STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2006-A001-113
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 2-Period, Crossover Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Subjects With Moderate to Severe Obstructive Sleep Apnea and Adult and Elderly Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease
Date:	19 Aug 2020
Version:	Version 1.0

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AHI	apnea hypopnea index
ANOVA	analysis of variance
ATC	anatomical therapeutic class
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
EOS	end of study
E-R	exposure response
GOLD	Global Initiative for Chronic Obstructive Lung Disease
MedDRA	Medical Dictionary for Regulatory Activities
NREM	non rapid eye movement
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PSG	polysomnography
REM	rapid eye movement
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	Système International
SOC	system organ class

Abbreviation	Term
SpO_2	mean oxygen saturation
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
TST	total sleep time
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-A001-113.

3.1 Study Objectives

3.1.1 Primary Objectives

OSA Cohort:

- Using polysomnography (PSG), determine whether lemborexant increases the apnea hypopnea index (AHI) on Day 8 of treatment in adult and elderly subjects (adults ≥45 to <65 years; elderly ≥ 65 to 90 years) with moderate to severe obstructive sleep apnea (OSA) compared with placebo

COPD Cohort:

- Using pulse oximetry, determine whether lemborexant decreases mean oxygen saturation (SpO2) during TST on Day 8 of treatment in adult and elderly subjects with moderate to severe chronic obstructive pulmonary disease (COPD) compared with placebo

3.1.2 Secondary Objectives

OSA Cohort:

- Using PSG, determine whether lemborexant increases the AHI on Day 1 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant decreases the mean oxygen saturation (SpO2) during total sleep time (TST) on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant increases the percentage of TST during which the SpO2 is <90%, <85%, and <80% on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant decreases the mean oxygen desaturation index (ODI) during TST on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant decreases the absolute number of desaturations (≥3% reduction from Baseline SpO2) during TST on Days 1 and 8 of treatment compared with placebo
- Evaluate safety and tolerability of lemborexant compared with placebo

COPD Cohort:

- Using pulse oximetry, determine whether lemborexant decreases mean SpO2 during TST on Day 1 of treatment compared with placebo
- Using PSG, determine whether lemborexant increases the AHI on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant increases the percentage of TST during which the SpO2 is <90%, <85%, and <80% on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant decreases the mean oxygen desaturation index (ODI) on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant decreases the absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment compared with placebo
- Evaluate safety and tolerability of lemborexant compared with placebo

3.1.3 Exploratory Objectives

OSA and COPD Cohorts:

Explore the effects of lemborexant compared with placebo on the following for Days 1 and 8 of treatment:

- The mean SpO2 during rapid eye movement (REM) sleep, non-REM (NREM) sleep, and wake
- The mean ODI during REM sleep and NREM sleep
- The absolute number of desaturations during REM sleep and NREM sleep
- AHI during REM and NREM sleep
- Determine whether lemborexant increases the AHI, and decreases the mean SpO2 during TST separately for adult and elderly subjects
- Determine whether lemborexant increases the mean ODI, and increases the absolute number of desaturations, during TST separately for adult and elderly subjects

In addition, explore the following pharmacokinetic (PK) endpoints for both OSA and COPD Cohorts:

- Plasma concentrations of lemborexant and its metabolites (M4, M9, and M10)
- Exposure-response (E-R) relationships between lemborexant concentrations and pharmacodynamic (PD) variables, including but not limited to respiratory safety variables (AHI, mean SpO2 during TST, percentage of TST in which SpO2 is <90%, <85%, and <80%, means ODI, and absolute number of desaturations).

3.2 Overall Study Design and Plan

In the OSA and COPD Cohorts, this will be a randomized, double-blind, placebo-controlled, 2-period crossover study. There will be 2 phases, Prerandomization and Randomization. The Prerandomization Phase will last up to 21 days and will consist of the Screening Period and Baseline Period. The Randomization Phase will comprise 2 Treatment Periods, each of 8 days duration, separated by a washout interval of at least 14 days, and a Follow-Up Period of 14 days. Twenty-eight days after the final study dose, there will be an end of study (EOS) Visit.

4 DETERMINATION OF SAMPLE SIZE

OSA Cohort:
A mean difference between treatments in AHI >5 is considered clinically meaningful in studies of the respiratory safety of sleep agents in OSA (Kruger, et al., 2007, Sun, et el., 2016). The within-subject variance is assumed to be 25.34 for AHI for adult subjects (Sun, et al., 2016) and 30.41 for AHI for elderly subjects (where the elderly within-subject variance is estimated from adult data +20%, Mitterling, et al, 2015; Lee, et al, 2016). Assuming the true difference in AHI (lemborexant –placebo) on Day 8 is as high as 1.5, a total of 30 subjects completing the study (20 adult, 10 elderly), provides 82% power that the upper bound of the 90% CI for the treatment difference in AHI (lemborexant − placebo) on Day 8 would be less than 5.

Description	Combined within-subject variance of AHI	Adult N	Elderly N	Total N	Total Power (%)
80% overall power with 20 adult subjects	**26.96**	**20**	**10**	**30**	**82**
85% overall power with 20 adult subjects	27.38	20	14	34	86
80% overall power with 20 elderly subjects	28.54	12	20	32	82
85% overall power with 20 elderly subjects	28.16	16	20	36	86
Equal number of subjects	27.875	20	20	40	90

COPD Cohort:

A 2% decrease in mean SpO2 during TST is considered a clinically meaningful change. For the primary hypothesis (mean SpO2 during TST on Day 8), assuming a true within subject variance of 1.07% for mean SpO2, a significance level of 0.05, and a true difference of -1 percent point, a total of 30 subjects completing the crossover study provides 99% power that the lower bound of the 90% confidence interval for the mean difference in mean SpO2 (LEM- placebo) on Day 8 would be greater than -2 percent points. The true difference could be as low as -1.23% and the study still would have had 80% power to support the hypothesis.

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. All analyses will be performed separately for OSA and COPD cohorts.

5.1 Study Endpoints

5.1.1 Efficacy Endpoints

Not applicable.

5.1.2 Safety Endpoints

OSA AND COPD COHORTS

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, electrocardiograms, and clinical laboratory tests separately for each cohort.

5.1.3 Pharmacokinetic (PK) Endpoints

OSA AND COPD COHORTS

Lemborexant plasma concentrations at all days assessed for separately both cohorts

5.1.4 Pharmacodynamic (PD) Endpoints

PRIMARY ENDPOINT (OSA COHORT)

- AHI on Day 8 of treatment

SECONDARY ENDPOINTS (OSA COHORT)

- AHI on Day 1 of treatment
- Mean SpO2 during TST on Day 1 and Day 8 of treatment

- The percentage of TST during which the SpO2 is <90%, <85% and <80% on Day 1 and Day 8 in of treatment

- Mean oxygen desaturation index (ODI) on Days 1 and 8 of treatment
- Absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment

PRIMARY ENDPOINT (COPD COHORT)

- Mean SpO2 during TST on Day 8 of treatment

SECONDARY ENDPOINTS (COPD COHORT)

- Mean SpO2 during TST on Day 1 of treatment
- AHI on Day 1 and Day 8 of treatment
- The percentage of TST during which the SpO2 is <90%, <85% and <80% on Day 1 and Day 8 of treatment
- Mean oxygen desaturation index (ODI) on Days 1 and 8 of treatment
- Absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment

EXPLORATORY ENDPOINTS (OSA AND COPD COHORTS)

- Mean SpO2 during REM sleep, NREM and wake on Day 1 (and Day 8 for OSA Cohort) of treatment separately for each cohort
- AHI during REM and NREM sleep on Day 1 and Day 8 of treatment separately for each cohort
- AHI separately for adult and elderly subjects at all days assessed separately for each cohort
- Mean SpO2 during TST separately for adult and elderly subjects at all days assessed separately for each cohort

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

Enrolled subjects will be defined as all subjects who provided informed consent. The two cohorts will be treated separately for all summaries and analyses. For the purposes of analysis the following analysis sets have been identified separately for each cohort:

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

- The PK Analysis Set for each cohort is the group of subjects who received at least 1 dose of lemborexant and had at least 1 quantifiable plasma concentration after dosing with lemborexant.
- The Pharmacodynamic Analysis Set for each cohort is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.

5.2.2 Subject Disposition

Reasons for screening failure will be summarized.

The number and percentage of subjects who completed the study will be summarized by treatment group and by sequence, and the number who discontinued prematurely will be summarized by reason for discontinuation by treatment group and by sequence.

5.2.3 Protocol Deviations

Major protocol deviations will be presented as a listing.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each sequence and for all study drug groups combined using descriptive statistics. Continuous demographic and baseline variables include age, height, BMI, and weight variables; categorical variables include sex, age group (adults ≥45 to <65 years; elderly ≥ 65 to 90 years), race, and ethnicity.

MEDICAL HISTORY

A subject data listing of medical and surgical history will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (March 2019 or later). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications are defined as medications that (1) started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug to the last dose day plus 14 days. A concomitant medication in Treatment Period 1 is counted up to predosing of Treatment Period 2; a concomitant medication in Treatment Period 2 is counted up to the final study visit.

All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Compliance for the both the OSA and COPD cohorts for each study drug will be calculated on the basis of the number of tablets dispensed, lost and returned, for all randomized subjects.

$$\text{Compliance} = \frac{\text{Number of tablets dispensed - number of tablets returned or lost}}{\text{Number of tablets expected to be taken by the subject for the treatment period}} \times 100$$

If subject's treatment period was extended for any reason then the number of tablets expected to be taken will be increased appropriately. Summaries will provide descriptive summary statistics and number (percentage) of subjects using the categories <80%, >= 80% to <= 100%, >100% to <= 120%, and > 120% for each treatment group.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

The randomization stratification by age group will be reflected in models for the analysis of the primary and secondary PD endpoints by incorporating age group as a fixed effect.

5.3.3 Multiple Comparisons/Multiplicity

No multiplicity adjustments will be made for this is a Phase 1 safety study.

5.3.4 Examination of Subgroups

Separate analyses will be performed for the 2 age groups (≥45 and <65 years and ≥65 to 90 years) for the primary and secondary PD endpoints in addition to the analyses in which age group is treated as a covariate. Separate analyses also will be performed for subjects with moderate OSA (15≤AHI<30) and severe OSA (AHI≥30) and for subjects with moderate COPD (GOLD 2 Classification) and severe COPD (GOLD 3 Classification) if there are sufficient numbers of subjects in the subgroups.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

In general, missing values due to subject discontinuation, missed or unusable assessments will not be imputed.

Incomplete/Missing data will not be imputed, unless otherwise specified; i.e., all missing values will remain as missing in all statistical analyses and listings, unless otherwise specified.

No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

5.3.6 Other Considerations

The OSA and COPD cohorts will be analyzed separately. If one of the cohorts completes earlier than the other, the database may be locked for that cohort and the data analyzed before the database is locked for the other cohort.

Individual subject data in the database will be presented in data listings.

For the analyses of the primary and secondary endpoints the estimands will be the difference between lemborexant and placebo for the difference from baseline. The PD analysis set will be used for these analyses and since the endpoints are safety endpoints, the assignment of treatment group will be the treatment actually received. Any missing values will be considered to be missing at random. In a previous lemborexant study in subjects with OSA, missing values were due to dropout for administrative reasons.

5.4 Efficacy Analyses

No efficacy data will be collected in this study.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

The Safety Analysis Set will be used for individual lemborexant and M4, M9 and M10 plasma concentration listings. The PK Analysis Set will be used for summaries of lemborexant and M4, M9 and M10 plasma concentrations. Since only 1 blood sample for PK determination will be obtained on each study day, no PK parameters will be calculated.

5.5.1 Pharmacodynamic Analyses

The following analysis will be performed on the PD Analysis Set for each cohort.

Analysis for the Primary Endpoint

OSA Cohort: Mean AHI will be analyzed on the PD Analysis Set using repeated measures ANOVA, for Day 8 of each treatment period. The model will include fixed effects for age group, sequence, period, and treatment, and a random effect for subject within sequence. The following will be presented: LS means, difference in LS mean of lemborexant 10 mg compared to placebo, and the two-sided 90% CI (equivalent to a one-sided upper 95% CI) for the true mean difference (lemborexant − placebo) in AHI. If the upper bound of the one-sided 95% CI of the treatment difference of AHI is less than 5, this will provide evidence that the given dose of lemborexant does not result in a clinically significant increase in AHI with mild OSA compared with placebo.

Plots of AHI treatment difference data (both individual and LS Mean) will be used to explore the results.

COPD Cohort: Mean SpO2 will be analyzed on the PD Analysis Set using repeated measures ANOVA, of values on Day 1 of each treatment period. The model will include

fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. The following will be presented: least squares (LS) means, difference in LS mean of lemborexant 10 mg compared to placebo, and the two-sided 90% CI (equivalent to a one-sided lower 95% CI) for the true mean difference (lemborexant − placebo) in SpO2. If the lower bound of the one-sided 95% CI of the treatment difference of SpO2 is greater than -2 (for active – placebo), this will provide evidence that the given dose of lemborexant does not result in a clinically significant decrease in SpO2 compared to placebo.

Plots of SpO2 treatment difference data (both individual and LS Mean) will be used to explore the results.

Analysis for the Secondary Endpoints

The secondary endpoints will be analyzed using the same model as the primary endpoint.

5.5.2 Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/Pharmacodynamic (Exposure-Response) Analyses

The exposure-response (E-R) relationship between plasma concentrations of lemborexant after PSG, and selected PD parameters including but not limited to the respiratory safety variables (including AHI, mean SpO2 during TST, ODI, absolute number of desaturations, and percentage of TST in which SpO2 is <90%, <85%, and <80%) will be explored graphically. Any emergent relationship may be followed using population model-based analysis. The potential effect of covariates (eg, age) on the E-R relationship may be tested. The PK Analysis Set will be used for these assessments.

5.5.3 Pharmacogenomic/Pharmacogenetic and Other Biomarker Analyses

Not applicable.

5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group, will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, and the C-SSRS. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

The incidence of AEs, out-of normal-range markedly abnormal laboratory variables, out-of-range vital signs, and suicidality variables (C-SSRS) will be summarized by treatment for OSA and COPD cohorts using descriptive statistics.

5.6.1 Extent of Exposure

The extent of exposure (mean daily dose, cumulative dose [calculated as the sum of the daily doses], and duration of exposure) to each treatment will be summarized descriptively by treatment and cohort, and a listing will also be provided.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 19.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerged during treatment, having been absent at pretreatment (Baseline) or

- Reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE was 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 TEAEs will be summarized by treatment group separately for each cohort. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with 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) *(or* by highest CTCAE grade).

A TEAE in Treatment Period 1 is counted up to predosing of Treatment Period 2 a TEAE in Treatment Period 2 is counted up to the final study visit.

Separate listings will be provided for subjects with deaths, SAEs, and AEs leading to discontinuation.

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 cohort using descriptive statistics (eg, mean, SD, median, minimum, maximum for continuous variables, and number and percentage for categorical variables) for the laboratory parameters and changes from baseline.

Qualitative parameters listed in protocol Section 9.5.1.5 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.

Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the clinical study report for this study. 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-cohort comparisons will be based on 3 by 3 tables (shift tables) that, for a particular laboratory test, compare the Study Baseline LNH classification to the LNH classification at end of study/early termination, by treatment group.

Clinical laboratory results postbaseline will be evaluated for markedly abnormal values. A laboratory test will be considered markedly abnormal if the result worsens to meet Eisai grading criteria for laboratory values limit of Grade 2 or higher. If the Grade 2 limit is missing, the Grade 1 limit will be considered. Appendix 13.1 presents the Eisai grading criteria for laboratory values that were used to identify subjects with markedly abnormal laboratory values. For the incidence of markedly abnormal laboratory values, each subject may be counted once in the laboratory parameter value high and in the laboratory parameter low categories as applicable.

5.6.4 Vital Signs

Descriptive summary statistics for vital sign parameters (diastolic and systolic blood pressure, pulse, and respiration rate) will be evaluated by treatment at predose and at postdose for Day 1 and Day 8. In addition, change from predose to each postdose time will be summarized by treatment. Baseline will be the pre-dose value in each treatment period. Each cohort will be analyzed separately.

Clinically notable ranges will be summarized by treatment and time point and will be defined as follows:

Table 1 Vital Sign Criteria

Variable	Criterion value[a]	Change relative to baseline[a]	Clinically notable range
Heart rate	>120 bpm	Increase of ≥ 15 bpm	H
	<50 bpm	Decrease of ≥15 bpm	L
Systolic BP	>180 mmHg	Increase of ≥20 mmHg	H
	<90 mmHg	Decrease of ≥20 mmHg	L
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L

BP = blood pressure, bpm = beats per minute, H = high, L = low.

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

Vital sign values will be listed on an individual basis by cohort, treatment and subject. Abnormal vital sign values will be identified on the listings as those above (H) or below (L) a clinically notable range.

5.6.5 Electrocardiograms

A 12-lead safety ECG will be recorded for all subjects at Screening, Baseline, and at follow-up. The overall number and percentage of subjects with normal, abnormal, clinically, and non clinically-significant ECG results will be summarized at Screening, Baseline, and at Follow-up. Investigator assessments of normality/abnormality will also be listed.

5.6.6 Other Safety Analyses

No other safety analyses are planned for this study.

5.7 Other Analyses

Not applicable.

5.8 Exploratory Analyses

Summaries and plots of all endpoints may be produced for appropriate subgroups (eg, age group, sex, BMI, race). Subgroup analyses will also be performed as appropriate on primary and secondary endpoints. Exploratory endpoints will be analyzed using the same model as the primary endpoints.

6 INTERIM ANALYSES

No interim analyses are planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

Not applicable.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

No missing data will be imputed.

8.1 Pharmacokinetic Data Handling

8.1.1 Lower Limit of Quantification of E2006 Plasma Concentration

The LLOQ of E2006 as well as metabolites M4, M9 and M10 plasma concentration is 0.0500 ng/mL.

8.1.2 BLQ Handling for Calculation of PK Parameters

Not applicable.

8.1.3 BLQ Handling for Developing Concentration-Time Profiles

Not applicable.

8.1.4 Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow the guidance in the NCA-MNL.

8.1.5 General Rules for Presentation of Drug Concentrations

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

8.1.6 General Rules for Presentation of PD Parameters

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

Typical variable	N	Digit rule	Raw Minimum Maximum	Mean Median	SD
AHI	X	Fixed decimal places	2	2	3
SpO2	…	Fixed decimal places	2	2	2
% of TST	X	Fixed decimal places	3	3	2
ODI	X	Fixed decimal places	2	2	2
Number of desaturations	X	Fixed decimal places	…	1	2

9 PROGRAMMING SPECIFICATIONS

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

All analysis will be done separately for each cohort.

All pharmacodynamic and safety data will be presented using nominal timepoint as reported in the data. No additional derivation will be performed for analysis visit window.

10 STATISTICAL SOFTWARE

Analysis will be performed using SAS (release 9.4 or newer), Phoenix WinNonlin (version 6.4 or newer), PDx-POP (version 5.2 or newer). Pharsight Knowledgebase Server (version 3.0 or newer), Microsoft Excel (2010 or newer), and NONMEM (version 7.3 or newer), R (3.3.2 or newer).

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

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C-SSRS Reference

http://www.cssrs.columbia.edu/scales_cssrs.html

GOLD 2019

https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 1.

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 2.5×ULN if baseline was normal; 2.0 – 2.5×baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
ALT	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
AST	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN if baseline was normal; 1.0 – 1.5×baseline if baseline was abnormal	>1.5 – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 10.0×ULN if baseline was normal; 3.0 – 10.0×baseline if baseline was abnormal	>10.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium <LLN - 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	<6.0 mg/dL <1.5 mmol/L Ionized calcium <0.8 mmol/L; life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium >ULN - 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	>13.5 mg/dL >3.4 mmol/L Ionized calcium >1.8 mmol/L; life-threatening consequences
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 - 3.0×baseline; >1.5 – 3.0×ULN	>3.0×baseline; >3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 2.5×ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Glucose, serum-high (hyperglycemia)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	life-threatening consequences; urgent intervention indicated
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L; intervention initiated	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	125-129 mmol/L and asymptomatic	<125 – 129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN without physiologic consequences	N/A	>ULN with physiologic consequences	life-threatening consequences

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

13.2 SAS Code for ANOVA

Proc Mixed can be used to analyze the crossover design data as follows:

```
proc mixed data=XXXX;
class sequence patient period treatment;
model Response= sequence period treatment /solution
ddfm=satterth;
random patient(sequence);
lsmeans treatment / pdiff cl e;
run;
```

For subgroup analyses use the above code with by variable.

SIGNATURE PAGE

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