Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Centanafadine (EB-1020)

REVISED CLINICAL PROTOCOL

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

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

CONFIDENTIAL — PROPRIETARY INFORMATION

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List of Abbreviations

Abbreviation	Definition
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APMP	abuse potential monitoring process
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
BID	twice daily
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
CTFG	Clinical Trial Facilitation Group
ECG	electrocardiogram
eCRF	electronic case report form
eICF	electronic informed consent form
EDC	electronic data capture
ESAM	events subject to additional monitoring
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identifier
IMP	investigational medicinal product
IND	investigational new drug
IR	immediate-release
IRB	Institutional Review Board
IRE	immediately reportable event
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhea method
MDD	major depressive disorder

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MHI	medication handling irregularities
NDA	new drug application
PK	pharmacokinetic
PORP	participants of reproductive potential
POCBP	participants of childbearing potential
PQC	product quality complaint
QD	once daily
SAE	serious adverse event
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
US	United States
Vz/F	volume of distribution after extravascular drug administration
XR	extended-release

1 Protocol Summary

1.1 Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Investigational Medicinal Product: Centanafadine (EB-1020)

Protocol No.: 405-201-00150

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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

Clinical Phase: 1

Planned Treatment/Indication: Attention-deficit/hyperactivity disorder (ADHD)

Trial Rationale:

As described in the Food and Drug Administration (FDA) Guidance for Industry, *Bioavailability and Bioequivalence Studies Submitted in NDAs and INDs-General Considerations* (April 2022)[1] a single-dose pharmacokinetic (PK) trial is recommended to assess bioavailability because single-dose trials are generally more sensitive in the assessment of rate and extent of release of the drug substance compared with multiple-dose trials. The bioavailability of the different lots of centanafadine once daily (QD) extended-release (XR) capsules will be evaluated under fasted conditions because fasted measurements generally provide a more sensitive method to assess differences between formulations.[2] A crossover design is typical for bioavailability trials and allows for participants to serve as their own controls. Randomization to treatment sequences for each arm is intended to reduce bias when collecting data and interpreting results.

Up to 4 arms of healthy adults will be included to evaluate the effects of different talcs and/or different % weight gain coating to the sustained-release (SR) bead component of the QD XR capsule on the PK performance of centanafadine QD XR capsules. The first arm will evaluate centanafadine QD XR capsules containing CCI talc versus the reference centanafadine QD XR capsule containing CCI talc, at dose strengths of 164.4 and 328.8 mg each in a 4-sequence, 4-period, crossover design.

Additional lots and dose strengths of centanafadine QD XR capsules may be evaluated in subsequent arms to determine if the PK profile following centanafadine QD XR capsules

with different brands of talc and/or different % weight gain coating to the SR bead component is similar to that following the administration of centanafadine as dosed in the pivotal trials. Furthermore, to support dosing recommendations for pediatrics, this trial may investigate the PK profile in healthy adults following administration of the capsule contents sprinkled on a tablespoon of applesauce and/or other food substances compared to that of the intact capsule. Doses of centanafadine QD XR will not exceed 328.8 mg administered once daily.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary: Evaluate the 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 lot of centanafadine QD XR capsules used in the pivotal pediatric trials.	Primary: The following PK parameters will be determined for centanafadine: • C_{max}, AUC_t, and AUC_∞
Secondary: 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 SR tablets and to assess the effect of sprinkling on applesauce and/or other food substances as compared to administration as an intact capsule	Secondary: The following PK parameters will be determined for centanafadine: • $AUC_{0\text{-}24h}$, t_{max}, CL/F, Vz/F, and $t_{1/2,z}$ For EB-10601 the same PK parameters may be calculated (except CL/F and Vz/F) as supported by the data
Safety: 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.	Safety: Reported AEs, clinical laboratory tests, vital signs, ECGs, C-SSRS

AE = adverse event; AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve calculated to the last observable concentration at time t; C_{max} = maximum (peak) plasma concentration; C-SSRS = Columbia-Suicide Severity Rating Scale; CL/F = apparent clearance of drug from plasma after extravascular administration; ECG = electrocardiogram; PK = pharmacokinetic; QD = once daily; $t_{1/2Z}$.= half-life of drug elimination during terminal phase, t_{max} = time to maximum (peak) plasma concentration; Vz/F = volume of distribution after extravascular drug administration; XR = extended release.

Trial Design:

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.

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).

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]

- Treatment A: centanafadine QD XR 164.4 mg containing CCI talc, as intact capsule under fasted conditions.
- Treatment B: centanafadine QD XR 328.8 mg containing CCI talc, as intact capsule under fasted conditions.
- Treatment C: centanafadine QD XR 164.4 mg containing CCI talc, as intact capsule under fasted conditions.
- Treatment D: centanafadine QD XR 328.8 mg containing CCI talc, as 2 × 164.4 mg capsules under fasted conditions.

Additional lots and dose strengths of centanafadine QD XR capsules may be evaluated in subsequent arms.

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.

Key Inclusion/Exclusion Criteria:

Male and female participants between the ages of 18 and 55 years (inclusive), with a body mass index (BMI) between 19 and 32 kg/m^2 (inclusive), who are in good health as determined by medical history, physical examination, ECG, serum/urine chemistry, hematology, and serology tests, and who are able to provide informed consent will be considered for inclusion in the trial.

Trial Site(s): This trial will take place at 1 site in the United States (US).

Trial Intervention(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

Trial interventions are all pre-specified IMPs intended to be administered to participants during the conduct of the trial.

In Arm 1, single doses of 164.4 mg and 328.8 mg of centanafadine QD XR capsules containing CCI talc will be compared to 164.4 mg and 328.8 mg of centanafadine QD XR capsules containing CCI talc.

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.

In additional arms, treatment regimen A to D may include retesting of QD XR lots from Arm 1 or inclusion of any of the following treatments:

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 and/or other food substances
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 and/or other food substances
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 and/or other food substances
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 and/or other food substances

Dose	Administration
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 and/or other food substances
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 and/or other food substances
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.

In each arm, 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

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

Trial Assessments:

Assessments for Pharmacokinetics (PK): blood sampling for plasma concentrations of centanafadine and metabolite(s).

Assessments for Safety: AEs, clinical laboratory tests, 12-lead ECG, vital signs, and physical examination findings, assessment of suicidality (C-SSRS).

Screening/Other: medical and medication history, urine drug and alcohol screening, pregnancy test, serology (human immunodeficiency virus [HIV], hepatitis B surface antigen (HBsAg), and hepatitis C virus [HCV]).

Independent Data Monitoring Committee: No

Statistical Methods:

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

The primary analysis of PK parameters (maximum [peak] plasma concentration of the drug [C_{max}], area under the concentration time curve calculated to the last observable concentration at time t [AUC_t], and area under the concentration-time curve from time zero to infinity [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.

The details of the analysis including the test and reference treatments will be described in the statistical analysis plan (SAP).

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

Trial Duration:

Each participant in this trial is expected to participate in the following periods of the trial (approximate durations listed):

Eligibility screening period (27 days [Day −28 to Day −2) and check-in to the clinic on Day −1)
Treatment period (in-clinic) (12 days [Days 1 to 12])
Post-treatment follow-up period (telephone call) (Day 17 + 2 days).

The trial start is defined as the date the first participant signs their informed consent form (ICF). Overall, the trial duration, from signing of the first participant's informed consent form to the last participant's final assessment, is expected to be 45 days.

Known and Potential Risks and Benefits:

Data from the completed phase 1, 2, and 3 trials indicate that centanafadine is safe and well-tolerated in healthy adults and adult participants with ADHD. Data from completed phase 2 and 3 trials demonstrate that centanafadine is effective in treating symptoms of ADHD, based on statistically significant improvements to the primary efficacy measure, the adult ADHD-Rating Scale-IV or ADHD Investigator Symptom Rating Scale total scores, compared to placebo. The data also suggest centanafadine may confer an improved safety profile and a lower potential for abuse compared to currently approved stimulant treatments for ADHD.

Based on final safety data from the adult phase 2 and 3 trials with the centanafadine SR tablet administered at total daily doses (TDDs) of 200 and 400 mg (with exposures similar to centanafadine QD XR 164.4 and 328.8 mg, respectively)[3] centanafadine was generally safe and well tolerated when administered to adult participants with ADHD. The most frequently reported treatment-emergent adverse events (treatment-emergent adverse events [TEAEs]; ≥ 5%) that occurred at higher incidence than the placebo group were headache, decreased appetite, nausea, diarrhea, and insomnia.

Rash has also been reported in participants who have been exposed to centanafadine; therefore, rash or other newly acquired, nontraumatic skin eruptions will be considered an adverse event of special interest (AESI) in this trial. The Rash and Skin Eruption AESI Plan will be followed. Considering that rash can be a sign of an allergic reaction, participants will be monitored closely for other symptoms of allergic reaction, including shortness of breath, difficulty breathing, swelling of the throat or mouth, swollen face, fever, or swollen lymph nodes.

1.2 Schema

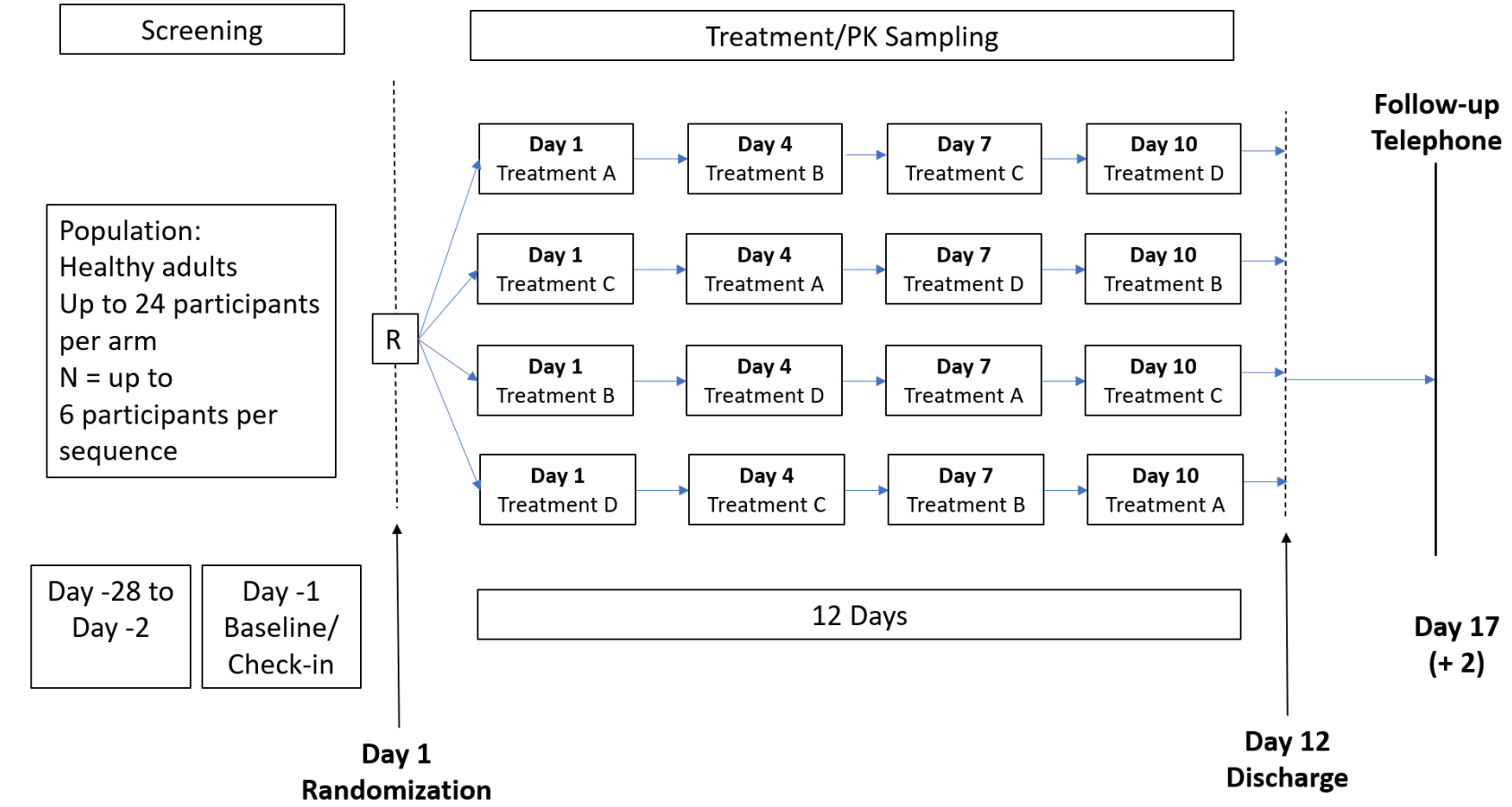


Figure 1.2-1 Trial Design Schematic for All Arms

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Assessments	Screening		Treatment Period												Follow-up Phone Call[a]	Notes
	Day −28 to Day −2	Day −1 (Baseline/ Check-in)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12/ET (Discharge)	Day 17 (+ 2)	
ENTRANCE/HISTORY																
Informed Consent	X															Section 10.1.2
Inclusion/Exclusion Criteria	X	X														Section 5.2
Demographic Information	X															Section 10.1.7.2
Medical History	X															Section 5.2
Height and BMI	X															Section 5.2
Body Weight	X	X												X		Section 5.2
Serology (HIV, Hepatitis)	X															Section 8.6.1
Alcohol, Drug, and Cotinine Screen	X	X														Section 5.2
Urine Pregnancy Test (All Females)	X	X												X		Section 10.3
FSH (Postmenopausal Females Only)	X															Section 10.3

Table 1.3-1 Schedule of Assessments

Assessments	Screening		Treatment Period												Follow-up Phone Call[a]	Notes
	Day −28 to Day −2	Day −1 (Baseline/ Check-in)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12/ET (Discharge)	Day 17 (+ 2)	
Randomization			X													Section 5.1 and Section 6.3
TRIAL RESIDENCY																
Check-in		X														-
Discharge														X		-
SAFETY																
Clinical Laboratory Assessments (Hematology, Serum Chemistry, and Urinalysis)	X	X												X		Section 8.6.1
Physical Examination	X	X												X		Section 8.6.2
Vital Signs (supine, standing)	X	X	X predose			X predose			X predose			X predose		X		Section 8.6.3
12-Lead ECG (single assessments except for where noted)	X	X (triplicate)												X		Section 8.6.4
C-SSRS	X[b]	X[c]												X[c]		Section 8.6.5

Table 1.3-1 Schedule of Assessments

Assessments	Screening		Treatment Period												Follow-up Phone Call[a]	Notes
	Day −28 to Day −2	Day −1 (Baseline/ Check-in)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12/ET (Discharge)	Day 17 (+ 2)	
Adverse Events								X								Section 8.7
Prior and Concomitant Medications								X								Section 6.6
IMP ADMINISTRATION																
Centanafadine Administration			X			X			X			X				Section 6
Medication Compliance Assessment			X			X			X			X				Section 6.4
PHARMACOKINETICS																
Blood Draw for Plasma PK[d]			X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2

BMI = body mass index; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; IMP = investigational medicinal product; PK = pharmacokinetic(s).

[a]A follow-up telephone call will be made 7 (+2) days after the last dose of IMP for completers.

[b]C-SSRS Baseline Version will be administered at screening.

[c]C-SSRS Since Last Visit Version will be administered on baseline/check-in (Day −1) and Day 12/ET.

[d]Blood samples for PK analysis will be collected at predose, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 30, 36 and 48 hours postdose /ET.

2 Introduction

Centanafadine (EB-1020) is being developed for the treatment of ADHD in adults and pediatrics.

Immediate-release (IR), SR, and XR formulations of centanafadine have been evaluated. As QD dosing is preferred, multiple XR formulations were tested. The final formulation is referred to as the centanafadine QD XR capsule and has been administered in adult phase 1 CCI [redacted], pediatric phase 1 (405-201-00046), adult proof of concept in major depressive disorder (MDD) (405-201-00062), and pediatric pivotal phase 3 trials (405-201-00016, 405-201-00017, and 405-201-00021).

In this trial, different lots of centanafadine QD XR capsules will be evaluated to explore the effect of different brands of US Pharmacopeia talc, an anti-tacking agent used in SR bead polymer coating, and/or different polymer percentage weight gain coating applied to the SR bead, on the PK of centanafadine. Talc is commonly used as an excipient in pharmaceutical products and is designated as Generally Recognized as Safe by the FDA.[4] CCI [redacted] This investigation is intended to ensure the robustness of centanafadine manufacturing in case of any future supply chain disruptions. Centanafadine concentrations following administration of new lots of capsules will be compared to the lot of capsules with CCI [redacted] talc used in the pivotal pediatric ADHD trials (reference) and may also be compared to concentrations obtained following administration of centanafadine SR tablets administered twice daily (BID) that were used in the pivotal adult ADHD trials.

2.1 Trial Rationale

As described in the FDA Guidance for Industry, *Bioavailability and Bioequivalence Studies Submitted in NDAs and INDs-General Considerations* (April 2022)[1] a single-dose PK trial is recommended to assess bioavailability because single-dose trials are generally more sensitive in the assessment of rate and extent of release of the drug substance compared with multiple-dose trials. The bioavailability of the different lots of centanafadine QD XR capsules will be evaluated under fasted conditions because fasted measurements generally provide a more sensitive method to assess differences between formulations.[2] A crossover design is typical for bioavailability trials and allows for participants to serve as their own controls. Randomization to treatment sequences for each arm is intended to reduce bias when collecting data and interpreting results.

Up to 4 arms of healthy adults will be included to evaluate the effects of different talcs and/or different % weight gain coating to the SR bead component of the centanafadine QD XR capsule on the PK performance of centanafadine QD XR capsules. The first arm will evaluate centanafadine QD XR capsules containing CCI talc versus the reference centanafadine QD XR capsule containing CCI talc, at dose strengths of 164.4 and 328.8 mg each in a 4-sequence, 4-period, crossover design.

Additional lots and dose strengths of centanafadine QD XR capsules may be evaluated in subsequent arms to determine if the PK profile following centanafadine QD XR capsules with different brands of talc and/or different % weight gain coating to the SR bead component is similar to that following the administration of centanafadine as dosed in the pivotal trials. Furthermore, to support dosing recommendations for pediatrics, this trial may investigate the PK profile in healthy adults following administration of the capsule contents sprinkled on a tablespoon of applesauce and/or other food substances compared to that of the intact capsule. Doses of centanafadine QD XR will not exceed 328.8 mg administered once daily.

2.2 Background

Centanafadine has inhibitory activity at norepinephrine, dopamine, and serotonin reuptake transporters. Centanafadine may offer effective treatment of ADHD with a better safety profile and lower abuse potential than currently available treatments for ADHD. Centanafadine was well-tolerated and effective in adult phase 2 and phase 3 trials in participants with ADHD.

Centanafadine PK following administration of the QD XR formulation has been evaluated in 5 previous trials, 2 trials in adults and 3 trials in pediatrics. Doses have ranged from 82.2 to 328.8 mg in adults and 41.1 to 328.8 mg in pediatrics. In all trials, doses were well-tolerated, and the safety was consistent with previous trials that evaluated the centanafadine SR tablet formulation. A thorough QT trial where centanafadine was administered as an 800 mg TDD indicated no effect on QT prolongation.

As of the Investigator's Brochure (IB) cutoff date of 12 Sep 2022, in total, 1815 participants have received at least 1 dose of centanafadine from completed and ongoing open-label trials including 440 healthy participants, 93 healthy adult participants who were experienced stimulant users, 16 adult participants with hepatic or renal impairment, 1056 adult participants with ADHD, 160 pediatric participants with ADHD, and 50 cigarette-smoking adults.

As of the IB cutoff date of 12 Sep 2022, 342 additional participants in 4 ongoing blinded trials were exposed to centanafadine or placebo including 22 healthy adults CCI 162 adolescent participants (13 to 17 years of age) with ADHD (Trial 405-201-00016), 11 pediatric participants (4 to 12 years of age) with ADHD (Trial 405-201-00021), and 147 adults with binge-eating disorder (Trial 405-201-00056).

Please refer to the centanafadine IB[5] for more detailed information on the chemistry, pharmacology, efficacy, and safety of centanafadine.

2.3 Known and Potential Risks and Benefits

Data from the completed phase 1, 2, and 3 trials indicate that centanafadine is safe and well-tolerated in healthy adults and adult participants with ADHD. Data from completed phase 2 and 3 trials demonstrate that centanafadine is effective in treating symptoms of ADHD, based on statistically significant improvements to the primary efficacy measure, the adult ADHD-Rating Scale-IV or ADHD Investigator Symptom Rating Scale total scores, compared to placebo. The data also suggest centanafadine may confer an improved safety profile and a lower potential for abuse compared to currently approved stimulant treatments for ADHD.

Based on final safety data from the adult phase 2 and 3 trials with the centanafadine SR tablet administered at TDDs of 200 and 400 mg (with exposures similar to QD XR 164.4 and 328.8 mg, respectively)[3] centanafadine was generally safe and well tolerated when administered to adult participants with ADHD. The most frequently reported TEAEs; $\geq$ 5% that occurred at higher incidence than the placebo group were headache, decreased appetite, nausea, diarrhea, and insomnia.

Rash has also been reported in participants who have been exposed to centanafadine; therefore, rash or other newly acquired, nontraumatic skin eruptions will be considered an AESI in this trial. The Rash and Skin Eruption AESI Plan will be followed. Considering that rash can be a sign of an allergic reaction, participants will be monitored closely for other symptoms of allergic reaction, including shortness of breath, difficulty breathing, swelling of the throat or mouth, swollen face, fever, or swollen lymph nodes.

The trial site will receive updated versions of the IB, when available, and the trial site should refer to the most current version as needed.

3 Objectives, Endpoints, and Estimands

Trial objectives and endpoints are summarized in Table 3-1.

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: Evaluate the 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 lot of centanafadine QD XR capsules used in the pivotal pediatric trials.	Primary: The following PK parameters will be determined for centanafadine: • C_{max}, AUC_t, and AUC_∞
Secondary: 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 SR tablets and to assess the effect of sprinkling on applesauce and/or other food substances as compared to administration as an intact capsule	Secondary: The following PK parameters will be determined for centanafadine: • $AUC_{0\text{-}24h}$, t_{max}, CL/F, Vz/F, and $t_{1/2,z}$ For EB-10601 the same PK parameters may be calculated (except CL/F and Vz/F) as supported by the data
Safety: 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.	Safety: Reported AEs, clinical laboratory tests, vital signs, ECGs, C-SSRS

AE = adverse event; AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve calculated to the last observable concentration at time t; C_{max} = maximum (peak) plasma concentration; C-SSRS = Columbia-Suicide Severity Rating Scale; CL/F = apparent clearance of drug from plasma after extravascular administration; ECG = electrocardiogram; PK = pharmacokinetic; QD = once daily; $t_{1/2z}$.= half-life of drug elimination during terminal phase, t_{max} = time to maximum (peak) plasma concentration; Vz/F = volume of distribution after extravascular drug administration; XR = extended release.

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 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.

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 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 ET. Safety assessments include monitoring of AEs, clinical laboratory tests, vital signs, physical examinations, baseline ECGs, and the C-SSRS.

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]

- Treatment A: centanafadine QD XR 164.4 mg containing CCI talc, as intact capsule under fasted conditions.
- Treatment B: centanafadine QD XR 328.8 mg containing CCI talc, as intact capsule under fasted conditions.
- Treatment C: centanafadine QD XR 164.4 mg containing CCI talc, as intact capsule under fasted conditions.
- Treatment D: centanafadine QD XR 328.8 mg containing CCI talc, as 2 × 164.4 mg capsules under fasted conditions.

Additional lots and dose strengths of centanafadine QD XR capsules may be evaluated in subsequent arms. A schematic of the trial design for all arms is provided in Figure 1.2-1.

4.2 Scientific Rationale for Trial Design

The goal of this trial is to evaluate the effects of different lots on the PK performance of centanafadine QD XR capsules.

Relative bioavailability findings will be used to support the bridging of the SR and QD XR formulations and product labeling for the centanafadine QD XR capsule.

The use of a crossover trial design allows for participants to each serve as their own control, improving data quality and consistency, particularly for the study of PK and bioavailability. Moreover, this trial design enables the capture of necessary data with the lowest number of participants.

4.3 Dosing Rationale

Once daily doses of centanafadine QD XR capsules (containing CCI talc) have been used in adult phase 1 CCI, pediatric phase 1b (405-201-00046), adult MDD phase 2 (405-201-00062) and pediatric phase 3 trials (405-201-00016, 405-201-00017, and 405-201-00021) and will be used in Arm 1 as the reference formulation.

In Arm 1, single doses of 164.4 and 328.8 mg of centanafadine QD XR capsules containing CCI talc will be compared to centanafadine QD XR 164.4 mg and 328.8 mg capsules containing CCI talc. Centanafadine QD XR containing CCI talc will be administered as a single capsule of 164.4 or 328.8 mg in the morning. Centanafadine QD XR containing CCI talc will be administered as single capsule of 164.4 mg or 2 × 164.4 mg capsules (for a dose of 328.8 mg) in the morning.

In additional arms, Treatments A to D may include retesting of QD XR lots from Arm 1 or inclusion of the following treatments:

- Centanafadine QD XR 164.4 mg or 328.8 mg [talc to be determined] capsules administered as single dose capsules (eg, 1 × 164.4 or 1 × 328.8 mg capsules) either taken as an intact capsule, or the capsule opened and the contents sprinkled on applesauce and/or other food substances.
- Centanafadine QD XR 164.4 mg or 328.8 mg (talc and % weight gain coating to be determined) capsules administered as single dose capsules (eg, 1 × 164.4 or 1 × 328.8 mg capsules) either taken as an intact capsule, or the capsule opened and the contents sprinkled on applesauce and/or other food substances.
- Centanafadine QD XR containing CCI talc will be administered as single capsule of 164.4 mg or 2 × 164.4 mg capsules (for a dose of 328.8 mg) with the capsule opened and the contents sprinkled on applesauce and/or other food substances.
- Doses up to 328.8 mg (comprised of 2 × 164.4 mg capsules or 4 × 82.2 mg capsules) of centanafadine QD XR capsules containing CCI.
- 200 mg TDD as centanafadine SR tablets (1 × 100 mg SR tablet administered BID, 5 hours apart)
- 400 mg TDD as centanafadine SR tablets (2 × 100 mg SR tablet administered BID, 5 hours apart)

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

4.4 Start and End-of-Trial Definitions

The trial start is defined as the first visit of the first participant, which is the date the first participant signs their ICF.

The end-of-trial date is defined as the last date of contact, or the date of final contact attempt as recorded on the post-treatment follow-up electronic case report form (eCRF) page for the last participant completing or withdrawing from the trial.

4.5 Definition of Trial Participant Completion

The treatment period is defined as the time period during which participants are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the participant actually takes all doses of the IMP. Participants who are evaluated at the last scheduled visit and complete contact for the follow-up telephone call (7 [+ 2 days] after the last dose of IMP) will be defined as trial completers.

5 Trial Population

An appropriate number of participants will be screened in order to enroll, randomize, and treat up to 96 healthy men and women (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.

5.1 Trial Participant Selection and Numbering

All participants will be given a unique subject identifier (ID; site number [3 digits] + subject number ['S' + 5 digits] upon providing consent [or assent, if applicable]). The site number will be designated by the sponsor. For each site, the subject number will be given sequentially from S00001.

Demographic information (collection date, date of birth, sex at birth, gender identity, childbearing potential, race, ethnicity, country) and medical history will be recorded in the eCRF at the screening visit.

Eligible participants who are enrolled in the trial will be assigned a unique subject randomization number for treatment sequence assignment. The randomization code will be generated in blocks of 4 with males randomized first followed by females. Neither sex will comprise more than 60% of participants per arm. Results of the eligibility assessment, date of randomization (or date of treatment assignment), and randomization number (or treatment group) will be recorded in the eCRF.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the medical monitor.

5.2.1 Inclusion Criteria

Participants are required to meet the following inclusion criteria when assessed:

1) Male or female participants between 18 and 55 years of age, inclusive.
2) Body mass index (BMI) between 19.0 to 32.0 kg/m^2 (inclusive).
3) In good health as determined by:
   - Medical history
   - Physical examination
   - Electrocardiogram (ECG)
   - Serum/urine chemistry, hematology, and serology tests.
4) Ability to provide written, informed consent prior to initiation of any trial-related procedures, and ability, in the opinion of the investigator, to comply with all the requirements of the trial.

5.2.2 Exclusion Criteria

Participants will be excluded if they meet any of the following exclusion criteria when assessed:

1) Clinically significant abnormality in past medical history, or at the screening physical examination, that in the investigators or sponsor's opinion may place the participant at risk or interfere with outcome variables including absorption, distribution, metabolism, and excretion of drug. This includes, but is not limited to, history of or concurrent cardiac, hepatic, renal, neurologic, endocrine, gastrointestinal, respiratory, hematologic, and immunologic disease or cholecystectomy.
2) Consumption of alcohol and/or food and beverages containing caffeine, methylxanthines (eg, coffee, chocolate) within 72 hours prior to dosing.
3) History of drug and/or alcohol abuse within 2 years prior to screening.
4) History of or current hepatitis or AIDS or carriers of hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (anti-HCV), or HIV antibodies.
5) History of any significant drug allergy or known or suspected hypersensitivity.
6) A positive urine or breath alcohol test and/or urine drug screen for substance of abuse at screening or upon admission to the trial site.
7) Participants having taken an investigational drug within 30 days prior to screening.
8) Any history of significant bleeding or hemorrhagic tendencies.

9) A history of difficulty in donating blood.
10) The donation of blood or plasma within 30 days prior to the first dose of IMP.
11) Use of prescription, over the counter, herbal medication or vitamin supplements within 14 days prior to the first dose of IMP and antibiotics within 30 days prior to the first dose of IMP. The sponsor may allow exceptions only if the medication's administration is deemed unlikely to impact the PK result.
12) Exposure to any substances known to stimulate hepatic microsomal enzymes within 30 days prior to screening through the end of the trial (eg, occupational exposure to pesticides, organic solvents, etc.).
13) Use of tobacco products or daily exposure to second-hand smoke within 2 months prior to the screening visit, urine cotinine concentrations > 200 ng/mL or serum cotinine concentrations > 20 ng/mL at screening or check-in.
14) Participants presenting with, or having a history of, uncontrolled hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in systolic blood pressure or a decrease of ≥ 20 mmHg in diastolic blood pressure after at least 3 minutes standing compared with the previous supine blood pressure, **OR** development of symptoms.
15) Participants who have a supine pulse rate, after resting for at least 3 minutes, outside the range of 50-90 bpm.
16) Abnormal ECG findings at screening or check-in, as follows:
    a. QTcF > 450 msec for male participants or > 470 msec for female participants
    b. QRS interval > 120 msec
    c. PR interval > 200 msec
17) History of unexplained syncope.
18) History of serious mental disorders, that, in the opinion of the investigator, would exclude the participant from participating in this trial.
19) Participants with no permanent place of residence.
20) Any participant who, in the opinion of the investigator, should not participate in the trial.
21) Previous exposure to centanafadine
22) Female participants who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
23) Participants of reproductive potential (PORP) / participants of childbearing potential (POCBP) who do not agree to practice 2 different effective and/or highly effective methods of birth control or remain fully abstinent from sexual activity with the potential for conception, per the guidelines in Section 10.3.
24) Participants who do not agree to refrain from donating sperm or eggs from trial screening through 90 days for sperm and 30 days for eggs after the last dose of IMP.
25) Any of the following:

- A significant risk of committing suicide based on history and the investigator's clinical judgment, or routine psychiatric status examination
- Current suicidal behavior
- Imminent risk of injury to self
- Active suicidal ideation as it is evidenced by an answer of "yes" on Questions 4 or 5 (over the last 6 months) on the suicidal ideation section of the Baseline/Screening version of the C-SSRS
- Any history of suicidal behavior in the past 2 years as detected by the Baseline/Screening version of the C-SSRS

Note: Participants excluded for positive drug/alcohol screen are not eligible to be re-screened for participation in the trial, however participants excluded for any other reasons may be re-screened at any time if the exclusion characteristic has changed. In the event that the participant is re-screened, a new ICF must be signed, and a new screening number assigned.

Definitions of reproductive potential and childbearing potential can be found in Section 10.3.

Participants must agree to follow restrictions to medications and lifestyle described in Section 6.6 and Section 5.3, respectively.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Refer to Section 6.1 for fasting requirements prior to and after IMP administration.

5.3.2 Caffeine, Alcohol, and Tobacco

The consumption of alcohol and/or food and beverages containing caffeine and methylxanthines (eg, coffee, chocolate) is prohibited within 72 hours prior to dosing and for the duration of participation.

The use of tobacco products or daily exposure to second-hand smoke within 2 months prior to the screening visit is prohibited.

5.3.3 Physical Activity

Participants will not be permitted to participate in strenuous exercise for 72 hours before Day −1 until discharge from the trial site.

Participants will remain either in a seated or semi-recumbent position for the first 4 hours following dosing, except during brief periods when protocol-related procedures need to

be performed. Restroom visits must be supervised during the 4 hours postdose and should be brief (< 10 minutes). In addition, during the 4-hour period after oral dosing, the participant's toilet use must be supervised to prevent self-induced emesis resulting in loss of the oral dose. Following the 4-hour postdose period, participants will be allowed to ambulate, but should not exercise strenuously.

5.4 Screen Failures

A screen failure is a participant from whom informed consent is obtained and is documented in writing (ie, participant signs an ICF), but who is not randomized or assigned trial intervention(s). Any untoward medical occurrence that occurs in a screen failure is considered a screen failure AE. All screen failure AEs must be recorded in the source document after participant informed consent/assent has been obtained. A screen failure AE must be recorded on an immediately reportable event (IRE) form to the sponsor if the screen failure AE meets the IRE criteria defined in Section 8.7.

If the participant meets the definition of a screen failure in this trial, the following information will be recorded in the eCRF:

- Date of ICF signature
- Visit date (screening visit)
- Demographics (collection date, date of birth, sex at birth, gender, race, ethnicity, country)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure
- Any screen failure AEs

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Participants with a positive drug or alcohol screen are not eligible to be rescreened for participation in the trial; however, participants excluded for other reasons may be rescreened at any time, at the discretion of the medical monitor, if the exclusion characteristic has changed or resolved. If a participant is rescreened for trial participation and the rescreening is not completed within the original screening window, a new ICF must be signed. Rescreened participants should also be assigned a new subject number for every screening/rescreening event. A participant may not rescreen more than once.

6 Trial Intervention(s) and Concomitant Therapy

6.1 Trial Intervention(s) Administered

Trial interventions are all pre-specified IMPs intended to be administered to participants during the conduct of the trial.

In Arm 1, single doses of 164.4 mg and 328.8 mg of centanafadine QD XR capsules containing CCI talc will be compared to 164.4 mg and 328.8 mg of centanafadine QD XR capsules containing CCI talc (Table 6.1-1).

Table 6.1-1 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.

In additional arms, treatment regimen A to D may include retesting of QD XR lots from Arm 1 or inclusion of any of the following treatments (Table 6.1-2):

Table 6.1-2 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 and/or other food substances
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 and/or other food substances
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 and/or other food substances
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 and/or other food substances
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 and/or other food substances
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 and/or other food substances
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

Table 6.1-2 Dosing Schedule - Additional Arms

Dose	Administration
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.

In each arm, 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

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

For additional information regarding the dosage regimen and treatment period(s), including any follow-up period(s) for each treatment group/arm of the trial, see Section 4.1.

6.2 Management of Trial Intervention(s)

For full details on management of trial intervention(s), please refer to the trial-specific operations manual.

6.2.1 Packaging and Labeling

The IMP will be provided by the sponsor or designated agent to the investigators and the persons designated by the investigator(s) or institution(s). The IMP will be supplied as bottles. Each bottle used in the dosing period will be labeled to clearly disclose the compound ID, trial number, sponsor's name and address, lot number, instructions for use, route of administration, and appropriate precautionary statements and other information required by local regulatory authorities.

6.2.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees.

The IMP will be stored according to the conditions indicated on the IMP label.

The trial site staff will maintain a temperature log in the IMP storage area to record the temperature.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of received, dispensed, used, and destroyed. Neither the investigator nor any designees may provide IMP to any person not participating in this trial.

6.2.4 Returns and Destruction

The IMP may only be destroyed by the trial site(s) if approved by the sponsor and if the IMP destruction meets all local regulations. The IMP will be destroyed by the clinical trial site following completion and verification of accountability of the IMP by the assigned clinical monitor. The trial site(s) may utilize qualified third-party vendors for IMP destruction. A certificate of destruction should be filed in the trial master file.

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication provided by a healthcare professional, consumer, clinical trial participant, medical representative, regulatory agency, partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device or medicinal product or a falsified, tampered, or diverted product after it is released for distribution.

Examples include, but are not limited to, communications involving:

- Failure/malfunction of a medicinal product to meet any of its specifications

- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product, no safety seal)
- Blister defects (eg, missing, empty blisters)
- Storage temperature discrepancies
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record each PQC identified through any means from the receipt of the trial intervention(s) from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including participant dosing.

The investigator or designee must notify the sponsor (or sponsor's designee) within 24 hours of becoming aware of the PQC. The PQC reporting information should be sent to the Otsuka Pharmaceutical Development & Commercialization, Inc IMP complaints mailbox e-mail: **IMP-PQC@otsuka-us.com**. The information should also indicate whether or not the complaint sample is available for return.

Identification of a PQC by the participant should be reported to the site investigator, who should then follow the reporting mechanism above.

6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, participant, investigator, site, etc)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures of complaint sample (if available)
- Availability of complaint sample for return
- Was any participant at risk due to the identified issue?

6.2.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the sponsor will provide return instructions, when applicable.

It must be documented in the site accountability record that the complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

6.2.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

6.3 Measures to Minimize/Avoid Bias

This is an open-label trial.

Participants will be randomized to 1 of 4 treatment sequences on Day 1. Eligible participants who are enrolled in the trial will be assigned a unique subject randomization number for treatment or treatment sequence assignment. The randomization numbers will be created by the sponsor following its standard operating procedures.

6.4 Trial Participant Compliance

The time and dose of each trial intervention administration will be recorded in the eCRF. Information regarding any missed or inappropriately administered doses will also be documented in the eCRF. All doses of IMP will be administered while the participants are in the clinic; compliance will be ensured by a mouth check during the oral dosing administration of IMP.

6.5 Dose Modification

Not applicable.

6.6 Prior/Concomitant Medications or Therapies

The investigator will record all medications (including, but not limited to, prescription medications, over-the-counter medications, vitamins, herbal remedies, etc) and therapies taken by the participant from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which participants are evaluated for primary and/or secondary objectives) in the eCRF. The investigator will also record all medications and therapies taken by the participant for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the eCRF.

For concomitant medications, the following will be recorded in the eCRF: medication, indication, dose, frequency, route, start date and end date. For concomitant therapy, the following will be recorded in the eCRF: therapy, indication, start date and end date.

6.6.1 Prohibited Medications or Therapies

No medications other than the protocol-specific trial IMP may be taken during the trial (with the exception of birth control). The use of prescription, over-the-counter, or herbal medications or vitamin supplements within 14 days prior to dosing of IMP and antibiotics within 30 days prior to the first dose of IMP is prohibited. The sponsor may allow exceptions only if the medication is unlikely to affect the PK result.

6.7 Intervention After the End of the Trial

Not applicable.

7 Discontinuation of Trial/Treatment and Participant Discontinuation/Withdrawal

7.1 Entire Trial or Treatment

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, the Institutional Review Board (IRB), and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site Discontinuation

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP). The investigator will notify the sponsor promptly if the investigator or the IRB at the site discontinues participation in the trial.

7.3 Discontinuation of Trial Intervention

After treatment assignment, a participant may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a participant who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. If participants discontinue treatment, their participation in the trial will be discontinued. Participants who discontinue from the trial should be encouraged to complete all ET and follow-up assessments with ET assessments conducted as soon as possible.

See the schedule of assessments for data to be collected at the time of discontinuation of trial intervention and follow-up and for any further evaluations that need to be completed. If a participant discontinues trial intervention due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized.

For each participant who discontinues trial intervention, the main reason for discontinuation will be recorded in the eCRF (refer to Section 7.4.1 Documenting Reasons for Participant Discontinuation/Withdrawal).

7.4 Participant Discontinuation/Withdrawal from the Trial

- A participant may withdraw from the trial at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the trial, if possible, an early discontinuation visit should be conducted, as shown in the schedule of assessments (Table 1.3-1). Also see the schedule of assessments for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.
- If a participant withdraws consent from the trial, the participant will be permanently discontinued from all trial interventions and the trial.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before the withdrawal of consent.
- If a participant withdraws from the trial, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

Complete withdrawal of consent requires a participant's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).
- Contact of the participant by trial site staff, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the participant's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a participant's intended withdrawal need to be completely understood,

documented, and managed to protect the rights of the participant and the integrity of the trial. A participant may initially express their desire to discontinue trial intervention administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3). A participant may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should determine if the participant can continue participation in the trial if modifications to the participant's treatment and/or schedule of assessments can be accommodated. Only participants who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

7.4.1 Documenting Reasons for Participant Discontinuation/Withdrawal

A participant may discontinue trial intervention(s) and thereby withdraw from the trial for the reasons listed below:

- Adverse event
  - Continuing IMP places the participant at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
  - Serious adverse event (SAE)
  - Other potentially IMP-related safety concerns or AEs
- Death
- Lost to follow-up
- Noncompliance with IMP
- Physician decision
- Pregnancy
- Protocol deviation
- Protocol-specific withdrawal criterion met
- Site terminated by sponsor
- Withdrawal by subject

7.5 Lost to Follow-up

Participants who cannot be contacted on or before Day 17 (+2) during the trial intervention period, who do not have a known reason for discontinuation (eg, withdrew consent/assent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up." Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death

(ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the participant, medical records, successful telephone contact with the participant, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the participant by telephone and in the event the site is unable to reach the participant by telephone, the site will attempt to contact the participant via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

If the participant was classified as "lost to follow-up," the following information will be recorded in the eCRF: "Date of final contact attempt" and "Contact method."

8 Trial Procedures

The expected duration for trial participation will be up to approximately 45 days, including a screening period lasting up to 27 days (Days −28 to −2), a baseline/check-in visit on Day −1, a 12 day in-clinic treatment period (Day 1 to 12), and a safety follow-up telephone call 7 days +2 after the last dose of IMP (Day 17 [+2]).

The assessments to be conducted during the trial are summarized in Table 1.3-1.

The total amount of blood to be drawn for the entirety of the trial is estimated to be below 250 mL per participant. Repeat or unscheduled blood draws may occur, if applicable.

8.1 Efficacy Assessments

Not applicable.

8.2 Pharmacokinetic Assessments

8.2.1 Pharmacokinetic Plasma Samples

Pharmacokinetic samples will be collected at the time points described in the schedule of assessments (Table 1.3-1). These samples should be collected within ± 3 minutes of the nominal time. Predose samples should be collected within 60 minutes before administration of the IMP.

When vital signs are scheduled at the same nominal time as PK sample collections, vital signs should be measured before PK samples are collected. The actual date and time of the PK sample collection will be recorded in the eCRF.

Blood samples (4 mL) will be collected in vacutainers containing dipotassium ethylenediaminetetraacetic acid and processed into plasma to determine the concentrations of centanafadine and metabolite(s). CCI

CCI

After processing into plasma, aliquots will be placed into appropriately labeled tubes and will be placed in a freezer set at −70°C unless otherwise instructed in the trial-specific operations/laboratory manual.

All PK samples will be shipped to the bioanalytical laboratory. Additional information will be provided in the trial-specific laboratory manual.

CCI

8.6 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.7.

8.6.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the schedule of assessments (Table 1.3-1) to perform the clinical laboratory assessments described in Section 10.2.

Refer to the trial-specific laboratory manual for information on how to identify laboratory values outside of normal reference ranges and for instructions on how to assess for potential clinical significance. The total volume of blood to be collected during the trial will be documented in the ICF.

8.6.2 Physical Examination

Physical examinations will be performed at the time points described in the schedule of assessments (Table 1.3-1).

A complete physical examination will include height (screening only), weight, and calculation of BMI (at visits indicated in Table 1.3-1) as well as an assessment of the head, eyes, ears, nose, and throat; thorax; abdomen; skin and mucosae; neurological system; and extremities.

Directed physical examinations in response to reported AEs will be conducted as necessary. Any abnormalities that are observed after the screening period and are considered by the investigator to be clinically significant, are to be recorded as AEs on the source documents and in the eCRF.

8.6.3 Vital Signs

Vital signs (including blood pressure, pulse, and body temperature) will be collected at the time points described in the schedule of assessments (Table 1.3-1) and will be performed before PK samples are collected on IMP dosing days.

Blood pressure and heart rate 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. Participants' vital signs should be monitored and assessed for potential clinical significance. Any post screening abnormalities considered by the investigator to be clinically significant are to be recorded as AEs in the eCRF.

8.6.4 Electrocardiogram

Electrocardiograms will be performed in the supine position at the time points described in the schedule of assessments (Table 1.3-1). The 12-lead ECGs will be single assessments for screening and discharge (Day 12)/ET and will be performed in triplicate at check-in to the inpatient facility (Day −1).

Participants' ECGs should be monitored and assessed for potential clinical significance. Any post screening abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the eCRF.

8.6.5 Suicidality Monitoring

Suicidality monitoring will occur at the time points described in the schedule of assessments (Table 1.3-1).

Suicidality will be monitored during the trial using the CSSRS. The C-SSRS is a semistructured interview that captures the occurrence, severity, and frequency of suicide related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide related thought or behavior has occurred. The interview and rating for the

C-SSRS must be completed by a licensed clinician or designee who has completed the required rater training to complete this assessment and who has been approved by the sponsor to administer this assessment. Documentation of training should be maintained in the trial site's files.

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 all other time points. There are required items to be completed, potential additional items if there is a positive response to a required item, and items for suicide/suicide behavior present during the interview. The C-SSRS uses dichotomous scales (ie, yes or no), Likert scales, and text or narrative to further describe the thoughts or behaviors.

8.6.6 Other Safety Assessments

No other safety variables are applicable for this trial.

8.7 Adverse Events

8.7.1 Definitions

Trial interventions are all pre-specified, investigational medicinal products intended to be administered to the participants during the conduct of the trial.

Adverse Event: an AE is defined as any untoward medical occurrence in a clinical trial participant administered a trial intervention, and which does not necessarily have a causal relationship with this intervention. Adverse events would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred.

An adverse reaction is any untoward and unintended response to a trial intervention related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the trial intervention caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the trial intervention and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of IMP treatment. In more detail, TEAEs are all AEs which started after the start of IMP; or if the event was continuous from baseline and was worsening, serious, IMP-related, or resulted in death, discontinuation, interruption, or reduction of IMP.

A serious adverse event (SAE) includes any event that results in any of the following outcomes:

- Death
- Life-threatening, ie, the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the participant, and may require medical or surgical intervention to prevent one of the outcomes listed above, eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Adverse Events of Special Interest (AESIs): a noteworthy event for the particular IMP or class of products that a sponsor may wish to monitor carefully. All AESIs are to be reported as immediately reportable events (IREs).

Immediately Reportable Event (IRE):

- Any SAE.
- Any AESIs (see Section 8.7.5).
- Potential serious hepatotoxicity (see Section 8.7.7).
- Any AE related to occupational exposure (eg, an investigator getting a skin rash after exposure to a medication). Non-participant AEs would not be recorded on the eCRF form but must be recorded on an IRE form to the sponsor.
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, pregnancy of a trial participant will mandate trial intervention discontinuation and pregnancy of a participant or a participant's partner must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. Pregnancy will only be

documented on the AE eCRF if the pregnancy occurs in a trial participant and there is an abnormality or complication (see Section 10.3).

Clinical Laboratory Test Value Changes: it is the investigator's responsibility to review the results of laboratory tests for each individual participant as they become available. This review will be documented by the investigator's dated signature on the laboratory report. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant (ie, clinically significant) by the investigator (participant is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: adverse events will be graded on a 3-point scale and reported as indicated in the eCRF. The severity of an adverse experience is defined as follows:

1 = Mild: discomfort noticed, but no disruption to daily activity.

2 = Moderate: discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: inability to work or perform normal daily activity.

Investigational Medicinal Product Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.

Not Related: There is no temporal or causal relationship between the IMP and the AE.

8.7.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess participants for the occurrence of AEs. To avoid bias in eliciting AEs, participants should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the participant must be recorded on the source documents and in the eCRF provided by the sponsor. Adverse event collection will begin after a participant signs the ICF and will continue until the participant's last scheduled contact unless the AE must be followed further. All screen failure AEs will be recorded as described in Section 5.4.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

Medical or surgical procedures (eg, endoscopy, appendectomy) should not be reported as AEs; however, the condition that led to the procedure may be reported as an AE.

If a reported AE undergoes a change or worsening in severity, seriousness, or toxicity, it should be reported as a new AE in the eCRF.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 8.7.3. Special attention should be paid to recording hospitalization and concomitant medications.

The AE, start date, end date (if possible, start date and time, end date and time), seriousness, severity, relationship to IMP (causality), action taken with IMP, and outcome will be recorded on the source documents and in the eCRF.

Note: start time should be recorded in the event an AE such as vomiting occurs. When capturing start/end time, at a minimum, the hour should be captured in the event it is difficult to specify in hours and minutes.

Regarding SAE, relationship to, and action taken with trial intervention(s) other than IMP will also be evaluated per each intervention. These evaluations will be recorded in the source documents and in the eCRF and will be reported using the IRE form (see Section 8.7.3).

8.7.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, after the investigator or site personnel become aware of any IRE (SAE, AE related to occupational exposure, AESI, potential serious hepatotoxicity, or confirmed pregnancy), by telephone, fax, or e-mail to the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE eCRF). Participant confidentiality must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding Safety Information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.7.9.2.

8.7.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.7.5 Adverse Events of Special Interest

Newly acquired, nontraumatic skin eruptions are considered as AESIs. The following examples would not be considered as AESIs: contact dermatitis, insect bites and stings, poison plant intoxication (eg, poison ivy), skin reactions to ECG electrodes or similar adhesive tape, or chemical or thermal burns. 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, nonserious lesions are also eligible).

Rash/Skin Eruption AESI Workup Instructions are in place to monitor AESIs. The instructions explain the whole process, providing step-by-step instructions, and comprise the following basic components:

- AESI Form
- IRE Form
- Remote Electronic Virtual Assessment Application to capture and securely transmit the skin eruption photographs
- Clinical research site personnel
- Central dermatologist
- Local dermatologist or teledermatology service
- Sponsor medical monitor and contract research organization medical monitor
- Sponsor pharmacovigilance representatives
- Stopping rules for the IMP in case there is an AESI
- Blood work including the steps in bullous eruption or potential drug reaction with eosinophilia and systemic symptoms / drug-induced hypersensitivity syndrome scenarios
- Biopsy-related instructions when applicable

In addition, skin checks must be conducted during each physical exam and the presence of rash during AE monitoring must be inquired.

The trial site will have a local designated dermatologist available for consultation as needed for these AESIs.

All AESIs should be reported as IREs (see Section 8.7.3).

8.7.6 Abuse Potential Monitoring Process, Events Subject to Additional Monitoring, and Medication Handling Irregularities

A key objective of the Abuse Potential Monitoring Process (APMP) is to monitor for instances of abuse or diversion of the IMP and other psychoactive substances. In addition to monitoring for irregularities in medication handling, AEs that may be suggestive of a developing abuse issue will also receive special attention. As part of the APMP, medication handling irregularities (MHIs) must be reported, and AEs related to abuse potential and AEs involving MHIs must be reported as Events Subject to Additional Monitoring (ESAMs) with detailed narratives. Investigators and site staff at the trial site will be trained on reporting potentially abuse-related AEs (eg, recording a description of the event in the participant's own words in the source documents as well as eCRF, in addition to the clinical term, and to be aware that a participant's report may encompass more than one event and that these should be recorded separately). The investigators will be provided with examples of potentially abuse-related AEs and trained on how to handle such events (eg, additional monitoring).[6] While the investigators will be provided with examples of AE terms as a guide during trial conduct, the analysis of potentially abuse-related AEs will be based on a search of all Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, all verbatim terms, and any open text fields within the AE data to identify text strings suggestive of abuse potential, in line with the 2017 US FDA guidance (Assessment of Abuse Potential of Drugs).

Refer to the separate APMP documentation for complete details on MHIs and ESAMs, including documenting and reporting procedures, examples of potentially abuse-related AE terms that meet the criteria for ESAM reporting, and guidance for the training of investigators and trial site staff.

8.7.7 Potential Serious Hepatotoxicity

For a participant who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 3 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and report as an AE in the eCRF.

8.7.8 Procedure for Breaking the Blind

This trial does not use blinding procedures.

8.7.9 Follow-up of Adverse Events

8.7.9.1 Follow-up of Nonserious Adverse Events

With the exception of screen failures, nonserious AEs that are identified at any time during the trial must be recorded in the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in the eCRF. For any AE having been identified throughout the trial, additional relevant medical history information may be requested by the sponsor during analysis of the event, to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation). All screen failure AEs will be recorded as described in Section 5.4.

8.7.9.2 Follow-up of Immediately Reportable Events

This trial requires that participants be actively monitored for IREs up to 7 (+2) days after the last trial intervention is administered.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such in the AE eCRF and on the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a participant's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded in the AE eCRF and on the IRE form, according to the appropriate reporting procedures described in Section 8.7.3.

It is expected that the investigator will provide or arrange appropriate supportive care for the participant and will provide prompt updates on the participant's status to the sponsor. The investigator will follow the IREs until:

- The events are resolved,
- The events have stabilized,
- The participant is lost to follow-up, or
- The participant has died.

Resolution means that the participant has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the participant's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the participant is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for participants that become pregnant or for pregnant partners of trial participants.

8.7.9.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact

Any new IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the trial intervention(s), should be reported to the sponsor according to the procedures outlined in Section 8.7.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. Any significant follow-up information should continue to be reported to the sponsor until the events are resolved or stabilized, or the participant is lost to follow-up or has died.

8.8 Treatment of Overdose

Not applicable.

8.9 Participant Assessments

Not applicable.

8.10 Other Assessments

Not applicable.

9 Statistical Considerations

9.1 Sample Size

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

9.2 Datasets for Analysis

The randomized dataset includes all participants who are randomized in the trial.

The safety dataset includes all participants that were administered at least one dose of IMP.

The PK dataset includes all participants with evaluable plasma concentration data and PK parameters.

9.3 Handling of Missing Data for Primary Endpoint Analysis

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

9.4 Statistical Analyses

9.4.1 Primary Endpoints Analyses

The primary analysis of PK parameters (C_{max}, AUC_t, and AUC_∞) will be calculated for Test (T) and Reference (R); the 90% 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.

The details of the analysis including the test and reference treatments will be described in the SAP.

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

9.4.2 Secondary Endpoints Analyses

See Section 9.4.5.2 for the PK analysis and Section 9.4.4 for the safety analyses.

9.4.3 Control of Experiment-wise Type 1 Error

Not applicable.

9.4.4 Safety Analyses

9.4.4.1 Adverse Events

All AEs will be coded by system organ class and MedDRA preferred term. The incidence of the following events will be summarized by treatment group for each arm:

- TEAEs
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- TEAEs causally related to the IMP
- AESIs

9.4.4.2 Clinical Laboratory Data

Clinical laboratory test results (observed and change from baseline data) will be summarized by treatment sequence for each arm. The incidence of potentially clinically relevant clinical laboratory test results will also be summarized by treatment sequence for each arm. All clinical laboratory test results will be presented in a listing by arm.

9.4.4.3 Physical Examination and Vital Signs Data

Physical examination data will be presented in a listing.

Vital signs results (observed and change from baseline data) will be summarized by treatment for each arm. The incidence of potentially clinically relevant vital sign results will also be summarized by treatment for each arm. All vital sign test results will be presented in a listing.

9.4.4.4 Electrocardiogram Data

Electrocardiogram results at baseline will be summarized for all participants. All ECG test results will be presented in a listing. Baseline will be determined by the average of the triplicate ECGs.

Electrocardiogram results (observed and change from baseline data) will be summarized by treatment sequence for each arm. The incidence of potentially clinically relevant clinical laboratory test results will also be summarized by treatment sequence for each arm. All ECG test results will be presented in a listing.

9.4.4.5 Other Safety Data

9.4.4.5.1 Suicidality

Suicidality will be monitored during the trial using the C-SSRS. The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide related thought or behavior has occurred. The interview and rating for the C-SSRS must be completed by a licensed clinician or designee who has completed the required rater training to complete this assessment and who has been approved by the sponsor to administer this assessment. Documentation of training should be maintained in the trial site's files. 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 all other time points. There are required items to be completed, potential additional items if there is a positive response to a required item, and items for suicide/suicide

behavior present during the interview. The C-SSRS uses dichotomous scales (ie, yes or no), Likert scales, and text or narrative to further describe the thoughts or behaviors.

9.4.5 Other Analyses

9.4.5.1 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, sex at birth, weight, height, and BMI for the enrolled and randomized participants will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable).

9.4.5.2 Pharmacokinetic Analyses

The PK of centanafadine and EB-10601 from different lots of centanafadine QD XR capsules (eg, manufactured using different brands of talc, different % weight gain coating) may be compared to the lot of capsules with CCI talc used in the pivotal pediatric ADHD trials and may also be compared to PK obtained following administration of centanafadine SR tablets that were used in the pivotal adult ADHD trials or to other lots of capsules.

Centanafadine and EB-10601 plasma concentrations will be summarized by treatment, analyte, and timepoint using descriptive statistics (mean, median, standard deviation, percentage coefficient of variation, geometric mean, minimum, maximum).

Noncompartmental PK analysis will be performed to estimate the PK parameters for centanafadine and EB-10601. Estimated PK parameters will be summarized by treatment and analyte using the same descriptive statistics as for concentrations, except for time to maximum (peak) plasma concentration (t_{max}) which will be reported as median, minimum, and maximum. Other parameters may be calculated as supported by the data collected.

9.5 Interim Analysis

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, applicable International Council for Harmonisation (ICH) GCP guidance, international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling the eCRF, IRE and any safety information, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting the privacy of trial participants. To this end, a subject ID will be used to identify each participant.

Financial aspects, participant insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

Diversity and inclusion are essential in all aspects of clinical trials to generate evidence-based approaches that are generalizable and applicable to the populations that are most likely to benefit from the medications or products being studied. Clinical trials must be inclusive of underrepresented racial and ethnic populations and other minority groups to account for diverse lived experiences. Otsuka is committed to promoting an inclusive environment that engages a diversity of participants, sites, investigators, and site staff in the execution of its clinical trials.

10.1.2 Informed Consent

Informed consent will be freely obtained from all participants (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB that approves this protocol.

Each ICF will comply with the ICH GCP Guidelines, and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF used in the trial before submission to the IRB. In support of the site's standard process for administering informed consent, this trial will also allow for electronic informed consent form (eICF) as a tool within applicable regions and trial sites. The eICF utilizes the IRB-approved site-specific ICF to offer participants an

enhanced platform to review and understand their rights as a research trial participant as well as required trial procedures. When possible, trial sites will have participants review and sign the eICF prior to starting any trial procedures; however, if local regulations do not allow for use of the electronic format, participants may continue in the trial utilizing the standard paper and wet ink signature process.

Investigators may discuss trial availability and the possibility for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential participants are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the participant by the investigator (or a qualified designee), and it has been documented that the participant has had the opportunity to ask questions and have those questions answered, the IRB-approved paper ICF will be signed and dated by both the participant and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB. The participant will receive a copy of the signed ICF; the original shall be kept on file by the investigator. Participants may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the participants, so that they can make a knowledgeable and voluntary decision on continued trial participation. If a partner of a trial participant becomes pregnant during the course of the trial, the nonparticipant partner may be asked to sign an ICF in order to collect additional information regarding the nonparticipant partner and fetus.

10.1.3 Recruitment Strategy

Methods for participant recruitment may include, but are not limited to: media (ie, television, radio, and newspaper), physician referrals, press releases, fliers, random mailings, cold calls, and the internet. Methods will be selected before the start of the trial and may be added as the trial progresses.

10.1.4 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Participant confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor

personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All trial intervention(s), participant bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Participants will be identified only by their unique subject ID in the eCRF. If further participant identification is required, participants' full names may be made known to a regulatory agency or other authorized officials, if necessary, subject to local regulations.

The contract between sponsor and trial sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store trial-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

If trial intervention monitoring will be conducted by an innovative application, the retention and use of images and data will be in accordance with the terms of the master service agreement with the vendor.

10.1.5 Quality Control and Quality Assurance

10.1.5.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the applicable ICH GCP guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.5.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, trial intervention supply, presence of required documents, the informed consent/assent process, site operations, delegation of authority and training, and a review of the eCRF with source documents, as applicable. The investigator will agree to cooperate and participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.1.6 Protocol Deviations

In the event of a significant/major deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, trial intervention dispensing or participant dosing error, treatment assignment error, participant enrolled in violation of eligibility criteria or concomitant medication criteria]), the investigator or designee will contact the sponsor or designee at the earliest possible time by telephone or via e-mail. The investigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the participant's continuation in the trial. This decision will be documented by the investigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation.

10.1.7 Records Management

10.1.7.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, screening logs, progress notes, paper-based assessments and scales, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, participant confidentiality must be maintained in accordance with local regulatory requirements.

10.1.7.2 Data Collection

During each participant's visit to the site, an investigator or their designee participating in the trial will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent/assent process, including any revised ICFs;
- Documentation of the investigator's decision to enroll the participant into the trial, the review of all inclusion/exclusion criteria prior to trial intervention administration, and confirmation of the participant's actual participation in the trial;
- Documentation of baseline and demographic characteristics (eg, age, weight, BMI, sex at birth, gender, race, ethnicity)
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General participant status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to trial intervention must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed, including dosing and trial intervention compliance;
- The signature (or initials) and date of the investigator (or designee) who made an entry in the medical record.
- The time of last food eaten prior to IMP dosing, the time of meal provided on dosing days, the actual time of IMP dosing and PK sample collection will all be recorded in the eCRF.

In addition, any contact with the participant via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Information from medical records and other source documents will be entered by investigative site personnel onto eCRFs in the sponsor's electronic data capture (EDC) system that is 21 CRF Part 11 compliant. Changes to the data will be captured by an automatic audit trail in the EDC system.

Electronic data not entered on eCRF, such as data received from central laboratories and central ECG readers, will be reconciled using key data fields by the sponsor or the clinical research organization with the eCRF data to ensure consistency.

10.1.7.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with applicable ICH GCP guidance and as required by applicable local regulations. The

investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.1.7.4 Records Retention at the Trial Site

Food and Drug Administration (FDA) regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

A period of at least 2 years after the date on which a New Drug Application (NDA) is approved by the FDA;

A period of 2 years after the sponsor has notified the FDA that investigation with this drug is discontinued.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10.1.7.5 Dissemination of Clinical Trial Data

Registration and disclosure of this trial is not required per local regulations.

10.1.7.6 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other personnel involved in the conduct of the trial who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other personnel involved in the conduct of the trial consent to such acknowledgement in any publications resulting from its conduct.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Hematology: Erythrocytes Hematocrit Hemoglobin Leukocytes count with differential Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelets Urinalysis: Bilirubin Color Glucose Ketones Microscopic analysis, white blood cell/red blood cell counts per high powered field, casts, crystals, squamous cells Occult blood pH Protein Specific gravity Specimen appearance Urobilinogen	Serum Chemistry: Alkaline phosphatase ALT AST Bilirubin, total Blood urea nitrogen Calcium Carbon dioxide Cholesterol, total Chloride Creatine phosphokinase Creatinine Gamma glutamyl transferase Glucose Lactic dehydrogenase Potassium Protein, total Sodium Triglycerides Drug Screen (all items in urine except where noted): Alcohol (breath or urine) Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Cotinine (urine or serum) Methadone Opiates Phencyclidine Propoxyphene Additional Tests: FSH for postmenopausal females Urine or serum pregnancy test for all females Viral serology (HIV, HBsAg, anti-HCV)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

DEFINITIONS:

Participants of reproductive potential (PORP) are defined as those participants who have reached onset of menarche or clear onset of puberty (Tanner stage B3 or stage G3) and who are not documented as sterile (eg, have had a bilateral orchiectomy or have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months).

Participants of childbearing potential (POCBP) are those for whom menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months).

CONTRACEPTIVE GUIDANCE:

For PORP and POCBP and their partners, who are sexually active, there must be a documented agreement that the participant and their partner will take measures (ie, 2 different effective and/or highly effective methods of birth control per below table or remain abstinent from sexual activity with the potential for conception) to prevent pregnancy during the course of the trial and for 90 days for males and 30 days for females after the last trial intervention administration.

The contraceptive method(s) will be documented in the eCRF. All PORP must also agree not to donate sperm or eggs from trial screening through 90 days for sperm and 30 days for eggs after the last trial intervention administration.

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the POCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*)*
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – Oral – Intravaginal – Transdermal – Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – Oral – Injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from sexual activity with the potential for conception during the entire period of risk associated with the trial intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant.*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
Progestogen-only oral hormonal contraception where inhibition of ovulation isn't the primary mode of action
External or internal condom with or without spermicide
Cervical cap, diaphragm, or sponge with spermicide
A combination of external condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

a) Contraceptive use by PORP should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c) External condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
d) Considered effective, but not highly effective - failure rate of ≥ 1% per year.

NOTE: periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. External condom and internal condom should not be used together (due to risk of failure from friction).

PROCESSES:

Before enrolling participants in this clinical trial, investigators must review the following information about trial participation as part of the ICF process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, PORP and POCBP and their partners must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Participants must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine or serum pregnancy test for human chorionic gonadotropin will be performed at screening and at check-in on Day −1 and discharge/ET on all POCBP. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all POCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). All PORP must also be instructed to contact the investigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle) with their child.

If a POCBP is suspected to be pregnant before receiving trial intervention(s), the intervention administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the participant must not receive the trial

intervention(s) and must not be enrolled in the trial. If pregnancy is suspected while the participant is taking trial intervention(s), the intervention(s) must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the trial intervention(s) will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety) and the participant will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with trial intervention exposure during the trial and for at least 30 days after the last trial intervention administration for female participants and 90 days after the last trial intervention administration for female partners of male participants and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

Protocol required procedures for trial discontinuation and follow-up must be performed on the participant unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

10.4 Appendix 4: Protocol Amendments

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Non-substantial amendments are defined as having no effect on the safety of participants, conduct or management of the trial, trial design, or the quality or safety of intervention(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to participants should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the participant, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written informed consent/assent will be obtained from currently enrolled participants in the trial before the amendment-specified changes in the trial are implemented.

10.4.1 Protocol Amendment(s)

CCI

[redacted]

10.4.1.2 Protocol Amendment 2

CCI



11 References

1 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Bioavailability Studies Submitted in NDAs or INDs — General Considerations Guidance for Industry. www.fda.gov/media/121311/download. Published April 2022. Accessed 29 September 2023.

2 US Food and Drug Administration Draft Guidance for Industry. Assessing the effects of food on drugs in INDs and NDAs - clinical pharmacology considerations. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM631941.pdf. Published February 2019. Accessed 30 April 2019.

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4 US Food and Drug Administration. SCOGS Select Committee on GRAS Substances. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=SCOGS&sort=Sortsubstance&order=ASC&startrow=1&type=basic&search=talc. Updated July 31, 2020. Accessed October 20, 2023.

5 Otsuka Pharmaceutical Development and Commercialization. Centanafadine (EB-1020) Investigator's Brochure, Edition 12. Otsuka Report, issued 08 Feb 2023.

6 FDA Center for Drug Evaluation and Research. Guidance for Industry: Assessment of Abuse Potential of Drugs. January 2017. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf.

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational medicinal product, centanafadine, any other trial interventions or concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the IRB responsible for such matters in the clinical trial facility where centanafadine will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on eCRF by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for participants screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to participants, I will implement the amendment immediately, and provide the information to the Health Authority and IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all participants with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: Protocol 405-201-00150 Amendment 2

Document Number: 1000272628

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Biostatistics Approval	11-Jul-2024 16:32:49
PPD	Clinical Approval	15-Jul-2024 13:43:18
PPD	Clinical Pharmacology Approval	11-Jul-2024 15:35:30