16.1.9   Documentation of Statistical Methods

The final approved Statistical Analysis Plan and other statistical documents, as applicable, for this study are provided in the following pages.

- Statistical Analysis Plan Version 1.0 May 21, 2020

- Adjudication Committee Charter Version 3.0 Sept 3, 2019

STATISTICAL ANALYSIS PLAN

Study Protocol Number: E2006-A001-312

Study Protocol Title: A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia

Date: May 21, 2020

Version: Final Version 1

1 TABLE OF CONTENTS

2 STANDARD LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	anatomical therapeutic class
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
DMC	data monitoring committee
DSMB	data safety monitoring board
FAS	full analysis set
LOCF	last observation carried forward
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
NI	noninferiority
PD	pharmacodynamic
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SI	Système International
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
WHO	World Health Organization

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-A001-312.

3.1   Study Objectives

3.1.1   Primary Objective

The primary objective of the study is to evaluate the proportion of adult (≥18 years) subjects with insomnia disorder taking zolpidem tartrate immediate release (ZOL-IR) or zolpidem tartrate extended release (ZOL-ER), intermittently or frequently, who successfully transition to lemborexant 5 mg (LEM5) or 10 mg (LEM10), after 2 weeks of receiving lemborexant (LEM).

3.1.2   Secondary Objectives

- To evaluate the proportion of subjects who increase from LEM5 to LEM10 or decrease from LEM10 to LEM5 during the 2-week Titration Period

- To evaluate the subjects' impression of treatment using the Patient Global Impression of Insomnia (PGI-I) at the end of the 2-week Titration Period

- To evaluate the safety and tolerability of LEM in subjects previously taking ZOL

3.1.3   Exploratory Objectives

- To evaluate LEM5 or LEM10 scores on the Insomnia Severity Index (ISI) compared with Baseline at the end of the 2-week Titration Period

- To evaluate LEM5 or LEM10 scores on the Quality of Sleep Rating scale compared with Baseline at the end of the 2-week Titration Period

- To compare nights on which an evening dose of LEM5, or LEM10 was taken, to nights on which an evening dose of ZOL was taken, for the following sleep-related actigraphy variables:
  - Total Sleep Time (TST)
  - Sleep Efficiency (SE)
  - Wake After Sleep Onset (WASO)
  - Wake Bouts

- To compare the daytime after an evening dose of LEM5, or LEM10 was taken, to the daytime after an evening dose of ZOL was taken, for the following wake-related actigraphy variable, Sleep Bouts.

3.2   Overall Study Design and Plan

E2006-A001-312 is a multicenter Phase 3b pilot study evaluating the transition of LEM when administered as a replacement for ZOL-IR or ZOL-ER.

The study will consist of 3 phases: a Pretreatment Phase (consisting of up to a 3-week Screening Period and a 1-day Baseline Period), a Treatment Phase (consisting of a 2-week Titration Period), and an Extension Phase consisting of the Maintenance Period up to 12 weeks. The 4 week Follow-up Period will occur immediately following the end of the Treatment Phase for those not continuing into the Maintenance Period or after the Maintenance Period for those who continue.

The Pretreatment and Treatment Phases will comprise the Titration Period. A Follow-up Period visit occurring 4 weeks after the end of the Extension Phase (or Treatment Phase, for subjects not entering the Extension Phase) will be conducted. An overview of the study design is presented in Figure 1.

Figure 1   Study E2006-A001-312 – Study Design

LEM5 = Lemborexant 5 mg, LEM5 = Lemborexant 5 mg, R = Randomization

Screening Period

During the Screening Period, subjects will continue to take ZOL at the dosage strength prescribed by their health-care provider. Subjects must enter data into the data collection system for at least 14 (preferably contiguous) days out of the allowable 21-day Screening

Period in order to be eligible for study inclusion. Actigraph data will be downloaded and transmitted to the central reader at the end of screening, along with the sleep log of bedtimes, morning wake times, and the approximate times when the actigraph was replaced on the subject's wrist.

Based on ZOL use during the Screening Period, subjects will be assigned to either Cohort 1 (Intermittent ZOL Use) or Cohort 2 (Frequent ZOL Use).   The subjects who meet both criteria for intermittent and frequent ZOL use for 1 week each of the last 2 weeks of the 3-week Screening Period will be assigned to Cohort 1 and referred to as Cohort 1-Mixed (group 1B).

All subjects in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). For Cohort 2, subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio. Upon completion of the Baseline Period (1-day), subjects who remain eligible will enter the Titration Period.

Titration Period

During the 2-week Titration Period, subjects will follow the following schedule:

Cohort 1 (Only Intermittent use or Mixed Use; Treatment groups 1A and 1B): Subjects in this cohort will decide when to take LEM according to their usual pattern, with the requirement that they take LEM at least once per week during the 2-week Titration Period.

Cohort 2 (Frequent Use 5mg or 10 mg, Treatment Groups 2A and 2B): Subjects in these cohorts will take LEM at least 5 nights per week during the 2-week Titration Period.

For subjects with a starting dose of LEM5 in Cohorts 1 and 2, subjects will be encouraged (but not mandated) to remain on their assigned dose for 7 days before calling the site should they feel that LEM5 is not fully effective for treatment of their insomnia.

For subjects with a starting dose of LEM10 in Cohort 2, subjects will be encouraged to remain on their assigned dose for 7 days before calling the site should they feel that LEM10 should be reduced.

At the time of LEM dose change during the Titration Period, the reason for the dose change will be recorded in the case report form (CRF). Subjects will be allowed 1 LEM dose adjustment during the Titration Period. Every morning, subjects will enter their insomnia drug use data into the data collection system and record their sleep log data, and, provided an insomnia drug was taken the night prior, PGI-I and Quality of Sleep Rating will be completed. The ISI will be completed at each study visit except Follow-up Visit.

Upon completion of the Titration Period, actigraphs will be returned to the study site, and subjects will be considered for eligibility to enter the Extension Phase.

Extension Phase

Maintenance Period

During the 12-week Maintenance Period, subjects will continue on the dose of LEM that they took at the end of the Titration Period. LEM dose changes may be implemented during the maintenance period as clinically determined by the investigator with input from the subject.

Follow-up Period

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for all subjects.

The end of the study will be the date of the last study visit for the last subject in the study.

4   DETERMINATION OF SAMPLE SIZE

As a pilot study, sample size estimates are not based on statistical calculations.

This study will enroll approximately 60 subjects across 3 treatment arms (Cohort 1 (A and B), Cohort 2A, and Cohort 2B) to evaluate the proportion of subjects who transition to LEM as a substitute for zolpidem. Approximately twenty subjects will be assigned to Cohort 1 (Intermittent ZOL Use), and approximately 40 subjects will be assigned to Cohort 2 (Frequent ZOL Use).

This study is designed to reflect clinical practice, in which patient satisfaction of the treatment after switching is an important consideration for maintaining a patient on that treatment. This was the basis for defining the outcome of transition to Lemborexant. While sleep quality assessments are included as secondary outcomes in this pilot study to supplement the Phase 3 clinical trial data, it is not necessary to establish the absolute amount of improvement in sleep parameters, but rather whether the subject is satisfied enough to continue treatment with Lemborexant.

Hence this sample size is deemed sufficient to inform whether the proposed strategies are sufficient to evaluate whether alternative strategies would be required to help understand how best to recommend safe and effective methods for transitioning from ZOL to LEM.

5   STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects. The study endpoints for efficacy and safety will be presented by treatment group (LEM5 and LEM10) and by pooling across treatments within each cohort and overall.

5.1   Study Endpoints

5.1.1   Primary Endpoint(s)

The primary endpoint is the proportion of overall subjects who successfully transition to LEM at the end of the Titration Period.

Transition to LEM is defined as a subject who remains on LEM at the end of the 2-week Titration Period and either 1) enters the Extension Phase, or 2) chooses to not enter the Extension Phase for reasons not related to LEM (including, but not limited to, time commitment related to the study, study-related travel expenses, or preference to continue insomnia management with another health care provider).

5.1.2   Secondary Endpoint(s)

The secondary endpoints are as follows:

- The proportion of subjects who transition to LEM at the end of the 2-week Titration Period within each Cohort.
- The proportion of subjects in the LEM5 treatment groups with dose increasing to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 treatment group with dose decreasing to LEM5 at the end of the Titration Period in Cohort 2.
- The proportion of subjects with positive medication effect rating on each PGI-I item at the end of the 2-week Titration Period by Cohort and overall using the value at the end of the Titration Period.

5.1.3   Exploratory Endpoint(s)

The exploratory endpoints are as follows:

- The change from Baseline in mean ISI score at the end of the Titration Period by Cohort and overall using end of the Titration Period.
- The change from baseline in mean Quality of Sleep Rating at the end of the Titration Period by cohort and overall using end of the Titration Period.
- To compare nights on which an evening dose of LEM5, or LEM10 was taken, to nights on which an evening dose of ZOL was taken, for the following sleep-related actigraphy variables:
  - Mean TST
  - Mean SE
  - Mean WASO

- Number of Wake Bouts

• To compare the daytime after an evening dose of LEM5, or LEM10 was taken, to the daytime after an evening dose of ZOL was taken, for the following wake-related actigraphy variable:

- Mean Duration of Sleep Bouts

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

<u>Safety Analysis Set (SAS)</u> –The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

<u>Full Analysis Set (FAS)</u> – All subjects who received at least 1 dose of LEM will be included in the Full Analysis Set.

Analyses based on FAS and SAS will use the "as treated" Cohort/Dose. Additional sensitivity analysis will be conducted using "as planned" Cohort/Dose.

5.2.2 Subject Disposition

The number of subjects screened and the number failing screening (overall and by reason for failure) will be summarized. Screen failure data will be listed. The number of subjects treated along with the number of subjects in each of the study populations will also be presented.

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 and treatment discontinuation. Other reasons for study treatment and study terminations will also be summarized. These tabulations will be produced for all treated subjects by cohort.

Listing and disposition summary for the subjects related to COVID-19 will be created.

5.2.3 Protocol Deviations

Criteria for determining major protocol deviations are defined in "Study 312 deviation table" and placed in eTMF.

The following categories are identified for determining the major protocol violations:

• Violations of inclusion/exclusion criteria

• Noncompliance of study drug/dosage intervention

• Use of prohibited concomitant medications

• Subject assigned to incorrect cohort

- Missing baseline and post-baseline study visits

Individual subjects with these protocol deviations will be listed.

5.2.4   Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized by cohort and overall Dose using descriptive statistics. Continuous demographic variables include age, height, weight, and BMI; categorical variables include sex, age group (<65 years old; ≥65 years old), BMI group (<18.5, 18.5 to <25, 25 to ≥30), race, and ethnicity. Medical History will be summarized using MedDRA SOC and PT.

Characteristics of insomnia at Study Baseline will be summarized using ISI, PGI-I, and Quality of Sleep Rating.

5.2.5   Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization WHO Drug Global October 2019 or later. The number (percentage) of subjects who took prior and concomitant medications, and prior and concomitant sleep medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO-DD PT.

Prior medications are defined as medications that stopped before the first dose of study drug (Lemborexant).

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

5.2.6   Treatment Compliance

Number of subjects with last dose will be summarized along with Percentage of dose taken.

5.3   Data Analysis General Considerations

5.3.1   Pooling of Centers

Subject distribution across sites will be investigated. Subjects from all centers will be pooled for all analyses.

5.3.2   Adjustments for Covariates

Not applicable as no modelling for the data is planned.

5.3.3   Multiple Comparisons/Multiplicity

No multiplicity adjustment is planned for this open-label pilot study.

5.3.4   Examination of Subgroups

No subgroup analyses are planned for this study.

5.3.5   Handling of Missing Data, Dropouts, and Outliers

No handling of missing data is planned for this study.

5.4   Efficacy Analyses

All efficacy analyses will be conducted on the FAS.

5.4.1   Primary Efficacy Analyses

The analysis of the primary endpoint will be conducted on Titration Period only.

- The proportion of overall subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed using frequency and percentages by cohort using the last dose. Last dose is the dose taken by the subjects at the time of discontinuation or at the time when they entered the extension period.

5.4.2   Secondary Efficacy Analyses

The analysis of the secondary endpoints will be conducted on Titration Period only.

- The proportion of subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed within each cohort using frequency and percentages.

- The proportion of subjects in LEM5 who increased the dose to LEM10 at the end of the Titration Period by Cohort and overall using frequency and percentages.

- The proportion of subjects in LEM10 who decreased the dose to LEM5 at the end of the Titration Period will be displayed in Cohort 2 using frequency and percentages.

- Proportion of subjects in each of the 4 items of the PGI-I will be summarized using frequency and percentages separately within each scale over time by cohort and overall using end of the Titration Period dose groups.

- The proportion of subjects whose response on the first 3 items of the PGI-I (medication effect) was neutral or negative at Baseline, but who recorded a positive effect on these items at the end of the Titration Period, and the proportion of subjects who rated the drug as being too strong or too weak at Baseline, but whose rating was "just right" at the end of the Titration Period (as data allow) will be reported using frequency and percentages.

5.4.3   Other Efficacy Analyses

Time to first dose change will be summarized. Dose changes made by the investigator (planned) and dose changes listed in the diary (actual) will be summarized using number of subjects that made the change. Dose changes over time will be listed along with the number of days when the change was made since the start of study.

A graphical representation of changes between the 5 and 10 mg dose groups in each of the cohorts may be presented.

No other efficacy analyses are planned for this study. Exploratory objectives are presented in Section 5.8.

5.5   Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

5.6   Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables). Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

Safety variables include incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

5.6.1   Extent of Exposure

The cumulative extent of exposure (days of exposure) to study drug will be summarized descriptively. Number of doses taken/week will be summarized by cohort for the study drug and zolpidem.

5.6.2   Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 22.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A 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.

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

The incidence of AEs will be summarized by end of Titration Period dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and by PT will be calculated. Incidence (%) by causal relationship with study drug and by severity will also be calculated.

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

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related])

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

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

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

The number (percentage) of subjects with TEAEs of cataplexy or other events that are characterized according to a Customized MedDRA Query (CMQ) PT as cataplexy-related events, as well drug abuse liability will be summarized separately. The number of adjudicated events based on the report of the Adjudication Committee will also reported separately. In addition, at each visit, subjects will be asked whether they have had a fall since the previous visit. If yes, supplemental information must be obtained to support a

narrative for the event, as per the Adjudication Committee description. For clinically significant events, time of onset, and recovery will be reported.

AEs summaries, and abnormal findings will also be displayed based on the dose that the subjects were taking at the time of the findings.

5.6.3   Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate.

For all quantitative parameters listed in protocol Section 9.5.1.5 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics.

Qualitative parameters listed in protocol Section 9.5.1.5 Safety Assessments (Laboratory Measurements) will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will be used to compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

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

5.6.4   Vital Signs

Mean changes from baseline in vital signs (i.e., systolic and diastolic BP, pulse, respiratory rate, body temperature, and weight) and out-of-range vital signs will be summarized by end of Titration Period dose groups by cohort using descriptive statistics.

Clinically notable vital sign values will be identified on the listings as those above (H) or below (L) a clinically notable range (Table 1). Changes from baseline in clinical notable vital signs will be summarized, and number and percent of subjects who fall outside the

clinically notable vital sign ranges will also be presented for change from study Baseline for Safety Analysis Set by cohort using end of Titration Period dose.

Table 1   Clinically Notable Vital Sign Criteria

Variable	Criterion Value[a]	Change Relative to Study Baseline[a]	Clinically Notable Range
Heart rate	>120 bpm	Increase of 15 bpm	H
	<50 bpm	Decrease of ≥15 bpm	L
Systolic BP	>180 mmHg	Increase of ≥20 mmHg	H
	<90 mmHg	Decrease of ≥20 mmHg	L
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L

BP = blood pressure, 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 Study Baseline.

5.6.5   Electrocardiograms

ECG assessments will be performed at Screening and at the end of the Titration Period. Mean changes from baseline in ECG findings will be summarized by end of Titration Period dose by cohort using descriptive statistics. Shift tables will present changes from baseline in ECG interpretation (categorized as normal and abnormal).

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

Absolute QTc interval prolongation:

* QTc interval >450 ms

* QTc interval >480 ms

* QTc interval >500 ms

Change from baseline in QTc interval:

* QTC interval increases from baseline >30 ms

* QTC interval increases from baseline >60 ms

5.6.6   Other Safety Analyses

The results of C-SSRS assessments will be listed for each subject. The incidence of suicidal ideation or suicidal behavior will be summarized by treatment group as appropriate.

Urine drug test results and pregnancy test results will also be listed.

5.7   Other Analyses

The proportion of overall subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed using frequency and percentages by cohort using Modal dose at the time of discontinuation or at the time when they entered extension. Modal dose is the dose taken by subjects for the majority of days during the Titration Period on the nights when they took the study drug.

Additional safety analyses may also be conducted using Modal dose as appropriate.

Sensitivity analysis will be conducted by summarizing disposition, transition and Adverse Event incidence table using the planned cohort/dose group,

Findings from the Sleep drug experience interview will be summarized for ZOL and LEM along with the summaries for chief complaint related to sleep drugs.

5.8   Exploratory Analyses

- Change from Baseline of the total score from items 1 to 7 as well as items 4 to 7 on the ISI will be summarized at the end of the Titration Period by Cohort and overall using end of the Titration Period dose groups.

- The change from baseline in mean Quality of Sleep Rating score for subjects at the end of the Titration Period will be summarized by cohort and overall using end of the Titration Period dose groups.

- Average value of following sleep-related actigraphy variables will be summarized by treatment over the nights on which an evening dose of LEM5, LEM10, and ZOL was taken using end of the Titration Period dose groups.
    - Mean TST
    - Mean SE
    - Mean WASO
    - Number of Wake Bouts

- Average value of wake-related actigraphy variable, mean duration of Sleep Bouts, will be summarized by treatment over the daytime after an evening dose of LEM5, LEM10, and ZOL was taken using end of the Titration Period dose groups.

Exploratory endpoints will also be analyzed using Modal Dose. Additional efficacy endpoints may be analyzed as appropriate. Any exploratory analyses that are performed will be appropriate titled and labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

5.9   Extension Phase Analyses

Subjects who complete the Titration Period and wish to continue taking LEM will enter the 12-week Extension Phase. Subjects will continue the LEM dose and regimen established during the Titration Period; however, the dose may be titrated up or down depending on response and tolerability, per subject input and investigator judgement. For subjects who are eligible for the Extension Phase but who do not wish to continue study participation, the reason for discontinuation from the study will be recorded. At the end of the Extension Phase, the Follow-up Period will begin, and last for 4 weeks.

Extension Phase Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post-dose safety assessment for the extension phase.

The primary focus of data summarization for the Extension Phase will be on safety and tolerability. The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized by cohort using descriptive statistics.

Evaluation of data will be performed on the extension phase safety analysis set over the entire study (Titration Period plus Extension period) using modal dose. Modal dose for extension period is the dose taken by subjects for majority of days during the entire study period on the nights when they took the study drug.

Additional summaries of data for the extension period will include the following: Disposition information, concomitant medications, and prior sleep related concomitant medications will be summarized. A list of major protocol deviations as defined as above for the core study period will be created. Treatment compliance will be summarized using % of dose taken similar to the Titration period.

Time to first dose change will be summarized. Dose changes made by the investigator (planned) will be summarized using number of subjects that made the change. Dose changes over time will be listed along with the number of days when the change was made since the start of study. The cumulative extent of exposure (days of exposure), and number of doses taken/week of study drug will be summarized by cohort.

6   INTERIM ANALYSES

No interim analyses is currently planned for this study.

7   CHANGES IN THE PLANNED ANALYSES

There are no changes to the planned analyses.

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 (i.e., study visit captured on the CRF) will be used as the analysis visits in all by-visit summaries. Where applicable, the Early Term visit will be used along with last visit for completers as the End of Treatment visit for the safety analyses.

8.2   Baseline Assessment

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

9   PROGRAMMING SPECIFICATIONS

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

10   STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS 11.1 or later.

11   MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG 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

Study protocol E2006-A001-312: A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia. (V4.0), 01 Oct 2019 (Amendment 02)

13 APPENDICES

13.1 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 – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <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

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

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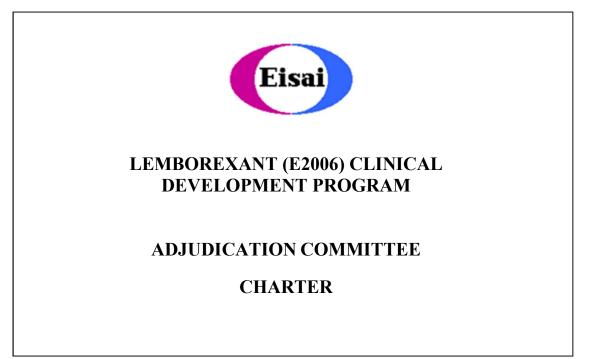Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

SIGNATURE PAGE

Remove table rows that are not applicable. For example, if there is only 1 author delete the table rows for the second author.

Author(s): *If there is 1 author, remove "(s)" in the heading; if there is more than 1 author, remove the parentheses around the "s."*

Study Statistician signs here

<Name, degree(s)>	Date
<title>	

(Note: There may be more than 1 SAP author, eg, a CRO statistician may also be an author of the SAP.)

If applicable, the second author signs here

<Name, degree(s)>	Date
<title>	
<legal name of non-Eisai company>*(if applicable)*	

Approval:

The biostatistics head signs here

Biostatistics Head of <insert therapeutic area>	Date
<Name, degree(s)>	
<title, department>	

The study director signs here

Study Director	Date
<Name, degree(s)>	
<title, department>	

Additional approver(s) as per local SOP or as otherwise required.

<Function title>	Date
<Name, degree(s)>	
<title, department>	

1   TITLE PAGE

LEMBOREXANT (E2006) CLINICAL DEVELOPMENT PROGRAM

ADJUDICATION COMMITTEE

CHARTER

CONFIDENTIAL

This is an Eisai, Inc. document that contains confidential information. Nothing herein is to be disclosed without written consent from Eisai, Inc.

Note: This Charter will serve as the Standard Operating Procedure (SOP) for the Adjudication Committee.

CHARTER SIGNATURE PAGE

<div align="center">

Eisai

LEMBOREXANT (E2006) CLINICAL DEVELOPMENT PROGRAM

CHARTER SIGNATURE PAGE

</div>

Reviewed and Approved by:

PPD

17 Sept 2019
_____
                    Date

Reviewed and Approved by:

PPD

03 Sept 2019

_____
                    Date

2   TABLE OF CONTENTS

LIST OF APPENDICES

3   LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AC	Adjudication Committee
CRO	contract research organization

4   INTRODUCTION

The adjudication of adverse events that may represent cataplexy or seizure by an expert Adjudication Committee ("AC") is being done in order to provide standardized, systematic, and independent assessments of these adverse events in the lemborexant clinical trials.

This charter defines the membership, roles, responsibilities and deliverables of the AC. This charter also provides the procedures for ensuring confidentiality, the purpose and timing of reviews for adjudication and the deliverables generated by the AC. Reference materials that may be provided to the Committee include copies of the final protocols for the clinical trials from which events will be adjudicated.

5   COMPOSITION OF THE ADJUDICATION COMMITTEE

This Committee will comprise 3 physicians (inclusive of the Chair), drawn from the field of sleep medicine and/or neurology. The committee members will be independent from the clinical trials in which the adverse events for adjudication will be reported. Each event to be adjudicated will require review by and input from all 3 members.

6   INDEPENDENCE OF THE ADJUDICATION COMMITTEE

It is essential that the judgment of members of the AC not be influenced by factors other than those necessary to adjudicate the reviewed events. The membership has been restricted to individuals free of apparent significant conflicts of interest. Independence is essential to ensure the AC is objective and capable of an unbiased assessment of the adverse events being adjudicated. The following will ensure the independence of the AC:

- Members will not have participated as investigators in the studies from which events are being adjudicated
- Members must not have a direct interest in knowing or influencing the clinical development program outcome or have a financial interest in the outcome of the program
- Members may not hold a significant equity or other financial interest in Eisai, Inc.

Each member will be responsible for declaring potential conflicts. A verbal confirmation of any changes in each member's Conflict of Interest will be addressed prior to each adjudication review cycle, and documented in the review cycle's minutes, or at a minimum once a year, whichever is more frequent. Members of the AC who develop potential or significant perceived conflicts of interest will be asked to resign. A replacement member will be selected prior to the next review cycle if necessary.

7   CONFIDENTIALITY PROCEDURES

As part of the consulting agreement detailing the services provided as members of the AC, which must be fully executed prior to the first review cycle, each member provided a confidentiality agreement.

8   RESPONSIBILITIES OF THE ADJUDICATION COMMITTEE

8.1   Primary objective

- Adjudicate each adverse event from any clinical trial with lemborexant that is coded to a customized list of preferred terms that can potentially be considered to be an adverse event of cataplexy or seizure as well as any adverse event (as reported) of cataplexy or seizure to confirm agreement with the coded term or adjudicate that the event was instead cataplexy or seizure

8.2   General responsibilities

- Fully accepts and understands role as AC member
- Reviews all documents provided in the AC adjudication packets
- Protects the confidentiality of the data from the clinical trials and the AC discussions
- Ensures the outcomes of the AC are based upon an unbiased evaluation of the materials provided (e.g., narratives)

9   ADJUDICATION COMMITTEE CHAIR RESPONSIBILITIES

- Presides over the AC review cycles and ensures that the review cycle minutes and adjudication outcome(s) are appropriately documented
- Serves as the primary contact person for the AC
- Reviews and approves the AC Charter
- Communicates the adjudication process, including any revisions necessary during the course of the trial
- Participates in the resolution of any adjudication disagreements

10   EISAI RESPONSIBILITIES

- Selects and approves Chair and members
- Makes final versions of clinical study protocols and/or clinical study reports and the IB available
- Drafts, reviews and approves AC Charter
- Manages AC honoraria, contracts, and approved incidental expenses

11   AC COORDINATOR ADMINISTRATIVE RESPONSIBILITIES

- Provides final versions of clinical study protocols and/or clinical study reports and the IB to the AC
- Receives a narrative for each event and builds the adjudication packets for submission to the AC members as directed by the charter

- Facilitates the collection of additional source documents requested from the AC

- As applicable for ongoing studies, follows up with site and clinical teams (i.e., Phase 1 unit, CRO, and/or Eisai clinical team) for documents to complete the adjudication packets or for supplemental information requested by the AC for a particular subject whose adverse event is being adjudicated

- Assists the Chair in the preparation of the AC Charter

- In conjunction with the Chair, coordinates the AC review cycles, distributing adjudication packet materials to the AC as appropriate

- Tracks decisions of the AC members during each review cycle

12 ADVERSE EVENTS TO BE REVIEWED

The AC will review, in a blinded manner, adverse events that could potentially be considered cataplexy or seizure. A set of preferred terms constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query for cataplexy is used to identify events for adjudication. The customized MedDRA query includes the following terms:

cataplexy, seizure, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, fall, atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia, transient ischemic attack, and convulsions [SMQ narrow and broad]

Investigators participating in lemborexant clinical studies can also identify AEs that they believe are related to cataplexy beyond those listed above.

Subject narratives are written for each subject in whom one or more of the adverse events has been identified.

To assist in the preparation of narratives about such events and to support the adjudication process, investigators and site personnel are instructed to query subjects who report any of the above events for supplemental information about the events. This supplemental information is obtained using a questionnaire with the supplemental information obtained subsequently entered into the electronic case report form. Investigators and site personnel may also provide any supplemental information on the Serious Adverse Events reporting form for any of the above events considered serious.

13 REVIEW PROCESS

The schematic below depicts the adjudication review process for studies that are ongoing.

Site
- Obtains AE reports and supplemental information
- Enters information into eCRF
- Responds to queries with additional documents or eCRF details

AC Coordinator
- Liaises with sites to compile adjudication packets
- Responsible for coordinating workflow among all parties
- Compiles adjudication packets and provides to AC Members
- Responsible for transferring adjudication results to Eisai

AC Chair and Members
- Reviews materials in adjudication packets, decides whether there is agreement with verbatim term from investigator, or if in disagreement, whether the event is cataplexy
- Iteratively discusses as necessary to achieve consensus, or decides consensus cannot be achieved
- Chair relays adjudication result for each event to AC Coordinator

AC Coordinator
- Compiles and transfers all AC results to Eisai via data transfer

For studies that are ongoing, narratives for events that have already been adjudicated may be updated with new information and re-adjudicated by the Committee. Narratives for previously adjudicated events will be updated if any of the following details of the previously adjudicated event have changed:

- Start date of the event
- End date of the event
- Severity of the event
- Verbatim adverse event terms within the narrative
- Serious criteria
- Event outcome
- Date of outcome

In addition, if a subject has an additional event that would require adjudication, the original narrative will be updated with the details of the new event. All events will be adjudicated. The narratives that require re-adjudication will be provided to the Committee with the treatment assignment blinded.

In each adjudication packet, each committee member will receive one Adjudication Form for each event. In the case of multiple events, the same narrative will be provided, but the determination will be made on an event-by-event basis. An example of the Adjudication Form is in Appendix 3. The AC member is to decide whether or not the event under review represents cataplexy or seizure. If there is disagreement with the investigator's verbatim term (reported term), the AC member is to (1) provide a basis for disagreeing with the accuracy of the investigator's verbatim term and (2) specify how they would have reported the adverse event on the basis of the information available.

The AC Chair will receive an Adjudication Consensus Form with the adjudication packet for each event. An example of the Adjudication Consensus Form is in Appendix 4. On the Adjudication Consensus Form, the AC Chair will provide the adjudicated result. The possible outcomes are:

- *The verbatim term was not cataplexy or seizure, and the event does not represent cataplexy or seizure*
- *The verbatim term was not cataplexy or seizure, but the event represents cataplexy*
- *The verbatim term was not cataplexy or seizure, but the event represents seizure*
- *The verbatim term was cataplexy, but the event does not represent cataplexy or seizure*
- *The verbatim term was cataplexy, but the event represents seizure*
- *The verbatim term was cataplexy, and the event represents cataplexy*
- *The verbatim term was seizure, but the event does not represent seizure or cataplexy*
- *The verbatim term was seizure, but the event represents cataplexy*
- *The verbatim term was seizure, and the event represents seizure*
- *Consensus Not Achieved*
- *Not Enough Information*

Each Adjudication Form and Adjudication Consensus Form must also denote whether the event is a re-adjudication of a previously adjudicated event (No or Yes).

14 TRANSFER OF ADJUDICATED RESULTS TO EISAI

In order to permit the result of the adjudication for each event to be included in the clinical database for the ongoing study in which the event was reported, the decision of the AC's review of the event will be provided to Eisai by the Chair. The AC Coordinator will obtain the Adjudication Result Form for each event from the AC Chair. The AC Coordinator will generate a listing of all adjudicated results, prepared according to agreed data transfer specifications, and will transfer these data to Eisai.

The adjudicated results of events from completed studies will be reported in the Integrated Summary of Safety in new drug applications for registration purposes; study level databases

will not be updated with the adjudicated information.

15 COMMUNICATION

The AC Coordinator will keep track of all AC member correspondence, comments, and iterative discussions and from these, will generate minutes for each AC review cycle for inclusion in AC Master File.

16 TIMING OF REVIEW CYCLES

It is anticipated that narratives will be reviewed by the AC members prior to database lock. If no event requiring adjudication is reported in a given clinical trial, no review cycle is required.

17 REVISIONS TO THE CHARTER

In the event revisions are necessary after original Charter approval, the revised Charter, designated as Version 4.0, will be sent to AC for approval and signature.

The AC Coordinator will distribute the final revision of the Charter as appropriate.

The above process will be followed for subsequent revisions, with the version number increasing sequentially.

18 COMPLETION OF AC ACTIVITIES

The duration of AC activities will continue until the clinical development program for lemborexant has been completed.

19 DOCUMENT RETENTION

The AC Coordinator will compile and maintain the following documents:

- All versions of the Charter
- The minutes of each AC review cycle
- Copies of all adjudication packets provided to the AC
- Copies of relevant correspondence related to this AC
- Upon completion of the activities of the AC, the documents will be forwarded to Eisai, Inc. for archiving.

Appendix 1   Charter Signature Page Template

Due to the geographically dispersed Adjudication Committee, a separate signature page was created for each member.

LEMBOREXANT (E2006) CLINICAL DEVELOPMENT PROGRAM

ADJUDICATION COMMITTEE

Member Information

Role: Chair

Name: PPD

Specialty:

Affiliation: PPD

I have reviewed the Adjudication Committee Charter (Version 3.0, 03 September 2019) and approve it as written. I understand my role as the Chair of this Committee.

PPD

Signature: _____**Date:** _____**03 Sept 2019** _____

LEMBOREXANT (E2006) CLINICAL DEVELOPMENT PROGRAM

ADJUDICATION COMMITTEE

Member Information

Role: Member

Name: PPD

Specialty: PPD

Affiliation:

I have reviewed the Adjudication Committee Charter (Version 3.0, 03 September 2019) and approve it as written. I understand my role as a Member of this Committee.

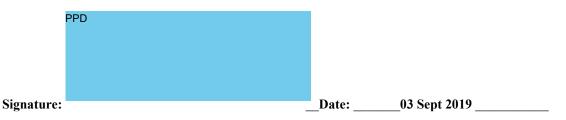**Signature:** PPD   **Date:** 9/5/19

Eisai

LEMBOREXANT (E2006) CLINICAL DEVELOPMENT PROGRAM

ADJUDICATION COMMITTEE

Member Information

Role: Member

Name: PPD

Specialty:

Affiliation

I have reviewed the Adjudication Committee Charter (Version 3.0, 03 September 2019) and approve it as written. I understand my role as a Member of this Committee.

Signature: PPD _____ **Date:** 09/17/2019

Appendix 2   Adjudication Committee Roster

Adjudication Committee Members			
Title	**Name/Affiliation**	**Address**	**Telephone number/ E-mail**
PPD			

Appendix 3   Adjudication Form

Adjudication Form
Lemborexant Clinical Trials

Subject #   **E2006-A001-312 ########** _____

Event #   _____

Event Verbatim Term   _____

Based on the subject narrative with information about this event, which of the following is accurate?

☐ **The verbatim term was not cataplexy or seizure, and the event does not represent cataplexy or seizure**

☐ **The verbatim term was not cataplexy or seizure, but the event represents cataplexy**

☐ **The verbatim term was not cataplexy or seizure, but the event represents seizure**

☐ **The verbatim term was cataplexy, but the event does not represent cataplexy or seizure**

☐ **The verbatim term was cataplexy, but the event represents seizure**

☐ **The verbatim term was cataplexy, and the event represents cataplexy**

☐ **The verbatim term was seizure, but the event does not represent seizure or cataplexy**

☐ **The verbatim term was seizure, but the event represents cataplexy**

☐ **The verbatim term was seizure, and the event represents seizure**

If you disagree with the investigator's verbatim term, please provide the basis for this.

☐ **Not enough information**

☐ **Other** _____

If you disagree with the investigator verbatim term, please specify how you would have reported the adverse event on the basis of the information available.

_____

Is this a re-adjudication of a previously adjudicated event? ☐ No   ☐ Yes

Adjudication Committee Member

Signature _____   **Date:** _____

Appendix 4   Adjudication Consensus Form

Lemborexant Clinical Trials

Subject #   **E2006-A001-312 ########_____**

Event #   **_____**

Event Verbatim Term   **_____**

The result of adjudication of this event by the Adjudication Committee members is:

☐   **The verbatim term was not cataplexy or seizure, and the event does not represent cataplexy or seizure**

☐   **The verbatim term was not cataplexy or seizure, but the event represents cataplexy**

☐   **The verbatim term was not cataplexy or seizure, but the event represents seizure**

☐   **The verbatim term was cataplexy, but the event does not represent cataplexy or seizure**

☐   **The verbatim term was cataplexy, but the event represents seizure**

☐   **The verbatim term was cataplexy, and the event represents cataplexy**

☐   **The verbatim term was seizure, but the event does not represent seizure or cataplexy**

☐   **The verbatim term was seizure, but the event represents cataplexy**

☐   **The verbatim term was seizure, and the event represents seizure**

☐   **Consensus Not Achieved**

☐   **Not Enough Information**

Is this a re-adjudication of a previously adjudicated event?   ☐ **No**   ☐ **Yes**

Adjudication Committee Chair

Signature_____   **Date: _____**