Official Title:	An Open-label, 52-Week, Multicenter Trial Evaluating the Long-term Safety and Tolerability of Centanafadine Sustained-Release Tablets in Adults with Attention-Deficit/Hyperactivity Disorder
NCT Number:	NCT03605849
Document Date:	Protocol Amendment Version 2: 02 Jun 2020

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Otsuka Pharmaceutical Development & Commercialization, Inc

Investigational Medicinal Product

Centanafadine (EB-1020)

REVISED CLINICAL PROTOCOL

An Open-label, 52-Week, Multicenter Trial Evaluating the Long-term Safety and Tolerability of Centanafadine Sustained-Release Tablets in Adults with Attention-Deficit/Hyperactivity Disorder

Protocol No. 405-201-00015
IND No. 119,361

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, Maryland 20850
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety CCI [redacted]
Issue Date:	07 Mar 2018
CCI [redacted]	
Version No.:	4.0

Protocol 405-201-00015

Trial Conduct for COVID-19

All procedures and assessments in this protocol are to be followed to the fullest extent possible. The sponsor, in coordination with the site, investigator(s), and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it relates to COVID-19. If any protocol-specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, refer to the COVID-19 Addendum for the appropriate measures to be followed. Appropriate measures may include replacing in-person visits with virtual visits (phone or video) as deemed necessary by the investigator to ensure subject safety and maintain protocol requirements.

Protocol 405-201-00015

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc Name of Investigational Medicinal Product: Centanafadine (EB-1020)	Protocol No.: 405-201-00015 IND No.:119,361
Protocol Title:	An Open-label, 52-Week, Multicenter Trial Evaluating the Long-term Safety and Tolerability of Centanafadine Sustained-Release Tablets in Adults with Attention-Deficit/Hyperactivity Disorder
Clinical Phase/Trial Type:	3
Treatment Indication:	Adults with attention-deficit/hyperactivity disorder (ADHD)
Objective:	To assess the long-term safety and tolerability of centanafadine sustained-release (SR) tablets administered twice daily (BID) (400 mg total daily dose [TDD]) in the treatment of adults with ADHD.
Trial Design:	Multicenter, open-label
Subject Population:	The trial population will include rollover subjects from Trial 405-201-00013 or Trial 405-201-00014 and de novo subjects. De novo 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. Approximately 720 subjects will be enrolled in this trial, with the expectation that approximately 300 subjects will achieve 6-month exposure and approximately 100 subjects will achieve 52-week exposure.

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Inclusion/Exclusion Criteria:	Key inclusion criteria for rollover subjects from double-blind phase 3 trial (ie, Trial 405-201-00013 or Trial 405-201-00014) include the following: • Subjects who completed the 6-week double-blind treatment period and 7-day follow-up after last dose of investigational medicincal product (IMP) in double-blind trials and who, in the opinion of the investigator, could potentially benefit from centanafadine for ADHD. • Subjects who, during the double-blind trials, demonstrated adequate compliance with medication and protocol requirements, per investigator's judgment. Key inclusion criteria for de novo subjects include the following (other than the key criteria described under Subject Population in this Synopsis): • Subjects are 18 to 55 years of age, inclusive, at the time of consent. • Subjects have BMI of 18 to 40, inclusive. • Subjects are willing to discontinue all prohibited psychotropic medications starting from the time of signing the informed consent and up to the 10-day safety follow-up period. Key exclusion criteria for rollover subjects from double-blind phase 3 trial (ie, Trial 405-201-00013 or Trial 405-201-00014) include the following: • Subjects who experienced, in the opinion of the investigator, poor tolerability to trial medication or whose safety assessments resulted in new concerns that would suggest the subject may not be appropriate for a 52-week treatment with trial medication. • Subjects who have re-initiated any therapy for adult ADHD during the 7-day follow-up period after the Week 6 visit of the double-blind phase 3 trial. • 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 medications at baseline will not be permitted to continue participation in Trial 405-201-00015.

	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. Key exclusion criteria for de novo subjects include the following: • Subject has a DSM-5 diagnosis of Other Specified or Unspecified Attention-Deficit/Hyperactivity Disorder as confirmed by ACDS Version 1.2. • Subject has a current comorbid psychiatric disorder that is either controlled with medications prohibited in this trial or is uncontrolled and associated with significant symptoms, including but not limited to: a current major depressive episode (as per DSM-5 criteria), current symptoms (past 90 days) meeting the DSM-5 criteria for a diagnosis of generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, or posttraumatic stress disorder, as established by the MINI. Note: Subjects with mild mood or anxiety symptoms that do not meet criteria for diagnosis, who do not require treatment based on the Investigator's assessment, and do not confound efficacy or safety assessments in the opinion of the examining Investigator, may be included. • 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.
Trial Site(s):	An estimated 115 sites in the United States (US) will enroll subjects.

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Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Centanafadine will be provided as 100 mg SR tablets. After the completion of baseline evaluations (Day -1), all subjects will receive a starting dose of 200 mg TDD of centanafadine SR tablets from Days 1 to 7, followed by a titration to 400 mg TDD of centanafadine SR tablets on Day 8. Subjects will continue at 400 mg TDD for the rest of the open-label treatment period. From Days 1 to 7, all doses of open-label IMP will be taken orally BID, with 1 centanafadine SR tablet taken in the morning and 1 centanafadine SR tablet taken 4 to 6 hours after the first dose. From Day 8 to Week 52/early termination (ET), all doses of open-label IMP will be taken orally BID, with 2 centanafadine SR tablets taken in the morning and 2 centanafadine SR tablets taken 4 to 6 hours after the first dose. Every effort should be made to administer the IMP at the same times every day.
Trial Assessments:	*Primary:* Adverse event (AE) reporting. *Additional Safety:* Clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs, physical examination, Columbia-Suicide Severity Rating Scale (C-SSRS), and Study Medication Withdrawal Questionnaire (SMWQ). *Efficacy:* Adult ADHD Investigator Symptom Rating Scale (AISRS), Clinical Global Impression-Severity of Illness Scale (CGI-S) and ADHD Impact Module - Adult (AIM-A). *Screening/Other:* Medical, psychiatric, and medication history, urine drug and alcohol screening, urine pregnancy test, MINI, and ACDS Version 1.2.

Criteria for Evaluations:	**Primary Endpoint:** The long-term safety and tolerability of centanafadine SR tablets administered BID (400 mg TDD) will be assessed by the frequency and severity of treatment-emergent AEs (TEAEs). **Additional Safety Endpoints:** Additional safety variables will include clinically significant changes in: laboratory tests (hematology, serum chemistry, coagulation parameters, and urinalysis), physical examinations, vital sign measurements, electrocardiograms (ECGs). The C-SSRS will be used to assess and classify reported suicidal behavior. By-subject listings of physical examination findings will be provided as a further assessment of safety. Assessments of withdrawal symptoms will be evaluated using SMWQ. Abuse-related AEs and AEs involving medication irregularities will be recorded verbatim on source documentation with detailed narratives.

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Statistical Methods:	The sample size is not based on statistical power considerations but on International Council for Harmonisation/Good Clinical Practice (ICH/GCP) requirements. The trial population will be derived from eligible subjects from double-blind phase 3 trial (ie, Trial 405-201-00013 or Trial 405-201-00014) and de novo subjects from selected sites. It is expected that approximately 560 completing subjects from double-blind phase 3 trial (Trial 405-201-00013 or Trial 405-201-00014) and approximately 145 de novo subjects will be enrolled into this trial. **Primary Endpoint Analysis:** The primary safety analysis is the frequency and severity of AEs in this trial. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of TEAEs will include the following summaries: • 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 medication handling irregularities A TEAE is defined as an AE that starts after the first dose of IMP or an AE that is reported at baseline and increases in intensity or becomes serious or trial drug-related or results in death, discontinuation, interruption, or reduction of IMP. Descriptive statistics will be provided for each endpoint, and will be summarized at each trial visit using the observed cases (OC) dataset and at the last visit using the last observation carried forward (LOCF) dataset. Baseline is defined as the last available measurement prior to the first dose of open-label IMP in the open-label treatment phase.

Trial Duration:	Individual participation for rollover subjects who complete the trial without early withdrawal will be approximately 54 weeks, consisting of a 52-week open-label treatment period, and 10-day safety follow-up after the last dose of IMP. Individual participation for de novo subjects who complete the trial without early withdrawal will be approximately 58 weeks, consisting of a screening period of up to 28 days, a 52-week open-label treatment period, and a 10-day safety follow-up 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
AST	Aspartate aminotransferase
BID	Twice daily
BMI	Body mass index
CCI	[redacted]
CGI-S	Clinical Global Impression-Severity of Illness Scale
CPK	Creatine phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DRESS	Drug rash with eosinophilia and systemic symptoms
ECG	Electrocardiogram
eCRF	Electronic case report form
eICF	Electronic informed consent form
ESAM	Events Subject to Additional Monitoring
ET	Early termination
CCI	[redacted]
FDA	Food and Drug Administration
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
HbA_1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational medicinal product

IND	Investigatinal new drug
IR	Immediate-release
IRB	Institutional review board
IRE	Immediately reportable event
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MHI	medication handling irregularities
MINI	Mini International Neuropsychiatric Interview
OC	Observed-case
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc
OTC	Over-the-counter
PK	Pharmacokinetic
PO	by mouth
PQC	Product quality complaint
PT	Preferred terms/international normalized ratio
PT/INR	prothrombin time
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
QTcN	QT interval corrected for heart rate by the FDA Neuropharm Division formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SMWQ	Study Medication Withdrawal Questionnaire
SR	Sustained-release
T_4	Free thyroxine
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States of America/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 85% 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 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. This 52-week, open-label, multicenter, trial will evaluate the long-term safety and tolerability of a 400 mg total daily dose (TDD) of centanafadine SR for the treatment of adult subjects with ADHD.

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 01 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 5 phase 1 trials and 120 subjects with ADHD received centanafadine in 2 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 adult subjects with ADHD.

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. Centanafadine may also confer an improved safety profile and 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 subjects and subjects with ADHD have been conducted with centanafadine. A total of 140 healthy subjects received centanafadine in 5 phase 1 trials and 120 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 and/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/kg). Neither subject who received 400 mg/day discontinued dosing due to the rash nor were the rashes in these subjects consistent with the drug eruptions seen in subjects who received 600 mg or 800 mg. All of the rashes were nonserious and all but 1 resolved within 12 days of treatment with IMP withdrawal or dose reduction. The 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

Attention-deficit hyperactivity disorder is an increasingly recognized and heterogeneous disorder characterized by the 3 core symptoms of hyperactivity, inattentiveness, and impulsivity[1]. Recent estimates of the prevalence of adult ADHD range from 2% to 6% of the adult population.[26]

While the currently recommended treatments for ADHD include stimulants (eg, methylphenidate and amphetamines) and nonstimulants (eg, atomoxetine, guanfacine, and clonidine)[17,18] there still remains a need for safer, more effective therapies to expand the current options.

Centanafadine SR is a novel triple reuptake inhibitor developed for the treatment of ADHD. The purpose of this proposed open-label, multicenter trial is to evaluate the long-term safety and tolerability of a 400 mg TDD centanafadine SR in adult subjects with ADHD.

2.2 Dosing Rationale

In this trial, centanafadine will be provided as 100 mg SR tablets.

After the completion of baseline evaluations (Day -1), all subjects will receive a starting dose of 200 mg TDD of centanafadine SR tablets from Days 1 to 7, followed by a titration to 400 mg TDD of centanafadine SR tablets on Day 8. Subjects will continue at 400 mg TDD for the rest of the open-label treatment period until Week 52/ET.

From Days 1 to 7, all doses of open-label IMP will be taken orally twice daily (BID), with 1 centanafadine SR tablet taken in the morning and 1 centanafadine SR tablet taken 4 to 6 hours after the first dose.

From Day 8 to Week 52/ET, all doses of open-label IMP will be taken orally BID, with 2 centanafadine SR tablets taken in the morning and 2 centanafadine SR tablets taken 4 to 6 hours after the first dose.

During the treatment period, subjects should make every effort to administer the open-label IMP at the same times every day.

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 Rating Scale IV (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 centanfadine will be included in this study to confirm the long-term safety and tolerability of the previously-established maximum tolerated dose.

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

2.3 Trial Objective

2.3.1 Primary Objective

The primary objective of this trial is to assess the safety and tolerability of centanafadine SR tablets administered BID (400 mg TDD) in the treatment of adults with ADHD.

3 Trial Design

3.1 Type/Design of Trial

This is a phase 3, 52-week, open-label, multicenter trial to assess the long-term safety and tolerability of centanafadine SR tablets (400 mg TDD) for the treatment of adults with ADHD. The trial population will include male and female subjects 18 to 55 years of age (inclusive) who meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) as confirmed by the Adult ADHD Clinical Diagnostic Scale (ACDS) Version 1.2. Subjects who rollover from the double-blind phase 3 trial (ie, Trial 405-201-00013 or Trial 405-201-00014) and de novo subjects from selected sites are permitted to enroll in this trial.

This trial will have 3 periods for rollover subjects:

1. Baseline;
2. Open-label treatment; and
3. Follow-up.

The trial will have 4 periods for de novo subjects:

1. Screening and washout;
2. Baseline;
3. Open-label treatment; and
4. Follow-up.

The trial will be organized as follows:

Rollover Subjects from Double-blind Phase 3 Trial (ie, Trial 405-201-00013 or Trial 405-201-00014)

Open-label Screening/Baseline: Subjects who completed one of the double-blind phase 3 trials may be eligible to enroll in this trial; subjects who discontinued will not be eligible. Subjects who complete both the 6-week double-blind treatment period and the 7-day follow-up visit are eligible to enroll into this trial. Subjects will be evaluated for eligibility at the 7-day follow-up visit of the double-blind phase 3 trial, and informed consent will be obtained before any procedures for the open-label trial are conducted. Therefore the assessments from the 7-day follow-up visit of the double-blind phase 3 trial may serve as the baseline assessments for the open-label trial.

CCI [redacted]

Open-label Treatment: Eligible subjects from the double-blind phase 3 trial will receive daily treatment with open-label centanafadine SR tablets as described in Section 3.2.

During the open-label treatment period, subjects will return to the clinic for evaluations at the end of Weeks 1, 2, 4, 8, 12, 16, 20, 26, 32, 38, 44, and 52/ET. A Week 48 visit will be conducted via telephone, web, or other acceptable means of contact.

Follow-up: If any subject discontinues the trial early, every effort should be made to complete the early termination (ET) evaluations as soon as possible and, whenever possible, prior to starting any new medication or treatment. All subjects (completers and early withdrawals) will be evaluated for safety during a 10-day follow up (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, in-clinic visits 2 and 7 days after the last dose of IMP, and a follow-up telephone call [or web, or other acceptable means of contact] 10 days after the last dose of IMP).

De Novo Subjects

Screening and Washout: De novo subjects must meet the DSM-5 criteria for ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) 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.

Subjects will be screened to establish eligibility for trial participation. The length of screening (Day –28 to Day –2) will include a washout period (if needed), which will range from 7 to 28 days. The investigator or his/her designee must obtain informed consent from the subject prior to any trial-related procedures being performed. An identification (ID) number will be assigned for each subject with documented consent. Those subjects who meet eligibility requirements will undergo ADHD medication washout, if applicable. If subjects are taking disallowed medications and 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 baseline. A complete washout schedule, including common excluded medications and herbal preparations, is provided in Table 4.1-1 of the protocol. The screening visit may take place over multiple days to accommodate the subject's schedule, if needed.

Baseline: Following medication washout, subjects will return to the clinic for reassessment of eligibility criteria and establishment of baseline measurements. The interval between the first day of the screening visit (informed consent date) and the baseline visit (Day –1) must not exceed 28 days. Subjects who meet relevant entry criteria by the time they leave the clinic on the day of the baseline visit will be dispensed the trial medication.

CCI [redacted]

Open-Label Treatment: After completing the baseline assessments, eligible subjects will receive daily treatment with open-label centanafadine SR tablets during the open-label treatment period, as described in Section 3.2.

During the open-label treatment period, subjects will return to the clinic for evaluations at the end of Weeks 1, 2, 4, 8, 12, 16, 20, 26, 32, 38, 44, and 52/ET. A Week 48 visit will be conducted via telephone, the web, or other acceptable means of contact.

Follow-up: If any subject discontinues the trial early, every effort should be made to complete the Week 52/ET evaluations as soon as possible and whenever possible prior to starting any new medication or treatment. All subjects (completers and early withdrawals) will be evaluated for safety during a 10-day follow up (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, in-clinic visits 2 and 7 days after the last dose of IMP, and a follow-up telephone call [or web, or other acceptable means of contact] 10 days after the last dose of IMP).

See Figure 3.1-1 and Figure 3.1-2 for schematics of the trial design for rollover and de novo subjects, respectively.

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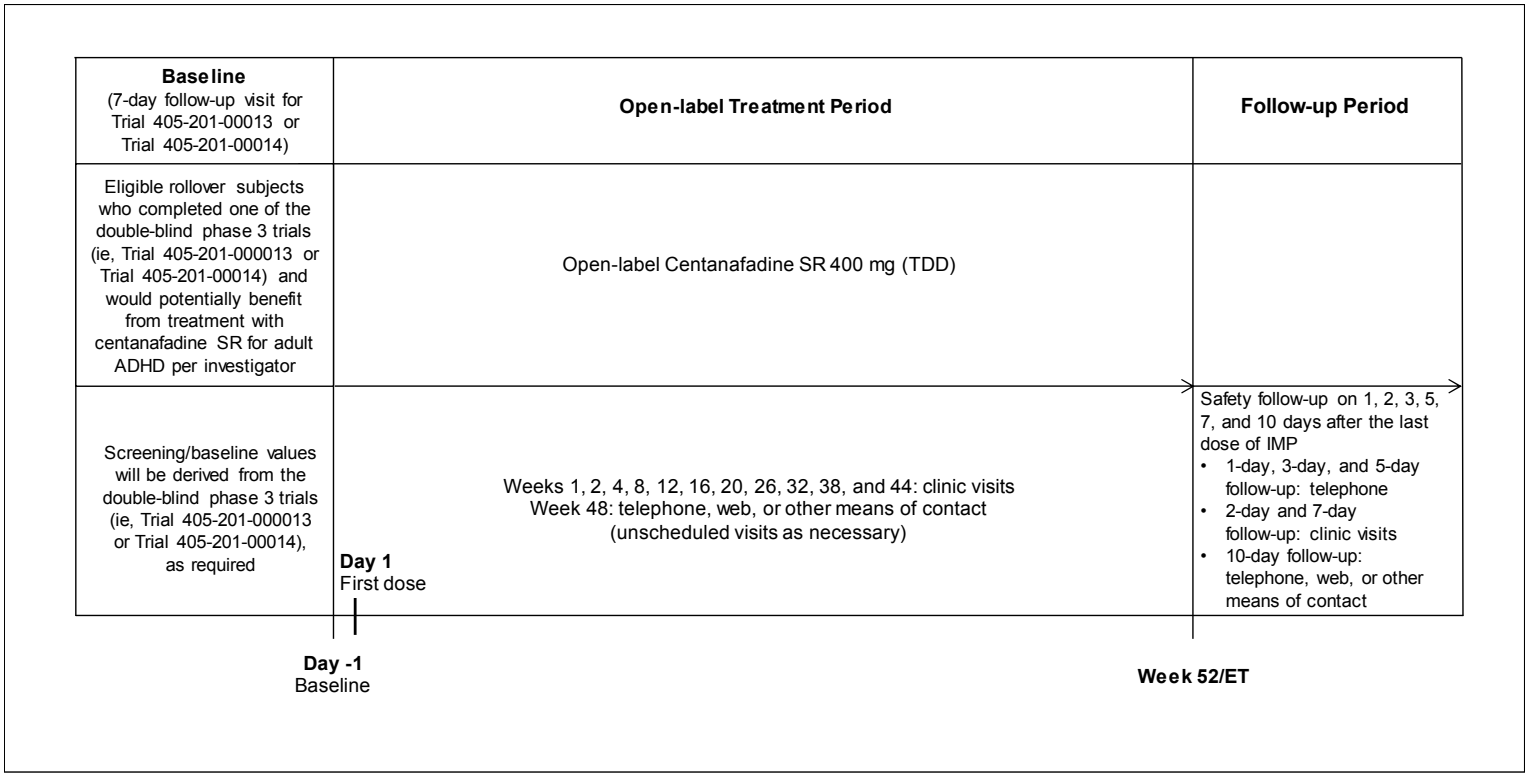

Figure 3.1-1 Trial Design Schematic - Rollover Subjects from Trial 405-201-00013 or Trial 405-201-00014

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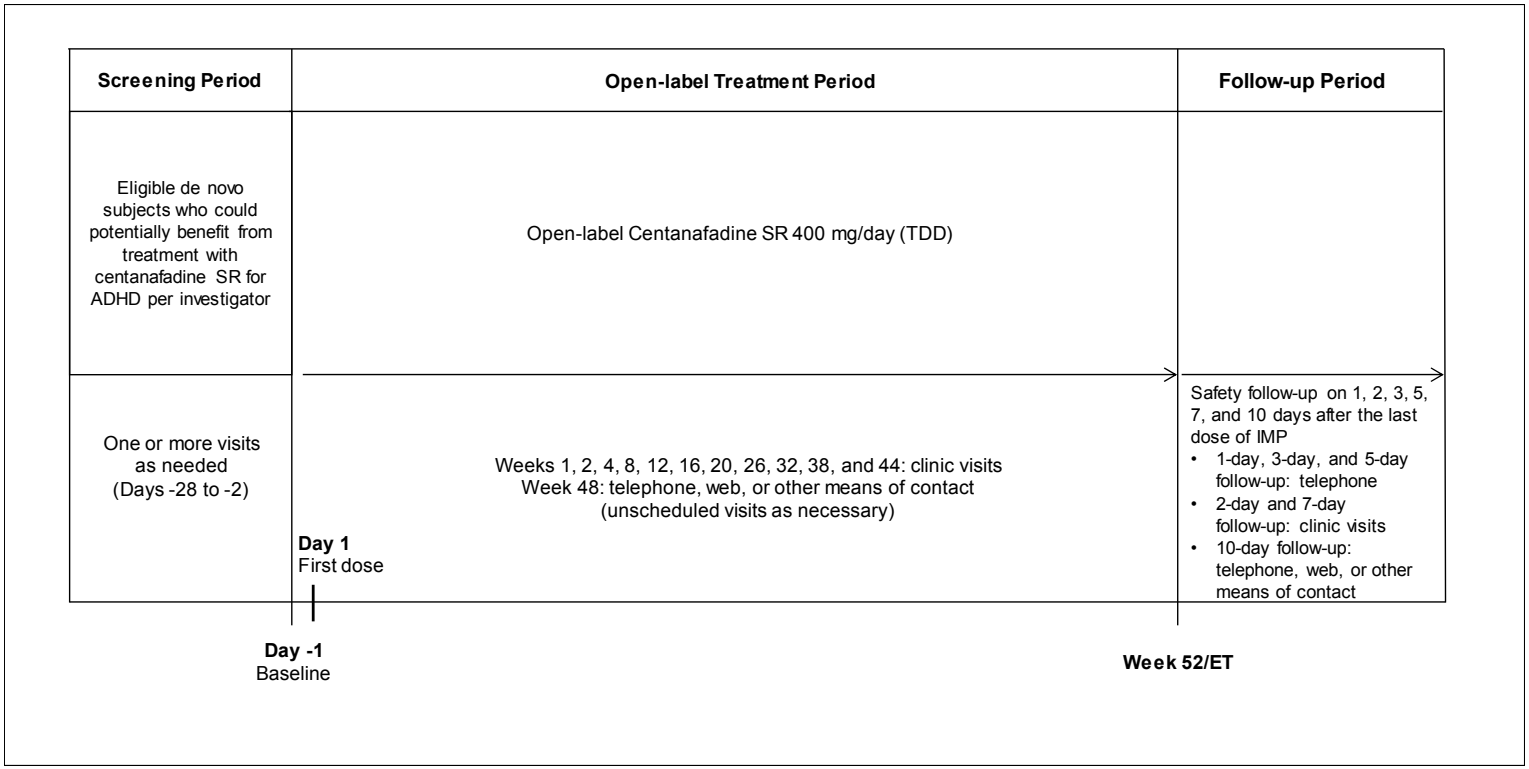

Figure 3.1-2 Trial Design Schematic - De Novo Subjects

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3.2 Trial Treatments

After the completion of baseline evaluations on Day -1, all subjects will follow a dose-escalation schedule starting on Day 1 (the day after the baseline visit) to increase their dose of the IMP to the target dose of 400 mg TDD by Day 8, as presented in Table 3.2-1 below:

Table 3.2-1 Titration Schedule for Centanafadine SR Tablets

Days	Time	Total Daily Dose	
1 to 7	1 tablet PO in morning 1 tablet PO 4 to 6 hours later	1 × 100 mg tablet 1 × 100 mg tablet	200 mg
8 and thereafter	2 tablets PO in morning 2 tablets PO 4 to 6 hours later	2 × 100 mg tablets 2 × 100 mg tablets	400 mg

PO = by mouth.

Subjects will continue to dose with 400 mg TDD for the remainder of the open-label treatment period starting on Day 8. If there are any tolerability issues at the 400 mg TDD, the dose may be temporarily decreased to 200 mg TDD, based on the clinical judgment of the investigator. If an investigator reduces the TDD of a subject due to an adverse event, once the AE resolves, the dose should increase back to 400mg TDD. If tolerability issues emerge once the dose has been brought back to 400mg TDD, then the dose may be reduced again. If the dose is reduced from 400mg for ≥ 5 days in total, the medical monitor should be contacted to discuss continuation in the study.

Every effort should be made to administer the IMP at the same times every day.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

A total of approximately 720 male and female subjects with a current diagnosis of ADHD are anticipated to be enrolled with the expectation that at least 300 subjects will achieve 6-month exposure and 100 subjects will achieve 52-week exposure.

The trial population will include approximately 560 completing rollover subjects from double-blind phase 3 trials (ie, Trial 405-201-00013 or Trial 405-201-00014) and approximately 145 de novo subjects between the ages of 18 and 55 years, inclusive, at the time of informed consent; de novo subjects must meet the 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.

De novo subjects must washout of any prohibited medications prior to baseline (Table 4.1-2). Rollover subjects have already met the diagnostic criteria for ADHD (ie, DSM-5 criteria for ADHD as confirmed by the ACDS Version 1.2) as a part of their screening for the double-blind phase 3 trial (ie, Trial 405-201-00013 or Trial 405-201-00014) and have already been washed out of any prohibited medications prior to the start of the double-blind trial treatment phase, which will be confirmed prior to baseline of Trial 405-201-00015 via concomitant medication reporting and urine drug screening.

Subjects who roll over from Trial 405-201-00013 or Trial 405-201-00014 who turned 56 years old during that trial are also permitted to enroll in this trial.

3.3.2 Subject Selection and Numbering

At screening, only de novo subjects will be assigned a unique subject ID number upon signing the electronic informed consent form (eICF) based on sequential enrollment in the trial. The clinical site will maintain a list identifying all subjects by their subject ID number and initials. Subjects that rollover from Trials 405-201-00013 or 405-201-00014 will retain their subject ID number from the prior trial upon entry in to Trial 405-201-00015.

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[27] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written 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

3.4.2.1 Rollover Subjects

Subjects are required to meet the inclusion criteria presented in Table 3.4.2.1-1.

Table 3.4.2.1-1 Inclusion Criteria for Rollover Subjects from Trial 405-201-00013 or Trial 405-201-00014

1.	Subjects who completed the 6-week double-blind treatment period and 7-day follow-up after last dose of IMP in double-blind phase 3 trial, (ie, Trial 405-201-00013 or Trial 405-201-00014) and who, in the opinion of the investigator, could potentially benefit from centanafadine for ADHD.
2.	Subjects who are able to complete the consent process and/or consent obtained from a legally acceptable representative (as required by IRB) prior to the initiation of any protocol-required procedures.
3.	Subjects who, during the double-blind trials, demonstrated adequate compliance with medication and protocol requirements, per investigator's judgment.
4.	Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, and discontinuation of prohibited medication, and to read and understand the written word in order to be reliably rated on assessment scales.

FOCBP = females of childbearing potential.

3.4.2.2 De Novo Subjects

Subjects are required to meet the inclusion criteria presented in Table 3.4.2.2-1.

Table 3.4.2.2-1 Inclusion Criteria for De Novo Subjects

1.	Subjects with a current primary DSM-5 diagnosis of ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) as confirmed by the ACDS Version 1.2.
2.	Subjects are 18 to 55 years of age, inclusive, at the time of consent.
3.	Subjects have BMI of 18 to 40, inclusive.
4.	Subjects are able to swallow multiple tablets.
5.	Subjects are willing and able to comply with all testing and requirements as defined in this protocol.
6.	Subjects are 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.
7.	Subjects are willing to discontinue all prohibited psychotropic medications (Section 4) starting from the time of signing the informed consent and up to the 10-day safety follow-up period.
8.	Subjects are 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.

BMI = body mass index.

3.4.3 Exclusion Criteria

3.4.3.1 Rollover Subjects

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3.1-1.

Table 3.4.3.1-1 Exclusion Criteria for Rollover Subjects from Trial 405-201-00013 or Trial 405-201-00014

1.	Subjects who, during the double-blind phase 3 trial, (ie, Trial 405-201-00013 or Trial 405-201-00014), experienced, in the opinion of the investigator, poor tolerability to trial medication or whose safety assessments resulted in new concerns that would suggest the subject may not be appropriate for a 52-week treatment with trial medication.
2.	Subjects who have demonstrated noncompliance, based on investigator's judgment to follow trial procedures during the course of their participation in the double-blind phase 3 trial, (ie, Trial 405-201-00013 or Trial 405-201-00014). The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.
3.	Subjects who have re-initiated any therapy for adult ADHD during the 7-day follow-up period after the Week 6 visit in Trial 405-201-00013 or Trial 405-201-00014.
4.	Females who have a positive pregnancy test result prior to receiving IMP.

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Table 3.4.3.1-1 Exclusion Criteria for Rollover Subjects from Trial 405-201-00013 or Trial 405-201-00014	
5.	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, females who have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or males 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.
6.	Following responses from the "Since Last Visit" version of the C-SSRS 7-day follow-up visit of double-blind pahse 3 trial, (ie, Trial 405-201-00013 or Trial 405-201-00014): • Subjects with a response of "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) at entry, **OR** • Subjects with a response of "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) at entry, **OR** • Subjects with a response of "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) at entry, **OR** Subjects who, in the opinion of the investigator (including consideration of responses on the C-SSRS throughout Trial 405-201-00013 or Trial 405-201-00014), present a serious risk of suicide. Note: "Entry" is defined as the 7-day follow-up of Trial 405-201-00013 or Trial 405-201-00014.
7.	Subjects with newly developed psychiatric or medical condition that would be exclusionary under the criteria listed for Trial 405-201-00013 or Trial 405-201-00014.
8.	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 medications at baseline will not be permitted to continue participation in Trial 405-201-00015. 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.
9.	Any new or developing safety concerns related to vital signs in the opinion of the investigator during the baseline visit.

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Table 3.4.3.1-1	**Exclusion Criteria for Rollover Subjects from Trial 405-201-00013 or Trial 405-201-00014**
10.	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) Abnormal free T_4 (free T_4 is measured only if result for TSH is abnormal) 9) QTcF and/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. Eligibility should be based on the last available measurement during Trial 405-201-00013 or Trial 405-201-00014, as applicable. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.
11.	Subjects receiving any of the prohibited medications within the specified period prior to the first dose of trial medication or who would be likely to require prohibited concomitant therapy during the trial (Section 4).
12.	Subjects who have previously been enrolled in this trial and subsequently withdrawn.
13.	Any subject who, in the opinion of the investigator, should not participate in the trial.

ALT = alanine aminotransferase; anti-HCV = hepatitis C antibodies; AST = asparatate aminotransferase; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; 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 using Bazett's formula; QTcF = QT interval corrected using Fridericia's formula; T_4 = free thyroxin; TSH = thyroid stimulating hormone.

3.4.3.2 De Novo Subjects

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3.2-1.

Table 3.4.3.2-1 Exclusion Criteria for De Novo Subjects

1.	Females who are breast-feeding and/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, females who have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or males 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.	Subjects with DSM-5 diagnosis of Other Specified or Unspecified Attention-Deficit/Hyperactivity Disorder as confirmed by ACDS Version 1.2.
4.	Subjects with life-time history of electroconvulsive therapy, or a life-time history of vagal nerve stimulation or deep brain stimulation for the treatment of depression.
5.	Subjects with 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.
6.	Subjects with a clinically significant current DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, histrionic, narcissistic, avoidant, or dependent personality disorders.
7.	Subjects who meet the following criteria for "Baseline/Screening" version of the C-SSRS: • Suicidal Ideation Items 4 or 5 within the last 6 months **OR** • 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 **OR** Subjects who, in the opinion of the investigator, present a serious risk of suicide.
8.	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.
9.	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.
10.	Subject has a life-time history of a pattern of abuse or diversion of stimulants.
11.	Subjects with any current or suspected drug or alcohol use disorder or have met the DSM-5 criteria for a substance use disorder in the past 6 months. Nicotine use disorder is not exclusionary.

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Table 3.4.3.2-1 Exclusion Criteria for De Novo Subjects	
12.	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.
13.	Subjects with known intellectual disability (intellectual developmental disorder), including mild adaptive functioning impairment, or clinical evidence of intellectual disability based on the opinion of the investigator.
14.	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.
15.	Subjects presenting with, or having a history of, uncontrolled hypertension (systolic blood pressure > 140 mmHg and/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 and/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.
16.	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.
17.	The following laboratory test and ECG results are exclusionary at screening: 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 and/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.
18.	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 T_4 at screening (free T_4 is measured only if result for TSH is abnormal).

Table 3.4.3.2-1 Exclusion Criteria for De Novo Subjects	
19.	Subjects receiving any of the prohibited medications within the specified period prior to the first dose of trial medication or who would be likely to require prohibited concomitant therapy during the trial (Section 4).
20.	Subjects with a history of prior exposure to centanafadine.
21.	Subjects with a history of dermatologic adverse reactions or anaphylaxis secondary to drug exposure.
22.	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).
23.	Subjects who have previously been enrolled in this trial and subsequently withdrawn.
24.	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.
25.	Any subject who, in the opinion of the investigator, should not participate in the trial.

See Section 3.9 for details regarding screen failures.

Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months.

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

3.5 Endpoints

3.5.1 Primary Endpoint

The primary endpoint in this trial is the long-term safety and tolerability of centanafadine SR tablets administered BID (400 mg TDD), as assessed by the frequency and severity of treatment-emergent adverse events (TEAEs).

3.5.2 Secondary Endpoints

None.

3.5.3 Exploratory Endpoint(s)

Exploratory efficacy endpoints for the open-label treatment period are as follows:

- Change from baseline in Adult ADHD Investigator Symptom Rating Scale (AISRS) Total Score, by trial visit and at the last visit (ie, Week 52/ET);
- Change from baseline Clinical Global Impression-Severity of Illness Scale (CGI-S), by trial visit and at the last visit (ie, Week 52/ET);
- Change from baseline in ADHD Impact Module - Adult (AIM-A) Score by trial visit and at the last visit;

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3.5.4 Additional Safety Endpoints

Additional safety variables will include clinically significant changes in: clinical laboratory tests (hematology, serum chemistry, coagulation parameters, and urinalysis), physical examinations, vital sign measurements, and electrocardiograms (ECGs).

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to assess and classify reported suicidal behavior. By-subject listings of physical examination findings will be reviewed as a further assessment of safety.

Assessments of withdrawal symptoms will be performed using Study Medication Withdrawal Questionnaire (SMWQ).

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

3.6 Measures to Minimize/Avoid Bias

Not applicable; this is an open-label trial.

3.7 Trial Procedures

Individual participation for rollover subjects who complete the trial without early withdrawal will be approximately 54 weeks, consisting of a 52-week open-label treatment period, and 10-day safety follow-up period after the last dose of IMP. Individual participation for de novo subjects who complete the trial without early withdrawal will be approximately 58 weeks, consisting of a screening period of up to 28 days, a 52-week open-label treatment period, and a 10-day safety follow-up after the last dose of IMP.

Trial assessment time points are summarized in Table 3.7-1 and Table 3.7-2 (rollover subjects from Trial 405-201-00013 or Trial 405-201-00014) and Table 3.7-3 and Table 3.7-4 (de novo subjects).

In addition to the trial assessment time points summarized (Table 3.7-1 and Table 3.7-2 for rollover subjects and Table 3.7-3 and Table 3.7-4 for de novo subjects CCI [redacted]

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Table 3.7-1	**Schedule of Assessments - Rollover Subjects from Trial 405-201-00013 or Trial 405-201-00014 - Baseline Through End of Treatment**									
	Baseline	**52-Week Open-label Treatment Period**								
	7-day follow-up visit from Trial 405-201-00013 or Trial 405-201-00014/ Baseline for Trial 405-201-00015[a]	**W 1 & 2** (± 3 days)	**W 4, 8, 12 & 16** (± 3 days)	**W 20** (± 3 days)	**W 26** (± 3 days)	**W 32** (± 3 days)	**W 38** (± 3 days)	**W 44** (± 3 days)	**W 48[b]** (± 3 days)	**End of Treatment** **W 52/ET** (± 3 days)
Visit	**1**	**2 & 3**	**4, 5, 6, & 7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
ENTRANCE/HISTORY										
Informed consent	X									
Inclusion/exclusion criteria	X									
Concomitant medication(s)	X[c]	X	X	X	X	X	X	X	X	X
HIV/HBsAg/ anti-HCV	X									
Urine pregnancy test[d]	X	X	X	X	X	X	X	X		X
SAFETY										
Adverse events	X[c]	X	X	X	X	X	X	X	X	X
Physical examination	X[e]		X[f]		X					X
Vital signs	X[c]	X	X	X	X	X	X	X		X
12-lead ECG	X	X	X[g]		X		X			X

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Table 3.7-1	**Schedule of Assessments - Rollover Subjects from Trial 405-201-00013 or Trial 405-201-00014 - Baseline Through End of Treatment**									
	Baseline	**52-Week Open-label Treatment Period**								
	7-day follow-up visit from Trial 405-201-00013 or Trial 405-201-00014/ Baseline for Trial 405-201-00015[a]	**W 1 & 2** (± 3 days)	**W 4, 8, 12 & 16** (± 3 days)	**W 20** (± 3 days)	**W 26** (± 3 days)	**W 32** (± 3 days)	**W 38** (± 3 days)	**W 44** (± 3 days)	**W 48[b]** (± 3 days)	**End of Treatment** **W 52/ET** (± 3 days)
Visit	**1**	**2 & 3**	**4, 5, 6, & 7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Clinical laboratory tests (hematology, serum chemistry [including HbA1c and TSH], and urinalysis)	X		X[f]		X		X			X
PT/INR	X				X					X
SMWQ										X
Urine drug screen	X[c]		X[h]		X					X
Alcohol testing[i]	X[c]		X[h]		X					X
C-SSRS	X[c]	X	X	X	X	X	X	X		X
EFFICACY										
AISRS	X[c]	X	X	X	X	X	X	X		X
CGI-S	X	X	X	X	X	X	X	X		X
AIM-A	X				X					X
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Table 3.7-1	**Schedule of Assessments - Rollover Subjects from Trial 405-201-00013 or Trial 405-201-00014 - Baseline Through End of Treatment**									
	Baseline	**52-Week Open-label Treatment Period**								
	7-day follow-up visit from Trial 405-201-00013 or Trial 405-201-00014/ Baseline for Trial 405-201-00015[a]	**W 1 & 2** (± 3 days)	**W 4, 8, 12 & 16** (± 3 days)	**W 20** (± 3 days)	**W 26** (± 3 days)	**W 32** (± 3 days)	**W 38** (± 3 days)	**W 44** (± 3 days)	**W 48[b]** (± 3 days)	**End of Treatment** **W 52/ET** (± 3 days)
Visit	**1**	**2 & 3**	**4, 5, 6, & 7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
OTHER										
IMP dispensing	X	X	X	X	X	X	X	X		
IMP return and accountability		X	X	X	X	X	X	X		X

AIM-A = ADHD Impact Module – Adult; AISRS = Adult ADHD Investigator Rating Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; PT/INR = prothrombin time/international normalized ratio; W = week.

[a]Dosing will commence the day after the baseline visit.

[b]Telephone, web, or other acceptable means of contact.

[c]Assessments may be conducted at the 7-day follow-up visits of Trial 405-201-00013 or Trial 405-201-00014, and the information can be carried over into Trial 405-201-00015 for the baseline visit.

[d]If the urine pregnancy test is positive, the result will be confirmed with a serum pregnancy test.

[e]Physical examination at baseline will include height measurements.

[f]Week 8 only.

[g]Weeks, 4, 8, and 16 only.

[h]Weeks 4 and 12 only.

[i]Alcohol testing may be conducted via a blood test or using a breathalyzer.

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Table 3.7-2	**Schedule of Assessments - Rollover Subjects from Trial 405-201-00013 or Trial 405-201-00014 - Follow-up**					
Period	**Follow-up[a]**					
	1 (+1) days 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	**15**	**16**	**17**	**18**	**19**	**20**
ENTRANCE/HISTORY						
Concomitant medication(s)	X	X	X	X	X	X
EFFICACY						
AISRS		X			X	
SAFETY						
Adverse events	X	X	X	X	X	X
Vital signs		X			X	
SMWQ	X	X	X	X	X	X
Urine drug screen		X			X	
Alcohol testing[b]		X			X	
C-SSRS		X			X	

[a]Follow-up telephone calls will be conducted at 1, 3, and 5 days after the last dose of IMP, in-clinic visits on 2 and 7 days after the last dose of IMP, and a follow-up telephone call [or web, or other acceptable means of contact] 10 days after the last dose of IMP).

[b]Alcohol testing may be conducted via a blood test or using a breathalyzer.

Table 3.7-3	**Schedule of Assessments - De Novo Subjects - Baseline Through End of Treatment**										
			52-Week Open-label Treatment Period								
	Screening[a]	**Baseline**[b]	**W 1 & 2** (± 3 days)	**W 4, 8, 12, & 16** (± 3 days)	**W 20** (± 3 days)	**W 26** (± 3 days)	**W 32** (± 3 days)	**W 38** (± 3 days)	**W 44** (± 3 days)	**W 48**[c] (± 3 days)	**End of Treatment W 52/ET** (± 3 days)
Visit	**1**	**2**	**3 & 4**	**5, 6, 7, & 8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
ENTRANCE/HISTORY											
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X
Medical history	X										
ACDS	X										
Identification of comorbidities using MINI	X										
Psychiatric history	X										
HIV/HBsAg/ anti-HCV	X										
Urine pregnancy test[d]	X	X	X	X	X	X	X	X	X		X
SAFETY											
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X[e]	X		X[f]		X					X
Vital signs	X	X	X	X	X	X	X	X	X		X
12-lead ECG	X	X	X	X[g]		X		X			X

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Table 3.7-3 Schedule of Assessments - De Novo Subjects - Baseline Through End of Treatment

			52-Week Open-label Treatment Period								
	Screening[a]	Baseline[b]	W 1 & 2 (± 3 days)	W 4, 8, 12, & 16 (± 3 days)	W 20 (± 3 days)	W 26 (± 3 days)	W 32 (± 3 days)	W 38 (± 3 days)	W 44 (± 3 days)	W 48[c] (± 3 days)	End of Treatment W 52/ET (± 3 days)
Visit	**1**	**2**	**3 & 4**	**5, 6, 7, & 8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Clinical laboratory tests (hematology, serum chemistry [including HbA1c and TSH], and urinalysis)	X	X		X[f]		X		X			X
PT/INR		X				X					X
SMWQ											X
Urine drug screen	X	X		X[h]		X					X
Alcohol testing[i]	X	X		X[h]		X					X
C-SSRS	X	X	X	X	X	X	X	X	X		X
EFFICACY											
AISRS		X	X	X	X	X	X	X	X		X
CGI-S		X	X	X	X	X	X	X	X		X
AIM-A		X				X					X
CCI [redacted]											

Table 3.7-3	**Schedule of Assessments - De Novo Subjects - Baseline Through End of Treatment**										
			52-Week Open-label Treatment Period								
	Screening[a]	**Baseline**[b]	**W 1 & 2** (± 3 days)	**W 4, 8, 12, & 16** (± 3 days)	**W 20** (± 3 days)	**W 26** (± 3 days)	**W 32** (± 3 days)	**W 38** (± 3 days)	**W 44** (± 3 days)	**W 48**[c] (± 3 days)	**End of Treatment W 52/ET** (± 3 days)
Visit	**1**	**2**	**3 & 4**	**5, 6, 7, & 8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
OTHER											
IMP dispensing		X	X	X	X	X	X	X	X		
IMP return and accountability			X	X	X	X	X	X	X		X

CCI [redacted]

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

[b]Dosing will commence the day after the Baseline visit.

[c]Telephone, web, or other acceptable means of contact.

[d]If the urine pregnancy test is positive, the result will be confirmed with a serum pregnancy test.

[e]Physical examination at screening will include height measurements.

[f]Week 8 only.

[g]Weeks 4, 8, and 16 only.

[h]Weeks 4 and 12 only.

[i]Alcohol testing may be conducted via a blood test or using a breathalyzer.

CCI [redacted]

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Table 3.7-4 Schedule of Assessments - De Novo Subjects - Follow-up

Period	**Follow-up[a]**					
	1 (+1) days 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	**16**	**17**	**18**	**19**	**20**	**21**
ENTRANCE/HISTORY						
Concomitant medication(s)	X	X	X	X	X	X
EFFICACY						
AISRS		X			X	
SAFETY						
Adverse events	X	X	X	X	X	X
Vital signs		X			X	
SMWQ	X	X	X	X	X	X
Urine drug screen		X			X	
Alcohol testing[b]		X			X	
C-SSRS		X			X	

[a]Follow-up telephone calls will be conducted at 1, 3, and 5 days after the last dose of IMP, in-clinic visits on 2 and 7 days after the last dose of IMP, and a follow-up telephone call [or web, or other acceptable means of contact] 10 days after the last dose of IMP).

[b]Alcohol testing may be conducted via a blood test or using a breathalyzer.

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3.7.1 Schedule of Assessments

3.7.1.1 Screening and Baseline

3.7.1.1.1 Rollover Subjects

Screening for rollover subjects occurs simultaneously with baseline at the 7-day follow-up visit after Week 6/ET visit (Week 6) of double-blind phase 3 trial, (ie, Trial 405-201-00013 or Trial 405-201-00014) (Table 3.7-1) (Visit 1). Rollover subjects entering from double-blind phase 3 trial must sign the eICF for the open-label trial (ie, Trial 405-201-00015), before any procedures specific to Trial 405-201-00015 can be performed. Subjects will retain the same subject ID number assigned in Trial 405-201-00013 or Trial 405-201-00014. The following screening/baseline assessments may be conducted at the 7-day follow-up visits of Trial 405-201-00013 or Trial 405-201-00014, and the information can be carried over into Trial 405-201-00015 for the baseline visit: concomitant medications, AEs, vital signs, urine drug screen, alcohol testing, C-SSRS, and AISRS. The additional procedures to be performed for rollover subjects at baseline of the open-label trial are as follows:

- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- Medical history from Trial 405-201-00013 or Trial 405-201-00014 will be retained, but will be updated if necessary.
- A qualified rater will administer the CGI-S.
- Subjects will complete the AIM-A.
- CCI [redacted]
- A physical examination including height measurements will be performed.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.
- Blood samples will be collected for clinical laboratory tests, including hematology and serum chemistry (with glycosylated hemoglobin [HbA_1c], and thyroid-stimulating hormone [TSH and free thyroxine [T_4]). Blood will be drawn after a minimum 8-hour fast, if at all possible (see Section 3.7.4.2). See Table 3.4.3.1-1 for exclusions based on outcome of screening clinical laboratory tests. Vital sign and ECG assessments should be completed before any blood samples are collected.
- Blood samples will be drawn for human immunodeficiency virus (HIV) serology and the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV).
- 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.

- .AE recording will begin with the signing of the eICF for Trial 405-201-00015.
- Open-label centanafadine SR will be dispensed to the subject and subjects will be instructed to take their 2 doses at approximately the same time every day starting from Day 1 (day after baseline visit).

3.7.1.1.2 De Novo Subjects

De novo subjects did not participate in Trial 405-201-00013 or Trial 405-201-00014; therefore, they must attend separate screening and baseline visits to allow for completion of eligibility assessments and washout of prohibited concomitant medications, if applicable (Table 3.7-3).

3.7.1.1.2.1 Screening

For de novo subjects, the screening period begins after informed consent has been obtained and will take place between Day –28 and Day –1 prior to enrollment (Visit 1). Although the screening period continues up to administration of the first dose of IMP, screening procedures should be initiated with a sufficient amount of time allotted in order to obtain laboratory results and ECG results from the central reader prior to dosing. Completion of screening activities may require more than 1 visit. All procedures outlined for screening in the Schedule of Assessments (Table 3.7-3) will be performed. Screening evaluations will include the following:

- CCI [redacted]
- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- Demographic data will be recorded.
- Medical and psychiatric history will be recorded, including the DSM-5 diagnosis of ADHD using the ACDS Version 1.2 and MINI will be administeered to rule out other comorbid diagnoses.
- The investigator (or qualified designee) will complete the "Baseline/Screening" C-SSRS form.
- A physical examination including height measurements will be performed.
- Vital sign measurements will be recorded. See Table 3.4.3.2-1 for exclusions based on outcome of screening vital sign measurements.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.

- Blood samples will be collected for clinical laboratory tests, including hematology and serum chemistry (with HbA_1c and TSH and T_4). Blood will be drawn after a minimum 8-hour fast, if at all possible (see Section 3.7.4.2). See Table 3.4.3.2-1 for exclusions based on outcome of screening clinical laboratory tests. Vital sign and ECG assessments should be completed before any blood samples are collected.
- Blood samples will be drawn for HIV serology and the presence of HBsAg and anti-HCV.
- Alcohol testing will be conducted via a blood test or using a breathalyzer.
- A urine pregnancy test will be performed for all 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.
- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse. See Table 3.4.3.2-1 for exclusions based on outcome of urine drug screen(s).
- 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 1 week off stimulants and 3 weeks off nonstimulants will be required before baseline. A complete washout schedule, including common excluded medications and herbal preparations, is provided in Section 4.1.
- AE recording will begin with the signing of the eICF for Trial 405-201-00015.

The sponsor reserves the right to utilize external quality oversight methods to ensure the validity of diagnosis, severity of illness, and other factors determining appropriateness of subject selection.

3.7.1.1.2.2 Baseline

If the subject is found to be eligible for the trial during the screening, the subject will attend a baseline visit (Visit 2) during which the following procedures will be completed prior to the subject starting open-label IMP:

- Inclusion/exclusion criteria will be verified. Review of inclusion/exclusion criteria at the baseline visit will be based on assessments performed during screening.
- Medications taken during the screening period will be reviewed and documented.
- A qualified rater will administer the AISRS.
- A qualified rater will administer the CGI-S.
- The investigator (or qualified designee) will complete the “Since Last Visit” C-SSRS form.
- Subjects will complete the AIM-A.
- CCI [redacted]
- A physical examination will be performed.

- Vital sign measurements will be recorded.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.
- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry [including HbA_1c, TSH, and PT/INR]) after a minimum 8-hour fast. Vital sign and ECG assessments should be completed before any blood samples are collected.
- Alcohol testing will be conducted via a blood test or using a breathalyzer.
- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse. See Table 3.4.3.2-1 for exclusions based on outcome of urine drug screen(s).
- A urine pregnancy test will be performed for all FOCBP. The result must be negative prior to dosing. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
- Blood samples for FBR will be collected, if FBR consent was obtained.
- AEs and concomitant medications will be recorded.
- Open-label centanafadine SR will be dispensed to the subject and subjects will be instructed to take their 2 doses at approximately the same time every day starting on Day 1 (the day after the baseline visit).

3.7.1.2 Open-label Treatment Period

3.7.1.2.1 Weeks 1 and 2

Weeks 1 and 2 (± 3 days) will be Visits 2 and 3 for rollover subjects and Visits 3 and 4 for de novo subjects.

The following procedures will be performed at Week 1 and 2 visits (± 3 days):

- A qualified rater will administer the AISRS.
- A qualified rater will administer the CGI-S.
- The investigator (or qualified designee) will complete the “Since Last Visit” C-SSRS form.
- Vital sign measurements will be recorded.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.
- A urine pregnancy test will be performed for all FOCBP. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
- AEs and concomitant medications will be recorded.
- Drug accountability will be performed.

- Open-label centanafadine SR will be dispensed to the subject and subjects will be instructed to take their 2 doses at approximately the same time every day.

3.7.1.2.2 Weeks 4, 8, 12 and 16

Weeks 4, 8, 12 and 16 (± 3 days) will be Visits 4, 5, 6, and 7 for rollover subjects and Visits 5, 6, 7, and 8 for de novo subjects.

The following procedures will be performed at the Week 4, 8, 12, and 16 visits (± 3 days):

- A qualified rater will administer the AISRS.
- A qualified rater will administer the CGI-S.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- A physical examination will be performed (Week 8 only).
- Vital sign measurements will be recorded.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn (Weeks 4, 8, and 16 only).
- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry [including HbA_1c, and TSH]) after a minimum 8-hour fast. Vital sign and ECG assessments should be completed before any blood samples are collected (Week 8 only).
- Alcohol testing may be conducted via a blood test or using a breathalyzer (Weeks 4 and 12 only).
- Urine will be collected for urinalysis (Week 8 only).
- Urine will be collected for urine screen(s) for drugs of abuse (Weeks 4 and 12 only).
- A urine pregnancy test will be performed for all FOCBP. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
- AEs and concomitant medications will be recorded.
- Drug accountability will be performed.
- Open-label centanafadine SR will be dispensed to the subject and subjects will be instructed to take their 2 doses at approximately the same time every day.

3.7.1.2.3 Week 20

Week 20 (± 3 days) will be Visit 8 for rollover subjects and Visit 9 for de novo subjects.

The following procedures will be performed at the Week 20 visit (± 3 days):

- A qualified rater will administer the AISRS.

- A qualified rater will administer the CGI-S.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- Vital sign measurements will be recorded.
- A urine pregnancy test will be performed for all FOCBP. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
- AEs and concomitant medications will be recorded.
- Drug accountability will be performed.
- Open-label centanafadine SR will be dispensed to the subject and subjects will be instructed to take their 2 doses at approximately the same time every day.

3.7.1.2.4 Week 26

Week 26 (± 3 days) will be Visit 9 for rollover subjects and Visit 10 for de novo subjects.

The following procedures will be performed at the Week 26 visit (± 3 days):

- A qualified rater will administer the AISRS.
- A qualified rater will administer the CGI-S.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- Subjects will complete the AIM-A.
- CCI [redacted]
- A physical examination will be performed.
- Vital sign measurements will be recorded.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.
- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry [including HbA_1c, TSH, and PT/INR]) after a minimum 8-hour fast. Vital sign and ECG assessments should be completed before any blood samples are collected.
- Alcohol testing may be conducted via a blood test or using a breathalyzer.
- Urine will be collected for urinalysis and urine screen(s) for drugs of abuse.
- A urine pregnancy test will be performed for all FOCBP. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
- AEs and concomitant medications will be recorded.
- Drug accountability will be performed.
- Open-label centanafadine SR will be dispensed to the subject and subjects will be instructed to take their 2 doses at approximately the same time every day.

3.7.1.2.5 Week 32

Week 32 (± 3 days) will be Visit 10 for rollover subjects and Visit 11 for de novo subjects.

The following procedures will be performed at the Week 32 visit (± 3 days):

- A qualified rater will administer the AISRS.
- A qualified rater will administer the CGI-S.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- Vital sign measurements will be recorded.
- A urine pregnancy test will be performed for all FOCBP. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
- AEs and concomitant medications will be recorded.
- Drug accountability will be performed.
- Open-label centanafadine SR will be dispensed to the subject and subjects will be instructed to take their 2 doses at approximately the same time every day.

3.7.1.2.6 Week 38

Week 38 (± 3 days) will be Visit 11 for rollover subjects and Visit 12 for de novo subjects.

The following procedures will be performed at the Week 38 visit (± 3 days):

- A qualified rater will administer the AISRS.
- A qualified rater will administer the CGI-S.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- Vital sign measurements will be recorded.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.
- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry [including HbA_1c and TSH]) after a minimum 8-hour fast. Vital sign and ECG assessments should be completed before any blood samples are collected.
- A urine pregnancy test will be performed for all FOCBP. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
- AEs and concomitant medications will be recorded.
- Drug accountability will be performed.
- Open-label centanafadine SR will be dispensed to the subject and subjects will be instructed to take their 2 doses at approximately the same time every day.

3.7.1.2.7 Week 44

Week 44 (± 3 days) will be Visit 12 for rollover subjects and Visit 13 for de novo subjects.

The following procedures will be performed at the Week 44 visit (± 3 days):

- A qualified rater will administer the AISRS.
- A qualified rater will administer the CGI-S.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- Vital sign measurements will be recorded.
- A urine pregnancy test will be performed for all FOCBP. The result must be negative prior to dosing. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
- AEs and concomitant medications will be recorded.
- Drug accountability will be performed.
- Open-label centanafadine SR will be dispensed to the subject and will be instructed to take their 2 doses at approximately the same time every day.

3.7.1.2.8 Week 48

Week 48 (± 3 days) will be Visit 13 for rollover subjects and Visit 14 for de novo subjects.

Week 48 visit (± 3 days) will be conducted via telephone, web, or other acceptable means of contact. The following procedures will occur for all subjects:

- AEs and concomitant medications will be recorded.

3.7.1.2.9 Week 52/Early Termination (End of Treatment)

Week 52/ET (± 3 days) will be Visit 14 for rollover subjects and Visit 15 for de novo subjects.

The following procedures will be performed at the Week 52/ET visit (± 3 days):

- A qualified rater will administer the AISRS.
- A qualified rater will administer the CGI-S.
- The SMWQ questionnaire will be completed.

- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- Subjects will complete the AIM-A.
- CCI [redacted]
- A physical examination will be performed.
- Vital sign measurements will be recorded.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.
- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry [including HbA_1c, TSH, and PT/INR]) after a minimum 8-hour fast. Vital sign and ECG assessments should be completed before any blood samples are collected.
- Alcohol testing will be conducted via a blood test or using a breathalyzer.
- Urine will be collected from all subjects for urinalysis and urine screen(s) for drugs of abuse.
- A urine pregnancy test will be performed for all FOCBP. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
- AEs and concomitant medications will be recorded.
- Drug accountability will be performed.
- Subjects will be instructed not to initiate a different ADHD therapy until follow-up visit is completed 10 days after the last dose of IMP (Week 52/ET + 14 days).

3.7.1.3 Follow-up Period

All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation during a 10-day follow up period (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, in-clinic visits 2 and 7 days after the last dose of IMP, and a follow-up telephone call [or web, or other acceptable means of contact] 10 days after the last dose of IMP).

The following procedures will be performed at the 1-day, 3-day, and 5-day follow-up visit:

- The SMWQ questionnaire will be completed remotely.
- AEs will be recorded.
- Concomitant medications will be recorded.

The following procedures will be performed at the 2-day and 7-day follow-up visit:

- A qualified rater will administer the AISRS.
- The SMWQ questionnaire will be completed in-clinic.
- Vital sign measurements will be recorded.
- Alcohol testing may be conducted via a blood test or using a breathalyzer.
- Urine will be collected for urine screen(s) for drugs of abuse.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- AEs and concomitant medications will be recorded.

The following procedures will be performed at 10-day follow-up contact:

- The SMWQ questionnaire will be completed remotely.
- AEs and concomitant medications will be recorded.

Depending upon the type of follow-up required, other evaluations or tests may be conducted or performed.

3.7.2 Efficacy Assessments

It is required that adequately trained and experienced clinicians administer the AISRS, CGI-S, MINI, and ACDS Version 1.2. 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 more accurately reflects the impact and severity of ADHD among adults. The scale will be administered as described in the Schedule of Assessments (Table 3.7-1 and Table 3.7-2 for rollover subjects and Table 3.7-3 and Table 3.7-4 for de novo subjects). It is a clinician-administered scale that measures all 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.[28]

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 for rollover subjects and Table 3.7-3 for de novo subjects) is an observer-rated scale that will be used to measure symptom severity.[29] To perform this assessment, the investigator or rater will respond to the following question: "Considering your total clinical experience with the 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.[30]

3.7.3 Other Assessments

CCI

3.7.3.2 Mini International Neuropsychiatric Interview

The MINI[31,32,33] will be conducted for de novo subjects at screening to rule out exclusionary comorbid psychiatric diagnoses. Detailed instructions for administration of this structured interview will be provided.

3.7.3.3 Adult Attention-deficit/Hyperactivity Disorder Clinical Diagnostic Scale

The ACDS Version 1.2 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.[34] The ACDS will be administered to de novo subjects at screening.

3.7.3.4 Attention-Deficit Hyperactivity Disorder Impact Module - Adult

The AIM-A 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.[35]

3.7.3.5 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/or secondary objectives) on the electronic case report form (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 until the end of the trial (defined as the last date of contact or date of final contact attempt) on the eCRF.

3.7.4 Safety Assessments

3.7.4.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.4.2 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 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, non-fasting blood samples may be obtained initially for determining eligibility for the trial. A fasting blood sample is required at baseline prior to dosing. Clinical laboratory tests at other visits should be drawn fasting, if possible, but must be drawn after a minimum 8-hour fast at Week 52/ET. Vital sign measurements and ECG assessments should be completed before any blood samples are

collected. See exclusion criteria (Section 3.4.3) for laboratory tests. For de novo subjects, 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. 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 lab vendor's online portal and assessed by the investigator or qualified designee for clinical significance within eCRF.

Table 3.7.4.2-1 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 Blood alcohol test or breathalyzer	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 (females of childbearing potential), serum test will confirm positive urine test results PT/INR TSH, with reflex to free T_4 if TSH is abnormal HbA_1c CPK reflex for isoenzymes if CPK > 3 × ULN; serum and urine myogloblin collected if CPK > 5 × ULN Additional Tests (Baseline Only for Rollover Subjects and Screening Only for De Novo Subjects): HBsAg Anti-HCV HIV

CPK = creatine phosphokinase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RBC = red blood cell; 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. For de novo subjects, 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. The baseline laboratory test results will be available after the subject has initiated the IMP; therefore, if results come back meeting any of the 'exclusionary' ranges (see Table 3.4.3.1-1 for rollover subjects and Table 3.4.3.2-1 for de novo subjects), the subject's eligibility to continue the trial will be determined after discussing with 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 can be performed at any point during the trial if pregnancy is suspected. Urine pregnancy tests will be conducted in FOCBP per the Schedule of Assessments (Table 3.7-1 and Table 3.7-2 for rollover subjects and Table 3.7-3 and Table 3.7-4 for de novo subjects).

3.7.4.3 Physical Examination and Vital Signs

3.7.4.3.1 Physical Examination

A complete physical examination will be performed at screening for de novo subjects and at baseline for rollover subjects (ie, Trial 405-201-00013 or Trial 405-201-00014), 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 for rollover subjects and Table 3.7-3 for de novo subjects). A complete physical examination will include height (baseline and screening only for rollover subjects and de novo subjects, respectively), weight, waist circumference, and calculation of body mass index (BMI) (baseline and screening only for rollover subjects and de novo subjects, respectively, and Week 52/ET for all subjects); and assessment of the head, eyes, ears, nose, throat, thorax, abdomen, urogenital, skin and mucosae, neurological, and extremities. Any abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF.

3.7.4.4 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 for rollover subjects and Table 3.7-3 and Table 3.7-4 for de novo subjects). 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. At baseline, predose vital signs will be measured before dosing. Vital signs are to be completed before any blood is drawn.

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).

3.7.4.5 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 for rollover subjects and Table 3.7-3 for de novo subjects). All ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an ET. Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator or qualified designee will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis.

If, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the subject and/or the interpretation of the trial results) or meets an exclusion criterion (see Table 3.4.3.1-1 for rollover subjects and Table 3.4.3.2-1 for de novo subjects), the subject should be excluded from the trial. For de novo subjects, abnormal results for ECGs should be repeated once at screening with 3 consecutive ECG recordings to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. Each ECG recording should be taken approximately 5 minutes apart (the ECG result reported will be evaluated at each

time point). The central ECG service will provide the corrections for the 3 ECGs performed. Based on the QT interval corrected for heart rate by Fridericia's formula (QTcF) reported by the central service, a subject will be excluded if the corrections are ≥ 450 msec in men and ≥ 470 msec in women for 2 of the 3 time points of the ECGs done, unless due to ventricular pacing. If only 1 ECG time point has a QTcF of ≥ 450 msec in men and ≥ 470 msec in women, and this is not reproduced at either of the other 2 time points, the subject can be included in the trial.

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.

3.7.4.6 Other Safety Assessments

3.7.4.6.1 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 for rollover subjects and Table 3.7-3 and Table 3.7-4 for de novo subjects). 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.

3.7.4.6.2 Suicidality

Suicidality will be monitored during the trial (Table 3.7-1 and Table 3.7-2 for rollover subjects and Table 3.7-3 and Table 3.7-4 for de novo subjects) 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.

This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version, which assesses the life-time experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events or ideation

within a specified time period prior to entry into the trial, will be completed for all de novo subjects at the screening visit to determine the eligibility. Any subject with active suicidal ideation within the last 30 days, suicidal behaviors within the last year, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (see Table 3.4.3.1-1 for rollover subjects and Table 3.4.3.2-1 for de novo subjects). The "Since Last Visit" C-SSRS form will be completed at all other in-clinic visits for all subjects (rollover and de novo).

3.7.5 Pharmacokinetic/Pharmacodynamic Assessments

3.7.5.1 Pharmacokinetic Assessment

Not applicable.

CCI

[redacted]

3.7.6 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.

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 Interruption

All attempts should be made to avoid treatment interruption during the trial. For subjects who have an interruption of treatment, the investigator or designee will contact the sponsor at the earliest possible time to discuss. The sponsor should be notified when there is a planned or inadvertent treatment interruption of 4 days or more in a 7-day period. 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. The treatment interruption will be recorded in the eCRF and also recorded as a protocol deviation (Section 3.13).

3.8.3.2 Treatment Discontinuation

After starting open-label IMP, 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 3.8.3.5. Refer to the Schedule of Assessments (Table 3.7-1 and Table 3.7-2 for rollover subjects and Table 3.7-3 and Table 3.7-4 for de novo subjects) for a description of follow-up procedures.

If a subject discontinues from the trial prematurely, the reason must be fully evaluated and recorded appropriately in source documents and in eCRF. If the subject is being withdrawn because of an AE, that AE should be indicated as the reason for withdrawal. All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary.

3.8.3.3 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
    - Other potentially IMP-related safety concerns or AEs
- 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

Subjects withdrawn prior to Week 52 must complete the Week 52/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 days and 7 days after the last dose of the IMP, and 10 days via telephone, web, or other acceptable means of contact 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 after enrollment 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. Subjects will be instructed not to start

alternative ADHD therapy until Week 52/ET visit and appropriate follow-up visits are completed.

3.8.3.4 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 [interrupt or] discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.1 and Section 3.8.3.2). 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 3.8.3.3 to

determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.8.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be given instructions to 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 started on open-label treatment. For the purposes of this trial, treatment begins with the first dose of open-label oral centanafadine SR.

Subjects who sign an eICF but who are not started on-treatment may be permitted to be rescreened. In the event that the subject is rescreened for trial participation, and the rescreening is not completed within the original screening window, a new eICF must be signed.

De Novo Subjects

If a subject fails to qualify for the trial during the 28-day screening period for a reason other than a positive screen for cocaine, or other illicit drugs (excluding marijuana), the subject is permitted to be rescreened at a later date. Screen failures previously excluded for a positive blood alcohol test or breath alcohol test or a positive urine drug screen due to use of prescription or over-the-counter (OTC) medications or products may be retested or rescreened for participation in the trial only with the explicit consent of the medical monitor. 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 subjects again test positive at baseline visit, authorization to proceed for an additional washout and continuation to the treatment period requires explicit authorization from the medical monitor. Screen failures excluded for any other reasons may be rescreened at any time if the exclusion characteristic has

changed. In the event that the subject is rescreened for trial participation, 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 objective 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 Week 52/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 Week 52/ET visit 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 for rollover subjects and Table 3.7-3 for de novo subjects). 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.

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 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

Rollover subjects who enrolled from Trial 405-201-00013 or Trial 405-201-00014 will washout from centanafadine for at least one week before the baseline visit of the open-label trial. Rollover subjects who are willing to enroll in this trial must not start any new medication for ADHD after the Week 6 visit in Trial 405-201-00013 or Trial 405-201-00014.

De novo subjects who are currently taking any medication for adult ADHD at screening will washout from their current ADHD medication before the baseline (Day -1) visit. De novo 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 the first dose of IMP.

Table 4.1-1 Washout of Prohibited Medications Required Before the Trial - De Novo Subjects

	Medication	Required Washout Prior to Dosing
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), unless meeting critieria in Table 4.1-2 (1. [j])	7 days
7.	Antihypertensives Clonidine Propranolol Guanfacine	21 days
8.	Anorexics (weight loss supplements)	7 days

Table 4.1-2 lists all medications prohibited during the trial, including exceptions, where appropriate. Prohibited medications may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) in short-term basis and must not be prescribed as a treatment for a chronic disease.

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) Antihistamines: Sedating (eg, diphenhydramine, hydroxyzine, chlorpheniramine): Permitted if subject can provide a valid prescription, or if taken OTC to treat an established medical history of insomnia or as a decongestant. Non-sedating (eg, Claritin, Alegra): Subjects are permitted to use during trial
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]Limited use of oral benzodiazapines as rescue medication for the short-term management of AEs of anxiety, agitation, and insomnia will be allowed during the trial. The prescribed benzodiazepine should be discontinued as soon as the AE for which it was initiated subsides, as per the investigator's discretion to avoid any withdrawal effects. 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

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 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 or breathalyzer at any time during the trial if there is a suspicion of illicit drug or alcohol 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. The AEs 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:

- Any SAE.
- Any AE of special interest (AESI) (see Section 5.4)
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.6).
- Pregnancies are also defined as immediately reportable events (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, and/or fulfills a seriousness criterion, this is considered an AE.

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

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/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 AESI.

All AESI 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 and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months).

For FOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or 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, females who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or males 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 and/or serum pregnancy test for human chorionic gonadotropin will be performed at screening on FOCBP subjects. 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

Not applicable; this is an open-label trial.

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 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

No PK or pharmacogenomic analysis is planned.

7 Statistical Analysis

7.1 Sample Size

The sample size is not based on statistical power considerations but on ICH/GCP requirements. The trial population will be derived from eligible subjects from the, double-blind phase 3 trial (ie, Trial 405-201-00013 or Trial 405-201-00014) and de novo subjects from selected sites. It is expected that approximately 560 completing rollover subjects from double-blind phase 3 trial (Trial 405-201-00013 or Trial 405-201-00014) and approximately 145 de novo subjects will be enrolled into this trial.

7.2 Datasets for Analysis

The following samples are defined for this trial:

- Enrolled Sample, which comprises all subjects who sign an eICF for the trial;
- Safety Sample, which comprises all subjects that will receive at least 1 dose of IMP;
- Efficacy Sample, which comprises those subjectsin the Safety Sample who have at least 1 post baseline efficacy evaluation of AISRS Total Score.

7.3 Handling of Missing Data

In order to assess the sensitivity of results due to missing data, 2 types of analyses will be performed: last observation carried forward (LOCF) and observed cases (OC). The OC dataset will consist of the actual observations recorded at each visit. The LOCF dataset will include data recorded at a scheduled visit, ie, all OC data, or, if no observation is recorded at that visit, data will be carried forward from the previously scheduled visit. Baseline data will not be carried forward to impute missing values for the LOCF dataset. The OC dataset will be used for analyzes at each trial visit and the LOCF dataset will be used for analyzes at the last visit.

7.4 Primary, Secondary, and Exploratory Endpoint Analyses

7.4.1 Primary Endpoint Analysis

The primary (safety) endpoint analysis is the frequency and severity of AEs (including evaluations of rash and abuse potential) in the open-label treatment period. All AEs will be coded using the MedDRA PTs. The incidence of TEAEs will include the following summaries:

- 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 medication handling irregularities

A TEAE is defined as an AE that starts after the first dose of IMP or an AE that is reported at baseline and increases in intensity or becomes serious or trial drug-related or results in death, discontinuation, interruption, or reduction of IMP.

7.4.2 Secondary Endpoint Analysis

Not applicable.

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7.4.3 Exploratory Endpoint Analysis

Exploratory (efficacy) endpoints for the open-label trial are:

- Change from baseline in AISRS Total Score, by trial visit and at the last visit (ie, Week 52/ET);
- Change from baseline CGI-S, by trial visit and at the last visit (ie, Week 52/ET);
- Change from baseline in AIM-A Score by trial visit and at the last visit;
- CCI

Descriptive statistics will be provided for each endpoint, and will be summarized at each trial visit based on the Efficacy Sample using the OC dataset and at the last visit using the LOCF dataset. Baseline is defined as the last available measurement prior to the first dose of open-label IMP in the open-label treatment period.

7.4.4 Interim Analysis

No interim analysis is planned for this trial.

7.5 Analysis of Demographic and Baseline Characteristics

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

7.6 Additional Safety Endpoint Analysis

Standard safety variables to be analyzed include clinical laboratory tests, vital signs, ECGs, and physical examinations. In addition, data from the following safety scales will be evaluated: abuse liability, assessments of suicidality (C-SSRS), and assessment of withdrawal (SMWQ).

Safety analysis will be conducted based on the Safety Sample defined in Section 7.2. 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 analyzes are provided in the statistical analysis plan (SAP).

7.6.1 Abuse Liability Analysis

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

7.6.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements will be provided. In addition, the incidence of potentially clinically relevant values identified using prospectively defined in the SAP criteria for laboratory tests will be summarized.

7.6.3 Physical Examination and Vital Signs Data

Physical examination findings will be listed by-subject. Potentially clinically relevant results in vital signs and body weight will also be summarized.

Summary statistics for change from baseline in vital signs and body weight will be provided.

7.6.4 Electrocardiogram Data

Mean change from baseline will be summarized by visit.

The incidence of clinically relevant changes will be calculated for ECG parameters and summarized by visit.

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:

1) QTcB is the length of the QT interval corrected for heart rate by the Bazett's 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: $QTcN=QT/(RR)^{0.37}$

Results will be summarized by visit.

7.6.5 Study Medication Withdrawal Symptoms

Medication withdrawal symptoms for all subjects will be assessed using SMWQ. Summary statistics for SMWQ total scores at the scheduled visit(s) will be provided.

7.6.6 Columbia-Suicide Severity Rating Scale

Suicidality (eg, C-SSRS) will be summarized by treatment group by descriptive statistics. Details are described in the SAP.

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. Trial medication 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 (including investigational or active control) 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(s). The IMP may only be destroyed by the trial site(s), if approved by the sponsor and if the IMP destruction meets all local regulations.

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 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 Product Quality Complaint (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 CCI
- Phone: CCI

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 complaint
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

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 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 regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years after the date on which a New Drug Application is approved by the FDA;
- A period of 2 years after the sponsor has notified the FDA that investigation with this drug is discontinued.

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

10 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 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 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 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, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject 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, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved eICF will require similar modification. In such cases, after approval/favorable opinion of the new eICF by the IRB, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

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.

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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 and/or a decrease of ≥ 20 mmHg in diastolic blood pressure after at least 3 minutes of standing compared to the previous supine blood pressure	Not applicable (baseline status not considered)
Orthostatic tachycardia	≥ 25 bpm increase in heart rate from supine to standing	Not applicable (baseline status not considered)
Weight	–	≥ 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 ECG 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 405-201-00015, issued 7 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.
- Revised the last day of subject contact from Day +14 to Day +10 after the last dose of IMP.
- Added criteria excluding de novo subjects only 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).
- Added wording in the clinical laboratory table indicating that a CPK reflex for isoenzymes if CPK > 3 × ULN; serum and urine myoglobin collected if CPK > 5 × ULN, and that the urine drug screen should include methylphenidate (ritalinic acid) and not "stimulants (including those for the treatment of ADHD)."
- Revised exclusion language regarding participating in other prior clinical trials for de novo subjects only.
- 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.
- Updated assignment of subject ID numbers for de novo and rollover subjects.
- Clarified that SMWQ will be completed by the subject at the site and completed remotely for non-site visits.

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- Removed CYP2D6 inhibitors and substrates from the Washout of Prohibited Medications Required Before the Trial - De Novo Subjects 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 405-201-00015, originally issued on 07 Mar 2018 and amended on 18 May 2018, were made to address administrative changes and correct minor errors.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Changed the FBR blood volume collection from "up to 10 mL" to "approximately 10 mL".
- Changed "birth control depot injection" to "birth control injection".
- Removed the medication adherence platform for IMP accountability and compliance, as that will not be used in this trial.
- Clarified that vital signs will be performed in the supine and standing positions only, and not the sitting position, consistent with Trials 405-201-00013 and 405-201-00014.
- Clarified that the fasting blood sample test results for rollover subjects do not need to be reviewed by the investigator prior to the administration of IMP, because the results will not be available until after the subject has started IMP.
- Added footnotes to the Schedule of Assessments to clarify that the following assessments may be conducted at the 7-day follow-up visits of Trials 405-201-00013 or 405-201-00014, and the information can be carried over into Trial 405-201-00015 for the baseline visit: concomitant medications, AEs, vital signs, urine drug screen, alcohol testing, C-SSRS, and AISRS.
- Updated the email address for reporting IREs.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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Amendment Number: 2

Issue Date: 02 Jun 2020

PURPOSE:

The purpose of this protocol amendment is to introduce a COVID-19 Addendum for any protocol-specified activities that are not able to be performed or cannot be performed due to COVID-19 considerations. Refer to the COVID-19 Addendum for the appropriate measures to be followed.

BACKGROUND:

These changes to clinical trial protocol 405-201-00015, originally issued on 07 Mar 2018 and amended on 18 May 2018 and 30 Aug 2018, were made to introduce a COVID-19 Addendum. No other changes were made.

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

Document Name: 405-201-00015 Protocol Amendment 2

Document Number: CCI [redacted]

Document Version: 5.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Clinical Approval	02-Jun-2020 18:08:33
PPD	Biostatistics Approval	02-Jun-2020 19:52:30
PPD	Clinical Pharmacology Approval	02-Jun-2020 19:55:32
PPD	Safety Approval	03-Jun-2020 03:06:33

Otsuka Pharmaceutical Development & Commercialization, Inc

Investigational Medicinal Product

Centanafadine (EB-1020)

ADDENDUM FOR CLINICAL PROTOCOL FOR TRIAL 405-201-00015

An Open-label, 52-Week, Multicenter Trial Evaluating the Long-term Safety and Tolerability of Centanafadine Sustained-Release Tablets in Adults with Attention-Deficit/Hyperactivity Disorder

Protocol No. 405-201-00015
IND No. 119,361

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, Maryland 20850
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety Fax: CCI E-mail: CCI
Issue Date:	02 Jun 2020
Version No.:	1.0

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Trial Conduct for COVID-19

All procedures and assessments in the protocol are to be followed to the fullest extent possible. The sponsor, in coordination with the site, investigator(s), and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it relates to COVID-19. If any protocol-specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, the appropriate measures to be followed will be provided in this document.

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List of In-text Figures

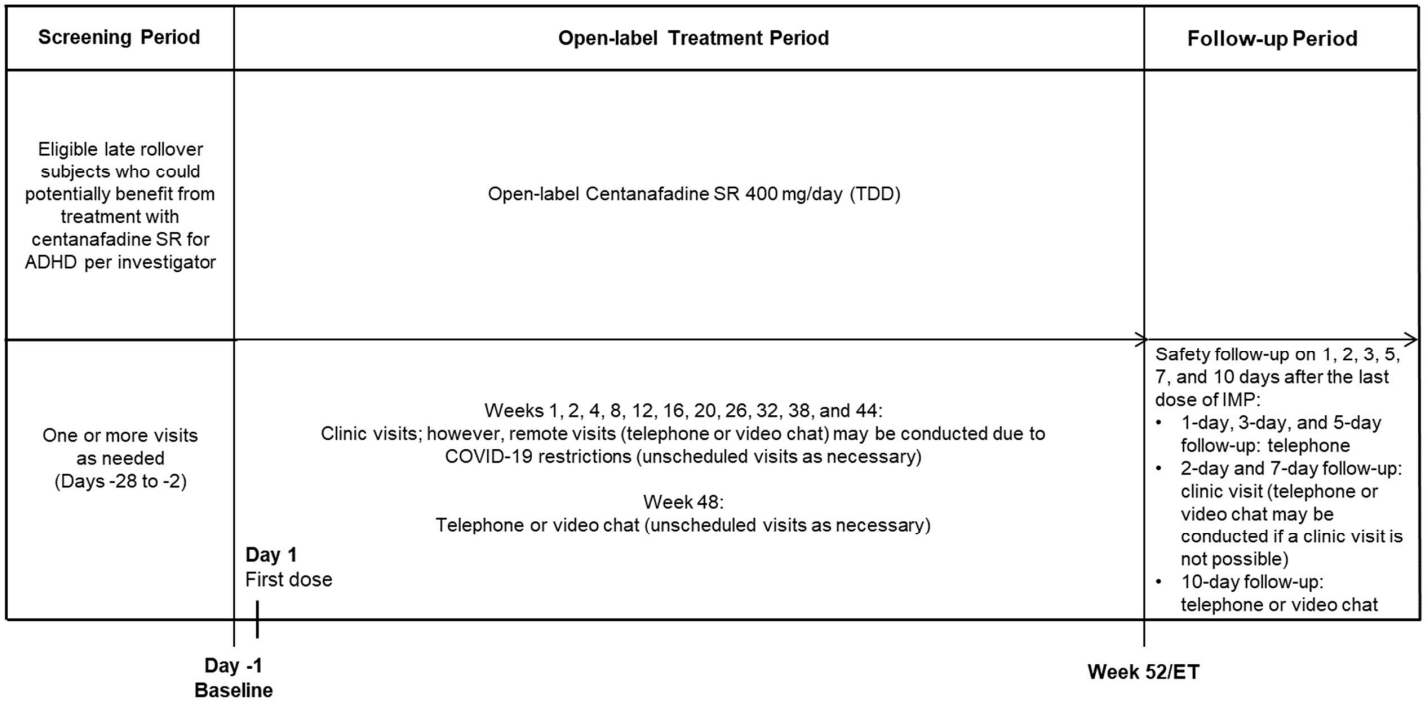
List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACDS	Adult ADHD Clinical Diagnostic Scale
ADHD	Attention-deficit hyperactivity disorder
AE	Adverse event
AIM-A	ADHD Impact Module - Adult
AISRS	Adult ADHD Investigator Symptom Rating Scale
ALT	Alanine aminotransferase
Anti-HCV	Hepatitis C antibodies
AST	Aspartate aminotransferase
CCI	[redacted]
CGI-S	Clinical Global Impression-Severity of Illness Scale
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
ET	Early termination
FOCBP	Females of childbearing potential
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
MINI	Mini International Neuropsychiatric Interview
PRO	Patient-reported outcome
PT	Prothrombin time
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
SAE	Serious adverse event
SMWQ	Study Medication Withdrawal Questionnaire
SR	Sustained-release
T_4	Free thyroxine
TDD	Total daily dose
TSH	Thyroid-stimulating hormone

Protocol 405-201-00015

1 Trial 405-201-00015 COVID-19 Protocol Summary

1.1 Trial Design Schematic



ADHD = attention deficit hyperactivity disorder; ET = early termination; IMP = investigational medicinal product; SR = sustained release; TDD = total daily dose.

Figure 1.1-1 COVID-19 Impact Trial Design Schematic

1.2 Schedule of Assessments

Table 1.2-1 COVID-19 Impact Schedule of Assessments (Baseline Through End of Treatment)

			52-Week Open-label Treatment Period								
	Screening	Baseline[a]	W 1 & 2 (± 3 days)	W 4, 8, 12, & 16 (± 3 days)	W 20 (± 3 days)	W 26 (± 3 days)	W 32 (± 3 days)	W 38 (± 3 days)	W 44 (± 3 days)	W 48[b] (± 3 days)	End of Treatment W 52/ET (± 3 days)
Visit	**1**	**2**	**3 & 4**	**5, 6, 7, & 8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
ENTRANCE/HISTORY											
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X
Medical history	X										
ACDS	X										
Identification of comorbidities using MINI	X										
Psychiatric history	X										
HIV/HBsAg/anti-HCV	X										
Urine pregnancy test[c]	X	X	X	X	X	X	X	X	X		X
SAFETY											
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X[d]	X		X[e,f]		X[f]					X[f]
Vital signs	X	X	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]		X[g]
12-lead ECG	X	X	X[f]	X[f,h]		X[f]		X[f]			X[f]
Clinical laboratory tests (hematology, serum chemistry [including HbA1c and TSH], and urinalysis)	X	X		X[e,f]		X[f]		X[f]			X[f]

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Table 1.2-1 COVID-19 Impact Schedule of Assessments (Baseline Through End of Treatment)

			52-Week Open-label Treatment Period								
	Screening	Baseline[a]	W 1 & 2 (± 3 days)	W 4, 8, 12, & 16 (± 3 days)	W 20 (± 3 days)	W 26 (± 3 days)	W 32 (± 3 days)	W 38 (± 3 days)	W 44 (± 3 days)	W 48[b] (± 3 days)	End of Treatment W 52/ET (± 3 days)
Visit	**1**	**2**	**3 & 4**	**5, 6, 7, & 8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
PT/INR		X				X[f]					X[f]
SMWQ											X
Urine drug screen	X	X		X[f,i]		X[f]					X[f]
Alcohol testing[j]	X	X		X[f,i]		X[f]					X[f]
C-SSRS	X	X	X	X	X	X	X	X	X		X
EFFICACY											
AISRS		X	X	X	X	X	X	X	X		X
CGI-S		X	X	X	X	X	X	X	X		X
AIM-A		X				X					X
CCI											
OTHER											
IMP dispensing		X	X	X	X	X	X	X	X		
IMP return and accountability			X	X	X	X	X	X	X		X

ACDS = Adult ADHD Clinical Diagnostic Scale; AIM-A = ADHD Impact Module - Adult; AISRS = Adult ADHD Investigator Symptom Rating Scale; anti-HCV = hepatitis C antibodies; CCI ; CGI-S = Clinical Global Impression-Severity of Illness Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; HbA1c = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; INR = international normalized ratio; MINI = Mini International Neuropsychiatric Interview; PT = prothrombin time; SMWQ = Study Medication Withdrawal Questionnaire; TSH = thyroid-stimulating hormone.

Note: If an in-person screening and baseline visit cannot be performed, then the subject cannot continue or be enrolled in the trial. The postbaseline visits should also be conducted in person; however, they may be conducted remotely due to COVID-19 restrictions. Subjects may miss up to 2 consecutive in-person assessments due to COVID-19 restrictions. The medical monitor must be consulted if the subject will miss more than 2 consecutive visits and determine whether or not the subject can continue on IMP. During the trial, if efficacy/safety assessments are unable to be obtained, the subject may

continue in the trial; however, if a subject is unable to collect a urine pregnancy test, the medical monitor must be contacted. At all postbaseline visits conducted remotely, the assessments will be done by telephone or video chat.

[a]Dosing will commence the day after the baseline visit.

[b]Telephone or video chat.

[c]If the urine pregnancy test is positive, see Section 4.1.2 for additional details.

[d]Physical examination at screening will include height measurements.

[e]Week 8 only.

[f]These assessments will be conducted at in-person visits only and will not be conducted remotely.

[g]At all postbaseline visits, subjects may collect their own vital signs using an appropriate device at home, if available; see Section 4.1.1 for additional details. For subjects who cannot obtain vital signs, a maximum of 2 consecutive months of missed vital sign assessments are permitted. If a subject cannot be seen in the clinic or cannot obtain vital signs remotely through available collection devices after that point, the medical monitor must be consulted to ascertain whether the subject should be discontinued from the trial.

[h]Weeks 4, 8, and 16 only.

[i]Weeks 4 and 12 only.

[j]Alcohol testing may be conducted via a blood test or using a breathalyzer.

CCI

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Table 1.2-2 COVID-19 Impact Schedule of Assessments (Follow-up)

	Follow-up[a]					
	1 (+1) days 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	**16**	**17**	**18**	**19**	**20**	**21**
ENTRANCE/HISTORY						
Concomitant medication(s)	X	X	X	X	X	X
EFFICACY						
AISRS		X			X	
SAFETY						
Adverse events	X	X	X	X	X	X
Vital signs		X[b]			X[b]	
SMWQ	X	X	X	X	X	X
Urine drug screen		X[c]			X[c]	
Alcohol testing[d]		X[c]			X[c]	
C-SSRS		X			X	

[a]Follow-up telephone calls will be conducted at 1, 3, and 5 days after the last dose of IMP, and a follow-up telephone call or video chat will be conducted 10 days after the last dose of IMP. At 2 and 7 days after the last dose of IMP, subjects should be seen in person; however, if a clinic visit is not possible, these visits may be conducted remotely (telephone or video chat).

[b]Subjects may collect their own vital signs using an appropriate device at home, if available; see Section 4.1.1 for additional details.

[c]These assessments will be conducted at in-person visits only and will not be conducted remotely.

[d]Alcohol testing may be conducted via a blood test or using a breathalyzer.

2 General Considerations

2.1 Telemedicine

Guidance will be provided to sites on whether use of telephone is acceptable, or if video is required. Sites will be instructed to attempt to standardize collection via telephone or video depending on the requirements of the trial to minimize confusion and risk of errors of utilizing varying collection strategies. All applicable country-by-country guidances and local regulations will be followed when implementing telemedicine options.

2.2 Reconsent

If there is an immediate need to reconsent subjects during the period of COVID-19 restrictions, a paper reconsent process will be followed and sites are encouraged to contact the contract research organization (CRO) and sponsor with questions. In regions where remote capacity exists to collect remote eConsent, the necessary information will be provided by the CRO and sponsor.

2.3 Protocol Deviations

Protocol deviations that occur as a direct result of the COVID-19 pandemic must be recorded in eSource separately from other protocol deviations as soon as they are identified and will be recorded as “Major” in eSource for data capture purposes. Examples of the types of COVID-19 related deviations to be reported may include: missed visits, missed assessments, assessments performed remotely (completed outside of protocol procedure), missed investigational medicinal product (IMP) dose, IMP dispensed/returned via courier, IMP not returned to site, site unable to verify IMP compliance, out of window visits, and prohibited concomitant medications. A “direct result” is defined as being due to actual illness, or as a result of quarantine, social distancing, or site closures. All other deviations will follow the normal deviation process described in the protocol and should not be entered proactively by sites.

2.4 Guidance to Record Adverse Events and Discontinuations Due to COVID-19

If a subject tests positive OR is presumed positive with COVID-19, the subject must be discontinued from the trial and an adverse event (AE) of “Coronavirus Infection” OR “Coronavirus Positive Test Result” should be recorded on the AE page of the electronic case report form. A positive test result or a presumed positive subject is not automatically a serious adverse event (SAE), unless an SAE criterion is met (eg, hospitalization).

If a subject discontinues due to COVID-19 either because the subject tests positive OR is presumed positive with COVID-19, then the primary reason for discontinuation should be reported as "Adverse Event" and indicate the AE number in the "Specify the reason for discontinuation" space that corresponds with the AE of "Coronavirus Infection" OR "Coronavirus Positive Test Result." Be sure to remember to enter an AE in the AE form for the "Coronavirus Infection" OR "Coronavirus Positive Test Result."

If a subject discontinues due to COVID-19 other than the subject testing positive OR being presumed positive with COVID-19, then the primary reason for discontinuation should be reported as "Other." Be sure to specify the reason as "COVID-19" followed by the reason ensuring that the prefix of the description includes "COVID-19." Do note that the reason "Other" should be selected even if the subject decides to withdraw consent or if the investigator decides to withdraw the subject due to COVID-19 concerns.

2.5 Statistical Analyses

Any impact of COVID-19 on the planned statistical analyses for the trial will be described in the final statistical analysis plan.

3 Trial Population

3.1 Inclusion Criteria

Late rollover subjects (ie, those who were unable to rollover from Trial 405-201-00013 or Trial 405-201-00014 due to the inability of an in-person baseline visit in Trial 405-201-00015) are required to meet the inclusion criteria presented in Table 3.1-1.

Table 3.1-1 Inclusion Criteria for Late Rollover Subjects From Trial 405-201-00013 or Trial 405-201-00014

1.	Subjects who completed or were administratively early terminated from the double-blind phase 3 trial (ie, Trial 405-201-00013 or Trial 405-201-00014) within the period restricting rollover due to the COVID-19 pandemic and who, in the opinion of the investigator, could potentially benefit from centanafadine for ADHD.
2.	Subjects who are able to complete the consent process and/or consent obtained from a legally acceptable representative (as required by the IRB) prior to the initiation of any protocol-required procedures.
3.	Subjects who, during the double-blind trials, demonstrated adequate compliance with medication and protocol requirements, per the investigator's judgment.
4.	Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, and discontinuation of prohibited medications, and to read and understand the written word in order to be reliably rated on assessment scales.
5.	Subjects who are willing to discontinue all prohibited psychotropic medications (refer to Section 4.1 of the protocol) starting from the time of signing the informed consent and up to the 10-day safety follow-up period.

IRB = institutional review board.

3.2 Exclusion Criteria

Late rollover subjects (ie, those who were unable to rollover from Trial 405-201-00013 or Trial 405-201-00014 due to the inability of an in-person baseline visit in Trial 405-201-00015) will be excluded if they meet any of the exclusion criteria presented in Table 3.2-1.

Table 3.2-1 Exclusion Criteria for Late Rollover Subjects From Trial 405-201-00013 or Trial 405-201-00014

1.	Subjects who, during the double-blind phase 3 trial (ie, Trial 405-201-00013 or Trial 405-201-00014), experienced, in the opinion of the investigator, poor tolerability to the IMP or whose safety assessments resulted in new concerns that would suggest the subject may not be appropriate for a 52-week treatment with IMP.
2.	Subjects who have demonstrated noncompliance, based on the investigator's judgment, to follow trial procedures during the course of their participation in the double-blind phase 3 trial (ie, Trial 405-201-00013 or Trial 405-201-00014). The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.
3.	Females who have a positive pregnancy test result prior to receiving IMP.
4.	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, females who have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchiectomy) 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 will also be excluded.
5.	Following responses from the "Since Last Visit" version of the C-SSRS (subjects should reference their last visit on Trial 405-201-00013 or Trial 405-201-00014): • Subjects with a response of "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) at entry, **OR** • Subjects with a response of "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) at entry, **OR** • Subjects with a response of "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) at entry, **OR** Subjects who, in the opinion of the investigator (including consideration of responses on the C-SSRS throughout Trial 405-201-00013 or Trial 405-201-00014), present a serious risk of suicide.
6.	Subjects with a newly developed psychiatric or medical condition that would be exclusionary under the criteria listed for Trial 405-201-00013 or Trial 405-201-00014.
7.	Subjects that have a positive alcohol test (via breathalyzer or blood), or a positive drug screen for cocaine or other illicit drugs (excluding marijuana). Subjects with a positive drug screen for confirmed prescription medications at baseline will not be permitted to continue participation in Trial 405-201-00015. 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 requires explicit approval from the medical monitor.
8.	Any new or developing safety concerns related to vital signs in the opinion of the investigator during the baseline visit.

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Table 3.2-1	Exclusion Criteria for Late Rollover Subjects From Trial 405-201-00013 or Trial 405-201-00014
9.	The following laboratory test and ECG results are exclusionary: 1) Platelets ≤ 75000/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) HbA1c ≥ 7% 8) Abnormal free T_4 (free T_4 is measured only if result for TSH is abnormal) 9) QTcF and/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 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. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.
10.	Subjects receiving any of the prohibited medications within the specified period prior to the first dose of IMP or who would be likely to require prohibited concomitant therapy during the trial (refer to Section 4.1 of the protocol).
11.	Subjects who have previously been enrolled in this trial and subsequently withdrawn.
12.	Any subject who, in the opinion of the investigator, should not participate in the trial.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; FOCBP = females of childbearing potential; QTcB = QT interval corrected for heart rate by Bazett's formula; QTcF = QT interval corrected for heart rate by Fridericia's formula; T_4 = free thyroxine.

4 Trial Procedures

If an in-person screening and baseline visit cannot be performed, then the subject cannot continue or be enrolled in the trial. The postbaseline visits should also be conducted in person; however, they may be conducted remotely due to COVID-19 restrictions. Subjects may miss up to 2 consecutive in-person assessments due to COVID-19 restrictions. The medical monitor must be consulted if the subject will miss more than 2 consecutive visits and determine whether or not the subject can continue on IMP. During the trial, if efficacy/safety assessments are unable to be obtained, the subject may continue in the trial; however, if a subject is unable to collect a urine pregnancy test, the medical monitor must be contacted. At all postbaseline visits conducted remotely, the assessments will be done by telephone or video chat.

4.1 Safety Assessments

4.1.1 Vital Signs

Blood pressure, heart rate, weight, and temperature may be measured as described in the protocol at the time points defined in this COVID-19 Addendum Schedule of Assessments (Table 1.2-1 and Table 1.2-2) with the following changes:

- Subjects will be asked to use their own collection device, if available. (Device(s) may be provided to subjects).
- Subjects will be instructed to be as consistent as possible regarding the time of day the measurement is taken, and to notify the site staff of the measurement results via telephone, or other means, on the appropriate visits.
- Site staff will be instructed to record the measurement in eSource, and if there are believed to be any errors, inconsistencies, or safety concerns with the reported home measurement, the medical monitor should be notified.

For subjects who cannot obtain vital signs, a maximum of 2 consecutive months of missed vital sign assessments are permitted. If a subject cannot be seen in the clinic or cannot obtain vital signs remotely through available collection devices after that point, the medical monitor must be consulted to ascertain whether the subject should be discontinued from the trial.

4.1.2 Pregnancy

Pregnancy tests will be performed as described in the protocol at the time points defined in this COVID-19 Addendum Schedule of Assessments (Table 1.2-1) with the following changes:

- For planned visits that require a pregnancy test for females of childbearing potential (FOCBP), the site will provide the necessary tests and instructions so the test may be performed at home.
- Applicable subjects will perform a pregnancy test prior to dosing with IMP, ensuring a date and time-stamped picture or video of the result is taken. The subject will notify the site staff of the test results by telephone and send the time-stamped picture or video to the site staff by email.
  - If negative, site to inform the subject to proceed with dosing.
  - If positive, the site must instruct the subject to immediately stop taking IMP, and the site will refer to the Pregnancy section of the protocol for appropriate immediately reportable event reporting.
    - Further instruction must be agreed upon in consultation with the sponsor.

4.2 Clinical Outcomes

4.2.1 General Considerations

Attempt to standardize the method of administration for a scale across subjects (eg, video chat or telephone) to decrease variability, and consult trial-specific guidance for recommendations on preferred methods for a given outcome. Prior to starting the remote visit, the subject should be informed of the estimated amount of time the visit is expected to take, and confirm subject access to a sufficient mobile or Wi-Fi signal and that the subject's device has an adequate charge. Any potential distractions should be addressed proactively to ensure the subject is not distracted during the remote visit. Assessments should be administered by the same qualified/trained rater who rated the subject previously; if this is not possible due to staff availability and/or technological limitations, discuss relevant information with previous raters to obtain clinical context (note that per protocol, raters must be trained/qualified to conduct assessments in all cases). Do your best to conduct all assessments during the same call/video chat, on the same day. Video chat is the preferred method for the Adult ADHD Investigator Symptom Rating Scale (AISRS), while other assessments can be completed by telephone or video chat.

All site staff will adhere to all Good Clinical Practice Guidelines, including Good Documenting Practices. Any factors that may potentially affect the subject's report (eg, unavoidable distractions, rater assessment of subject's level of engagement, any unexpected modifications to procedures) should be documented in eSource, along with how an assessment was completed (eg, via video, telephone, etc) and any modifications or accommodations performed. All assessment start times should be documented (including those that are interview based). If any AE-related information is reported, standard procedures for remote AE assessments with evaluation and follow-up with the medical monitor, as necessary, should be followed and documented accordingly.

4.2.2 Semi-Structured Interviews

Those administering scales must follow scale administration, training guidelines, and rating conventions as much as possible as provided by the sponsor, and ensure they maintain neutrality/research rapport as usual. Careful attention must be provided to subject engagement to try to ascertain whether the subject is distracted or minimizing, and efforts must be made to redirect the subject and ask additional questioning, if needed. Things to pay attention to are, but not limited to, the following: tone of voice, cadence, volume, and rate of speech if visual cues are not available (ie, if administered by telephone). Assessment start-stop times will be documented in eSource. The interviewer will be asked to "Rate what you see" and "Rate what you hear", and should not discount

symptoms on the assumption that they are caused or exacerbated by COVID-19 or changes in life circumstances.

4.2.3 Subject or Caregiver Reported Outcomes

Patient-reported outcomes (PROs) are to be completed by subjects on paper rather than be administered by raters over the telephone or teleconference platform. The subject should complete the paper scale during the telephonic/video conference assessment visit to ensure the correct date and time for PRO completion. It is recommended to use the video conference platform to observe the subject completing the paper PROs in a manner that does not allow the site staff to see the subject's responses but rather to ensure that the ratings are completed by the subject themselves. If this is not feasible, before ending the assessment visit, ask the subject to check if they have completed the PRO forms and to check again for completeness. Documentation must clearly detail the mode of administration and data entry. All assessments, including paper reports, should be completed during the telephonic/video conference visit.

4.2.4 Global Assessments of Severity and Subject Status

Sites will use all available sources of information to complete global assessments of severity, change/improvement, or subject status (eg, subject report, informant report, medical records if available, other assessment data if allowed per protocol). Site staff will be asked to conduct a general relatively unstructured evaluation and utilize informants as needed, ensuring that informants are also in a quiet and private place during evaluation. Attempt to complete global assessments after other assessments have been completed so all information from the visit is available, if allowed per protocol and per sponsor team instruction. The raters will be asked to "Rate what you see" and "Rate what you hear", and not rate according to what might be reasonable/expected due to COVID-19 as the rater must make a clinical assessment of subject status regardless of cause.

4.2.5 Suicidal Behavior and Suicidal Ideation

Evaluations of suicidality should be completed similar to how it is described in the protocol.

If suicidal ideation or behavior is reported, conduct further risk evaluation as per typical procedures and follow site processes and utilize emergency services or crisis lines, as needed. The medical monitor should be contacted for immediate guidance and support.

5 Investigational Medicinal Product

Given the ongoing COVID-19 restrictions, clinical sites are permitted to ship IMP directly to subjects.

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Document Name: 405-201-00015 Protocol Addendum

Document Number: CCI [redacted]

Document Version: 2.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Clinical Pharmacology Approval	02-Jun-2020 19:55:58
PPD	Biostatistics Approval	02-Jun-2020 19:55:56
PPD	Clinical Approval	02-Jun-2020 18:08:00
PPD	Safety Approval	03-Jun-2020 03:05:58