Statistical Analysis Plan

An Open-label, Parallel-Group Study to Evaluate the Pharmacokinetics of Lemborexant and its Metabolites in Subjects with Mild and Moderate Hepatic Impairment Compared to Healthy Subjects

Protocol Number: E2006-A001-104

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Previous Versions

Not Applicable

SAP Amendments before database lock

Version	Issue Date	Section	Revision/Addition	Rationale

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1 INTRODUCTION

This document details the planned statistical analyses for Eisai protocol E2006-A001-104.

The proposed analyses are based on the contents of V2.0 of the protocol (dated 28-Feb-2018).

This is a multicenter, single dose, open-label, parallel-group study in subjects with mild and moderate hepatic impairment and healthy control subjects matched with regard to age [±10 years], sex, and body mass index [BMI, ±20%]. The study will enroll a total of 24 subjects, including 16 subjects with impaired hepatic function; 8 subjects each in of Child-Pugh class A (mild) and B (moderate). At least 8 healthy subjects will be dosed as one control cohort to match (1:1) to the subjects with hepatic impairment in each Child-Pugh class with regard to age, sex, and BMI.

The study will consist of 2 phases: Prerandomization and Treatment. The Prerandomization Phase will include 2 study periods; Screening and Baseline (Day -1). The subjects will be admitted to the clinical facility on Day -1, remain confined to the clinic until Day 8, and then return to the clinical facility for additional pharmacokinetic (PK) sampling as outpatients until Day 14. In the event of early discontinuation of the subjects, the subjects with Child Pugh Class A and B (Cohorts A and B) and the matched controls (Cohort C) may be replaced. On Day 1, the subjects will be administered a single 10-mg dose of lemborexant with approximately 240 mL of water in the morning after an overnight fast. The blood samples for PK assessments will be collected at prespecified intervals up to 312 hours postdose administration. The subjects will be discharged on Day 14 of the study. In addition, the blood samples for plasma protein binding assessments of lemborexant will be collected from each subject at 2 time points; approximately 1 hour and 24 hours postdose.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the effect of mild and moderate hepatic impairment on the PK of lemborexant after a single dose administration.

2.2 Secondary Objectives

- To evaluate the effects of hepatic impairment on the PK of lemborexant metabolites M4, M9, and M10.
- To evaluate the relationship between the PK parameters of lemborexant and its metabolites and the Child-Pugh Classification score, serum albumin, total bilirubin, and prothrombin time.

- To assess safety and tolerability of lemborexant following a single dose administration in subjects with mild and moderate hepatic impairment and healthy subjects.

2.3 Exploratory Objectives

To explore the relationship between the PK parameters of lemborexant and its metabolites and the model of end stage liver disease (MELD) score.

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}	maximum observed concentration
t_{max}	time at which the highest drug concentration occurs
$AUC_{(0\text{-}72)}$	area under the concentration-time curve from zero time to 72 hours postdose
$AUC_{(0\text{-}t)}$	area under the concentration-time curve from zero time to time of last quantifiable concentration
$AUC_{(0\text{-}inf)}$	area under the concentration-time curve from zero time extrapolated to infinite time
AUC_{ex}	the percentage of $AUC_{(0\text{-}inf)}$ based on extrapolation
$t_{1/2}$	terminal elimination phase half-life
CL/F	apparent total body clearance (lemborexant only)
V_z/F	apparent volume of distribution (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
fu	Plasma protein fraction unbound
AUCu	$AUC_{(0\text{-}inf)}$ values adjusted by unbound fraction in plasma (for lemborexant only)
CLu/F	Apparent clearance relative to the unbound plasma concentration based on AUCu (for lemborexant only)

Lemborexant and its metabolites plasma concentrations will be listed and tabulated.

$AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} of lemborexant are the primary PK parameters. The rest of the parameters, including the PK parameters of the metabolites, are 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, Electrocardiogram (ECG) and the performance of physical examinations.

4 SAMPLE SIZE

A sample size of 8 subjects per each cohort of mild and moderate hepatic impairment, as defined by Child-Pugh classes A or B, is based on the recommendations in regulatory guidelines for a minimum number of subjects to be enrolled for moderate liver impairment cohort (FDA, 2003). Additionally, from single-dose studies of the 10-mg tablet (E2006-A001-004, E2006-A001-005, and E2006-A001-008), the pooled between-subject standard deviations of logarithmically transformed C_{max} and $AUC_{(0-inf)}$ of lemborexant were 0.334 and 0.391 respectively. With a sample size of 8 subjects in each Child-Pugh category and at least 8 matched controls, a 2-sided 90% confidence interval (CI) for the ratio for $AUC_{(0-inf)}$ will extend 0.322 from the observed mean difference on the log scale.

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 he/she has provided informed consent.

6.1.2 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set is the group of subjects who dosed with the test drug and had sufficient PK data to derive at least 1 PK parameter.

6.1.3 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 MELD Score

The MELD score at Screening for each subject (in each of the three cohorts) will be calculated as follows per the OPTN policy, January 2016 (pages 4-5)[2]:

First the initial MELD score will be calculated:

$$MELD(i) = [0.957 \times \log_e(Creatinine)] + [0.378 \times \log_e(bilirubin)] + [1.120 \times \log_e(INR)] + 0.643$$

This value will be rounded to two decimal places and multiplied by 10.

If calculated value for *MELD(i)* is > 11, the additional MELD calculation will be performed:

$$MELD = MELD(i) + [1.32 \times (137 - Serum\ Sodium)] - [0.033 \times MELD(i) \times (137 - Serum\ Sodium)]$$

This recalculated MELD value will be rounded to the nearest integer. If MELD(i) ≤ 11 then the recalculated MELD value will equal the initial MELD value.

The following scheduled screening values are used:

- Creatinine in mg/dL
- Bilirubin in mg/dL
- INR
- Sodium in mmol/L

Where the scheduled screening value is missing the first non-missing repeat scheduled value will be used.

The following additional rules will be followed:

- If the Bilirubin, Creatinine, or INR value is <1.0 a value of 1.0 will be used in the calculation.
- If Creatinine>4.0 mg/dL, a value of 4.0 will be used in the calculation
- If Sodium <125 mmol/L, a value of 125 will be used in the calculation.
- If Sodium >137 mmol/L a value of 137 will be used in the calculation.

The maximum MELD score is 40.

6.2.3 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, Pharsight Corporation), 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 or more 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
$AUC_{(0-72)}$	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
$AUC_{(0-t)}$	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, 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; calculated for lemborexant only
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 λz.

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 Vz/F will be reported based on the pharmacokineticist's judgment.

6.2.4 Baseline

Baseline for the safety variables is defined as the last non missing 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.

6.2.5 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.

6.2.6 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).

6.2.7 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.

6.2.8 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, Pharsight Corporation).

Listings will be sorted in the following order: cohort (Child Pugh Class A, Child Pugh Class B, followed by Healthy Subject cohort), subject, parameter, and day, unless otherwise stated. All data will be listed.

Continuous variables will be summarized by the number of non missing 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 non missing 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 cohort 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 cohort and overall.
- The number of early terminations and the primary reasons for terminations will be tabulated for all enrolled subjects by cohort 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 DB 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 cohort 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)
- Child Pugh Score
- Recalculated MELD Score (Initial MELD score will be listed only)
- Serum Albumin at Screening
- Total Bilirubin at Screening
- PT at Screening
- INR at Screening
- Creatinine at Screening

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 before the first dose of study drug and were continuing at the time of the first dose of study drug, or 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, 48, 72, 96, 120, 144, 168, 216, 264, and 312 hours postdose. In addition, blood samples for protein binding (12 mL per time point) of lemborexant and metabolites 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.

PK parameters for lemborexant and its metabolites (M4, M9, and M10) will be calculated as described in section 6.2.3.

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 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 WCT 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.

Protein binding will be calculated for metabolites without any assessment of PK parameters.

Evaluation of the impact of hepatic impairment on drug exposure:

The effect of hepatic impairment on the PK of lemborexant, the primary PK parameters based on total C_{max}, $AUC_{(0\text{-}72h)}$, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$ will be compared between the cohort of healthy normal controls and the cohorts of subjects with mild and moderate hepatic impairment as defined by Child-Pugh classes A or B. A general linear model of logarithmically transformed values with hepatic function class as a fixed effect will be utilized to estimate the geometric mean ratio (and two-sided 90% confidence intervals) of subjects with mild/normal and moderate/normal hepatic function. Similar statistical analyses will be conducted for the PK parameters of the metabolites and unbound lemborexant as secondary endpoints. Protein binding will be calculated for metabolites without any assessment of PK Parameters. Summary statistics will be generated for each of the PK parameters for each Child-Pugh class and healthy controls

Scatter plots of PK parameters (C_{max}, $AUC_{(0-72)}$, $AUC_{(0-t)}$ and $AUC_{(o-inf)}$) of lemborexant and its metabolites versus Child-Pugh Score at Screening will be provided. The association between the primary PK parameters and Child-Pugh Score will be evaluated by regression analysis (the PK parameter as a dependent variable and Child-Pugh Score as an independent variable). For subjects in the Healthy cohort the Child-Pugh score will be set to zero in the scatter plots and regression analysis. Similar analyses will be performed for the following measurements at Screening: MELD score, serum albumin, total bilirubin, PT, and creatinine. Additionally, association between the PK parameters and liver transaminase levels at Screening (ALT and AST) will be performed, if deemed necessary.

6.16 Pharmacogenomic Analysis

Not Applicable.

6.17 Safety Analyses

The safety analyses will be presented by cohort 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 cohort 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 6.2.8).
- 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 -.
- 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

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.

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

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 cohort at each scheduled assessment and Early Termination (if applicable) for each hematology, serum chemistry, urinalysis, and coagulation 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 cohort 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 cohort and overall.

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

There is no data safety monitoring board (DSMB) for this study.

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

None.

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
[2] https://optn.transplant.hrsa.gov/media/1575/policynotice_20151101.pdf

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.

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14.2.2.2	Descriptive Statistics for Percent Bound and Unbound of Lemborexant and Metabolites in Plasma after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) PK Analysis Set
14.2.3.1	Descriptive Statistics for Pharmacokinetic Parameters of Lemborexant after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) PK Analysis Set
14.2.3.2	Descriptive Statistics for Pharmacokinetic Parameters of M4 after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) PK Analysis Set
14.2.3.3	Descriptive Statistics for Pharmacokinetic Parameters of M9 after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic

Figure Number	Figure Title
14.2	**PK Analysis**
14.2.2.1	Mean Lemborexant and Metabolites Concentration-Time Profiles after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) on Linear and Semi-Logarithmic Scales PK Analysis Set
14.2.2.2	Lemborexant and Metabolites Concentration-Time Profiles for All Subjects after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A) on Linear and Semi-Logarithmic Scales Safety Analysis Set
14.2.2.3	Lemborexant and Metabolites Concentration-Time Profiles for All Subjects after Administration of Lemborexant 10 mg to Subjects with Moderate Hepatic Impairment (Cohort B) on Linear and Semi-Logarithmic Scales Safety Analysis Set
14.2.2.4	Lemborexant and Metabolites Concentration-Time Profiles for All Subjects after Administration of Lemborexant 10 mg to Subjects with Normal Hepatic Function (Cohort C) on Linear and Semi-Logarithmic Scales Safety Analysis Set
14.2.2.5	Concentration-Time Profiles after Administration of Lemborexant and Metabolites with Linear Regression for Estimating the Terminal Elimination Rate Safety Analysis Set
14.2.2.6	Box Plot Comparing Lemborexant and Metabolites C_{max} Values after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) PK Analysis Set
14.2.2.7	Box Plot Comparing Lemborexant and Metabolites $AUC_{(0-72)}$ Values after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) PK Analysis Set
14.2.2.8	Box Plot Comparing Lemborexant and Metabolites $AUC_{(0-t)}$ Values after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) PK Analysis Set

Listing Number	Listing Title
16.2.1	**Subject Disposition**
16.2.1.1	Subjects Disposition Enrolled Subjects
16.2.2	**Protocol Deviations**
16.2.2.1	Protocol Deviations Safety Analysis Set
16.2.2.2	Inclusion/Exclusion Not Met
16.2.3	**Demography, Baseline Characteristics, Treatment Compliance, and Analysis Populations**
16.2.3.1	Analysis Populations Enrolled Subjects
16.2.4.1	Demographics Enrolled Subjects
16.2.4.2	Child Pugh Classification Safety Analysis Set
16.2.4.3	Previous Medical History Safety Analysis Set
16.2.4.4	Ongoing Medical History Safety Analysis Set
16.2.4.5	Prior Medications Safety Analysis Set
16.2.4.6	Concomitant Medications Safety Analysis Set
16.2.5.1	Dosing Information Safety Analysis Set
16.2.6	**PK**
16.2.6.1	Lemborexant and Metabolites Concentration-Time and Protein Binding Data Listing by Subject Safety Analysis Set
16.2.6.2	Lemborexant Pharmacokinetic Parameter Listing by Subject PK Analysis Set
16.2.6.3	M4, M9, and M10 Pharmacokinetic Parameter Listing by Subject PK Analysis Set
16.2.6.4	Terminal Elimination Rate of Lemborexant and Metabolites for Individual Subjects after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic

STATISTICAL ANALYSIS PLAN

POST DATABASE LOCK ADDENDUM

An Open-label, Parallel-Group Study to Evaluate the Pharmacokinetics of Lemborexant and its Metabolites in Subjects with Mild and Moderate Hepatic Impairment Compared to Healthy Subjects

Protocol Ref: E2006-A001-104

Version: 1.0

Date effective: 24-JUL-2018

SUMMARY OF SECTIONS

1. INTRODUCTION

This document is a post database lock addendum to the statistical analysis plan dated 11 May 2018 which details the planned statistical analyses for the Eisai protocol E2006-A001-104.

2. CHANGES/ADDITIONS TO EXISTING ANALYSIS PLAN

Section 6.2.3 Pharmacokinetic Parameters

The following parameter was added during the pharmacokinetic analysis, and included in subsequent comparisons across treatments.

$AUC_{(0-8)}$	Area under the plasma concentration–time curve from time zero to 8 h post dose; calculated using the linear-log trapezoidal rule (linear-up log-down), reported to 3 significant figures

Section 6.15 Pharmacokinetic Analysis

Descriptive statistics for unbound fraction protein were added. Additional figures; Scatterplots for Pharmacokinetic Parameters of Lemborexant and Metabolites versus Cohort, Scatterplots for Pharmacokinetic Parameters Adjusted by Unbound Fraction in Plasma, Protein binding box plots, AUC0-8 box plots comparing Lemborexant and Metabolites, and mean profiles truncated to 24 hours Postdose were added.

Section 12, LIST OF TABLES, FIGURES AND LISTINGS:

Minor updates were made to the order, numbering, and/or titles of the planned tables, listings, and figures containing pharmacokinetic data (concentration-time data, pharmacokinetic parameters, statistical analysis), and new outputs were added.

The pharmacokinetic tables in Section 16 were updated as follows:

Table added:

Table	Title
14.2.2.3	Descriptive Statistics for the Unbound Fraction (%) of Lemborexant and Metabolites in Plasma after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate

	Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) - PK Analysis Set
14.2.2.4	Descriptive Statistics for the Percent Unbound Fraction of Lemborexant and Metabolites in Plasma after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) with Averaged Time Points (1h and 24h) - PK Analysis Set
14.2.2.5	Descriptive Statistics for the Fraction Unbound Protein of Lemborexant and Metabolites in Plasma after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) with Averaged Time Points (1h and 24h) - PK Analysis Set
14.2.3.5	Descriptive Statistics for Pharmacokinetic Parameters of Lemborexant Adjusted by Unbound Fraction in Plasma after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) - PK Analysis Set

The pharmacokinetic listings in Section 16 were updated as follows:

Revised title:

Listing	**Title**
16.2.6.6	Lemborexant ANOVA SAS Output Text – PK Analysis Set

New Listings:

Listing	**Title**
16.2.6.7	M4 ANOVA SAS Output Text – PK Analysis Set
16.2.6.8	M9 ANOVA SAS Output Text – PK Analysis Set
16.2.6.9	M10 ANOVA SAS Output Text – PK Analysis Set
16.2.6.10	Lemborexant and Metabolites Pharmacokinetic Parameters Adjusted by Unbound Fraction in Plasma by Subject - PK Analysis Set

The pharmacokinetic figures in Section 14 were updated to the following:

Population changed:

Figure	Title
14.2.2.5	Concentration-Time Profiles after Administration of Lemborexant and Metabolites with Linear Regression for Estimating the Terminal Elimination Rate - PK Analysis Set

Figure added:

Figure	Title
14.2.2.7	Box Plot Comparing Lemborexant and Metabolites $AUC_{(0-8)}$ Values after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) - PK Analysis Set

Figures renumbered:

Figure	Title
14.2.2.8	Box Plot Comparing Lemborexant and Metabolites $AUC_{(0-72)}$ Values after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) - PK Analysis Set
14.2.2.9	Box Plot Comparing Lemborexant and Metabolites $AUC_{(0-t)}$ Values after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) - PK Analysis Set
14.2.2.10	Box Plot Comparing Lemborexant and Metabolites $AUC_{(0-inf)}$ Values after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) - PK Analysis Set

Figures added:

Figure	Title
14.2.2.11	Protein Binding (Percent Bound) Box Plots Comparing PBE2006A, PBM4A, PBM9A and PBM10A Values after Administration of

	Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) for 1 and 24 hours - PK Analysis Set
14.2.2.12	Scatterplots for Pharmacokinetic Parameters of Lemborexant and Metabolites versus Cohort - PK Analysis Set
14.2.2.13	Scatterplots for Pharmacokinetic Parameters Adjusted by Unbound Fraction in Plasma for Lemborexant and Metabolites versus Cohort - PK Analysis Set
14.2.2.14	Mean and Mean (SD) Lemborexant and Metabolites Concentration-Time Profiles after Administration of Lemborexant 10 mg to Subjects with Mild Hepatic Impairment (Cohort A), Moderate Hepatic Impairment (Cohort B), or Normal Hepatic Function (Cohort C) Truncated to 24 hours Postdose on Linear and Semi-Logarithmic Scales - PK Analysis Set

Figures renumbered:

Figure	**Title**
14.2.2.15	Scatterplot and Regression Analysis for Pharmacokinetic Parameters of Lemborexant and Metabolites versus Child-Pugh Score at Screening PK Analysis Set
14.2.2.16	Scatterplot and Regression Analysis for Pharmacokinetic Parameters of Lemborexant and Metabolites versus MELD Score at Screening PK Analysis Set
14.2.2.17	Scatterplot and Regression Analysis for Pharmacokinetic Parameters of Lemborexant and Metabolites versus Serum Albumin at Screening PK Analysis Set
14.2.2.18	Scatterplot and Regression Analysis for Pharmacokinetic Parameters of Lemborexant and Metabolites versus Total Bilirubin at Screening PK Analysis Set
14.2.2.19	Scatterplot and Regression Analysis for Pharmacokinetic Parameters of Lemborexant and Metabolites versus Prothrombin Time at Screening PK Analysis Set
14.2.2.20	Scatterplot and Regression Analysis for Pharmacokinetic Parameters of Lemborexant and Metabolites versus Creatinine at Screening PK Analysis Set
14.2.2.21	Scatterplot and Regression Analysis for Pharmacokinetic Parameters of Lemborexant and Metabolites versus ALT at Screening

	PK Analysis Set
14.2.2.22	Scatterplot and Regression Analysis for Pharmacokinetic Parameters of Lemborexant and Metabolites versus AST at Screening PK Analysis Set

Approval for implementation of
Statistical Analysis Plan Post Database Lock Addendum

Title: **An Open-label, Parallel-Group Study to Evaluate the Pharmacokinetics of Lemborexant and its Metabolites in Subjects with Mild and Moderate Hepatic Impairment Compared to Healthy Subjects**

Protocol Reference: **E2006-A001-104**

Sponsor: **Eisai, Inc.**

Addendum No: **1.0**

Date effective: **24-JUL-2018**

Author: PPD

Author:

WCT reviewer:

Author's signature: **Date:** 24 Jul 2018

Author's signature: **Date:** 24 Jul 2018

Reviewer's signature: **Date:** 24 July 2018

The above Statistical Analysis Plan Post Database Lock Addendum has been reviewed and approved by the Sponsor:

Name of Approver: PPD

Position:

Signature for sponsor: _____ Date: 24-Jul-2018