Statistical Analysis Plan

An Open-label, Parallel-Group Study to Evaluate the Pharmacokinetics of Lemborexant and Its Metabolites in Subjects with Normal Renal Function or with Severe Renal Impairment

Protocol Number: E2006-A001-105

Version 2.0

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Previous Versions

Version 1.0 25-MAY-2018

SAP Amendments before database lock

Version	Issue Date	Section	Revision/Addition	Rationale
2.0	08-AUG-2018	6.1.2	Definition of Pharmacokinetic Analysis Set updated	The definition of the PK analysis set was edited for consistency with the hepatic impairment study.
		3.1, 6.2.2, 6.15 and 12	Calculation of PK parameter $AUC_{(0-8)}$ added. $AUC_{(0-8)}$ included in all listings, summary statistics, figures and statistical analysis tables. Box plots of $AUC_{(0-8)}$ added (Figure 14.2.2.7)	$AUC_{(0-8h)}$ was added to represent the total exposure over the time the subject would be sleeping.
		6.2.2 and 6.15	Calculation of AUCu added for metabolites as well as lemborexant. Descriptive statistics for unbound fraction protein AUCu of lemborexant and metabolites added (Table 14.2.2-5 and Table 14.2.3.5). Boxplots added (Figure 14.2.2.11)	AUCu was calculated for metabolites to assess changes in protein binding of each metabolite over time after dosing.
		6.15	Scatterplots for PK parameters by renal impairment group added (Figure 14.2.2.12)	Scatterplots for PK parameters vs. renal impairment were added for consistency with the hepatic impairment study. Scatterplots represent a visual assessment of how drug exposure is affected by renal impairment.
		6.15	Scatterplots for PK parameters adjusted by Unbound Fraction added (Figure 14.2.2.13)	Scatterplots for PK parameters adjusted by unbound fraction vs. renal impairment were added for consistency with the hepatic impairment study. Scatterplots represent a visual assessment of how

				unbound drug exposure is affected by renal impairment.
		6.15	Mean profiles for PK concentration data truncated to 24 hours added (Figure 14.2.22)	Mean profiles were truncated to 24 h in order to better assess the concentration time profile during the first 24 hours of exposure.
		6.2.2	Molecular weights for lemborexant and metabolites added into definition of MPR $AUC_{(0\text{-inf})}$	MPR was molecular-weight corrected to better assess direct comparisons of total exposure for metabolite and parent.
		12	Title for table 14.2.2.1 updated to include data for both renal groups, Table 14.2.2.2 removed as a result of this change.	Tables 14.2.2.1 and 14.2.2.2 were merged for consistency with the hepatic impairment study.
		12	Analysis Set for Figure 14.2.2.5 (Concentration-Time Profiles after Administration of Lemborexant and Metabolites with Linear Regression for Estimating the Terminal Elimination Rate) changed from Safety Analysis Set to PK Set	Figure 14.2.2.5 was updated with the safety analysis set for consistency with the hepatic impairment study.
		6.17.2 and 12	Summary and listing of Coagulation laboratory data removed	Coagulation data not collected
		12	Numbering adjusted throughout to accommodate above changes	

Table of Contents

1 INTRODUCTION

This document details the planned statistical analyses for the Eisai protocol E2006-A001-105.

The proposed analyses are based on the contents of V2.0 of the protocol (dated 02 April 2018).

This is a multi-center, single dose, open-label, parallel-group study in subjects with severe renal impairment and matched (with regard to age [± 10 years], race, sex, and body mass index [BMI, ± 20%]) healthy control subjects. The study will be conducted in 2 phases: Prerandomization Phase (containing the Screening Period and Baseline Period [Day -1]) and a Treatment Phase. The Screening Period will last up to 20 days, the Baseline Period will be 1 day, and the Treatment Period will be 11 days. Subjects will remain in the clinic until approximately 7 days after dosing (will be discharged from clinic after the Day 8 pharmacokinetic (PK) blood draw) and will return on Day 11 for end-of-study assessments/study discharge.

Subjects will be assigned to 1 of 2 groups: Subjects with severe renal impairment will be Group 1, and subjects with normal renal function demographically matched to subjects with severe impairment will be Group 2. The number of subjects per group and estimated glomerular filtration rate (eGFR) values used to assign each subject to a renal function group are shown below:

Classification of Renal Function Study Groups		
Population	**eGFR[a] (mL/min/1.73 m^2)**	**Number of Subjects per Group**
Group 1: Severe renal impairment	<30 and not on dialysis	8
Group 2: Normal renal function	≥90	8

[a] Day -1 estimated glomerular filtration rate (eGFR) will determine the renal category group to which a subject is assigned. If the Day -1 eGFR value places the subject into a different renal category group from that calculated at screening, the value can be repeated once within 24 to 48 hours. If eGFR variability across these scheduled and repeat time points indicates the subject does not consistently meet the criteria for one renal category group, subject enrollment into a renal category group will be at the discretion of the Medical Monitor and investigator, in consultation with the sponsor.

The eGFR is determined by the Modification of Diet in Renal Disease (MDRD) formula:

$$MDRD\ formula\ (mL/min/1.73m^2) = 175 \times (serum\ creatinine)^{-1.154} \times (age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ African\ American)$$

Group 1 subjects (severe renal impairment) will be enrolled first. Group 2 subjects (normal renal function) will be matched according to age, race, sex, and BMI.

Subjects determined eligible for study participation will receive a single 10 mg oral dose of lemborexant on Day 1. During the Treatment Period, plasma will be obtained over 11 days for the determination of lemborexant and metabolite concentrations M4, M9 and M10. Standard safety assessments will be measured before, during, and at the conclusion of the study.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the effect of severe renal impairment on the PK of lemborexant after a single dose administration.

2.2 Secondary Objectives

- To assess the effect of severe renal impairment on the PK of the unbound fraction of lemborexant.
- To assess the effect of severe renal impairment on the PK of metabolites (M4, M9, and M10) of lemborexant.
- To assess the safety and tolerability of lemborexant in subjects with normal renal function or with severe impaired renal function.

3 ENDPOINTS

3.1 Pharmacokinetic Endpoints

The endpoints are PK parameters derived by noncompartmental analysis using plasma concentrations of lemborexant and its metabolites. These parameters include, but are not limited to: C_{max}, t_{max}, $AUC_{(0\text{-}8h)}$, $AUC_{(0\text{-}72h)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, AUC_{ex}, $t_{1/2}$, CL/F, V_z/F, MPR $AUC_{(0\text{-}inf)}$, fu, AUCu, and CLu/F. PK parameters are defined in Section 6.2.2.

$AUC_{(0\text{-}72h)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, and C_{max} of lemborexant are the primary PK parameters. The rest of the parameters including the PK parameters of the metabolites, will be secondary endpoints.

3.2 Safety Endpoints

Safety will be assessed by monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), regular monitoring of hematology and blood chemistry, regular measurement of vital signs, electrocardiograms (ECG) and the performance of physical examinations.

4 SAMPLE SIZE

A sample size of 8 subjects for each cohort is based on the recommendations in Food and Drug Administration Guidance 10, and should provide estimates to assess whether dose adjustment is required for subjects with renal impairment.

Based on data from single dose studies of the 10 mg tablet (E2006-A001-004, E2006-A001-005, and E2006-A001-008), the pooled between-subject standard deviation of logarithmically transformed $AUC_{(0\text{-}inf)}$ values of lemborexant is 0.391. With a sample size of 8 subjects with severe renal impairment and 8 matched controls, the 2-sided 90% confidence interval (CI) for the geometric mean ratio for $AUC_{(0\text{-}inf)}$ would extend from 0.72 to 1.38 (for a mean ratio of 1.0). Similar precision is expected for the 2-sided 90% CI for the ratio for $AUC_{(0\text{-}t)}$.

5 RANDOMIZATION

Not Applicable.

6 PLANNED ANALYSES

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

6.1 Analysis Sets

6.1.1 Enrolled Subjects

A subject is considered to be enrolled in the study if they have provided informed consent.

6.1.2 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set is the group of subjects who dosed with the test drug and

6.1.3 had sufficient PK data to derive at least 1 PK parameter. Safety Analysis Set

The Safety Analysis Set is the group of subjects who dosed with the test drug and had at least 1 postdose safety assessment.

6.2 Derived Data

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

6.2.1 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled "Multiple" in the summary tables. The listings will reflect the original selected categories.

6.2.2 Pharmacokinetic Parameters

Concentration time data for lemborexant and its metabolites will be provided following database lock and will be analyzed by non-compartmental methods using Phoenix™ WinNonlin® (Version 6.3 or later, Certara USA, Inc., Princeton, NJ), in accordance with Eisai 302-104.00-MNL Non-Compartmental Pharmacokinetic Analysis (effective date 08 Jun 2016).

Concentrations that are below the limit of quantification (BLQ) will be treated in accordance with Section 2.5.1 of Eisai 302-104.00-MNL. During the pharmacokinetic analysis, BLQ values at predose up to the first quantifiable concentration will be set to zero; BLQ values between 2 quantifiable concentrations will be set to "missing"; and quantifiable concentrations preceded by 2 consecutive BLQ values in the terminal phase will be set to "missing".

The following PK parameters will be calculated for lemborexant and its metabolites (as data permit):

C_{max}	Maximum plasma concentration determined directly from individual concentration-time data, reported to 3 significant figures
t_{max}	Time to reach maximum plasma concentration determined directly from individual concentration-time data, reported to 2 decimal places
$AUC_{(0\text{-}8h)}$	Area under the plasma concentration–time curve from time zero to 8 hours postdose; calculated using the linear-log trapezoidal rule (linear-up log-down), reported to 3 significant figures
$AUC_{(0\text{-}72h)}$	Area under the plasma concentration–time curve from time zero to 72 hours postdose; calculated using the linear-log trapezoidal rule (linear-up log-down), reported to 3 significant figures
$AUC_{(0\text{-}t)}$	Area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration; calculated using the linear-log trapezoidal rule (linear-up log-down), reported to 3 significant figures
$AUC_{(0\text{-}inf)}$	Area under the plasma concentration–time curve extrapolated to infinity, reported to 3 significant figures and calculated as:

	$AUC_{(0\text{-}inf)} = AUC_{(0\text{-}t)} + C_{last}/\lambda z$
AUC_{ex}	The percentage of $AUC_{0\text{-}inf}$ based on extrapolation, reported to 3 significant figures and calculated as: $\%AUC_{ex}=(AUC_{(0\text{-}inf)} - AUC_{(0\text{-}t)})/AUC_{(0\text{-}inf)}*100$
$t_{½}$	The observed terminal elimination half-life, calculated as: $t_{½}= \ln(2)/\lambda_z$; see additional criteria below, reported to 3 significant figures
λ_z	The observed elimination rate constant; estimated by linear regression through at least three data points (not including t_{max}) in the terminal phase of the log concentration-time profile; see additional criteria below, reported to 3 significant figures
CL/F	Apparent body clearance, reported to 3 significant figures and calculated as: $CL/F = Dose/AUC_{(0\text{-}inf)}$; calculated for lemborexant only
V_z/F	Apparent volume of distribution based on the terminal phase, reported to 3 significant figures and calculated as: $Dose/(\lambda_z \times AUC_{(0\text{-}inf)})$; calculated for lemborexant only
MPR $AUC_{(0\text{-}inf)}$	Ratio of $AUC_{(0\text{-}inf)}$ of individual metabolite to $AUC_{(0\text{-}inf)}$ of lemborexant, corrected for molecular weights (E2006 = 411; M4, M9, and M10 = 427), reported to 3 significant figures
fu	plasma protein unbound fraction, reported to 3 significant figures
AUCu	$AUC_{(0\text{-}inf)}$ values adjusted by unbound fraction in plasma, reported to 3 significant figures
CLu/F	Apparent clearance relative to the unbound plasma concentration based on AUCu, reported to 3 significant figures (for lemborexant only)

At least 3 time points with quantifiable plasma concentrations will be required for the calculation of $AUC_{(0\text{-}t)}$. Individual $AUC_{(0\text{-}inf)}$ values for which AUC_{ex} >20% will be retained in the end of text tables and will not be included in the summary statistics. Individual $AUC_{(0\text{-}inf)}$ values for which AUC_{ex} >20% may be included in the summary statistics if approved by the Sponsor.

At least 3 time points (of which the first time point must be greater than t_{max}) with quantifiable plasma concentrations will be required for the calculation of λ_z.

No value for λ_z and other λ_z-related parameters ($AUC_{(0\text{-}inf)}$, $t_{1/2}$, CL/F, etc.) will be reported for lemborexant and its metabolites if the PK Analyst or the Sponsor decides a reliable estimate of λ_z is not possible after considering the following factors:

1) The duration of time over which λ_z is estimated (λ_z range) is less than twice the subsequently estimated terminal elimination phase half-life ($t_{½}$).

2) The adjusted regression coefficient (R^2 adj) is not ≥ 0.90; and

3) The concentration profiles do not exhibit a terminal elimination phase in the concentration versus time profile.

4) If the % extrapolation is > 20, related parameters $AUC_{(0\text{-inf})}$, CL/F, and V_z/F will be reported based on the pharmacokineticist's judgment.

6.2.3 Baseline

Baseline for the safety variables is defined as the last nonmissing value (either scheduled, unscheduled or repeat) before the subject receives the dose of lemborexant on Day 1. For laboratory variables, only results provided by the Worldwide Clinical Trials laboratory will be used as baseline values.

6.2.4 Duration/Study Day/Time

Study day will be calculated as the number of days from the dose of lemborexant on Day 1 using the following rules:

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

6.2.5 Conventions for Missing and Partial Dates

All dates presented in the individual subject listings will be as recorded on the electronic case report form (eCRF).

6.2.6 Unscheduled Visits

Only scheduled post baseline laboratory and vital signs values will be tabulated. Post baseline repeat/unscheduled assessments will be disregarded unless otherwise stated, although these post baseline assessments will be listed in Appendix 16.2.

6.2.7 Potential Cataplexy AEs

Potential AEs of Cataplexy are identified as those AEs with a verbatim term coded to one of the following MedDRA preferred terms:

Cataplexy	Dysarthria	Apallic syndrome	Presyncope
Muscle fatigue	Slow speech	Consciousness fluctuating	Transient ischaemic attack
Muscular weakness	Heteronymous diplopia	Depressed level of consciousness	Amaurosis fugax
Muscular tone disorder	Homonymous diplopia	Lethargy	Capsular warning syndrome
Hypotonia	Eyelid myoclonus	Loss of consciousness	Reversible ischaemic neurological deficit
Drop attack	Myoclonus	Sopor	
Slurred speech	Opsoclonus myoclonus	Stupor	
Diplopia	Clonus	Transient global amnesia	
Falls	Altered state of consciousness	Syncope	

Such AEs are identified on the eCRF by an answer of 'Yes' to the question 'Potential Cataplexy AE?'.

6.3 Conventions

All data listings, summaries, figures and statistical analyses will be generated using SAS[1] version 9.4 or higher or Phoenix™ WinNonlin® (Version 6.3 or later, Certara USA, Inc., Princeton, NJ).

Listings will be sorted in the following order: renal function group, subject, parameter, and day, unless otherwise stated. All data will be listed.

Continuous variables will be summarized by the number of nonmissing observations, mean, median, standard deviation (SD), and minimum and maximum. For all tabulations of changes from baseline data, the lower and upper 95% confidence limits for the mean for the individual treatments will be given. In addition, PK parameter data will have the geometric mean and coefficient variation (CV%) presented. CV% will be calculated as sqrt(exp[SD^2 of log transformed data]-1)*100.

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

6.3.1 Decimal Places

For pharmacokinetic data, when presenting individual/raw (raw, hereafter) values and summary statistics, the following rules will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD, and CV%) will have 3 significant digits. For t_{max}, raw values and summary statistics will be presented to 2 decimal places.

The adjusted regression coefficient (R^2 adj) will be presented to 3 significant digits. The number of time points used in the lambda-z estimates will be presented as an integer number. Lower and upper times of the lambda-z range will be presented to the same precision as the actual sampling time after dosing used for the calculation of PK parameters.

For all other data, means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

6.4 Subject Disposition

Subject disposition will be listed and summarized as follows:

- The number of subjects who are in each analysis set will be summarized for all enrolled subjects by renal function group and overall.
- The number of subjects who failed screening and the reasons for failure will be tabulated overall.
- The number of subjects who complete the study will be tabulated for all enrolled subjects by renal function group and overall.
- The number of early terminations and the primary reasons for terminations will be tabulated for all enrolled subjects by renal function group and overall. Secondary reasons for termination will be listed.
- Disposition data for all subjects screened will be listed.

6.5 Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2. Protocol deviations will be categorized as either major or minor by Eisai prior to database lock.

6.6 Inclusion and Exclusion Criteria

A listing of violators of the inclusion and exclusion criteria will be provided within Appendix 16.2.

6.7 Baseline Assessments

Standard continuous or categorical variable summaries will be presented by renal function group and overall for the following variables based on the Safety Analysis Set.

- Demographic data, data for all screened subjects will be listed.
- Weight at screening (kg)
- Height at screening (cm)
- BMI at screening (kg/m^2)
- eGFR ($mL/min/1.73\ m^2$) at Day -1

6.8 Medical History

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. Separate listings of previous and ongoing conditions at screening will be presented for the Safety Analysis Set. Conditions will be coded using the Medical Dictionary of Regulated Activities (MedDRA) primary system organ class and preferred term.

6.9 Prior and Concomitant Medications

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) drug codes. Non pharmacological procedures will be recorded in the CRF but not coded. Prior and concomitant medications will be listed. Prior medications will be defined as medications that stopped before the first dose of lemborexant. Concomitant medications will be defined as medications that started after the date of the first dose of study drug.

6.10 Viral Serology

A listing of viral serology results will be provided within Appendix 16.2.

6.11 Urine drug and alcohol screening

A listing of urine drug and alcohol screening results will be provided within Appendix 16.2.

6.12 Pregnancy Test

A listing of serum and urine pregnancy test results will be provided within Appendix 16.2.

6.13 Exposure to Study Drug

A listing of dosing information will be provided within Appendix 16.2.

6.14 Efficacy Analyses

Not Applicable

6.15 Pharmacokinetic Analysis

The Safety Analysis Set will be used for individual plasma concentration listings. The PK Analysis Set will be used for summaries of plasma concentrations and for analyses, summaries, and listings of PK parameters.

Blood samples (4 mL each) for PK assessments of lemborexant and its metabolites (M4, M9, and M10) will be collected at predose (0 hour), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168 and 240 hours postdose. In addition, blood samples for protein binding (12 mL per time point) of lemborexant will be collected at 1 and 24 hours postdose matching the PK sample collection at those time points.

For presentation of the individual data, BLQ values prior to the first non-zero concentration will be set to zero in the linear plots; BLQ values after the first non-zero concentration will be set to missing in the linear plots; and all BLQ values will be set to missing in the semi-logarithmic plots.

For calculation of mean concentrations, all BLQ values will be assigned as zero. If the proportion of values reported as BLQ is more than 50% or if the calculated mean is less than the lower limit of quantification (LLOQ) at a given sampling time, the mean will be treated as follows: zero for time points prior to the first non-zero mean concentrations in the linear plots' missing for time points after the first non-zero mean concentration in the linear plots; and missing for all BLQ values in the semi-logarithmic plots.

Plasma concentration data will be tabulated by nominal time and summarized by analyte and group using descriptive statistics [number of observations (n), arithmetic mean, standard deviation (SD), minimum (min), median and maximum (max)].

Mean plasma concentration-time data (using linear and semi-logarithmic scales) will be presented graphically; mean data will be plotted using nominal sample times. Additionally, mean profiles will be presented with the x-axis truncated to 24 hours postdose.

PK parameters for lemborexant and its metabolites (M4, M9, and M10) will be calculated as described in Section 6.2.2.

The adjusted regression coefficient (R^2 adj), number of time points used in the lambda-z estimates, and the lower and upper times of the lambda-z range will also be listed.

PK parameters will be summarized overall by treatment and by treatment stratified by analyte and group using descriptive statistics (n, mean, SD, min, median, max, geometric mean, CV%, calculated as: sqrt(exp[std^2 of log transformed data]-1)*100]).

The rules for presenting raw individual values and summary statistics for PK concentration and parameter data are provided in Section 6.3.1.

Protein Binding

Blood samples for plasma protein binding for lemborexant and metabolites will be collected for each subject at 2 time points: 1 hour and 24 hours postdose. Protein binding data will be provided by the vendor to Worldwide Clinical Trials as a percentage; if more than one value is available for either time point, the average of the protein binding values will be used in the calculations. Protein binding results will be presented as fractions and percentages and will be summarized for each time point (1 hour and 24 hour). Additionally, the average of the 2 timepoints (1 hour and 24 hour) will be calculated for each subject and summarized. The average of the 1 hour and 24 hour timepoints will be used to calculate the unbound PK parameters (AUCu and CLu/F).

Protein binding results for 1 h and 24 h will be summarized using the following descriptive statistics: n, mean, SD, minimum, median, and maximum. Protein binding results (averaged timepoints at 1 h and 24 h) will be summarized using the following descriptive statistics: n, mean, SD, CV%, minimum, median, maximum, and geometric mean.

Box plots will be created for the percent bound comparing lemborexant and metabolites across groups. Scatterplots will also be created for lemborexant and metabolite AUCu adjusted by the unbound fraction in plasma.

Evaluation of the impact of renal impairment on drug exposure:

The effect of renal impairment on the PK of lemborexant will be assessed using a linear model with renal impairment group as a factor. Logarithmically transformed values of the primary PK parameters C_{max}, $AUC_{(0\text{-}8h)}$, $AUC_{(0\text{-}72h)}$, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$ will be utilized to estimate the geometric mean ratio (and two-sided 90% confidence intervals) of subjects with severe renal impairment versus subjects with normal renal function. Similar statistical analyses will be conducted for the PK parameters of the metabolites and unbound lemborexant. In addition,

summary statistics for PK parameters in each renal function group will be tabulated. Box plots will be provided. The relationship between each of the PK parameters and the estimated renal function will be also presented graphically through the use of scatterplots of each PK parameter.

If the 90% confidence intervals indicate that there is an effect of renal impairment on the primary PK parameters, relationships between the individual subject PK parameters (C_{max}, $AUC_{(0-8h)}$, $AUC_{(0-t)}$, $AUC_{(0-72)}$, $AUC_{(0-inf)}$, and CL/F, both free and total) and individual subject estimated renal function (eGFR estimated by the MDRD) will be explored utilizing linear regression models with the PK parameter as the dependent variable and eGFR at Day -1 as the independent variable. Point estimates and 95% CIs of the intercept and slope will be presented.

6.16 Pharmacogenomic Analysis

Not Applicable.

6.17 Safety Analyses

The safety analyses will be presented by the renal function group for the Safety Analysis Set.

6.17.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during

treatment, having been absent at pretreatment (Baseline) or

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

The following tables will be presented for AEs:

Overall incidence by renal function group in

- the number of TEAEs, SAEs and events associated with special situations, AEs related to study treatment, SAEs that are related to study treatment, AEs leading to discontinuation and potential cataplexy AEs (as defined in Section 6.2.7).
- TEAEs by system organ class and preferred term - incidence.
- TEAEs by system organ class, preferred term and maximum severity - incidence
- Treatment-related TEAEs by system organ class and preferred term - incidence.
- SAEs and deaths by system organ class and preferred term – incidence overall and for those related to treatment.

- Treatment emergent, non-serious AEs, by system organ class and preferred term – incidence overall and for those related to treatment.

A subject will only be counted once within a specific system organ class and preferred term, even if the subject experienced more than one TEAE within that specific system organ class and preferred term.

Listings of adverse events will be provided in the following categories:

- TEAEs
- Non treatment-emergent AEs
- Deaths
- Serious TEAEs and events associated with special situations
- AEs leading to discontinuation
- Potential Cataplexy AEs

For Potential Cataplexy AEs data from the supplemental information questionnaire will be listed.

If an AE has missing relationship it is assumed to be related to the study drug for the purpose of summarizing the data. For an AE with missing severity the severity will be reported as "missing" if the subject has not reported another AE within the same level of summarization (i.e. system organ class or preferred term). If the subject has reported more than one AE within the same level then the worst severity will be used in the tabulation.

6.17.2 Laboratory Data

Laboratory data at Day -1 was analyzed by both a local laboratory and Worldwide Clinical Trials laboratory. Data from both laboratories will be listed but summary tables will only include data provided by Worldwide Clinical Trials.

All laboratory data will be listed and summarized using the International System of Units (SI). For continuous variables descriptive statistics of the observed values and change from baseline will be presented by renal function group at each scheduled assessment and Early Termination (if applicable) for each hematology, serum chemistry, and urinalysis parameter. For categorical variables the number and percentage of subjects in each reported level will be presented. Each hematology, serum chemistry, and urinalysis measurement will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each post baseline assessment and Early Termination (if applicable) will be presented.

A listing of any markedly abnormal laboratory measurements (defined as meeting the criteria for grade 2 or higher in the sponsors grading of laboratory values presented in Appendix 1 to the study protocol) that were recorded throughout the study will be presented. The incidence of markedly abnormal laboratory results over the course of the study will be listed.

6.17.3 Vital Signs

Descriptive statistics of the observed values and change from baseline will be presented by renal function group and timepoint for the following:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration Rate (breaths/min)
- Body Temperature (degrees Celsius)

The incidence of subjects reporting an increase or decrease greater than 20mmHg in systolic or 15 mmHg in diastolic blood pressure relative to baseline will be summarized at each post baseline assessment.

Weight at Day -1 will be listed only.

6.17.4 Electrocardiogram Data

Shift tables in relation to the overall interpretation (Normal, Abnormal Not Clinically Significant [NCS], and Abnormal Clinically Significant [CS]) from baseline to each post baseline assessment will be presented by renal function group.

6.17.5 Physical Examination

Significant findings at the Screening physical examination will be recorded on the Medical History and Current Medical Conditions CRF page and changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF, this data will be listed as described in the previous sections.

7 INTERIM ANALYSIS

No interim analyses are planned.

8 DATA SAFETY MONITORING BOARD ANALYSIS

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

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

The protocol states that if the 90% confidence intervals indicate that there is an effect of renal impairment on the primary PK parameters, relationships between the individual subject PK parameters (C_{max}, $AUC_{(0-t)}$, $AUC_{(0-72)}$, $AUC_{(0-inf)}$, and CL/F, both free and total) and individual subject estimated renal function (eGFR estimated by the MDRD) will be explored utilizing linear regression models with the log transformed PK parameter as the dependent variable and eGFR at Day -1 as the independent variable. The regression model will in fact be fitted with non log transformed PK parameter values as the dependent variable.

10 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

10.1 Pharmacokinetic Data Handling

10.1.1 Lower Limit of Quantification of Plasma Concentration

The LLOQ for lemborexant and its metabolites (M4, M9, and M10) is 0.0500 ng/mL in plasma.

11 REFERENCES

[1] SAS Institute Inc. Cary, NC, SAS Institute Inc

12 LIST OF TABLES, FIGURES AND LISTINGS

Please note: Table, Listing, and Figure titles are subject to change upon final analysis. Tables, Listings, and Figures may be consolidated as necessary.

	Safety Analysis Set
14.3.1.3.1	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term Safety Analysis Set
14.3.1.3.2	Serious Adverse Events and Deaths by Primary System Organ Class and Preferred Term Safety Analysis Set
14.3.1.4.1	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Severity Safety Analysis Set
14.3.1.5.1	MedDRA Summary of Treatment-Emergent Treatment-related Adverse Events by Primary System Organ Class and Preferred Term Safety Analysis Set
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14.3.4.2.2.1 Normal Range Shifts in Chemistry from Baseline to each Follow-up Assessment
Safety Analysis Set

14.3.4.3.1.1 Summary Statistics for the Change from Baseline in Urinalysis at each Follow-up Assessment
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Figure Number	Figure Title
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Listing Number	Listing Title
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