtpn avisitn trtpn* avisitn
        / dist=normal link=identity;
    REPEATED subject = subjid / within = avisitn corr=un;
    LSMEANS trtpn*avisitn /DIFF cl ;
    ODS output LSMeans=<dataset2> Diffs=<dataset3>;
run;
```

3.4 Maintenance of description from SAP version 3.0

Below table summarized to edit description in SAP Ver 3.0. Analysis purpose is not change.

Section in SAP Ver 3.0	Ver 3.0	Correction
5.4.3	Percentage of the change from baseline of total duration of sleep stage of non-REM (N1, N2, N3 separately and combined) and REM	~~Percentage of the~~ Change from baseline of total duration of sleep stage of non-REM (N1, N2, N3 separately and combined) and REM
	The change from Baseline (at Screening) for BDI-II and BAI on Day31 will be analyzed using ANCOVA including age group (<65 years; and ≥65 year), site (North, East, South), treatment and Baseline.	The change from Baseline (at Screening) for BDI-II and BAI on Day31 will be analyzed using ANCOVA including factor of age group (<65 years; and ≥65 year), site (North, East, South), treatment and Baseline.
	Subject listing of individual visit results and averaged analysis results for polysomnography parameter (Other) and for morning sleepiness in clinic, BDI-II and BAI will be provided	Subject listing of individual visit results and averaged analysis results for polysomnography parameter (Other) and for morning sleepiness ~~in clinic~~, BDI-II and BAI will be provided

4 REFERENCE LIST

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