Official Title:	**A Phase 3, Randomized, Double-blind, Multicenter, Placebo-controlled, Parallel-group Trial Evaluating the Efficacy, Safety, and Tolerability of Centanafadine Sustained-release Tablets in Adults With Attention-deficit/Hyperactivity Disorder**
NCT Number:	NCT03605680
Document Date:	Protocol Version 4.0: 15 January 2020

Otsuka Pharmaceutical Development & Commercialization, Inc

Investigational Medicinal Product

Centanafadine (EB-1020)

REVISED CLINICAL PROTOCOL

A Phase 3, Randomized, Double-blind, Multicenter, Placebo-controlled, Parallel-group Trial Evaluating the Efficacy, Safety, and Tolerability of Centanafadine Sustained-release Tablets in Adults with Attention-deficit/Hyperactivity Disorder (Trial 405-201-00013)

Protocol No. 405-201-00013
IND No. 119361

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	Syneos Health Research Pharmacovigilance & Drug Safety Fax: [redacted] E-mail: [redacted]
Issue Date:	8 Mar 2018
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Protocol 405-201-00013

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Centanafadine (EB-1020)	Protocol No.: 405-201-00013 IND No.: 119361
Protocol Title:	A Phase 3, Randomized, Double-blind, Multicenter, Placebo-controlled, Parallel-group Trial Evaluating the Efficacy, Safety, and Tolerability of Centanafadine Sustained-release Tablets in Adults with Attention-deficit/Hyperactivity Disorder (Trial 405-201-00013)
Clinical Phase/Trial Type:	3
Treatment Indication:	Adult Attention-deficit/Hyperactivity Disorder (ADHD)
Objective(s):	Primary: To confirm the efficacy of centanafadine sustained-release (SR) tablets administered twice-daily (BID; 200 mg or 400 mg total daily doses [TDDs]) compared to placebo in the treatment of adults with ADHD Secondary: To confirm the safety and tolerability of centanafadine SR tablets administered BID (200 mg or 400 mg TDDs) compared to placebo in the treatment of adults with ADHD
Trial Design:	This trial is a phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial to confirm the efficacy, safety, and tolerability of centanafadine SR (200 mg TDD or 400 mg TDD) compared to placebo for the treatment of adults with ADHD. The trial will have 4 periods: (1) screening and washout; (2) 1-week single-blind placebo run-in; (3) 6-week double-blind treatment; and (4) 7-day follow-up period (follow-up telephone calls at 1, 3, and 5 days after the last dose of investigational medicinal product (IMP), and in-clinic visits 2 and 7 days after the last dose of IMP) for subjects who complete the trial, and decide to enroll in Trial 405-201-00015. For subjects who terminate early, decide to not enroll in Trial 405-201-00015, or who are not eligible to enroll in Trial 405-201-00015, they will be required to participate in the 7-day follow-up period as well as participate in an additional follow-up telephone call 10 days after the last dose of IMP. Subjects randomized to receive a TDD of 200 mg centanafadine SR will start at their target dose at the start of the double-blind treatment period.

	Subjects randomized to receive 400 mg TDD centanafadine SR will start the double-blind treatment period at the TDD of 200 mg centanafadine SR for 7 days, before they are escalated to their target TDD of 400 mg for a total of approximately 42 days of treatment. Subjects will be required to visit the site up to 12 times over the trial. Subjects who complete both the 6-week double-blind treatment period and the 7-day follow up (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, and in-clinic visits 2 and 7 days after the last dose of IMP), and refrain from using prohibited medications after the IMP is stopped may be eligible to enroll into Trial 405-201-00015, which is a 12-month, observational, open-label trial to evaluate the long term safety and tolerability of subjects with ADHD who previously participated in Trials 405-201-00013 or 405-201-00014. Subjects who terminate early, decide to not enroll in Trial 405-201-00015, or who are not eligible to enroll in Trial 405-201-00015, will be required to participate in the 7-day follow-up period as well as participate in an additional follow-up telephone call 10 days after the last dose of IMP. For subjects who early terminate or decline participation in the open-label trial, they will be instructed to refrain from utilizing prohibited concomitant medications (Section 4.1), including ADHD treatments, until after the follow-up telephone call 10 days after the last dose of IMP.
Subject Population:	A total of up to 1150 male and female subjects with current diagnosis ADHD and between the ages of 18 and 55 years, inclusive, are planned to be screened in order to randomize approximately 450 subjects to yield 292+ completers. Subjects must meet the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria for ADHD (including predominantly inattentive presentation, hyperactive presentation, or combined presentation) as confirmed by the Adult ADHD Clinical Diagnostic Scale (ACDS) Version 1.2. To confirm that ADHD is the primary diagnosis, the Mini International Neuropsychiatric Interview (MINI) will be used to identify and exclude other psychiatric conditions which would preclude enrollment.

	Subjects who were not receiving any pharmacological treatment for ADHD must have an Adult ADHD Investigator Symptom Rating Scale (AISRS) score of ≥ 28 at screening and baseline. Subjects who were receiving pharmacological treatment for ADHD at screening must have a minimum AISRS score of ≥ 22 at screening, and a score of ≥ 28 at baseline. All subjects must be willing to discontinue all prohibited psychotropic medications (Section 4) starting from the time of signing the informed consent through the 7-day follow-up period. Subjects that do not rollover into Trial 405-201-00015 must be willing to discontinue all prohibited psychotropic medications starting from the time of signing the informed consent until after the follow-up telephone call 10 days after the last dose of IMP. Subjects must have a Clinical Global Impression-Severity of Illness Scale (CGI-S) score of ≥ 4 (≥ moderate impairment) at baseline.
Inclusion/Exclusion Criteria:	Key inclusion criteria are described under Subject Population in this synopsis. Key exclusion criteria include the following: **Screening:** • Subject has a DSM-5 diagnosis of Other Specified or Unspecified Attention Deficit/Hyperactivity Disorder. • Subject has a current comorbid psychiatric disorder that either could be expected to require treatment with medications prohibited in this trial, or to confound efficacy or safety assessments. Examples include, but are not limited to, psychotic disorder (current or lifetime), bipolar disorder (current or lifetime), generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, a current major depressive episode, or posttraumatic stress disorder, as established by the MINI. • In the opinion of the investigator, subject has not derived significant therapeutic benefit from 2 or more ADHD therapies of 2 different classes (eg, amphetamine and methylphenidate, or amphetamine and atomoxetine) given with an acceptable dose and duration during adulthood (aged 18 or older). NOTE: If subject has not derived significant therapeutic benefit due to an inability to tolerate side effects, eligibility can be discussed on case-by-case basis with the medical monitor.

	• Subjects that have a positive alcohol test (via breathalyzer or blood), a positive drug screen for cocaine, or other illicit drugs (excluding marijuana). Subjects with a positive drug screen for confirmed prescription or over-the-counter (OTC) use of ADHD medications at screening will be required to undergo a washout period. NOTE: Subjects that test positive for marijuana may be permitted to be enrolled if they have no evidence of a substance use disorder, and if they agree to refrain from use for the duration of the trial. Allowance for subjects testing positive for marijuana at screening require explicit approval from the medical monitor. **Single-blind placebo run-in:** • Subjects who have a positive alcohol test (via breathalyzer or blood), a positive drug screen assessed prior to Visit 2 for cocaine, other illicit drugs (including marijuana), or prescription or OTC ADHD medications will be screen failed. This includes medications such as opioids or benzodiazepines taken without prescription. • Subjects with a ≥ 30% improvement in the (18 item) ADHD Symptoms score of the Adult ADHD Self Report Scale (ASRS) compared with the score at screening will be screen failed, and not eligible for rescreening. **Baseline:** • Subjects who have a positive alcohol test (via breathalyzer or blood), a positive drug screen assessed prior to the baseline visit for cocaine, other illicit drugs (including marijuana), or prescription or OTC ADHD medications will be early terminated. This includes medications such as opioids or benzodiazepines taken without prescription. • Subjects with a ≥ 30% improvement in the (18 item) ADHD Symptoms score of the ASRS compared with the score at the start of single-blind placebo run-in will be early terminated. • In the opinion of the investigator, the subject is unable to adhere to the treatment regimen or other requirements outlined in the protocol.
Trial Site(s):	The trial is expected to enroll subjects at approximately 40 sites in the United States.

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Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:

The IMP will be supplied as weekly blister cards. All subjects will begin oral BID dosing with single-blind matching placebo on Visit 2 (Day −7) and continue through Visit 3 (baseline).

Trial assignments for the double-blind treatment period will be made once eligibility is confirmed. Eligible subjects will be randomized in a 1:1:1 ratio at baseline (Visit 3) to one of the following 3 treatment groups:

- Centanafadine SR 200 mg
- Centanafadine SR 400 mg
- Matching placebo

Subjects randomized to receive the target TDD of 200 mg centanafadine SR will start at the target dose on Day 1 of the double-blind treatment period and remain there for the duration of the trial. Subjects randomized to receive a TDD of 400 mg centanafadine SR will receive a TDD of 200 mg centanafadine SR on Day 1 of the double-blind treatment period for 7 days before they are escalated to their target TDD of 400 mg on Day 8 for the duration of the trial.

		Total Daily Dose	
Day(s)	**Time**	**200 mg Target**	**400 mg Target**
1 through 7	2 tablets orally in morning	1 × 100 mg + 1 × PBO tablet	1 × 100 mg + 1 × PBO tablet
	2 tablets orally 4-6 hr later	1 × 100 mg + 1 × PBO tablet	1 × 100 mg + 1 × PBO tablet
8 and thereafter	2 tablets orally in morning	1 × 100 mg + 1 × PBO tablet	2 ×100 mg
	2 tablets orally 4-6 hr later	1 × 100 mg + 1 × PBO tablet	2 ×100 mg

PBO = placebo.

Neither the investigator nor the subject will be aware of the treatment assignment after randomization. All doses of centanafadine SR and matching placebo should be taken orally BID and can be administered without regard to meals, and should be taken at approximately the same time each day, with the first dose taken in the morning. The second dose should be taken 4 to 6 hours after the morning dose is administered.

The total duration of the double-blind treatment period will be 6 weeks for all randomized subjects.

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Trial Assessments:	*Efficacy*: AISRS, CGI-S, Clinical Global Impression (CGI) Change from Baseline *Pharmacokinetic*: Sparse pharmacokinetic (PK) samples will be taken for determination of concentrations of centanafadine and metabolite(s) in plasma on Days 7, 14, 28, 42/end of treatment/early termination (ET), and 49/7-day follow-up. Samples collected at Day 14 and Day 42/ET should be taken concurrently with the serum chemistry sample. *Safety*: Adverse event (AE) reporting (including evaluations for rash, AEs related to abuse potential, and AEs involving medication handling irregularities), clinical laboratory tests, physical examinations, vital sign measurements, electrocardiograms (ECGs), assessments of withdrawal (Study Medication Withdrawal Questionnaire [SMWQ]), and suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]). *Screening/Other*: ADHD Impact Module - Adult (AIM-A) and ASRS. A whole blood sample to extract deoxyribonucleic acid (DNA) for genotyping and a future biospecimen research sample will be collected at baseline.
Criteria for Evaluation:	**Primary Efficacy Endpoint:** The primary efficacy endpoint is the change from baseline at Day 42 in the AISRS total score. **Key Secondary Efficacy Endpoint:** The key secondary efficacy endpoint is change from baseline at Day 42 on the CGI-S. **Other Efficacy Endpoints:** • Change from baseline in AISRS total score for every scheduled visit; • Change from baseline in the Inattentive subscale and Hyperactivity-Impulsive subscale scores of the AISRS for every scheduled visit; • Change from baseline in CGI-S score for every scheduled visit; • CGI Change from Baseline score at each scheduled visit; • Percentage of responders at each post-baseline visit, where a responder is defined as a subject with a CGI Change from Baseline score of 1 or 2 OR a ≥ 30% improvement in ADHD symptoms compared with baseline as measured by the AISRS total score.

	Exploratory Efficacy Endpoints: The exploratory endpoints are the change from baseline to Day 28 and Day 42 in the AIM-A and the ASRS total score and subscale scores. **Safety Endpoints:** Standard safety variables will include AEs (including evaluations for rash, AEs related to abuse potential, and AEs involving medication handling irregularities), clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, vital sign measurements, ECGs, assessments of withdrawal (SMWQ), and suicidality (C-SSRS). Abuse-related AEs and AEs involving medication irregularities will be recorded verbatim on source documentation with detailed narratives.
Statistical Methods:	A sufficient number of subjects will be enrolled and randomized to achieve approximately 405 evaluable subjects in the double-blind treatment period (ie, subjects with an AISRS total score at baseline and at least 1 subsequent AISRS total score in the double-blind treatment period). After allowance of 10% nonevaluable subjects in the double-blind treatment period, the total number of subjects to be randomized is 450 subjects (150 subjects in each treatment arm). In order to ensure 405 evaluable subjects, the number of nonevaluable subjects will be monitored in a blinded manner on an ongoing basis during the trial. The power and sample size were obtained using the PASS 14 (2015) statistical computing software. The primary efficacy endpoint is the change from baseline to Day 42 in AISRS total score. The estimand for the primary efficacy analysis is the difference in outcome improvement if all subjects tolerated and adhered to their treatment. This approach is Estimand #3, recommended by the 2010 National Academy of Sciences' National Research Council report on prevention and treatment of missing data and International Council for Harmonisation E9 (R1) "Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials". This estimand focuses on the efficacy of centanafadine (SR 200mg TDD or SR 400mg TDD) in change from the baseline in AISRS total score. The objective of this trial is consistent with the election of an efficacy rather than effectiveness estimand.

	The primary efficacy analysis will be performed by fitting a mixed-effect model repeated measures analysis with an unstructured variance covariance structure in which the change from baseline in AISRS total score at the scheduled double-blind treatment period visits will be the dependent variable based on the observed-case data set. The model will include fixed class effect terms for treatment, trial center, visit day, and an interaction term of treatment by visit day. The model will also include baseline values of AISRS total score and the interaction term of baseline values of AISRS total score by visit day as covariates. The primary comparison between the centanafadine (200 mg TDD or 400 mg TDD group) and the placebo group at Day 42 in the double-blind treatment phase will be estimated as the difference between Least Squares means utilizing the computing software SAS procedure PROC MIXED. The comparison between centanafadine 200 mg TDD or 400 mg TDD group and placebo group will be tested at a significance level of 0.05 (2-sided) in the order of 1) 400 mg versus placebo, and 2) 200 mg versus placebo. Additional details will be provided in the statistical analysis plan (SAP). Based on the results at various dose strengths from phase 2 centanafadine trials, it is reasonable to expect a treatment difference of 5 points with a standard deviation (SD) of 12.5 in the mean change from baseline to Day 42 on AISRS total score in either the 200 mg TDD or 400 mg TDD arms. The planned sample size of 405 evaluable subjects (135 in each treatment arm) will yield at least 90% power to detect the treatment effects at a 2-tailed significance level of 0.05. The 2-sided alpha level for the final analysis is 0.05. Descriptive statistics will be provided for all efficacy and safety variables in general. Continuous variables will be summarized by tabulations of mean, median, range, and SD. Tabulations of frequency distributions will be provided for categorical variables.

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Trial Duration:	A total of up to 1150 male and female subjects are planned to be screened in order to randomize approximately 450 subjects to yield approximately 292 completers. Individual participation for all subjects in the trial is 12 to 13 weeks, consisting of an up to 28-day screening period, a 1-week single-blind placebo run-in period, a 6-week double-blind treatment period, and a 7-day follow-up period (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, and in-clinic visits 2 and 7 days after the last dose of IMP) for all subjects. For subjects who early terminate or decline participation in the open-label trial, they will be required to participate in an additional follow-up telephone call 10 days after the last dose of IMP.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACDS	Adult ADHD Clinical Diagnostic Scale
ADHD	Attention-deficit/hyperactivity disorder
ADHD-RS-IV	ADHD Rating Scale Version IV
AE	Adverse event
AESI	Adverse event of special interest
AIM-A	ADHD Impact Module - Adult
AISRS	Adult ADHD Investigator Symptom Rating Scale
ALT	Alanine aminotransferase
Anti-HCV	Hepatitis C antibodies
APMP	Abuse Potential Monitoring Plan
ASRS	Adult ADHD Self Report Scale
AST	Aspartate aminotransferase
BID	Twice daily
BMI	Body mass index
CGI	Clinical Global Impression
CGI-S	Clinical Global Impression-Severity of Illness Scale
CMH	Cochran Mantel Haenszel
CPK	Creatine phosphokinase
CRO	Clinical research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CST	Clinical Surveillance & Training
CTN SR	Centanafadine sustained release
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
eICF	Electronic informed consent form
ESAM	Events Subject to Additional Monitoring
ET	Early termination
FAS	Full Analysis Set
FBR	Future biospecimen research
FDA	Food and Drug Administration
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
GEE	Generalized estimating equations
HbA_{1c}	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HDL	High-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus

IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRE	Immediately reportable event
ITT	Intent-to-treat
LOCF	Last-observation-carried-forward
LDL	Low-density lipoprotein
LOE	Lack of efficacy
MAR	Missing at random
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MHI	Medication handling irregularities
MI	Multiple Imputation
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed-effect model repeated measures
MNAR	Missing not at random
OC	Observed-case
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc
OTC	Over-the-counter
PBO	Placebo
PK	Pharmacokinetic
PQC	Product Quality Complaint
PT	Prothrombin time
QTcB	QT interval corrected for heart rate by the Bazett formula
QTcF	QT interval corrected for heart rate by the Fridericia formula
QTcN	QT interval corrected for heart rate by the FDA Neuropharm Division formula
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SMWQ	Study Medication Withdrawal Questionnaire
SR	Sustained release
T4	Thyroxine
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
UDS	urine drug screen
ULN	Upper limit of normal
US	United States
WBC	White blood cell

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1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is an increasingly recognized and heterogeneous disorder characterized by 3 core symptoms of hyperactivity, inattentiveness, and impulsivity.[1] Depending on the ADHD subtype, sex, and presence of comorbid disorders, individuals with ADHD may display considerably different symptomatology, even within a particular age cohort.[2]

Although ADHD is still considered primarily a childhood disorder, the advent of consensus diagnostic criteria for ADHD in conjunction with more rigorous prospective research has documented the persistence of this disorder into adolescence in up to 70% and into adulthood in up to 66% of childhood cases.[3,4] More recently, 2 follow-up trials of children with ADHD from child mental health clinics in southeast England and the Netherlands showed persistence of ADHD into young adulthood in 79% to 86.5% of individuals, respectively.[5,6] Long-term follow-up trials report the persistence of this disorder into adulthood in as many as 65% of childhood cases.[7,8] There is mounting evidence that supports adult ADHD is a combination of both childhood ADHD persisting into adulthood and adult-onset ADHD without childhood diagnosis.[9] Fayyad et al (2007) estimated adult (18 to 44 years) ADHD prevalence determined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria to be 3.4%.[10] Kessler et al (2006) determined adult ADHD prevalence to be 4.4% using the National Comorbidity Survey Replication, a lay-administered household survey.[11]

The exact pathophysiology of ADHD remains uncertain although it is believed that a dysregulation of neurotransmitters, specifically dopamine and norepinephrine, in the frontostriatal region of the brain are involved.[12,13] This hypothesis is based primarily on knowledge of the mechanism of action of drugs found to be effective in treating ADHD and further supported by molecular genetics and neuroimaging studies.[12,14] Environmental and perinatal complications may also be contributing factors.[15,16]

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[17] and alpha-adrenergic agonists such as guanfacine and clonidine.[18] Stimulants have a rapid onset of action in ADHD, are effective in all 3 core deficits of the disorder[17], and have a response rate of about 70%.[19] However, their usefulness is limited by adverse reactions, by lack of effect on or exacerbation of comorbidities, and by abuse

liability (ie, risks of abuse, dependence, and diversion) with resultant drug prescribing restrictions.[17]

The first nonstimulant drug approved in the United States (US) was atomoxetine. Although atomoxetine is an acceptable option for some patients with ADHD, it is generally less effective than treatment with stimulant therapy. In an atomoxetine/methylphenidate comparison trial, the response rate for atomoxetine was superior to placebo, 45% to 24%, respectively. However, the response rate for methylphenidate was superior to atomoxetine (56% to 45%).[20] In addition, atomoxetine is associated with cardiovascular and nervous system adverse events (AEs) and has a boxed warning from the Food and Drug Administration (FDA) for increased risk of suicidal ideation in children or adolescents.[21]

Immediate-release 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.[22] In addition, patient responses to alpha-2 adrenergic agonists have been shown to be not as strong as stimulants. An effect size of 0.58 for clonidine was seen compared to 0.82 for stimulants in a meta-analysis of ADHD treatment trials. Therefore, as a first line treatment immediate release alpha-2 adrenergic agonists are usually not considered for ADHD.[23,24]

Clinical data available to date suggest that centanafadine sustained release (SR) has the potential to be more effective than nonstimulant therapies, with a better side-effect profile, and lower abuse potential than currently available stimulant therapies. In the current trial a 200 mg and a 400 mg total daily dose (TDD) of centanafadine SR will be evaluated against placebo.

Please refer to the Investigator's Brochure (IB) for more detailed information about the investigational medicinal product (IMP).[25]

1.1 Nonclinical Data

A complete description of the available efficacy and safety pharmacology data from nonclinical studies, including pharmacokinetic (PK) and toxicology studies in different animal species can be found in the current IB.[25]

1.2 Clinical Data

As of the IB data cutoff of 1 Apr 2017, 7 clinical trials in 260 subjects have been conducted with centanafadine. A total of 140 healthy subjects or recreational stimulant users received centanafadine in five phase 1 trials and 120 subjects with ADHD received centanafadine in two phase 2 trials.

Data from the 2 completed phase 2 trials (EB-1020-SR-ADHD-201 and NVI-EB-1020-202) demonstrated the efficacy of centanafadine SR in the treatment of adult subjects with ADHD. Trial EB-1020-SR-ADHD-201 was an exploratory, single-blind pilot trial to evaluate flexible doses (100 to 500 mg) of centanafadine SR. Trial NVI-EB-1020-202 was a randomized, double-blind, multicenter, 2-period, 2-treatment, crossover trial. Due to tolerability issues observed at high doses of centanafadine SR (800 and 600 mg), the trial was amended to the maximum TDD of 400 mg for further evaluation. For both trials, there was a statistically significant difference in the primary endpoint using the adult ADHD Rating Scale Version IV (ADHD-RS-IV) for subjects that received centanafadine SR compared to placebo ($p < 0.001$). Safety data collected from the complete phase 2 trials indicated that centanafadine SR is well tolerated up to 400 mg in subjects with ADHD.

Please refer to the IB for a detailed summary of available clinical data.[25]

1.3 Known and Potential Risks and Benefits

Based on the IB, data from the completed phase 1 and 2 trials indicate that centanafadine is safe and well-tolerated in healthy adult subjects and adult subjects with ADHD. Data from the completed phase 2 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 ADHD-RS-IV. 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. The abuse potential for centanafadine is continuing to be evaluated.

Seven clinical trials in 260 healthy adult subjects and adult subjects with ADHD have been conducted with centanafadine. A total of 140 healthy adult subjects received centanafadine in 5 phase 1 trials and 120 adult subjects with ADHD received centanafadine in 2 phase 2 trials. The most common AEs reported in trials with centanafadine SR at TDDs ranging from 25 to 800 mg were gastrointestinal (nausea, diarrhea, and dry mouth), metabolism/nutrition-related (decreased appetite), and nervous system disorders (headache, dizziness, and insomnia). In general, these AEs were mild and resolved. To date, 1 serious AE (SAE) (ischemic cardiovascular accident) occurred in

a subject with ADHD (initial dosage of centanafadine SR 100 mg, titrated to 500 mg) 6 days after completing treatment, but it was not considered related to centanafadine treatment.

Based on the outcome of the phase 2 trials, treatment with centanafadine may be associated with increases in blood pressure, heart rate and 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 has been observed in subjects who received centanafadine. One subject experienced mild rash that was considered related to treatment after taking 500 mg centanafadine SR TDD for 4 days (Trial NVI-EB-1020-201). The rash resolved in 8 days with no change in the dose and the subject completed the trial. Eight subjects reported rash after multiple doses of centanafadine SR in Trial NVI-EB-1020-202. Rashes resulted in discontinuation of dosing for 5 subjects and dose interruption or dose reduction for 3 subjects. The severity of the rash in subjects who discontinued IMP ranged from moderate to severe. The majority of subjects who experienced rash were exposed to doses greater than 400 mg/day (2 subjects received 800 mg/day; 4 subjects received 600 mg/day; 2 subjects received 400 mg/day). Neither subject who received 400 mg/day discontinued dosing due to the rash nor were the rashes in these subjects consistent with the drug eruptions seen in subjects who received 600 mg or 800 mg. All of the rashes were nonserious and all but one resolved within 12 days of treatment with IMP withdrawal or dose reduction. The one exception was a severe rash lasting over 2 months that was considered likely due to an existing cutaneous condition and exacerbated by the drug eruption. The dermatologic experts who reviewed these AEs concluded that none exhibited a profile consistent with a rash that would progress to a serious or otherwise life-threatening AE.

Considering that rash can be a sign of an allergic reaction, subjects 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 (see Section 5.4). A comprehensive rash monitoring plan will be followed.

Please refer to the IB for more detailed information about the known and potential risks and benefits of centanafadine.[25]

2 Trial Rationale and Objectives

2.1 Trial Rationale

This phase 3 registrational trial, in conjunction with other registrational trials, is part of the centanafadine clinical development program that has been designed to confirm the efficacy and safety of centanafadine for the treatment of adults experiencing ADHD symptoms. As efficacy is dependent on both treatment duration and dose, a fixed-dose, parallel-group approach represents the optimal trial design to evaluate efficacy.

This trial is being conducted to obtain information on the efficacy, safety, and tolerability of TDDs of 200 mg and 400 mg centanafadine SR compared to placebo in adults with ADHD. A double-blind, randomized design will be used to minimize bias while collecting data and when interpreting the results. A single-blind placebo run-in will also be used to exclude likely placebo responders before randomization to minimize the impact of a placebo-effect on determining the efficacy of centanafadine SR on ADHD symptoms during the double-blind treatment period.

2.2 Dosing Rationale

In the current trial, centanafadine will be administered twice daily (BID) as multiple 100 mg SR tablets to achieve TDDs of 200 mg or 400 mg.

In the phase 2 NVI-EB-1020-202 trial, centanafadine SR was initially administered at a target dose of 800 mg/day. This dose was revised down to 600 mg/day given the incidence of gastrointestinal AEs and 3 reported cases of rash. After an additional 5 cases of rash were reported at the revised maximal dose of 600 mg/day centanafadine SR, the dose was further reduced to 400 mg/day. The primary endpoint, ADHD-RS-IV total score, was met in subjects that received 400 mg TDD centanafadine compared to those that received placebo ($p < 0.001$). Given the separation of 400 mg centanafadine from placebo, and the positive benefit/risk profile, it was concluded that the maximum tolerated dose is 400 mg/day. A TDD of 400 mg centanafadine will be included in this trial to further confirm the efficacy, safety, and tolerability of the previously-established maximum tolerated dose.

During the NVI-EB-1020-202 trial, subjects that received 100 to 200 mg/day while titrating up to the maximum dose of centanafadine exhibited a statistically significant separation from placebo at Day 7 ($p < 0.001$), suggesting a TDD of 200 mg centanafadine may also be effective for the treatment of ADHD symptoms. A TDD of 200 mg

centanafadine will be included in this trial to further explore the efficacy, safety, and tolerability of a minimum effective dose of centanafadine.

Please refer to the IB for additional information about the IMP.[25]

2.3 Trial Objectives

Primary: To confirm the efficacy of centanafadine SR tablets administered BID (200 mg or 400 mg TDDs) compared to placebo in the treatment of adults with ADHD

Secondary: To confirm the safety and tolerability of centanafadine SR tablets administered BID (200 mg or 400 mg TDDs) compared to placebo in the treatment of adults with ADHD

3 Trial Design

3.1 Type/Design of Trial

This trial is a phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial to confirm the efficacy, safety, and tolerability of centanafadine SR (200 mg TDD or 400 mg TDD) compared to placebo for the treatment of adults with ADHD. The trial population will include male and female subjects 18 to 55 years of age (inclusive) with a current diagnosis of ADHD as confirmed by the Adult ADHD Clinical Diagnostic Scale (ACDS) Version 1.2 at screening.

The trial will have 4 periods: (1) screening and washout; (2) 1 week single-blind placebo run-in; (3) 6-week double blind treatment; and (4) 7-day follow-up period (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, and in-clinic visits 2 and 7 days after the last dose of IMP) for subjects who complete the trial, and decide to enroll in Trial 405-201-00015. For subjects who terminate early, decide to not enroll in Trial 405-201-00015, or who are not eligible to enroll in Trial 405-201-00015, they will be required to participate in the 7-day follow-up period as well as participate in an additional follow-up telephone call 10 days after the last dose of IMP. Subjects randomized to receive a TDD of 200 mg centanafadine SR will start at their target dose at the start of the double-blind treatment period. Subjects randomized to receive a TDD of 400 mg centanafadine SR will start the double-blind treatment period at the TDD of 200 mg centanafadine SR for 7 days, before they are escalated to their target TDD of 400 mg for a total of approximately 42 days of treatment. Subjects will be required to visit the site up to 12 times over the trial. See Figure 3.1-1 for a schematic of the trial design.

Subjects who complete both the 6-week double-blind treatment period and the 7-day safety follow-up period (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, and in-clinic visits 2 and 7 days after the last dose of IMP), and refrain from using prohibited medications (Section 4.1) after the IMP is stopped may be eligible to enroll into Trial 405-201-00015, which is a 12-month, observational, open-label trial to evaluate the long-term safety and tolerability of subjects with ADHD who previously participated in Trials 405-201-00013 or 405-201-00014. Subjects who terminate early, decide to not enroll in Trial 405-201-00015, or who are not eligible to enroll in Trial 405-201-00015, will be required to participate in the 7-day follow-up period as well as participate in an additional follow-up telephone call 10 days after the last dose of IMP. For subjects who early terminate or decline participation in the open-label trial, they will be instructed to refrain from utilizing prohibited concomitant medications (Section 4.1), including ADHD treatments, until after the follow-up telephone call 10 days after the last dose of IMP.

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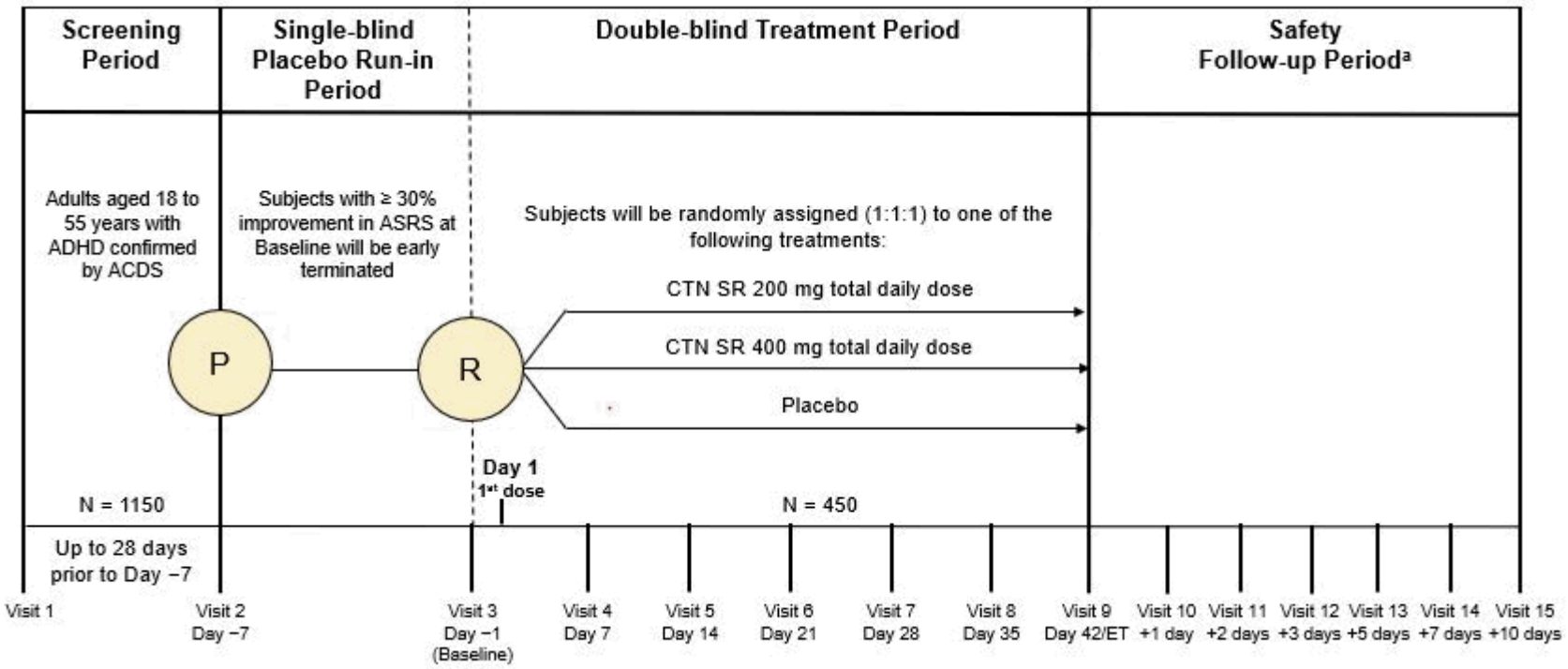

Figure 3.1-1 Trial Design Schematic

ASRS = Adult ADHD Self Report Scale; CTN SR = centanafadine sustained release; ET = early termination; P = placebo administration; R = randomization.

[a]All subjects will be required to participate in the 7-day follow-up period (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, and in-clinic follow-up visits at 2 and 7 days after the last dose of IMP). Subjects who terminate early, decide to not enroll in Trial 405-201-00015, or who are not eligible to enroll in Trial 405-201-00015, will be required to participate in an additional follow-up telephone call 10 days after the last dose of IMP.

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3.2 Trial Treatments

3.2.1 Single-blind Placebo Run-in Period

All subjects will begin BID dosing with single-blind matching placebo on Visit 2 (Day −7) and continue through Visit 3 (baseline) (Section 3.7.1.2). Two tablets of matching placebo should be taken orally in the morning followed by an additional 2 tablets 4 to 6 hours later. The morning and subsequent dose of matching placebo should be taken at approximately the same time each day. All subjects must be unaware of the single-blind placebo run-in period so that it is indistinguishable from the double-blind treatment period.

3.2.2 Double-blind Treatment Period

Trial assignments for the double-blind treatment period will be made once eligibility is confirmed. Eligible subjects will be randomized in a 1:1:1 ratio at baseline (Visit 3) to one of the following 3 treatment groups:

- Centanafadine SR 200 mg TDD
- Centanafadine SR 400 mg TDD
- Matching placebo

Neither the investigator nor the subject will be aware of the treatment assignment after randomization. All doses of centanafadine SR and matching placebo should be taken orally BID and can be administered without regard to meals, and should be taken at approximately the same time each day, with the first dose taken in the morning. The second dose should be taken 4 to 6 hours after the morning dose is administered.

Subjects randomized to receive the target TDD of 200 mg centanafadine SR will start at the target dose on Day 1 of the double-blind treatment period and remain at that dose for the duration of the trial (Table 3.2.2-1). Subjects randomized to receive a TDD of 400 mg centanafadine SR will receive a TDD of 200 mg centanafadine SR on Day 1 of the double-blind treatment period for 7 days before they are escalated to their target TDD of 400 mg on Day 8 for the duration of the trial (Table 3.2.2-1).

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Table 3.2.2-1 Dosing Schedule for Centanafadine SR Tablets

		Total Daily Dose	
Day(s)	**Time**	**200 mg Target**	**400 mg Target**
1 through 7	2 tablets orally in morning	1 × 100 mg + 1 × PBO tablet	1 × 100 mg + 1 × PBO tablet
	2 tablets orally 4-6 hr later	1 × 100 mg + 1 × PBO tablet	1 × 100 mg + 1 × PBO tablet
8 and thereafter	2 tablets orally in morning	1 × 100 mg + 1 × PBO tablet	2 ×100 mg
	2 tablets orally 4-6 hr later	1 × 100 mg + 1 × PBO tablet	2 ×100 mg

PBO = placebo.

For subjects randomized to placebo, they will take 2 placebo tablets in the morning and 2 tablets in the afternoon for the duration of treatment.

Once the subject is at the target dose, further dose modification is not permitted. Dose modification is not allowed at any time during the trial.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

A total of up to 1150 male and female subjects with current diagnosis ADHD and between the ages of 18 and 55 years, inclusive, are planned to be screened in order to randomize approximately 450 subjects to yield 292+ completers.

Subjects must meet the DSM Fifth Edition (DSM-5) criteria for ADHD (including predominantly inattentive presentation, hyperactive presentation, or combined presentation) as confirmed by the ACDS Version 1.2. To confirm that ADHD is the primary diagnosis, the Mini International Neuropsychiatric Interview (MINI) will be used to identify and exclude other psychiatric conditions which would preclude enrollment.

Subjects who are not receiving any pharmacological treatment for ADHD must have an Adult ADHD Investigator Symptom Rating Scale (AISRS) score of ≥ 28 at screening and baseline. Subjects who are receiving pharmacological treatment for ADHD at screening must have a minimum AISRS score of ≥ 22 at screening, and a score of ≥ 28 at baseline (Section 3.4.2). Subjects must washout of their current ADHD therapy, if applicable, and any prohibited medications prior to baseline (Table 4.1-1).

3.3.2 Subject Selection and Numbering

At screening, subjects will be assigned a unique subject identification (ID) number upon signing the electronic informed consent form (eICF) based on sequential enrollment in the trial. Subjects will be assigned a randomization number upon randomization

(Section 3.6.1), at the baseline visit (Day −1). The clinical site will maintain a list identifying all subjects by their subject ID number and initials.

3.4 Eligibility Criteria

3.4.1 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 institutional review board (IRB) that approves this protocol.

Each eICF will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[26] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any site-specific eICF used in the trial prior to submission to the IRB.

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

Potential 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 participants will be provided with controlled access to the eICF application by trial site staff. When the trial site staff and the participant agree that the participant has enough information to make an informed decision to participate, the participant 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.

Subjects may be asked to sign additional eICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

Screening	
1.	Subjects with a current primary DSM-5 diagnosis of ADHD (including predominantly inattentive presentation, hyperactive presentation, or combined presentations) as confirmed by the ACDS Version 1.2.
2.	Subjects who are not receiving any pharmacological treatment for ADHD must have an AISRS score of ≥ 28 at screening. Subjects who are receiving pharmacological treatment for ADHD at screening must have a minimum AISRS score of ≥ 22 at screening.
3.	Subject is 18 to 55 years of age, inclusive, at the time of consent.
4.	Subject has a BMI of 18 to 40, inclusive.
5.	Subject is able to swallow multiple tablets.
6.	Subject is willing and able to comply with all testing and requirements as defined in this protocol.
7.	Subject is able to provide electronic informed consent to participate in the trial in accordance with the ICH GCP Guidance E6 and applicable regulations before completing any trial-related procedures.
8.	Subject is willing to discontinue all prohibited psychotropic medications (Section 4) starting from the time of signing the informed consent and up to the 7-day follow-up period. Subjects that do not rollover into Trial 405-201-00015 must be willing to discontinue all prohibited psychotropic medications starting from the time of signing the informed consent until after the follow-up telephone call 10 days after the last dose of IMP.
9.	Subject is able to read English or Spanish well enough to understand the nature of the trial and to read and understand the written word in order to complete subject-reported outcome measures and be able to communicate effectively to be reliably rated on assessment scales; must be able and agree to comply with all protocol requirements, including the prescribed dosage regimens, discontinuation of prohibited medications, and report for regularly scheduled office visits.
Inclusion Criteria Assessed at Baseline	
10.	Subjects who were not receiving any pharmacological treatment for ADHD at screening must have an AISRS score of ≥ 28 at baseline. Subjects who were receiving pharmacological treatment for ADHD at screening must also have a minimum AISRS score of ≥ 28 at baseline.
11.	Subject must have a CGI-S score of ≥ 4 (≥ moderate impairment) at baseline.

BMI = body mass index; CGI-S = Clinical Global Impression-Severity of Illness Scale.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria

Screening	
1.	Females who are breast-feeding or who have a positive pregnancy test result prior to receiving IMP.
2.	Sexually active males or FOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the course of the trial and for 30 days after the last dose of IMP for female subjects, and 90 days after the last dose of IMP for male subjects and their partners who are FOCBP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control injection, birth control implant, birth control patch, condom with spermicide, or sponge with spermicide. Male subjects who do not agree to refrain from donating sperm from screening through 90 days after the last dose of IMP.
3.	Subject has a DSM-5 diagnosis of Other Specified or Unspecified Attention Deficit/Hyperactivity Disorder.
4.	Subject has initiated, changed, or discontinued receiving psychological (eg, supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) interventions for ADHD within the 60 days before the screening visit, or are anticipated to start new treatment during the trial. Subjects who are receiving psychotherapy that was initiated > 60 days before the screening visit will be allowed to continue to receive their psychotherapy during the trial only if they agree to not make any changes in the frequency or nature of their psychotherapy during the course of this trial.
5.	Subject has a lifetime history of electroconvulsive therapy, or a lifetime history of vagal nerve stimulation or deep brain stimulation for the treatment of depression.
6.	Subject has a current comorbid psychiatric disorder that either could be expected to require treatment with medications prohibited in this trial, or to confound efficacy or safety assessments. Examples include, but are not limited to, psychotic disorder (current or lifetime), bipolar disorder (current or lifetime), generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, a current major depressive episode, or posttraumatic stress disorder, as established by the MINI.
7.	Subjects with a clinically significant current DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, histrionic, narcissistic, avoidant, or dependent personality disorders.
8.	Subjects who meet criteria for C-SSRS Suicidal Ideation Items 4 or 5 within the last 6 months prior to screening or subjects who meet criteria for any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years prior to screening, **OR** Subjects who, in the opinion of the investigator, present a serious risk of suicide.
9.	Subject has any medical or psychological condition(s) or state(s) that in the investigator's opinion would prohibit the subject from completing the trial or would go against the subject's best interest with his/her participation in the trial. This would include any significant illness or unstable medical condition that could lead to difficulty complying with the protocol. This would also include most bariatric surgeries, with the only exception being those where there has been no breach of the gastrointestinal wall (ie, uncomplicated lap band surgery) AND no sign of malabsorption.
10.	Subject has a history of epilepsy, seizures (other than infantile febrile seizures), syncope, Tourette's Disorder, serious neurological disease, history of significant head trauma with clinically significant loss of consciousness, dementia, cerebrovascular disease, Parkinson's disease, or intracranial lesions.

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Table 3.4.3-1 Exclusion Criteria	
11.	Subject has a life-time history of a pattern of abuse or diversion of stimulants.
12.	Subject has any current or suspected drug or alcohol use disorder. Subject has met the DSM-5 criteria for a substance use disorder in the past 6 months. Nicotine use disorder is not exclusionary.
13.	Subjects that have a positive alcohol test (via breathalyzer or blood), a positive drug screen for cocaine, or other illicit drugs (excluding marijuana). Subjects with a positive drug screen for confirmed prescription or OTC use of ADHD medications at screening will be required to undergo a washout period (Section 4). NOTE: Subjects that test positive for marijuana may be permitted to be enrolled if they have no evidence of a substance use disorder, and if they agree to refrain from use for the duration of the trial. Allowance for subjects testing positive for marijuana at screening require explicit approval from the medical monitor.
14.	Subjects with a known intellectual disability or clinical evidence of intellectual disability based on the opinion of the investigator.
15.	Subjects with insulin-dependent diabetes mellitus are excluded. Subjects with non-insulin-dependent diabetes mellitus may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria: • Screening glucose (non-fasting) < 200 mg/dL. (If the non-fasting glucose is ≥ 200 mg/dL, subjects must be retested in the fasting state. Fasting glucose must be ≤ 125 mg/dL.), • Subject has been maintained on a stable regimen of oral anti-diabetic 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, • Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, **AND** • Subject's diabetes is not newly diagnosed during screening for the trial.
16.	Subjects presenting with, or having a history of, uncontrolled hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in systolic blood pressure or a decrease of ≥ 20 mmHg in diastolic blood pressure after at least 3 minutes standing compared with the previous supine blood pressure, **OR** development of symptoms.
17.	Subjects with known ischemic heart disease or history of myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, coronary artery bypass surgery, or other serious cardiac problems that would place him/her at increased vulnerability to the sympathomimetic effects of a stimulant medication.
18.	The following laboratory test and ECG results are exclusionary: 1) Platelets ≤ 75,000/mm^3 2) Hemoglobin ≤ 9 g/dL 3) Neutrophils, absolute ≤ 1000/mm^3 4) AST > 2 × upper limit of normal 5) ALT > 2 × upper limit of normal 6) Creatinine ≥ 2 mg/dL 7) HbA_{1c} ≥ 7% 8) QTcF or QTcB > 450 msec for males or > 470 msec for females NOTE: In addition, subjects should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which in the investigator's judgment are medically significant and that would impact the safety of the subject or the interpretation of the trial results. Tests with abnormal results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.
19.	Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days) or an abnormal result for free T4 at screening (free T4 is measured only if result for TSH is abnormal).

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Table 3.4.3-1 Exclusion Criteria	
20.	Subjects receiving any of the prohibited medications within the specified period prior to the start of the single-blind placebo run-in period, or who would be likely to require prohibited concomitant therapy during the trial (Section 4).
21.	Subject has a history of prior exposure to centanafadine.
22.	Subject has a history of dermatologic adverse reactions secondary to any drug exposure or anaphylaxis (or some type of systemic allergic reaction) to any substance.
23.	Subject has participated in a clinical trial involving either an investigational medication or a non-medication intervention within the last 60 days prior to screening or has participated in more than 2 clinical trials involving either an investigational medication or non-medication intervention within the past year.
24.	Subject has previously been randomized in this trial and subsequently withdrawn.
25.	In the opinion of the investigator, subject has not derived significant therapeutic benefit from 2 or more ADHD therapies of 2 different classes (eg, amphetamine and methylphenidate, or amphetamine and atomoxetine) given with an acceptable dose and duration during adulthood (aged 18 or older). NOTE: If subject has not derived significant therapeutic benefit due to an inability to tolerate side effects, eligibility can be discussed on case-by-case basis with the medical monitor.
26.	Any subject who, in the opinion of the investigator, should not participate in the trial.
27.	Subjects with HIV seropositive status/acquired immunodeficiency syndrome, seropositive status for hepatitis B (ie, HBsAg positive), or hepatitis C (ie, anti-HCV positive and HCV RNA positive).
Exclusion Criteria Assessed Prior to Start of the Single-blind Placebo Run-in	
28.	Subjects who have a positive alcohol test (via breathalyzer or blood), a positive drug screen assessed prior to Visit 2 for cocaine, other illicit drugs (including marijuana), or prescription or OTC ADHD medications will be screen failed. This includes medications such as opioids or benzodiazepines taken without prescription.
29.	Subjects with a ≥ 30% improvement in the (18 item) ADHD Symptoms score of the ASRS compared to the score at screening will be screen failed, and not eligible for rescreening.
Exclusion Criteria Assessed at Baseline	
30.	Subjects who have a positive alcohol test (via breathalyzer or blood), a positive drug screen assessed prior to the baseline visit for cocaine, other illicit drugs (including marijuana), or prescription or OTC ADHD medications will be early terminated. This includes medications such as opioids or benzodiazepines taken without prescription.
31.	Subjects with a ≥ 30% improvement in the (18 item) ADHD Symptoms score of the ASRS compared to the score at the start of single-blind placebo run-in will be early terminated.
32.	In the opinion of the investigator, the subject is unable to adhere to the treatment regimen or other requirements outlined in the protocol.

ALT = alanine aminotransferase; anti-HCV = hepatitis C antibodies; ASRS = Adult ADHD Self Report Scale; AST = aspartate aminotransferase; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FOCBP = females of childbearing potential; HbA_{1c} = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; OTC = over-the-counter; QTcB = QT interval corrected for heart rate by the Bazett formula; QTcF = QT interval corrected for heart rate by the Fridericia formula; RNA = ribonucleic acid; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Please refer to Section 3.9 for details regarding screen failures.

Subjects must agree to restrictions to medications and lifestyle as described in Section 4.

3.5 Endpoints

3.5.1 Primary Endpoint

3.5.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline at Day 42 in the AISRS total score.

3.5.2 Secondary Endpoints

3.5.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is change from baseline at Day 42 on the Clinical Global Impression-Severity of Illness Scale (CGI-S).

3.5.2.2 Other Efficacy Endpoints

- Change from baseline in AISRS total score for every scheduled visit;
- Change from baseline in the Inattentive subscale and Hyperactivity-Impulsive subscale scores of the AISRS for every scheduled visit;
- Change from baseline in CGI-S score for every scheduled visit;
- Clinical Global Impression (CGI) Change from Baseline score at each scheduled visit;
- Percentage of responders at each post-baseline visit, where a responder is defined as a subject with a CGI Change from Baseline score of 1 or 2 OR a ≥ 30% improvement in ADHD symptoms compared with baseline as measured by the AISRS total score;

3.5.3 Exploratory Endpoints

The exploratory endpoints are the change from baseline to Day 28 and Day 42 in the ADHD Impact Module - Adult (AIM-A) and the Adult ADHD Self Report Scale (ASRS) total score and subscale scores.

3.5.4 Safety Endpoints

Standard safety variables will include AEs (including evaluations for rash, an AE of special interest [AESI]), clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, vital sign measurements, electrocardiograms (ECGs), assessments of withdrawal (Study Medication Withdrawal Questionnaire [SMWQ]), and suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]).

Abuse-related AEs and AEs involving medication irregularities will be recorded verbatim on source documentation with detailed narratives (see Section 5.5).

3.6 Measures to Minimize/Avoid Bias

3.6.1 Randomization

During the trial, administration of the IMP will be double-blind. In other words, neither the investigator nor the subject will have knowledge of the treatment assignment (eg, centanafadine SR 200 mg, 400 mg, or placebo). Treatment assignments will be based on a computer-generated randomization code provided by the Otsuka Pharmaceutical Development & Commercialization, Inc (OPDC) Biometrics Department. Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. The bioanalytical laboratory will also be sent the randomization code. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging trial medication, operating electronic case report form (eCRF), and reporting SAEs to regulatory agencies. The randomization will be stratified by trial site and designed to allocate subjects in a 1:1:1 ratio to centanafadine SR 200 mg/day or 400 mg/day or placebo.

3.7 Trial Procedures

The time from enrollment of the first subject to the last subject's last trial visit will be approximately 12 months. Individual participation for subjects who complete the trial will be approximately 12 weeks, consisting of a 28-day screening and washout period, a 1-week single-blind placebo run-in period, a baseline day, a 6-week double-blind treatment period, and a 7-day follow-up period (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, and in-clinic visits 2 and 7 days after the last dose of IMP). For subjects who terminate early, decide to not enroll in Trial 405-201-00015, or who are not eligible to enroll in Trial 405-201-00015, they will be required to participate in the 7-day follow-up period as well as participate in an additional follow-up telephone call 10 days after the last dose of IMP.

When Trial 405-201-00013 reaches its conclusion, all subjects participating in the trial, regardless of trial period, may be eligible to enroll into Trial 405-201-00015, which is a 12-month, observational, open-label trial (Section 3.1). All subjects will be required to comply with the appropriate follow-up procedures described in Section 3.7.1.5 and Section 3.7.1.6.

Trial assessment time points are summarized in Table 3.7-1 and Table 3.7-2.

Table 3.7-1 Schedule of Assessments - Screening Through End of Treatment

Period	Screening[a]	PBO Run-in[b]	Double-blind Treatment							
	Days −35 to −8	Day −7	Baseline Day −1	Day 7 +1 Day	Day 14 ±2 Days	Day 21 ±2 Days	Day 28 ±2 Days	Day 35 ±2 Days	Day 42/ET ±2 Days	NOTES
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
ENTRANCE/HISTORY										
Informed consent	X									Section 3.4.1
Inclusion/exclusion criteria	X	X	X							Section 3.4
Demography	X									
Concomitant medication(s)	X	X	X	X	X	X	X	X	X	
Medical history	X	X	X							
ACDS	X									
Identification of comorbidities using MINI	X									
Psychiatric evaluation	X									
HIV/HBsAg/anti-HCV	X									Section 3.7.5.2
Randomization			X							Section 3.6.1
Urine pregnancy test	X	X	X	X	X	X	X	X	X	Section 3.7.5.2 Section 5.7
EFFICACY										
AISRS	X	X	X	X	X	X	X	X	X	Section 3.7.2.1
CGI-S			X	X	X	X	X	X	X	Section 3.7.2.2
CGI Change from Baseline				X	X	X	X	X	X	Section 3.7.2.3
SAFETY										
Adverse events	X	X	X	X	X	X	X	X	X	Section 5.2
Physical examination	X					X			X	Section 3.7.5.3.1
Vital signs	X	X	X	X	X	X	X	X	X	Section 3.7.5.3.2
12-lead ECG	X	X	X	X	X		X		X	Section 3.7.5.4
Clinical laboratory tests	X	X	X		X				X	Section 3.7.5.2
SMWQ								X	X	Section 3.7.5.5.1

Table 3.7-1 Schedule of Assessments - Screening Through End of Treatment

Period	Screening[a]	PBO Run-in[b]	Double-blind Treatment							
	Days −35 to −8	Day −7	Baseline Day −1	Day 7 +1 Day	Day 14 ±2 Days	Day 21 ±2 Days	Day 28 ±2 Days	Day 35 ±2 Days	Day 42/ET ±2 Days	NOTES
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
UDS/alcohol testing via breathalyzer or blood	X	X	X	X	X	X	X	X	X	Section 3.7.5.2
C-SSRS	X	X	X	X	X	X	X	X	X	Section 3.7.5.5.2
PHARMACOKINETIC/PHARMACOGENOMIC										
PK blood sample				X	X		X		X	Section 3.7.6.1
Pharmacogenomic and FBR samples			X							Section 3.7.6.2 Section 3.7.6.3
EXPLORATORY										
AIM-A		X	X				X		X	Section 3.7.3.1
ASRS	X	X	X				X		X	Section 3.7.3.4
OTHER										
IMP/placebo dispensing		X	X	X	X	X	X	X		
IMP/placebo return and accountability			X	X	X	X	X	X	X	Section 8.4 Section 3.12

anti-HCV = hepatitis C antibodies; FBR = future biospecimen research; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; UDS = urine drug screen.

[a]Screening will include a washout period that can range from 7 to 28 days

[b]See Section 3.7.1.2

Table 3.7-2 Schedule of Assessments - Follow-up

Period	Follow-up[a]						NOTES
	1 (+1) day after the last dose of IMP	2 (+1) days after the last dose of IMP	3 (+ 1) days after the last dose of IMP	5 (+ 1) days after the last dose of IMP	7 (+ 2) days after the last dose of IMP	10 (+ 2) days after the last dose of IMP	
Visit	**10**	**11**	**12**	**13**	**14**	**15**	
ENTRANCE/HISTORY							
Concomitant medication(s)	X	X	X	X	X	X	
EFFICACY							
AISRS		X			X		Section 3.7.2.1
SAFETY							
Adverse events	X	X	X	X	X	X	Section 5.2
Vital signs		X			X		Section 3.7.5.3.2
SMWQ	X	X	X	X	X	X	Section 3.7.5.5.1
UDS/alcohol testing via breathalyzer or blood		X			X		Section 3.7.5.2
C-SSRS		X			X		Section 3.7.5.5.2
PHARMACOKINETIC/PHARMACOGENOMIC							
PK blood sample					X		Section 3.7.6.1

[a]All subjects will be required to participate in the 7-day follow-up period (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, and in-clinic follow-up visits at 2 and 7 days after the last dose of IMP). Subjects who terminate early, decide to not enroll in Trial 405-201-00015, or who are not eligible to enroll in Trial 405-201-00015, will be required to participate in an additional follow-up telephone call 10 days after the last dose of IMP.

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3.7.1 Schedule of Assessments

3.7.1.1 Visit 1 (Screening)

The screening period begins after consent is obtained and will take place between Day −35 and Day −8 prior to the initiation of the single-blind placebo run-in period. Completion of screening activities may require more than 1 visit. All procedures outlined for screening in the Schedule of Assessments (Table 3.7-1) will be performed. The following should also be noted:

- The investigator or his/her designee must obtain informed consent from the subject prior to any trial-related procedures being performed.
- A urine drug screen will be collected and sent to the central lab for evaluation. If subjects are taking disallowed medications and they are able to taper appropriately and safely, they will do so during the screening period. If medication taken is for ADHD, a minimum of 7 days off stimulants and 21 days off nonstimulants will be required before the single-blind placebo run-in period. A complete washout schedule, including common excluded medications and herbal preparations, is provided in Section 4.1. A subject who tested positive for any prohibited medications at the screening visit must have a repeat urine drug screen that is confirmed as negative prior to performing Visit 2.
- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- Medical and psychiatric history will be recorded, including the DSM-5 diagnosis of ADHD using the ACDS Version 1.2.
- Subjects will be administered the ASRS.
- A urine pregnancy test will be performed for all females of childbearing potential (FOCBP). If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test. Subjects with a positive serum test result will be excluded from the trial.

External quality oversight methods will be used by Clinical Surveillance & Training (CST) to promote appropriate subject enrollment. Such methods will require sites to communicate certain aspects of subject data during the screening period to CST as detailed in the Operations Manual. Subjects cannot be randomized until approval from CST has been received. The investigator is responsible for ensuring that subjects are eligible for enrollment into the trial and for assessing subject safety throughout the trial.

3.7.1.2 Visit 2 (Single-blind Placebo Run-in)

After the subject has completed the medication washout period (if applicable), the Visit 2 (Day −7) assessments described in the Schedule of Assessments (Table 3.7-1) will be performed. The following should also be noted:

- Urine drug screen results from the previous visit will be reviewed. If the subject is positive for any prohibited medications at screening (including medications for the treatment of ADHD, see Section 4.1), and has not had a negative repeat urine drug screen confirmed since, the subject will be screen failed.
- Subjects will be administered the ASRS prior to the start of the single-blind placebo run-in period, and those with a ≥ 30% improvement in the (18-item) ADHD Symptoms score compared to the score at screening will be screen failed, and not eligible for rescreening.
- All subjects must be unaware of the single-blind placebo run-in period so that it is indistinguishable from the double-blind treatment period. All subjects must be under the impression that they are starting to receive randomized treatment at the time of Visit 2 (Day −7).
- Placebo will be dispensed for the single-blind placebo run-in period, and subjects will be instructed to take their first dose from the dosing card in the clinic. Subjects will be instructed to take their doses at approximately the same time every day.
- The subject will download the AiCure Platform (Section 3.12) or receive a provisioned device with the AiCure Platform predownloaded, and will be trained on IMP compliance using this application.

  Subjects who discontinue the trial during the single-blind placebo run-in period should be considered early termination subjects, and should proceed with the early termination visit (Section 3.7.1.4.2) and follow-up procedures (Section 3.7.1.5 and Section 3.7.1.6).

3.7.1.3 Visit 3 (Baseline)

After the subject has completed the single-blind placebo run-in period, the Visit 3 (Day −1) assessments described in the Schedule of Assessments (Table 3.7-1) will be completed.

The following should also be noted:

- Urine drug screen results from the previous visit will be reviewed. If the subject is positive for any prohibited medications (including medications for the treatment of ADHD, see Section 4.1), the subject will be early terminated, and the procedures outlined in Section 3.7.1.4.2 will be completed.
- Subjects will be administered the ASRS, and those with a ≥ 30% improvement in the (18-item) ADHD Symptoms score compared to the score at the start of single-blind placebo run-in will be early terminated.

- Subjects who do not meet eligibility (see Exclusion Criteria #30, #31, and #32) at the baseline visit are considered early termination subjects, and should proceed with the early termination visit (Section 3.7.1.4.2) and follow-up procedures (Section 3.7.1.5 and Section 3.7.1.6).
- Dosing cards from the single-blind run-in period will be returned; accountability and compliance will be verified.
- Blood samples for genotyping and for future biospecimen research (FBR) will be collected.
- Subjects entering the double-blind treatment period will be randomized (1:1:1) to receive centanafadine SR 200 mg TDD, 400 mg TDD, or placebo.
- Subjects will receive a dosing card for dosing on Days 1 to 7, and will be instructed to start dosing from the new card on the following day (Day 1), and to take their doses at approximately the same time every day.

3.7.1.4 Double-Blind Treatment Period

3.7.1.4.1 Visits 4 through 8

The assessments described for Visits 4 through 8 (Days 7-35) in the Schedule of Assessments (Table 3.7-1) will be completed. The following should also be noted:

- Urine drug screen results from the previous visit will be reviewed. If the subject is positive for any prohibited medications (including medications for the treatment of ADHD, see Section 4.1), the subject will be early terminated, and the procedures outlined in Section 3.7.1.4.2 will be completed.
- At each visit dosing cards from the prior week will be returned; accountability and compliance will be verified.
- Sparse PK samples will be collected at Visits 4 (Day 7), 5 (Day 14), and 7 (Day 28).
- Subjects will receive a dosing card for dosing at each visit for the next week, and will be instructed to start dosing from the new card on the following day, and to take their doses at approximately the same time every day.

3.7.1.4.2 Visit 9/End of Treatment/Early Termination

The assessments described for Visit 9 (Day 42/early termination [ET]) in the Schedule of Assessments (Table 3.7-1) will be completed. If a subject discontinues early before Day 42, procedures noted for Day 42 must be completed at the ET visit. Attempts should be made to complete **ALL** evaluations, particularly efficacy assessments (ie, AISRS, CGI Change from Baseline, CGI-S, ASRS, and AIM-A), for the Day 42/ET visit prior to the administration of any new ADHD medications. However, if the subject receives a new ADHD medication or has a urine drug screen positive for any new ADHD medication prior to the conduct of ET procedures, no efficacy assessments should be performed.

The following should also be noted:

- Urine drug screen results from the previous visit will be reviewed. If the subject is positive for any new ADHD medication, no efficacy assessments should be conducted.
- Subjects will return their dosing card from the prior week, accountability, and compliance will be verified.
- Sparse PK sample will be collected.
- For all subjects who complete the trial (Section 3.10) and are considering entry into the open-label rollover trial, they will be instructed to refrain from utilizing prohibited concomitant medications (Section 4.1), including ADHD treatments, during the 7-day safety follow-up period. For subjects who early terminate or decline participation in the open-label trial, they will be instructed to refrain from utilizing prohibited concomitant medications (Section 4.1), including ADHD treatments, until after the follow-up telephone call 10 days after the last dose of IMP.
- For subjects who early terminate or decline participation in the open-label trial, future treatment options will be discussed, and subjects will complete follow-up visits and procedures described in Section 3.7.1.5 and Section 3.7.1.6.

3.7.1.5 Visits 10 Through 14 (Follow-up)

All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation for 7 days (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, and in-clinic visits 2 and 7 days after the last dose of IMP). The assessments described in the Follow-up Schedule of Assessments (Table 3.7-2) will be completed. The following should also be noted:

Subjects who complete both the 6-week double-blind treatment period, the 7-day follow-up period (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, and in-clinic visits 2 and 7 days after the last dose of IMP), and who refrain from using prohibited medications (Section 4.1) after the IMP is stopped, may be eligible to enroll into Trial 405-201-00015, which is a 12-month, observational, open-label trial to evaluate the long-term safety and tolerability of subjects with ADHD who previously participated in Trials 405-201-00013 or 405-201-00014. For subjects who early terminate or decline participation in the open-label trial, they will be instructed to refrain from utilizing prohibited concomitant medications (Section 4.1), including ADHD treatments, until after the follow-up telephone call 10 days after the last dose of IMP (Section 3.7.1.6). Subjects who will be rolling over into the open-label trial will need to sign the Trial 405-201-00015 informed consent form prior to activities performed at the 7-day follow-up visit of Trial 405-201-00013.

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3.7.1.6 Visit 15 (Follow-up)

Subjects who terminate early, decide to not enroll in Trial 405-201-00015, or who are not eligible to enroll in Trial 405-201-00015, will be required to participate in an additional follow-up via telephone call 10 days after the last dose of IMP. For subjects who early terminate or decline participation in the open-label trial, they will be instructed to refrain from utilizing prohibited concomitant medications (Section 4.1), including ADHD treatments, until after the follow-up telephone call 10 days after the last dose of IMP. The assessments described in the Follow-up Schedule of Assessments (Table 3.7-2) will be completed.

3.7.2 Efficacy Assessments

It is required that adequately trained and experienced clinicians administer the ACDS, MINI, AISRS, CGI-S, and CGI Change from Baseline. All individuals performing these assessments must be pre-approved by the sponsor or designee.

3.7.2.1 Adult Attention-deficit/Hyperactivity Disorder Investigator Symptom Rating Scale

The AISRS is a modified version of the ADHD Rating Scale that reflects the impact and severity of ADHD among adults, and will be administered as described in the Schedule of Assessments (Table 3.7-1 and Table 3.7-2). It is a clinician-administered scale that measures the 18 symptoms of adult ADHD using a Likert scale: 0 (none); 1 (mild); 2 (moderate); and 3 (severe), and uses a semi-structured interview methodology with suggested prompts for each item to improve interrater reliability. The scale's 18 items directly correspond to the 18 DSM-5 symptoms of ADHD where 9 inattentive items alternate with 9 hyperactive impulsive items. The maximum total score for the scale is 54 points, with 27 points for each subscale. The total score is the sum of both the Inattentive and Hyperactive Impulsive subscales.[27]

3.7.2.2 Clinical Global Impression-Severity of Illness Scale - Modified for Attention-deficit/Hyperactivity Disorder

The CGI-S modified (Table 3.7-1) is an observer-rated scale that will be used to measure symptom severity.[28] To perform this assessment, the investigator or rater will respond to the following question: “Considering your total clinical experience with adult ADHD, how mentally ill is the patient at this time?” Response choices include: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.[29]

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3.7.2.3 Clinical Global Impression Change from Baseline

The CGI Change from Baseline (Table 3.7-1) is an observer-rated scale that will be used to measure the subject's total improvement compared to before trial drug treatment was initiated.[28] The rater or investigator will rate the subject's total improvement relative to baseline. Response choices include: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.[29]

3.7.3 Other Assessments

3.7.3.1 Mini International Neuropsychiatric Interview

The MINI[30,31,32] will be conducted as outlined in the Schedule of Assessments (Table 3.7-1) to rule out exclusionary comorbid psychiatric diagnoses. Detailed instructions for administration of this structured interview will be provided.

3.7.3.2 Adult ADHD Clinical Diagnostic Scale

The ACDS Version 1.2 (Table 3.7-1) is a clinician-administered, semistructured interview assessment used to establish the presence of current adult symptoms of ADHD, with suggested age-specific prompts for rating both childhood and adult symptoms. The ACDS includes a retrospective assessment of all childhood ADHD symptoms as well as an assessment of recent (last 6 months) adult ADHD symptoms that includes 9 criterion symptoms of inattention, 9 criterion symptoms of hyperactivity and impulsivity, and 14 non-DSM symptoms believed to be relevant to adult ADHD.[33]

3.7.3.3 Attention-deficit/Hyperactivity Disorder Impact Module - Adult

The AIM-A (Table 3.7-1) is a subject self-report questionnaire which assesses quality of life in adults with ADHD. The questionnaire has 4 global quality of life items, 5 economic impact items, and 5 multi-item scales that assess the following key concepts: Living with ADHD, General Well-Being, Work, Home and School Performance and Daily Functioning. Additionally, Relationships and Communication, and Impact of Symptoms are also included.[34]

3.7.3.4 Adult Attention-deficit/Hyperactivity Disorder Self-Report Scale, Expanded Version

The ASRS Version 1.1, (Table 3.7-1) is a self-report questionnaire developed by the WHO. The subject will answer 31 questions. Of those 31, 18 of the questions pertain to the 18 DSM-5 ADHD symptoms (ADHD Symptoms). The expanded version includes 9 additional items that assess Executive Function Deficits, and 4 items that assess Emotional Dyscontrol.[35]

3.7.4 Prior and Concomitant Medications

The investigator will record all medications 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 secondary objectives) on the eCRF. Details of prohibited and restricted medications are provided in Section 4.1. The investigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) on the eCRF.

3.7.5 Safety Assessments

3.7.5.1 Adverse Events

Refer to Section 5.

3.7.5.2 Clinical Laboratory Assessments

A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow up, if needed). In cases where an immediate result is required for a particular laboratory test, the sample should be divided and sent to both a local laboratory and the designated central laboratory. Urine will be collected and blood will be drawn from each subject during screening prior to treatment with the IMP. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. If a fasting blood sample was obtained at the screening visit and less than 14 days have elapsed since the screening visit, clinical laboratory tests (hematology, serum chemistry, and urinalysis) do not need to be repeated at the baseline visit. The results of these tests must be reviewed by the investigator prior to initiation of the administration of the IMP. Clinical laboratory tests at other visits should be drawn fasting, if possible, but must be drawn after a minimum 8-hour fast at Day 42/ET. All blood collections must occur after the

administration of efficacy assessments and safety assessments (eg, AE monitoring, physical examination, vital sign measurements, ECGs, medication withdrawal scales, and suicidality) at any given visit. See exclusion criteria (Section 3.4.3) based on screening laboratory tests. 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 retained electronically within the laboratory vendor's online portal and assessed by the investigator or qualified designee for clinical significance within the eCRF.

Table 3.7.5.2-1 Clinical Laboratory Assessments

Hematology: Hematocrit Hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Mean corpuscular volume Platelet count RBC count WBC count with differential Urinalysis: Color Bilirubin Blood Glucose Ketones Leukocyte esterase Microscopic analysis, WBC/RBC counts per high powered field Nitrite pH Protein Specific gravity Urobilinogen Urine Drug Screen Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Marijuana Methadone Methylphenidate (ritalinic acid) Opiates Phencyclidine Propoxyphene Other Alcohol testing via breathalyzer or blood	Serum Chemistry: Albumin Alkaline phosphatase ALT AST Bicarbonate Bilirubin, total Blood urea nitrogen Calcium Cholesterol (total, HDL, LDL) Chloride CPK Creatinine Gamma glutamyl transferase Glucose Magnesium Potassium Phosphorus Protein, total Sodium Triglycerides Uric acid Additional Tests: Urine pregnancy (FOCBP), serum test will confirm positive urine test results PT and INR (screening, baseline, and Day 42/ET) CPK reflex for isoenzymes if CPK > 3 × ULN; serum and urine myogloblin collected if CPK > 5 × ULN Additional Tests (Screening Only) HBsAg Anti-HCV HIV TSH, with reflex to free T4 if TSH is abnormal HbA_{1c}

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CPK = creatine phosphokinase; HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; PT = prothrombin time; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell.

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

Any value outside the normal range will be flagged for the attention of the investigator who must indicate whether or not a flagged value is of clinical significance. If one or more values are questionable, the test(s) may be repeated. If the result of any test (or repeat test, if done) is indicated as clinically significant in the samples taken during the screening period, the subject will NOT be enrolled into the trial without the permission of the medical monitor. In addition, unscheduled laboratory tests should be performed if clinically significant abnormalities are observed. Unscheduled laboratory tests may be repeated at any time at the discretion of the investigator for appropriate medical care. Refer to Appendix 2 for criteria for identifying values of potential clinical relevance.

A pregnancy test will be conducted in all FOCBP prior to trial intervention; results must be available prior to the administration of the IMP. All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at screening must not be enrolled. Subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial. Pregnancy tests will be performed in FOCBP at each visit during the trial. An additional pregnancy test will be conducted in FOCBP at the Day 42/ET visit.

3.7.5.3 Physical Examination and Vital Signs

3.7.5.3.1 Physical Examination

A complete physical examination will be performed at screening, and a targeted physical examination to address any new concerns will be performed at all other visits indicated in the Schedule of Assessments (Table 3.7-1). A complete physical examination will include height (screening only), weight, waist circumference, and calculation of body mass index (BMI) (screening and Day 42/ET only); and assessment of the head, eyes, ears, nose, throat, thorax, abdomen, urogenital, skin and mucosae, neurological, and extremities. Examinations with abnormal results that are deemed clinically significant should be repeated to ensure reproducibility of the abnormality. Any abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF.

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3.7.5.3.2 Vital Signs

Vital signs including systolic blood pressure and diastolic blood pressure, heart rate, respiratory rate, and body temperature will be measured at the time points described in the Schedule of Assessments (Table 3.7-1 and Table 3.7-2). 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.

Subjects should be monitored for potentially clinically significant vital signs values (Appendix 3). Abnormal results that are deemed clinically significant should be repeated to ensure reproducibility of the abnormality. Any abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF (Section 5.2).

3.7.5.4 Electrocardiogram Assessments

The 12-lead ECGs will be performed in the supine position at the time points described in the Schedule of Assessments (Table 3.7-1).

Subjects should be monitored for potentially clinically significant ECG results (Appendix 4). Tests with abnormal results that are deemed clinically significant should be repeated to ensure reproducibility of the abnormality. Any abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF.

3.7.5.5 Other Safety Assessments

3.7.5.5.1 Study Medication Withdrawal Questionnaire

The SMWQ is a questionnaire to assess withdrawal symptoms that will be completed as described in the Schedule of Assessments (Table 3.7-1 and Table 3.7-2). The SMWQ is a modification of the Amphetamine Withdrawal Questionnaire in which the terms "amphetamines and methamphetamine" are replaced with the term "the study medication."[36,37,38] At the site, the subject will complete the SMWQ, and on non-site days, subjects will complete the SMWQ remotely.

3.7.5.5.2 Columbia-Suicide Severity Rating Scale

Suicidality will be monitored during the trial (Table 3.7-1 and Table 3.7-2) using the C-SSRS.[39] 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.[39] 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.

The C-SSRS has a "Screening/Baseline" version, which will be completed at screening and a "Since Last Visit" version that will be completed at all other visits (including the ET visit, if applicable). There are a maximum of 19 items to be completed: 7 required, 10 potential additional items if there is a positive response to a required item, and 2 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.

3.7.6 Pharmacokinetic and Pharmacogenomic Assessments

All blood collections must occur after the administration of efficacy assessments and safety assessments (eg, AE monitoring, physical examination, vital sign measurements, ECGs, medication withdrawal scales, and suicidality) at any given visit.

3.7.6.1 Pharmacokinetic Assessments

3.7.6.1.1 Pharmacokinetic Blood Samples

Five sparse PK samples will be taken for determination of concentrations of centanafadine and metabolite(s) in plasma. Blood samples will be collected by trial centers that have appropriate facilities. A 2-mL sample will be collected at the time points presented in the Schedule of Assessments (Table 3.7-1). Samples collected at Day 14 and Day 42/ET should be taken concurrently with the serum chemistry sample. The actual date and time of the PK sample collection must be recorded on the eCRF. The exact timing of sampling relative to previous dose is not critical and can vary as much as is operationally practical. Preferentially, 3 of the 4 PK samples taken during the treatment period per subject should be taken as follows:

- At least 1 sample should be taken prior to the first morning dose (trough concentration) at either Day 7, Day 14, or Day 28
- At least 1 sample should be taken at least 1 hour after the morning dose
- At least 1 sample should be taken after the afternoon dose

All plasma samples will be shipped to the central laboratory. Detailed handling and shipping instructions are in Appendix 1.

3.7.6.2 DNA Blood Samples for Pharmacogenomic Testing

A blood sample will be collected at the time point presented in the Schedule of Assessments (Table 3.7-1) in order to extract deoxyribonucleic acid (DNA) and determine the genotypes related to drug metabolizing enzymes and transporters to determine the genotypes of genes related to absorption, distribution, metabolism, and excretion. Genotypes and estimated phenotypes may be included as part of a population PK analysis to be reported separately. All samples will be shipped to the central laboratory. Detailed handling and shipping instructions are provided in Appendix 1.

3.7.6.3 Future Biospecimen Research

A blood sample will be collected at the time point presented in the Schedule of Assessments (Table 3.7-1) only from those subjects that provided consent for FBR sample collection. Research performed on this sample may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics 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 appropriately consented subjects. The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and their therapeutic treatments. Processing, storage, and shipping instructions for FBR samples are provided in Appendix 1.

3.7.7 End of Trial

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 eCRF page for the last subject completing or withdrawing from the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

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. Subjects who remain in the trial when the trial reaches its conclusion may be eligible to enter an open-label rollover trial (Trial 405-201-00015) if they meet all of the inclusion/exclusion criteria for that trial.

3.8.2 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 GCP. The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After randomization, 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. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.4. Refer to Table 3.7-2 for a description of follow-up procedures.

A urine drug screen will be collected and sent to the central lab at the time points described Table 3.7-1 and Table 3.7-2. At the start of the single-blind placebo run-in period through the Day 42/ET visit, if the subject is tests positive for any prohibited medications (including medications for the treatment of ADHD, see Section 4.1), the subject will be early terminated, and the procedures outlined in Section 3.7.1.4.2 will be completed.

At the baseline visit only, if subjects have a ≥ 30% improvement in the ASRS (18 item) ADHD Symptoms score compared to the score at the start of the single-blind placebo run-in, they will be early terminated.

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3.8.3.2 Documenting Reasons for Treatment Discontinuation

A subject may discontinue IMP for a number of reasons including those listed below:

- Reasons related to AE:
  - Subject decides to discontinue because of annoyance or discomfort due to a non-serious 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
- Death
- Reasons unrelated to medical condition (provide detail and review AE history with subject)
- Withdrawal of informed consent (complete written withdrawal of consent form)
- Lost to follow-up
- Rash (regardless of severity or seriousness) (see Section 5.4)
- Pregnancy (see Section 5.7)
- Termination of all or part of the trial by the sponsor
- Lack of efficacy (LOE)

Subjects withdrawn prior to Day 42 must complete the Day 42/ET evaluations at the time of withdrawal. In addition, all subjects who withdraw prematurely from the trial will be assessed by telephone 1, 3, and 5 days after the last dose of IMP, in the clinic 2 and 7 days after the last dose of the IMP, and 10 days via telephone after the last dose of the IMP. Three attempts will be made to contact the subject by telephone; 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.

Meeting a screening exclusion criterion post-randomization does not require an automatic discontinuation of the subject. The investigator should assess the change for clinical significance, determine if an AE should be reported, and make a determination of subject continuation based on subject safety. The investigator will consult with the medical monitor to determine subject continuation in the trial.

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 5.9 must be followed.

3.8.3.3 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent 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 requires a subject's refusal of ALL of the following methods of follow up (these methods of follow up will also be noted in the trial eICF):

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

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a 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 3.8.3.1). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.4 to determine if the subject can continue participation in the trial if modifications to his/her treatment or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above

degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.8.3.4 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an eICF), but who is not randomized or assigned to trial treatment.

For this trial, treatment begins with the first dose of the IMP in the single-blind placebo run-in period. Subjects that have a positive alcohol test (via breathalyzer or blood), or positive drug screen for cocaine, or other illicit drugs (excluding marijuana) are not eligible to be retested or rescreened, and will be considered screen failures. Subjects that test positive for marijuana may be permitted to be enrolled if they have no evidence of a substance use disorder, and if they agree to refrain from use for the duration of the trial. Allowance for subjects testing positive for marijuana at screening require explicit approval from the medical monitor. Subjects that test positive for confirmed prescription use of ADHD medications at screening will be required to undergo a washout period (Section 4.1). If after the allotted washout period, a subject tests positive for ADHD medications prior to the start of the single blind placebo run-in period, subjects will be screen failed, and not permitted to rescreen. Screen failures previously excluded for a positive urine drug screen due to use of prescription or over-the-counter (OTC) medications or products not used for the treatment of ADHD, may be retested or rescreened for participation in the trial only with the explicit consent of the medical monitor. Subjects will be administered the ASRS prior to the start of the single-blind placebo run-in period, and those with a ≥ 30% improvement in the (18-item) ADHD Symptoms score compared to the score at screening will be screen failed, and not eligible for rescreening. Screen failures excluded for any other reasons may be rescreened at any time if the exclusion characteristic has changed. In the event that a screen failure is rescreened a new eICF must be signed, a new screening number assigned, and all screening procedures repeated.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete the Day 42/ET visit will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Day 42/ET during the treatment period, 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" as the reason for discontinuation. 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.

3.12 Subject Compliance

Responsible trial personnel will dispense the IMP according to the visits outlined in the Schedule of Assessments (Table 3.7-1). Accountability and compliance verification will be monitored with a medication adherence monitoring platform, and results should be documented in the subject's trial records. Subjects 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.

3.12.1 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 preloaded on a smartphone, or subjects will download the AiCure Platform onto their own mobile device at the start of the single-blind placebo run-in period (Day −7).

When at home, subjects will receive an IMP reminder at a time within a predefined window. This notification reminds subjects to take their IMP dose while using the AiCure Platform. Subjects 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 may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with subjects, 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.

3.12.2 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.

3.12.3 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 subject Informed Consent, 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, or Ethics Committee(s). 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.

3.13 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. The investigator and sponsor 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, and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

Subjects who are currently taking any therapy for ADHD at screening will washout from their current ADHD therapy (see Table 4.1-1) before the start of the single-blind placebo run-in period (Day −7). All subjects must agree to discontinue all prohibited medications during the screening period. Table 4.1-1 provides the required duration of washout for selected prohibited medications. All other prohibited medications must be discontinued at least 24 hours before Day −7.

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Table 4.1-1 List of Medications Prohibited Before the Trial		
Medication		**Required Washout Prior to Start of Placebo Run-in Period**
1.	Antidepressants Fluoxetine All other antidepressants	 28 days 14 days
2.	Benzodiazepines	7 days
3.	Hypnotics, including non-benzodiazepine sleep aids	7 days
4.	ADHD medications Stimulants Nonstimulants	 7 days 21 days
5.	Sedating antihistamines (eg, diphenhydramine, hydroxyzine, chlorpheniramine)	7 days
6.	Antihypertensives Clonidine Propranolol Guanfacine	21 days
7.	Anorexics (weight loss supplements)	7 days
8.	Investigational compounds	7 days

Table 4.1-2 lists all medications prohibited during the trial, including exceptions, where appropriate.

Table 4.1-2 List of Medications Prohibited During the Trial	
1.	All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including depot formulations b) Anticonvulsants c) Antidepressants d) Mood stabilizers (ie, lithium) e) Benzodiazepines[a] f) Hypnotics g) All medications intended for the treatment or management of ADHD symptoms (on or off label use), including but not limited to any form of: amphetamine (mixed salts), atomoxetine, clonidine, dexmethylphenidate, guanfacine, lisdexamfetamine, and methylphenidate h) Opioid analgesics, unless permission is obtained from the medical monitor. Permission for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency. i) Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, omega-3 fatty acids, melatonin, kava extracts, GABA supplements, etc) j) Sedating antihistamines (eg, diphenhydramine, hydroxyzine, chlorpheniramine)
2.	Investigational agents
3.	Barbiturates, except for the treatment of migraine headaches, provided that in the opinion of the investigator the dosing is medically appropriate.
4.	The following antihypertensive medications: propranolol, clonidine, guanfacine
5.	Varenicline or similar medications, excluding nicotine replacement products
6.	Anorexics (weight loss supplements)

[a]Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted for the treatment of insomnia AEs.

4.2 Other Restrictions

4.2.1 Restricted Therapies and Precautions

St. John's Wort (*Hypericum perforatum*) is prohibited for 14 days prior to IMP administration and during the trial. Investigators should inform subjects that normal consumption of caffeine is permitted.

The subject's best medical interests should guide the investigator in the management of conditions that are pre-existing or that develop during the trial (intercurrent illness or AEs). The investigator should examine the acceptability of all concomitant medications not explicitly prohibited. In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medications (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) without prior consultation with the investigator. All trial personnel should be familiar with the content of the centanafadine IB in order to manage the subject's condition adequately and select appropriate concomitant medications, if needed.

4.2.2 Non-therapy Precautions and Restrictions

4.2.2.1 Precautions

Subjects should not undergo any elective medical procedure without prior consultation with the investigator. An elective procedure (minor surgery, dental surgery, orthopedic surgery, etc) that might require hospitalization or general anesthesia should be deferred until after the trial whenever clinically appropriate.

4.2.2.2 Restrictions

Subjects may only receive psychotherapy for ADHD (eg, supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) if they have been participating in the therapy regularly (ie, at consistent intervals) for at least 60 days prior to screening and commit to maintain their participation during the course of the trial with no changes unless permission is obtained from the medical monitor.

Subjects will be instructed to refrain from drinking alcoholic beverages or using illicit drugs (including marijuana) during participation in the trial. The investigator may request a blood or urine drug screen at any time during the trial if there is a suspicion of illicit drug use.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product 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 preplanned 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.

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 in-patient 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 non-medical need) are not considered SAEs.
- 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 adverse events are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AESI (see Section 5.4).
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.6).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. 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 by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eCRF. The intensity 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.

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRF provided by the sponsor. Serious AE collection is to begin after a subject has signed the eICF.

Use medical terminology in 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 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator or site personnel become aware of any 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. An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor or designee. (Please note that the IRE form is NOT the AE eCRF.)

Subjects experiencing SAEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal or have otherwise been explained. 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 or designee.

5.4 Adverse Events of Special Interest

Newly acquired skin eruptions that are non-traumatic 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 or removal of lead adhesive.

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

All AESIs should be reported as IREs (Section 5.3).

5.5 Abuse Potential Monitoring Plan, Events Subject to Additional Monitoring, and Medication Handling Irregularities

A key objective of the Abuse Potential Monitoring Plan (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 own words in the source documents as well as the eCRF, in addition to the clinical term, and to be aware that a subject'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).[40] 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.

5.6 Potential Serious Hepatotoxicity

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

5.7 Pregnancy

Females of childbearing potential are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 consecutive months).

For FOCBP and for males who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP for female subjects, and 90 days after the last dose of IMP for male subjects and their partners who are FOCBP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control injection, birth control implant, birth control patch, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit. Male subjects must also agree not to donate sperm from screening through 90 days after the last dose of IMP.

Before enrolling FOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all FOCBP. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form stating that the above-mentioned risk factors and the consequences were discussed with her.

A urine or serum pregnancy test for human chorionic gonadotropin will be performed at screening on all subjects that are FOCBP. If a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.

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

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.

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP for female subjects, and for 90 days after the last dose of IMP for partners of male subjects, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) 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 appropriate 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.

5.8 Procedure for Breaking the Blind

The investigator is encouraged to contact the sponsor/clinical research organization (CRO) medical monitor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the

personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.9 Follow-up of Adverse Events

5.9.1 Follow-up of Nonserious Adverse Events

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

5.9.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

This trial requires that subjects that complete the trial be actively monitored for SAEs and IREs up to 7 days after the last dose of IMP is administered. Subjects that decide to not enroll in Trial 405-201-00015, or for subjects that do not complete Trial 405-201-00013, will be actively monitored for SAEs and IREs up to 10 days after the last dose of IMP is administered.

Serious AEs and nonserious IREs that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eCRF page. If updated information (eg, resolved status) on SAE or 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 according to the appropriate reporting procedures. The investigator will follow SAEs until the events are resolved, stabilized, or 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.

5.9.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring after Last Scheduled Contact

Any new SAEs or 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. This may include SAEs or IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs or IREs identified 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.

6 Pharmacokinetic/pharmacogenomic Analysis

The PK samples will be analyzed for centanafadine (EB-1020) and its metabolite(s) concentrations. Times postdose will be determined from the date and time of first pill captured by AiCure for the dose prior to the PK sample and the sampling date and time captured in the eCRF; for the sample taken 7 days after the last dose of IMP (Day 49 for completers), the date and time of the first pill from last dose taken (on Day 42 for completers) will be used as the date and time of the dose prior to the sample. No formal statistical comparisons are planned. A separate population or PK/pharmacogenomic modeling may be performed using the data from this trial and other trials.

7 Statistical Analysis

7.1 Sample Size

The primary efficacy endpoint is the change from baseline at Day 42 in AISRS total score. The trial will compare the placebo arm to the centanafadine dose arms, randomized at a ratio of 1:1:1, with an overall alpha of 0.05 for the primary endpoint.

Based on the results at various dose strengths from phase 2 centanafadine trials, it is reasonable to expect a treatment difference of 5 points with a standard deviation (SD) of 12.5 in the mean change from baseline to Day 42 on AISRS total score in either the 200 mg TDD or 400 mg TDD arms. The planned sample size of 405 evaluable subjects (135 in each treatment arm) will yield at least 90% power to detect the treatment effects at a 2-tailed significance level of 0.05. The 2-sided alpha level for the final analysis is 0.05.

A sufficient number of subjects will be enrolled and randomized to achieve approximately 405 evaluable subjects in the double-blind treatment period (ie, subjects with an AISRS total score at baseline and at least 1 subsequent AISRS total score in the

double-blind treatment period). After allowance of 10% nonevaluable subjects in the double-blind treatment period, the total number of subjects to be randomized is 450 subjects (150 subjects in each treatment arm). In order to ensure 405 evaluable subjects, the number of nonevaluable subjects will be monitored in a blinded manner on an ongoing basis during the trial. The power and sample size were obtained using the PASS 14 (2015) statistical computing software.

7.1.1 Datasets for Analysis

The following samples are defined for this trial:

- Enrolled Sample: comprises all subjects who signed an eICF for the trial and enrolled into the single-blind placebo run-in period
- Randomized Sample: comprises of all subjects who were randomized in the double-blind treatment period. Subjects are considered randomized when they are assigned a treatment group by eCRF at the end of the single-blind placebo run-in period. A subject receiving IMP outside of the eCRF will not be considered randomized, but safety will be reported.
- Safety Sample: comprises those randomized subjects in the double-blind treatment period who receive at least 1 dose of double-blind IMP as indicated on the dosing record. Subjects will only be excluded from this population if there is documented evidence (ie, drug dispensed = drug returned or no IMP dispensed) that the subject did not take IMP. If a subject is dispensed IMP and is lost to follow-up, he/she will be considered exposed.
- Efficacy Sample: the Full Analysis Set (FAS) comprises all subjects in the Safety Sample who have a baseline value and at least 1 valid post-randomization efficacy evaluation for AISRS total score in the double-blind treatment period.

The core dataset for all efficacy analyses is the FAS, which is created based on the intent-to-treat (ITT) principle. However, as will be described below, in order to handle missing data and restrictions imposed by different types of analyses (eg, change from baseline analysis), datasets derived from the FAS dataset will be used for the efficacy analysis.

7.2 Handling of Missing Data

The AISRS is utilized as the primary efficacy assessment of a subject's level of ADHD symptoms. This 18-item scale directly corresponds to the 18 DSM-5 symptoms of ADHD where 9 Inattentiveness items alternate with 9 Hyperactivity/Impulsivity items. Each item is scored as follows: 0 (none), 1 (mild), 2 (moderate), 3 (severe). For all items, 0 is the "best" rating and 3 is the "worst" rating. The maximum total score for the scale is 54 points, with 27 points for each subscale. The AISRS total score is the sum of the Inattentiveness and Hyperactivity/Impulsivity subscale scores. The range of the AISRS

total score is from 0 to 54. The AISRS Inattentive subscale score and Hyperactivity/Impulsivity subscale score, as well as the AISRS total score is set to be missing if more than one item of a subscale is missing for Inattentiveness subscale or Hyperactivity/Impulsivity subscale, separately. If one item is missing for a given subscale (Inattentiveness or Hyperactivity/Impulsivity), then the subscale score will be derived as the mean of scores for non-missing items multiplied by 9. All imputed scores are rounded to the first decimal place.

The mixed-effect model repeated measures (MMRM) assumes data are missing at random (MAR), which is a reasonable assumption in longitudinal clinical trials in ADHD. However, the possibility of "missing not at random" (MNAR) data can never be ruled out. As sensitivity analyses, either selection model[41] pattern-mixture model[42,43,44,45] or shared parameter model[46] will be used to explore data missing mechanisms of MNAR and investigate the response profile of dropout reason. Pattern Mixture Models based on Multiple Imputation (MI) with mixed missing data mechanisms will be used to investigate the response profile of dropout subjects by last dropout reason under MNAR mechanism for the following 3 scenarios: 1) Dropout reasons due to either AE or lack of efficacy as MNAR, 2) Dropout reasons due to either AE or lack of efficacy or subject withdrew consent as MNAR, 3) All dropouts as MNAR using both 1) Delta adjustment imputation method which is to departure from MAR assumption by progressively increasing the delta until conclusion from the primary analysis is overturned, and 2) Placebo based imputation methods in which missing data for both placebo and drug group are imputed based on the imputation model derived from placebo data. If drug improved outcomes prior to dropout, this benefit is carried into subsequent imputed values, but will diminish over time in accordance with the correlation structure. Details of these exploratory analyses will be provided in the statistical analysis plan (SAP).

7.3 Primary, Secondary, and Exploratory Endpoint Analyses

7.3.1 Primary Efficacy Endpoint Analysis

The objective of the primary efficacy analysis is to compare the efficacy between centanafadine (SR 200 mg TDD or SR 400 mg TDD) and placebo. The primary efficacy endpoint is the change from baseline to Day 42 in AISRS total score. For analysis of the double-blind treatment period data, baseline is defined as the last available measurement prior to the first dose of double-blind IMP in the double-blind treatment period.

The estimand for the primary efficacy analysis is the difference in outcome improvement if all subjects tolerated and adhered to their treatment. This approach is Estimand #3,

recommended by the 2010 National Academy of Sciences' National Research Council report on prevention and treatment of missing data and ICH E9 (R1) "Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials".

This estimand focuses on the efficacy of centanafadine (SR 200 mg TDD or SR 400 mg TDD) in change from the baseline in AISRS total score. The objective of this trial is consistent with the election of an efficacy rather than effectiveness estimand.

The primary analysis will be performed on the Efficacy Sample which includes all randomized subjects who took at least 1 dose of IMP in the double-blind treatment period and who have both baseline and at least 1 post-randomization AISRS total score during the double-blind treatment period. The primary efficacy analysis will be performed by fitting a MMRM analysis with an unstructured variance covariance structure in which the change from baseline in AISRS total score at the scheduled double-blind treatment period visits will be the dependent variable based on the observed cases (OC) data set. The model will include fixed class effect terms for treatment, trial center, visit day, and an interaction term of treatment by visit day. The model will also include baseline values for the double-blind treatment period of AISRS total score and the interaction term of baseline values of AISRS total score by visit day as covariates. The primary comparison between the centanafadine (400 mg TDD group or 200 mg TDD group) and the placebo group at Day 42 in the double-blind treatment phase will be estimated as the difference between Least Squares means utilizing the computing software SAS procedure PROC MIXED. The comparison between the centanafadine (400 mg TDD group or the 200 mg TDD group) and the placebo group will be tested at a significance level of 0.05 (2-sided) in the order of 1) 400 mg versus placebo, and 2) 200 mg versus placebo. If there is a convergence problem with the unstructured variance covariance matrix of the MMRM model, the following structures other than unstructured will be used in order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry and the first (co)variance structure converging to the best fit will be used as the primary analysis. If a structured covariance has to be used, the "sandwich" estimator of the standard error of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix. Details of this analysis will be provided in the SAP.

Small centers will be defined as centers that do not have at least 1 evaluable subject (evaluable with regard to the primary efficacy variable) in each treatment arm in the double-blind treatment period. All small centers will be pooled to form "pseudo centers" for the purpose of analysis according to the following algorithm. Small centers will be

ordered from the largest to the smallest based on the number of evaluable subjects (ie, subjects who have baseline and at least 1 post-baseline value for the primary endpoint in the double-blind treatment period). The process will start by pooling the largest of the small centers with the smallest of the small centers until a non-small center is formed. This process will be repeated using the centers left out of the previous pass. In case of ties in center size, the center with the smallest center code will be selected. If any centers are left out at the end of this process, they will be pooled with the smallest pseudo centers, or if no pseudo centers exist, they will be pooled with the smallest non-small center.

In the case of gross violations of the linear model assumptions, nonparametric van Elteren test will be performed to compare the treatment effect at Day 42 in the double-blind treatment period on both last-observation-carried-forward (LOCF) and MI data. Details will be provided in the SAP.

7.3.1.1 Sensitivity Analyses

7.3.1.1.1 Sensitivity Analyses for Missing at Random Assumption

Traditionally the dropout mechanisms are divided into 3 types[43]: (1) missing completely at random (MCAR), in which the probability of dropout doesn't depend on the observed data and the missing data; (2) MAR, in which the probability of dropout depends on the observed data, and (3) MNAR, where the probability of dropout depends on the missing data and possibly the observed data.

Most of MNAR methods[41] have treated all observations with dropout as if they fall within the same dropout type. In practice, we would find that different dropout reasons may be related to the outcomes in different ways, for example, detailed dropout reasons for this trial are: AE, LOE, death, reasons unrelated to medical condition, withdrawal of informed consent, lost to follow-up, rash, pregnancy, and termination of all or part of the trial by sponsor. Dropout due to an AE, rash, and LOE may lead to MNAR dropout. Subjects that withdrew consent may also lead to MNAR dropout. However, it is debatable whether a dropout caused by subjects that withdrew consent are MAR or MNAR. Except AE, rash, LOE, and subjects that withdrew consent, all the other dropout reasons may be assumed as either MCAR or MAR dropout.

As sensitivity analyses for MAR assumptions, analyses for MNAR will be carried out. Pattern Mixture Models based on MI with mixed missing data mechanisms will be used

to investigate the response profile of dropout subjects by last dropout reason under the MNAR mechanism for the following 3 scenarios:

1) Dropout reasons due to either AE, rash, or LOE as MNAR
2) Dropout reasons due to either AE, rash, or LOE or subject withdrew consent as MNAR
3) All dropouts as MNAR

Delta Adjustment Imputation Methods

This MNAR sensitivity analysis will be performed to address a departure from the MAR assumptions by progressively increasing the delta until the conclusion from the primary analysis is overturned. The delta is 0%, 10%, 20%, 30%, .., 100% of the expected treatment difference of 5 points and/or the observed treatment difference between centanafadine and placebo from the primary analysis of MMRM model until the conclusion of the primary analysis is overturned. When delta=0 it is MAR. When delta > 0 it is MNAR.

1) Using Monte Carlo Markov Chain methodology from PROC MI to impute the intermittent missing data to a monotone missing pattern;
2) Using a standard MAR-based multiple imputation approach from PROC MI to impute the monotone missingness data
3) For subjects in the treated group and with a dropout reason of AE or LOE or subject withdrew consent, a delta will be added for all the values after the dropout time.
4) Using MMRM model in the primary analysis to analyzed the completed data using PROC MIXED on the multiple imputed data
5) Obtaining the overall results using PROC MIANALYZE

Placebo Based Imputation Methods

The placebo-based imputation methods will be similar to the "Standard" multiple imputations method, except the parameters for the imputation model will only be obtained from the placebo (control) group. Missing data for both the placebo and drug groups are imputed based on the imputation model derived from placebo data. If drug improved the outcomes prior to dropout, this benefit is carried into subsequent imputed values, but will diminish over time in accordance with the correlation structure.

In addition, model based MNAR methods such as the shared parameter model[46] and random coefficient pattern mixture model[44] will be also performed.

7.3.1.1.2 Sensitivity Analyses for Violation of Normality Assumption

The primary endpoint MMRM analysis is a maximum likelihood method that relies on the normality assumption. Residual analyses will be carried out to examine model assumption.

In the case of gross violations of the normality assumptions, nonparametric van Elteren test[47] will be performed to compare treatment effect at Day 42 on both LOCF dataset and MI data. The van Elteren test is a generalized Cochran Mantel Haenszel (CMH) procedure useful for stratified continuous data in non-normal setting. It belongs to a general family of Mantel-Haenszel mean score tests. The test is performed via SAS procedure PROC FREQ, by including CMH2 and SCORES=MODRIDIT options in the TABLE statement. The stratification factor is trial center.

In addition, other methods that are robust to distributional assumption will also be performed to provide different views on the primary efficacy result, these include generalized estimating equations (GEE), weighted GEE, and MI-robust regression.[48]

For MI-van Elteren test and MI-robust regression, imputation datasets will be generated with SAS MI procedure, each dataset will be analyzed, and then an overall estimate is derived with SAS MIANALYZE procedure.

7.3.2 Secondary Efficacy Endpoint Analyses

7.3.2.1 Key Secondary Efficacy Endpoint Analysis

The key secondary efficacy endpoint is the change from baseline to Day 42 between treatment groups using the CGI-S. The estimand for the key secondary efficacy analysis is also the difference in outcome improvement if all subjects tolerated and adhered to their treatment. This approach is Estimand #3 recommended by the 2010 National Academy of Sciences' National Research Council report on prevention and treatment of missing data and ICH E9 (R1) Addendum. This key secondary efficacy endpoint will be analyzed by fitting the same MMRM model described in the primary analysis.

To control the overall experiment-wise type I error at 0.05 level, a fixed-sequence testing approach will be applied.

The statistical test will be performed in the following order:

1) Change from baseline to Day 42 in the double-blind treatment period in AISRS total score between centanafadine 400 mg TDD and placebo;
2) Change from baseline to Day 42 in CGI-S score between centanafadine 400 mg TDD and placebo;

3) Change from baseline to Day 42 in the double-blind treatment period in AISRS total score between centanafadine 200 mg TDD and placebo;
4) Change from baseline to Day 42 in CGI-S score between centanafadine 200 mg TDD and placebo.

7.3.2.2 Other Efficacy Endpoint Analyses

Other efficacy analyses are listed below. All other efficacy variables will be evaluated at a nominal 0.05 level (2-sided) without adjusting for multiplicity.

1) Change from baseline in AISRS total score for every scheduled visit during the double-blind treatment period other than the Day 42 visit;
2) Change from baseline for the Inattentive subscale and Hyperactive-Impulsive subscale of the AISRS for scheduled visits during the double-blind treatment period, separately at every visit
3) Change from baseline in CGI-S for every scheduled visit during the double-blind treatment period other than the Day 42 visit
4) CGI Change from Baseline at each scheduled visit
5) Percentage of responders at each post-baseline visit, where a responder is defined as a subject with a CGI Change from Baseline score of 1 or 2 OR a ≥ 30% improvement in ADHD symptoms compared with baseline as measured by the AISRS total score

Variable (1) through variable (3) will be evaluated using the same MMRM model described in the primary analysis. Variable (4) will be evaluated by the CMH Row Mean Score Differ Test controlling, in LOCF analysis, for trial center. Variable (5) will be evaluated by the CMH General Association Test controlling, in LOCF analysis, for trial center. An OC analysis will also be conducted for variables (4) and (5), but will not control for trial center. Statistical significance for analysis of all other efficacy variables will be evaluated at a nominal 0.05 level (2-sided).

7.3.3 Exploratory Efficacy Endpoint Analyses

Statistical analysis of the exploratory endpoints will be further described in the SAP.

7.4 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height, and BMI for the randomized subjects will be summarized by descriptive statistics (frequency, mean, median, SD, maximum, minimum, and percentage when applicable).

Baseline disease severity and medical history will be also be summarized by descriptive statistics for the Safety Sample to identify any potential lack of balance between the treatment groups.

7.5 Safety Analysis

Safety analysis regarding safety and tolerability in the double-blind treatment period will be conducted based on the Safety Sample defined in Section 7.1.1. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, and body weight. Details of safety analysis will be provided in the SAP.

7.5.1 Adverse Events

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

- Treatment-emergent AEs (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
- Abuse-related AEs and AEs involving MHIs

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

7.5.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements will be provided. In addition, potentially clinically significant laboratory results will be identified using criteria prospectively defined in the SAP, and will be summarized.

7.5.3 Physical Examination and Vital Signs Data

By-subject listings will be provided for physical examination findings. Summary statistics for changes from baseline in vital signs and body weight will be provided. Potentially clinically significant results in vital signs and body weight will also be summarized. The SAP will define other information to be analyzed for physical examination data.

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7.5.4 Electrocardiogram Data

Mean change from baseline and incidence of clinically significant changes will be calculated for ECG parameters.

For the analysis of QT and QTc, data from 3 consecutive complexes (representing 3 consecutive heart beats) will be measured to determine average values. The following QT corrections will be used for reporting purposes in the clinical trial report:

1) QTcB is the length of the QT interval corrected for heart rate by the Bazett formula: $QTcB = QT / (RR)^{0.5}$
2) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: $QTcF = QT / (RR)^{0.33}$
3) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN = QT / (RR)^{0.37}$

7.5.5 Other Safety Data

Medication withdrawal symptoms assessed by SMWQ total scores at the scheduled visit(s) will be summarized by treatment group by descriptive statistics. Details will be described in the SAP.

Suicidality monitored during the trial using the C-SSRS will be summarized by treatment group by descriptive statistics. Details will be described in the SAP.

7.5.6 Abuse Liability Analysis

Abuse potential will be assessed through the active monitoring of ESAMs (eg, AEs related to abuse potential and AEs involving MHI).

8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the centanafadine IB.[25]

8.1 Packaging and Labeling

Trial medication will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The IMP will be supplied as weekly blister cards. Each blister card used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP will be stored at controlled room temperature conditions as per the clinical label on the IMP. The clinical site staff will ensure that the temperature log is maintained in the drug storage area and that the temperature is recorded at least once each working day. The clinical site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day.

8.3 Accountability

The investigator or designee must maintain an inventory record of IMP received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMP, and partially used IMP must be returned to the sponsor or a designated agent, or destroyed at the trial site. The IMP may only be destroyed by the trial site, if approved by the sponsor and if the IMP destruction meets all local regulations.

All IMP returned to the sponsor must be accompanied by the appropriate documentation and be clearly identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor will facilitate the return or destruction of used IMP containers, unused IMP, and partially-used IMP.

8.5 Reporting of Product Quality Complaints

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

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)

- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Online: Send information required for reporting purposes (listed below) to [redacted]
- Phone: [redacted] at [redacted]

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

8.5.2 Information Required for Reporting Purposes

- Description of compliant
- 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 or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

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

8.5.4 Assessment/Evaluation

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

9 Records Management

9.1 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 progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

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

9.2 Data Collection

During each subject's visit to the clinic, a clinician participating in the trial will record progress notes 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;
- The signature (or initials) and date of each clinician (or designee) who made an entry in the progress notes.

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 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. Changes to the data will be captured by an automatic audit trail.

The trial site will be given a tablet to directly record subject data and clinical observations on electronic forms. Designated trial site staff will not be given access to the 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 by the trial clinical research associate, 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 clinician.

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.

9.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6[26] and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

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

- A period of at least 2 years after the date on which a New Drug Application 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 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated 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 clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 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, and comparison of the eCRF with source documents. The investigator agrees to participate with audits.

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

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling the eCRF, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject ID code 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.

12 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, 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 numbers in eCRF. If further subject ID is required, subjects’ full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). 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, or the sponsor conclude that the protocol amendment substantially alters the trial design 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.

14 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 participants 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 participants consent to such acknowledgement in any publications resulting from its conduct.

15 References

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Appendix 1 Collection, Handling, and Shipment of Bioanalytical Samples

Pharmacokinetic Sample Collection

Blood (2 mL) will be collected for the determination of plasma concentrations of centanafadine (EB-1020) and its metabolite(s).

The PK samples will be collected into 2-mL Vacutainer® tubes containing potassium ethylenediaminetetraacetic acid (K_2EDTA). Each tube must be gently inverted at least 8 times. Within 60 minutes of collection, the blood tubes must be centrifuged at 2000 to 3000 rpm for 10 to 15 minutes at 4°C (± 3°C). The rpm, time and temperature should remain the same throughout the trial. Within 90 minutes of collection, the separated plasma from the tube should then be transferred to the bar-code labeled transfer or plasma tube.

All tubes must be labeled using the labels provided by the sponsor or sponsor designee. If information needs to be written on the tube label, then the pen will need to use waterproof ink and the label must be covered with transparent tape, or other means, in order to prevent damage to the label during freeze/thaw cycles. An electronic manifest must be provided with all sample shipments and must be approved by the sponsor prior to sample shipment.

The sample must be stored at −70°C (± 10°C). If a −70°C freezer is not available, the PK samples must be shipped on dry ice to the central laboratory on the day of collection, otherwise samples should be shipped on dry ice within 1 month of collection.

Pharmacogenomic Sample Collection

A 4-mL whole blood sample for the pharmacogenomic determination of drug metabolizing enzymes and transporters will be collected by venipuncture into one 4-mL K_2EDTA Vacutainer tube. Each tube should be gently inverted 10 times to ensure proper mixing with the anticoagulant. Refrigerate the whole blood samples at 4°C (± 3°C) for at least 1 day (but no longer than 4 days). Then, the samples should be stored upright at −20°C (± 10°C) or below. If refrigerating is not possible, samples can be frozen directly from ambient. The tube will be shipped on dry ice to the central laboratory.

Blood Samples for Future Biospecimen Research

Blood (approximately 10 mL) will be collected into an evacuated collection tube(s). The trial site is expected to follow the instructions for collection, processing, storage, and shipment of blood samples. The FBR samples will be shipped to the central laboratory.

The FBR samples will be stored for potential analysis for up to 20 years from acquisition. The specimens will be stored under strict supervision in a limited access facility which operates to ensure the integrity of the specimens.

Sample Shipment

Plasma samples must be neatly packed in a Styrofoam container which should be completely filled with dry ice to avoid air spaces that allow evaporation of the dry ice. The Styrofoam container should be sealed with tape and placed in a cardboard box. The recipient of the samples must be alerted of sample shipment. Packages will be shipped via an overnight carrier and must not be shipped on Thursdays, Fridays, Saturdays, or any day prior to a holiday without the expressed consent of the sponsor. The names and addresses of the laboratories for shipping purposes will be provided in the Operations Manual.

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Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST	≥ 3 × ULN
ALT	≥ 3 × ULN
Alkaline phosphatase	≥ 3 × ULN
Blood urea nitrogen	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
Creatine phosphokinase	> 3 × ULN
Hematology	
Hematocrit	
Men	≤ 37% and decrease of ≥ 3 percentage points from baseline
Women	≤ 32% and decrease of ≥ 3 percentage points from baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
WBC count	≤ 2,800 mm^3 or ≥ 16,000 mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Absolute neutrophil count	≤ 1,500/mm^3
Platelet count	≤ 75,000/mm^3 or ≥ 700,000/mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 100 mg/dL
Nonfasting	≥ 200 mg/dL
Total cholesterol, fasting	≥ 240 mg/dL
LDL cholesterol, fasting	≥ 160 mg/dL
HDL cholesterol, fasting	
Men	< 40 mg/dL
Women	< 50 mg/dL
Triglycerides, fasting	≥150 mg/dL

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Appendix 3 Criteria for Identifying Vital Signs of Potential Clinical Relevance

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

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

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

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Appendix 4 Criteria for Identifying Electrocardiogram Measurements of Potential Clinical Relevance

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

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

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

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

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

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Appendix 5 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue Date: 18 May 2018

PURPOSE:

This amendment serves to provide clarifications, additions, and subtractions to trial procedures intended to gather additional safety data during the follow-up period. In addition, administrative clarifications were made, including corrections to typographical, punctuation, and formatting errors. These changes were minor and do not change the design or content of the protocol, and therefore, are not summarized in this appendix.

BACKGROUND:

These changes to clinical trial protocol 405-201-00013, issued 08 Mar 2018, were made to address preliminary FDA comments received on 27 Apr 2018 in regards to the Type C briefing package, and to address other minor administrative changes.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Added additional follow-up contacts to be conducted via telephone on 1, 3, and 5 days after the last dose of IMP for all subjects enrolled in Trial 405-201-00013.
- Revised the last day of subject contact from Day +14 to Day +10 for subjects that do not complete Trial 405-201-00013, are not eligible for, or do not rollover to Trial 405-201-00015.
- Added criteria excluding subjects with HIV seropositive status/acquired immunodeficiency syndrome, seropositive status for hepatitis B (ie, HBsAg positive), or hepatitis C (ie, anti-HCV positive and HCV RNA positive).
- Clarified that pregnancy testing at screening should only be performed on FOCBP.
- Added wording in the clinical laboratory table indicating that a CPK reflex for isoenzymes if CPK > 3 × ULN; serum and urine myogloblin collected if CPK > 5 × ULN, and that the urine drug screen should include methylphenidate (ritalinic acid).
- Revised exclusion language regarding participating in other prior clinical trials.
- Added statistical language to address new requirements set forth by the ICH E9(R1) Addendum.
- Removed Appendices 5-8 from the protocol and replaced in-text references to these appendices with reference to external documentation.
- Revised postmenopausal criteria to be aligned with template text.

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- Clarified that SMWQ will be completed by the subject at the site and completed remotely for non-site visits.
- Removed CYP2D6 inhibitors and substrates from the List of Medications Prohibited Before the Trial table and the List of Medications Prohibited During the Trial table.
- Corrected various typographical errors and provided clarifications to text.

ADDITIONAL RISK TO THE SUBJECT:
There is no additional risk to the subjects.

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Administrative Change Number: 1

Issue Date: 30 Aug 2018

PURPOSE:

The purpose of this administrative change is to provide clarifications to trial procedures.

This administrative change will not affect the safety of subjects, the scope of the investigation, or the scientific quality of the trial.

BACKGROUND:

These changes to clinical trial protocol 405-201-00013, originally issued on 08 Mar 2018 and amended on 18 May 2018, were made to address administrative changes and correct minor errors.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Updated the email address for reporting IREs.
- Changed the FBR blood volume collection from “up to 10 mL” to “approximately 10 mL”.
- Changed “birth control depot injection” to “birth control injection”.
- Clarified that some clinical laboratory assessments (alcohol testing) are not performed at screening only.
- Added clarification that subjects who will be rolling over into the open-label trial will need to sign the Trial 405-201-00015 informed consent form prior to activities performed at the 7-day follow-up visit of Trial 405-201-00013.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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Amendment Number: 2

Issue Date: 15 Jan 2020

PURPOSE:

The purpose of this protocol amendment is to remove the mention of the interim analysis and provide revisions and clarifications to exclusion criteria. In addition, there are revisions to a number of planned screen subjects and clarifications around the drug screening.

BACKGROUND:

These changes to clinical trial protocol 405-201-00013, originally issued on 08 Mar 2018, amended on 18 May 2018, and an administrative change on 30 Aug 2018, were made to remove the interim analysis based on FDA comments received, and to address other administrative changes.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Number of planned screened subjects revised from 900 to 1150 in Section 3.3.1.
- The statement added to exclusion criteria 9 "This would also include most bariatric surgeries, with the only exception being those where there has been no breach of the gastrointestinal wall (ie, uncomplicated lap band surgery) AND no sign of malabsorption".
- Exclusion criteria 22 revised to provide clarity to the text.
- Exclusion criteria 28 and 30 revised to clarify that a drug screen will be assessed prior to Visit 2 and baseline visit, respectively, and clarification added that the criteria include medications such as opioids or benzodiazepines taken without prescription.
- Interim analysis was removed from the following:
  - Section 3.7 Trial Procedures
  - Section 3.7.8 Interim Analysis Review Committee
  - Section 3.8.1 Entire Trial or Treatment Arm(s)
  - Section 7.1 Sample Size
  - Section 7.3.2.1 Key Secondary Efficacy Endpoint Analysis
  - Section 7.3.4 Interim Analysis
- Clarification around positive drug screenings and negative repeat screens added to Section 3.7.1.1, Visit 1 (Screening) and Section 3.7.1.2, Visit 2 (Single-blind Placebo Run-in).
- Statement added in Section 3.7.1.1, Visit 1 (Screening) "a urine drug screen will be collected and sent to the central lab for evaluation" for clarity.

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- Removed language that urine drug screen should be performed prior to the start of any other screening procedures added to Section 3.7.1.1.1, Visit 1 (Screening).
- Removed language that urine drug screen should be performed prior to the start of any other screening procedures and added a clarifier that urine drug screen results from the previous visit will be reviewed. Revisions were made in the following sections:
  - Section 3.7.1.2, Visit 2 (Single-blind Placebo Run-in)
  - Section 3.7.1.3, Visit 3 (Baseline)
  - Section 3.7.1.4.1, Visits 4 through 8
  - Section 3.7.1.4.2, Visit 9/End of Treatment/Early Termination
- Revisions for clarification around blood samples for genotyping made to Section 3.7.6.2, DNA Blood Samples for Pharmacogenomic Testing and Section 3.7.1.3, Visit 3 (Baseline).
- Corrected various typographical errors.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the 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 (EB-1020), 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) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where centanafadine (EB-1020) 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- or IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms 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/IEC 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/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC 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 sub-investigators 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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SIGNATURE PAGE

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