Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Centanafadine (EB-1020)

REVISED CLINICAL PROTOCOL

A Phase 1b, Multicenter, Open-label, Multiple Ascending Dose Trial to Assess the Pharmacokinetics, Safety, and Tolerability of Centanafadine Extended-release Capsules after Oral Administration in Pediatric Subjects (4 to 12 years, inclusive) With Attention-deficit Hyperactivity Disorder

Open-label, Multiple Ascending Dose Trial to Assess the Pharmacokinetics, Safety, and Tolerability of Centanafadine Extended-release Capsules in Pediatric Subjects With Attention-deficit Hyperactivity Disorder

Protocol No. 405-201-00046
IND No. 119,361

CONFIDENTIAL — PROPRIETARY INFORMATION

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List of Abbreviations

Abbreviation	Definition
ADHD	Attention-deficit hyperactivity disorder
ADHD-RS-5	Attention-deficit hyperactivity disorder Rating Scale - 5
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
Anti-HCV	Hepatitis C antibodies
APMP	Abuse Potential Monitoring Process
AST	Aspartate aminotransferase
AUC_{0-24h}	Area under the concentration-time curve from time 0 to 24 hours
BMI	Body mass index
C_{24h}	Concentration of drug in plasma at 24 hours
CGI-S	Clinical Global Impression - Severity
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Science
C_{max}	Maximal peak plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
DA	Dopamine
DL	Drug load
DNA	Deoxyribonucleic acid
DR	Delayed release
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders - 4th Edition*
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders - 5th Edition*
ECG	Electrocardiogram
eICF	Electronic informed consent
ESAM	Events Subject to Additional Monitoring
ET	Early termination
FBR	Future biospecimen research
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H/I	Hyperactivity/impulsivity
HbA_{1c}	Glycated hemoglobin
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IA	Inattentive
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IDDM	Insulin dependent diabetes mellitus
IMP	Investigational medicinal product
IND	Investigational New Drug

Abbreviation	Definition
IR	Immediate release
IRB	Institutional review board
IRE	Immediately reportable event
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
MedDRA	Medical Dictionary for Regulatory Activities
MHI	Medication handling irregularities
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
NE	Norepinephrine
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PQC	Product quality complaint
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SMWQ	Study medication withdrawal questionnaire
SR	Sustained release
$t_{1/2,z}$	Terminal elimination half-life
T_4	Thyroxine
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum (peak) plasma concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual analog scale
XR	Extended release

1 Protocol Summary

1.1 Synopsis

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

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

Protocol No.: 405-201-00046

IND No.: 119,361

Protocol Title: A Phase 1b, Multicenter, Open-label, Multiple Ascending Dose Trial to Assess the Pharmacokinetics, Safety, and Tolerability of Centanafadine Extended-release Capsules after Oral Administration in Pediatric Subjects (4 to 12 years, inclusive) with Attention-deficit Hyperactivity Disorder

Protocol Lay Person Short Title: Open-label, Multiple Ascending Dose Trial to Assess the Pharmacokinetics, Safety, and Tolerability of Centanafadine Extended-release Capsules in Pediatric Subjects With Attention-deficit Hyperactivity Disorder

Clinical Phase: 1b

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

Objectives and Endpoints:

Objectives	Endpoints
Primary: To characterize the multiple-dose (14-day regimen) PK of centanafadine in ADHD pediatric subjects 4 to 12 years of age, inclusive.	Primary Outcome Endpoints: • C_{max} and AUC_{0-24h} on Day 14 for centanafadine. • Apparent clearance and apparent volume of distribution of centanafadine for Day 14.

Objectives	Endpoints
Secondary: • To assess the safety and tolerability of multiple-dose centanafadine XR or QD XR in ADHD pediatric subjects 4 to 12 years of age, inclusive. • To characterize the multiple-dose PK of metabolites of centanafadine. • To assess the ability of the pediatric subjects to swallow an empty capsule. • To assess the palatability of the centanafadine XR capsule or QD XR capsule and centanafadine XR capsule contents or QD XR capsule contents sprinkled on applesauce. • To assess efficacy of centanafadine in ADHD pediatric subjects 4 to 12 years of age, inclusive. • To obtain samples to determine if centanafadine plasma concentrations collected using a microsampling technique are similar to those following venous blood collection (Cohort 1 only; results to be reported separately).	Other Outcome Endpoints: • Reported AEs, clinical laboratory assessments, physical examinations, vital signs, body weight, ECGs, C-SSRS, sleep diary. • Ability to swallow the empty capsule of centanafadine. • Palatability of the centanafadine XR capsule or QD XR capsule and centanafadine XR capsule contents or QD XR capsule contents sprinkled on applesauce as assessed by VAS. • Mean change from baseline to Day 7 and Day 14 in investigator-rated ADHD-RS-5 total score and CGI-S. Other PK Endpoints: • C_{max} of centanafadine on Day 1. • t_{max} of centanafadine on Day 1 and Day 14. • AUC_{0-24h} of centanafadine on Day 1. • C_{24h} on Day 1 and Day 14. • $t_{1/2,z}$ of centanafadine on Day 14. • Accumulation ratios of C_{max}, AUC_{0-24h}, and C_{24h} for Day 14/Day 1. • PK parameters will be estimated (t_{max}, C_{max}, AUC_{0-24h}, $t_{1/2,z}$) for EB-10601 and other metabolites, as data allow.

ADHD-RS-5 = Attention-deficit Hyperactivity Disorder Rating Scale - 5, AE = adverse event; AUC_{0-24h} = area under the concentration-time curve from time 0 to 24 hours; C_{24h} = concentration of drug in plasma at 24 hours; CGI-S = Clinical Global Impression - Severity; C_{max} = maximal peak plasma concentration; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; PK = pharmacokinetic; $t_{1/2,z}$ = terminal elimination half-life; t_{max} = time to maximal peak plasma concentration; VAS = visual analog scale; XR = extended-release.

Trial Design: This is a phase 1b, multicenter, open-label, multiple-dose trial in pediatric subjects (4 - 12 years of age, inclusive) with a confirmed diagnosis of ADHD.

A washout of a minimum of 7 days for subjects on stimulants and nonstimulants will be required before centanafadine extended-release (XR) dosing on Day 1.

The ability of a subject to swallow intact capsules will be assessed during the screening phase. Each subject will be administered 1 empty capsule to determine their ability to swallow intact capsules. Based on this assessment, subjects will either be instructed to take centanafadine XR or QD XR as an intact capsule or the capsule contents sprinkled on applesauce for the entire trial duration.

Eligible subjects will check into the trial site clinic on Day −1, the day before Day 1 of the treatment phase, and may be released from the trial site clinic on Day 2 after the 24-hour pharmacokinetic (PK) sample collection following the Day 1 dose and administration of Day 2 dose. Alternatively, subjects may remain in the trial site clinic for the duration of treatment and PK sampling following dosing on Day 14. Subjects who are released from the trial site clinic on Day 2 will return on Day 7 for an outpatient visit for PK, efficacy, and safety assessments and on Day 13 for check-in to the clinic for dosing on Day 14 and subsequent PK sampling. Overnight stays (ie, on Day −1, Day 1, Day 13, Day 14, and Day 15), will be optional per the preference of the subject and/or caregiver(s) with agreement of the investigator.

Palatability of the centanafadine XR capsule or QD XR capsule and capsule contents sprinkled on applesauce (if applicable) will be captured following dosing on Day 1.

For subjects released from the trial site clinic on Day 2, the subject and/or caregiver(s) will be responsible for daily administration of the centanafadine XR or QD XR dose from Day 3 through Day 13. For all subjects, whether they remain in the trial site clinic for the duration of the treatment period or are discharged home following the Day 2 dose to Day 13, an investigational medicinal product (IMP) adherence monitoring platform, AiCure, will be utilized to confirm that centanafadine XR or QD XR is administered daily to the subjects.

Centanafadine XR or QD XR will be administered to the subjects in the trial site clinic on Day 14 and PK, efficacy, and safety assessments will be conducted.

The trial population of subjects aged 4 to 12 years will be evaluated separately in 3 subgroups:

- 4 to 5 years, inclusive
- 6 to 8 years, inclusive

- 9 to 12 years, inclusive

Weight-adjusted doses of centanafadine XR and QD XR that produce exposures similar to 400-mg adult centanafadine sustained-release (SR) tablet doses will be evaluated in separate cohorts of subjects aged 9 to 12 years. Similarly, weight-adjusted doses of centanafadine QD XR that produce exposures similar to 200 and 400-mg adult centanafadine SR tablet doses will be evaluated in separate cohorts of subjects aged 6 to 8 years and subjects aged 4 to 5 years.

Safety and tolerability will be reviewed for each cohort after all subjects enrolled and dosed in that cohort have been administered their last dose of IMP.

In Cohort 1, subjects aged 9 to 12 years will be administered the 400-mg weight-adjusted adult equivalent dose of centanafadine XR once daily for 14 days. Up to 12 subjects will be enrolled in Cohort 1 to ensure 10 completers with evaluable PK and safety profiles.

If the dose administered in Cohort 1 is determined to be safe and tolerable, then subjects aged 6 to 8 years will be administered the 200-mg weight-adjusted adult equivalent dose of centanafadine QD XR once daily for 14 days in Cohort 2. Up to 8 subjects will be enrolled in Cohort 2 to ensure 5 completers with evaluable PK following dosing on Day 14; at least 6 subjects must be evaluable for safety.

If the dose administered in Cohort 2 is determined to be safe and tolerable, another cohort of subjects aged 6 to 8 years will be administered the 400-mg weight-adjusted adult equivalent dose of centanafadine QD XR once daily for 14 days in Cohort 3. Up to 8 subjects will be enrolled in Cohort 3 to ensure 5 completers with evaluable PK following dosing on Day 14; at least 6 subjects must be evaluable for safety.

If the doses administered to subjects aged 6 to 8 years in Cohorts 2 and 3 are determined to be safe and tolerable, then subjects aged 4 to 5 years will be administered the 200-mg weight-adjusted adult equivalent dose of centanafadine QD XR once daily for 14 days in Cohort 4. Up to 5 subjects will be enrolled in Cohort 4 to ensure 3 completers with evaluable PK and safety profiles.

If the dose administered in Cohort 4 is determined to be safe and tolerable, another cohort of subjects aged 4 to 5 years will be administered the 400-mg weight-adjusted adult equivalent dose of centanafadine QD XR once daily for 14 days in Cohort 5. Up to 5 subjects will be enrolled in Cohort 5 to ensure 3 completers with evaluable PK and safety profiles.

In Cohort 6, subjects aged 9 to 12 years will be administered the 400-mg weight-adjusted adult equivalent dose of centanafadine QD XR once daily for 14 days. Up to 12 subjects

will be enrolled in Cohort 6 to ensure 10 completers with evaluable PK and safety profiles. Cohort 6 will be initiated before Cohorts 4 and 5.

Safety and tolerability of subjects will be reviewed by the investigator, contract research organization medical monitor, and Otsuka Pharmaceutical Development & Commercialization, Inc. staff, including the project leader, Clinical Safety & Pharmacovigilance representative, medical monitor, and the clinical pharmacology representative. Dose escalation may be modified or stopped based upon sponsor or investigator's clinical judgment at any time. Additional subjects or cohorts may be added at the discretion of the safety review team to further evaluate a given dose. Each subject in the cohort will be evaluated by the investigator at the site to assess the subject's tolerability to the dose. Dose toleration is defined as follows: during the course of the trial, the subject does not experience any moderate or severe AEs or potentially clinically significant changes from baseline in clinical laboratory assessment values, vital signs, or electrocardiogram (ECG) tracings, which are assessed as related to the IMP, and would warrant a dose decrease or discontinuation of the IMP. Dose toleration must be observed in at least 6 subjects in Cohort 2 and at least 3 subjects in Cohort 4 to warrant dose escalation to the next cohort. Pharmacokinetic information will also be considered prior to making the dose escalation decision.

Subjects and/or their parents/guardians will be contacted 7 (+ 2) days after the last dose of IMP on Day 14 to assess any new or ongoing adverse events (AEs) and to record concomitant medications.

Trial Population: Up to 12 subjects will be enrolled in each of the 9 to 12 years age cohorts (Cohorts 1 and 6), up to 8 subjects will be enrolled in each of the 6 to 8 years age cohorts (Cohorts 2 and 3), and up to 5 subjects will be enrolled in each of the 4 to 5 years age cohorts (Cohorts 4 and 5). Additional subjects may be enrolled as necessary.

Key Inclusion/Exclusion Criteria: The trial population will include male and female subjects 4 to 12 years of age, inclusive, who are in good health and meet the following criteria: a clinical diagnosis of any ADHD subtype based on *Diagnostic and Statistical Manual of Mental Disorders - 5th Edition* (*DSM-5*) criteria and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). Written informed consent obtained from a legally acceptable representative (eg, parent/guardian) and assent must be obtained from the subject prior to the initiation of any protocol-required procedures.

Trial Site(s): This is a multicenter trial in United States.

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration: Investigational medicinal product for Cohort 1 will be supplied as centanafadine XR capsules of 52.5 mg, 78.8 mg, and 210 mg. Investigational medicinal product for Cohorts 2 to 6 will be supplied as centanafadine QD XR capsules of 41.1 mg and 164.4 mg.

Doses of centanafadine XR or QD XR will be taken once daily in the morning on Days 1 through 14. All doses should be taken at approximately the same time each day, with the dose taken in the morning upon awakening. The IMP should not be taken with a high-fat meal.

The fixed-dose strengths will be administered according to body weight.

The centanafadine XR capsule or QD XR capsule can be administered as intact capsules or the capsule contents can be sprinkled on 1 tablespoon of applesauce and ingested immediately with up to 120 mL of room temperature water (suggested for subjects 4 - 8 years of age) or 120 to 240 mL of room temperature water (suggested for subjects 9 - 12 years of age).

On PK sampling days (Days 1 and 14), doses will be administered after an 8-hour fast and food will be restricted until 2 hours postdose with a snack permitted at 2 hours postdose and lunch at 4 hours postdose. On Days 1 and 14, water will be restricted for 1 hour prior to dosing and until 2 hours postdose. Doses of centanafadine XR or QD XR should not be taken with a high fat meal.

Trial Assessments:

Assessments for Efficacy: investigator-rated ADHD Rating Scale – 5 (ADHD-RS-5) and Clinical Global Impression - Severity (CGI-S).

Assessments for Pharmacokinetics: blood samples will be taken for the determination of centanafadine and metabolite(s) plasma concentrations. Pharmacokinetic blood samples will also be collected using a microsampling technique (Cohort 1 only).

Assessments for Safety: monitoring of AE, clinical laboratory assessments, vital signs, physical examinations, 12-lead ECGs, assessments of suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]), and sleep diary.

Screening/Other: serology, pregnancy testing, urine drug screen/alcohol testing, MINI-KID, palatability visual analog scale, optional Future Biospecimen Research (FBR), blood collection experience survey, and study medication withdrawal questionnaire (SMWQ).

Data Monitoring Committee: There is no data monitoring committee for this trial; however, the safety and tolerability of subjects will be reviewed after each cohort.

Statistical Methods: Ten subjects in the 9 to 12 years age group and 10 subjects in the 6 to 8 years age group (including both dose levels) are sufficient to obtain a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with at least 80% power for a PK variability of 42% (coefficient of variation). Up to 12 subjects will be enrolled in the 9 to 12 years age cohort (Cohorts 1 and 6), up to 8 subjects will be enrolled in each of the 6 to 8 years age cohorts (Cohorts 2 and 3), and up to 5 subjects will be enrolled in each of the 4 to 5 years age cohorts (Cohorts 4 and 5). Additional subjects may be enrolled as necessary.

Noncompartmental PK analysis will be performed. Plasma concentrations of centanafadine and metabolites will be summarized by age group, centanafadine dose, treatment day, and time point. Pharmacokinetic parameters will be summarized by age group, centanafadine dose, treatment day and analyte using descriptive statistics.

Concentration and PK data may be summarized by mode of administration (intact capsule versus applesauce) based on the data.

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

- Screening: Days −28 to −2
- Check-in: Day −1
- Treatment Period: Days 1 to 16 (dosing on Days 1 to 14)
- Follow-up: Day 21 (7 days [+ 2 days] after the last dose of IMP)

Overall the trial duration, from signing of the first informed consent form to the final subject assessment, is expected to be 51 days.

1.2 Schema

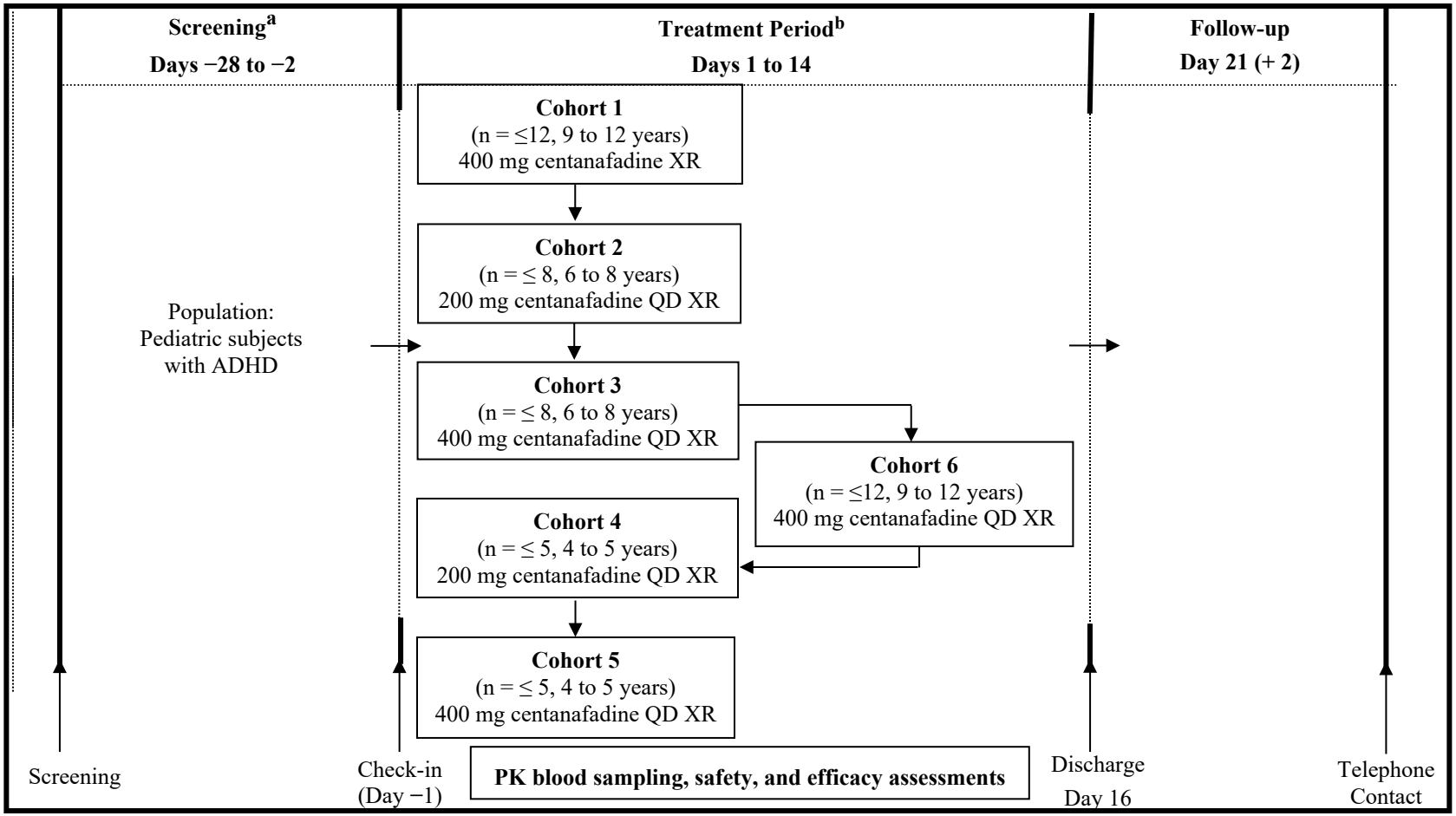

Figure 1.2-1 Trial Design Schematic

IMP = investigational medicinal product; n = number of subjects; QD = per day; XR = extended release.
Note: Cohorts 1 through 3 will be dosed sequentially, followed by Cohort 6, then Cohorts 4 and 5. The safety and tolerability of each cohort will be reviewed before dosing is started in the next cohort.

All doses of centanafadine XR and QD XR are equivalents by body weight that are predicted to produce exposures similar to 200 or 400 mg centanafadine sustained-release tablets in adults.

[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]Subjects may be discharged from the trial site clinic after the collection of the 24-hour PK sample and after dosing on Day 2. Alternatively, subjects may remain in the trial site clinic for the duration of treatment and PK sampling following dosing on Day 14.

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Period	Screening	Baseline	Treatment Period									Follow-up Phone Call	Notes
Visit													
Trial Day	Day −28 to Day −2	Day −1	Day 1	Day 2	Days 3, 4, 5, and 6	Day 7	Days 8, 9, 10, 11, and 12	Day 13	Day 14	Day 15	Day 16/ ET	Day 21 (+ 2)	
ENTRANCE/HISTORY													
Informed consent/assent	X												Section 10.1.2
Demographics	X												
Inclusion/ exclusion criteria	X												Section 5.2
Medical history	X												
Confirmation of diagnosis of ADHD by *DSM-5*	X												
MINI-KID	X												Section 8.10.1
Serology testing	X												Section 10.2
Drug screen for methylphenidate and amphetamines	X	X				X		X					Section 10.2
Pregnancy test (female subjects in Cohorts 1 and 6 only)	X	X									X		Section 10.2 Section 10.3
Empty capsule swallow test	X												

Table 1.3-1 Schedule of Assessments

Period	Screening	Baseline	Treatment Period									Follow-up Phone Call	Notes
Visit													
Trial Day	Day −28 to Day −2	Day −1	Day 1	Day 2	Days 3, 4, 5, and 6	Day 7	Days 8, 9, 10, 11, and 12	Day 13	Day 14	Day 15	Day 16/ ET	Day 21 (+ 2)	
TRIAL RESIDENCY[a]													
Admission		X						X					
Discharge				X							X		
IMP ADMINISTRATION AND COMPLIANCE													
Administration of centanafadine			X	X	X	X	X	X	X				Section 6.1
AiCure platform		X											Section 6.4
AiCure compliance check			X	X	X	X	X	X	X				Section 6.4
EFFICACY													
ADHD-RS-5		X				X			X				Section 8.1.1
CGI-S		X				X			X				Section 8.1.2
SAFETY													
Adverse events	X	X	X	X	X[b]	X	X[b]	X	X	X	X	X	Section 8.8
Clinical laboratory assessments	X	X				X			X[c]		X		Section 8.7.1
Physical examination[d]	X	X				X			X		X		Section 8.7.2
Vital signs[e]	X	X	X	X	X[b]	X	X[b]	X	X	X	X		Section 8.7.3

Table 1.3-1 Schedule of Assessments

Period	Screening	Baseline	Treatment Period									Follow-up Phone Call	Notes
Visit													
Trial Day	Day −28 to Day −2	Day −1	Day 1	Day 2	Days 3, 4, 5, and 6	Day 7	Days 8, 9, 10, 11, and 12	Day 13	Day 14	Day 15	Day 16/ ET	Day 21 (+ 2)	
12-Lead ECG[f]	X	X	X	X		X			X		X		Section 8.7.4
C-SSRS[g]	X	X		X		X		X		X	X (ET only)		Section 8.7.5
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X		Section 6.5
Sleep diary		X	X	X	X	X	X	X	X				Section 8.7.6.1
PHARMACOKINETICS													
PK blood draw[h]			X	X		X			X	X	X		Section 8.2.1
PK sample collection using a microsampling technique[i]			X	X					X	X			Section 8.2.2
PHARMACODYNAMICS													
Palatability VAS[j]			X										Section 8.3
OTHER PROCEDURES													
FBR[k]		X											Section 8.6
SMWQ										X	X	X	Section 8.10.2
Blood collection experience survey (Cohort 1 only)			X	X					X	X			Section 8.10.3

ET = early termination; VAS = visual analog scale.

[a]Subjects may be released from the trial site clinic after the collection of the 24-hour PK sample and after dosing on Day 2. Alternatively, subjects may remain in the trial site clinic for the duration of treatment and PK sampling following dosing on Day 14. Subjects who are released from the trial site clinic on Day 2 will return on Day 7 for an outpatient visit and on Day 13 for check-in to the trial site clinic. Overnight stays (ie, on Day −1, Day 1, Day 13, Day 14, and Day 15), are optional per the preference of the subject and/or caregiver(s) with agreement of the investigator.

[b]For in-clinic subjects. If a subject is released from the trial site clinic but returns to the trial site clinic on Days 3 to 6 or Day 8 to 12, assessments planned for in-clinic subjects should also be performed on the subjects that come in to the trial site clinic on those days.

[c]Predose.

[d]Complete physical examinations will be conducted at screening (including height and weight), check-in (including weight), Day 7 (including weight), predose on Day 14 (including weight), Day 16/ET (including weight). Directed physical examinations in response to AEs will be conducted as necessary.

[e]Vital sign assessments will be performed at screening and on Day −1, Day 1 (8 hours postdose), Day 2 (24 hours postdose), Day 7 (postdose), Day 13, Day 14 (predose), Day 15, and Day 16/ET. Vital sign assessments will also be performed once daily on Days 3 to 6 and Day 8 to 12 for subjects admitted to the trial site clinic.

[f]Electrocardiogram measurements will be performed at screening and on Day −1, Day 1 (8 hours postdose), Day 2 (24 hours postdose), Day 7 (postdose), Day 14 (predose and 8 hours postdose), and Day 16/ET.

[g]On Day 15, the C-SSRS will be administered 24 hours after the Day 14 dose.

[h]Blood samples for PK analysis will be collected on Days 1, 2, 7, 14, 15, and 16 as follows: on Day 1 at 1, 2, 3, 4, 6, 8, and 12 hours postdose; on Day 2 at 24 hours after the Day 1 dose; on Day 7 at predose (preferred) or anytime postdose; on Day 14 at predose, 1, 2, 3, 4, 6, 8, and 12 hours postdose; on Day 15 at 24, 30, and 36 hours after the dose on Day 14; and on Day 16 at 48 hours after the Day 14 dose.

[i]Cohort 1 only. Using the microsampling technique, blood samples for PK analysis will be collected on Days 1, 2, 14, and 15: on Day 1 at 2 and 8 hours postdose; on Day 2 at 24 hours after the dose on Day 1; on Day 14 at 2 and 8 hours postdose; and on Day 15 at 30 hours after the dose on Day 14.

[j]Palatability will be assessed following the first dose on Day 1.

[k]FBR sampling can be done at the time of another blood draw if not done at check-in on Day −1.

2 Introduction

Centanafadine (EB-1020) is being developed for the treatment of attention-deficit hyperactivity disorder (ADHD) in adults (≥ 18 years) and in children (4 to 17 years, inclusive). 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 (NE [noradrenaline]) and dopamine (DA).[1,2,3] Centanafadine, is a potent inhibitor of the uptake of NE, DA, and serotonin (5-hydroxytryptamine [5-HT]) in vitro and in vivo.

Attention-deficit hyperactivity disorder is an increasingly recognized and heterogeneous disorder characterized by 3 core symptoms of hyperactivity, inattentiveness, and impulsivity.[4] Depending on the ADHD subtype, sex of the individual, and presence of comorbid disorders, individuals with ADHD may display considerably different symptomatology, even within a particular age cohort.[5]

Attention-deficit hyperactivity disorder is typically viewed as a childhood/adolescent disorder.[6] ADHD frequently begins between 2 and 4 years of age[7,8] and it is most commonly diagnosed between ages 7 and 10 years. The diagnosis and treatment of ADHD of a very young child represents a diagnostic challenge.[9] 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.[10] In addition, symptoms of ADHD, even at a young age, are frequently associated with social impairment, such as emotional distress for the child and the parents.[11] A literature review of ADHD studies using the *Diagnostic and Statistical Manual of Mental Disorders - 4th Edition* (*DSM-IV*) diagnostic criteria in preschool aged children found that preschoolers with ADHD look similar to older children with the disorder, with respect to symptom presentations and prognosis, and that boys and older preschoolers are more likely to meet criteria for ADHD. In addition, preschoolers with ADHD are significantly impaired in their relationships with adults and other children and in their functioning at home and outside the home.[12] Similarly, in preschool children who met the *DSM-IV* diagnostic criteria for ADHD, 79.2% exhibited global academic and social impairment 3 years later.[13] Clinical practice guidelines indicate that the *DSM-IV* criteria can be applied to preschool aged children and appropriately identify patients in this age group; however, they note that the Diagnostic and Statistical Manual of Mental Disorders subtypes may not be valid for this population and these patients are less likely to have a qualified separate observer to support the diagnosis.[14] They recommend the use of focused checklists validated for use in

preschoolers, such as the ADHD Rating Scale, to help clinicians in making an accurate diagnosis and offset some of these diagnostic challenges in young children.

With the exception of clonidine and guanfacine, which are alpha-2 adrenoceptor agonists, all of the established drugs for the treatment of ADHD act indirectly to potentiate and prolong the neurochemical signaling of the catecholamines (ie, NE and DA) by virtue of stimulating their release from presynaptic nerve terminals, by delaying their clearance from the synapse by inhibition of monoamine reuptake, or inhibiting their catabolism by monoamine oxidase. Thus, the pharmacotherapy of ADHD consequently relies on 2 major classes of drugs: (1) stimulants, such as methylphenidate and amphetamines, and (2) nonstimulants, such as atomoxetine[15] and alpha-adrenergic agonists such as guanfacine and clonidine.[16] The stimulants used to treat ADHD have a rapid onset of action, are effective in all 3 core deficits of the disorder and have a response rate of about 70%[2,3,17] but their usefulness is impaired by dose-limiting adverse events (AEs) and by abuse liability with resultant drug prescribing restrictions.[2,3,15] Atomoxetine is associated with cardiovascular and nervous system AEs and has a boxed warning from the Food and Drug Administration (FDA) for increased risk of suicidal ideation in children or adolescents.[18] Immediate-release (IR) clonidine and guanfacine have been evaluated as monotherapy in ADHD; however, rapid clearance and absorption, negative side effects, and reduced efficacy compared with stimulants has limited their usage.[19] In addition, patient responses to alpha-2 adrenergic agonists have been shown to be not as strong as stimulants. Therefore, as a first line treatment, IR alpha-2 adrenergic agonists are usually not considered for ADHD.[20,21]

Based on the shortcomings of current pharmacotherapy for ADHD, there is a need for new drugs that combine the effectiveness and rapid onset of the stimulants (methylphenidate and amphetamines), but lack their liability for abuse and dependence, notwithstanding their potential cardiovascular and eating disorders effects.

In vivo microdialysis studies with centanafadine demonstrate that it produces moderate, but therapeutically relevant, increases in the extracellular concentrations of NE and DA in the rat prefrontal cortex.[22] The magnitude of the increases in NE and DA efflux produced by centanafadine is broadly similar to those reported for atomoxetine. However, although the increases of NE and DA are pharmacologically relevant, they are relatively modest (< 500% of baseline) with clear evidence of a dose-effect ceiling. In contrast, methylphenidate is capable of rapidly increasing synaptic DA by > 500% and there is no dose ceiling to its effect.[23] Thus, centanafadine may be comparably efficacious to C-II stimulants with a lower potential for abuse.

Please refer to the centanafadine Investigator's Brochure (IB) for more detailed information.[24]

Phase 3 adult ADHD efficacy trials for centanafadine have been completed. Based on the agreed pediatric study plan with the FDA, a pharmacokinetic (PK), safety, and tolerability trial will be conducted prior to conducting pediatric efficacy trials. This trial is being conducted to evaluate the PK, safety, and tolerability of the centanafadine once daily extended-release (XR) capsule in pediatric subjects (4 - 12 years, inclusive) with ADHD; the FDA has agreed that PK in adolescents (13 - 17 years) does not need to be determined prior to starting pediatric efficacy trials.

2.1 Trial Rationale

A trial (Trial 405-201-00010) to assess the PK, safety, and tolerability of twice-daily XR capsules, consisting of a combination of IR beads and 9% polymer coated extended-release beads (XR-9PF) is ongoing in pediatric subjects (4 - 12 years, inclusive). Safety and tolerability data from 6- to 12-year-old subjects in Trial 405-201-00010 will be leveraged in this trial (Trial 405-201-00046).

A new once a day XR capsule consisting of a combination of IR beads, sustained-release beads (SR) beads, and delayed-release (DR) beads is under development. The primary purpose of this trial is to evaluate the PK of centanafadine and its metabolites following administration of the new centanafadine once daily XR capsule in children (4 -12 years, inclusive). The PK information will help in optimizing the dose for pediatric efficacy trials.

Adolescents aged 13 to 17 years will not be studied in this trial based on the publication by Momper et al.[25] In this article, the authors reviewed 126 unique products with pediatric trials submitted to the FDA since the FDA Amendments Act of 2007, of which 92 had at least 1 adolescent indication concordant with an adult indication. Of these 92 products, 87 (94.5%) had equivalent dosing for adults and adolescent patients. The FDA agrees with not conducting a dedicated PK trial in an adolescent population; however, sparse PK will be collected in adolescents in the registration trials.

2.2 Background

A complete description of the available efficacy and safety pharmacology data from nonclinical studies, including PK and toxicology studies in different animal species, can be found in the centanafadine IB.[24]

As of the IB data cutoff of 12 Sep 2019, centanafadine has been or is currently being evaluated in 17 clinical trials; 822 subjects have been treated with at least 1 dose of

centanafadine. A total of 405 healthy adult subjects or recreational stimulant users received centanafadine in 12 phase 1 trials and 417 adult subjects with ADHD received centanafadine in 2 phase 2 trials and one open-label phase 3 trial. A total of 5 phase 1 trials (EB-1020-101, EB-1020-102, and EB-1020-IR-103, 405-201-00001, and 405-201-00019) and 1 phase 2 trial (NVI-EB-1020-202) were placebo-controlled. Additionally, 2 phase 3 trials (405-201-00013 and 405-201-00014) were placebo-controlled.

Centanafadine active pharmaceutical ingredient in a capsule (IR formulation) has been administered in phase 1 trials. The centanafadine SR tablet formulation has been administered in phase 1, 2, and 3 trials.

An open-label, phase 1 trial (Trial 405-201-00036) evaluating once daily administration of the centanafadine XR formulation has been conducted in adult subjects. At the time of finalization of this protocol, the clinical study report for Trial 405-201-00036 is under development.

A pilot phase 2a, open-label, single-dose trial to assess the PK of centanafadine XR capsules to pediatric subjects with ADHD (Trial 405-201-00037) has been completed. The age range of the subjects was 9 to 12 years, inclusive, and 13 subjects were treated. A single dose of 55 mg centanafadine was well tolerated by all subjects; there was 1 reported treatment-emergent adverse event (TEAE) in the trial (vessel puncture site bruise). The TEAE was not serious and not related to the investigational medicinal product (IMP).

A phase 1b, open-label, multiple ascending dose trial to assess the PK of centanafadine XR capsules given twice daily (BID) to pediatric subjects with ADHD (Trial 405-201-00010) is currently ongoing. The sponsor plans to discontinue the trial, as development of the BID formulation will not continue. At the time of finalization of this protocol amendment, the first 3 cohorts of subjects aged 9 to 12 years, inclusive, have been completed and data following 100 mg, 200 mg, and 400-mg adult equivalent doses have been reviewed. The 100-mg adult equivalent dose cohort of subjects aged 6 to 8 years, inclusive, has been completed and the data have been reviewed.

2.2.1 Pharmacokinetics

An open-label, phase 1 trial (Trial 405-201-00036) evaluating the PK of the once daily administration of the centanafadine XR formulation has been conducted in healthy adult subjects. The preliminary median concentration-time profile following a single 210 mg dose of the once daily centanafadine XR formulation under fasted conditions as intact capsules or capsule contents sprinkled on one tablespoon of applesauce in Trial 405-201-00036 is shown in Figure 2.2.1-1.

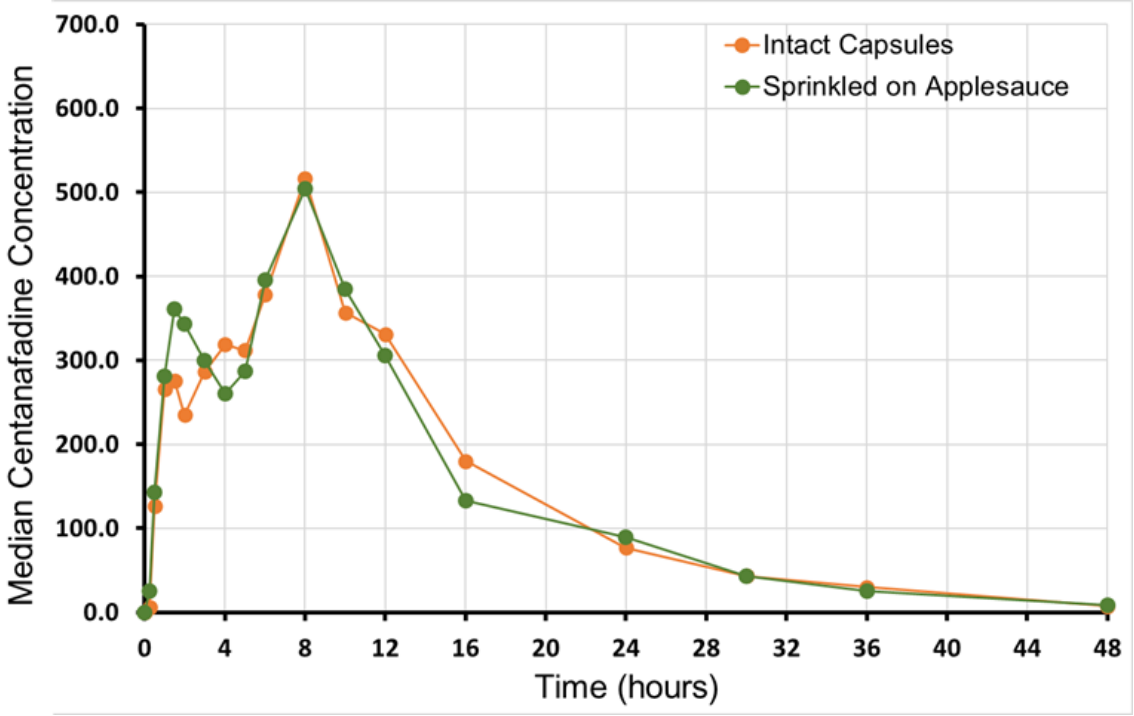

Figure 2.2.1-1 **Median Centanafadine Concentrations Following a Single Dose of 210 mg Once Daily Extended-release Capsules Administered under Fasted Condition as Intact Capsules or Capsule Contents Sprinkled on Applesauce in Healthy Adults**

Note: Lower limit of quantification for centanafadine in plasma was 5 ng/mL.
N = 17 subjects for intact capsules and N = 18 for applesauce with 16 subjects taking both treatments.

2.3 Known and Potential Risks and Benefits

Data from the completed phase 1, 2, and 3 trials indicate that centanafadine is safe and well-tolerated in healthy adult subjects and adult subjects with ADHD. Data from the completed phase 2 and 3 trials demonstrate that centanafadine is effective in treating symptoms of ADHD, based on the positive effect of centanafadine SR on the primary efficacy measure, the adult investigator-rated ADHD Rating Scale - 4. Preliminary data suggest centanafadine may also confer an improved safety profile and a lower potential for abuse compared to currently approved Schedule II stimulant treatments for ADHD.

Following administration of the centanafadine SR formulation in the phase 2 and phase 3 trials in adults with ADHD, the most frequently reported TEAEs (and at a higher incidence than the placebo group) included decreased appetite, nausea, diarrhoea, insomnia, dry mouth, upper respiratory tract infection, anxiety, irritability, fatigue, nasopharyngitis, dizziness, and rash. TEAEs that occurred in ≥ 2% of pediatric subjects with ADHD following administration of centanafadine XR adult equivalent doses in phase 1 and phase 2 trials included somnolence, decreased appetite, and irritability.

A total of 23 serious adverse events (SAEs) have been reported in phase 2 and 3 trials in adult subjects. These SAEs included angina pectoris, angioedema, bronchitis, cerebrovascular accident, diverticulitis, drug abuse, influenza, intraductal proliferative breast lesion, intentional self-injury (twice), malignant melanoma in situ, mood swings, metabolic surgery, obesity, pneumonia, sepsis, stress urinary incontinence, suicidal ideation, suspected COVID-19, upper respiratory tract infection, ureterolithiasis, vertigo positional, and viral gastroenteritis. Except for the angioedema case that was judged related, all of the other SAEs were considered not related to centanafadine by the investigator. No SAEs have been reported in pediatric subjects.

Treatment with centanafadine may be associated with increases in blood pressure and heart rate as well as orthostatic blood pressure changes. 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 will be measured prior to initiation of therapy, and periodically while on therapy. Subjects will 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).

Rash was reported in 29 adult subjects who were exposed to centanafadine SR in phase 1, phase 2, and phase 3 trials. The majority (16/29) of the adult subjects with rashes received doses of 400 mg. In ongoing pediatric Trial 405-201-00010, rash was reported in 1 pediatric subject who was exposed to centanafadine XR adult equivalent 200 mg dose. The dermatologic experts who reviewed these rashes concluded that none exhibited a profile consistent with a rash that would progress to an SAE or otherwise life-threatening AE.

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

Please refer to the IB for more detailed information about the known and potential risks of centanafadine.[24] Trial sites will receive updated versions of the IB, when available, and trial sites should refer to the most current version as needed.

3 Objectives and Endpoints

The trial objectives and endpoints are presented in Table 3-1.

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: To characterize the multiple-dose (14-day regimen) PK of centanafadine in ADHD pediatric subjects 4 to 12 years of age, inclusive.	Primary Outcome Endpoints: • C_{max} and AUC_{0-24h} on Day 14 for centanafadine. • Apparent clearance and apparent volume of distribution of centanafadine for Day 14.
Secondary: • To assess the safety and tolerability of multiple-dose centanafadine XR or QD XR in ADHD pediatric subjects 4 to 12 years of age, inclusive. • To characterize the multiple-dose PK of metabolites of centanafadine. • To assess the ability of the pediatric subjects to swallow an empty capsule. • To assess the palatability of the centanafadine XR capsule or QD XR capsule and centanafadine XR capsule contents or QD XR capsule contents sprinkled on applesauce. • To assess efficacy of centanafadine in ADHD pediatric subjects 4 to 12 years of age, inclusive. • To obtain samples to determine if centanafadine plasma concentrations collected using a microsampling technique are similar to those following venous blood collection (Cohort 1 only; results to be reported separately).	Other Outcome Endpoints: • Reported AEs, clinical laboratory assessments, physical examinations, vital signs, body weight, ECGs, C-SSRS, and sleep diary. • Ability to swallow the empty capsule of centanafadine. • Palatability of the centanafadine XR capsule or QD XR capsule and centanafadine XR capsule contents or QD XR capsule contents sprinkled on applesauce as assessed by VAS. • Mean change from baseline to Day 7 and Day 14 in investigator-rated ADHD-RS-5 total score, and CGI-S. Other PK Endpoints: • C_{max} of centanafadine on Day 1. • t_{max} of centanafadine on Day 1 and Day 14. • AUC_{0-24h} of centanafadine on Day 1. • C_{24h} on Day 1 and Day 14. • $t_{1/2,z}$ of centanafadine on Day 14. • Accumulation ratios of C_{max}, AUC_{0-24h}, and C_{24h} for Day 14/Day 1. • PK parameters will be estimated (t_{max}, C_{max}, AUC_{0-24h}, $t_{1/2,z}$) for EB-10601 and other metabolites, as data allow.

ADHD-RS-5 = Attention-deficit Hyperactivity Disorder Rating Scale - 5, AUC_{0-24h} = area under the concentration-time curve from time 0 to 24 hours; C_{24h} = concentration of drug in plasma at 24 hours; CGI-S = Clinical Global Impressions − Severity; C_{max} = maximal peak plasma concentration; C-SSRS = Columbia − Suicide Severity Rating Scale; ECG = electrocardiogram; $t_{1/2,z}$ = terminal elimination half-life; t_{max} = time to maximal peak plasma concentration; VAS = visual analog scale.

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This is a phase 1b, multicenter, open-label, multiple-dose trial in pediatric subjects (4 - 12 years of age, inclusive) with a confirmed diagnosis of ADHD. This trial consists of a screening period (Day −28 to Day −2, including a washout phase), check-in (Day −1), a 14-day treatment phase, and a safety follow-up phone call 7 (+ 2) days after the last dose. The total duration of the trial will be approximately 51 days.

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.

Subjects with a confirmed diagnosis of ADHD will be enrolled in the trial. A washout of a minimum of 7 days for subjects on stimulants and nonstimulants will be required before centanafadine XR or QD XR dosing on Day 1.

The ability of a subject to swallow intact capsules will be assessed during the screening phase. Each subject will be administered 1 empty capsule to determine their ability to swallow intact capsules. Based on this assessment, subjects will either be instructed to take centanafadine XR or QD XR as an intact capsule or the capsule contents sprinkled on applesauce for the entire trial duration.

Eligible subjects will check into the trial site clinic on Day −1, the day before Day 1 of the treatment phase, and may be released from the trial site clinic on Day 2 after the 24-hour PK sample collection following the Day 1 dose and administration of Day 2 dose. Alternatively, subjects may remain in the trial site clinic for the duration of treatment and PK sampling following dosing on Day 14. Subjects who are released from the trial site clinic on Day 2 will return on Day 7 for an outpatient visit for PK, efficacy, and safety assessments and on Day 13 for check-in to the clinic for dosing on Day 14 and subsequent PK sampling. Overnight stays (ie, on Day −1, Day 1, Day 13, Day 14, and Day 15), will be optional per the preference of the subject and/or caregiver(s) with agreement of the investigator.

Palatability of the centanafadine XR capsule or QD XR capsule and capsule contents sprinkled on applesauce (if applicable) will be captured following dosing on Day 1.

For subjects released from the trial site clinic on Day 2, the subject and/or caregiver(s) will be responsible for daily administration of the centanafadine XR or QD XR dose from Day 3 through Day 13. For all subjects, whether they remain in the trial site clinic for the duration of the treatment period or are discharged home following the Day 2 dose to Day 13, an IMP adherence monitoring platform, AiCure, will be utilized to confirm that centanafadine XR or QD XR is administered daily to the subjects. Bottle(s) of centanafadine XR capsules or QD XR capsules and instructions for the number of capsules to be taken daily from each bottle will be provided to the subjects and their parent/guardian based on the subject's centanafadine XR or QD XR dose. Instructions for use for administration of the capsule or the capsule contents sprinkled on applesauce will be provided.

Centanafadine XR or QD XR will be administered to the subjects in the trial site clinic on Day 14 and PK, efficacy, and safety assessments will be conducted.

The trial population of subjects aged 4 to 12 years will be evaluated separately in 3 subgroups:

- 4 to 5 years, inclusive
- 6 to 8 years, inclusive
- 9 to 12 years, inclusive

Weight-adjusted doses of centanafadine XR and QD XR that produce exposures similar to 400-mg adult centanafadine SR tablet doses will be evaluated in separate cohorts of subjects aged 9 to 12 years. Similarly, weight-adjusted doses of centanafadine QD XR that produce exposures similar to 200 and 400-mg adult centanafadine SR tablet doses will be evaluated in separate cohorts of subjects aged 6 to 8 years and subjects aged 4 to 5years.

Safety and tolerability will be reviewed for each cohort after all subjects enrolled and dosed in that cohort have been administered their last dose of IMP.

In Cohort 1, subjects aged 9 to 12 years will be administered the 400-mg weight-adjusted adult equivalent dose of centanafadine XR once daily for 14 days. Up to 12 subjects will be enrolled in Cohort 1 to ensure 10 completers with evaluable PK and safety profiles.

If the dose administered in Cohort 1 is determined to be safe and tolerable, then subjects aged 6 to 8 years will be administered the 200-mg weight-adjusted adult equivalent dose of centanafadine QD XR once daily for 14 days in Cohort 2. Up to 8 subjects will be

enrolled in Cohort 2 to ensure 5 completers with evaluable PK following dosing on Day 14; at least 6 subjects must be evaluable for safety.

If the dose administered in Cohort 2 is determined to be safe and tolerable, another cohort of subjects aged 6 to 8 years will be administered the 400-mg weight-adjusted adult equivalent dose of centanafadine QD XR once daily for 14 days in Cohort 3. Up to 8 subjects will be enrolled in Cohort 3 to ensure 5 completers with evaluable PK following dosing on Day 14; at least 6 subjects must be evaluable for safety.

If the doses administered to subjects aged 6 to 8 years in Cohorts 2 and 3 are determined to be safe and tolerable, then subjects aged 4 to 5 years will be administered the 200-mg weight-adjusted adult equivalent dose of centanafadine QD XR once daily for 14 days in Cohort 4. Up to 5 subjects will be enrolled in Cohort 4 to ensure 3 completers with evaluable PK and safety profiles.

If the dose administered in Cohort 4 is determined to be safe and tolerable, another cohort of subjects aged 4 to 5 years will be administered the 400-mg weight-adjusted adult equivalent dose of centanafadine QD XR once daily for 14 days in Cohort 5. Up to 5 subjects will be enrolled in Cohort 5 to ensure 3 completers with evaluable PK and safety profiles.

In Cohort 6, subjects aged 9 to 12 years will be administered the 400-mg weight-adjusted adult equivalent dose of centanafadine QD XR once daily for 14 days. Up to 12 subjects will be enrolled in Cohort 6 to ensure 10 completers with evaluable PK and safety profiles. Cohort 6 will be initiated before Cohorts 4 and 5.

The trial design schematic is shown in Figure 1.2-1.

Safety and tolerability of subjects will be reviewed by the investigator, contract research organization medical monitor, and Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) staff, including the project leader, Clinical Safety & Pharmacovigilance representative, medical monitor, and the clinical pharmacology representative. Dose escalation may be modified or stopped based upon sponsor or investigator's clinical judgment at any time. Additional subjects or cohorts may be added at the discretion of the safety review team to further evaluate a given dose. Each subject in the cohort will be evaluated by the investigator at the site to assess the subject's tolerability to the dose. Dose toleration is defined as follows: during the course of the trial, the subject does not experience any moderate or severe AEs or potentially clinically significant changes from baseline in clinical laboratory assessment values, vital signs, or electrocardiogram (ECG) tracings, which are assessed as related to the IMP, and would warrant a dose decrease or discontinuation of the IMP. Dose toleration must be observed

in at least 6 subjects in Cohort 2 and at least 3 subjects in Cohort 4 to warrant dose escalation to the next cohort. Pharmacokinetic information will also be considered prior to making the dose escalation decision.

Subjects and/or their parents/guardians will be contacted 7 (+ 2) days after the last dose of IMP on Day 14 to assess any new or ongoing AEs and to record concomitant medications.

4.2 Scientific Rationale for Trial Design

The focus of this trial is to assess the safety and tolerability of once daily XR capsules in pediatric subjects (4 - 12 years of age, inclusive); therefore, the trial design is a 14-day multiple-dose trial. In addition, the primary goal is to assess the single- and multiple-dose PK profile in pediatric subjects. The PK samples will be collected until 48 hours after dosing, ie, 5-half-lives following the Day 14 dose for adequate estimation of half-life.

A 400-mg adult equivalent dose of IR beads (50% by weight or 10% by weight) + XR-9PF beads (9% Kollicoat IR pore former) (IR+XR-9PF) formulation administered 8 hours apart, with a second dose at half of the first dose in subjects aged 9 to 12 years was found to be safe and well tolerated (Trial 405-201-00010). Hence, a 400-mg adult equivalent dose of the once daily XR formulation will be evaluated in subjects aged 9 to 12 years in this trial as the exposures are expected to be similar.

Body weight-adjusted doses in subjects 9 to 12 years of age produced concentrations similar to those observed in adults for 2 previously studied XR formulations. Therefore, the doses of centanafadine QD XR to be administered in this trial will be selected based on body weight adjustments from the 164.4 mg and 328.8-mg adult doses (comparable to 200 mg and 400 mg total daily doses of SR tablet, respectively) utilized in the 405-201-00047 trial. The 405-201-00047 trial was conducted in healthy adult subjects to determine the dose proportionality and multiple dose PK of once daily centanafadine XR capsules, to evaluate the effect of food or sprinkling on applesauce on the relative bioavailability of once daily centanafadine XR capsules, and to directly compare the PK of the final QD XR capsule versus the SR tablet.

Cohorts of subjects aged 6 to 8 years will be enrolled in this trial, once the 100-mg adult equivalent dose of IR+XR-9PF beads in 6 - 8 year olds (Trial 405-201-00010) and the 400-mg adult equivalent dose of the once daily XR formulation in 9 - 12 year olds (Cohort 1) is found safe and well tolerated. Initially, a 200-mg adult equivalent dose of the QD XR formulation will be evaluated to assess safety and tolerability in subjects aged 6 to 8 years, followed by the 400-mg adult equivalent dose administered to a second cohort of subjects.

Cohorts of subjects aged 4 to 5 years old will be enrolled in this trial once the 200 and 400-mg adult equivalent dose of the QD XR formulation in 6 to 8 year olds (Cohorts 2 and 3) is found safe and well tolerated, and it has been confirmed that there are no concerns that preclude the administration of IMP to subjects aged 4 to 5 years. A 200-mg adult equivalent dose of QD XR formulation will be evaluated to assess safety and tolerability in subjects aged 4 to 5 years, followed by the 400-mg adult equivalent dose administered to a second cohort of subjects.

4.3 Dosing Rationale

In adults, doses up to 400 mg total daily dose (TDD) administered as the SR tablet have been well tolerated. Total daily doses of 200 and 400 mg were shown to be efficacious in phase 3 adult ADHD trials. Doses of the once daily XR capsule that approximate daily exposures following 200 and 400 mg SR tablets in adults will be investigated in this trial in pediatric subjects.

The highest dose to be tested will be expected to produce mean peak centanafadine concentrations of about 1.4 µg/mL, the approximate mean peak concentration following the 400 mg TDD of the SR tablet formulation used in a phase 2 trial in ADHD adults (Trial NVI-EB-1020-202).

The target adult equivalent doses in pediatric subjects was derived as follows:

1. The actual dose of centanafadine once daily XR capsule in pediatric subjects was calculated based on matching exposures to centanafadine SR tablets dosed in adults. The dose was adjusted based on relative bioavailability of once daily XR compared with SR tablets in adults. Allometric scaling with a coefficient of 0.75 was used to calculate pediatric clearance. Allometric scaling can be adequately used to design PK trials in pediatric subjects aged 2 years and older based on the publication by Liu et al.[26] The median weight of adults from trials in adult subjects was used to scale dosing in pediatric subjects.
2. The actual dose for a particular weight (allometric derived) was then matched to the available dose strength (administered dose). In general, the dose strength and weight bins were selected such that the exposures are within 34% of the expected exposures from allometric scaling. The weight-based dosing is summarized in Table 6.1-1 (Cohort 1) and Table 6.1-2 (Cohorts 2-5).

The data collected following administration of the XR formulation dosed twice daily in Trial 405-201-00010 has supported dosing at the target exposures in the current trial, which utilizes the once daily XR formulation and QD XR formulation of centanafadine. The sponsor has stopped development of the twice daily XR formulation so future dosing

decisions will be based on results following dosing with the once daily formulation of centanafadine QD XR.

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 eSource 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 consumes all doses of the IMP. Subjects who are evaluated at the last scheduled visit will be defined as trial completers. For purposes of this trial, subjects who complete the discharge assessments (at least 24 hours after dosing on Day 14 and following PK sampling) will be defined as trial completers.

5 Trial Population

The trial population will include male and female subjects 4 to 12 years of age, inclusive, who meet the following criteria: a clinical diagnosis of any ADHD subtype based on *Diagnostic and Statistical Manual of Mental Disorders - 5th Edition* (*DSM-5*) criteria and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).

Every effort will be made to ensure that both genders and the entire age range are represented.

5.1 Subject Selection and Numbering

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

Demographic information (collection date, date of birth, sex, childbearing potential, race, and ethnicity) and medical history will be recorded in eSource 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 when assessed:

1) Written informed consent obtained from a legally acceptable representative (eg, parent/guardian) and assent must be obtained from the subject prior to the initiation of any protocol-required 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) to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens and discontinuation of prohibited concomitant medication, to reliably return for scheduled visits, and to be reliably rated on assessment scales.
3) Male or female subjects 4 to 12 years of age, inclusive, at the time of informed consent/assent.
4) Subjects must weigh ≥ 13 kg.
5) 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:
   a) Medical history
   b) Clinical laboratory assessment determination
   c) ECGs
   d) Physical examination
6) Subjects with a diagnosis of any ADHD subtypes based on *DSM-5* criteria and confirmed by the MINI-KID.
7) For female subjects and male subjects, 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 the last dose of IMP for subjects of childbearing potential and for 90 days following the last dose of IMP for male subjects and their partners who are of childbearing potential.
8) Subject is judged by the investigator to be clinically stable, and has not had any psychiatric hospitalizations within the past 12 weeks prior to screening.
9) Subjects with non-insulin dependent diabetes mellitus (IDDM) may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria:
   a) Glycated hemoglobin (HbA_{1c}) < 6.5%, AND
   b) Screening glucose must be ≤ 125 mg/dL or ≤ 6.94 mmol/L (fasting) or < 200 mg/dL or < 11.1 mmol/L (nonfasting). If the nonfasting screening glucose is ≥ 200 mg/dL or ≥ 11.1 mmol/L, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL or ≤ 6.94 mmol/L, AND

c) Subject has been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening, AND

d) Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, AND

e) Subject's diabetes is not newly diagnosed during screening for the trial.

10) Subjects and their legally acceptable representative (eg, parent/guardian) must be able and willing to utilize the AiCure Platform for each daily dose.

11) Body mass index (BMI) ≥ the fifth percentile of the Centers for Disease Control and Prevention clinical growth charts for age and sex.

5.2.2 Exclusion Criteria

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

1) Females who are breast-feeding and/or who have a positive pregnancy test result (Cohorts 1 and 6 only) 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 (medication, illicit drug use, etc); or subjects with a clinical presentation or history of psychotic symptoms.
3) Subjects with developmental disorders, such as autism spectrum disorder.
4) Subjects with a history of intellectual disability as determined by at least 1 of the following: intelligence quotient < 70, or clinical evidence, or a social or school history that is suggestive of intellectual disability.
5) Subjects who have any of the following:
   a) A significant risk of committing suicide based on history and the investigator's clinical judgment, or routine psychiatric status examination
   b) Current suicidal behavior
   c) Imminent risk of injury to self
   d) Active suicidal ideation as evidenced by an answer of "yes" on Questions 4 or 5 (over the last 6 months) on the suicidal ideation section of the "Baseline/Screening" version of the C-SSRS
   e) 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 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.
6) Subjects with a lifetime history of a substance use disorder (as determined by *DSM-5* criteria), or current substance misuse including alcohol and benzodiazepines, but excluding caffeine and nicotine.

7) Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least 90 days prior to first dose of IMP) or an abnormal result for free thyroxine (T_4) at screening. Eligibility of subjects excluded based on an abnormal free T_4 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 T_4 is measured only if result for thyroid-stimulating hormone [TSH] is abnormal.)
8) 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 adverse event 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.
9) Subjects with IDDM (ie, any subjects using insulin).
10) 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.).
11) Any major surgery within 30 days prior to the first dose of IMP.
12) Any history of significant bleeding or hemorrhagic tendencies.
13) Blood transfusion within 30 days prior to the first dose of IMP.
14) Subjects with a positive drug screen for methylphenidate or amphetamines resulting from the confirmed use of prescription or over-the-counter medications may continue evaluation for the trial, following consultation and approval by the medical monitor. Subjects that test positive for confirmed prescription use of ADHD medications at screening will be required to undergo a washout period.
15) Subjects who have taken antibiotics within 30 days prior to the first dose of IMP.
16) Consumption of alcohol and/or food and beverages containing methylxanthines (eg, coffee, chocolate) (because of stimulant activity) within 72 hours prior to dosing.
17) The following laboratory test and ECG results are exclusionary:
    a) Platelets $\leq 130 \times 10^3/\mu L$
    b) Hemoglobin ≤ 11.2 g/dL
    c) Absolute neutrophil count $\leq 1.00 \times 10^3/\mu L$
    d) Aspartate aminotransferase (AST) $> 2 \times$ upper limit of normal (ULN)
    e) Alanine aminotransferase (ALT) $> 2 \times$ ULN
    f) Creatinine ≥ 1.4 mg/dL

g) $HbA_{1c} \geq 6.5\%$

h) Creatine phosphokinase ≥ 2 × ULN, unless discussed with and approved by the medical monitor.

i) QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 450 msec for males and ≥ 470 msec for females using the QTcF correction

NOTE: Subjects should be excluded if they have any other abnormal clinical laboratory assessments, 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 check-in should be taken approximately 5 minutes apart. Based on the QTcF correction, a subject will be excluded if the correction is ≥ 450 msec for more than 1 of the 3 time points of triplicate ECGs done for males or ≥ 470 msec for more than 1 of the 3 time points of triplicate ECGs done for females.

18) Subjects who have supine or standing diastolic blood pressure, after resting for at least 3 minutes, > 80 mmHg.

19) 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.

20) Subjects who have had any previous exposure to centanafadine.

21) 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.

22) Subjects with a history of allergic reaction or a known or suspected sensitivity to any substance that is contained in the IMP formulation.

23) Subjects who do not tolerate venipuncture or have poor venous access that would cause difficulty for collecting blood samples.

24) Prisoners or subjects who are compulsorily detained (eg, juvenile detention, court-mandated treatment) for any reason.

25) Subjects who are on probation or parole.

26) Any subject who, in the opinion of the investigator, should not participate in the trial.

27) Relatives of trial site employees.

28) Subjects who have history of clinically significant tachycardia or hypertension.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

On PK sampling days (Days 1 and 14), doses will be administered after an 8-hour fast and food will be restricted until 2 hours postdose with a snack permitted at 2 hours postdose and lunch at 4 hours postdose. On Days 1 and 14, water will be restricted for 1 hour prior to dosing and until 2 hours postdose. Doses of centanafadine XR or QD XR should not be taken with a high fat meal.

Subjects should be fasting for a minimum of 8 hours prior to the blood draws for clinical laboratory assessments, if possible.

Consumption of alcohol and/or food and beverages containing methylxanthines (eg, coffee, chocolate) are prohibited within 72 hours prior to dosing.

5.3.2 Activity

Subjects will be asked to abstain from strenuous or sustained physical activity for 48 hours prior to check-in and for the duration of the dosing and PK sampling period.

5.4 Screen Failures

Subjects for whom the electronic informed consent form (eICF) and assent form are signed but who are not started on treatment are permitted to be rescreened. In the event that the subject is rescreened for trial participation, and the rescreening was not completed within the original screening window, a new eICF and assent form must be signed by the parent/guardian and subject, respectively.

A screen failure is a subject from whom informed consent/assent is obtained and is documented in writing (ie, parent/guardian signs an eICF and subject signs an assent form), but who is not assigned trial treatment. All AEs must be reported after informed consent/assent has been obtained, including screening failures due to AEs, irrespectively of IMP administration.

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

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

6 Trial Treatments

6.1 Trial Treatments Administered

Investigational medicinal product for Cohort 1 will be supplied as centanafadine XR capsules of 52.5 mg, 78.8 mg, and 210 mg. Investigational medicinal product for Cohorts 2 to 6 will be supplied as centanafadine QD XR capsules of 41.1 mg and 164.4 mg.

Doses of centanafadine XR or QD XR will be taken once daily in the morning on Days 1 through 14. All doses should be taken at approximately the same time each day, with the dose taken in the morning upon awakening. The IMP should not be taken with a high-fat meal.

The fixed dose strengths will be administered according to body weight as shown in Table 6.1-1 (Cohort 1) and Table 6.1-2 (Cohorts 2 to 5).

Table 6.1-1 Weight-based Dosing of Centanafadine XR - Cohort 1

Weight Bin	Doses in Children
	400 mg Adult Equivalent
≥ 13 to 16 kg	105 mg
> 16 to 25 kg	157.6 mg
> 25 to 40 kg	210 mg
> 40 to 60 kg	288.8 mg
> 60 kg	420 mg

Table 6.1-2 Weight-based Dosing of Centanafadine QD XR - Cohorts 2 to 6

Weight Bin	Doses in Children	
	200 mg Adult Equivalent	400 mg Adult Equivalent
13 to < 20 kg	41.1 mg	82.2 mg
20 to < 35 kg	82.2 mg	164.4 mg
35 to 50 kg	123.3 mg	246.6 mg
> 50 to 89 kg	164.4 mg	328.8 mg

The weight bins may be adjusted based on safety or PK data collected during this trial.

The centanafadine XR capsule or QD XR capsule can be administered as intact capsules or the capsule contents can be sprinkled on 1 tablespoon of applesauce and ingested immediately with up to 120 mL of room temperature water (suggested for subjects 4 - 8 years of age) or 120 to 240 mL of room temperature water (suggested for subjects

9 - 12 years of age). Food and water restrictions on Day 1 and Day 14 are described in Section 5.3.1.

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.[24]

6.2.1 Packaging and Labeling

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

6.2.2 Storage

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

The IMP will be stored at controlled room temperature conditions as per the clinical label on the IMP. The trial site staff will maintain a temperature log in the IMP storage area to record the temperature.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of IMP 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 may only be destroyed by the trial site(s), if approved by the sponsor and if the IMP destruction meets all local regulations. The IMP will be destroyed by the clinical trial site following completion and verification of accountability of the IMP by the assigned trial monitor. The trial site(s) may utilize qualified third-party vendors for IMP destruction. A certificate of destruction should be filed within the IMP accountability.

6.2.5 Reporting of Product Quality Complaints

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

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

- Failure/malfunction of a product or medical device to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Bottle defects (eg, under-fill, over-fill, no safety seal)
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record each PQC identified through any means from the receipt of the 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) within 24 hours of becoming aware of the PQC according to the procedure outlined below.

Send PQC reporting information to the Otsuka IMP complaints mailbox e-mail: IMP-PQC@otsuka-us.com. Also indicate whether or not the complaint sample is available for return.

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

6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, 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 of complaint sample (if available)

- Availability of complaint sample for return
- Was any subject at risk due to the identified issue?

6.2.5.3 Return Process

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

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

6.2.5.4 Assessment/Evaluation

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

6.3 Measures to Minimize/Avoid Bias

This is an open-label trial.

6.4 Subject Compliance

The time and dose strength of each IMP administration will be recorded in eSource. Information regarding any missed or inappropriately administered doses will also be documented in eSource.

Accountability and compliance verification will be monitored with a medication adherence monitoring platform, and the results documented in the subject's trial records. Subjects and their parents/guardians must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance), discontinuation of the subject from the trial should be considered.

Details on the AiCure technology to be used in this trial to assess IMP compliance are provided below.

6.4.1 AiCure Investigational Medicinal Product Adherence and Reminder System

This trial will employ an IMP adherence monitoring platform ("AiCure Platform") for all subjects in the trial. The AiCure Platform uses artificial intelligence on smartphones to confirm IMP ingestion. In addition, built-in reminders and a communication system allow real time intervention in case of IMP interruptions.

Use of this AiCure Platform will in no way supersede or replace the physician or prescribed IMP protocol of the subjects. Because the AiCure Platform does not change the IMP protocol of the subjects, but rather encourages adherence to the predefined protocol, use of this AiCure Platform presents minimal risk to the subjects. Use of the AiCure Platform will be required for all subjects in the trial.

The monitoring AiCure Platform requires that all subjects take each dose of the IMP while using a smartphone. The AiCure Platform will be provided to subjects and their parents/guardians preloaded on a smartphone, or subjects and their parents/guardians will download the AiCure Platform onto their own mobile device at the baseline visit (Day −1).

When at home, subjects and their parents/guardians will receive an IMP reminder at a time within a predefined window. This notification reminds subjects and their parents/guardians to take their IMP dose while using the AiCure Platform. Subjects and their parents/guardians will follow a series of prescribed steps in front of the front facing webcam to visually confirm their ingestion of the IMP. The application on the smartphone will make an automated determination of whether the subject has properly taken their IMP at the prescribed time. There is no need for the trial site staff to review the administration, nor would the trial site staff need to be available at the time the subject takes their IMP. The amount of guidance that the device provides to the subjects is automatically reduced as the subject becomes more proficient at using the application.

After the device confirms proper IMP ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrollment. The captured data and video are reviewable through a roles and rules restricted system ensuring privacy of the information. The system is compliant with the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information.

Phone numbers of the subjects/parents/guardians may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with subjects and their parents/guardians, including automated messaging from the AiCure Platform device and contact by the trial site staff or other monitoring personnel. At no time is the phone number visible to the trial site staff or monitoring personnel on the AiCure Platform. Individuals outside the trial site will not be provided with subject names, nor will they be given access to subject medical records.

6.4.2 AiCure Subject Risk

The AiCure Platform provides no more than minimal risk to subjects. This protocol only introduces a smartphone-based monitoring application that prompts the user to take their IMP, verifies ingestion, and stores encrypted data securely for analysis. When functioning properly, use of the AiCure Platform does not affect titration, dosage, route of administration, or treatment duration, conforming to any trial requirements as noted by trial site staff.

It is possible, though very unlikely, that the AiCure application can fail to remind subjects to take the IMP or tell them to take their IMP when not required. To date, AiCure has not encountered such a malfunction.

All trial data, including any identifiable subject information, will be obtained and encrypted by the application. Subjects will be coded according to the protocol and their identity will not be stored with the trial data obtained. After the subject has taken the IMP and confirmation of proper ingestion has been completed, the encrypted data will be automatically forwarded to a secure server. The server is compliant with the HIPAA, which protects the privacy and security of healthcare information. The data will be securely stored and only accessible to the trial site staff and other authorized personnel through two-way authentication.

The data may also be retained in a secure manner beyond the term of the trial and utilized to improve the operation of the AiCure Platform, categorize adherence activity by disease state or other useful categories, or for regulatory filings by the AiCure Platform Provider to support future applications for the AiCure Platform Provider's product. Individuals who are not associated with the care and treatment of subjects will not have access to subject identity or any medical records.

6.4.3 AiCure Subject Confidentiality

The AiCure Platform Provider will protect subjects' personal information to the full extent required by law. However, information from this trial, including de-identified video recording(s) of subject performance of various actions, may be submitted to the trial site, and potentially to the FDA. Both information obtained by the application, and information in the eICF or assent form, may be examined by the trial site or the trial site's representatives, and may also be reviewed by the FDA and other regulatory agencies, IRBs. All of these parties are bound to safeguard the rights, safety, and well-being of all clinical trial subjects, and to maintain all information in confidence, with special consideration given to trials that may include vulnerable subjects.

The results of this trial may be presented at meetings or in publications; however, specific subjects will not be identified by name in these presentations or publications. Information from this trial may also be retained by the AiCure Platform Provider for the purpose of improving the AiCure Platform, to allow for future analysis of various facial and other parameters, the reporting of high level statistical analysis of the AiCure Platform, to improve the internal workings of the system running on the smartphone device, or for regulatory filings by the AiCure Platform Provider to support future applications for the Provider's product.

6.5 Concomitant Medications or Therapies

The investigator will record all medications (including prescription medications, over-the-counter medications, herbal remedies, etc) and therapies taken by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) in eSource. 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) in eSource.

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

6.5.1 Prohibited Medications or Therapies

No medications other than planned IMP may be taken during the trial, with the exception of the medications described in Section 6.5.2. A washout of a minimum of 7 days for subjects on stimulants and nonstimulants, including propranolol, guanfacine, and clonidine, will be required before centanafadine XR or QD XR dosing on Day 1. Subjects taking fluoxetine must undergo a washout period of at least 28 days prior to centanafadine XR or QD XR dosing on Day 1.

The use of nonpermitted prescription, over-the-counter, or herbal medications or vitamin supplements is prohibited within 14 days prior to the first dose of IMP and the use of antibiotics is prohibited within 30 days prior to the first dose of IMP. The sponsor may allow exceptions only if the medication is unlikely to affect the PK or pharmacodynamic (PD) result. Some concomitant medications may be permitted but a decision should be made in consultation with the medical monitor.

6.5.2 Permitted Medications or Therapies

Subjects who have been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to screening and subjects with hypothyroidism or hyperthyroidism whose condition has been stabilized with medications for at least 90 days prior to first dose of IMP may continue those medications.

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

Dose escalation from Cohort 2 to Cohort 3 or from Cohort 4 to Cohort 5 may be stopped following a review of the safety and tolerability data as described in Section 4.1.

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

A subject may be discontinued from the trial for the reasons listed below:

- Resting, supine, and confirmed on 2 readings, systolic blood pressure > 130 mmHg and an increase from baseline by 25 mmHg
- Resting, supine, and confirmed on 2 readings, diastolic blood pressure > 90 mmHg and an increase from baseline by 15 mmHg
- Resting, supine, and confirmed on 2 readings, pulse > 120 beats per minute (bpm) and an increase from baseline by 30 bpm
- Skin eruptions that are classified as severe (defined as the inability to perform normal daily activity) or that meet the criteria for an SAE
- Neutropenia with an absolute neutrophil count < $1.00 \times 10^3/\mu L$ per microliter

7.3.1 Treatment Interruption

Not applicable.

7.3.2 Treatment Discontinuation

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. If a subject discontinues treatment, their participation in the trial will be discontinued. Discontinued subjects 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 IMP 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
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAE
    - Other potentially IMP-related safety concerns or AEs
- Death
- Disease relapse
- Lost to follow-up
- Noncompliance with IMP
- Physician decision
- Pregnancy (see Section 10.3)
- Progressive disease
- Protocol deviation
- Protocol violation
- Protocol-specific withdrawal criterion met
- Trial site terminated by sponsor
- Trial terminated by sponsor
- Technical problems
- Withdrawal by parent/guardian

- Withdrawal by subject
- Other

If the subject discontinues IMP 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

Each parent/guardian and subject has the right to withdraw their consent or assent from further participation in the trial at any time without prejudice. Parents/guardians and subjects can withdraw consent or assent for use of data which has not previously been anonymously transferred into trial data sets collected as part of the trial and can only withdraw consent for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the parent/guardian or subject provides their written withdrawal of consent or 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 or assent requires a parent's/guardian's or subject's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and trial site staff).
- Contact of the parent/guardian or 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 or 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 or 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 IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3.2). A subject may, however, indicate that further trial participation is creating a burden on their school or social schedule. Therefore, 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 treatment and/or 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 to participate in the trial.

Details on the withdrawal of consent or assent from the optional Future Biospecimen Research (FBR) substudy are provided in the eICF.

7.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent/assent withdrawal, investigators will be instructed to meet and discuss (without undue coercion) with the subject (and their parent/guardian) their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the parent's/guardian's/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 21 (+ 2 days) for the final follow-up telephone call, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up". Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

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 eSource.

8 Trial Procedures

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

8.1 Efficacy Assessments

8.1.1 Attention-deficit Hyperactivity Disorder Rating Scale - 5

The Attention-deficit Hyperactivity Disorder Rating Scale – 5 (ADHD-RS-5) will be administered by trial site staff at the time points described in the schedule of assessments (Table 1.3-1).

The ADHD-RS-5 is a scale based on the *DSM-5* criteria for ADHD that provides a rating of inattentive (IA) and hyperactivity/impulsivity (H/I) symptoms for children and adolescents, based on gender and age. An additional set of 12 items assessing IA- and H/I-related impairment are answered after the symptoms items and are scored separately. Response options for the symptoms items use a 4-point Likert scale where 0 = “never or rarely”, 1 = “sometimes”, 2 = “often”, and 3 = “very often”. Impairment items are rated on a 4-point Likert scale where 0 = “no problem”, 1 = “minor problem”, 2 = “moderate problem”, and 3 = “severe problem”. Raw summed scores are converted to percentiles. Clinicians should score the highest score that is generated for the prompts for each item. Significant symptoms and impairments are generally considered at least a “2” (moderate).

It is required that adequately trained and experienced clinicians administer the ADHD-RS-5. All individuals performing these assessments must be preapproved by the sponsor or designee.

8.1.2 Clinical Global Impression - Severity (Attention-deficit Hyperactivity Disorder Version)

The Clinical Global Impression - Severity (CGI-S) will be administered by trial site staff at the time points described in the schedule of assessments (Table 1.3-1).

The ADHD version of the CGI-S will be administered and is a single-item clinical rating of the subject’s severity of ADHD symptoms in relation to the clinician’s total experience with ADHD patients. Severity is rated on a 7-point scale (1 = normal, not at all ill; 7 = among the most extremely ill patients).

It is required that adequately trained and experienced clinicians administer the CGI-S. All individuals performing these assessments must be preapproved by the sponsor or designee.

8.2 Pharmacokinetic Assessments

8.2.1 Pharmacokinetic Blood Plasma Samples

Pharmacokinetic blood samples will be collected at the time points described in the schedule of assessments (Table 1.3-1). Blood samples (3 mL) will be collected in vacutainers containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) and processed into plasma to determine the concentrations of centanafadine and its metabolite EB-10601. Additional metabolites that are not identified in the protocol may also be analyzed, if needed. In addition, PK samples may be used for the investigation of a bioanalytical method, if needed.

The samples should be collected within ± 3 minutes of the nominal time. Predose samples should be collected within 60 minutes before administration of the IMP. After the first dose, predose samples will be taken within 10 minutes prior to the dose.

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.

The actual date and time of the PK sample collection will be recorded in eSource.

After processing into plasma, aliquots will be placed into appropriately labeled tubes and will be placed in a freezer set at −70°C or −20°C, unless otherwise instructed in the Laboratory Manual.

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

8.2.2 Pharmacokinetic Blood Sample Collection Using a Microsampling Technique

For subjects in Cohort 1 only, blood samples will be collected at the time points outlined in the schedule of assessments (Table 1.3-1) using a microsampling technique to determine if centanafadine and metabolite(s) concentrations are comparable to those obtained from venous collection. Additional information will be provided in the Laboratory Manual. A numbing agent may be used for the microsampling blood collection to determine if the numbing agent has any effect on the concentration measurement.

8.3 Pharmacodynamic Assessments

Palatability, including flavor, smell, sweetness, overall liking (immediate), and overall liking (2 to 5 minutes later) of the centanafadine XR capsule or QD XR capsule, or

centanafadine XR capsule contents or QD XR capsule contents sprinkled on to the applesauce will be assessed by visual analog scale (VAS).[27]

8.4 Pharmacogenomic Assessments

Not applicable.

8.5 Biomarker Assessments

Not applicable.

8.6 Future Biospecimen Research Samples

Future biospecimen research samples will be collected at the time points described in the schedule of assessments (Table 1.3-1). Participation in the FBR is optional.

8.6.1 Scope of Future Biospecimen Research

Future biospecimen research samples will be collected from subjects who consent to this sample collection. Research performed on these samples may include genetic analyses including whole genome analysis (deoxyribonucleic acid [DNA]), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics, and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from subjects who have provided appropriate consent. The objective of collecting specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments.

8.6.2 Summary of Procedures for Future Biospecimen Research Samples

All subjects enrolled in the clinical trial will be considered for enrollment in the optional FBR substudy.

After obtaining informed consent, the following FBR specimen will be obtained:

- Blood (4 mL K_2EDTA tube) for DNA analysis

If a parent/guardian and subject provides consent/assent to FBR collection, back-up PK samples may be used for FBR. The date and time of the sample collection will be recorded in eSource. Additional information will be provided in the Laboratory Manual. If a FBR substudy is planned, a separate document describing the analysis may be prepared and the results may be reported separately from the clinical study report.

8.7 Safety Assessments

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. The total volume of blood to be collected during the trial will be documented in the eICF.

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.

Exclusion criteria for screening laboratory tests are listed in Section 5.2.2. 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 eSource.

Subjects should be monitored for potentially clinically significant clinical laboratory values (Section 10.4).

A urine or serum pregnancy test for females will be performed in Cohorts 1 and 6 only at the time points described in the schedule of assessments (Table 1.3-1). On suspicion of pregnancy, an unscheduled urine or serum pregnancy test will be performed. Positive urine pregnancy tests must be confirmed with a serum pregnancy test. The investigator (or appropriate site staff) is advised to counsel participants on the risk of pregnancy while participating in a clinical trial as well as ensuring the child understands how pregnancies occur and can be avoided. This should be documented in the eSource. Results of the pregnancy test must be available prior to the administration of the IMP.

A urine drug screen will be performed at the time points described in the schedule of assessments (Table 1.3-1). 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. Subjects that test

positive for confirmed prescription use of ADHD medications at screening will be required to undergo a washout period.

8.7.2 Physical Examination

Physical examinations 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 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 AE will be conducted as necessary.

Any abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eSource.

8.7.3 Vital Signs

Vital signs will be collected at the time points described in the schedule of assessments (Table 1.3-1).

Vital signs include blood pressure, heart rate, respiratory rate, and body temperature. 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. Temperature and respiratory rate will be taken with the subject in the supine position. Predose vital signs will be measured within 2 hours before dosing.

Subjects should be monitored for potentially clinically significant vital signs values (Section 10.5).

8.7.4 Electrocardiogram

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

The 12-lead ECGs will be performed in the supine position. Predose 12-lead ECGs conducted at baseline (Day −1) will be performed in triplicate, taken approximately 5 minutes apart. The average of the 3 values will be the baseline value. Based on QTcF, a subject will be excluded if the correction is ≥ 450 msec for more than 1 of the 3 time points of triplicate ECGs done for males or ≥ 470 msec for more than 1 of the 3 time points of triplicate ECGs done for females. A single ECG will be measured at all other time points.

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.

Subjects should be monitored for potentially clinically significant ECG results (Section 10.6). Any abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eSource.

8.7.5 Suicidality Monitoring

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

The pediatric version of the Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered for subjects 4 to 5 years of age[28] and the adult version of the C-SSRS will be administered for subjects ≥ 6 years of age. The "Baseline/Screening" version will be completed at the screening visit and the "Since Last Visit" version will be completed at all subsequent assessments.

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 investigational site's files.

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

8.7.6.1 Sleep Diary

The subject's parent/guardian or in-clinic overnight staff will complete a sleep diary for the subject using the AiCure Platform at the time points described in the schedule of assessments (Table 1.3-1).

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 are defined as AEs with an onset date on or after the start of open-label treatment. In more detail, TEAEs are all AEs which 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, discontinuation, interruption, or reduction of IMP.

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 eICF 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: A noteworthy event for the particular product/IMP or class of products that a sponsor may wish to monitor carefully. All adverse events of special interest (AESIs) are to be reported as IREs.

Immediately Reportable Event:

- Any SAE.
- Any AE related to occupational exposure.
- Any AESIs
- Potential serious hepatotoxicity (see Section 8.8.7).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an immediately reportable event (IRE) form and the Pregnancy Surveillance Form(s) to the sponsor. This includes pregnancy of the subject or the partner of the subject. Pregnancy will only be documented on the AE eSource if the pregnancy occurs in a female subject and there is an abnormality or complication.

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 in the eSource. 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 eSource. Adverse event collection will begin after a guardian/subject provides consent/assent, and will continue until the subject's at the last scheduled contact unless the AE must be followed further (see Section 8.8.3). All AEs must be reported after subject informed consent has been obtained, including screening failures due to AEs, irrespective of IMP administration.

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.

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 adverse event, start date, end date, 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 eSource.

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 eSource). Subject confidentiality must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding safety information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.8.9.2

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 monitoring plan for complete details, including reporting forms, on extra measures that must be performed to characterize any skin AESI of a newly acquired skin eruption that is nontraumatic. The trial site will identify a local dermatologist for consultation as needed for these AESIs. All AESIs should be reported as IREs (Section 8.8.5).

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

A key objective of the Abuse Potential Monitoring Process (APMP) is to monitor for instances of abuse or diversion of the trial medication and other psychoactive substances. In addition to monitoring for irregularities in medication handling, AEs that may be suggestive of a developing abuse issue will also receive special attention. As part of the APMP, medication handling irregularities (MHIs) must be reported, and AEs related to abuse potential and AEs involving MHIs must be reported as Events Subject to Additional Monitoring (ESAMs) with detailed narratives.

Investigators and site staff at each trial site will be trained on reporting potentially abuse-related AEs (eg, recording a description of the event in the subject's/caregiver's own words in the source documents as well as eSource, in addition to the clinical term, and to be aware that a subject's/caregiver's report may encompass more than one event and that these should be recorded separately). The investigators will be provided with examples of potentially abuse-related AEs, and trained on how to handle such events (eg, additional monitoring). While the investigators will be provided with examples of AE terms as a guide during trial conduct, the analysis of potentially abuse-related AEs will be based on a search of all Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, all verbatim terms, and any open text fields within the AE data to identify text strings suggestive of abuse potential, in line with the 2017 FDA guidance (Assessment of Abuse Potential of Drugs).[29] Refer to the separate APMP documentation for complete details on MHIs and ESAMs, including documenting and reporting

procedures, examples of potentially abuse-related AE terms that meet the criteria for ESAM reporting, and guidance for the training of investigators and trial site staff.

8.8.7 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 in the eSource.

8.8.8 Procedure for Breaking the Blind

This trial does not use blinding procedures.

8.8.9 Follow-up of Adverse Events

8.8.9.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eSource with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in the eSource. 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).

8.8.9.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 30 days after the last dose of IMP is administered.

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

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

Any new IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the 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

Not applicable.

8.10 Subject Assessment Recording

8.10.1 Mini International Neuropsychiatric Interview for Children and Adolescents

The MINI-KID, a structured diagnostic interview that assesses the 30 most common and clinically relevant disorders or disorder subtypes in pediatrics mental health, will be utilized for both diagnosis and to exclude comorbid conditions.

8.10.2 Study Medication Withdrawal Questionnaire

The study medication withdrawal questionnaire (SMWQ) will be completed by the subject or their parent/guardian at the time points described in the schedule of assessments (Table 1.3-1).

The SMWQ is a questionnaire to assess withdrawal symptoms and is a modification of the Amphetamine Withdrawal Questionnaire in which the terms "amphetamines and methamphetamine" are replaced with the term "the study medication."

8.10.3 Blood Collection Experience Survey

The blood collection experience survey will be completed by subjects in Cohort 1 and trial site staff at the time points described in the schedule of assessments (Table 1.3-1).

The blood collection experience survey assesses if the PK blood collections from the subject's arm and finger were painful, as well as which site the subject would prefer blood to be collected from.

8.11 Other Assessments

Not applicable.

9 Statistical Considerations

9.1 Sample Size

Ten subjects in the 9 to 12 years age group and 10 subjects in the 6 to 8 years age group (including both dose levels) are sufficient to obtain a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with at least 80% power for a PK variability of 42% (coefficient of variation).[30] Up to 12 subjects will be enrolled in each of the 9 to 12 years age cohorts (Cohorts 1 and 6), up to 8 subjects will be enrolled in each of the 6 to 8 years age cohorts (Cohorts 2 and 3), and up to 5 subjects will be enrolled in each of the 4 to 5 years age cohorts (Cohorts 4 and 5). Additional subjects may be enrolled as necessary.

9.2 Datasets for Analysis

The PK data set includes all subjects that are administered a dose of IMP and have at least 1 postdose evaluable plasma concentration.

The safety dataset includes all subjects that are administered at least one dose of IMP.

9.3 Handling of Missing Data for Primary 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

9.4.1.1 Clinical Global Impression - Severity

Mean change from baseline to Day 7 and Day 14 in CGI-S score will be summarized descriptively by age and dose group.

9.4.1.2 Attention-deficit Hyperactivity Disorder Rating Scale - 5

Mean change from baseline to Day 7 and Day 14 in investigator-rated ADHD-RS-5 total score as well as the ADHD-RS-5 inattention and hyperactivity subscale scores will be summarized descriptively.

9.4.2 Safety Analysis

9.4.2.1 Adverse Events

All AEs will be coded by system organ class and MedDRA preferred term. The incidence of the following events will be summarized by age group and dose level within the age group (as applicable):

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

9.4.2.2 Clinical Laboratory Data

Clinical laboratory assessments (observed and change from baseline data) will be summarized by age group and dose level within the age group (as applicable). The incidence of potentially clinically relevant clinical laboratory tests will be summarized by dose level within each age group.

9.4.2.3 Physical Examination and Vital Signs Data

Vital signs (observed and change from baseline data) and the incidence of potentially clinically relevant vital signs will be summarized by age group and dose level within the age group (as applicable).

9.4.2.4 Electrocardiogram Data

Electrocardiograms (observed and change from baseline data) and the incidence of potentially clinically relevant ECGs will be summarized by age group and dose level within the age group (as applicable).

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 age group and dose level within the age group (as applicable) and presented in a listing.

9.4.2.5.2 Sleep Diary

Sleep diary data will be by age group and dose level within the age group (as applicable).

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height, and BMI for the enrolled subjects will be summarized by descriptively. Summary statistics will consist of mean, median, minimum, maximum, and standard deviation for continuous variables and tabulations of frequency distributions for categorical variables.

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

9.4.3.2 Pharmacokinetic Analysis

Noncompartmental analysis will be performed. Plasma concentrations of centanafadine and metabolites will be summarized by age group, centanafadine dose, treatment day, and time point. Pharmacokinetic parameters will be summarized by age group, centanafadine dose, treatment day and analyte using descriptive statistics.

Concentration and PK data may be summarized by mode of administration (intact capsule versus applesauce) based on the data.

Dried blood samples collected from microsampling in Cohort 1 subjects will be summarized by treatment day and time point. However, a comparison of plasma concentrations from microsampling to those obtained by venipuncture will be reported separately.

9.4.3.3 Pharmacodynamic Analysis

The VAS scores for palatability, including the flavor, smell, sweetness, overall liking (immediate), and overall liking (2 to 5 minutes later) after dosing of centanafadine XR capsule or QD XR capsule, or centanafadine XR capsule contents or QD XR capsule contents sprinkled on to the applesauce for the first dose on Day 1 will be summarized descriptively.

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 Abuse Liability Analysis

Abuse potential will be assessed through the active monitoring of ESAMs (eg, AEs related to abuse potential and AEs involving MHI), which will be summarized descriptively and presented in a listing as well.

9.4.3.8 Study Medication Withdrawal Questionnaire

The SMWQ data will be summarized by age group and dose level within the age group (as applicable).

9.4.3.9 Blood Collection Experience Survey

The blood collection experience survey data from Cohort 1 will be summarized by collection technique.

9.5 Interim Analysis and Adaptive Design

No interim analysis or adaptive design are applicable.

9.5.1 Data Monitoring Committee

There is no data monitoring committee for this trial; however, the safety and tolerability of subjects will be reviewed after each cohort as described in Section 4.1.

10 Supporting Documentation and Operational Considerations

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

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, applicable ICH GCP guidance, 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 eSource, IRE and any safety information, 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 all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The eICF will be approved by the same IRB that approves this protocol. Subjects will provide informed assent per local law, and the subject must be able to understand that he or she can withdraw from the trial at any time and for any reason.

Each eICF will comply with the International Council for Harmonisation (ICH) GCP Guidelines, and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written trial site-specific eICF used in the trial before submission to the IRB. In support of the trial site’s standard process for administering informed consent, this trial will also allow for eICF as a tool within applicable regions and trial sites. The eICF utilizes the IRB-approved site-specific eICF 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 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 a potential subject without first obtaining consent or assent. However, informed consent and 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 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 and the subject agree that the subject has enough information to make an informed decision to participate, the subject will electronically sign in the eICF application and an electronic date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the eICF. 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 their parent/guardian by the investigator (or a qualified designee), and it has been documented that the subject and their parent/guardian has had the opportunity to ask questions, the IRB-approved eICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB. The IRB-approved assent will be signed and dated by both the subject and the person obtaining assent (investigator or designee), as well as by any other parties required by the IRB. The guardian/subject will receive a copy of the signed eICF and assent; the original shall be kept on file by the investigator.

Guardians/subjects may be asked to sign additional eICFs/assents if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the guardians/subjects, 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, and their guardians if required by local guidelines, may be asked to sign additional eICFs and assents in order to collect additional information regarding the nonsubject partner and fetus.

A separate and similar consent/assent process will be followed for the optional blood samples for FBR. Consent and assent must be obtained before a blood sample is collected.

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

10.1.4.2 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 process, site operations, delegation of authority and training, and a review of the eSource with source documents, as applicable. The investigator will agree to cooperate and participate with audits.

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

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent 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 eSource 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, logs, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the eICF. 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 process, including any revised consents;
- 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, including dosing and IMP compliance;
- 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 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 applicable ICH GCP guidance and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.1.6.4 Records Retention at the Trial Site

Food and Drug Administration 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 the sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10.1.6.5 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: Hemoglobin Hematocrit Mean corpuscular hemoglobin concentration Mean corpuscular volume Red blood cell count White blood cell count (absolute and differential) Platelets Urinalysis: Specimen appearance Color Occult blood Glucose Microscopic analysis, if indicated, WBC/RBC counts per high powered field pH Protein Specific gravity Drug Screen Amphetamines Methylphenidate (including ritalinic acid metabolite)	Serum Chemistry: Alkaline phosphatase ALT AST Bicarbonate Bilirubin Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Creatine phosphokinase Gamma glutamyl transferase Glucose Lactate dehydrogenase Potassium Protein Sodium Triglycerides Additional Tests: Anti-HCV HbA_{1c} HBsAg HIV Prothrombin time and international normalized ratio TSH, with reflex to free T_4 if TSH is abnormal Urine or serum pregnancy for females (Cohorts 1 and 6 only)

anti-HCV = hepatitis C antibodies; HBsAg = hepatitis B surface antigen.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

For males and females, or their partners, 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 remain fully abstinent) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP for subjects of childbearing potential and for 90 days following the last dose of IMP for male subjects and their partners who are of childbearing potential. 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 for 30 days after the last dose of IMP for subjects of childbearing potential and for 90 days following the last dose of IMP for male subjects and their partners who are of childbearing potential, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, birth control implant, birth control depot injection, birth control patch, 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 eSource.

Before enrolling males and females in this clinical trial, investigators must review the below information about trial participation as part of the eICF 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 females must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the eICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine or serum pregnancy test will be performed as shown in the schedule of assessments (Table 1.3-1) for female subjects in Cohorts 1 and 6 only. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all female subjects 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 while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and 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 the last dose of IMP for subjects of childbearing potential and for 90 days following the last dose of IMP for male subjects and their partners who are of childbearing potential, 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: Criteria for Identifying Clinical Laboratory Values of Potential Clinical Relevance

Table 10.4-1 Criteria for Identifying Clinical Laboratory Values of Potential Clinical Relevance

Clinical Laboratory Tests	Criteria for Subjects 4 to 12 Years of Age[31,32,33]
Serum Chemistry	
AST	≥ 2 × ULN
ALT	≥ 2 × ULN
Alkaline phosphatase	≥ 2 × ULN
Blood urea nitrogen	≥ 24 mg/dL
Uric acid	≥ 6.7 mg/dL
Creatinine	≥ 1.4 mg/dL
Bilirubin (total)	≥ 1.6 mg/dL
Creatine phosphokinase	≥ 2 × ULN
Prolactin	≥ 21.00 ng/dL
Hematology	
Hematocrit	≤ 33 %
Hemoglobin	≤11.2 g/dL
White blood count	≤ 4.35 × 10^3/uL
Eosinophils	≥ 4.8%
Neutrophils	≤ 40.5%
Absolute neutrophil count	≤ 1.00 × 10^3/uL or ≥ 9.00 × 10^3/uL
Platelets	≤ 130 × 10^3/uL
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
Nonfasting	≥ 139 mg/dL
Total cholesterol, fasting	≥ 217 mg/dL
Low density lipoprotein cholesterol, fasting	≥ 130 mg/dL
High density lipoprotein cholesterol, fasting	≤ 34 mg/dL
Triglycerides, fasting	≥ 131 mg/dL
TSH	≤ 0.34 mIU/mL or ≥ 5.40 mIU/mL
Free T_4	≤ 9 pmol/L or ≥ 30 pmol/L
Prothrombin time	≥ 12.3 seconds
Activated partial thromboplastin time	≥ 29.4 sec
International normalized ratio Not taking anticoagulants Taking anticoagulants	 ≥ 1.2 ≥ 3.0

10.5 Appendix 5: Criteria for Identifying Vital Signs of Potential Clinical Relevance

Table 10.5-1 Criteria for Identifying Vital Signs Outside of Normal Range Values and of Potential Clinical Relevance

Variable	Criterion Value	Change Relative to Baseline
Heart Rate[34]	< 60 bpm or > 110 bpm	Increase or decrease of ≥ 15 bpm
Systolic Blood Pressure[35]		
4 - 5 year olds	< 80 mmHg or > 115 mmHg	Increase or decrease of ≥ 20 mmHg
6 - 9 year olds	< 85 mmHg or > 115 mmHg	Increase or decrease of ≥ 20 mmHg
10 - 12 year olds	< 90 mmHg or > 120 mmHg	Increase or decrease of ≥ 15 mmHg
Diastolic Blood Pressure[35]		
4 - 5 year olds	< 45 mmHg or > 80 mmHg	Increase or decrease of ≥ 15 mmHg
6 - 9 year olds	< 50 mmHg or > 80 mmHg	Increase or decrease of ≥ 15 mmHg
10 - 12 year olds	< 60 mmHg or > 80 mmHg	Increase or decrease of ≥ 15 mmHg

Note: 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.

10.6 Appendix 6: Criteria for Identifying Electrocardiogram Measurements of Potential Clinical Relevance

Table 10.6-1 Criteria for Identifying Electrocardiogram Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rhythm[36]		
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[36]		
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
Preexcitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 120 msec	increase of ≥ 20 msec
Infarction[36]		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post-trial entry
ST/T Morphological[36]		
Myocardial Ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc < 12 years ≥ 12 years	 QTcF ≥ 450 msec QTcF ≥ 460 msec	 increase of 60 msec from baseline

[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.

10.7 Appendix 7: 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 eICF will require similar modification. In such cases, after approval/favorable opinion of the new eICF by the IRB, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

10.7.1 Protocol Amendment(s)/Administrative Change(s)

10.7.1.1 Protocol Amendment 1

Amendment 1 Approval Date: 25 Jan 2021

PURPOSE:

The main purpose of this protocol amendment was to separate dosing in 4 to 5 year old subjects to occur following dosing in 6 to 8 year old subjects, add a BMI index cut-off to the inclusion criteria, update contraceptive requirements, update the exclusion criteria, add time points for safety assessments, add text to state that PK data may be summarized by mode of administration (intact capsule versus applesauce), add individual subject discontinuation criteria, and update text in the introduction section. Additionally, since the protocol was being amended, various other necessary updates and revisions were made, including:

- State that pregnancy tests will be only performed for female subjects in Cohort 1
- Remove the Weiss Functional Impact Rating Scale - Parent and Attention-deficit Hyperactivity Disorder Impact Module - Child scales
- Add the blood collection experience survey and SMWQ
- Delete the composition details for the XR capsules
- Change the duration for completion of the sleep diary
- Add text to allow a numbing agent to be used for the microsampling blood collection
- Update the FBR sample requirements
- Add criteria for identifying clinical laboratory values and ECG measurements of potential clinical relevance

BACKGROUND:

The protocol was amended to incorporate necessary updates to improve safety data collection and ensure consistency across centanafadine protocols. Most importantly, revise that older-age cohorts must be completed and safety/tolerance evaluated for each of these cohorts before dosing may commence for any younger-age cohorts, as well as separate dosing in 4 to 5 year old subjects to occur following dosing in 6 to 8 year old subjects. In addition, inclusion criterion number 7 and contraceptive requirements were updated; inclusion criterion number 11 was added to specify a BMI cutoff; exclusion criterion number 2 was updated to exclude subjects with a clinical presentation or history of psychotic symptoms; exclusion criterion number 28 was added to exclude subjects who have a history of clinically significant tachycardia or hypertension; safety assessment time points were added for vital signs, ECGs, and the C-SSRS; individual

subject discontinuation criteria were added; and criteria to identify clinical laboratory values and ECG measurements of potential clinical relevance were added.

To be consistent with the IB (Edition 9), the description of SAEs reported in centanafadine trials was updated.

To allow for the comparison of endpoints for subjects receiving intact capsules versus applesauce, text was added to state that PK data may be summarized by mode of administration.

It was specified that a pregnancy test will only be performed for subjects in Cohort 1 as pregnancy tests will only be required for subjects in this cohort.

The Weiss Functional Impact Rating Scale - Parent and Attention-deficit Hyperactivity Disorder Impact Module - Child scales were removed to reduce subject burden.

The blood collection experience survey was added to evaluate which approach to blood collection is better. The SMWQ was added to collect data around abuse potential for consistency with other centanafadine protocols.

The duration of the collection of the sleep diary was corrected.

The composition details for the XR capsule were deleted as this is proprietary information.

The PK background text describing Trial 405-201-00036 was updated for consistency with other centanafadine protocols.

The microsampling text was updated to state a numbing agent may be used, as it may be necessary to determine if a numbing agent has any effect on the concentration measurement.

The volume of blood required for FBR sampling, the tube to be used, and sample analysis text was updated per the requirements of the Laboratory Manual.

All other changes were made to improve overall clarity or correct typographical errors.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Separated dosing in subjects aged to 4 to 5 years to occur following dosing in subjects aged 6 to 8 years, and added text to state cohorts will be dosed sequentially.
- Clarified in the schedule of assessments that Day 21 is a follow-up telephone call.
- Removed the WFIRS-P and AIM-C scales from the protocol.
- Added vital sign assessments to be performed on Days 3 to 6 and Days 8 to 12 for in-clinic subjects, as well as Days 13 and 15 for all subjects.

- Added a footnote to the schedule of assessments to state that if a subject is released from the trial site clinic but returns to the trial site clinic on Days 3 to 6 or Days 8 to 12, the assessments planned for in-clinic subjects should also be performed for the subject on those days.
- Added an ECG measurement at 8 hours postdose on Day 14.
- Added C-SSRS assessments on Days 2 and 13.
- The completion of the sleep diary was changed from being completed throughout the trial to being completed from Day −1 to Day 14. The row for the sleep diary was also moved to the safety assessments section of the schedule of assessments.
- A SMWQ was added on Days 15, 16, and 21.
- A blood collection experience survey was added on Days 1, 2, 14, and 15 following collection of the blood samples for PK analysis (including using the microsampling technique).
- The PK background text describing Trial 405-201-00036 in the introduction was updated and Figure 2.2.1-1 was replaced.
- The text in the introduction describing the SAEs reported in centanafadine trials was updated.
- Updated exclusion criterion number 1 and text in the protocol to state pregnancy tests will only be performed for female subjects in Cohort 1.
- Updated inclusion criterion number 7 and text in the protocol to state that all subjects will take effective measures to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP.
- Inclusion criterion number 11 was added to include subjects with a BMI ≥ the fifth percentile of the Centers for Disease Control and Prevention clinical growth charts for age and sex.
- Exclusion criterion number 2 was updated to exclude subjects with a clinical presentation or history of psychotic symptoms.
- Exclusion criterion number 28 was added to exclude subjects who have history of clinically significant tachycardia or hypertension.
- The composition details for the XR capsule were deleted.
- Added text to allow a numbing agent to be used for the microsampling blood collection.
- Added individual subject discontinuation criteria.
- Added appendices summarizing the criteria for identifying clinical laboratory values and ECG measurements of potential clinical relevance.
- Clarified that the subject diary will be completed using the AiCure platform.
- Deleted text from the footnotes of the schedule of assessments that was already referred to and stated in the body of the protocol.

- Changed the volume of blood for the FBR sample from 2.5 to 4 mL, the sample tube from a PaxGene RNA tube to a K_2EDTA tube, and specified that the sample will be for DNA analysis. Deleted text describing the sample for measurement of proteins, sugars, and other molecules.
- Added text to state concentration and PK data may be summarized by mode of administration (intact capsule versus applesauce) based on the data.
- Fixed typographical errors.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

10.7.1.2 Protocol Amendment 2

Amendment 2 Approval Date: 09 Feb 2022

PURPOSE:

The purpose of this protocol amendment was to update information regarding the use of 405-201-00010 trial data to inform the current trial, to update 405-201-00010 trial status, and to update the weight-based dosing for subjects in Cohorts 2 to 5. Other revisions were made to present updated safety information following centanafadine administration in phase 1, phase 2, and phase 3 trials, to add a description of a previous centanafadine trial, to omit PK blood sample collection using a microsampling technique in subjects in Cohorts 2 to 5, and to revise the table with potential clinical relevance criteria for laboratory values.

BACKGROUND:

The protocol was revised to update information regarding Trial 405-201-00010 status and the use of trial data, as Trial 405-201-00010 will be discontinued and safety and tolerability data from Trial 405-201-00010 will not be utilized to inform dosing of 4- to 5-year-old subjects in Trial 405-201-00046. The protocol was amended to update the weight-based dosing information to reflect administration of the final QD XR capsule formulation to subjects in Cohorts 2 to 5; results from healthy adult subjects (Trial 405-201-00047) indicated that, following manufacturing at a larger scale than the batch sizes used in Trial 405-201-00037, bioavailability of centanafadine was increased and a dose reduction of approximately 20% (210 mg to 164.4 mg) would produce concentrations comparable to the SR tablet 200 mg total daily dose.

PK blood sample collection using a microsampling technique was omitted, as early results from Cohort 1 and from other studies indicated that concentrations in blood

microsamples from children were not correlating well with venous plasma sample concentrations so this line of enquiry has been stopped.

As additional safety information has become available, the protocol was updated to present the current safety results. The table presenting criteria for identifying clinical laboratory values of potential clinical relevance was updated for accuracy.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Specified that centanafadine XR and centanafadine QD XR will be administered during the trial.
- Specified that safety and tolerability data from 6- to 12-year-old subjects in Trial 405-201-00010 will be leveraged in the current trial.
- Stated that trial 405-201-00010 will be discontinued.
- Updated the status of the 405-201-00010 trial to indicate that the first 3 cohorts in subjects aged 9 to 12 years, inclusive, have been completed and the data reviewed, and the 100-mg adult equivalent dose cohort of subjects aged 6 to 8 years, inclusive, has been completed and the data reviewed.
- Updated the most commonly reported TEAEs, all reported SAEs, and rash events to present data from all completed trials. Revised text to indicate that centanafadine may be associated with increases in blood pressure and heart rate as well as orthostatic blood pressure changes without specifying that this was based on phase 2 trial data.
- Added a description of the 405-201-00047 trial and background information regarding centanafadine QD XR, which is to be administered to subjects in the 6- to 8-year-old cohorts and in the 4- to 5-year-old cohorts.
- Updated text to indicate that the dose strength and weight bins were selected such that the exposures are within 34% of the expected exposures from allometric scaling.
- Indicated that dosing decisions for 4- and 5-year-old subjects will be based on data from this trial only, as development of the BID formulation used in Trial 405-201-00010 is being discontinued in favor of development of a once daily formulation.
- Included the capsule strengths for IMP supplied for Cohort 1 and for Cohorts 2 to 5.
- Specified that the original weight bins and 400-mg adult equivalent doses identified were applicable to Cohort 1 (Table 6.1-1). Included revised weight bins and 200 mg and 400-mg adult equivalent doses to be administered to subjects in Cohorts 2 to 5 based on the new centanafadine QD XR formulation (Table 6.1-2).
- Specified that PK blood sample collection using a microsampling technique will be performed for subjects in Cohort 1 only.
- The normal ranges were removed from the table presenting criteria for identifying clinical laboratory values of potential clinical relevance.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

10.7.1.3 Protocol Amendment 3

Amendment 3 Approval Date: 25 Jul 2022

PURPOSE:

The purpose of this protocol amendment was to include an additional cohort of up to 12 subjects aged 9 to 12 years to be administered the 400-mg weight-adjusted adult equivalent dose of centanafadine QD XR.

BACKGROUND:

The inclusion of a cohort to test the centanafadine QD XR formulation in the 9-to-12-year age group will provide dense PK sampling information on the same formulation being used in the ADHD pivotal trials for this age group.

MODIFICATIONS TO PROTOCOL:

- Text has been revised throughout to include Cohort 6 where applicable.
- The PK analysis section has been corrected to indicate that dried blood samples rather than plasma samples collected from microsampling in Cohort 1 subjects will be summarized by treatment day and time point.
- The Schedule of Assessments and relevant body text of the protocol were revised to indicate that the Blood Collection Experience Survey is only applicable to Cohort 1.
- The Known and Potential Risks and Benefits section was revised to include new serious adverse events that have occurred in other trials since this trial was initiated.
- Clarified that CGI-S results will be presented by age and dose.
- Minor typographical and grammatical issues have been corrected.

ADDITIONAL RISK TO THE SUBJECT:

The updated safety profile is still acceptable so there is no additional risk to subjects.

10.7.1.4 Protocol Amendment 4

Amendment 4 Approval Date: 15 Sep 2022

PURPOSE:

The purpose of this protocol amendment was to update exclusion criterion 1 for breast-feeding and pregnancy to be applicable to females in Cohort 6 and to update exclusion criterion 17(f) for serum creatinine to ≥ 1.4 mg/dL from 0.7 mg/dL.

This protocol amendment was also to revise the required period from 30 days to 90 days following the last dose of IMP for male subjects and their partners who are of childbearing potential to practice 2 different approved methods of birth control or remain fully abstinent, and to report a pregnancy.

BACKGROUND:

The pregnancy testing was updated to be applicable for females in both Cohorts 1 and Cohort 6 since both cohorts have subjects 9 to 12 years of age.

The creatinine exclusion criteria was broadened because additional safety information in pediatric subjects indicate that centanafadine has no effect on renal function, suggesting that there is no increased risk in broadening the criteria. The amended criteria allows for a broader evaluation of the pediatric population with ADHD to be representative to inform product review for marketing authorization. Further, the criteria are consistent with other pediatric trials in the centanafadine clinical development program, enabling rollover of subjects from Trial 405-201-00046 to the long term safety trial, 405-201-00017.

The required time period for male abstinence, contraception, and reporting a pregnancy was updated to encompass a minimum one sperm cycle (defined as 90 days).

MODIFICATIONS TO PROTOCOL:

- Exclusion criterion number 1 was updated to exclude females who are breast-feeding and/or who have a positive pregnancy test result in Cohort 6 prior to receiving IMP, in addition to those previously covered in Cohort 1. The applicable change was updated globally.
- Exclusion criterion number 17(f) was updated to exclude subjects with creatinine ≥ 1.4 mg/dL. This change was also updated in Appendix 4, Table 10.4-1 (Criteria for Identifying Clinical Laboratory Values of Potential Clinical Relevance).
- The required period following the last dose of IMP for male subjects and their partners who are of childbearing potential to practice 2 different approved methods of birth control or remain fully abstinent was updated from 30 to 90 days globally.
- The required period following the last dose of IMP for male subjects and their

- partners who are of childbearing potential to report a pregnancy was updated from 30 days to 90 days.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to subjects.

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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 in eSource 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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