Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Centanafadine (EB-1020)

Protocol No. 405-201-00150
IND No. 119361

Protocol Title: A Phase 1, Open-label, Randomized Trial to Evaluate the Relative Bioavailability of Centanafadine QD XR Oral Capsules in Healthy Adults

Protocol Lay Person Short Title: A Trial to Compare the Amount of Centanafadine that Enters the Bloodstream for Different Lots of Centanafadine QD XR

Statistical Analysis Plan

Phase 1
Version: Final
Date: 8 Mar 2024

Protocol Version: Amendment 1 18 Dec 2023

Confidential
May not be used, divulged, published, or otherwise disclosed without the prior written consent of Otsuka Pharmaceutical Development & Commercialization, Inc.

Table of Contents

Table of Contents 2
List of In-text Tables 4
List of In-text Figures 5
List of Appendices 6
List of Abbreviations 7
1 Introduction 8
2 Trial Objectives 8
3 Trial Design 8
3.1 Type/Design of Trial 8
3.2 Trial Treatments 11
3.3 Trial Population 12
4 Sample Size 12
5 Statistical Analysis Datasets 12
5.1 Randomized Dataset 12
5.2 Safety Dataset 12
5.3 Pharmacokinetic Dataset 13
5.4 Handling of Missing Data 13
5.4.1 Missing Data 13
5.4.2 Incomplete Dates 13
6 Primary and Secondary Outcome Variables 13
6.1 Primary Endpoints 13
6.2 Secondary Endpoints 13
6.3 Safety Endpoints 14
7 Disposition and Demographic Analysis 14
7.1 Participant Disposition 14
7.2 Demographic and Baseline Characteristics 14
7.3 Medical History 14
7.4 Treatment Compliance 14
7.5 Prior and Concomitant Medications 15

7.6 Protocol Deviations 15
8 Safety Analyses 15
8.1 Extent of Exposure 15
8.2 Adverse Events 15
8.3 Clinical Laboratory Data 16
8.4 Vital Sign Data 16
8.5 Physical Examination Data 17
8.6 Electrocardiogram Data 17
8.7 Potential Serious Hepatotoxicity 17
8.8 Columbia-Suicide Severity Rating Scale 17
9 Pharmacokinetics Analysis 18
CCI
12 Interim Analysis 19
13 Changes in the Planned Analyses 19

List of In-text Tables

Table 3.2-1 Dosing Schedule - Arm 1 11

Table 3.2-2 Dosing Schedule - Additional Arms 11

List of In-text Figures

Figure 3.1-1 Trial Design Schematic for All Arms.....10

List of Appendices

Appendix 1	Criteria for Identifying Laboratory Values of Potential Clinical Relevance	20
Appendix 2	Criteria for Identifying Vital Signs of Potential Clinical Relevance	21
Appendix 3	Criteria for Identifying ECG Measurements of Potential Clinical Relevance	22

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{∞}	area under the concentration-time curve from time zero to infinity
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
BMI	body mass index
CI	confidence interval
CL/F	apparent clearance of drug from plasma after extravascular administration
C_{max}	maximum (peak) plasma concentration of the drug
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
IMP	investigational medicinal product
IND	investigational new drug
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
PK	pharmacokinetic
POCBP	participants of childbearing potential
QD	once daily
SAP	statistical analysis plan
SR	sustained-release
$t_{1/2z}$	half-life of drug elimination during the terminal phase
TDD	total daily dose
TEAE	treatment-emergent adverse event
t_{max}	time to maximum (peak) plasma concentration
ULN	upper limit of normal
Vz/F	volume of distribution after extravascular drug administration
XR	extended-release

1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of safety and pharmacokinetic (PK) data of Trial 405-201-00150.

This SAP is prepared based on the protocol amendment 1 dated 18 Dec 2023.

2 Trial Objectives

Primary Objective

To evaluate the relative bioavailability of lots of centanafadine once daily (QD) extended-release (XR) capsules containing different talcs and/or different % weight gain coating to the bead capsules compared to the lot of centanafadine QD XR capsules used in the pivotal pediatric trials.

Secondary Objective

To evaluate relative bioavailability of lots of centanafadine QD XR capsules containing different talcs and/or different % weight gain coating to the bead capsules compared to the centanafadine sustained-release (SR) tablets and to assess the effect of sprinkling on applesauce as compared to administration as an intact capsule.

Safety Objective

To evaluate the safety and tolerability of lots of centanafadine QD XR capsules containing different talcs and/or different % weight gain coating to the bead capsules in healthy adults.

3 Trial Design

3.1 Type/Design of Trial

This is a phase 1, open-label, randomized, single-center, multi-arm trial for the evaluation of the relative bioavailability of different lots of centanafadine QD XR capsules in healthy adults.

Participants in each arm will receive 4 treatments in a 4-sequence, 4 period, crossover design. Up to 4 arms, each with as many as 24 participants (with neither sex comprising more than 60% of participants per arm), may be enrolled. Participants in each arm will undergo the same trial procedures. Participants will be randomized to 1 of 4 treatment sequences for 4 dosing periods separated by 72-hour washout, as follows:

- Sequence 1 (n = up to 6): A, B, C, D
- Sequence 2 (n = up to 6): C, A, D, B
- Sequence 3 (n = up to 6): B, D, A, C
- Sequence 4 (n = up to 6): D, C, B, A

Each arm will be comprised of a screening period lasting up to 27 days, a baseline/check-in visit on Day −1, a 12-day in-clinic treatment period, and a safety follow-up telephone contact 7 (+2) days after the last dose of investigational medicinal product (IMP), for a total of up to 45 days of participation in the trial.

All participants will check-in to the clinic on Day −1. On the morning of Days 1, 4, 7, and 10, participants will receive IMP after a 10-hour overnight fast. Serial PK samples will be collected for the determination of centanafadine and metabolite concentrations in plasma over the 48-hour period following administration of IMP. Participants will be discharged from the clinic after collection of the 48-hour PK sample on Day 12 or at early termination (ET). Safety assessments include monitoring of adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, baseline electrocardiograms (ECGs), and the Columbia-Suicide Severity Rating Scale (C-SSRS).

See Figure 3.1-1 for schema of the trial design.

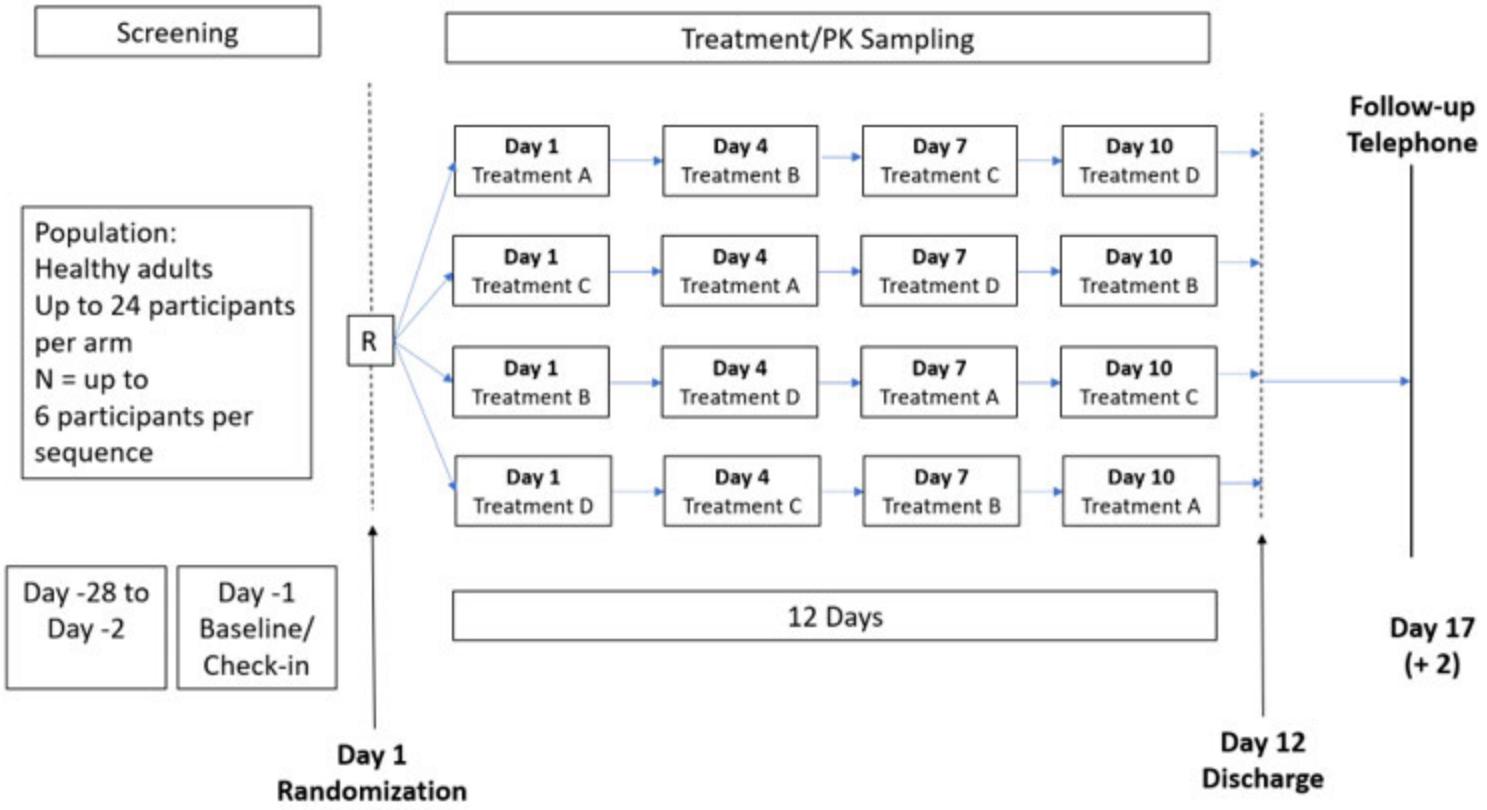


Figure 3.1-1 Trial Design Schematic for All Arms

3.2 Trial Treatments

In Arm 1, participants will receive single 164.4 mg and 328.8 mg doses of centanafadine QD XR capsules containing CCI talc [test formulations] and will be compared to 164.4 mg and 328.8 mg (as 2 × 164.4 mg capsules) centanafadine QD XR capsules containing CCI talc [reference formulations].

Table 3.2-1 Dosing Schedule - Arm 1

Treatment	Dose	Administration
A	Centanafadine QD XR 164.4 mg containing CCI talc	Single dose (1 × 164.4 mg capsule) in the morning
B	Centanafadine QD XR 328.8 mg containing CCI talc	Single dose (1 × 328.8 mg capsule) in the morning
C	Centanafadine QD XR 164.4 mg containing CCI talc	Single dose (1 × 164.4 mg capsule) in the morning
D	Centanafadine QD XR 328.8 mg containing CCI talc	Single dose (2 × 164.4 mg capsule) in the morning

QD = once daily; XR = extended release.

Additional lots and dose strengths of centanafadine QD XR capsules may be evaluated in subsequent arms. In additional arms, Treatments A to D may include retesting of QD XR lots from Arm 1 or inclusion of the following treatments:

Table 3.2-2 Dosing Schedule - Additional Arms

Dose	Administration
Centanafadine QD XR 164.4 mg (talc to be determined)	Single dose (1 × 164.4 mg capsule) in the morning administered as intact capsules or sprinkled on applesauce
Centanafadine QD XR 328.8 mg (talc to be determined)	Single dose (1 × 328.8 mg capsule) in the morning administered as intact capsules or sprinkled on applesauce
Centanafadine QD XR 164.4 mg (talc and % weight gain coating to be determined)	Single dose (1 × 164.4 mg capsule) in the morning administered as intact capsules or sprinkled on applesauce
Centanafadine QD XR 328.8 mg (talc and % weight gain coating to be determined)	Single dose (1 × 328.8 mg capsule) in the morning administered as intact capsules or sprinkled on applesauce
Centanafadine QD XR 164.4 mg containing CCI talc	Single dose (1 × 164.4 mg capsule) in the morning administered as intact capsules or sprinkled on applesauce
Centanafadine QD XR 328.8 mg containing CCI talc	Single dose (2 × 164.4 mg capsules) in the morning administered as intact capsules or sprinkled on applesauce
Centanafadine QD XR 328.8 mg containing CCI talc	Single dose (eg, 2 × 164.4 mg capsules or 4 × 82.2 mg capsules) in the morning
Centanafadine SR 200 mg TDD	1 × 100 mg SR tablet administered in the morning followed by 1 × 100 mg SR tablet administered 5 hours later
Centanafadine SR 400 mg TDD	2 × 100 mg SR tablets administered in the morning followed by 2 × 100 mg SR tablets administered 5 hours later

SR = sustained release; TDD = total daily dose; QD = once daily; XR = extended release.

Note: doses will not exceed centanafadine QD XR 328.8 mg or centanafadine SR 400 mg TDD, or equivalent.

Centanafadine QD XR capsules will be administered in the morning following a minimum 10-hour fast. Similarly, if selected for a later arm, centanafadine SR tablets may be administered in the morning, following a minimum 10-hour fast, with the second centanafadine SR tablet dose administered 5 hours after the first dose. All doses of centanafadine will be administered with approximately 240 mL of still, room temperature water. No additional water will be permitted for 1 hour before and after morning dosing. A meal will be provided after the 4-hour PK blood draw.

Being able to sprinkle the formulation on applesauce is important for the pediatric population, so the PK following administration of centanafadine sprinkled on applesauce may also be tested. For testing with applesauce, participants should be fasted. The contents of the QD XR capsule will be sprinkled onto 1 tablespoon of applesauce (applesauce to be provided by the site) and consumed immediately, followed by water as above.

3.3 Trial Population

An appropriate number of participants will be screened in order to enroll, randomize, and treat up to 96 healthy men and women (participants of childbearing potential [POCBP] are required to use an acceptable form of contraception) between 18 and 55 years of age, inclusive, with no more than 24 participants per arm and neither sex comprising more than 60% of participants in each arm. Discontinued participants may be replaced at the sponsor's discretion.

4 Sample Size

This trial is exploratory in nature; a sample size of up to 24 participants per arm was chosen for practical considerations.

5 Statistical Analysis Datasets

5.1 Randomized Dataset

The Randomized dataset will consist of all participants who are randomized in the trial.

5.2 Safety Dataset

The Safety dataset will consist of all participants who are randomized and receive at least 1 dose administration of IMP.

5.3 Pharmacokinetic Dataset

The Pharmacokinetic dataset will consist of all participants with evaluable plasma concentration data and PK parameters.

5.4 Handling of Missing Data

5.4.1 Missing Data

Both the PK and safety analyses will be based on observed (non-missing) data and no data imputation will be performed in this trial. The handling of concentrations below the lower limit of quantitation will be according to the sponsor's data handling processes.

5.4.2 Incomplete Dates

The general rule for imputing incomplete dates in safety datasets when the year is present is to use January if only the month is missing and the first day of a month if only the day is missing. If both month and day are missing but the year is available, January 1 is imputed. If the year is unknown, the date will be considered as missing.

No date imputation will be performed for PK sampling.

6 Primary and Secondary Outcome Variables

6.1 Primary Endpoints

The following PK parameters will be determined for centanafadine:

- Maximum (peak) plasma concentration of the drug (Cmax)
- Area under the concentration-time curve calculated to the last observable concentration at time t (AUC_t)
- Area under the concentration-time curve from time zero to infinity (AUC_∞)

6.2 Secondary Endpoints

The following PK parameters will be determined for centanafadine:

- Time to maximum (peak) plasma concentration (t_{max})
- Area under the concentration-time curve calculated to 24 hour ($AUC_{0\text{-}24h}$)
- Volume of distribution after extravascular drug administration (Vz/F)
- Terminal-phase elimination half-life ($t_{1/2,z}$)
- Apparent clearance of drug from plasma after extravascular administration (CL/F)

For EB-10601 the same PK parameters may be calculated (except CL/F) as supported by the data.

6.3 Safety Endpoints

- Reported AEs
- Clinical laboratory assessments
- Vital signs
- 12-lead ECGs
- C-SSRS

7 Disposition and Demographic Analysis

7.1 Participant Disposition

The number of participants who have been screened, the number of participants who are randomized, the number of participants who are treated, the number of participants who discontinue from the trial, and the number of participants who complete the trial will be tabulated by sequence for each arm.

The number and percentage of participants who discontinue from the trial are to be summarized by discontinuation reason and sequence for the randomized dataset of each arm.

7.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics (age, sex assigned at birth, race, ethnicity, weight, height, and body mass index [BMI]) will be summarized using descriptive statistics (number of participants, mean, standard deviation [SD], median, minimum, and maximum for continuous variables, and the proportion of participants for categorical variables). The summary will be based on the randomized dataset and by sequence for each arm.

7.3 Medical History

Listings for general medical history based on safety dataset will be provided.

7.4 Treatment Compliance

The time and dose of each IMP administration will be recorded on the electronic case report form (eCRF). A listing of treatment compliance for each participant based on safety dataset will be provided.

7.5 Prior and Concomitant Medications

The count and proportion of participants taking concomitant medications will be tabulated by drug classification using the latest version of World Health Organization Drug Dictionary for the randomized dataset. The concomitant medications tabulation will be summarized as follows: prior to start of IMP, during IMP, and post IMP for the randomized dataset. During IMP is designed as if participant takes any medication between Day 1 and Day 12.

In addition, listings of concomitant mediations will be provided.

7.6 Protocol Deviations

Major protocol deviation data will be summarized by type of deviation (eg, violation of informed consent process, IMP dispensing or participant dosing error, treatment assignment error, participant enrolled in violation of eligibility criteria or concomitant medication criteria) and by sequence for the randomized dataset of each arm. In addition, a participant listing will be provided describing the major deviations for each participant.

8 Safety Analyses

All safety analyses will be conducted based upon the safety dataset Safety variables to be analyzed include treatment exposure, AEs, clinical laboratory tests, physical examinations, vital signs, ECGs, and suicidality via the C-SSRS.

8.1 Extent of Exposure

Extent of exposure to IMP will be provided with descriptive statistics (n, percentage) by day and treatment. A listing recording date, time and dosage will be provided as well.

8.2 Adverse Events

All treatment-emergent adverse events (TEAEs) will be coded by Medical Dictionary for Regulatory Activities (MedDRA; Version 26.0 or later), System Organ Class (SOC), and MedDRA preferred term.

Treatment-emergent adverse events are defined as those AEs with an onset date on or after the start of IMP treatment, or if the event was continuous from baseline and was worsening, serious, IMP related, or resulted in death, discontinuation, interruption, or reduction of IMP.

Newly acquired, nontraumatic skin eruptions will be considered AEs of special interest (AESIs). Some examples of AESIs should include but are not limited to newly acquired maculopapular, macular, papular, papulosquamous, urticarial, acneiform, mucosal,

cutaneous, mucocutaneous, vesicular, pustular, bullous, squamous, exfoliative, pruritic or non-pruritic, erythematous, exanthematous also known as morbilliform rashes or skin eruptions which are localized or generalized, regardless of severity (mild, moderate, severe) or seriousness (ie, non-serious lesions are also eligible).

An overall summary of the AEs by treatment group will be provided for each arm. The incidence and percentage of participants with the following events will be summarized by SOC, MedDRA preferred term, severity, and treatment:

- TEAEs
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- AESIs
- Non-serious TEAEs of at least 5%

All TEAEs will be presented in listings. The listings of death, serious AEs, AEs leading to discontinuation of the IMP, and AESIs will also be provided as well.

8.3 Clinical Laboratory Data

For clinical laboratory tests data, the baseline value is defined as the last non-missing value obtained before dosing for the first period.

The potentially clinically significant laboratory test abnormalities will be listed by participant and by test. Clinical laboratory tests (observed and change from baseline data) will be summarized by time point and treatment sequence. The incidence of potentially clinically relevant clinical laboratory tests as defined in Appendix 1 will be summarized by sequence. Shift tables will be produced assessing status (low-normal-high) changes from baseline using the laboratory reference range provided by the site lab.

When laboratory test is repeated, the last repeat value will be used in the summary for that visit. Unscheduled laboratory data will not be summarized in the change from baseline table but will be included in incidence table. All clinical laboratory test results will be presented in a listing.

8.4 Vital Sign Data

Blood pressure and pulse measurements will be made in the supine and standing positions after the participant has been in each position for at least 3 minutes. The supine measurements will be performed first followed by the standing measurements.

The baseline of vital sign is defined as the last non-missing value obtained before dosing in the first period. If the predose assessment for the first period is missing, the baseline value will be based on the check-in visit on Day -1.

Vital sign data (observed and change from baseline data) will be summarized by time point and treatment sequence. The incidence of potentially clinically relevant vital signs, as defined in Appendix 2 will be summarized by sequence as well. The potentially clinically significant vital sign abnormalities will be listed by participant. All vital sign test results will be presented in a listing.

When vital sign is repeated, the last repeat value will be used in the summary for that visit. Unscheduled vital sign data will not be summarized in the change from baseline table but will be included in incidence table.

8.5 Physical Examination Data

Physical examination data will be presented in a listing.

8.6 Electrocardiogram Data

Baseline value will be the average of the triplet assessments on Day -1. If all assessments are not available on Day -1, the baseline value will be based on the screening value.

Descriptive statistics of ECG values (observed and change from baseline data) will be provided by time point and sequence. The incidence of potentially clinically relevant ECGs will be summarized by sequence as well. Criteria for Identifying ECG Measurements of Potential Clinical Relevance are provided in Appendix 3. All ECG test results will be presented in a listing.

8.7 Potential Serious Hepatotoxicity

A listing will be provided to present the incidence of participants who experience an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 3 times the upper limit of normal (ULN) and total bilirubin is ≥ 2 times the ULN.

8.8 Columbia-Suicide Severity Rating Scale

Suicidality will be assessed based on C-SSRS data. Data for the “Baseline/Screening” version of the C-SSRS and the “Since Last Visit” version of the C-SSRS will be summarized descriptively and presented in a listing.

The “Baseline/Screening” version of the C-SSRS will be completed at the screening visit and the “Since Last Visit” version of the C-SSRS will be completed at check-in on

Day −1, and Day 12 or early termination. Baseline and post-baseline C-SSRS data will be summarized by treatment sequence using safety dataset to report the incidence of:

- Suicidality
- Suicidal behavior (and its 4 types)
- Suicidal ideation (and its 5 types)

Suicidality is defined as reporting at least 1 occurrence of any suicidal behavior or suicidal ideation. Suicidal behavior is defined as reporting any type of suicidal behaviors (actual attempt, interrupted attempt, aborted attempt and preparatory acts or behavior). Suicidal ideation is defined as reporting any type of suicidal ideation. In addition to these 3 incidences, C-SSRS data collected post-baseline will also be summarized by treatment sequence using SAS to report the incidence of:

- Completed suicide
- Emergence of suicidal ideation
- Emergence of serious suicidal ideation
- Worsening of suicidal ideation
- Emergence of suicidal behavior

Any completed suicide is considered as complete suicidality. Emergence of suicidal ideation is defined as having no suicidal ideation at screening and baseline and reporting any type of ideation during treatment. Emergence of serious suicidal ideation is defined as having no suicidal ideation at screening and baseline and reporting any type of suicidal ideation with ideation severity rating of 4 or 5 during treatment. Worsening of suicidal ideation is defined as occurring when the most severe suicidal ideation rating during treatment is more severe than its worst rating at screening and baseline. Emergence of suicidal behavior is defined as having no suicidal behavior at screening and baseline and reporting any type of suicidal behavior during treatment.

9 Pharmacokinetics Analysis

Centanafadine and its metabolite(s) plasma concentrations will be summarized using descriptive statistics (mean, median, standard deviation, percentage coefficient of variation, geometric mean, minimum, maximum) by treatment and timepoint. A noncompartmental PK analysis will be performed to estimate the PK parameters for centanafadine and its metabolite(s).

Values of C_{max}, AUC_t, AUC_∞, t_{max}, $AUC_{0\text{-}24h}$, $t_{1/2,z}$, CL/F, and Vz/F are planned. Other parameters, including those for metabolites, may be reported depending on the concentration data collected. T_{max} will be summarized by median, min and max only.

The primary analysis of PK parameters (C_{max}, AUC_t, and AUC_∞) will be calculated for Test (T) and Reference (R); the 90% confidence interval (CI) for the difference in the means of the log transformed data will be calculated using a linear mixed effect model (PROC MIXED in SAS Version 9.1 or higher). The mixed effects model for each parameter will include sequence, treatment, and period as fixed effects, and a term for participants as a random effect. The anti-log of the difference and CI derived from the previous step will provide the estimate and 90% CI for the ratio of the geometric means for each treatment comparison.

Only participants that have PK parameters determined for the treatments being compared will be included in the analysis.

CCI

[redacted]

12 Interim Analysis

There is no interim analysis for this trial.

13 Changes in the Planned Analyses

None.

Appendix 1 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST	≥ 3 × ULN
ALT	≥ 3 × ULN
Alkaline phosphatase P	≥ 3 × ULN
Blood urea nitrogen	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Bilirubin	≥ 2.0 mg/dL
Creatine kinase	> 3 × ULN
Hematology	
Hematocrit	
Males	≤ 37% and decrease of ≥ 3 percentage points from baseline
Females	≤ 32% and decrease of ≥ 3 percentage points from baseline
Hemoglobin	
Males	≤ 11.5 g/dL
Females	≤ 9.5 g/dL
Leukocyte count	≤ 2,800 mm^3 or ≥ 16,000 mm^3
Platelet	≤ 75,000/mm^3 or ≥ 700,000/mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Additional Criteria	
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
Nonfasting	≥ 200 mg/dL
Cholesterol, fasting	≥ 240 mg/dL
Triglycerides, fasting	≥ 150 mg/dL

ULN=upper limit of normal, AST= Aspartate aminotransferase, ALT= alanine transaminase.

Appendix 2 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart rate[b]	> 90 bpm < 50 bpm	≥ 10 bpm increase ≥ 10 bpm decrease
SBPb	> 140 mmHg Supine ≤ 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
DBP[b]	> 90 mmHg Supine < 60 mmHg	≥ 10 mmHg increase ≥ 10 mmHg decrease
Orthostatic hypotension	≥ 30 mmHg decrease in SBP and/or a decrease of ≥ 20 mmHg in DBP 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

SBP= Systolic blood pressure, DBP= diastolic blood pressure.

[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 participant'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 New Drug Application Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Conduction		
1 atrioventricular block	PR ≥ 200 msec	increase of ≥ 50 msec
Other intraventricular conduction block[b]	QRS ≥ 120 msec	increase of ≥ 20 msec
ST/T Morphological		
Increase in QTc	QTcF > 450 msec (males) QTcF > 470 msec (females)	

QTc = corrected QT interval.

[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 participant's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

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

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: P40520100150_Statistical_Analysis_Plan

Document Number: 1000293425

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Biostatistics Approval	20-Mar-2024 12:32:27
PPD	Clinical Pharmacology Approval	20-Mar-2024 18:14:41
PPD	Clinical Approval	20-Mar-2024 19:04:29