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Clinical Study Protocol

Study Title:	Efficacy of Centanafadine SR as a potential smoking cessation treatment
Protocol Number:	Protocol # 405-201-00055
Compound:	Centanafadine Sustained release Tablets (EB-1020)
IND Number:	155242
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
IRE Contact:	Rose Research Center PPD Email: PPD Phone: PPD
Version Number:	Version 3.0 – Amendment 1
Version Date:	August 16, 2021
Principal Investigator:	PPD
Medical Supervision:	PPD
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EXPLANATION OF TERMS

The following special terms are used in this protocol:

Baseline Visit	The baseline visit for this study is defined a V2.
Baseline Value	The baseline value is defined as the value at V2 unless otherwise specified.
End of Study	The end of study (EOS) for a subject is defined as the date of safety follow-up or the date of early termination of the subject.
Combustible cigarette	The term 'combustible cigarette' (CC) refers to commercially available, combustible cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine containing products.
Volunteer	A volunteer is an individual who has expressed interest in participating in a clinical research study.
Candidate	Individuals who completed a pre-screening evaluation with a member of the Rose Research Center recruitment team. They have been deemed as pre-qualified to come in for a physical screening visit to determine further eligibility.
Participant	A volunteer who has signed the study consent form. Once an individual signs the study consent form and receives a participant number, they are considered a Participant. The term "Subject" can and has historically been used interchangeably with Participant but for the purposes of communication, RRC has adopted the term participant as a global term for this status.

ABBREVIATIONS

5-HT	Serotonin
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
APMP	Abuse Potential Monitoring Process
AST	Aspartate aminotransferase
BID	Twice daily
BL	Baseline
BMI	Body mass index
BUN	Urea nitrogen
CBP	Childbearing potential
CC	Combustible cigarette
CFR	Code of Federal Regulations
CO	Carbon monoxide
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DA	Dopamine
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
FBR	Future biospecimen research
FDA	Food and Drug Administration
ESAM	Events Subject to Additional Monitoring
FTND	Fagerström test for nicotine dependence

GCP	Good Clinical Practice
HBA1c	Hemoglobin A1c
HCG	Human chorionic gonadotropin
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRE	Immediately Reportable Event
kg	Kilograms
Lbs	pounds
MAOI	Monoamine Oxidase Inhibitor
mCEQ	Modified Cigarette Evaluation Questionnaire.
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mg	Milligram
MHI	Medication handling irregularity
mL	Milliliter
MNWS	Minnesota Nicotine Withdrawal Scale
NE	Norepinephrine
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PPM	Parts per million
PQC	Product Quality Complain
QTc	Corrected QT interval
RBC	Red blood cell
RCT	Randomized Control Trial
RNA	Ribonucleic acid

RRC	Rose Research Center, LLC.
SaaS	Software-as-a-Service
SAE	Serious adverse event
SMS	Short Message Service
SNRI	Selective Norepinephrine Reuptake Inhibitor
SOP	Standard operating procedure
SR	Sustained Release
SSL	Secure Sockets Layer
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TDD	Total daily dose
TLS	Transport Layer Security
WBC	White blood cell
WHO	World Health Organization

SUMMARY OF CHANGES

AMENDMENT 1 – PROTOCOL VERSION 3.0 – 16 AUG 2021

- Clarification of "smoking cessation treatments" in Exclusion #14.
- Clarification of exclusionary medications in Exclusion #7.
- The PHQ-9 has been replaced with the C-SSRS based on recommendations from the FDA. **Section 9.1.5 Psychiatric Adverse Events** was added.
- Additional questionnaire added to assess use of other forms of nicotine between study visits.
- Clarification of laboratory tests ordered to properly characterize non-traumatic lesions. (**Section 9.5 – Adverse Events of Special Interest**)

SYNOPSIS

SPONSOR

Otsuka Pharmaceutical
Development & Commercialization, Inc.
2440 Research Boulevard
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INVESTIGATIONAL PRODUCT

Centanafadine Sustained release Tablets (EB-1020)

STUDY TITLE

Efficacy of centanafadine SR as a potential smoking cessation treatment

PROTOCOL NUMBER

405-201-00055

EXECUTIVE SUMMARY

This single-group, open-label study of 50 subjects will explore the potential of centanafadine in promoting smoking abstinence in adult smokers seeking to quit. The efficacy and tolerability of centanafadine at a dose of 400 mg total daily dose (TDD) (200 mg twice daily [BID]) approximately 4 to 6 hours apart (during a 7-week treatment period) will be compared with a benchmark of abstinence based on historical data from clinical trials of varenicline, viewed as the most efficacious pharmacotherapy currently approved by the FDA.

OBJECTIVES AND ENDPOINTS

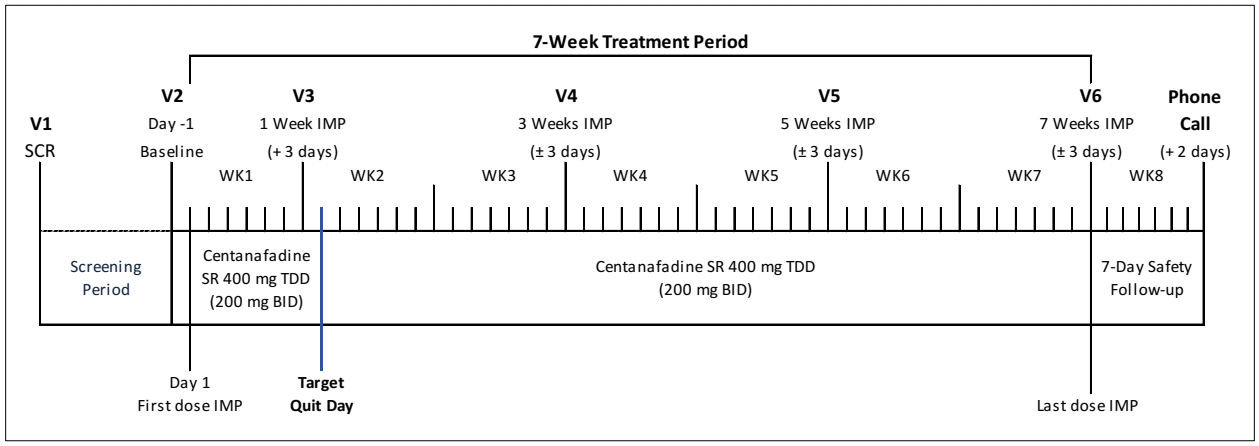
The primary endpoint is the four-week continuous abstinence rate of subjects with the treatment of centanafadine during weeks 4-7. A participant is considered abstinent from combustible cigarettes if he or she self-reports tobacco abstinence (no cigarette smoking, not even a puff) assessed by responses to daily messages throughout the period and has an exhaled carbon monoxide (CO) level of less than 5 ppm using the Vitalograph BreathCO monitor in the office at Visit 5 and Visit 6.

A secondary objective will be to determine if centanafadine yields equivalent efficacy to that of varenicline, with a significant reduction in the incidence of nausea the most prevalent side effect reported following varenicline treatment. Incidence rate of nausea is assessed by self-reported side effects collected via an open-ended question at each study visit.

STUDY DESIGN

This single-group, small-scale, open-label study (N= 50) will evaluate centanafadine SR (400 TDD) as a potential smoking cessation treatment. Participants enrolled in the study will be given centanafadine SR at a dose of 400 mg TDD (200 mg BID) approximately 4 to 6 hours apart for seven weeks.

The study will consist of up to a 28-day screening period, a baseline visit, a 7-week treatment period, and a 7-day safety follow-up period.



DOSING RATIONALE

The 400 mg TDD of centanafadine SR oral tablets (200 mg BID) will be evaluated in this study. This dose was found to produce a significant blockade (>10%) of transporters for serotonin, dopamine, and norepinephrine as well as alleviating symptoms of inattention and hyperactivity/impulsivity in patients with ADHD, without inducing a high incidence of nausea and headache that occur with doses as high as 800 mg.[1]

SAMPLE SIZE ESTIMATION

Given the conditional logic of the phase one analyses, Monte Carlo simulations based on a sample size of 50 were conducted to determine the significance thresholds for the binomial tests so that the overall Type I error rate across all tests would be 10% (9.87% of 100,000 simulated datasets), assuming the null hypothesis that centanafadine yields a four-week continuous smoking abstinence rate of 50% and an overall incidence of nausea of 30%. The power of the phase one analyses (probability of moving to phase two) was also determined by Monte Carlo simulations for three scenarios. In the first scenario, the treatment has a higher four-week continuous abstinence rate at 6 weeks post target quit date (65%) than varenicline, but an equivalent rate of nausea (30%). Power under this scenario is about 74%. In the second scenario, the treatment has the same four-week continuous abstinence rate at 6 weeks post target quit date as varenicline (50%) but has a lower nausea rate (15%). Power under this scenario is about 76%. Last, if the treatment generates both a higher four-week continuous abstinence rate at 6 weeks post target quit date (65%) and a lower rate of nausea (15%) then power is about 94%.

STATISTICAL METHODS

The estimation of the four-week continuous smoking abstinence rate at 6 weeks post target quit date is around 50% and 30% of treated individuals experiencing nausea from varenicline treatment based on the historical studies.[2] The smoking abstinence rate during weeks 4-7 will be calculated with 90% binomial confidence intervals, and the incidence rate of nausea will be tabulated, which will be compared with the thresholds established for efficacy and tolerability.

1 INTRODUCTION

1.1 BACKGROUND

Cigarette smoking remains the leading cause of preventable death in the United States, and is one of the leading causes of preventable morbidity and mortality.[3,4] An estimated 540,000 smokers die each year from smoking-related diseases.[5] Existing treatments for tobacco cessation yield, on average, less than 25% long-term abstinence rates, with many of the cessation failures occurring within the first month of abstinence.[6] There is an urgent need to develop new therapies for smoking cessation.[7] Current pharmacological approaches are efficacious for smoking cessation, but continue to have poor long-term abstinence rates, with potentially concerning adverse events.

There are currently seven Food and Drug Administration (FDA)-approved smoking cessation medications, which fall into three main categories: nicotine replacement therapy (NRT) including nicotine patch, gum, lozenge, inhaler, and nasal spray; varenicline (Chantix); and bupropion (Zyban/Wellbutrin). Among US smokers, 29.1% use NRT when attempting to quit smoking whereas only 7.9% use varenicline and 2.4% use bupropion.[8,9] Two other medications that show some efficacy, clonidine and nortryptyline, are not FDA approved, and account for less than 1% of smoking cessation treatment.[10] None of the current treatments yields sustained abstinence rates of over 25% at one year, but varenicline is the most efficacious. Varenicline is a full agonist on α7-nicotinic acetylcholine receptors (nAChRs) and a partial agonist on the α4β2, α3β4, and α6β2 subtypes.[2,11,12] Smoking abstinence rates at weeks 9-12 in two Phase III trials of varenicline were nearly identical at 44%. Given that four-week continuous abstinence at weeks 4-7 will be taken to be the primary abstinence outcome in the present study, and modeling relapse curves over the initial weeks of abstinence suggests that abstinence rates are ~5% higher at 6 weeks than at 12 weeks after the target quit-smoking date,[13] in this study a slightly higher rate of 50% abstinence will be taken to be the benchmark criterion to meet or exceed. Common adverse events associated with varenicline include nausea, insomnia, abnormal dreams, headaches, and nasopharyngitis.[14] The most common adverse reaction reported is nausea, with 30-40% of participants in randomized control trials reporting mild to moderate levels of nausea.[15] Discontinuation/drop-out rates of nearly 10% have been noted during clinical trials due to these adverse effects.[16] In real-world settings, discontinuation of varenicline treatment may be as high as 57%.[8]

Nicotine inhaled from cigarette smoke reaches the brain rapidly[17] and acts on nicotinic acetylcholine receptors to release several neurotransmitters involved in arousal, attention and mood regulation. Among these are the monoamines dopamine, norepinephrine and serotonin.[18,19] When dependent smokers abstain from smoking, nicotine withdrawal symptoms are experienced, including difficulty concentrating, irritability, and depressed mood,[20] which are thought to be due in part to a deficit in monoamine neurotransmitter activity. Centanafadine is a triple monoamine transporter inhibitor that acts to block re-uptake of norepinephrine, dopamine and serotonin (half-maximal inhibitory concentration [IC_{50}] 6 nM), dopamine (IC_{50} 38 nM), and serotonin (IC_{50} 83 nM),[21] and thus may counteract the withdrawal-induced deficit in these neurotransmitters accompanying smoking cessation. Indeed, bupropion, which is an efficacious smoking cessation treatment, is thought to exert its therapeutic actions by inhibiting re-uptake of dopamine and norepinephrine.CCI [redacted]

CCI [redacted] Additionally, smoking relapse is hypothesized to result in part from impulsivity, which has been shown to be reduced by centanafadine treatment.[1]

1.2 Study Rationale

Smokers that go through nicotine withdrawal often experience difficulty concentrating, hypoarousal, and negative mood, which could be alleviated by centanafadine's effect in enhancing monoamine neurotransmitter activity.

This trial will explore the potential of centanafadine in promoting smoking abstinence in adult smokers seeking to quit. The efficacy and tolerability of centanafadine at a dose of 400 mg per day will be compared with a benchmark of abstinence based on historical data from clinical trials of varenicline, viewed as the most efficacious pharmacotherapy currently approved by the FDA.

This single-group, open-label study of 50 participants will evaluate oral administration of centanafadine sustained-release tablets (EB-1020), to help smokers abstain from smoking combustible cigarettes during a 7-week study period.

2 Study Objectives and Endpoints

2.1 Primary Objective: Smoking Abstinence

The primary objective will be to determine whether centanafadine yields a superior four-week continuous smoking abstinence rate compared to varenicline during weeks 4-7. Abstinence will be defined as self-report of no cigarette smoking (not even a puff), confirmed by an expired air CO reading of less than 5 ppm at week 7.

2.1.1 Endpoints

- Self-report of no cigarette smoking (not even a puff), assessed by responses on daily messages.
- Expired air CO reading of less than 5 ppm, assessed in office using the Vitalograph BreathCO monitor.

2.2 Secondary Objective: Reduction in Incidence of Nausea

A secondary objective will be to determine if centanafadine yields equivalent efficacy to that of varenicline), with a significant reduction in the incidence of nausea, the most prevalent side effect reported following varenicline treatment.

2.2.1 Endpoint

Self-report of side effects assessed by open-ended question at each study visit.

3 INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This single-group, small-scale, open-label, phase 2 study (N= 50) will evaluate centanafadine as a potential smoking cessation treatment. The dose of centanafadine SR that will be evaluated in this trial will be 400 mg TDD (200 mg BID) approximately 4 to 6 hours apart for seven weeks.

The study will consist of a 14-day screening period, a baseline visit, a 7-week treatment period, and a 7-day safety follow-up period. Participants will visit the study center a total of six times, including a screening visit (V1), baseline visit (V2), a visit one week (+ 3 days) after starting the study drug (V3), three weeks (± 3 days) after starting the study drug (V4), five weeks (± 3 days) after starting the study drug (V5), and seven weeks (± 3 days) after starting the study drug (V6). All participants will be requested to participate in a 7-day safety follow up period, which will consist of telephone contact seven days (+2 days) after the last dose of investigational product.

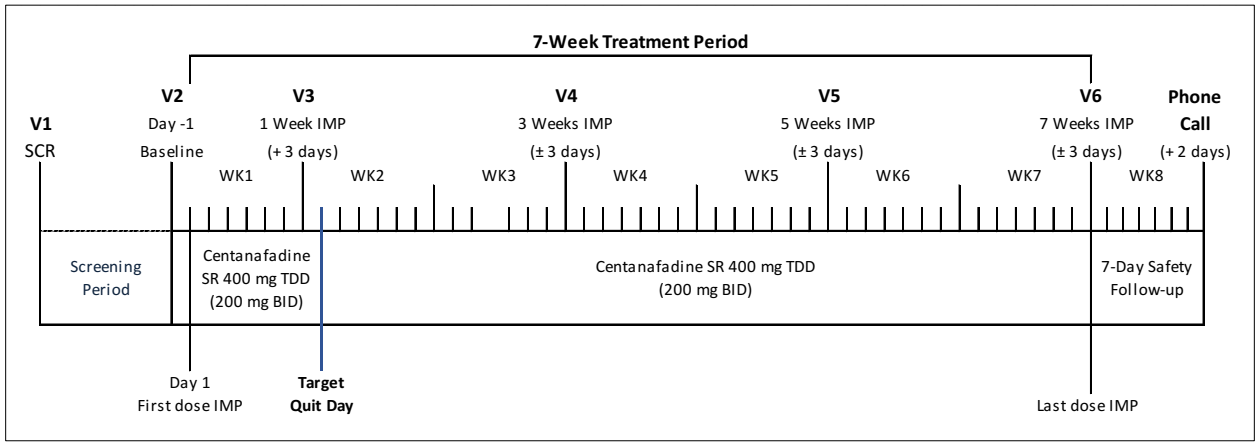


Figure 1 - Overall Study Design and Plan, 7-Week Treatment Period

3.2 STUDY AND SESSION DURATIONS

The total duration for a participant will be approximately 10 weeks. The Screening Session (Visit 1) will last approximately 2 ½ to 3 hours. The other study sessions will last approximately 1 to 1 ½ hours.

4 PARTICIPANT INVOLVEMENT

The study population will include fifty (50) cigarette smoking adults, between 21 and 65 years of age, inclusive, with no restriction on gender, race and ethnicities, or social-economic status, who have smoked an average of at least 10 commercially available cigarettes per day for the last 12 months.

4.1 POINT OF ENROLLMENT

Participants will be enrolled at V2, after all safety laboratory results have been received and reviewed by the medical staff (MD or PA).

4.2 INCLUSION CRITERIA

Inclusion Criteria	
1.	Has signed the ICF and is able to read and understand the information provided in the ICF.
2.	Smokers 21 to 65 years of age (inclusive) at screening.
3.	Smokes an average of at least 10 commercially available cigarettes per day for the last 12 months.
4.	Has an expired air CO reading of at least 10 ppm at screening.
5.	At screening, express a desire to quit smoking within the next 30 days.
6.	BMI of 18 to 40 kg/m^2, inclusive at screening.
7.	Willing and able to comply with the requirements of the study.
8.	Owns a smart phone with text message and data capabilities compatible with necessary surveys.

4.3 EXCLUSION CRITERIA

Exclusion Criteria	
1.	Participants of childbearing potential (CBP) who are breast-feeding and/or have a positive pregnancy test result.
2.	Participant presenting with, or having a history of, uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 95 mmHg) or symptomatic hypotension.
3.	Participants 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.
4.	History of seizures (after the age of 17 years).
5.	Participants of CBP or sexually active participants unless they 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 Investigation Medicinal Product (IMP) for participants of CBP, and 30 days after the last dose of IMP for participants with partners who are of CBP. Unless the participant is sterile (i.e., participants who have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or participants 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. Participants who do not agree to refrain from donating sperm from screening through 30 days after the last dose of IMP.
6.	Participant has a history of dermatologic adverse reactions secondary to any drug exposure or any active/uncontrolled dermatologic disease.
7.	Currently taking antidepressants (e.g., SSRI's SNRI's, TCA's or MAOI's), antipsychotics (such as butyrophenones, thioxanthines, atypical antipsychotics or other heterocyclics), benzodiazepines, hypnotics, or medications that prolong QTc. MAOI's taken within 30 days of screening.
8.	Screening (Visit 1) or Baseline (Visit 2) C-SSRS score greater than 0 (any answer "Yes") for the *SUICIDAL IDEATION* section or greater than 0 for the *SUICIDAL BEHAVIOR* section (any answer "Yes")
9.	Substance use disorder within 12 months prior to screening.
10.	Participants that have a positive alcohol test (via breathalyzer or blood), a positive drug screen for illicit drugs (Table 6.3.5) at screening or baseline. NOTE: Participants who test positive for marijuana at screening may 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.
11.	Any participant who has any other medical or physical condition(s) that, in the opinion of the investigator, may prevent the participant from completing the trial or would go against the participant's best interest with participation in the trial. This would include any significant illness or unstable medical condition that could lead to difficulty complying with the protocol.

Exclusion Criteria	
12.	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) HbA1c ≥ 7% 8) QTcF > 450 msec for males or > 470 msec for females NOTE: In addition, participants 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 participant or the interpretation of the trial results.
13.	Participants with a history of prior exposure to centanafadine.
14.	Use of smokeless tobacco (chewing tobacco, snuff), cigars (except for "Black & Mild" cigars or Cigarillos), pipes, hookah, e-cigarettes, nicotine replacement therapy or other smoking cessation treatments (e.g., bupropion as Zyban, or varenicline) within 14 days of screening.
15.	Participants who participated in a clinical trial and were exposed to interventional trial medication within the last 30 days prior to screening or who participated in more than 2 interventional clinical trials within the past year.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBP = childbearing potential; HbA1c = glycosylated hemoglobin; QTcF = QT interval corrected for heart rate by the Fridericia formula.

4.3.1 Participants of Childbearing Potential (CBP)

Participants of CBP are defined as participants 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 participants of CBP and for participants who are sexually active, there must be a documented agreement that the participant and/or their partner will take effective measures (i.e., double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the participant is sterile (i.e., 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 participants must also agree not to donate sperm from screening through 30 days after the last dose of IMP.

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

A serum pregnancy test (screening visit only) or urine pregnancy test (all other visits) for human chorionic gonadotropin will be performed on participants who have the potential to become pregnant. If a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.

4.4 RECRUITMENT STRATEGIES

CCI [redacted]

4.4.1 Pre-Screening

Pre-screening will be completed prior to V1 for all participants. Participants will be provided with a set of IRB approved questions directly related to the inclusion and exclusion criteria. Based upon the outcome of these questions, potential participants may be scheduled for a screening visit (V1).

4.5 PARTICIPANT RETENTION IN THE STUDY

All candidates who schedule a screening visit (V1) will receive a series of email, text, and telephone reminders; participants are also permitted through these communications to confirm, cancel, or reschedule all their appointments.

4.6 DISCONTINUATION OF PARTICIPANTS FROM STUDY

Discontinued participants will include both participants who withdraw from the study (participant's decision) or participants who are discontinued from the study (following Investigator's decision). A participant can only be discontinued from the study after the IMP is dispensed to them. Participants that are not dispensed the IMP are considered screen failures.

Participants will be informed that they are free to withdraw from the study at any time. Participants should be questioned for the reason of premature withdrawal from the study, although they are not obliged to disclose it.

Participants discontinued from the study cannot re-enter the study.

Participants will be discontinued from the study for any of the following reasons:

- Withdrawal of informed consent.
- Any adverse effect or condition that would jeopardize continued safe study participation.
- Discontinuation is considered to be in the best interest for the participant or for other participants participating in the study, as judged by the Investigator or designee.

Participants may be discontinued from the study for any of the following reasons based on the judgment of the Investigator:

- No-show to appointments and unable to reschedule within the visit window.
- The misuse or abuse of study related equipment.
- Potential loss of the participant's data validity.
- Unwilling or unable to comply with study procedures.

4.7 Lost to Follow-up

For participants lost to follow-up, three attempts to contact the participant (including written correspondence and/or phone calls) will be made and documented in the source documents. The date of the last contact (e.g., last visit, last phone call) will be recorded in the source document. When the PI (or designee) declares a participant is lost to follow-up, the lost to follow-up date will be recorded and will correspond to the date of the End of Study (EOS) of the participant.

4.8 Violation of Inclusion/Exclusion Criteria

Participants who, after signing the ICF, do not meet the inclusion and exclusion criteria will be considered screen failures. Re-screening for the study is not permitted.

4.9 Session and Response Windows

4.9.1 V2 Session Window

Participants may attend V2 up to 28 calendar days post Screening Session (V1).

4.9.2 V3 Session Window

Participants may attend V3 up to 3 calendar days post scheduled visit.

4.9.3 All other visit Windows

Participants may attend sessions up to three calendar days pre or post the scheduled visit.

4.9.4 Daily Message Response Window

The survey response window will be open until the next survey response message is sent.

5 Investigational Medicinal Product (IMP)

5.1 Centanafadine SR (EB-1020)

Centanafadine is an investigational drug that has inhibitory activity at norepinephrine (NE), dopamine (DA), and serotonin (5-HT) reuptake transporters.[1] It has the highest activity for inhibition for norepinephrine reuptake (half-maximal inhibitory concentration [IC_{50}] 6 nM), but also inhibits dopamine (IC_{50} 38 nM) and serotonin (IC_{50} 83 nM) transporter reuptake.[23]

Two phase 2 trials showed that the SR version of centanafadine was safe and well tolerated in adults with attention deficit hyperactivity disorder (ADHD). The first study administered up to a TDD of 500 mg

(split into twice daily dosing) for two weeks.[21] The second study compared TDDs of 400 mg, 600 mg, and 800 mg in terms of safety and efficacy for reducing ADHD symptoms. Both studies concluded that centanafadine SR 400 mg TDD (200 mg BID) was effective and well tolerated and did not result in sleep disturbances, and there were no signs of abuse or diversion.[21] The most common adverse events reported were headache (20%, placebo = 9%), decreased appetite (16%, placebo = 0%), and upper respiratory tract infection (16%, placebo = 11%).[21]

5.1.1 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 trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

5.2 Dosing Regimen

Centanafadine SR will be administered orally at a 400 mg TDD (200 mg BID) approximately 4 to 6 hours apart for a total of seven weeks. Doses of centanafadine SR can be taken without regard to meals and should be taken at approximately the same time each day, with the first dose taken in the morning. The second dose should be taken 4 to 6 hours after the first dose. If a subject forgets to take their second dose, they can take it up to 7 hours after their first dose; if they remember after 7 hours, they should skip the dose and resume dosing the next day.

5.2.1 Dosing Rationale

The 400 mg dose of centanafadine SR will be evaluated in this study. This dose was found to produce a significant blockade (>10%) of transporters for serotonin, dopamine, and norepinephrine as well as alleviating symptoms of inattention and hyperactivity/impulsivity in patients with ADHD, without inducing a high incidence of nausea and headache that occur with doses as high as 800 mg.[1]

5.2.2 Dose Adjustment Procedures

The IMP dose may be considered for a one time dose decrease based on tolerability and/or adverse events. A one-time dose decrease to 200mg TDD (one pill in am and one pill in pm), based on the clinical judgement of the investigator. The subject would remain on the decreased dose (200mg TDD) for the remainder of trial participation. If tolerability / AE does not resolve, post IMP dose-reduction, the subject should be considered for trial discontinuation, based on investigator judgement.

5.3 Storage and Accountability

5.3.1 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 participant not participating in this protocol.

The IMP will be stored at controlled room temperature conditions as per the clinical label on the IMP. The IMP storage location will be monitored by TempAlert, temperatures will be recorded every 10 minutes, with alerts triggered (via email, SMS, and phone call) when a temperature falls out-of-threshold (Severity 3), when a temperature is at risk of going out-of- range (Severity 2), and when a

temperature has gone out-of-range (Severity 1). For detailed information about temperature monitoring, please refer to RRC's *SOP CLN040 – Facility Temperature Procedures with TempAlert.*

5.3.2 Accountability

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

5.3.3 Destruction

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

5.4 PRODUCT QUALITY COMPLAINTS

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

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

- Failure of a product to meet any of its specifications
- Packaging defects (e.g., damaged, dirty, crushed, missing product or component, incorrect or missing labeling)
- Product defects (e.g., odor, chipped, broken, damaged, crushed, embossing illegible, under-filled bottle, over-filled bottle, empty bottle, no safety seal)
- Loss or theft of product

5.4.1 Eliciting and Reporting a PQC

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

Send PQC reporting information to Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) IMP PQC mailbox email: **IMP-PQC@otsuka-us.com**. Also indicate whether or not the complaint sample is available for return.

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

5.4.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (e.g., investigator, site, etc.)
- Reporter contact information (e.g., address, phone number, e-mail address)
- Subject number

- Clinical site number
- ID of material (product/compound name, lot/batch number, shipment number, expiry date)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures of complaint sample (if available)
- Availability of complaint sample for return

5.4.3 Return Process for Complaint Sample

Indicate during the report of the PQC if the complaint sample is available for return.

If complaint sample is available but not at the clinical site, please instruct participant to bring the complaint sample to their next site visit.

If complaint sample is available for return, the return instructions will be provided by the sponsor.

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

5.4.4 Assessment and Evaluation

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

6 STUDY PROCEDURES AND ACTIVITIES

Personnel performing study assessments must have appropriate and documented training. An overview of all study assessments is shown in the Schedule of Events. Study personnel will adhere to standard operating procedures (SOPs) for all activities. Appropriate medical advice will be provided by qualified staff (licensed providers) to the participant in case of any medical findings requiring health care.

6.1 INFORMED CONSENT AND GUIDANCE

Prior to any study assessments being performed, the participant will be asked to provide their written consent to participate in the study on an informed consent form (ICF). All assessments must start after the time of ICF signature by the participant for study participation.

Designated staff, under the supervision of the Principal Investigator, will obtain informed consent from each participant. The person obtaining consent provides the participants with a printed document that explains the procedures and risks. Designated staff will answer any questions. A signed copy of the informed consent form will be given to each participant. Participants are informed that they may withdraw from participation in the study at any time without penalty.

6.2 VIRTUAL SCREENING PROCEDURES

To protect against unnecessary risk in the COVID-19 environment, many aspects of screening may be conducted virtually. Potential participants will be sent the IRB approved consent form via electronic signature. Consenting will take place via virtual meeting where information about the study will be explained to potential participants, with adequate time allowed for questions to be answered. Once the consent form is signed, the participant will be sent a secure link to complete screening questionnaires.

These questionnaires will be reviewed by medical and research staff to determine eligibility prior to scheduling the On-Site Visit.

6.4 SAMPLINGS FOR PHARMACOKINETICS (PK)

Blood samples will be taken to determine concentrations of centanafadine and metabolites to assess compliance with dosing. The date and time of the sample collection and the date and time of last dose of IMP prior to sample collection will be recorded in the CRF. Concentrations of the IMP will be listed in the bioanalytical report.

6.5 SAFETY EVALUATIONS AND OTHER ASSESSMENTS

Clinical safety evaluations will be performed to ensure that participants meet the requirements of the study and to monitor participant safety. An overview of all assessments is provided in the schedule of events.

Urine will be collected, and blood will be drawn from each subject prior to treatment with centanafadine. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the laboratory will be assessed by the investigator or qualified designee for clinical significance.

The results of the clinical chemistry, hematology and urine analysis safety panel will not routinely be given to participants to send or be sent to their physician to include in their medical record. However, if the participant's laboratory results are clinically relevant (including positive pregnancy tests), the research medical staff will send the participant a copy of the laboratory results. Participants who are accepted into the study but need medical follow-up due to minor abnormalities in laboratory results (at any session) will also receive a copy of the laboratory results.

Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the laboratory will be assessed by the investigator or qualified designee for clinical significance.

6.5.1 Clinical Chemistry

Blood will be collected for Clinical Chemistry tests at the screening visit (V1), V4 and the final study visit (V6).

Clinical Chemistry	
Sodium	Chloride
Potassium	Carbon dioxide
Urea nitrogen (BUN)	Creatinine
Glucose	Calcium
Protein, total	Albumin
Bilirubin, total	Alkaline phosphatase (AP)
Aspartate aminotransferase (AST)	Alanine aminotransferase (ALT)
Glycosylated Hemoglobin (HbA1c; at screening only)	Gamma-glutamyl transferase (GGT)

Table 1 - Clinical Chemistry

6.5.2 Hematology

Blood will be collected for Hematology tests at the screening visit (V1), V4 and the final study visit (V6).

Hematology	
Red blood cell (RBC) count	WBC count
Hemoglobin	Differential white blood cell (WBC) count
Hematocrit	Platelet count
Mean corpuscular volume (MCV)	Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular hemoglobin (MCH)	

Table 2 - Hematology

6.5.3 Serum Pregnancy Test

Blood will be collected for a serum pregnancy test at the screening visit (V1) for all participants with the potential to become pregnant. In case of any positive pregnancy test, the Investigator or designee will inform the participant about the risks associated with smoking during pregnancy.

Serum Pregnancy Test
Quantitative human chorionic gonadotropin (HCG) test

Table 3 - Serum Pregnancy

6.5.4 Urinalysis

A urine sample will be collected for Urinalysis at the screening visit (V1) and the final study visit (V6).

Urinalysis	
pH	Glucose
Red blood cell traces	Specific gravity
Bilirubin	Nitrite
Protein	WBC Esterase

Table 4 - Urinalysis

6.5.5 Urine Drug Screen

A urine samples will be collected for a drug screen at the screening visit (V1), V4 and V5.

Drug Screening
Amphetamine
Cocaine
THC
Methamphetamine
Opiates

Table 5 - Drug Screening

6.5.6 Urine Pregnancy Test

A urine sample will be collected for a pregnancy test at all study visits (excluding screening). All positive urine pregnancy test results will be confirmed by a serum test. Participants with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial. The Investigator or designee will also inform the participant about the risks associated with smoking during pregnancy. For additional information please refer to **Section 9.8 Pregnancy after Enrollment**.

6.5.7 Electrocardiogram (ECG)

ECG recording will be performed and interpreted at RRC by qualified personnel. A standard 12-lead ECG will be recorded after the participant has rested for at least 5 minutes in a supine position.

Data and evaluations from ECGs will be reported on the individual participants' CRFs and transferred to Otsuka via the EDC database. Original ECG tracings will remain at the site (RRC) within the source documentation.

6.5.8 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate), will be measured in sitting position after the participant has rested for at least 5 minutes. After two minutes of standing, a second blood pressure reading (systolic and diastolic) and pulse rate will be obtained at the screening visit (V1).

6.5.9 Physical Examination

A complete physical examination, including auscultation and palpation will be performed. A complete physical examination will include review of general appearance, hair and skin, head, eyes, ears, nose and throat, neck, chest, abdomen, dentition, cardiovascular, musculoskeletal and neurological systems. The physical examination is to be conducted by a designated fully trained representative.

Appropriate medical recommendations will be provided to the participant if any medical findings requiring health care are identified.

6.5.10 Expired Air CO Breath Test

Carbon Monoxide (CO) in participant's exhaled breath (expressed as ppm) will be measured using a Vitalograph BreathCO Monitor. Participants must have an expired air CO reading at V1 of at least 10 ppm for inclusion into this study. This test will be repeated at each of the visits.

6.5.11 Medical History and Concomitant Disease

Relevant medical history and concomitant disease will be documented at the screening visit (V1). Medical history is defined as any condition that started and ended prior to screening. A concomitant

disease is defined as any condition that started prior to screening and is still ongoing at V2 (this may also include findings detected during the screening visit (V1)).

6.5.12 Prior and Concomitant Medication

All medication taken 30 days prior to the screening visit (V1) and during the study will be documented. Medications which are stopped before V2 will be considered as prior medications. Medications which are started prior to the screening visit (V1) and which are still being taken by the participant during the study, as well as medications that are initiated after the screening visit (V1) will be considered as concomitant medications. This applies to both prescription and over-the-counter products (e.g., vitamins).

Records of prior and concomitant medications taken include the drug name (preferably both generic and trade name), route of administration, dose/unit, frequency of use, indication, the start and, if applicable, the stop date. Any therapy changes (including changes of regimen) during the study will be documented.

6.5.13 Body Height and Body Weight

Body weight will be measured at each visit. Height and weight will be measured at screening, and body mass index (BMI) will be calculated.

6.5.14 Demographics

Sex assigned at birth, sex currently identified with, date of birth, race and ethnicity will be recorded for each participant according to the Schedule of Events.

6.5.15 AE/SAE Reporting

AEs/SAEs will be assessed using questionnaires and interviews at the indicated time points and spontaneous reporting from the time of ICF signature until the EOS for the participant the Schedule of Events.

6.5.16 Questionnaires

The questionnaires will be administered to the participants using paper questionnaires and/or an electronic data collection system. The questionnaires will be asked according to the Schedule of Events.

6.5.16.1 ***C-SSRS – The Columbia-Suicide Severity Rating Scale***

The C-SSRS is an assessment tool that evaluates suicidal ideation and behavior.[24] The "Screening" Version will be used for the first administration (at the screening visit). This version will include an assessment of suicidal ideations over the past 12-months and an assessment of suicidal behaviors over the past 24 months. Subsequent visits will utilize the "Since Last Visit" Version.

6.5.16.2 ***Modified Cigarette Evaluation Questionnaire Extended (mCEQE)***

The Cigarette Evaluation Questionnaire was initially developed in the PI's laboratory and used in numerous studies to assess the effects of pharmacological treatments on the rewarding effects of cigarette smoking. The mCEQE will be utilized to assess the degree to which participants experience the reinforcing of smoking, providing five subscale scores: smoking satisfaction (satisfying, tastes good, enjoy smoking), psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger), aversion (dizziness, nauseated), enjoyment of respiratory tract sensations (single-item assessment), craving reduction (single-item assessment). Participants will be asked to assess the 12

items of the questionnaire on a 7-point scale, ranging from “not at all” to “extremely”. These 12 items will be asked for the “first cigarette smoked”, “cigarette immediately after a meal”, and “all other cigarettes.”

6.5.16.3 *Modified Shiffman-Jarvik Withdrawal Scale*

The Modified Shiffman-Jarvik Withdrawal Scale is used to measure withdrawal symptoms and a participant’s desire to smoke. This scale consists of five subscales: craving, psychological symptoms, physical symptoms, sedation, and appetite.[25]

6.5.16.4 *Reasons to Smoke*

The Reasons to Smoke questionnaire is used to determine the most important reasons to smoke for each participant.

6.5.16.5 *The Fagerström Test for Nicotine Dependence (FTND)*

The Fagerström Test for Nicotine Dependence is a six-item questionnaire developed by Karl-Olov Fagerström and is used to determine someone’s level of nicotine dependence. The scores obtained on the test allow the classification of nicotine dependence in three different levels: mild (0-3 points), moderate (4-6 points), and severe (7 -10 points).

6.5.16.6 *Smoking History Questionnaire*

The Smoking History is a questionnaire designed to help assess the participant’s current and past smoking habits. This questionnaire will be administered at screening (V1) and will include questions about the number of years participants have smoked combustible cigarettes (CC), the number of CCs per day smoked over the last 12 months, brand of CCs, use of other tobacco products and use of nicotine replacement therapy or other smoking cessation treatments. This questionnaire will also be used to check eligibility criteria.

6.5.16.7 *Other Nicotine Use Questionnaire*

The Other Nicotine Use questionnaire will be used to capture information about the use of nicotine containing products (other than combustible cigarettes). This questionnaire will be given at V2 and all subsequent visits, including safety follow-up.

6.5.16.8 *Minnesota Nicotine Withdrawal Scale (MNWS)*

The MNWS is used to assess nicotine withdrawal symptoms including craving and mood effects. Participants will be asked to assess eight symptoms on a 5-point scale ranging from 0 to 4, where 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe.

6.5.16.9 *Study Drug Compliance*

Participants will be queried via electronic messages whether they have been compliant with taking the study drug. These messages will commence after the second visit (V2) and continue through the End of Study.

6.5.16.10 *Smoking Status*

Electronic messages will be sent to participants starting after the second visit (V2), through the End of Study, to ascertain the participants smoking status.

6.6 VISIT PROCEDURES

6.6.1 Screening (V1)

Eligibility of participants to participate in this study will be assessed at the screening visit (V1). The ICF will be signed, dated and timed prior to any other screening procedures. At the end of this visit, participants will be given instructions on the use of the messaging and questionnaire system that will be used daily to collect information about smoking status (starting the next day) and IMP compliance (after V2).

The sequence of the following questionnaires and assessments will be at the discretion of the Investigator (or designee) after signature of the ICF. Whenever possible, blood draws should be performed after all other assessments are complete.

6.6.1.1 ***Questionnaires***

- Smoking History
- Registration Form
- Medical History (with Review of Systems)

6.6.1.2 ***Assessments***

- Review of Prior and Concomitant Medication
- Review of Concomitant Disease and Medical History
- Expired air CO breath test
- Alcohol breath test
- Urine collection for urinalysis and drug screen
- Blood collection for safety laboratory testing (including pregnancy test for all females) and for future biospecimen research (for those participants who consented to this optional collection)
- Vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate), will be measured in sitting position after the participant has rested for at least 5 minutes. After two minutes of standing, a second blood pressure reading (systolic and diastolic) and pulse rate will be obtained.
- Height and weight / BMI
- Temperature
- Electrocardiogram (ECG) -- A standard 12-lead ECG will be recorded after the participant has rested for at least 5 minutes in a supine position.
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Physical examination

6.6.2 Baseline (V2) – Day -1

Visit 2 will occur within 28 days of the screening visit. Participants will come to the Center to complete questionnaires, assessments, and for dispensing of IMP. Participants will begin the study drug regimen the day after V2 (Day 1). Date and time of first dose will be collected via electronic message.

The sequence of the following questionnaires and assessments will be at the discretion of the Investigator (or designee).

6.6.2.1 ***Questionnaires***

- Reasons to Smoke
- Other Nicotine Use Questionnaire
- Modified Cigarette Evaluation Questionnaire Extended (mCEQE)
- Minnesota Withdrawal Questionnaire
- Modified Shiffman-Jarvik Withdrawal Scale
- Fagerström Test for Nicotine Dependence

6.6.2.2 ***Assessments***

- Review of Concomitant Medication
- Review of Concomitant Disease
- Expired air CO breath test
- Urine collection for pregnancy (all participants with the potential to become pregnant)
- Vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate), will be measured in sitting position after the participant has rested for at least 5 minutes.
- Weight
- Temperature
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Review of adverse events (as needed)
- Physical examination (as needed)

6.6.3 Day before Quit Day (V3) – 1 week on IMP

Six days (+ 3 days) after starting the study drug (one day prior to quit date), participants will return to the Center to complete questionnaires and assessments. Participants will also be asked to return unused IMP and will be dispensed enough IMP to last until the next scheduled visit.

The sequence of the following questionnaires and assessments will be at the discretion of the Investigator (or designee).

6.6.3.1 ***Questionnaires***

- Other Nicotine Use Questionnaire
- Modified Shiffman-Jarvik Withdrawal Scale
- Modified Cigarette Evaluation Questionnaire Extended (mCEQE)
- Minnesota Withdrawal Questionnaire

6.6.3.2 ***Assessments***

- Review of Concomitant Medication
- Review of Concomitant Disease
- Expired air CO breath test
- Urine collection for pregnancy (all participants with the potential to become pregnant)
- Vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate), will be measured in sitting position after the participant has rested for at least 5 minutes.
- Weight
- Temperature
- Columbia-Suicide Severity Rating Scale (C-SSRS)

- Review of adverse events (as needed)
- Physical examination (as needed)

6.6.4 Visit 4 (V4) – 3 weeks on IMP

Three weeks (± 3 days) after starting the study drug , participants will return to the Center for V4 to complete questionnaires and assessments. Participants will also be asked to return unused IMP and will be dispensed enough IMP to last until the next scheduled visit.

The sequence of the following questionnaires and assessments will be at the discretion of the Investigator (or designee).

6.6.4.1 ***Questionnaires***

- Other Nicotine Use Questionnaire
- Modified Shiffman-Jarvik Withdrawal Scale
- Modified Cigarette Evaluation Questionnaire Extended (mCEQE)
- Minnesota Withdrawal Questionnaire

6.6.4.2 ***Assessments***

- Review of Concomitant Medication
- Review of Concomitant Disease
- Expired air CO breath test
- Urine collection for drug screen and pregnancy (all participants with the potential to become pregnant)
- Blood collection for safety laboratory testing, pharmacokinetics, and future biospecimen research (for those participants who consented to this optional collection)
- Vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate), will be measured in sitting position after the participant has rested for at least 5 minutes.
- Weight
- Temperature
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Review of adverse events (as needed)
- Physical examination (as needed)

6.6.5 Visit 5 (V5) – 5 weeks on IMP

Five weeks (± 3 days) after starting the study drug, participants will return to the Center for V5 to complete questionnaires and assessments. Participants will also be asked to return unused IMP and will be dispensed enough IMP to last until the next scheduled visit.

The sequence of the following questionnaires and assessments will be at the discretion of the Investigator (or designee).

6.6.5.1 ***Questionnaires***

- Other Nicotine Use Questionnaire
- Modified Shiffman-Jarvik Withdrawal Scale
- Modified Cigarette Evaluation Questionnaire Extended (mCEQE)
- Minnesota Withdrawal Questionnaire

6.6.5.2 ***Assessments***

- Review of Concomitant Medication
- Review of Concomitant Disease
- Expired air CO breath test
- Urine collection for drug screen and pregnancy (all participants with the potential to become pregnant)
- Vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate), will be measured in sitting position after the participant has rested for at least 5 minutes.
- Weight
- Temperature
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Review of adverse events (as needed)
- Physical examination (as needed)

6.6.6 Final Study Visit (V6) – 7 weeks on IMP

Seven weeks (± 3 days) after starting the study drug, participants will return to the Center for V6 to complete questionnaires and assessments. Participants will also be asked to return all unused IMP.

The sequence of the following questionnaires and assessments will be at the discretion of the Investigator (or designee).

6.6.6.1 ***Questionnaires***

- Other Nicotine Use Questionnaire
- Modified Shiffman-Jarvik Withdrawal Scale
- Modified Cigarette Evaluation Questionnaire Extended (mCEQE)
- Minnesota Withdrawal Questionnaire
- Fagerström Test for Nicotine Dependence

6.6.6.2 ***Assessments***

- Review of Concomitant Medication
- Review of Concomitant Disease
- Expired air CO breath test
- Alcohol breath test
- Urine collection for urinalysis and pregnancy (all participants with the potential to become pregnant)
- Blood collection for safety laboratory testing, pharmacokinetics, and future biospecimen research (for those participants who consented to this optional collection)
- Vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate), will be measured in sitting position after the participant has rested for at least 5 minutes.
- Weight
- Temperature
- Electrocardiogram (ECG) -- A standard 12-lead ECG will be recorded after the participant has rested for at least 5 minutes in a supine position.
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Review of adverse events (as needed)

- Physical examination (as needed)

6.6.7 Telephone Contact

Participants will be contacted via phone on Day 1 (first day of IMP) and on weeks that they are not scheduled to visit the Center (Wk 2, Wk 4, and Wk 6) to ask how they are doing and answer any questions the participant may have.

6.6.8 Safety Follow-Up

Seven to 10 days after V6, participants will be contacted via phone for a safety follow-up.

6.6.8.1 ***Questionnaires***

- Other Nicotine Use Questionnaire
- Modified Cigarette Evaluation Questionnaire Extended (mCEQE)
- Minnesota Withdrawal Questionnaire

6.6.8.2 ***Assessments***

- Review of Concomitant Medication
- Review of Concomitant Disease
- Review of adverse events

6.7 DAILY MESSAGING

Rose Research Center will utilize eResearch, an IRB approved proprietary mobile electronic application for clinical research studies available in both the iOS and Android app stores. For the purposes of this protocol, the Survey's feature will be utilized to push the daily messages to enrolled participants.

Daily text reminders and/or push notifications may be paired with these daily messages in order to remind participants about the request to complete these assessments.

6.7.1 Daily Message (after screening, prior to V2)

Participants will receive a push notification with a prompt to a daily survey to access the following:

- Have you smoked any combustible cigarettes today?
  - If yes, how many cigarettes did you smoke?

6.7.2 Daily Message (Visit 2 through V6)

Participants will receive a push notification with a prompt to a daily survey to assess the following:

- Have you smoked any combustible cigarettes today?
  - If yes, how many cigarettes did you smoke?
- Did you take your 1st dose of study drug today?
- Did you take your 2nd dose of study drug today?
  - If yes, did you take the 2nd dose 4 to 6 hours after the 1st dose?

6.8 SCHEDULE OF EVENTS

Study Week	SCR	Wk 0 Baseline		Wk 1 (+ 3 days)	Wk 2 - Wk 3 (± 3 days)	Wk 4 - Wk 5 (± 3 days)	Wk 6 - Wk 7 (± 3 days)	Wk 8 (+ 2 days)
Visit	V1	V2		V3	V4	V5	V6	Safety Follow-up
IMP Timeline		Day -1	Day 1 IMP	Wk 1 IMP	Wk 3 IMP	Wk 5 IMP	Wk 7 IMP	
Informed Consent	x							
Inclusion/Exclusion Criteria	x	x						
Enrollment		x						
Visit Preparation	x	x		x	x	x	x	
Visit Reminder Calls	x	x		x	x	x	x	
Telephone Contact -(Day 1, Wk 2, Wk 4, Wk 6, and 7 day F/U)			x		x	x	x	x
Questionnaires								
Reasons to Smoke		x						
Smoking History	x							
Other Nicotine Use		x		x	x	x	x	x
Registration Form	x							
Medical History with Review of Systems	x							
Modified Cigarette Evaluation Questionnaire Extended (mCEQE)		x		x	x	x	x	x
The Fagerström Test for Nicotine Dependence (FTND)		x					x	
Modified Shiffman-Jarvik Withdrawal Scale		x		x	x	x	x	
Minnesota Withdrawal Questionnaire		x		x	x	x	x	x
The Columbia-Suicide Severity Rating Scale (C-SSRS)	x	x		x	x	x	x	
Smoking Status (via daily messages)	x	x	x	x	x	x	x	
Medication Adherence (via daily messages)		x	x	x	x	x	x	
Blood Samples								
Clinical Chemistry	x				x		x	
CBC w/Diff & Platelet Count	x				x		x	
Serum Pregnancy Test*	x							
HbA1c	x							
PK Blood Draws					x		x	
CCI								
Urine Samples								
Urinalysis Safety Panel	x						x	
Drug Screen	x				x	x		
Pregnancy		x		x	x	x	x	
Other Assessments								
Prior and Concomitant Medication Assessment and Medical Review	x	x		x	x	x	x	x
Concomitant Disease Assessment and Medical Review	x	x		x	x	x	x	
CO Breath Test	x	x		x	x	x	x	
ECG	x						x	
Blood Pressure - Sitting and Standing Positions	x	x		x	x	x	x	
Heart rate	x	x		x	x	x	x	
Temperature	x	x		x	x	x	x	
Respiratory rate	x	x		x	x	x	x	
Weight	x	x		x	x	x	x	
Physical Examination (as needed)	x	x		x	x	x	x	
Alcohol Breath Test	x							
Procedures								
AE Interview and Assessment		x		x	x	x	x	x
Collect Used/Unused IP				x	x	x	x	
Dispense IP		x		x	x	x		
IMP Dosing			x	x	x	x	x	

* Serum pregnancy test will be done if urine pregnancy test is positive

Table 6 - Schedule of Event

7 RISK / BENEFIT INFORMATION

7.1 POTENTIAL BENEFITS

The participants will be encouraged to quit smoking, which would significantly reduce their risk of smoking-related diseases.

7.2 IMPORTANCE OF KNOWLEDGE TO BE GAINED

The proposed study could lead to the development of a new approach to smoking cessation that would have a major positive impact on public health worldwide along with associated comorbid conditions.

7.3 POTENTIAL RISKS

7.3.1 Centanafadine SR

The most common adverse effects reported in other studies of centanafidine SR include: decreased appetite, headache, nausea, dry mouth diarrhea, fatigue, insomnia, rash (refer to Section 9.5 for additional information), dizziness, heart rate increase when standing from a sitting position, irritability, abdominal pain, change in sense of taste.[1]

7.3.2 Tobacco Withdrawal

To the extent that nicotine or other tobacco smoke constituent intake is reduced or eliminated, participants may experience tobacco withdrawal symptoms, including craving, difficulty concentrating, mood disturbance and increased appetite/weight gain.

7.3.3 Blood Draw

The risks associated with venipuncture are minimal and include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, and fainting are also possible, although unlikely.

7.4 CONCOMITANT MEDICATIONS

All medication taken 30 days prior to the screening visit (V1) and during the study will be documented using a source document. Medications which are stopped before V2 will be considered as prior medication. Medication which was started prior to V1 and which is still being taken by the subject during the study as well as medication that is initiated after V2 will be considered as a concomitant medication. This applies to both prescription and over-the-counter products (e.g., vitamins).

Records of prior and concomitant medications taken include the drug name (preferably both generic and trade name), route of administration, dose/unit, frequency of use, indication, the start and if applicable, the stop date. Any therapy changes (including changes of regimen) during the study have to be documented.

7.5 Protection Against Risks

Participants will be screened medically and monitored throughout the study. Study participants will receive detailed instructions on the use of the IMP distributed to them, in order to minimize the possibility of misuse. Participants will be instructed to keep the study drug away from children and pets.

Participants will be instructed to report any side effects to study staff, who will communicate these reports to the medical staff. The most appropriate course of action will be determined, which may include options for termination of exposure to the study drug. Participants will, however, be reminded that they have the option to withdraw from the study at any time. Participants will also be given a 24-hour emergency contact number in the event that side effects or adverse events occur between sessions.

7.5.1 Blood Pressure Monitoring

Cigarette smoking affects blood pressure in many ways, including stimulation of the sympathetic nervous system, but also through acute inflammation, impairment of endothelial function, and increased arterial stiffness.[26] In 2017, the American College of Cardiology set forth stricter recommendations for treatment of elevated blood pressure, with the goal of commencing treatment (lifestyle changes and/or medication) starting at 130/80, vice 140/90.[27] The definition of systemic arterial hypertension (commonly known as hypertension) did not change with these new recommendations from the American College of Cardiology. Hypertension is characterized by persistently high blood pressure in the systemic arteries, with an "Office BP" of $\geq$ 140 mmHg systolic and $\geq$ 90 mmHg diastolic.[28]

This study will use a blood pressure of 150/95 as a cutoff for eligibility, recognizing that most participants have recently smoked just prior to arriving for the screening process, and that many of them will have additional sympathetic activation through the ingestion of caffeinated beverages.

Any participant who presents with blood pressure > 140 mmHg systolic and/or > 90 mmHg diastolic will be counselled, with recommendations to monitor blood pressure at home and follow up with their primary care provider. Participants who enroll in the study will have blood pressure checks at every office visit.

8 Quality Control and Quality Assurance

8.1 Monitoring Activities

An independent Monitor will be contracted by RRC and will be responsible for the monitoring activities. Monitoring will be performed as per the agreed monitoring plan. A minimum of the following types of monitoring visits will occur for this study.

8.1.1 Site Initiation Visit (SIV)

A Site Initiation Visit will be conducted by the Monitor prior to site activation to confirm preparedness for protocol execution, satisfactory site facilities, clarify the applicable regulations and requirements of the protocol, carefully review the process of implementing the protocol at the site and conduct any necessary training prior to activating the site for enrollment.

8.1.2 Interim Monitoring Visits (IMVs)

Interim Monitoring Visits will be conducted to confirm participants' rights are being protected; the study is being conducted according to the protocol and applicable regulations; and to confirm accurate reporting of participant safety data and study endpoints.

8.1.3 Close-Out Visit (COV)

A Close-Out Visit will be conducted to ensure that all study data and other study documentation is complete and accurate and that all study records have been reconciled.

8.2 Training of Staff

The Investigator or designee will ensure that appropriate training relevant to the study is provided to all staff involved in the study, and that any new information relevant to the performance of this study is forwarded in a timely manner to the staff.

8.3 Audits and Inspections

Good Clinical Practice regulations require independent inspections of clinical program activities. Such inspections may be performed at any time before, during, and after the study.

Authorized representatives of the Sponsor, regulatory agencies and/or an IRB may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed and accurately reported, according to the protocol, ICH/GCP guidelines and any applicable regulatory requirements. The Investigator or designee will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative, and other regulatory agencies.

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical trial participant 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.

Any increase in the severity and/or the frequency of a concomitant disease is considered an AE.

9.1.2 Serious Adverse Event (SAE)

A Serious Adverse Event is any adverse event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

9.1.3 Nonserious Adverse Event

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

9.1.4 Immediately Reportable Event (IRE)

The following events will be reported immediately to the Sponsor.

- Any SAE.
- Any AE of special interest (AESI).
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity.
- Confirmed pregnancy.

9.1.5 Psychiatric Adverse Events

The investigator (or designee) will review participant responses to the C-SSRS. The C-SSRS will be used to screen for suicidal ideation within the last 12 months and suicidal behavior within the last 24 months from screening. Potential participants who score >0 on the screening C-SSRS for suicidal ideations (answer “Yes” to questions 1-5 in the *SUICIDAL IDEATION* section) or a score >0 for Suicidal Behavior (answer “Yes” to any questions in the *SUICIDAL BEHAVIOR* section) at screening (Visit 1) or at Baseline (Visit 2) will be excluded from study participation, and, at the discretion of the study physician/physician assistant, referred to appropriate psychiatric treatment. The C-SSRS will be administered by trained clinical research staff at every visit, including the screening visit (V1 through V6). The “Screening” version will be administered at V1, and the “Since Last Visit” version will be administered at V2 through

V6, inclusive. Any changes in the scoring will be evaluated by licensed medical professionals, with recommendations for referral to appropriate medical care provided to the participant when required, at the discretion of the study physician/physician assistant.

9.1.6 Changes in Clinical Laboratory Test Values

It is the investigator's (or designee'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 participant. 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 (participant is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

9.2 Collection of Safety Events from Participants

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

Information recorded when collecting AEs will include: thorough description of the AE, seriousness assessment, start and stop dates (if known), circumstances leading up to the event, clinical elements such as clinical course, specific vital signs and test results that may explain the pathophysiology of the event, as well as alternative explanations to its occurrence, the action taken with the investigation product/procedures due to the AE, the participant`s disposition in the study after the occurrence of the AE and the final outcome of the AE (if known).

Any exacerbation/worsening or increased frequency of an AE or pre-existing condition shall be evaluated and recorded.

9.2.1 Period of Collection

All existing health conditions identified during the Screening Period will be recorded as concomitant disease and the participant's eligibility will be reviewed. Any AEs which occur during the screening session will be captured by the study site staff and assessed by the Investigator or designee in order to establish relationship or relatedness in respect to study procedures.

Any new, clinically relevant, abnormal finding detected during the study or worsening of a pre-existing condition/concomitant disease will be documented as an AE or an SAE.

All ongoing AEs at the End of Study participation will be followed-up by the Investigator or designee until they have improved, resolved, stabilized (i.e., no worsening of condition), or until an acceptable explanation has been found. The Investigator or designee will refer the participant to their Primary Care Provider for follow up of those AE when appropriate.

9.3 Assessment of Adverse Events

9.3.1 Severity of Adverse Events

For each AE/SAE, the intensity will be graded on a 3-point intensity scale:

- Mild: The AE is easily tolerated and does not interfere with daily activity.
- Moderate: The AE interferes with daily activity, but the participant is still able to function.
- Severe: The AE is incapacitating and requires medical intervention.

9.3.2 IMP Causality

In general, all AEs and SAEs will be assessed by the Investigator or designee as either 'related' or 'not related'.

- Not related: The temporal relationship of the clinical event to study procedures and/or the study medication makes a causal relationship unlikely, or, concomitant medication, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
- Related: The temporal relationship of the clinical event to study procedures and/or the study medication makes a causal relationship possible, and concomitant medication, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

9.4 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.

9.5 Adverse Events of Special Interest

9.6 Abuse Potential Monitoring Plan

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

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

9.7 Potential Serious Hepatotoxicity

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

9.8 Pregnancy after Enrollment

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 30 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 should be followed for a minimum of 6 months from the date of birth, if consent is given to do so.

9.9 Follow-up of Non-serious 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).

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

This trial requires that participants be actively monitored for SAEs and IREs for 7-10 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 participant'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 participant is lost to follow up or has died. Resolution means that the participant has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the participant's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the participant is lost to follow-up, or has died.

9.11 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, stabilized, or the participant is lost to follow-up or has died.

10 Data Management

10.1 Data Collection Procedures

The results from the clinical assessments will be recorded in the source data file by the Investigator or their authorized designee and then captured in the case report forms (CRFs), unless otherwise specified in the final protocol. Trained study personnel will be responsible for capturing the data from the observations, tests, and assessments specified in the protocol and in the source documents. Study personnel will transfer the data to the CRFs.

The Investigator has ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. Any corrections made to source documents must be clearly recorded, without obscuring the original values and be accompanied by the date of change, reason for change, and identification of the person making the change. CRF data will be verified against the source documents at the study site by appropriate staff. Instances of missing or unclear data will be discussed with the Investigator for resolution.

10.2 Protocol Deviations / Noncompliance

Protocol deviations are defined as deviations from the study procedures as defined in this document, whether intentional or unintentional. Protocol deviations that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the data must be reported to the IRB within 10 business days of becoming aware of the deviation.

Noncompliance is defined as any action or activity involving human subjects that fails to comply with applicable regulations. Noncompliance that meets this definition must be reported to the IRB within 10 business days of becoming aware of the noncompliance.

10.3 Data Capture

All data are collected from participants using paper documents or an electronic data capture system. All applicable data, as specified in the protocol, will be transferred to the database or applicable Case Report Forms.

10.3.1 Pre-screening Data

Data will be collected for recruitment and screening purposes as stated within an Advarra IRB generic recruitment protocol. Unrelated to that recruitment protocol, pre-screening questionnaires will be attached to potential participant's records on whether they qualify or are disqualified for this study. Pre-Screening questionnaires utilized for this study will be permanently attached to that potential volunteer's record unless that information is requested to be removed by the participant.

10.3.2 At-home Data Collection

Electronic messaging will be utilized for the delivery of a link to a mobile device to collect study data. This data will be collected utilizing an electronic survey. The platform utilized for these messages will be eResearch, an IRB approved proprietary mobile research tool. Participants will be required to consent to use eResearch for daily at-home collection and be permitted to access the Survey functions for this protocol. The only other additional features available will be the standard publicly available ability to update and maintain their volunteer profile.

10.3.3 Electronic Data Capture System

All smoking behavioral and self-report measures will be captured using Medrio. All information collected within Medrio is compliant with 21 CFR 11 requirements.

10.4 Missing Data

Missing data will remain as missing, i.e., no attempt will be made to impute missing values.

10.5 Data Handling

Data of all participants enrolled including screening failures and AE/SAEs during the study (from the time of informed consent to the end of the study of the participant) will be captured in the source documents. For screening failures, only consent date and reason for screen failure will be added to the CRFs.

10.6 Data Validation

Data of all participants enrolled including screening failures and AE/SAEs during the study (from the time of informed consent to the end of the study of the participant) will be captured in the source documents.

10.7 Database Lock

Upon completion of the trial, after data entry is complete, the data has been cleaned, and the principal investigator has reviewed and provided approval, the database will be locked, and final write access will be removed.

11 PLANNED STATISTICAL METHODS

All data measures (e.g., withdrawal symptoms questionnaires, smoking history, self-report daily smoking messages, etc.) are captured initially using paper or an electronic data capture system. Verified data files will be analyzed using SAS (SAS Institute, Cary NC).

11.1 SAMPLE SIZE ESTIMATION

CCI

[redacted]

11.2 STATISTICAL METHODS

The estimation of the four-week continuous smoking abstinence rate at 6 weeks post target quit date is around 50% and 30% of treated individuals experiencing nausea from varenicline treatment based on the historical studies.[2] The smoking abstinence rate during weeks 4-7 will be calculated with 90% binomial confidence intervals, and the incidence rate of nausea will be tabulated, which will be compared with the thresholds established for efficacy and tolerability.

11.3 OUTCOMES

In general, descriptive statistics will be provided for all efficacy and safety outcomes when applicable. Details will be provided in statistical analysis plan (SAP).

11.3.1 Smoking Abstinence

Complete abstinence from combustible cigarette use at each time point will be defined by a self-report of no cigarette smoking (not even a puff) since the prior session, confirmed by an expired air CO reading of less than 5 ppm. The primary outcome will be four-week continuous smoking abstinence during weeks 4-7. An intent-to-treat approach will be taken in which any participants lost to follow-up after receiving the investigational product, or who have smoked during weeks 4-7 will be counted as non-abstinent.

11.3.2 Incidence of Nausea

A secondary outcome measure will be the incidence of nausea at any timepoint after drug administration begins.

12 ETHICS AND REGULATIONS

12.1 IRB APPROVAL

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF], questionnaires, subject recruitment materials [e.g., advertisements, phone screening script], written information to be provided to the subjects, Investigators' Brochure, the Investigator's and designee's curriculum vitae and/or other evidence of qualifications and any other documents requested by an Institutional Review Board [IRB], will be submitted for review and approval.

Any change to the protocol must be submitted to the IRB for review and approval before implementation. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately provided the reviewing IRB are notified within 10 working days.

12.2 INVESTIGATIONAL NEW DRUG APPLICATION

An Investigational New Drug (IND) application has been submitted to the FDA (IND 155242) for the use of centanafadine.

12.3 GCP AND REGULATORY REQUIREMENTS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study must be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and 56, applicable laws and the IRB requirements.

12.4 PARTICIPANT INFORMATION AND CONSENT

It is the responsibility of the investigator to provide each participant with full and adequate verbal and written information using the IRB-approved informed consent form (ICF), including the objective and procedures of the study and the possible risks involved before inclusion in the study. Informed consent must be obtained prior to performing any study-related procedures.

The signed and personally dated original and completed ICF(s) must be kept by the Investigator and filed in the Investigator study file at the site or with the participant's files and a copy must be given to the participant. The participant will be informed that if they discontinue from the study, the data collected until the point of discontinuation will be maintained as part of the study data and the samples collected prior to discontinuation will be analyzed, unless they refuse in writing.

12.5 AMENDMENT TO INFORMED CONSENT FORM

If a protocol amendment is required, an amendment may be required to the ICF. If revision of the ICF is necessary, the Investigator or designee will ensure that the documents have been reviewed and approved by the IRB before participants are informed and sign the amended ICF (including date and time).

13 ADMINISTRATIVE CONSIDERATIONS

13.1 PARTICIPANT CONFIDENTIALITY

All information obtained during the conduct of the study with respect to the participants' state of health will be regarded as confidential. A statement to this effect will be written in the information provided to the participant. An agreement to disclose any such information will be obtained from the participant in writing and signed by the participant, in compliance with all local and national data protection and privacy legislation.

Study records that identify participants will be kept confidential as required by law. Except when required by law, participants will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Rose Research Center. For records disclosed outside of Rose Research Center, participants will be assigned a unique code number. The key to the code will be kept separate from the locked file where the study records are stored.

13.2 RECORDS RETENTION

13.2.1 File Management at the Trial Site

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

13.2.2 Records Retention at the Trial Site

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

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

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

13.3 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:

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

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

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

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Appendix 1 - Columbia-Suicide Severity Rating Scale (C-SSRS), "Screening" and "Since Last Visit"

Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

PPD

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS-Screening - United States/English - Mapi.
ID040351 / C-SSRS-Screening_AU5.1_eng-USort.doc

Screening

 C-SSRS—Screening (Version 1/14/09) Page 1 of 2

Screening

Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

PPD

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C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AUS.1_eng-USori.doc

Since Last Visit

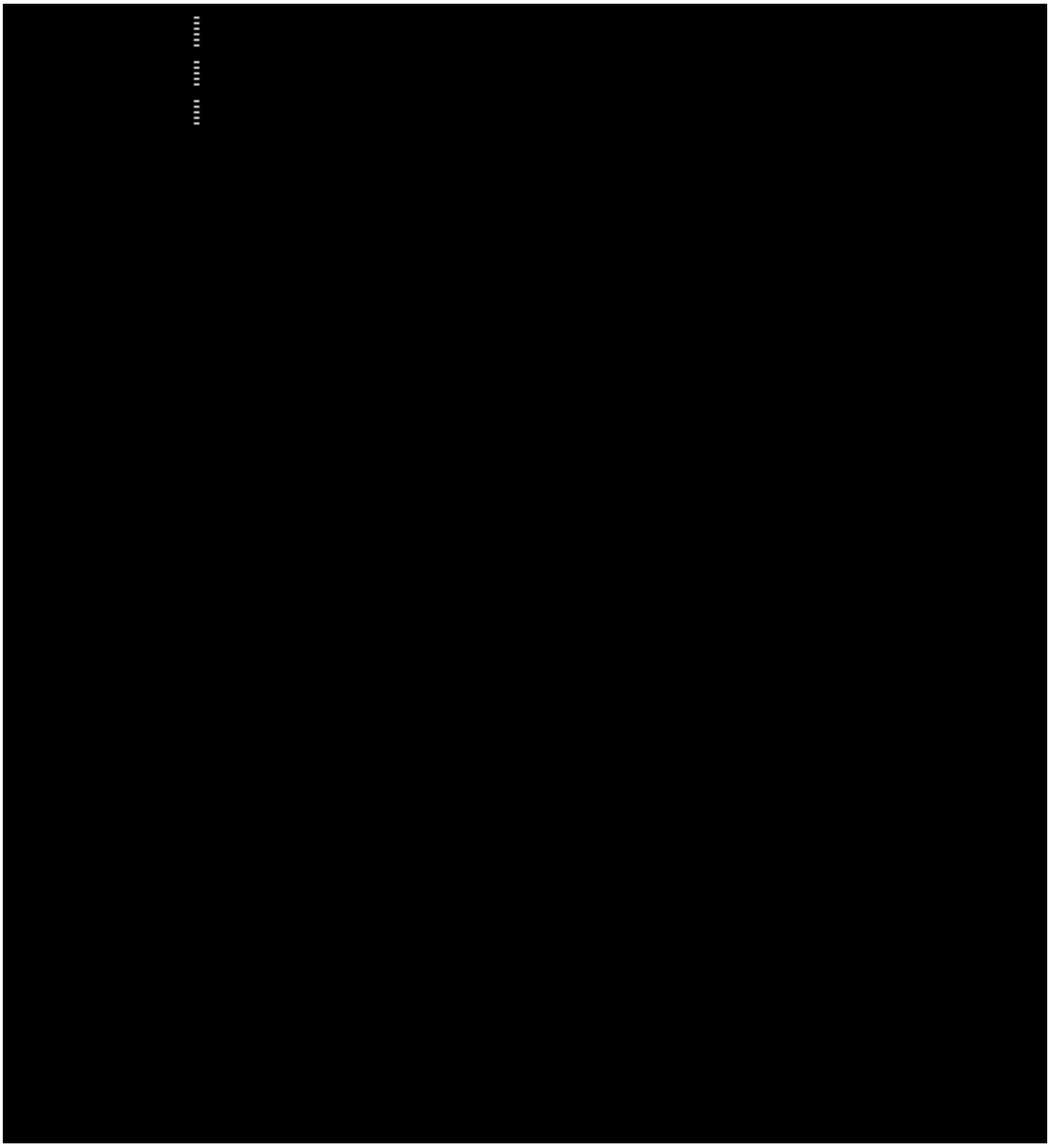
 C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

Since Last Visit

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

Appendix 2 – Fagerström Test for Nicotine Dependence (FTND)

Appendix 3 – Smoking History



Appendix 4 – Other Nicotine Use Questionnaire

Appendix 5 – Modified Cigarette Evaluation Questionnaire – Extended (mCEQE)

Appendix 6 – Reasons to Smoke

Appendix 7 – Shiffman Jarvik Withdrawal Scale

Appendix 8 – Minnesota Nicotine Withdrawal Scale

Rose Research Center, LLC Version 3.0 / 16 Aug 2021

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

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

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and 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.

PPD	PPD	PPD
Principal Investigator Print Name	Signature	Date
_____	_____	_____
Sponsor Representative Print Name	Signature	Date

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

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Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
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