Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational New Drug

Centanafadine Sustained Release Tablets (EB-1020)

Efficacy of Centanafadine SR as a Potential Smoking Cessation Treatment

Protocol No. 405-201-00055

IND No. 155242

STATISTICAL ANALYSIS PLAN

Version: 1.0

Date: May 9, 2022

Protocol Date: August 16, 2021

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice daily
BMI	Body mass index
CRF	Case report form
CO	Carbon monoxide
CCI	[redacted]
ECG	Electrocardiogram
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigative new drug
MedDRA	Medical Dictionary for Regulatory Activities
MHI	Medication handling irregularity
PE	Physical examination
SAE	Serious adverse event
SAP	Statistical analysis plan
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO	World health organization

1 Introduction

This statistical analysis plan (SAP) describes the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of data collected under the clinical protocol 405-201-00055. The SAP is consistent with latest version of protocol version 3.0 dated on 16 August 2021.

2 Study Objectives

2.1 Primary Objective

The primary objective is to determine whether centanafadine yields a superior four-week continuous smoking abstinence rate compared to varenicline during Week 4 to Week 7.

2.2 Secondary Objective

The secondary objective is to determine if centanafadine yields equivalent efficacy to that of varenicline, with less incidence of nausea, the most prevalent side effect reported following varenicline treatment.

3 Trial Design

3.1 Type/Design of Trial

This single-group, small-scale, open-label, phase 2 study evaluates centanafadine as a potential smoking cessation treatment. Participants enrolled in the study will be given centanafadine SR at a dose of 400 mg total daily dose (TDD) (200 mg twice daily [BID]) approximately 4 to 6 hours apart for seven weeks. The study consists of a 28-day screening period, a baseline visit, a 7-week treatment period, and a 7-day safety follow-up period. Participants visit the study center a total of 6 times, including a screening visit (V1), baseline visit (V2), a visit one week (+3 days) after starting the study drug (Week 1 visit V3), three weeks (±3 days) after starting the study drug (Week 3 visit V4), five weeks (±3 days) after starting the study drug (Week 5 visit V5), and seven weeks (±3 days) after starting the study drug (Week 7 visit V6). All participants are requested to participate in a 7-day safety follow up period, which will consist of telephone contact seven days (+2 days) after the last dose of investigational medicinal product (IMP).

A schematic of the trial design for this study is provided in Figure 3.1-1.

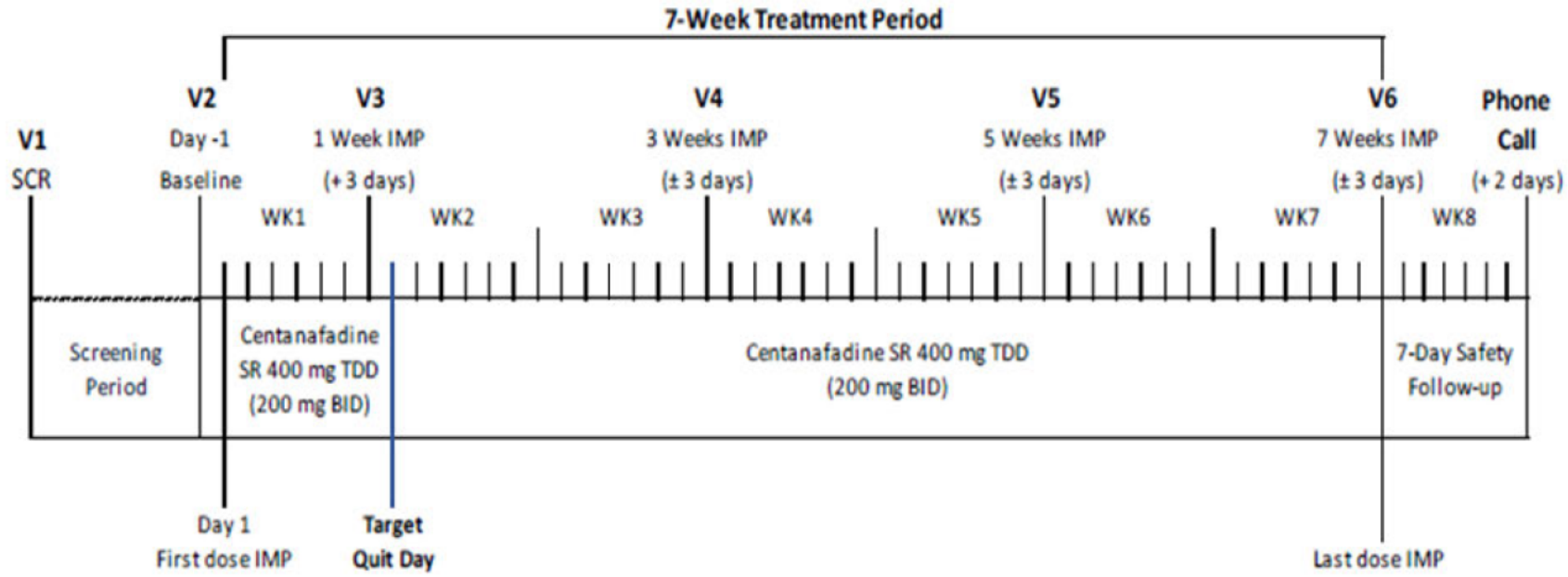

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

The dose of centanafadine SR that participants receive is 400 mg TDD (200 mg BID) approximately 4 to 6 hours apart for seven weeks.

The IMP dose may be considered for a one-time dose decrease based on tolerability and/or adverse events (AEs). A one-time dose decrease to 200mg TDD, based on the clinical judgement of the investigator, may be considered. The subject would remain on the decreased dose (200mg TDD) for the remainder of trial participation. If tolerability / AE does not resolve, post IMP dose-reduction, the subject should be considered for trial discontinuation, based on investigator judgement.

3.3 Trial Population

The study population includes 50 cigarette smoking adults. Smokers between 21 and 65 years of age (inclusive), 18 to 40 kg/m^2 (inclusive) of body mass index(BMI), with no restriction on gender, race and ethnicities, or social-economic status, and have smoked an average of at least 10 commercially available cigarettes per day for the last 12 months will be screened. Subjects who have an expired air carbon monoxide (CO) reading of at least 10 ppm at screening, express a desire to quit smoking within the next 30 days, and own a smart phone with text message and data capabilities compatible with necessary surveys will be eligible for inclusion.

4 Sample Size

This is a single-arm trial to assess the effect of centanafadine for a four-week continuous smoking abstinence rate during Week 4 to Week 7.

Table 4-1shows the 90% confidence interval for 50 subjects when the four-week continuous smoking abstinence rate is 0.3, 0.4, 0.45 and 0.5.[1]

Table 4-1 90% Confidence Interval for Sample Size of 50 Subjects

Confidence Level	Sample Size	Actual Width	Proportion	Lower Limit	Upper Limit
0.9	50	0.22885	0.3	0.19488	0.42373
0.9	50	0.24299	0.4	0.28313	0.52612
0.9	50	0.24639	0.45	0.32912	0.5755
0.9	50	0.24751	0.5	0.37625	0.62375

Lower limit and upper limit are 90% confidence interval of the proportion given the sample size and proportion of four-week continuous smoking abstinence.

5 Statistical Analysis Datasets

5.1 Enrolled Analysis Set

Enrolled Analysis Set includes all subjects who sign an informed consent form (ICF) for the trial and are assigned to treatment at the baseline visit.

5.2 Safety Analysis Set (SAS)

Safety Analysis Set includes all subjects who are administered at least one dose of IMP, regardless of any protocol violation.

5.3 Full Analysis Set (FAS)

Full Analysis Set includes all subjects who are administered at least one dose of IMP.

5.4 Trial Visit Window

The actual assessment date is mapped into the trial week based on Table 5.4-1. Trial days are derived from the formula: Trial Day = Date of assessment - Date of 1st IMP + 1. Based on the number of trial days, subjects are mapped to the corresponding trial week. In addition, only last observations within the same mapped weeks are reported in the summary tables by trial week.

Table 5.4-1 Mapped Trial Week Windows for Efficacy Analysis

Mapped Week	Mapped Trial Day Range[a,b]
Week 1	Day 1 - Day 7
Week 2	Day 8 - Day 14
Week 3	Day 15 - Day 21
Week 4	Day 22 - Day 28
Week 5	Day 29 - Day 35
Week 6	Day 36 - Day 42
Week 7	Day 43 - Day 49

[a] Relative days to the first day of IMP.

[b] Evaluations occurring more than three days after the last dosing date will be excluded from the analyses.

5.5 Handling of Missing Data

Missing data will not be imputed from analyses.

6 Primary and Secondary Outcome Variables:

6.1 Primary Outcome Variables

The primary outcome variable is four-week continuous smoking abstinence rate during Week 4 to Week 7.

6.2 Secondary Outcome Variables

Secondary outcome variable is the incidence of nausea at any timepoint after drug administration begins.

7 Disposition and Demographic Analysis

7.1 Subject Disposition

Subject disposition will be summarized by center.

Subject completion rate and reasons for discontinuation will be summarized for the enrolled analysis set.

7.2 Demographic and Baseline Characteristics

Baseline demographic characteristics include age, sex, race, ethnicity, height, weight, and BMI. For the enrolled analysis set, demographic characteristics will be summarized.

Mean, range and standard deviation will be used to describe continuous variables such as age. Frequency distributions will be tabulated for categorical variables such as race.

Baseline value is defined as the value at baseline visit (Day −1), if the value at the baseline visit is not available, the baseline value will be last evaluable assessment prior to the first dose of IMP.

7.3 Medical History

A summary of all medical history will be presented for the enrolled analysis set.

7.4 Treatment Compliance

Based on the IMP panel of the CRF, compliance in taking IMP is calculated by dividing the number of tablets taken by the total number of tablets the patients were scheduled to take during the study period. For lost-to-follow up patients, last IMP end date record will be used as the treatment end date. Treatment compliance will be summarized for the enrolled analysis set.

7.5 Prior and Concomitant Medications

The number and percentage of subjects taking concomitant medications will be tabulated by drug classification using the World Health Organization (WHO) drug dictionary for enrolled analysis set. Concomitant medications taken prior to start of treatment period and during treatment period will be summarized.

7.6 Protocol Deviation

Major protocol deviations will be summarized by type of deviation. In addition, a subject listing will be provided describing the deviations for each subject.

7.7 Smoking History

Smoking history will be summarized using descriptive statistics and reported for enrolled analysis set.

7.8 CCI

CCI

8 Efficacy Analysis

8.1 Primary Efficacy Endpoint

The primary outcome variable is four-week continuous smoking abstinence rate during Week 4 to Week 7.

8.1.1 Primary Efficacy Analyses

The primary endpoint with the treatment of centanafadine is the four-week continuous abstinence rate of subjects during Week 4 to Week 7. A participant is considered abstinent from combustible cigarettes if he or she self-reports tobacco abstinence (no cigarette smoking, not even a puff) assessed by responses to daily messages throughout the period and has an exhaled CO level of less than 5 ppm using the Vitalograph Breath CO monitor in the office at scheduled Week 5 and Week 7. An intent-to-treat approach is

taken in which any participants lost to follow-up / early termination after receiving the IMP, or who have smoked during Week 4 to Week 7 will be counted as non-abstinent.

Primary endpoint calculation:

- Set it as four-week continuous abstinence:
  - If there is no smoking in the self-report.
  - And if subject has exhaled CO level of less than 5 ppm using the Vitalograph BreathCO monitor in the office at scheduled Week 5 or Week 5 value is missing.
  - And if subject has exhaled level of less than 5 ppm using the Vitalograph BreathCO monitor in the office at scheduled Week 7.
  - Missing value check:
    - For CO value, only one missing value is allowed, and Week 7 value cannot be missing.
    - For self-report value, only one missing in each visit Week (7 days) is allowed. The missing value is checked per each week.

- All the others will be set as non-abstinent.
  - Week 7 CO value is missing
  - Two or more missing in self-report in each visit week (7 days)
  - Lost to follow-up/Early termination
  - Subjects with actual data that they were smoking. (CO value ≥ 5 ppm or any smoking record in self-report.)

A descriptive statistic will be provided for the continuous smoking abstinence rate during Week 4 to Week 7 with 90% binomial confidence intervals. For all binomial confidence intervals, it is based on normal approximation. If the number of abstinent or the number of non-abstinent ≤ 5, we will use the exact method.

8.1.2 Sensitivity Analysis I

Missing value is allowed. No need to check missing value. All the missing values during the treatment period will be considered as no-smoking.

Sensitivity analysis I endpoint calculation:

- Only subjects with adequate data that they were smoking during Week 4 to Week 7 are set as non-abstinent.
  - There is smoking in the self-report
  - Or subject has exhaled CO level of greater or equal to 5 ppm using the Vitalograph Breath CO monitor in the office at scheduled Week 5 and Week 7.

- Subjects lost to follow-up/Early termination will be set as non-abstinent.
- All other subjects having missing value in CO value and self-report will be set as abstinent.

A descriptive statistic will be provided with 90% binomial confidence intervals.

For all binomial confidence intervals, it is based on normal approximation. If the number of abstinent or the number of non-abstinent ≤ 5, we will use the exact method.

8.1.3 Sensitivity Analysis II

Two missing in self-report are allowed.

Sensitivity Analysis II endpoint calculation:

- Set it as four-week continuous abstinence:
  - If there is no smoking in the self-report.
  - And if subject has exhaled CO level of less than 5 ppm using the Vitalograph BreathCO monitor in the office at scheduled Week 5 or Week 5 value is missing.
  - And if subject has exhaled CO level of less than 5 ppm using the Vitalograph BreathCO monitor in the office at scheduled week 7
  - Missing value check:
    - For CO value, only one missing value is allowed, and Week 7 value cannot be missing.
    - For self-report value, only two missing in each visit week (7 days) is allowed.

- All the others will be set as non-abstinent.
  - Week 7 CO value is missing.
  - Three or more missing in Self-report every visit week (7 days)
  - Lost to follow-up/Early termination
  - Subjects with adequate data that they were smoking

A descriptive statistic will be provided with 90% binomial confidence intervals.

For all binomial confidence intervals, it is based on normal approximation. If the number of abstinent or the number of non-abstinent ≤ 5, we will use the exact method.

8.1.4 Sensitivity Analysis III

Three missing in self-report are allowed.

Sensitivity Analysis III endpoint calculation:

- Set it as four-week continuous abstinence:
  - If there is no smoking in the self-report.
  - And subject has exhaled CO level of less than 5 ppm using the Vitalograph BreathCO monitor in the office at scheduled Week 5 & Week 7
  - Missing value check:
    - For CO value, only one missing value is allowed, and Week 7 value cannot be missing.
    - For self-report value, only three missing in every visit week (7 days) is allowed.

- All the others will be set as non-abstinent.
  - Week 7 CO value is missing.
  - Four or more missing in self-report every visit week (7 days)
  - Lost to follow-up/Early termination
  - Subjects with adequate data that they were smoking

A descriptive statistic will be provided with 90% binomial confidence intervals.

For all binomial confidence intervals, it is based on normal approximation. If the number of abstinent or the number of non-abstinent ≤ 5, we will use the exact method.

8.2 Secondary Outcome Endpoint

Secondary outcome variable is the incidence of nausea at any timepoint after drug administration begins.

8.2.1 Secondary Efficacy Analysis

The nausea is only considered when it is a treatment-emergent adverse event (TEAE). The number of subjects with nausea is analyzed.The incidence rate of nausea will be tabulated in the frequency percentage.

8.3 Other Efficacy Analyses

The other efficacy endpoints include:

- CCI
- [redacted]
- [redacted]

- CCI
- [redacted]
- Abstinence rate by Week
- Four-week continuous abstinence rate using exhaled CO level
- Four-week continuous abstinence rate using self-report
- Summary of CO Level
- Number of cigarettes daily

8.3.1 CCI

CCI [redacted]

8.3.2 CCI

CCI [redacted]

CCI [redacted]

8.3.3 CCI [redacted]

CCI [redacted]

8.3.4 CCI [redacted]

CCI [redacted]

8.3.5 CCI [redacted]

CCI [redacted]

8.3.6 Abstinence Rate by Week

Abstinence rate calculation:

- If subject has exhaled CO level of less than 5 ppm using the Vitalograph BreathCO monitor and there is no smoking in the self-report, then set it as abstinence.
  - Missing value check:
    - For CO value, value can be missing.
    - For self-report value, only one missing in every visit week (7 days) is allowed.

- All the others will be set as non-abstinent.
  - There are two or more missing in self-report every visit week (7 days)
  - Lost to follow-up/Early termination
  - Subjects with adequate data that they were smoking

A descriptive statistic will be provided with 90% binomial confidence intervals by week.

For all binomial confidence intervals, it is based on normal approximation. If the number of abstinent or the number of non-abstinent ≤ 5, we will use the exact method.

8.3.7 Four-week Continuous Abstinence Rate Using Exhaled Carbon Monoxide Level

Endpoint calculation:

- If subject has exhaled CO level of less than 5 ppm using the Vitalograph Breath CO monitor in the office at scheduled Week 5 and Week 7, then set it as four-week continuous abstinence.
  - Missing value check:
    - For CO value, both Week 5 and Week 7 value are not missing.

- All the others will be set as non-abstinent.
  - Week 5 or Week 7 CO value is missing.
  - Lost to follow-up/Early termination
  - Subjects with adequate data that they were smoking

A descriptive statistic will be provided with 90% binomial confidence intervals.

For all binomial confidence intervals, it is based on normal approximation. If the number of abstinent or the number of non-abstinent ≤ 5, we will use the exact method.

8.3.8 Four-week Continuous Abstinence Rate Using Self-report

Endpoint calculation:

- If there is no smoking in the self-report, then set it as four-week continuous abstinence.
  - Missing value check:
    - For self-report value, only one missing value in every visit week (7 days) is allowed.

- All the others will be set as non-abstinent.

- There are two or more missing in Self-report every visit week (7 days)
- Lost to follow-up/Early termination
- Subjects with adequate data that they were smoking

A descriptive statistic will be provided with 90% binomial confidence intervals.

For all binomial confidence intervals, it is based on normal approximation. If the number of abstinent or the number of non-abstinent ≤ 5, we will use the exact method.

8.3.9 Summary of CO Level

The baseline for CO level analyses is defined as the last evaluable assessment prior to first IMP. The summary statistics for changes from baseline in the CO level will be provided. The incidences and percentage of subjects with CO level greater than or equal to 5 PPM will be summarized.

8.3.10 Number of Cigarettes Daily

The summary statistics for changes from baseline in the average number of cigarettes smoked per day will be provided.

9 Safety Analyses

Safety assessments including AEs, vital signs, ECGs, clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be summarized for the Safety Analysis Set.

In summarizing the incidence of clinically relevant abnormalities in clinical laboratory results, vital sign measurements and ECG measurements, a subject must have had an evaluation that meets the specified criteria. For clinical laboratory results and ECG measurements, incidence rate will be calculated as the number of subjects having at least one abnormality divided by the number of subjects in the Safety Analysis Set. For vital sign measurements, incidence rate will be calculated as the number of subjects having at least one abnormality divided by the number of subjects in the Safety Analysis Set.

9.1 Extent of Exposure

Number of subjects who were administered IMP will be summarized by duration of exposure and descriptive statistics (mean, maximum, and minimum) of daily dose will be calculated and summarized for safety analysis set.

9.2 Adverse Events

All AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as an AE which starts after start of first IMP or an AE continues from

baseline of the specific corresponding duration and was serious, trial drug-related or results in death, discontinuation, interruption or reduction of IMP.

The incidences of the following TEAEs will be reported:

- TEAEs
- TEAEs by severity
- Potentially drug-related TEAEs
- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs
- Treatment-emergent adverse events of special interest (AESI) related to CCI [redacted]
- TEAEs related to Abuse-Potential

9.3 Clinical Laboratory Data

Hematology and serum chemistry will be collected at screening visit, Week 3 visit and Week 7 visit. Urinalysis will be collected at screening visit and Week 7 visit. The baseline for laboratory analyses is defined as the last evaluable assessment prior to first IMP. The summary statistics for changes from baseline in the clinical laboratory measurements will be provided. The incidences and percentage of potentially clinically relevant laboratory tests abnormalities will be summarized. The potentially clinically relevant laboratory test abnormalities will be listed by subject and by test. The criteria for Identifying Laboratory Values of Potential Clinical Significance are provided in Appendix 2. Potential Hy's law cases will be displayed in a listing. The laboratory results for serum chemistry, hematology, and urinalyses will be listed.

If laboratory tests assessments are repeated for the same visit window, the last repeated values will be used for summary tables. This is accomplished by sorting patient data by visit date and visit time (if applicable) within same visit window. If the lab data are recorded as ranges (i.e., including < or > limit of quantification), these data are not included in the calculations for changes from baseline but included in the calculations for incidences.

9.4 Vital Sign Data

Vital signs include systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate. The potential clinically relevant vital sign abnormalities will be listed by subject. Criteria for the potentially clinically relevant vital sign abnormalities are provided in Appendix 1. Incidences of clinically relevant vital signs abnormalities based

on the observation from the scheduled visits and unscheduled post-baseline visits will be tabulated. In addition, vital sign parameters and changes from baseline at trial visits and last visit will be summarized.

If vital sign assessments are repeated for the same visit window, the last repeat values will be used for production of summary tables. This is accomplished by sorting patient data by visit date and visit time (if applicable) within the same visit window.

9.5 Physical Examination Data

A complete physical examination include review of general appearance, hair and skin, head, eyes, ears, nose and throat, neck, chest, abdomen, dentition, cardiovascular, musculoskeletal and neurological systems will be performed.

A listing of physical examination outcome will be provided.

9.6 Electrocardiogram Data

A standard 12-lead ECG will be recorded after the participant has rested for at least 5 minutes in a supine position. The RR, PR interval, QRS duration, QT intervals, and QTc are recorded. The corrected QT intervals for QTcF are defined as follows:

QTcF is the length of the QT interval corrected for heart rate by Fredericia's formula: $QTcF = QT / (RR)^{1/3}$.

The potentially clinically relevant ECG abnormalities will be listed by subject. Criteria for potentially clinically relevant ECG abnormalities are provided in Appendix 3. The incidences of abnormal ECGs of potentially clinical relevance based on the observation at the scheduled and the unscheduled post-baseline visits will be tabulated. Descriptive statistics of change from baseline in ECG intervals of PR, QRS, RR, QT, and QTcF at scheduled visits and last visit will be presented.

If ECG assessments are repeated for the same visit window, the last repeat values will be used for production of mean change from baseline. This is accomplished by sorting patient data by visit date and visit time (if applicable) within the same visit window.

9.7 Suicidality

Suicidality will be assessed based on Columbia-suicide severity rating scale (C-SSRS) data. Data for the "Baseline" Version of the C-SSRS and CCI [redacted]

The "Baseline" version of the C-SSRS will be completed at screening CCI [redacted]

CCI [redacted]

10 Pharmacokinetic Analyses

Blood samples will be taken to determine concentrations of centanafadine and metabolites to assess compliance with dosing.

11 Pharmacodynamic Analyses

No pharmacogenomic analyses is planned.

12 Pharmacogenomic Analyses

No pharmacogenomic analyses is planned.

13 Interim Analysis

No interim analyses are planned.

14 Changes in the Planned Analyses

None.

15 References

1 Reus VI, Obach RS, Coe JW, et al. Varenicline: new treatment with efficacy in smoking cessation. Drugs Today Barc Spain 1998. 2007;43(2):65-75. doi:10.1358/dot.2007.43.2.1069956

2 Lee YY, Khoo S, Morris T, et al. A mixed-method study of the efficacy of physical activity consultation as an adjunct to standard smoking cessation treatment among male smokers in Malaysia. SpringerPlus. 2016;5(1):2012. doi:10.1186/s40064-016-3675-2

3 Teo, E. W., Lee, Y. Y., Khoo, S., Morris, T. Translation and validation of the MALAY version OF Shiffman-Jarvik withdrawal scale and Cessation SELF-EFFICACY Questionnaire: A review of psychometric properties. Health and Quality of Life Outcomes. 2015; 13(1). https://doi.org/10.1186/s12955-015-0238-0

4 Toll BA, O'Malley SS, McKee SA, Salovey P, Krishnan-Sarin S. Confirmatory Factor Analysis of the Minnesota Nicotine Withdrawal Scale. Psychol Addict Behav J Soc Psychol Addict Behav. 2007;21(2):216-225. doi:10.1037/0893-164X.21.2.216

16 Potential Clinical Relevance Criteria

Appendix 1 Criteria for Identifying Vital Signs and Weight of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate [b]	> 100 bpm < 50 bpm	≥ 10 bpm increase ≥ 10 bpm decrease
Systolic Blood Pressure [b]	≥ 140 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic Blood Pressure [b]	≥ 90 mmHg < 60 mmHg	≥ 10 mmHg increase ≥ 10 mmHg decrease
Orthostatic Hypotension	≥ 30 mmHg decrease in systolic blood pressure or a ≥ 20 mmHg in diastolic blood pressure after at least 3 minutes of standing compared to the previous supine blood pressure.	Not Applicable (baseline status not considered)
Orthostatic Tachycardia	≥ 25 bpm increase in heart rate from supine to standing	Not Applicable (baseline status not considered)
Weight	-	≥ 7% increase ≥ 7% decrease

a In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

b As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Divisionof Neuropharmacological Drug Products draft (2/27/87).

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST (SGOT)	≥ 3 x upper limit of normal (ULN)
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric Acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
Creatine Phosphokinase (CPK)	> 3 x ULN
Hematology	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from Baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from Baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2,800/ mm^3 or ≥ 16,000/ mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Absolute neutrophil count	≤ 1,500/ mm^3
Platelet count	≤ 75,000/ mm^3 or ≥ 700,000/ mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 100 mg/dL
Non-Fasting	≥ 200 mg/dL
Total Cholesterol, Fasting	≥ 240 mg/dL
LDL Cholesterol, Fasting	≥ 160 mg/dL
HDL Cholesterol, Fasting	
Men	< 40 mg/dL
Women	< 50 mg/dL
Triglycerides, Fasting	≥ 150 mg/dL

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Bas
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bp
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bp
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpı
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bp
Supraventricular premature beat	all	not present → prese
Ventricular premature beat	all	not present → prese
Supraventricular tachycardia	all	not present → prese
Ventricular tachycardia	all	not present → prese
Atrial fibrillation	all	not present → prese
Atrial flutter	all	not present → prese
Conduction		
1° atrioventricular block	PR ≥ 200 msec	increase of ≥ 50 ms
2° atrioventricular block	all	not present → prese
3° atrioventricular block	all	not present → prese
Left bundle-branch block	all	not present → prese
Right bundle-branch block	all	not present → prese
Pre-excitation syndrome	all	not present → prese
Other intraventricular conduction block[d]	QRS ≥ 120 msec	increase of ≥ 20 msı
Infarction		
Acute or subacute	all	not present → prese
Old	all	not present → prese ≥ 12 weeks post study
ST/T Morphological		
Myocardial Ischemia	all	not present → prese
Symmetrical T-wave inversion	all	not present → prese
Increase in QTc	QTcF > 450 msec (men) QTcF > 470 msec (women)	

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c] No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d] No current diagnosis of left bundle branch block or right bundle branch block.

17 Proposed List of Summary Tables and Listings

Summary Clinical Tables:

CT-1.1 Subjects Disposition

CT-1.2 Subjects Disposition by Center

CT-1.3 Subject Completion Rates by Week (Enrolled Analysis Set)

CT-1.4 Enrollment By Country

CT-1.5 Enrollment By Country By Age Group

CT-2 Reasons for Discontinuation (Enrolled Analysis Set)

CT-3.1 Demographic Characteristics (Enrolled Analysis Set)

CT-3.2 Baseline Characteristics: Reasons to Smoke (Enrolled Analysis Set)

CT-3.3 Smoking History (Enrolled Analysis Set)

CT-3.4 Medical History (Enrolled Analysis Set)

CT-4.1 Concomitant Medications: Medications Taken Prior to Start of Study Therapy (Enrolled Analysis Set)

CT-4.2 Concomitant Medications: Medications Taken During Study (Enrolled Analysis Set)

CT-5.1.1.1 Smoking Continuous Abstinence Rate During Week 4-7 (Full Analysis Set)

CT-5.1.1.2 Smoking Continuous Abstinence Rate During Week 4-7 - Sensitivity Analysis I (Full Analysis Set)

CT-5.1.1.3 Smoking Continuous Abstinence Rate During Week 4-7 - Sensitivity Analysis II (Full Analysis Set)

CT-5.1.1.4 Smoking Continuous Abstinence Rate During Week 4-7 - Sensitivity Analysis III (Full Analysis Set)

CT-5.1.1.5 Smoking Continuous Abstinence Rate During Week 4-7-Using Only Exhaled Carbon Monoxide Level (Full Analysis Set)

CT-5.1.1.6 Smoking Continuous Abstinence Rate During Week 4-7 - Using Only Self-report (Full Analysis Set)

CT-5.1.2 Summary of Non-smoking Rate from Self-report and CO Level by Week (Full Analysis Set)

CT-5.1.3 Summary of Non-smoking Rate from Self-report by Week (Full Analysis Set)

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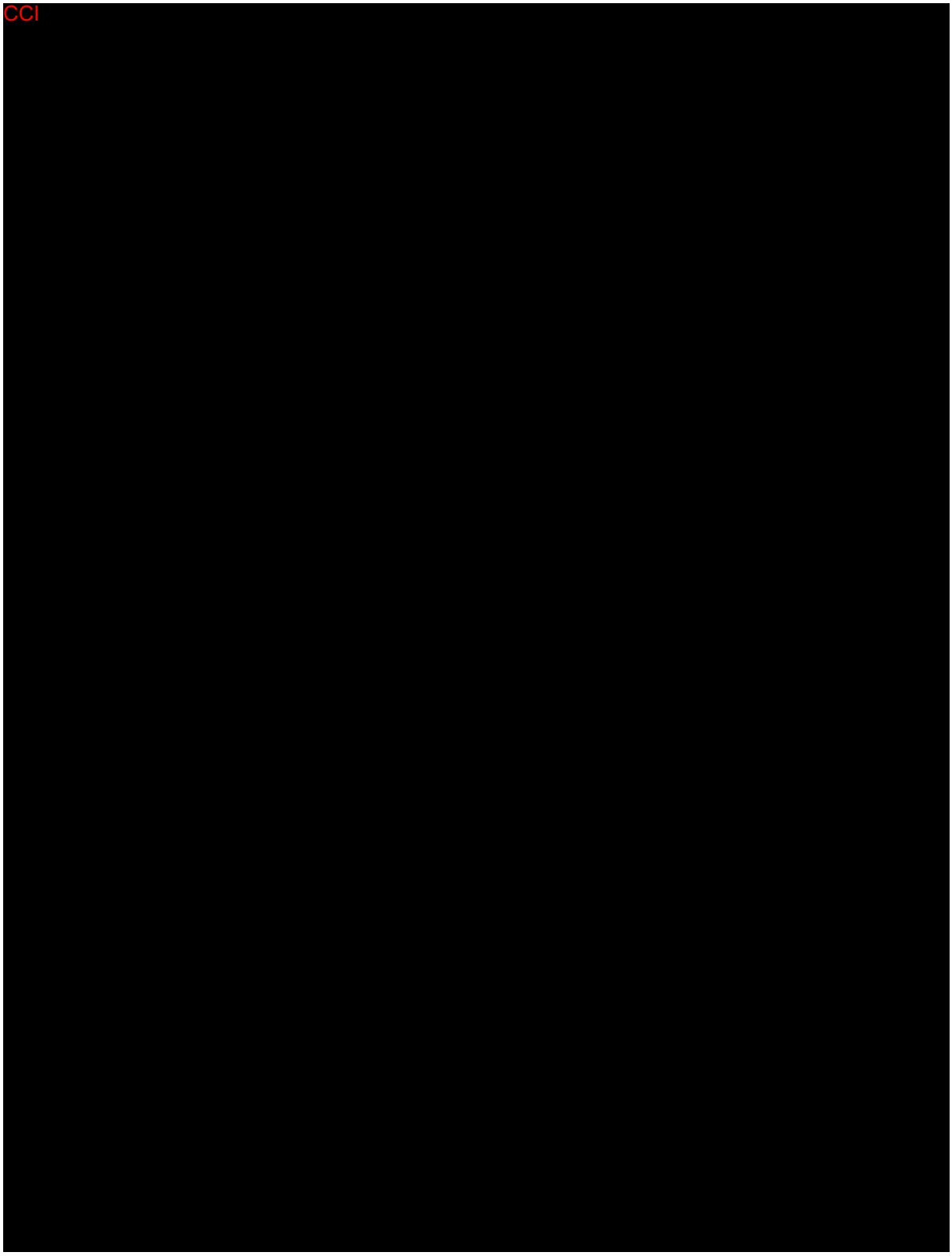

CT-6.1.1 Expired Air CO breath Test Result (Full Analysis Set)

CT-6.1.2 Summary of Subjects with CO Level Greater Than or Equal to 5 PPM (Full Analysis Set)

CT-6.2 Summary of Change from Baseline in Average Number of Cigarettes Smoked Per Day by Week (Full Analysis Set)

CT-7.1 Extent of Exposure (Safety Analysis Set)

CT-7.2 Number and Percentage of Subjects Receiving Study Medication and Mean and Range of Average Daily Dose (Safety Analysis Set)

CT-8.1 Incidence of Adverse Events (All Causalities) (Safety Analysis Set)

CT-8.2.1 Incidence of Treatment-emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.2.2 Incidence of Treatment-emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Severity (Safety Analysis Set)

CT-8.2.2.1 Incidence of Treatment-emergent Adverse Events Greater Than or Equal to 5% by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.2.2.2 Incidence of non-Serious Treatment-emergent Adverse Events Greater Than or Equal to 5% by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.2.3 Incidence of Treatment-emergent Adverse Events Greater Than or Equal to 2% by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.2.4 Incidence and Occurrence (Number of Events) of Potentially Drug-Related Serious TEAEs by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.2.5 Incidence and Occurrence (Number of Events) of Serious TEAEs by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.2.6 Incidence and Occurrence (Number of Events) of Non-Serious TEAEs by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.3.1 Incidence of Potentially Drug-related Treatment-emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.3.2 Incidence of Potentially Drug-related Treatment-emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Severity (Safety Analysis Set)

CT-8.4.1 Incidence of Deaths Due to Treatment-emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.4.2 Incidence of Deaths Due to Treatment-emergent Adverse Events by System Organ Class and MedDRA Preferred Term and Severity (Safety Analysis Set)

CT-8.5.1 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.5.2 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Severity (Safety Analysis Set)

CT-8.6.1 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuations of Trial Medication by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.6.2 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuations of Trial Medication by System Organ Class, MedDRA Preferred Term and Severity (Safety Analysis Set)

CT-8.7.1 Incidence of Treatment-emergent Adverse Events of Special Interests by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.7.2 Incidence of Treatment-emergent Adverse Events of Special Interests by System Organ Class and MedDRA Preferred Term and Severity (Safety Analysis Set)

CT-8.8.1 Incidence of Treatment-emergent Adverse Events related to Abuse-Potential by System Organ Class and MedDRA Preferred Term (Safety Analysis Set)

CT-8.8.2 Incidence of Treatment-emergent Adverse Events related to Abuse-Potential by System Organ Class and MedDRA Preferred Term and Severity (Safety Analysis Set)

CT-9.1 Listing of Deaths (Safety Analysis Set)

CT-9.2 Listing of Serious Adverse Events (Safety Analysis Set)

CT-9.3 Listing of Adverse Events Resulting in Discontinuations of IMP (Safety Analysis Set)

CT-9.4 Listing of Treatment-emergent Adverse Events of Special Interests (Safety Analysis Set)

CT-9.5 Listing of Treatment-emergent Adverse Events related to Abuse-Potential (Safety Analysis Set)

CT-10.1 Incidence of Laboratory Test Results of Potential Clinically Relevance (Safety Analysis Set)

CT-10.2.1 Laboratory Test Results for Chemistry - Mean Change from Baseline (Safety Analysis Set)

CT-10.2.2 Laboratory Test Results for Hematology - Mean Change from Baseline (Safety Analysis Set)

CT-10.2.3 Laboratory Test Results for Urinalysis - Mean Change from Baseline (Safety Analysis Set)

CT-10.2.4 Laboratory Test Results for Other Clinical Laboratory Tests - Mean Change from Baseline (Safety Analysis Set)

CT-10.2.5 Shift Tables of Clinical Laboratory Test Results - Chemistry (Safety Analysis Set)

CT-10.2.6 Shift Tables of Clinical Laboratory Test Results - Hematology (Safety Analysis Set)

CT-10.2.7 Shift Tables of Clinical Laboratory Test Results - Urinalysis (Safety Analysis Set)

CT-10.2.8 Shift Tables of Clinical Laboratory Test Results - Other Clinical Laboratory Tests (Safety Analysis Set)

CT-10.3.1 Listing of Laboratory Values of Potential Clinical Relevance by Subject (Safety Analysis Set)

CT-10.3.2 Listing of Laboratory Values of Potential Clinical Relevance by Test (Safety Analysis Set)

CT-10.5 Criteria for Laboratory Values of Potential Clinical Relevance

CT-10.6 Listing of Potential Hy's Law Cases by Subject (Safety Analysis Set)

CT-11.1 Incidence of Vital Signs of Potential Clinical Relevance (Safety Analysis Set)

CT-11.2 Vital Sign Parameters - Mean Change from Baseline (Safety Analysis Set)

CT-11.3 Listing of Vital Signs of Potential Clinical Relevance by Subject (Safety Analysis Set)

CT-11.4 Criteria for Potentially Clinically Relevant Vital Sign Abnormalities

CT-12.1 Incidence of ECG Measurements of Potential Clinical Relevance (Safety Analysis Set)

CT-12.2 ECG Parameters - Mean Change from Baseline (Safety Analysis Set)

CT-12.3 Listing of ECG Measurements of Potential Clinical Relevance (Safety Analysis Set)

CT-12.4 Criteria for ECG Measurements of Potential Clinical Relevance (Safety Analysis Set)

CT-13 Summary of Medication Handling Irregularity (Safety Analysis Set)

CT-14.1 Columbia-Suicide Severity Rating Scale (C-SSRS), Suicidality (Safety Analysis Set)

CT-14.2 Columbia-Suicide Severity Rating Scale (C-SSRS), Suicidality Behavior by Type (Safety Analysis Set)

CT-14.3 Columbia-Suicide Severity Rating Scale (C-SSRS) - Suicidal Ideation by Type (Safety Analysis Set)

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PATIENTS DATA LISITNG

Individual subject data listings will be provided.

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Document Name: P40520100055_Statistical Analysis Plan_03072022

Document Number: CCI

Document Version: CCI

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Clinical Pharmacology Approval	12-May-2022 13:14:14
PPD	Clinical Approval	12-May-2022 21:35:34
PPD	Biostatistics Approval	10-May-2022 00:27:46