Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Centanafadine (EB-1020)

REVISED CLINICAL PROTOCOL

A Pilot Phase 2a, Multicenter, Open-label, Single-dose Trial to Assess the Pharmacokinetics of Centanafadine Extended-release Capsules After Oral Administration in Pediatric Subjects (9 to 12 years, inclusive) With Attention-deficit Hyperactivity Disorder

Open-label, Single-dose Trial to Assess the Pharmacokinetics of Centanafadine Extended-release Capsules in Pediatric Subjects With Attention-deficit Hyperactivity Disorder

Protocol No. 405-201-00037
IND No. 119361

CONFIDENTIAL — PROPRIETARY INFORMATION

Drug Development Phase:	2a
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc.
Immediately Reportable Event	[redacted]
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1 Protocol Summary

1.1 Synopsis

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

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

Protocol No.: 405-201-00037

IND No.: 119361

Protocol Title: A Pilot Phase 2a, Multicenter, Open-label, Single-dose Trial to Assess the Pharmacokinetics of Centanafadine Extended-release Capsules After Oral Administration in Pediatric Subjects (9 to 12 years, inclusive) With Attention-deficit Hyperactivity Disorder

Protocol Lay Person Short Title: Open-label, Single-dose Trial to Assess the Pharmacokinetics of Centanafadine Extended-release Capsules in Pediatric Subjects With Attention-deficit Hyperactivity Disorder

Clinical Phase: 2a

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

Objectives and Endpoints:

Objectives	Endpoints
Primary: To characterize the single-dose concentration-time profile from 0 to 12 hours of centanafadine in pediatric subjects (9 to 12 years, inclusive) with ADHD.	Primary: • C_{max} of centanafadine • t_{max} of centanafadine • AUC_{0-12h} of centanafadine

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Objectives	Endpoints
Other: [redacted]	[redacted]

AE = adverse event; AUC_{0-12h} = area under the concentration-time curve from time 0 to 12 hours postdose; [redacted] C_{max} = maximum (peak) plasma concentration; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; IR = immediate-release; PK = pharmacokinetic; t_{max} = time to maximum concentration; VAS = visual analogue scale; XR = extended-release.

Trial Design:

This is a pilot phase 2a, multicenter, open-label, single-dose trial in pediatric subjects (9 to 12 years, inclusive) with a documented history of ADHD and confirmation of an ADHD prescription medication. This trial consists of a screening period (Day −21 to Day −2), check-in (Day −1 or Day 1), 2-day treatment period (Day 1: dosing, Day 2: end-of-treatment [EoT]), and a safety follow-up telephone call 7 (+ 2) days after dosing (Day 8). The screening period may be extended if additional time is needed to complete screening procedures, upon discussion with and approval by the medical monitor.

Eligible subjects will check-in either on Day −1 or Day 1, based on the investigator's decision. A single dose of centanafadine will be administered either as intact capsules or the capsule contents sprinkled on a tablespoon of applesauce on Day 1 in the morning. [redacted] Pharmacokinetic (PK) and safety assessments will be performed for approximately 24 hours postdose. Subjects may be released from the clinic after PK sample collection at 12 hours postdose to return the following morning or may remain in the clinic until 24 hours postdose, based on the investigator's decision. Subjects released on Day 1 will return to the clinic on Day 2 between 22 to 26 hours postdose for an outpatient visit, which will include EoT assessments and one PK sample. In-clinic subjects may leave the clinic on Day 2 after EoT assessments and PK sampling are complete.

Subjects and/or their caregivers will be contacted by telephone 7 days after dosing to assess any new or ongoing adverse events (AEs) and to record concomitant medications.

Trial Population:

The trial population will consist of males and females, aged 9 to 12 years (inclusive), who have a documented history of ADHD and confirmation of an ADHD prescription medication. Up to 12 subjects may be treated in the trial.

Key Inclusion/Exclusion Criteria:

Key inclusion criteria are noted above, under Trial Population. In addition, subjects must be in good physical health, as determined by no clinically significant deviation from normal for all of the following, prior to enrollment in the trial:

- Medical history
- Clinical laboratory determination
- Electrocardiograms (ECGs)
- Physical examinations

Key exclusion criteria are as follows:

- Subjects with a clinical presentation or history that is consistent with delirium, dementia, amnesia, or other cognitive disorders; subjects with psychiatric symptoms that are better accounted for by another general medical condition(s) or direct effect of a substance (ie, medication, illicit drug use, etc.).
- Subjects with a history of intellectual disability as determined by at least 1 of the following: an intelligence quotient (IQ) < 70, or clinical evidence, or a social or school history that is suggestive of an intellectual disability.

- Subjects who have any of the following:
  - A significant risk of committing suicide based on history and the principal 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 Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Any lifetime history of suicidal behavior detected by the "Baseline/Screening" version of the C-SSRS

  The subject should not be enrolled (eg, dosed) if any active suicidal ideation is present prior to dosing (as evidenced by a clinical examination or an answer of "yes" on Questions 4 or 5 of the C-SSRS "Since Last Visit" version) or suicidal behavior is present in the C-SSRS "Since Last Visit" version.
- Subjects who have supine or standing diastolic blood pressure, after resting for at least 5 minutes, ≥ 95 mmHg.
- Subjects who participated in a clinical trial and were exposed to investigational medicinal product (IMP) within the last 30 days prior to screening or who participated in more than 2 interventional clinical trials within the past year.
- Subjects with a history of true allergic response (ie, not intolerance) to a medication or a history of dermatologic adverse reactions or anaphylaxis secondary to drug exposure.
- Subjects with a history of allergic reaction or a known or suspected sensitivity to any substance that is contained in the IMP formulation.

Trial Site(s):

This will be a multicenter trial (at approximately 3 trial sites) conducted in the United States.

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

Centanafadine will be supplied as 1 capsule containing a 50-mg dose as extended-release with [redacted] beads and 1 capsule containing a 5-mg dose as IR beads for a total centanafadine dose of 55 mg. Both of the intact capsules or the capsule contents sprinkled on a tablespoon of applesauce will be taken orally in the morning [redacted] following a minimum 8-hour fast. A snack will be provided approximately 2 hours after dosing and lunch will be provided approximately 4 hours after dosing.

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Trial Assessments:

Assessments for Pharmacokinetics: blood sampling for centanafadine, EB-10601, [redacted].

Assessments for Safety: AEs, clinical laboratory tests, physical examinations (including body weight), vital signs, ECGs, and the C-SSRS.

Screening/Other: demographics, medical and medication history, serum hepatitis and human immunodeficiency virus (HIV) screen, breath or urine alcohol test and urine drug screen, urine pregnancy test, height, capsule swallow test, and palatability visual analogue scale (VAS).

Data Monitoring Committee: No

Statistical Methods:

Since this is an exploratory trial, no formal sample size calculations will be performed. Up to 12 subjects may be treated depending on the concentration data and the number of subjects completing through 24 hours.

A noncompartmental analysis will be performed. Plasma concentrations of centanafadine and metabolite(s) will be summarized by time point and mode of administration (intact capsules or capsule contents sprinkled on a tablespoon of applesauce). The PK parameters will be summarized by analyte and mode of administration using descriptive statistics.

No inferential statistical analysis will be conducted.

The following PK parameters will be summarized:

- Maximum (peak) plasma concentration (C_{max}) of centanafadine
- Time to maximum concentration (t_{max}) of centanafadine
- Area under the concentration-time curve from time 0 to 12 hours postdose (AUC_{0-12h}) of centanafadine
- [redacted]

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Trial Duration:

Each subject in this trial is expected to participate in the following periods of the trial (approximate durations listed), for up to 29 (+ 2) days:

- Eligibility screening period: 21 days (including optional check-in on Day −1)
- Treatment period: 2 days (Day 1: dosing, Day 2: EoT)
- Post-treatment follow-up: 7 (+ 2) days after the last dose of IMP

Overall, the trial duration from the first informed consent/assent to the final subject assessment is expected to be 3 months.

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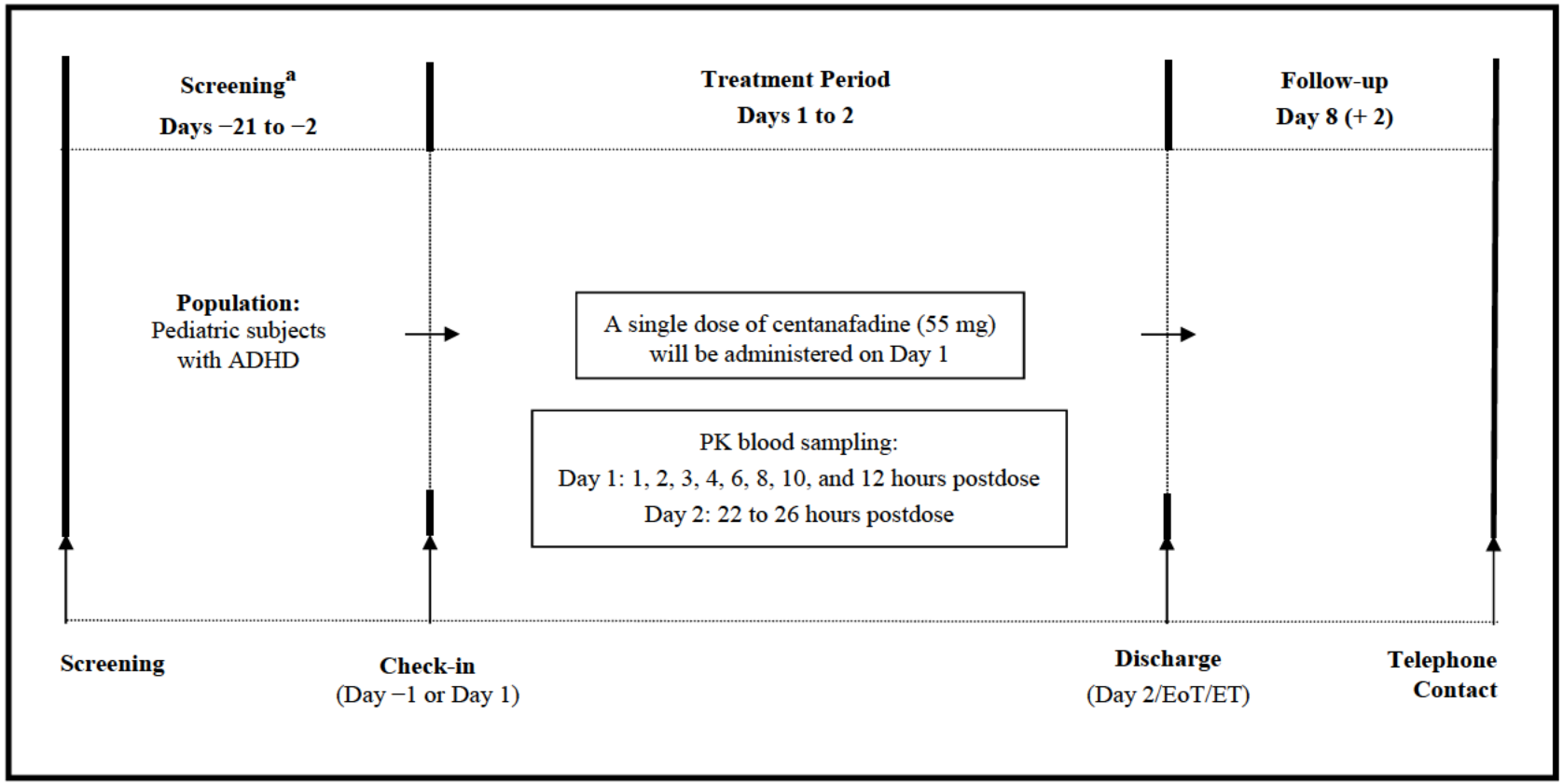
1.2 Schema



ET = early termination.

[a]The screening period may be extended if additional time is needed to complete screening procedures, upon discussion with and approval by the medical monitor.

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Assessment	Screening[a]	Check-in[b]	Treatment	Discharge	Follow-up Telephone Call[c]	Notes
	Day −21 to Day −2	Day −1	Day 1	Day 2/EoT/ET	Day 8 (+ 2)	
Screening						
Informed consent/assent	X					Section 10.1.2
Inclusion/exclusion criteria check	X					Section 5.2
Demographic information	X					
Medical history	X					
Height	X					Section 8.7.2
Serology (HIV, HBsAg, anti-HCV)	X					
[redacted]	[redacted]					[redacted]
Breath or urine alcohol test and urine drug screen	X					Section 10.2
Urine pregnancy test (for FOCBP)	X	X	X[d]	X		Section 10.3
Trial Residency						
Check-in[b]		X	X			
Meals			X			Section 6.1
Discharge from clinic			X[e]	X[e]		
IMP Administration						
Centanafadine			X			Section 6.1
Safety and Tolerability						
Record AEs	X	X	X	X	X	Section 8.8
Record concomitant medications	X	X	X	X	X	Section 6.5
Body weight	X	X	X[d]	X		Section 8.7.2
Physical examination	X	X	X[d]	X		Section 8.7.2
Vital signs	X	X[f]	X[f]	X		Section 8.7.3
12-lead ECG	X	X	X[d]	X		Section 8.7.4
Serum chemistry, hematology, and urinalysis	X	X	X[d]	X		Section 8.7.1

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Table 1.3-1 Schedule of Assessments

Assessment	Screening[a]	Check-in[b]	Treatment	Discharge	Follow-up Telephone Call[c]	Notes
	Day −21 to Day −2	Day −1	Day 1	Day 2/EoT/ET	Day 8 (+ 2)	
C-SSRS	X	X	X[d]	X		Section 8.7.5
Pharmacokinetics						
Centanafadine [redacted]) plasma concentrations			X	X		Section 8.2.1
Other Procedures						
[redacted]			[redacted]			[redacted]

anti-HCV = hepatitis C antibodies; FOCBP = females of childbearing potential; HBsAg = hepatitis B surface antigen.

[a]The screening period may be extended if additional time is needed to complete screening procedures, upon discussion with and approval by the medical monitor.

[b]Eligible subjects will check-in either on Day −1 or Day 1, based on the investigator's decision.

[c]A follow-up telephone call will be performed 7 (+ 2) days after dosing to assess AEs and record concomitant medications.

[d]Day 1 predose assessments will be performed only for those subjects who check-in on Day 1 (ie, subjects who check-in on Day −1 will have their predose assessments on Day −1).

[e]Subjects may be released from the clinic after PK sample collection at 12 hours postdose to return the following morning or may remain in the clinic until 24 hours postdose, based on the investigator's decision. Subjects released on Day 1 will return to the clinic on Day 2 between 22 to 26 hours postdose for an outpatient visit, which will include EoT assessments and one PK sample. In-clinic subjects may leave the clinic on Day 2 after the EoT assessments and PK sampling are complete.

[f]Vital signs will be assessed for all subjects at check-in, predose (within 2 hours before dosing) on Day 1, and 3 hours postdose on Day 1.

2 Introduction

Attention-deficit hyperactivity disorder (ADHD) is typically viewed as a childhood/adolescent disorder.[1] ADHD frequently begins between 2 and 4 years of age[2,3] and it is most commonly diagnosed between 7 and 10 years of age. The diagnosis and treatment of ADHD of a very young child represents a diagnostic challenge.[4] Because inattention, impulsivity, and hyperactivity can all be normal behaviors for a young child, making a diagnosis of ADHD often requires the degree and impairment of these symptoms to be beyond what is developmentally appropriate.[5]

It is widely believed that the core symptoms in ADHD result from dysregulation in the balance of 2 neurotransmitter systems in the prefrontal cortex, ie, norepinephrine (noradrenaline) and dopamine.[6,7,8]

Centanafadine (EB-1020), which is an inhibitor of the uptake of norepinephrine, dopamine, and serotonin (5-hydroxytryptamine) in vitro and in vivo, is a novel drug candidate that is being developed as a treatment for ADHD in adults (≥ 18 years) and in children (4 to 17 years, inclusive).

[redacted]

Please refer to the centanafadine Investigator's Brochure (IB) for more detailed information.[9]

2.1 Trial Rationale

Currently, the PK of centanafadine administered as IR/XR capsules is being evaluated in adults. It is possible that the PK (particularly absorption) of centanafadine following administration of the XR formulation may be different in children as compared to adults due to physiological differences in the gastrointestinal tract. Therefore, the primary purpose of this trial is to evaluate the PK of centanafadine [redacted] following administration of centanafadine capsules in pediatric subjects (9 to 12 years, inclusive) with ADHD and determine if the XR formulation is appropriate for further evaluation.

2.2 Background

[redacted]

[redacted]

2.2.2 Clinical

Centanafadine has been evaluated in 9 clinical trials (7 phase 1 trials and 2 phase 2 trials).

[redacted] Refer to the IB for more information.[9]

[redacted]

[redacted]

2.3 Known and Potential Risks and Benefits

The emerging safety profile of centanafadine is mainly based on trials in adult subjects using the SR formulation: the most common adverse events (AEs) reported in trials with centanafadine (IR and SR) at TDDs ranging from 25 to 800 mg were gastrointestinal (nausea, diarrhea, and dry mouth), metabolism/nutrition-related (decreased appetite), and nervous system disorders (headache, dizziness, and insomnia).[redacted]

Treatment with centanafadine may be associated with increases in blood pressure, heart rate, and orthostatic blood pressure changes. These increases appear to be dose-dependent.

Increases in blood pressure and heart rate were usually modest and asymptomatic; however, hypertension, tachycardia, and orthostasis have occurred. During clinical trials, heart rate and blood pressure should be measured prior to initiation of therapy and periodically while on therapy. Subjects should also be monitored for tachycardia or hypertension. Centanafadine should be used with caution in subjects with hypertension, tachycardia, or cerebrovascular disease or cardiovascular disease (eg, known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place a subject at increased vulnerability to noradrenergic effects).

Skin rashes ranging from mild pruritic rash, maculopapular rash to diffuse erythematous maculopapular rash have been observed in subjects who received multiple doses of centanafadine.

One subject experienced mild rash that was considered related to treatment after taking 500 mg centanafadine SR TDD for 4 days. The rash resolved in 8 days with no change in the dose and the subject completed the trial. Eight subjects reported rash after multiple doses of centanafadine SR. Rashes resulted in discontinuation of dosing for 5 subjects and dose interruption and/or dose reduction for 3 subjects. The severity of the rash in subjects who discontinued investigational medicinal product (IMP) ranged from moderate to severe.

The majority of subjects who experienced rash were exposed to centanafadine doses greater than 400 mg/day (2 subjects received 800 mg/day, 4 subjects received 600 mg/day, and 2 subjects received 400 mg/day). Neither subject who received 400 mg/day discontinued dosing due to the rash nor were the rashes in these subjects consistent with the drug eruptions seen in subjects who received 600 mg or 800 mg. All of the rashes were nonserious and all but 1 resolved within 12 days of treatment with IMP withdrawal or dose reduction. The 1 exception was a severe rash lasting over 2 months that was considered likely due to an existing cutaneous condition and exacerbated by the drug eruption. The dermatologic experts who reviewed these AEs concluded that none exhibited a profile consistent with a rash that would progress to a serious or otherwise life-threatening AE.

Considering that rash can be a sign of an allergic reaction, subjects should be monitored closely for other symptoms of allergic reaction including shortness of breath, itching and swelling of the throat or mouth, or difficulty breathing.

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

3 Objectives and Endpoints

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: To characterize the single-dose concentration-time profile from 0 to 12 hours of centanafadine in pediatric subjects (9 to 12 years, inclusive) with ADHD.	Primary: • C_{max} of centanafadine • t_{max} of centanafadine • AUC_{0-12h} of centanafadine
[redacted]	[redacted]

AUC_{0-12h} = area under the concentration-time curve from time 0 to 12 hours postdose [redacted]

C_{max} = maximum (peak) plasma concentration; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; t_{max} = time to maximum concentration; VAS = visual analogue scale.

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This is a pilot phase 2a, multicenter, open-label, single-dose trial in pediatric subjects (9 to 12 years, inclusive) with a documented history of ADHD and confirmation of an ADHD prescription medication. This trial consists of a screening period (Day −21 to Day −2), check-in (Day −1 or Day 1), 2-day treatment period (Day 1: dosing, Day 2: end-of-treatment [EoT]), and a safety follow-up telephone call 7 (+ 2) days after dosing (Day 8). The screening period may be extended if additional time is needed to complete screening procedures, upon discussion with and approval by the medical monitor.

Written informed consent will be freely obtained from all subjects' guardian(s) or legally acceptable representative(s), as applicable for local laws. Written informed assent will be freely obtained from all subjects.

Eligible subjects will check-in either on Day −1 or Day 1, based on the investigator's decision. A single dose of centanafadine will be administered either as intact capsules or the capsule contents sprinkled on a tablespoon of applesauce on Day 1 in the morning. [redacted] Pharmacokinetic and safety assessments will be performed for approximately 24 hours postdose. Subjects may be released from the clinic after PK sample collection at 12 hours postdose to return the following morning or may remain in the clinic until 24 hours postdose, based on the investigator's decision. Subjects released on Day 1 will return to the clinic on Day 2 between 22 to 26 hours postdose for an outpatient visit, which will include EoT assessments and one PK sample. In-clinic subjects may leave the clinic on Day 2 after EoT assessments and PK sampling are complete.

Subjects and/or their caregivers will be contacted by telephone 7 days after dosing to assess any new or ongoing AEs and to record concomitant medications.

A schematic of the trial design is provided in Figure 1.2-1.

4.2 Scientific Rationale for Trial Design

A single dose is expected to be predictive of multiple dosing; therefore, this trial will evaluate a single dose of centanafadine. The focus is on the evaluation of the centanafadine concentration-time profile through 12 hours postdose and measuring centanafadine concentrations at 24 hours postdose to determine the potential for accumulation following multiple doses; therefore, PK sampling through 24 hours is sufficient.

4.3 Dosing Rationale

In adults, dosing is started at a 200 mg TDD administered in divided doses, 5 hours apart, using SR tablets; this regimen has been well tolerated. The 200 mg dose of [redacted] produced centanafadine concentrations approximately 75% of the 200 mg TDD of SR. In this trial, a dose of 5 mg of IR beads and 50 mg of [redacted] beads will be administered, as the approximate median weight of 10- and 11-year-old pediatric subjects is 35 kg, based on the Centers for Disease Control and Prevention (CDC) growth charts.[10] As 75 kg is the approximate weight of adults from phase 1 and phase 2 trials, the expected centanafadine concentrations will be half of those observed in the PK Trial 405-201-00007. The same amount of dose will be administered to all subjects.

4.4 End of Trial Definition

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

4.5 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete Day 2 will be defined as trial completers.

5 Trial Population

The trial population will consist of males and females, aged 9 to 12 years (inclusive), who have a documented history of ADHD and confirmation of an ADHD prescription medication.

Up to 12 subjects may be treated in the trial. Subjects who discontinue for a reason other than a safety-related event may be replaced at the discretion of the sponsor.

5.1 Subject Selection and Numbering

All subjects will be given a unique subject identifier [redacted] upon providing consent/assent. The site number will be designated by the sponsor. The subject number will be given sequentially from [redacted] as the serial numbers in the trial sites.

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

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

Subjects are required to meet the following inclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

1) Written informed consent obtained from a legally acceptable representative (eg, parent/guardian) and assent obtained from the subject prior to the initiation of any trial-related procedures. The subject must provide informed assent at screening and must be able to understand that he or she can withdraw from the trial at any time. All informed consent/assent procedures must be in accordance with the trial site's institutional review board (IRB) and local regulatory requirements.
2) Ability, in the opinion of the investigator, of the subject and the subject's legally acceptable representative (eg, parent/guardian) or caregiver(s) to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens and discontinuation of prohibited concomitant medications, to reliably return for scheduled visits, and to be reliably rated on assessment scales.
3) Male or female subjects 9 to 12 years of age, inclusive, at the time of informed consent/assent.
4) Subjects with good physical health, as determined by no clinically significant deviation from normal for all of the following, prior to enrollment in the trial:
   - Medical history
   - Clinical laboratory determination
   - Electrocardiograms (ECGs)
   - Physical examinations
5) Subjects with documented history of ADHD and confirmation of an ADHD prescription medication.
6) For female subjects of childbearing potential (defined as post-menarche) who are also sexually active and male subjects who are sexually active, the ability to commit to remain fully abstinent (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] or withdrawal are not acceptable methods of contraception) or use 2 approved methods of birth control during the trial and for 30 days following dosing.
7) Subject is judged by the investigator to be clinically stable and has not had any psychiatric hospitalizations within the past 12 weeks.

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

1) Female subjects who are breast-feeding and/or have a positive pregnancy test result prior to receiving IMP.
2) Subjects with a clinical presentation or history that is consistent with delirium, dementia, amnesia, or other cognitive disorders; subjects with psychiatric symptoms that are better accounted for by another general medical condition(s) or direct effect of a substance (ie, medication, illicit drug use, etc.).
3) Subjects with a history of intellectual disability as determined by at least 1 of the following: an intelligence quotient (IQ) < 70, or clinical evidence, or a social or school history that is suggestive of an intellectual disability.
4) Subjects who have any of the following:
   - A significant risk of committing suicide based on history and the principal 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 Columbia-Suicide Severity Rating Scale (C-SSRS)
   - Any lifetime history of suicidal behavior detected by the "Baseline/Screening" version of the C-SSRS

   The subject should not be enrolled (eg, dosed) if any active suicidal ideation is present prior to dosing (as evidenced by a clinical examination or an answer of "yes" on Questions 4 or 5 of the C-SSRS "Since Last Visit" version) or suicidal behavior is present in the C-SSRS "Since Last Visit" version.
5) Subjects with a lifetime history of a substance use disorder (as determined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-5] criteria), or current substance misuse including alcohol and benzodiazepines, but excluding caffeine and nicotine.
6) Subjects with hypothyroidism or hyperthyroidism (unless the condition has been stabilized with medications for at least 90 days prior to dosing with the IMP) or an abnormal result for free thyroxine (T4) at screening. The eligibility of subjects excluded based on an abnormal free T4 result can be discussed with the medical monitor if, in the investigator's judgment, the subject is a suitable candidate for the trial. (Note: free T4 is measured only if the result for thyroid-stimulating hormone [TSH] is abnormal.)

7) Subjects who currently have clinically significant neurological, dermatological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as any history of myocardial infarction, congestive heart failure, human immunodeficiency virus (HIV) seropositive status/acquired immunodeficiency syndrome (AIDS), or chronic hepatitis B or C. Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with assessments during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.
8) Subjects with insulin-dependent diabetes mellitus (ie, any subjects using insulin).
9) Subjects with epilepsy or a history of seizures (except for a single seizure episode, for instance childhood febrile seizure or post traumatic) or a history of severe head trauma (eg, concussion with loss of consciousness) or cerebrovascular disease (eg, stroke, transient ischemic attack, etc.).
10) Any major surgery within 30 days prior to dosing with the IMP.
11) Any history of significant bleeding or hemorrhagic tendencies.
12) Blood transfusion within 30 days prior to dosing with the IMP.
13) Subjects with a positive drug screen for cocaine, marijuana (even if by prescription), or other illicit drugs, or alcohol, are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from the confirmed use of prescription or over-the-counter medications or products that in the investigator's documented opinion do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial, following consultation and approval by the medical monitor.
14) The following laboratory test and ECG results are exclusionary:
    - Platelet count $\leq 130 \times 10^3/\mu L$
    - Hemoglobin ≤ 11.2 g/dL
    - Absolute neutrophil count $\leq 1.00 \times 10^3/\mu L$
    - White blood cell count (WBC) $\leq 4.35 \times 10^3/\mu L$
    - Aspartate aminotransferase (AST) $> 2 \times$ upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) $> 2 \times$ ULN
    - Creatine phosphokinase (CPK) $> 2 \times$ ULN, unless discussed with and approved by the medical monitor
    - Creatinine ≥ 0.7 mg/dL
    - QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 450 msec for more than 1 of the 3 ECGs performed for subjects < 12 years old or QTcF ≥ 460 msec for more than 1 of the 3 ECGs performed for subjects ≥ 12 years old.

NOTE: Subjects should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which, in the investigator's judgment, are medically significant and would impact the safety of the subject or the interpretation of the trial results. Criteria will be provided to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation. Tests with abnormal results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. The 3 ECGs done at predose should be taken at least 1 minute apart following a 10-minute rest in the supine position.

15) Subjects who have supine or standing diastolic blood pressure, after resting for at least 5 minutes, ≥ 95 mmHg.
16) Subjects who participated in a clinical trial and were exposed to IMP within the last 30 days prior to screening or who participated in more than 2 interventional clinical trials within the past year.
17) Subjects with a history of true allergic response (ie, not intolerance) to a medication or a history of dermatologic adverse reactions or anaphylaxis secondary to drug exposure.
18) Subjects with a history of allergic reaction or a known or suspected sensitivity to any substance that is contained in the IMP formulation.
19) Subjects who do not tolerate venipuncture or have poor venous access that would cause difficulty for collecting blood samples.
20) Prisoners or subjects who are compulsorily detained (eg, juvenile detention, court-mandated treatment) for any reason.
21) Subjects who are on probation or parole.
22) Any subject who, in the opinion of the investigator, should not participate in the trial.
23) Consumption of alcohol and/or food and beverages containing methylxanthines (because of its stimulant activity) within 72 hours prior to dosing.
24) Relatives of the trial site employees cannot participate in the trial.

A definition of childbearing potential can be found in Section 10.3.

Subjects must agree to restrictions to medications and lifestyle described in Section 6.5.1 and Section 5.3, respectively.

5.3 Lifestyle Considerations

[redacted]

5.3.2 Caffeine, Alcohol, and Tobacco

The consumption of alcohol is prohibited within 72 hours prior to dosing and through the end of the 24-hour assessments. The use of tobacco following dosing through the end of the 24-hour assessments is prohibited.

5.3.3 Activity

Subjects will be asked to abstain from strenuous physical activity for 48 hours prior to check-in and for the duration of the dosing period and PK sampling period; subjects should also not start any new supplements during the trial.

5.4 Screen Failures

A screen failure is a subject from whom informed consent/assent is obtained and is documented in writing (ie, subject signs an informed consent form [ICF] or assent form), but who is not randomized or assigned trial treatment. Subjects who sign an ICF or assent form but who are not started on treatment are permitted to be rescreened. Subjects with a positive drug screen for cocaine, marijuana (even if by prescription), or other illicit drugs, or alcohol, may not be retested or rescreened; however, subjects 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. In the event that a subject is rescreened for trial participation, and the rescreening is not completed within the original protocol-specified screening period, a new ICF and assent form must be signed and screening procedures repeated.

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

- Date of informed consent/assent
- Visit date (screening visit)
- Demographics (collection date, birth date, sex, race, ethnicity, country)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure

6 Trial Treatments

6.1 Trial Treatments Administered

Centanafadine will be supplied as 1 capsule containing a 50-mg dose as [redacted] beads and 1 capsule containing a 5-mg dose as IR beads for a total centanafadine dose of 55 mg. Both of the intact capsules or the capsule contents sprinkled on a tablespoon of applesauce will be taken orally in the morning [redacted] following a minimum 8-hour fast. [redacted]

The ability of a subject to swallow the intact capsules will be assessed during the screening period with empty capsules. Based on this assessment, subjects will either be instructed to take the centanafadine capsules intact or the capsule contents sprinkled on a tablespoon of applesauce. An attempt will be made to administer the intact capsules to approximately half of the subjects and approximately half of the subjects will be administered the capsule contents sprinkled on a tablespoon of applesauce.

[redacted]

For further information regarding the treatment period, including the follow-up period, see Section 4.1.

6.1.1 Medical Devices

Not applicable.

6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the centanafadine IB.[9]

6.2.1 Packaging and Labeling

Investigational medicinal product will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The [redacted] Each[redacted] will be labeled to clearly disclose the compound ID, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

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. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

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

The clinical 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 IMP (ie, centanafadine) received, dispensed, administered, and destroyed. Neither the investigator nor any designees may provide IMP to any subject not participating in this protocol.

6.2.4 Returns and Destruction

The IMP will be destroyed by the clinical trial site. 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. Accountability of the IMP must be completed and verified by the assigned trial monitor prior to destruction. The trial site(s) may utilize qualified third-party vendors for IMP destruction.

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness, or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- [redacted]
- 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 all PQCs identified through any means from the receipt of the IMP from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

[redacted]

Identification of a PQC by the subject should be reported to the site investigator, who should then follow one of the reporting mechanisms above.

6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, subject, 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 (if available)
- Availability for return

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, return it in the product retrieval package, which will be provided by the sponsor.

It must be documented in the site accountability record that a 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.

6.4 Subject Compliance

The time and dose of each IMP administration will be recorded on the eCRF. Information regarding any missed or inappropriately administered doses will also be documented on the eCRF. Compliance will be ensured by a mouth check during the oral dosing administration of IMP.

6.5 Concomitant Medications or Therapies

The investigator will record all medications and therapies taken by the subject from 30 days prior to signing of informed consent/assent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) on the eCRF. The investigator will also record all medications and therapies taken by the subject 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) on 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.

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[redacted]

6.5.2 Permitted Medications

Not applicable.

6.5.3 Rescue Medications

Not applicable.

6.6 Intervention after the End of the Trial

Not applicable.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site

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 trial is terminated by the investigator or the IRB at the trial site.

7.3 Individual Subject Discontinuation

7.3.1 Treatment Interruption

Not applicable.

7.3.2 Treatment Discontinuation

As this is a single-dose trial, treatment discontinuation is not applicable. Subjects who discontinue from the trial should be encouraged to complete all early termination (ET) and follow-up assessments with ET assessments conducted as soon as possible after the subject is withdrawn.

7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

A subject may discontinue from the trial for the reasons listed below:

- Adverse event
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - SAE
  - Other potentially IMP-related safety concerns or AEs
- Death
- Lost to follow-up
- Physician decision
- Pregnancy (Section 10.3)
- Protocol deviation
- Protocol violation
- Protocol-specific withdrawal criterion met
- Recovery
- Site terminated by sponsor
- Trial terminated by sponsor
- Technical problems
- Withdrawal by parent/guardian
- Withdrawal by subject
- Other

If the subject discontinues from the trial due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 7.3.2 must be followed.

7.3.4 Withdrawal of Consent or Assent

All subjects have the right to withdraw their consent/assent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent/assent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject or the subject's legally acceptable representative (eg, parent/guardian) provides their written withdrawal of consent/assent, or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent/assent requires a subject's or a subject's legally acceptable representative's (eg, parent/guardian) 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 an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).
- Contact of the subject by trial personnel, 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 subject'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/assent 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/assent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue from the trial. As such, the investigator should follow the procedures outlined in Section 7.3.3 to determine if the subject can continue participation in the trial if modifications to his/her schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent/assent to participate in the trial.

7.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending trial discontinuation or withdrawal of consent/assent, investigators will be instructed to meet and discuss (without undue coercion) with the subject, and the subject's legally acceptable representative (eg, parent/guardian), their options of continuing in the trial. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent/assent.

7.4 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Day 8 (+ 2 days) or subjects who do not have a known reason for discontinuation (eg, withdrew consent/assent or AE) during the treatment period will be classified as "lost to follow-up".

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

If the subject was classified as "lost to follow-up", "Were you able to contact the subject?", "Date of contact/Date of final contact attempt", and "Contact method" will be recorded in the source documents.

8 Trial Procedures

Each subject's participation in the trial will be approximately 29 (+ 2) days in duration and will consist of a screening period (Day −21 to Day −2), check-in (Day −1 or Day 1), 2-day treatment period (Day 1: dosing, Day 2: EoT), and a safety follow-up telephone call 7 (+ 2) days after dosing (Day 8).

The total duration of the trial is expected to be approximately 3 months.

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

8.1 Efficacy Assessments

Not applicable.

[redacted]

8.2.1 Pharmacokinetic Blood Samples

Blood samples (4 mL, dipotassium ethylenediaminetetraacetic acid [K_2EDTA]) will be collected on Day 1 (1, 2, 3, 4, 6, 8, 10 and 12 hours postdose) and on Day 2 (one PK sample between 22 to 26 hours postdose), and will be processed into plasma for the determination of centanafadine, EB-10601, [redacted] The actual date and time of the PK sample collection will be recorded in the eCRF. When vital signs or ECGs are scheduled at the same nominal time as PK sample collections, vital signs should be measured and ECGs should be performed before PK samples are collected.

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 Operations/Laboratory Manual.

[redacted]

All plasma samples will be shipped to the bioanalytical laboratory for analysis. Additional information will be provided in the Operations/Laboratory Manual.

8.3 Pharmacodynamic Assessments

Not applicable.

8.4 Pharmacogenomic Assessments

Not applicable.

8.5 Biomarker Assessments

Not applicable.

8.6 Future Biospecimen Research Samples

Not applicable.

8.7 Safety Assessments

Safety assessments in this trial include AEs, clinical laboratory tests, physical examinations, vital signs, ECGs, and the C-SSRS.

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8.

8.7.1 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 Section 10.5 for criteria for identifying laboratory values of potential clinical relevance.

The total volume of blood to be collected during the trial will be documented in the ICF and assent form. The central laboratory will be used for all laboratory testing required during the trial.

Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. Vital sign measurements and ECG assessments should be completed before any blood samples are collected. See exclusion criteria in Section 5.2.2 based on screening laboratory tests. The results of these tests must be reviewed by the investigator prior to initiation of the administration of the IMP. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the central laboratory will be assessed by the investigator or qualified designee for clinical significance within the eCRF.

8.7.2 Physical Examination

A complete physical examination will be performed at the time points described in the schedule of assessments (Table 1.3-1). The complete physical examination will include height (screening only), weight, and calculation of body mass index (BMI) as well as assessment of the head, eyes, ears, nose, and throat; thorax; abdomen; skin and mucosae; neurological; and extremities. Directed physical examinations in response to reported AEs will be conducted as necessary.

Whenever possible, the same individual should perform all physical examinations for any individual subject throughout the course of the trial. Individuals performing the physical examination must be permitted to do so by local regulations, must be listed on the Food and Drug Administration (FDA) Form 1572 as principal investigator or subinvestigator, and must be listed on the trial site delegation of authority form as performing this function.

Any post-screening abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF.

8.7.3 Vital Signs

Vital signs (include systolic and diastolic blood pressure and heart rate) will be collected at the time points described in the schedule of assessments (Table 1.3-1). Subjects should be monitored for potentially clinically significant vital signs values (Section 10.6).

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

8.7.4 Electrocardiogram

Electrocardiograms will be performed at the time points described in the schedule of assessments (Table 1.3-1). Subjects should be monitored for potentially clinically significant ECG results (Section 10.7). Any abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF.

The 12-lead ECGs will be performed in the supine position. Predose 12-lead ECGs conducted at check-in (Day −1 or Day 1) will be performed in triplicate, taken at least 1 minute apart following a 10-minute rest in the supine position. The average of the 3 values will be the baseline value. Based on the QTcF, a subject will be excluded if the correction is ≥ 450 msec for more than 1 of the 3 time points of triplicate predose ECGs performed for subjects < 12 years old or ≥ 460 msec for more than 1 of the 3 time points of triplicate predose ECGs performed for subjects ≥ 12 years old.

A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the trial site to monitor safety during the trial.

8.7.5 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 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 who has been successfully trained to rate this scale by the sponsor or a designee, and is medically responsible for the subject. Documentation of trial 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 check-in (Day −1 or Day 1) and EoT/ET. 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.

8.7.6 Other Safety Variables

No other safety variables are applicable for this trial.

8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. 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 an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP 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 IMP 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 open-label treatment. In more detail, TEAEs are all AEs that started after the start of open-label IMP treatment; or if the event was continuous from baseline and was worsening, serious, IMP related, or resulted in death or discontinuation from the trial.

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject 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 and assent form should not be considered an SAE.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject 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 product/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 AE related to occupational exposure
- Any AESIs (see Section 8.8.5)
- Potential serious hepatotoxicity (see Section 8.8.6)
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate trial discontinuation and 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 there is an abnormality or complication. This includes pregnancy of the subject or the partner of the subject.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of laboratory tests for each individual subject 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 (subject 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 on 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.

IMP 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.

8.8.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRF provided by the sponsor. Adverse event collection will begin after a subject signs the ICF and assent form.

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.

An AE that undergoes a change in severity, seriousness, or toxicity should be reported as a new AE on 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 8.8.3. Special attention should be paid to recording hospitalization and concomitant medications.

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

8.8.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, after he/she 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.).

8.8.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.8.5 Adverse Events of Special Interest

Newly acquired skin eruptions that are nontraumatic will be considered AESIs. These may include, but are not limited to eruptions such as skin rashes, skin irritations, skin reactions, or acneiform lesions. This does not include localized contact irritation at ECG lead sites due to application/removal of lead adhesive.

Refer to the separate rash workup plan for complete details, including reporting forms, and extra measures that must be performed to characterize any skin AESI of a newly acquired skin eruption that is nontraumatic. The trial site will have a local designated dermatologist available for immediate consultation during the trial for these AESIs.

All AESIs should be reported as IREs (see Section 8.8.3).

8.8.6 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥ 3 times the 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 also report as an AE on the eCRF.

8.8.7 Procedure for Breaking the Blind

This trial does not use blinding procedures.

8.8.8 Follow-up of Adverse Events

8.8.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on 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 on the eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation).

8.8.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 7 (+ 2) days after dosing.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eCRF page and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a subject's last scheduled contact, this must be reported to the sponsor and recorded on the AE eCRF page and the IRE form, according to the appropriate reporting procedures described in Section 8.8.3.

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

- Resolved,
- Stabilized,
- The subject is lost to follow-up, or
- Has died.

Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject'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 subject is lost to follow-up or has died.

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

8.8.8.3 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 IMP, should be reported to the sponsor according to the procedures outlined in Section 8.8.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.9 Treatment of Overdose

For treatment of overdose, please refer to IB Section 6.4 (Overdose).

8.10 Subject Assessment Recording

Not applicable.

8.11 Other Assessments

8.11.1 Capsule Swallow Test

The ability of a subject to swallow the intact centanafadine XR capsule will be assessed during the screening period using a capsule swallow test. Based on this assessment, subjects will either be instructed to take the centanafadine capsules intact or the capsule contents sprinkled on a tablespoon of applesauce.

[redacted]

9 Statistical Considerations

9.1 Sample Size

Since this is an exploratory trial, no formal sample size calculations will be performed. Up to 12 subjects may be treated depending on the concentration data and the number of subjects completing through 24 hours.

9.2 Datasets for Analysis

The PK dataset will include all subjects who receive the single dose of centanafadine and have at least 1 postdose evaluable plasma concentration.

The safety dataset will include all subjects who receive the single dose of centanafadine.

9.3 Handling of Missing Data for Primary and Other Endpoint Analysis

No data imputation will be performed for missing PK data in this trial. The handling of concentrations below the lower limit of quantitation will be according to the sponsor's data handling processes.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Not applicable.

9.4.2 Safety Analysis

The safety analysis will be conducted on the safety dataset. Safety variables to be analyzed include AEs, clinical laboratory tests, physical examinations, vital signs, ECGs, and the C-SSRS. In general, baseline measurements of safety variables are defined as the last measurement prior to the dosing of IMP.

9.4.2.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized:

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

The TEAEs will also be presented in a listing.

9.4.2.2 Clinical Laboratory Data

Descriptive statistics will be used to summarize the change from baseline for laboratory tests. The incidence of potentially clinically relevant laboratory tests will be summarized by time point.

9.4.2.3 Physical Examination and Vital Signs Data

A listing of physical examination results will be provided.

Descriptive statistics will be used to summarize the change from baseline for vital signs. The incidence of potentially clinically relevant vital signs will be summarized by time point.

9.4.2.4 Electrocardiogram Data

Descriptive statistics will be used to summarize the change from baseline for ECGs. The incidence of potentially clinically relevant ECGs will be summarized by time point.

9.4.2.5 Other Safety Data

9.4.2.5.1 Columbia-Suicide Severity Rating Scale

Suicidality will be assessed based on the C-SSRS ("Baseline" Version and "Since Last Visit" Version). The incidence of suicidality, suicidal behavior, and suicidal ideation will be summarized descriptively by time point and presented in a listing.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, sex, weight, height, and BMI will be summarized by descriptive statistics for the enrolled subjects.

Baseline disease characteristics and psychiatric history will be also summarized by descriptive statistics.

9.4.3.2 Pharmacokinetic Analysis

A noncompartmental analysis will be performed. Plasma concentrations of centanafadine and metabolite(s) will be summarized by time point and mode of administration (intact capsules or capsule contents sprinkled on a tablespoon of applesauce). The PK parameters will be summarized by analyte and mode of administration using descriptive statistics.

No inferential statistical analysis will be conducted.

The following PK parameters will be summarized:

- Maximum (peak) plasma concentration (C_{max}) of centanafadine
- Time to maximum concentration (t_{max}) of centanafadine
- Area under the concentration-time curve from time 0 to 12 hours postdose ($AUC_{0\text{-}12h}$) of centanafadine

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- [redacted]

9.4.3.3 Pharmacodynamic Analysis

No pharmacodynamic (PD) analysis is planned.

9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

No PK/PD analysis is planned.

9.4.3.5 Pharmacogenomic Analysis

No pharmacogenomic analysis is planned.

9.4.3.6 Exploratory Endpoint Analysis

Not applicable.

9.4.3.7 Other Endpoint Analysis

The ability to swallow the centanafadine XR capsule will be summarized descriptively.

[redacted]

9.5 Interim Analysis and Adaptive Design

No interim analysis or adaptive design are applicable.

9.5.1 Data Monitoring Committee

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, International Council for Harmonisation (ICH) GCP: Consolidated Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) 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, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject ID will be used to identify each subject.

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

10.1.2 Informed Consent

Informed consent will be freely obtained from the guardian or legally acceptable representative of all subjects, as applicable for local laws. The ICF will be approved by the same IRB that approves this protocol. Subjects will provide informed assent, as applicable for local laws, and subjects must be able to understand that he or she can withdraw from the trial at any time and for any reason.

Each ICF will comply with the ICH GCP: Consolidated Guideline E6[12] 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 (eICF) as a tool within applicable regions and trial sites. The eICF utilizes the IRB-approved site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, trial sites will have subjects and their guardian or legally acceptable representative review and sign the eICF prior to starting any trial procedures; however, if local regulations do not allow for use of the electronic format, subjects 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 potential subjects and their guardian or legally acceptable representative without first obtaining consent/assent. However, informed consent/assent 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 subjects and their guardian or legally acceptable representative 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.

Prospective trial subjects will be provided with controlled access to the eICF application by trial site staff. When the trial site staff, subject, and the subject's guardian or legally acceptable representative agree that the subject and the guardian or legally acceptable representative has enough information to make an informed decision to participate, the subject's guardian or legally acceptable representative will electronically sign in the eICF application and an electronic date and timestamp will be applied to the signature; the subject will sign the assent form in the eICF application and an electronic date and timestamp will be applied to the signature. The subject and the subject's guardian or legally acceptable representative will be given a printed, signed copy of the ICF and assent. Any other parties required by the IRB (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the eICF in accordance with the ICH GCP guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.

Once appropriate essential information has been provided and fully explained in layman's language to the subject and the subject's guardian or legally acceptable representative by the investigator (or a qualified designee), and it has been documented that the subject and the subject's guardian or legally acceptable representative has had the opportunity to ask questions, the IRB-approved written ICF and assent will be signed and dated by the subject's guardian or legally acceptable representative and subject, respectively, and the person obtaining consent/assent (investigator or designee), as well as by any other parties required by the IRB. The subject the subject's guardian or legally acceptable representative will receive a copy of the signed ICF and assent; the original shall be kept on file by the investigator.

Subjects and their guardian or legally acceptable representative may be asked to sign additional ICFs or give additional assent if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects and their guardian or legally acceptable representative, so that they can make a

knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs or give additional assent in order to collect additional information regarding the nonsubject partner and fetus.

10.1.3 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. Subject 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 IMP, subject 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.

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

10.1.4 Quality Control and Quality Assurance

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH GCP: Consolidated Guideline (E6), 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.

10.1.4.2 Auditing

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

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of the informed consent/assent process, IMP dispensing or subject dosing error, treatment assignment error, subject 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 subject'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.

10.1.6 Records Management

10.1.6.1 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, and recorded data from automated instruments. 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, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.6.2 Data Collection

During each subject'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 consents/assents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject 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 IMP must also be recorded;

- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of the investigator (or designee) who made an entry in the medical record.

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

Source documents and source data will be captured electronically (where permitted by local regulation) in this trial and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected into a system that is fully validated according to 21 Code of Federal Regulations (CFR) Part 11. Changes to the data will be captured by an automatic audit trail.

Designated trial site staff will not be given access to the electronic source system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol-required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the trial site for data collected directly into the application, rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified per the monitoring plan and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator or their designee.

Another exception will be safety laboratory or central ECG data, where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source records will take place; however, on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess trial site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

10.1.6.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP: Consolidated Guideline (E6) and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.1.6.4 Records Retention at the Trial Site

The 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 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 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.

10.1.6.5 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 trial subjects 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 trial subjects 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: Hematocrit Hemoglobin Platelet count Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume RBC count WBC count with differential Microscopic urinalysis: Appearance Bilirubin Color Glucose Ketones Leukocyte esterase Leukocytes Nitrites Occult blood pH Protein Urobilinogen Specific gravity Microscopic analysis of RBC/WBC, per high powered field (casts, crystals, squamous cells) Additional Tests: TSH, with reflex to free T4 if TSH is abnormal HBsAg anti-HCV HIV Serum hCG/urine test pregnancy (for all female subjects ≥ 12 years of age and female subjects < 12 years of age who have started menstruating)	Serum Chemistry: Albumin ALP ALT AST Bicarbonate Bilirubin, total BUN Calcium Carbon dioxide Chloride Cholesterol (total, HDL, LDL) CPK Creatinine GGT Glucose LDH Magnesium Phosphorus Potassium Protein, total Sodium Uric acid Triglycerides Drug Screen (all items in urine except where noted): Alcohol (breath or urine) Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Cotinine (urine or serum) Marijuana Methadone Opiates Phencyclidine Propoxyphene

ALP = alkaline phosphatase; anti-HCV = hepatitis C antibodies; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HDL = high-density lipoprotein; LDH = lactic dehydrogenase; LDL = low-density lipoprotein; RBC = red blood cell count.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Females of childbearing potential (FOCBP) are females ≥ 12 years of age and females < 12 years of age whose 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).

For males and FOCBP, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remains fully abstinent) to prevent pregnancy during the course of the trial and for 30 days after dosing. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) or withdrawal are not acceptable methods of contraception. Unless the subject is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchiectomy) or remains fully abstinent during the trial and for 30 days after dosing, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pills, birth control implant, birth control depot injection, condom with spermicide, sponge with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the eCRF. Male subjects must also agree not to donate sperm from trial screening through 30 days after dosing.

Before enrolling males and females in this clinical trial, investigators must review the below information about trial participation as part of the ICF and assent process. The topics should generally include:

- General information
- Informed consent or assent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, males and FOCBP (and their guardian or legally acceptable representative) must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects and

their guardian or legally acceptable representative must sign the ICF and assent form confirming that the above-mentioned risk factors and the consequences were discussed.

A urine or serum pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening and check-in to the inpatient facility on all FOCBP (female subjects ≥ 12 years of age and all female subjects < 12 years of age, if menstruation has started). If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

The investigator (or appropriate trial site staff) is advised to counsel subjects (and their guardian or legally acceptable representative) on the risk of pregnancy while participating in a clinical trial as well as ensuring that the subject understands how pregnancies occur and can be avoided. This should be documented in the source records.

During the trial, all FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects must 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).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected after the subject has taken IMP, and the pregnancy is confirmed with serum pregnancy test results, the subject 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 IMP exposure during the trial and for at least 30 days after dosing, 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 subject 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: Abbreviations

Abbreviation	Definition
ADHD	Attention-deficit hyperactivity disorder
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-HCV	Hepatitis C antibodies
AST	Aspartate aminotransferase
AUC_{0-12h}	Area under the concentration-time curve from time 0 to 12 hours postdose
[redacted]	[redacted]
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
C_{max}	Maximum (peak) plasma concentration
CPK	Creatine phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
eICF	Electronic informed consent form
EoT	End-of-treatment
ET	Early termination
FDA	Food and Drug Administration
FOCBP	Females of childbearing potential
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
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
IQ	Intelligence quotient
IR	Immediate-release
IRB	Institutional review board
IRE	Immediately reportable event
LDH	Lactic dehydrogenase
LDL	Low-density lipoprotein

Abbreviation	Definition
PD	Pharmacodynamic
PK	Pharmacokinetic
PQC	Product Quality Complaint
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell count
SAE	Serious adverse event
SR	Sustained-release
T4	Thyroxine
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual analogue scale
WBC	White blood cell count
XR	Extended-release
[redacted]	[redacted]

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10.5 Appendix 5: Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria (Normal Ranges) for Subjects 9 - 12 Years Old[a,b]
Chemistry	
AST	≥ 2 × ULN
ALT	≥ 2 × ULN
ALP	≥ 2 × ULN
BUN	≥ 24 mg/dL (≤ 4 mg/dL or ≥ 24 mg/dL)
Creatinine	≥ 0.7 mg/dL (≤ 0.2 mg/dL or ≥ 0.7 mg/dL)
Uric acid	≥ 6.7 mg/dL (≤ 1.6 mg/dL or ≥ 6.7 mg/dL)
Bilirubin (total)	≥ 1.6 mg/dL (≤ 0.2 mg/dL or ≥ 1.6 mg/dL)
CPK	≥ 2 × ULN
Prolactin	≥ 21.00 ng/dL (≤ 2.63 ng/dL or ≥ 21.00 ng/dL)
Hematology	
Hematocrit	≤ 33% (≤ 33% or ≥ 44%)
Hemoglobin	≤ 11.2 g/dL (≤ 11.2 g/dL or ≥ 15.5 g/dL)
White blood count	≤ 4.35×10^3/μL (≤ 4.35×10^3/μL or ≥ 13.65×10^3/μL)
Eosinophils	≥ 4.8%
Neutrophils	≤ 40.5% (≤ 40.5% or ≥ 75.0%)
Absolute neutrophil count	≤ 1.00×10^3/μL or ≥ 9.00×10^3/μL
Platelet count	≤ 130×10^3/μL (≤ 130×10^3/μL or ≥ 570×10^3/μL)
Urinalysis	
Protein	Change from baseline
Glucose	Presence
Additional Criteria	
Chloride	≤ 94 mEq/L or ≥ 112 mEq/L
Potassium	≤ 3.3 mEq/L or ≥ 5.2 mEq/L
Sodium	≤ 132 mEq/L or ≥ 148 mEq/L
Calcium	≤ 8.3 mg/dL or ≥ 10.9 mg/dL
Glucose	
Fasting	≥ 100 mg/dL (≤ 70 mg/dL or ≥ 100 mg/dL)
Nonfasting	≥ 139 mg/dL (≤ 59 mg/dL or ≥ 139 mg/dL)
Total cholesterol, fasting	≥ 217 mg/dL (≤ 97 mg/dL or ≥ 217 mg/dL)
LDL cholesterol, fasting	≥ 130 mg/dL
HDL cholesterol, fasting	≤ 34 mg/dL (≤ 34 mg/dL or ≥ 75 mg/dL)
Triglycerides, fasting	≥ 131 mg/dL (≤ 30 mg/dL or ≥ 131 mg/dL)

[a]The recommended criteria represented in this table are intended to identify on-treatment outside of normal values that could potentially be clinically relevant. Variations based on local laboratory ranges may need to be considered.

[b]Information adapted from: 1. Soghier L, Pham K, Rooney S. Reference Range Values for Pediatric Care. The American Academy of Pediatrics. 2014; 2. Hughes HK, Kahl LK. The Johns Hopkins Hospital: The Harriet Lane Handbook. 21st edition. 2015; 3. Covance central laboratory reference ranges, 2019.

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10.6 Appendix 6: Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart rate at rest[b]	< 60 bpm or > 110 bpm	Increase or decrease of ≥ 15 bpm
Systolic blood pressure[c]		
School-age (6 to 9 years old)	< 85 mmHg or > 115 mmHg	Increase or decrease of ≥ 20 mmHg
Preadolescent (10 to 12 years old)	< 90 mmHg or > 120 mmHg	Increase or decrease of ≥ 15 mmHg
Diastolic blood pressure[c]		
School-age (6 to 9 years old)	< 50 mmHg or > 80 mmHg	Increase or decrease of ≥ 15 mmHg
Preadolescent (10 to 12 years old)	< 60 mmHg or > 80 mmHg	Increase or decrease of ≥ 15 mmHg
Orthostatic hypotension	≥ 30 mmHg decrease in systolic blood pressure and/or a decrease of ≥ 20 mmHg in diastolic blood pressure after at least 3 minutes of standing compared to the previous supine blood pressure	Not applicable (baseline status not considered)
Orthostatic tachycardia	≥ 25 bpm increase in heart rate from supine to standing	Not applicable (baseline status not considered)
Weight	Not applicable	Increase or decrease of ≥ 25%

bpm = beats per minute.

[a]The criterion value and change relative to baseline represented in this table are intended to identify on-treatment values outside of normal changes and that could potentially be clinically relevant. In order to be identified as potentially clinically relevant, the on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column. When evaluating these values, the emotional state of the subject must be taken into consideration (eg, crying, screaming) and documented as applicable.

[b]Information adapted from: Hughes HK, Kahl LK. The Johns Hopkins Hospital: The Harriet Lane Handbook. 21st edition. 2015.

[c]Information adapted from: Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents: American Academy of Pediatrics Subcommittee on Screening and Management of High Blood Pressure in Children. Pediatrics. 2017;140(3):1-72.

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10.7 Appendix 7: Criteria for Identifying ECG Measurements of Potential Clinical Relevance[13]

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rhythm		
Sinus tachycardia[b]	≥ 110 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 60 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1 atrioventricular block	PR ≥ 200 msec	increase of ≥ 50 msec
2 atrioventricular block	all	not present → present
3 atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 120 msec	increase of ≥ 20 msec
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post trial entry
ST/T Morphological		
Myocardial ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc		
< 12 years old	QTcF ≥ 450 msec	increase of 60 msec from baseline
≥ 12 years old	QTcF ≥ 460 msec	

QTc = corrected QT interval.

[a]The criterion value and change relative to baseline represented in this table are intended to identify on-treatment values outside of normal changes and that could potentially be clinically relevant. In order to be identified as potentially clinically relevant, the on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column. When evaluating these values, the emotional state of the subject must be taken into consideration (eg, crying, screaming) and documented as applicable.

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

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

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

10.8 Appendix 8: 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 "nonsubstantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects 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 subject, the currently approved written ICF and assent form will require similar modification. In such cases, after approval/favorable opinion of the new ICF and assent form by the IRB, repeat written informed consent/assent will be obtained from subjects enrolled in the trial and their guardian or legally acceptable representative before expecting continued participation and before the amendment-specified changes in the trial are implemented.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

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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 new drug, centanafadine, the 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 Institutional Review Board (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 subjects 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 subjects, I will implement the amendment immediately, and provide the information to the 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 subjects 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

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