Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Centanafadine (EB-1020)

REVISED CLINICAL PROTOCOL

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy, Safety, and Tolerability of Centanafadine Sustained-release Tablets After Oral Administration in Adult Subjects with Binge Eating Disorder

A Trial of Centanafadine Efficacy, Safety, and Tolerability in Adult Subjects with Binge Eating Disorder

Protocol No. 405-201-00056
IND No. 155,243

CONFIDENTIAL — PROPRIETARY INFORMATION

Drug Development Phase:	2
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	Global Pharmacovigilance Fax: +1 301-212-8626 Email: global_intake@otsuka-us.com
Amendment 2 Approval:	24 Jan 2022
Amendment 1 Approval:	28 Oct 2021
Approval:	07 Jul 2021

Protocol 405-201-00056

Table of Contents

Protocol 405-201-00056

Protocol 405-201-00056

Protocol 405-201-00056

Protocol 405-201-00056

List of In-text Tables

Protocol 405-201-00056

List of In-text Figures

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	Twice daily (or 2 times a day)
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CBP	Childbearing potential
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eICF	Electronic informed consent form
EDE	Eating Disorder Examination
EDE-Q	Eating Disorder Examination Questionnaire
EDE-Q7	Eating Disorder Examination Questionnaire - 7-Item Version
ESAM	Events subject to additional monitoring
ET	Early termination
CCI	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HAM-A	Hamilton Anxiety Rating Scale
HbA1c	Glycosylated hemoglobin
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRE	Immediately reportable event

Protocol 405-201-00056

Abbreviation	Definition
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
LDH	Lactic dehydrogenase
LOE	Lack of efficacy
MADRS	Montgomery-Asberg Depression Rating Scale
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCS	Mental Component Summary score
MedDRA	Medical Dictionary for Regulatory Activities
MHI	Medication handling irregularity
MMRM	Mixed-effect model repeated measures
MNAR	Missing not at random
OC	Observed cases
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc
PCS	Physical Component Summary score
PK	Pharmacokinetic
PQC	Product quality complaint
PT	Prothrombin time
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell count
RDW	Red cell distribution width
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SCID-5-CT	Structured Clinical Interview for DSM-5 Disorders, Clinical Trials Version
SF-36v2	36-item Short-Form Health Survey Version 2
SMWQ	Study Medication Withdrawal Questionnaire
T_4	Thyroxine
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell count

Protocol 405-201-00056

1 Protocol Summary

1.1 Synopsis

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

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

Protocol No.: 405-201-00056

IND No.: 155,243

Protocol Title: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy, Safety, and Tolerability of Centanafadine Sustained-release Tablets After Oral Administration in Adult Subjects with Binge Eating Disorder

Protocol Lay Person Short Title: A Trial of Centanafadine Efficacy, Safety, and Tolerability in Adult Subjects with Binge Eating Disorder

Clinical Phase: 2

Treatment/Indication: Binge eating disorder (BED)

Objectives and Endpoints:

Objectives	Endpoints
Primary: To assess the efficacy of 2 doses of centanafadine SR (200 and 400 mg TDD) compared with placebo in adults with moderate to severe BED.	Primary Efficacy: Change from baseline in binge eating days per week at Weeks 7-8, having binge eating day defined as a day with at least one binge eating episode Key Secondary Efficacy: • Change from baseline in CGI-S score at Week 8 Other Efficacy: • Change from baseline in CGI-S score at Weeks 1, 2, 3, 4, and 6 • CGI-C score • Change from baseline in Y-BOCS-BE score • Proportion of subjects with four-week cessation from binging at Week 8/ET • Change from baseline in number of binge episodes per week • Change from baseline in PGI-S score • PGI-C score • Change from baseline in SF-36v2 PCS and MCS scores • Change from baseline in EDE-Q7 total score

Protocol 405-201-00056

Objectives	Endpoints
Secondary: • To assess the safety and tolerability of centanafadine SR tablets administered daily (200 and 400 mg TDD) in the treatment of subjects with BED.	Safety: AEs (including AESIs [rash], abuse-related AEs, and AEs involving MHIs), clinical laboratory tests (hematology, serum chemistry [including change from baseline in total cholesterol and triglycerides], and urinalysis), vital sign measurements (including change from baseline in body weight and percent change from baseline in body weight), 12-lead ECGs, SMWQ, HAM-A, MADRS, and C-SSRS

AE = adverse event; AESI = adverse event of special interest; CGI-C = Clinical Global Impression - Change; CGI-S = Clinical Global Impression - Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDE-Q7 = Eating Disorder Examination Questionnaire - 7-Item Version; ET = early termination; HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MCS = Mental Component Summary score; MHI = medication handling irregularity; PCS = Physical Component Summary score; PGI-C = Patient Global Impression - Change; PGI-S = Patient Global Impression - Severity; SF-36v2 = 36-item Short-Form Health Survey Version 2; SMWQ = Study Medication Withdrawal Questionnaire; TDD = total daily dose; Y-BOCS-BE = Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating.

Trial Design: This will be a phase 2, multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy, safety, and tolerability of centanafadine SR tablets for the treatment of adult subjects with BED. The trial will consist of a 28-day screening period that includes completion of a binge eating diary for at least 14 days, a baseline visit, an 8-week (56-day) double-blind treatment period, and a 7-day safety follow-up period. All baseline assessments will be conducted prior to first dose of IMP.

Trial Population: Approximately 228 adult subjects with BED are anticipated to be screened with the expectation that approximately 126 subjects will be randomized (42 subjects per treatment arm).

Key Inclusion/Exclusion Criteria: Subjects will be 18 to 65 years of age (inclusive), with a primary diagnosis of BED of at least moderate severity, with a history of at least 2 binge eating days per week for 6 months prior to screening and at least 3 binge eating days in each week during the previous 14 days of a subject's screening period as reviewed at baseline (minimum screening period is 2 weeks), a rating of 4 or higher on the Clinical Global Impression - Severity (CGI-S) at screening and baseline, and a BMI of 18 to 45 kg/m^2, inclusive. Subjects with a lifetime history or current diagnosis of bulimia nervosa or anorexia nervosa will be excluded.

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

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration: IMP consisting of high dose centanafadine (400 mg total daily dose [TDD]), low dose centanafadine (200 mg TDD), or placebo will

be administered orally as 100 mg sustained-release (SR) tablets or matching placebo taken twice daily, approximately 4 to 6 hours apart.

Trial Assessments:

Assessments for Efficacy: Binge eating diary, CGI-S, Clinical Global Impression - Change (CGI-C), Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating (Y-BOCS-BE), Eating Disorder Examination Questionnaire (EDE-Q), Eating Disorder Examination Questionnaire - 7-Item Version (EDE-Q7), Patient Global Impression - Severity (PGI-S), Patient Global Impression - Change (PGI-C), 36-item Short-Form Health Survey Version 2 (SF-36v2)

Assessments for Pharmacokinetics and CCI [redacted] CCI [redacted]

Assessments for Safety: AEs (including AESI evaluations [rash], abuse-related AEs, and AEs involving medication handling irregularities [MHIs]), clinical laboratory tests (hematology, serum chemistry [including total cholesterol and triglycerides], and urinalysis), physical examinations, vital sign measurements (including body weight), electrocardiograms (ECGs), and assessments of suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]), withdrawal (Study Medication Withdrawal Questionnaire [SMWQ]), anxiety (Hamilton Anxiety Rating Scale [HAM-A]), and depression (Montgomery-Asberg Depression Rating Scale [MADRS]).

Screening/Other: pregnancy test, urine drug screen/alcohol testing via breathalyzer, blood, or urine, and psychiatric evaluation

Data Monitoring Committee: No

Statistical Methods: Assuming a treatment difference of 1.1 points with a standard deviation of 1.7 in the mean change from baseline in binge eating days per week at Weeks 7-8 in either centanafadine dose group (high dose centanafadine or low dose centanafadine) compared to the placebo group (effect size = 0.65), a sample size of 114 evaluable subjects (38 in each treatment arm) will yield at least 80% power to detect the treatment effects at a 2-tailed significance level of 0.05. Approximately 126 subjects will be randomized (42 in each treatment arm) to ensure 114 evaluable subjects in the study. The primary efficacy analysis will be performed by fitting a mixed-effect model repeated measures (MMRM) analysis with an unstructured variance covariance structure, in which change from baseline in binge eating days per week at the scheduled visits will be the dependent variable based on the observed cases (OC) data set. The model will

include fixed effect terms for treatment, trial center, visit week, and an interaction term of treatment by visit week. The model will also include the interaction term of baseline values of binge eating days per week by visit week as covariates. The primary comparison between centanafadine groups and the placebo group at Weeks 7-8 will be estimated as the difference between Least Squares means utilizing the computing software SAS procedure PROC MIXED. If there is a convergence problem with the unstructured variance covariance matrix of the MMRM model, the following structures other than unstructured will be used in order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry and the first (co)variance structure converging to the best fit will be used as the primary analysis. If a structured covariance has to be used, the "sandwich" estimator of the standard error of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix.

Trial Duration:

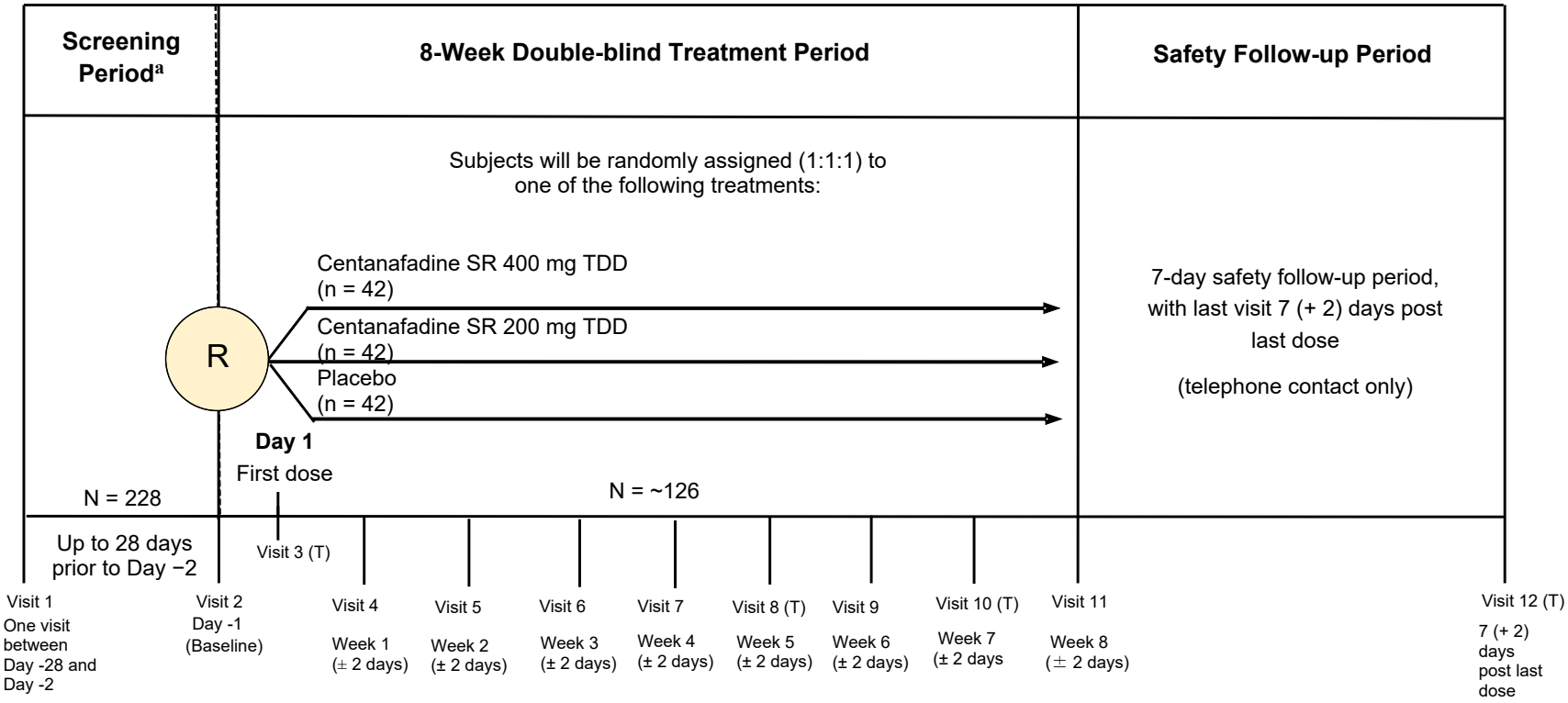
The anticipated duration for each participant to complete the trial is up to 13 weeks, which will include the following periods:

- Screening period: up to 4 weeks (28 days)
- Double-blind treatment period: 8 weeks
- Follow-up period: 7 (+ 2) days

Overall, the trial duration from signing of the first informed consent form to the final subject assessment is expected to be approximately 10 months.

Protocol 405-201-00056

1.2 Schema



N = number of subjects; R = randomization; T = telephone visit.
[a]Extension of screening may be requested and discussed with the medical monitor prior to the expiration of the screening period.

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

	Screening[a]	Baseline	Double-Blind Treatment Period									Safety Follow-up	
	Days −28 to −2	Day −1	First Dose Day 1	WK 1 (± 2 days)	WK 2 (± 2 days)	WK 3 (± 2 days)	WK 4 (± 2 days)	WK 5 (± 2 days)	WK 6 (± 2 days)	WK 7 (± 2 days)	WK 8/ET (± 2 days)	7 (+ 2) days post last dose	Notes:
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Type	**O**	**O**	**T**	**O**	**O**	**O**	**O**	**T**	**O**	**T**	**O**	**T**	
ENTRANCE CRITERIA													
Informed consent	X												Section 10.1.2
Inclusion/exclusion criteria	X	X											Section 5.2
Demographics	X												Section 5.1
Concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Medical history	X												Section 5.1
SCID-5-CT	X												Section 8.10.2
Urine pregnancy test	X	X					X				X		Section 10.3
UDS/alcohol testing[b]	X	X											Section 5.3.2 and Section 10.2
EFFICACY[c]													
Binge Eating Diary	<---------- daily completion by subject ----------> (severity criteria must be confirmed at baseline on previous 14 days of binge eating diary data)												Section 8.1.1
CGI-S	X	X		X	X	X	X		X		X		Section 8.1.2
CGI-C				X	X	X	X		X		X		Section 8.1.2.2
Y-BOCS-BE	X	X		X	X	X	X		X		X		Section 8.1.2.3
EDE-Q (full scale)	X												Section 8.1.1.2
EDE-Q7		X									X		Section 8.1.1.2
PGI-S	X	X		X	X	X	X		X		X		Section 8.1.1.3

Table 1.3-1 Schedule of Assessments

	Screening[a]	Baseline	Double-Blind Treatment Period									Safety Follow-up	
	Days −28 to −2	Day −1	First Dose Day 1	WK 1 (± 2 days)	WK 2 (± 2 days)	WK 3 (± 2 days)	WK 4 (± 2 days)	WK 5 (± 2 days)	WK 6 (± 2 days)	WK 7 (± 2 days)	WK 8/ET (± 2 days)	7 (+ 2) days post last dose	Notes:
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Type	**O**	**O**	**T**	**O**	**O**	**O**	**O**	**T**	**O**	**T**	**O**	**T**	
PGI-C				X	X	X	X		X		X		Section 8.1.1.4
SF-36v2		X					X				X		Section 8.1.1.5
SAFETY[c]													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.8
Clinical laboratory assessments[d,e]	X												Section 8.7.1
Clinical laboratory assessments, fasting[d]		X					X				X		Section 8.7.1
Urinalysis[d]	X	X					X				X		Section 8.7.1
Physical examination	X												Section 8.7.2
Height (screening only) and weight	X	X		X	X	X	X		X		X		Section 8.7.2
Vital signs[c]	X	X		X	X	X	X		X		X		Section 8.7.3
12-lead ECG[c,d]	X	X					X				X		Section 8.7.4
C-SSRS	X	X		X	X	X	X		X		X		Section 8.7.5
SMWQ											X	X	Section 8.7.6.1
HAM-A		X									X		Section 8.7.6.2
MADRS		X[f]									X		Section 8.7.6.3
PHARMACOKINETIC [redacted] CCI													
PK blood draws							X				X		Section 8.2.1
CCI [redacted]													

Table 1.3-1 Schedule of Assessments

	Screening[a]	Baseline	Double-Blind Treatment Period									Safety Follow-up	
	Days −28 to −2	Day −1	First Dose Day 1	WK 1 (± 2 days)	WK 2 (± 2 days)	WK 3 (± 2 days)	WK 4 (± 2 days)	WK 5 (± 2 days)	WK 6 (± 2 days)	WK 7 (± 2 days)	WK 8/ET (± 2 days)	7 (+ 2) days post last dose	Notes:
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Type	**O**	**O**	**T**	**O**	**O**	**O**	**O**	**T**	**O**	**T**	**O**	**T**	
CCI													
OTHER													
IMP dispensing		X		X	X	X	X		X				Section 6.2.3
IMP administration			X	X	X	X	X	X	X	X	X		Section 6.1
IMP return and accountability				X	X	X	X		X		X		Section 6.2.3 and Section 6.2.4

ET = early termination; O = office; SCID-5-CT = Structured Clinical Interview for DSM-5 Disorders, Clinical Trials Version; T = telephone; UDS = urine drug screen; WK = week.

[a]Extension of screening may be requested and discussed with the medical monitor prior to the expiration of the screening period.

[b]UDS is to be done on-site initially, with a confirmatory urine sample collected if needed for processing through the central lab. Alcohol test is to be conducted initially via breathalyzer, with confirmation via blood or urine sample through central lab processing. Additional UDS/alcohol testing can be performed during the double-blind treatment period at the investigator's discretion.

[c]Efficacy assessments should be completed prior to safety assessments and PK CCI blood draws. Vital signs and ECGs should be completed prior to any blood draws.

[d]Only if results are exclusionary at screening will a repeat test be performed prior to the baseline visit. Results must be available and inclusionary prior to randomization.

[e]Subjects are not required to be fasting for screening laboratory assessments.

[f]To be completed at the beginning of the baseline visit for confirmation of eligibility criteria.

Protocol 405-201-00056

2 Introduction

Centanafadine (EB-1020) is a triple monoamine reuptake inhibitor being developed for attention-deficit/hyperactivity disorder (ADHD). The current trial is designed to assess its efficacy as treatment of binge eating disorder (BED) in adults. This trial is intended to evaluate the efficacy and safety of centanafadine sustained release (SR) tablets compared to placebo for the treatment of BED in adult subjects who have a clinical diagnosis of moderate to severe BED based on the DSM-5 diagnosis criteria and confirmed by the Structured Clinical Interview for DSM-5 Disorders, Clinical Trials Version (SCID-5-CT).

2.1 Trial Rationale

Centanafadine is a new molecular entity with inhibitory activity at the norepinepherine (NE), dopamine (DA), and serotonin (5-HT)-reuptake transporters and has demonstrated safety and efficacy as a treatment of ADHD in adults. As positive results from phase 3 trials support the notion that DA and NE transmission plays in the etiology of both ADHD and BED, centanafadine is being evaluated for the treatment of BED (see Section 4.2). This Phase 2 proof-of-concept trial is designed to assess initial efficacy in reducing symptoms of BED in adults.

2.2 Background

Binge eating disorder is defined by the Diagnostic and Statistical Manual of Mental Disorders - 5th Edition (DSM-5) as a condition marked by recurrent episodes of eating large quantities of food that is accompanied by a sense of loss of control and followed by guilt, shame, or distress; and without common use of compensatory measures such as purging, restricting, or excessive exercising to counter binge episodes. According to the National Comorbidity Survey, the lifetime prevalence of BED is up to 3.5% in women and 2.0% in men in the United States, making it more common than anorexia and bulimia combined. Onset begins in late adolescence and occurs more frequently in women than in men.[1] A recent report suggests BED and other specified feeding or eating disorders are unrepresented in global estimates of disease burden.[2] Various behavioral therapies are utilized and off-label use of antidepressants or anticonvulsants are sometimes utilized.[3] Currently, only Vyvanse® (lisdexamfetamine) is approved for the treatment of BED.[4] Less than half of individuals with BED receive treatment specifically for this condition.[1] There are likely various reasons for this, including under-reporting of symptoms by patients who may feel shame, under-diagnosis of the condition which was only recently

identified as a distinct condition in the DSM-5, and evidence-based treatment options being limited to specialized psychotherapy and only a single approved medication.

The correlation between impulsivity in ADHD and BED has long been hypothesized and is supported by findings of numerous studies[5] including those showing shared neural circuitry.[6] The efficacy of lisdexamfetamine for both ADHD and BED further suggests treatments effective for one indication could provide efficacy for the other.

This trial is intended to evaluate the efficacy and safety of 2 oral doses of centanafadine SR tablets compared to placebo for the treatment of BED in adult subjects who have a clinical diagnosis of moderate to severe BED.

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

2.3 Known and Potential Risks and Benefits

The anticipated risks of centanafadine are described in detail in the currently approved version of the Investigator's Brochure. There are no unique risks anticipated in the BED population.

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

3 Objectives, Endpoints, and Estimands

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: To assess the efficacy of 2 doses of centanafadine SR (200 and 400 mg TDD) compared with placebo in adults with moderate to severe BED.	Primary Efficacy: Change from baseline in binge eating days per week at Weeks 7-8, having binge eating day defined as a day with at least one binge eating episode Key Secondary Efficacy: • Change from baseline in CGI-S score at Week 8 Other Efficacy: • Change from baseline in CGI-S score at Weeks 1, 2, 3, 4, and 6 • CGI-C score • Change from baseline in Y-BOCS-BE score • Proportion of subjects with four-week cessation from binging at Week 8/ET

Protocol 405-201-00056

Table 3-1 Trial Objectives and Endpoints	
Objectives	**Endpoints**
	• Change from baseline in number of binge episodes per week • Change from baseline in PGI-S score • PGI-C score • Change from baseline in SF-36v2 PCS and MCS scores • Change from baseline in EDE-Q7 total score
Secondary: • To assess the safety and tolerability of centanafadine SR tablets administered daily (200 and 400 mg TDD) in the treatment of subjects with BED.	Safety: AEs (including AESIs [rash], abuse-related AEs, and AEs involving MHIs), clinical laboratory tests (hematology, serum chemistry [including change from baseline in total cholesterol and triglycerides], and urinalysis), vital sign measurements (including change from baseline in body weight and percent change from baseline in body weight), 12-lead ECGs, SMWQ, HAM-A, MADRS, and C-SSRS

AE = adverse event; AESI = adverse event of special interest; CGI-C = Clinical Global Impression - Change; CGI-S = Clinical Global Impression - Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDE-Q7 = Eating Disorder Examination Questionnaire - 7-Item Version; HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MCS = Mental Component Summary score; MHI = medication handling irregularity; PCS = Physical Component Summary score; PGI-C = Patient Global Impression - Change; PGI-S = Patient Global Impression - Severity; SF-36v2 = 36-item Short-Form Health Survey Version 2; SMWQ = Study Medication Withdrawal Questionnaire; TDD = total daily dose; Y-BOCS-BE = Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating.

Section 9.4 describes the statistical analysis of the endpoints.

Primary Estimand

The primary clinical question of interest is: what is the treatment difference in binge eating days per week after 8 weeks of centanafadine treatment compared to placebo treatment in adult subjects with moderate to severe BED, where no subject would discontinue treatment due to any reason?

The primary estimand has the following attributes:

- Population: adult subjects with moderate to severe BED who meet the inclusion/exclusion criteria. Details are specified in Section 5.
- Endpoint: change from baseline in binge eating days per week at Weeks 7-8.
- Intercurrent events: premature treatment discontinuation.

Protocol 405-201-00056

- Treatment condition: one of the randomized treatment groups of the following per protocol: high dose centanafadine 400 mg TDD, low dose centanafadine 200 mg TDD, or placebo. Details can be found in Section 6.
- Population-level summary: difference in mean of endpoint between treatment conditions.
- Rationale for estimand: the hypothetical estimand is to evaluate the pharmacological effect if no withdrawals had occurred. It is justifiable since the focus is on the pharmacological effect of the drug additional to non-specific effects. Subjects who withdraw from a symptomatic IMP treatment either could have lost the treatment effect if the subjects had not taken any other symptomatic medication after withdrawal or could have the treatment effect masked if the subjects had taken other symptomatic medication after withdrawal. In those cases, any observations taken after subjects stop IMP will most likely not contribute to relevant information about the pharmacological effect of the drug. Therefore, the last collected efficacy assessment after premature trial discontinuation will be performed only once at the ET Visit.

Secondary and Other Estimands

The clinical question of interest for the key secondary estimand is: what is the treatment difference in CGI-S Score after 8 weeks of centanafadine treatment compared to placebo treatment in adult subjects with moderate to severe BED, where no subject would discontinue treatment due to any reason?

The key secondary estimand has similar attibutes to the primary estimand except that key secondary endpoint is change from baseline in CGI-S score at Week 8. Other estimands have similar attributes to the primary and key secondary estimands.

4 Trial Design

4.1 Type/Design of Trial

This will be a phase 2, multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy, safety, and tolerability of centanafadine SR tablets for the treatment of adult subjects with BED. Subjects with a primary clinical diagnosis of moderate to severe BED based on the DSM-5[7] diagnosis criteria and confirmed by the SCID-5-CT will be eligible for enrollment. The trial will consist of a screening period of up to 28 days that includes completion of a binge eating diary for at least 14 days (that shows at least 3 binge eating days in each week during the previous 14 days of a subject's screening period as reviewed at baseline [minimum screening period is 2 weeks]), a baseline visit, an 8-week (56-day) double-blind treatment period, and a 7-day safety follow-up period. All baseline assessments will be conducted prior to first dose of IMP.

Protocol 405-201-00056

Eligible subjects will be randomized 1:1:1 at baseline to receive 1 of 2 doses of centanafadine SR or placebo daily for 8 weeks. The doses of centanafadine SR that will be assessed in adult subjects during this trial were selected based on the efficacious and safe doses in the adult ADHD phase 2 and 3 trials.

Sparse pharmacokinetic (PK) blood samples will be taken. CCI [redacted] (Table 1.3-1).

All subjects who terminate early will be required to participate in a 7-day safety follow-up period, which will consist of telephone contact 7 (+ 2) days after the last dose of investigational medicinal product (IMP). For subjects who early terminate, they will be instructed to refrain from using prohibited concomitant medications, including BED treatments, until after the safety follow-up visit.

4.2 Scientific Rationale for Trial Design

Centanafadine, a new molecular entity with inhibitory activity at the NE, DA, and 5-HT-reuptake transporters, is being evaluated for the treatment of BED. In vivo studies have demonstrated that centanafadine is a monoamine reuptake inhibitor that differentially increases NE, DA, and 5-HT extracellular concentrations in the prefrontal cortex and DA in the striatum,[8] areas known to play a role in executive function, and impulsivity and reward in BED, respectively.[9]

Centanafadine has demonstrated efficacy in adult ADHD (Trial 405-201-00013 and Trial 405-201-00014) through increased neurotransmission of DA and NE (Trial 405-201-00022). Non-clinical studies[10,11,12,13,14] and clinical trial data (Trial 405-201-00019) suggests centanafadine may have a lower abuse potential compared to stimulants, which may support less restrictive scheduling, if any. The combined result may mean a safe and tolerable treatment option for this most common of eating disorders.

Lisdexamfetamine and dasotraline are 2 drugs that have positive results from large phase 3 trials in BED, as well as positive results from large phase 3 trials in adult ADHD, which supports the role that DA and NE transmission plays in the etiology of both disorders. Lisdexamfetamine remains the only Food and Drug Administration (FDA) approved drug for the treatment of BED and is limited by its restrictive scheduling and high side effect burden.[4]

Protocol 405-201-00056

Centanafadine sustained-release (SR) tablets administered orally as either 200 or 400 mg total daily doses (TDDs) have demonstrated efficacy in treating impulsive symptoms in adults with ADHD and was also reported to be generally safe and well tolerated as demonstrated by the low rate of reported treatment-emergent adverse events (TEAEs) that were dose-dependent, a low incidence of adverse events (AEs) of special interest (AESIs) (newly acquired, non-traumatic skin eruptions), and a low incidence of abuse potential-related AEs.[15] Its unique pharmacology, high tolerability, and the fact that it does not require titration could offer general psychiatrists or primary care physicians a distinct and potentially preferable alternative treatment option to the only currently approved medication. Having an accessible, approved treatment could go far to fill the unmet need of undertreated individuals struggling with BED. This Phase 2 proof-of-concept trial is designed to assess initial efficacy in reducing symptoms of BED in adults.

4.3 Dosing Rationale

The 2 doses of centanafadine SR that will be evaluated in this trial will be 200 mg and 400 mg TDD, administered as 100 mg BID (4 - 6 hours apart) and 200 mg BID (4 - 6 hours apart), respectively. These doses have demonstrated efficacy in phase 2 as well as in two phase 3 trials in adult ADHD. Dose-dependent increases in side effects were experienced in phase 2 trials at higher doses. While not considered dose-limiting, the efficacy at lower doses in ADHD supports assessing 200 mg and 400 mg before considering whether a higher dose is warranted.

4.4 End of Trial Definition

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

4.5 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumes all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the double-blind treatment period (Week 8) will be defined as trial completers.

5 Trial Population

The trial population will include adult subjects between 18 and 65 years of age, inclusive, at the time of informed consent with a clinical diagnosis of BED according to DSM-5

criteria and confirmed by the SCID-5-CT. Subjects may have a historical diagnosis or may be diagnosed at screening.

Approximately 228 subjects are anticipated to be screened with the expectation that approximately 126 subjects will be randomized (42 subjects per treatment arm).

5.1 Subject Selection and Numbering

All subjects will be given a unique subject identifier (ID; site number [3 digits] + subject number ['S' + 5 digits] upon providing consent). The site number will be designated by the sponsor.

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

Eligible subjects who are enrolled in the trial will be assigned a unique subject randomization number for treatment assignment. Subjects who discontinue from the trial will not be replaced.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the medical monitor.

5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria when assessed:

Table 5.2.1-1 Inclusion Criteria

1.	Adult subjects 18 to 65 years of age (inclusive) at the time of informed consent.
2.	A primary diagnosis of BED, or is diagnosed at screening, according to DSM-5 criteria and confirmed by the SCID-5-CT.
3.	BED with a history of at least 2 binge eating days per week for 6 months prior to screening.
4.	BED of at least moderate severity with at least 3 binge eating days in each week during the previous 14 days of a subject's screening period according to the subject's binge diary as reviewed at baseline (minimum screening period is 2 weeks).
5.	A rating of 4 or higher on the CGI-S at screening and baseline.
6.	BMI of 18 to 45 kg/m^2, inclusive.

BMI = body mass index

5.2.2 Exclusion Criteria

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

Table 5.2.2-1 Exclusion Criteria	
1.	Subjects of CBP who are breast-feeding and/or have a positive pregnancy test result prior to receiving IMP.
2.	Sexually active subjects or subjects of CBP who do not agree to practice 2 different methods of birth control or remain abstinent during the course of the trial and for 30 days after the last dose of IMP for subjects of CBP, and 30 days after the last dose of IMP for subjects and their partners who are subjects of CBP. Unless the subject is sterile (ie, subjects who have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or subjects 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. Subjects who do not agree to refrain from donating sperm from screening through 30 days after the last dose of IMP.
3.	Lifetime history of bulimia nervosa or anorexia nervosa.
4.	Started psychotherapy for BED within 3 months of screening.
5.	Participation in a formal weight loss program within 3 months of screening or planning to start a weight loss program during the trial.
6.	Lifetime history of major bariatric surgery, including gastro-jejunal bypass, roux-en-y gastric bypass, sleeve, and duodenal switch for weight loss at any time.
7.	Minor bariatric surgery, including lap band, in the past 2 years.
8.	Use of psychostimulant or mood stabilizer within 3 months of screening.
9.	Use of any other medications for treatment of BED, other eating disorder, or obesity; anorexics (weight loss supplements), or other weight management medications within the last 3 months, or started or changed dose of any other medication that can result in weight gain or weight loss within 3 months prior to screening.
10.	Lifetime history of psychotic disorder, bipolar disorder, hypomania, dementia, or ADHD according to DSM-5 criteria.
11.	Initiation of treatment for depression within 3 months prior to screening.
12.	MADRS score ≥ 18.
13.	Substance use disorder (as determined by DSM-5 criteria) within 12 months prior to screening.
14.	A positive alcohol test (via breathalyzer, blood, or urine), a positive drug screen for illicit drugs (excluding marijuana) at screening or baseline. NOTE: Subjects who test positive for marijuana at screening may be enrolled if they have no evidence of a substance use disorder, if they agree to refrain from use for the duration of the trial, and if they test negative prior to the baseline visit.
15.	Any of the following: • A significant risk of committing suicide based on history and the investigator's clinical judgment, or routine psychiatric status examination • Current suicidal behavior • Imminent risk of injury to self • Active suicidal ideation as it is evidenced by an answer of "yes" on Questions 4 or 5 (over the last 6 months) on the suicidal ideation section of the Baseline/Screening version of the C-SSRS • Any lifetime history of suicidal behavior detected by the Baseline/Screening version of the C-SSRS.

Protocol 405-201-00056

Table 5.2.2-1 Exclusion Criteria	
16.	Any other medical or physical condition(s) that, in the opinion of the investigator, may prevent the subject from completing the trial or would go against the subject'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.
17.	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, subjects should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which in the investigator's judgment are medically significant and that would impact the safety of the subject or the interpretation of the trial results. Tests with abnormal results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.
18.	A history of dermatologic adverse reactions secondary to any drug exposure or anaphylaxis (or some type of systemic allergic reaction) to any substance.
19.	A history of allergic reaction or a known or suspected sensitivity to any substance that is contained in the IMP formulation.
20.	A history of prior exposure to centanafadine.
21.	Participation in a clinical trial and exposure to interventional trial medication within the last 30 days prior to screening or participation 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.

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

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

5.3 Lifestyle Considerations

Not applicable.

5.3.1 Meals and Dietary Restrictions

Not applicable.

5.3.2 Caffeine, Alcohol, Tobacco, and Other Substances

Investigators should inform subjects that normal consumption of caffeine is permitted.

Instruction will be given to subjects to refrain from drinking alcoholic beverages or using illicit drugs (including marijuana) during participation in the trial.

Should the subject test positive for illicit drugs (including marijuana), the site will provide counseling to the subject on not using illicit drugs. A urine drug screen is required at the times designated in the Schedule of Assessments (Table 1.3-1), but the investigator may request a blood or urine drug screen at any time during the trial if there is a suspicion of illicit drug use in subjects. The UDS is to be done on-site initially, with a confirmatory urine sample collected if needed for processing through the central lab. Alcohol testing will be performed at screening and baseline via urine, blood, or breathalyzer test and is to be conducted initially via breathalyzer, with confirmation via blood or urine sample through central lab processing. Additional alcohol tests may be performed at the discretion of the investigator. Refer to Section 5.4 for additional details regarding positive alcohol or drug test results.

No restrictions for tobacco apply.

5.3.3 Activity

Subjects should not significantly alter their current activity levels or exercise routines. They should be encouraged to maintain their usual levels of physical activity throughout the trial.

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

5.4 Screen Failures

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

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

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

Protocol 405-201-00056

In the event that a subject cannot be randomized prior to the expiration of the 28-day screening period, additional extension of screening may be requested and discussed with the medical monitor. Any extension should be requested prior to the expiration of the screening period, as applicable. If no extension is granted, and the subject meets criteria for rescreening after the screening period has expired, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

In the case that subjects sign a consent form but have not started on treatment, subjects are permitted to be rescreened if exclusion criteria have changed and following consultation with the Medical Monitor. In the event that the subject is rescreened for trial participation, including after the 28-day screening period expires, a new consent form must be signed, a new screening number assigned, and all screening procedures repeated.

Subjects that have a positive alcohol test (via urine, blood, or breathalyzer), or positive drug screen for illicit drugs (excluding marijuana) are not eligible to be retested or rescreened, and will be considered screen failures. Subjects that test positive for marijuana at screening may be permitted to be enrolled if they have no evidence of a substance use disorder, agree to refrain from use for the duration of the trial, and test negative prior to baseline. Subjects that test positive for use of prohibited medications at screening will be required to undergo a washout period (Section 6.5.1). After the allotted washout period, if a subject tests positive for prohibited medications, the subject will be screen failed and not permitted to rescreen. Screen failures previously excluded for a positive urine drug screen due to use of prescription or over-the-counter medications or products not used for the treatment of BED, may be rescreened for participation in the trial only with the explicit consent of the medical monitor. Screen failures excluded for any other reasons may be rescreened at any time if the exclusion characteristic has changed.

6 Trial Treatments

6.1 Trial Treatments Administered

Eligible subjects will be randomized 1:1:1 at baseline to receive 1 of 2 doses of centanafadine SR or placebo daily for 8 weeks:

- High dose centanafadine: 400 mg centanafadine SR oral tablets TDD (2 × 100 mg BID, approximately 4 - 6 hours apart)
- Low dose centanafadine: 200 mg centanafadine SR oral tablets TDD (1 × 100 mg) + 1 placebo oral tablet (BID, approximately 4 - 6 hours apart)
- Placebo: 2 placebo oral tablets (BID, approximately 4 - 6 hours apart)

Neither the investigator nor the subject will be aware of the treatment assignment after randomization. IMP will be dispensed at the baseline visit and the first dose of IMP will be taken on the morning of Day 1, when the subjects will be home. A telephone call will be placed from site to subject to confirm dosing. The date and time of the first dose will be recorded.

All doses of centanafadine SR and matching placebo should be taken orally BID (with up to 240 mL of water). Doses should be taken at approximately the same time each day, with the first dose taken in the morning and the second dose taken 4 to 6 hours after the morning dose is administered. All doses can be administered without regard to meals.

If a subject forgets to take their morning dose at their normal dosing time, the subject should take the dose as soon as they remember that same day. If a subject forgets to take their second dose and 6 hours have elapsed since the time of the morning dose, they should skip the dose and resume dosing the next day. If a subject does not remember to take a missed dose on the same day it is missed, the subject should skip that dose and resume the normal dosing schedule for the following dose. Subjects should not take more than 2 doses in one day.

For information regarding the dose regimen and treatment period(s), including any follow-up period(s) for each treatment group/arm of the trial, see Section 4.1.

6.1.1 Medical Devices

Not applicable.

6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the centanafadine IB.[15]

6.2.1 Packaging and Labeling

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

6.2.2 Storage

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

The IMP will be stored according to the conditions indicated on the IMP label. The trial site staff will maintain a temperature log in the IMP storage area to record the temperature.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational or placebo) received, dispensed, administered, and returned. Neither the investigator nor any designees may provide IMP to any subject not participating in this protocol.

6.2.4 Returns and Destruction

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

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication provided by a healthcare professional, clinical trial subject, 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 (eg, damaged, dirty, crushed, missing product or component, incorrect or missing labeling)
- Product defects (eg, odor, chipped, broken, damaged, crushed, embossing illegible, under-filled bottle, over-filled bottle, empty bottle, no safety seal)
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

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

Protocol 405-201-00056

Send PQC reporting information to the Otsuka Pharmaceutical Development & Commercialization, Inc (OPDC) IMP complaints 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 subject should be reported to the site investigator, who should then follow the reporting mechanism above.

6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, investigator, site, etc.)
- Reporter contact information (eg, 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

6.2.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the sponsor will provide return instructions, when applicable. If complaint sample is available but not at the clinical site, please instruct subject to bring the complaint sample to their next site visit.

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

6.2.5.4 Assessment/Evaluation

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

6.3 Measures to Minimize/Avoid Bias

Treatment will be double-blind. Neither the investigator nor the subject will have knowledge of the treatment assignment.

Treatment assignments will be based on a computer-generated randomization code provided by the OPDC Biostatistics Department. Sponsor personnel, including those

involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. The bioanalytical laboratory will also be sent the randomization code. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging trial medication, and reporting serious adverse events (SAEs) to regulatory agencies. The randomization will be stratified by trial site and designed to allocate subjects in a 1:1:1 ratio to high dose centanafadine, low dose centanafadine, or placebo (see Section 6.1).

Procedures for breaking the blind can be found in Section 8.8.8.

6.4 Subject Compliance

Responsible trial personnel will dispense the IMP according to the visits outlined in the Schedule of Assessments (Table 1.3-1). Subjects must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance), discontinuation of the subject from the trial should be considered.

This trial will utilize IMP adherence monitoring for all subjects in the trial. Additional information is provided in the Operations Manual. Results should be documented in the subject's trial records. This compliance tool will not replace standard methods of IMP compliance (tablet count and reconciliation) utilized by the sites.

6.5 Concomitant Medications or Therapies

The investigator will record all medications (including prescription medications, over-the-counter medications, herbal remedies, etc) and therapies taken by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) in the eCRF. The investigator will also record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the eCRF.

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

6.5.1 Prohibited Medications or Therapies

All subjects must agree to discontinue all prohibited medications during the screening period, in order to meet the protocol-specified washout periods, and during the trial as shown in Table 6.5.1-1

Protocol 405-201-00056

Table 6.5.1-1 List of Medications or Therapies Prohibited/Restricted from the Screening Visit through the end of Safety Follow-Up
Prohibited/Restricted Medication
Antipsychotics (including depot formulations)
Anticonvulsants
Mood stabilizers (ie, lithium)
Benzodiazepines, except for sleep (see Table 6.5.2-1)
Stimulants (lisdexamfetamine, amphetamines, methylphenidates, modafinil, armodafinil)
Non-stimulant treatment for ADHD (atomoxetine, clonidine, guanfacine)
Medications for treatment of BED, other eating disorder, or obesity; anorexics (weight loss supplements), or other weight management medications (and for 3 months prior to screening)
Insulin (and for 3 months prior to screening)
Started or changed the dose of any medication that can result in either weight gain or weight loss (eg, liraglutide, metformin, Ozempic, and Rybelsus) (and for 3 months prior to screening)
Sedating antihistamines (eg, diphenhydramine, hydroxyzine, chlorpheniramine)
Investigational compounds (and for 30 days prior to screening)

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

Subjects should not start a weight loss program during the trial.

6.5.2 Permitted Medications or Therapies

The medications shown in Table 6.5.2-1 are permitted but this is not a comprehensive list.

Table 6.5.2-1 List of Medications Permitted During the Trial	
1.	Non-sedating antihistamine medication
2.	Saline and corticosteroid nasal sprays for the treatment of illness or seasonal allergies
3.	Stable, intermittent use of bronchodilators
4.	Opioids, with approval from the medical monitor for documented and clinically appropriate indications (ie, episodic pain condition, tooth extraction)
5.	Hormonal contraceptives
6.	Topical numbing agents

Protocol 405-201-00056

Table 6.5.2-1 List of Medications Permitted During the Trial	
7.	Sedative hypnotics at doses not greater than those indicated below, once nightly, not in combination: • Lorazepam 2 mg • Temazepam 30 mg • Eszopiclone 3 mg • Zaleplon 20 mg • Zolpidem 10 mg (males), 5 mg (females) • Zolpidem CR 12.5 mg (males), 6.25 mg (females) • Melatonin 5 mg
8.	Antidepressant medication that has been stable for 3 months prior to screening.

Psychotherapy, including cognitive behavioral therapy, is permitted if it has been stable in terms of type, intensity, and frequency for at least 3 months prior to screening and continues without change throughout the trial.

6.5.3 Rescue Medications

Not applicable.

6.6 Intervention After the End of the Trial

Not applicable.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

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

7.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB at the site.

7.3 Individual Subject Discontinuation

7.3.1 Treatment Interruption

All attempts should be made to avoid treatment interruption during the trial. If a subject's IMP treatment must be interrupted for medical or surgical reasons, for example, use of a prohibited concomitant medication or other reasons (eg, hospital admission for an invasive procedure, a major medical condition, surgery, dental work, or a temporary situation that prevents subject compliance with the IMP dosing schedule), the subject's IMP should be resumed as early as the situation allows. The investigator or designee will contact the medical monitor at the earliest possible time by telephone to discuss a subject's interruption of treatment. If 6 or more doses of IMP are missed in a 7-day period, a discussion must occur with the medical monitor to determine if the subject should be discontinued from the trial as a result of the treatment interruption. The treatment interruption will be recorded in the eCRF and will be reported as a protocol deviation.

7.3.2 Treatment Discontinuation

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 7.3.5.

7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

A subject may temporarily interrupt or discontinue IMP for the reasons listed below:

- Adverse event
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAE
    - Other potentially IMP-related safety concerns or AEs
- Death
- Reasons unrelated to medical condition (provide detail and review AE history with subject)

Protocol 405-201-00056

- Withdrawal by subject
- Lost to follow-up
- Rash (regardless of severity or seriousness) (see Section 8.8.5)
- Pregnancy (see Section 10.3)
- Site terminated by sponsor
- Study terminated by sponsor
- Lack of efficacy
- Noncompliance with study drug
- Physician decision
- Randomized by mistake
- Randomized by mistake with study treatment
- Other

If the subject temporarily interrupts or discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 7.3.1 and Section 7.3.2 must be followed.

7.3.4 Withdrawal of Consent

Each subject has the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects can withdraw consent for use of data which has not previously been anonymously transferred into trial data sets collected as part of the trial and can only withdraw consent for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and trial site staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.

- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to interrupt, modify, or discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3.1 and Section 7.3.2, respectively). A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should follow the procedures outlined in Section 7.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

CCI [redacted]

7.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be instructed to meet and discuss (without coercion) with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

7.4 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Visit 8 during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up". Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable

documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

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

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

8 Trial Procedures

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

8.1 Efficacy Assessments

Efficacy will be measured by the change from baseline in binge eating days per week, the change from baseline in the Clinical Global Impression – Severity (CGI-S) score, Clinical Global Impression – Change (CGI-C) score, the change from baseline in the Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) score, the proportion of subjects with four-week cessation from binging, the change from baseline in number of binge episodes per week, the change from baseline in the Eating Disorder Examination Questionnaire - 7-Item Version (EDE-Q7), Patient Global Impression - Severity (PGI-S), and Patient Global Impression - Change (PGI-C) after treatment with centanafadine compared to placebo. It is required that adequately trained and experienced individuals administer the clinician rating scales. All individuals performing these assessments must be pre-approved by the sponsor or designee.

Efficacy assessments should be completed prior to safety and PK assessments.

8.1.1 Patient-Reported Outcomes

8.1.1.1 Binge Eating Diary

All binge episodes will be captured daily by the subject in a binge eating diary; details about binge eating episodes per day will be recorded. At each visit, the investigator or designee will review the completed diary with the subject and assess the number of binges for each day. The investigator assessment of number of binges for each day will be recorded in the eCRF. Missing data, if any, will be reviewed by the clinical site staff with the subject and additional training on diary completion will be provided as needed.

Protocol 405-201-00056

8.1.1.2 Eating Disorder Examination Questionnaire and Eating Disorder Examination Questionnaire - 7-Item Version

The EDE-Q is a self-report version of the eating disorder examination (EDE) and measures eating-disorder psychopathology in the past 28 days and over longer intervals for diagnostic items.[16,17,18,19] The EDE-Q yields scores on subscales (dietary restraint, eating concern, weight concern, and shape concern) as well as a global score and binge eating frequency variables.

The EDE-Q7 is a brief version of the EDE-Q which comprises 7 items to generate a global score and 3 subscales (dietary restraint, shape/weight overvaluation, and body dissatisfaction). Severity rating ranges from 0 to 6, where 0 represents absence of the feature and 6 represents an extreme degree. Frequency ratings range from 0 to 6 where 0 = 'No days' or absence of the feature and 6 = 'every day'.

8.1.1.3 Patient Global Impression - Severity

The PGI-S is a single-item self-report of the patient's severity of symptoms.[20] Severity is rated on a 7-point scale (1 = no symptoms; 2 = minimal; 3 = mild; 4 = moderate; 5 = marked; 6 = severe; 7 = very severe).

8.1.1.4 Patient Global Impression - Change

The PGI-C is a single-item, 7-point patient self-report that requires the patient to assess how much his/her illness has improved or worsened relative to baseline, rated as: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; or 7 = very much worse.

8.1.1.5 36-Item Short-Form Health Survey

The 36-item Short-form Health Survey Version 2 (SF-36v2) is a patient-reported questionnaire with a standard recall period of 4 weeks which measures generic health-related quality of life on 2 broad domains, physical and mental composites, across eight health domain scales: physical functioning, pain, role physical, general health, vitality/fatigue, social functioning role emotional, and mental health.[21]

The SF-36v2 uses norm-based scoring to generate scores on a scale of 0 to 100 where lower scores on the physical component summary (PCS) and mental component summary (MCS) represent a lower health-related quality of life and a score of 50 references the normal US population. In addition to the composite scores and the individual health domain scores, the SF-36v2 provides a risk for depression score and the SF-6D health utility index on a scale form 0.0 (worst measured health state) to 1.0 (best

measured health state). The SF-36v2 will be administered on the visits as specified in Schedule of Assessments (Table 1.3-1).

8.1.2 Clinician Rating Scales

8.1.2.1 Clinical Global Impression - Severity

The CGI-S[20] will be administered by trial site staff at the time points shown in the schedule of assessments (Table 1.3-1). The CGI-S is a standardized, clinician-administered global rating scale that measures disease severity on a 7-point Likert scale. A higher score on the CGI-S represents a higher severity of disease (0 = not assessed; 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects).

8.1.2.2 Clinical Global Impression - Change

The CGI-C will be administered by trial site staff at the time points described in the schedule of assessments (Table 1.3-1). The CGI-C is a single-item, 7-point scale that requires the clinician to assess how much the subject's illness has improved or worsened relative to their baseline state at the beginning of treatment, rated as: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; or 7 = very much worse.

8.1.2.3 Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating

The Y-BOCS-BE[22,23] will be administered by trial site staff at the time points shown in the schedule of assessments (Table 1.3-1). The Y-BOCS-BE is a clinician-rated scale that assesses obsession with binge eating thoughts and compulsiveness of binge eating behaviors. It can be divided into 2 subscales: obsessions and compulsions. The Y-BOCS-BE is a 10-item scale, with each item rated from 0 (no symptoms) to 4 (extreme symptoms) and total scores ranging from 0 to 40. A score of 0 to 7 is sub-clinical; 8 to 15 is mild; 16 to 23 is moderate; 24 to 31 is severe; and 32 to 40 is extreme.

8.2 Pharmacokinetic Assessments

8.2.1 Pharmacokinetic Blood Samples

Two sparse PK samples per subject will be collected, one each at Weeks 4 and 8, to determine centanafadine and metabolite concentrations. Samples should be collected at the same time as the serum chemistry samples and following the administration of efficacy assessments and other safety assessments (AE monitoring, vital signs

measurements, ECGs, medication withdrawal scales, and suicidality assessment). Concentrations will be evaluated for compliance with dosing.

Samples will be collected using venipuncture (3 mL whole blood, K_2EDTA, processed into plasma). The actual date and time of the PK sample collection and dose taken prior to the PK sample will be recorded on the eCRF.

8.3 Pharmacodynamic Assessments

Not applicable.

8.4 Pharmacogenomic Assessments

Not applicable.

8.5 Biomarker Assessments

Not applicable.

CCI

CCI

Protocol 405-201-00056

CCI

8.7 Safety Assessments

Safety will be assessed by standard measurements including TEAEs, AESIs (rash), clinical laboratory tests (chemistry, hematology, and urinalysis), physical examinations, vital sign measurements, and 12-lead electrocardiograms (ECGs). The Study Medication Withdrawal Questionnaire (SMWQ), Hamilton Anxiety Rating Scale (HAM-A) score, Montgomery-Asberg Depression Rating Scale (MADRS), and the Columbia Suicide Severity Rating Scale (C-SSRS) will be used to assess safety. Abuse potential will be assessed through the active monitoring of Events Subject to Additional Monitoring (ESAMs) (eg, AEs related to abuse potential and AEs involving MHI). Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8.

8.7.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the schedule of assessments (Table 1.3-1) to perform the clinical laboratory assessments described in Section 10.2 and should be collected after efficacy assessments are completed if possible. Only if results are exclusionary at screening will a repeat test be performed prior to the baseline visit; the results must be available and inclusionary prior to randomization. The

total volume of blood to be collected during the trial will be documented in the electronic informed consent form (eICF).

Subjects are not required to be fasting for screening laboratory assessments. Laboratory assessments will be fasted if they are required to be repeated for baseline eligibility. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible.

See exclusion criteria (Section 5.2.2) based on screening laboratory tests or tests repeated for baseline eligibility as necessary. The results of these tests must be reviewed by the investigator prior to initiation of the administration of the IMP. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from laboratory tests will be assessed by the investigator or qualified designee for clinical significance.

Urine or serum pregnancy testing for subjects of CBP will be performed during the study. On suspicion of pregnancy, an unscheduled urine or serum pregnancy test will be performed. Positive urine pregnancy tests must be confirmed with a serum pregnancy test. The investigator (or appropriate site staff) is advised to counsel participants on the risk of pregnancy while participating in a clinical trial. This should be documented in source records. Results of the pregnancy test must be available prior to the administration of the IMP.

A drug screen will be performed at screening and baseline (Day −1); additional assessments can be conducted at any time at the discretion of the investigator. Subjects with a positive drug screen for confirmed use of prohibited medications at screening will be required to undergo a washout period. Subjects who have a positive drug screen for confirmed use of prohibited medications at the baseline visit will be considered screen failures and will not be permitted to rescreen.

8.7.2 Physical Examination

Physical examinations will be performed at the time point described in the schedule of assessments (Table 1.3-1). Physical examinations include height, weight, and BMI, as well as assessment of the head, eyes, ears, nose, and throat, thorax, abdomen, urogenital (at the discretion of the PI), skin and mucosae, neurological, and extremities. Directed physical examinations in response to reported AE will be conducted as necessary.

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

Protocol 405-201-00056

8.7.3 Vital Signs

Vital signs will be collected at the time points described in the schedule of assessments (Table 1.3-1). Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Blood pressure and heart rate measurements will be made in the supine and standing positions after the subject has been in each position for at least 3 minutes. The supine measurements will be performed first, followed by the standing measurements. Temperature and respiratory rate will be taken with the subject in the supine position. Vital signs scheduled for the same visit as blood samples should be completed before blood is drawn.

8.7.4 Electrocardiogram

Electrocardiograms will be performed at the time points described in the schedule of assessments (Table 1.3-1). ECGs scheduled for the same visit as blood samples should be completed before blood is drawn. The 12-lead ECGs will be performed in the supine position. 12-lead ECGs conducted at screening will be performed in triplicate, taken approximately 5 minutes apart. Based on the QTcF correction, a subject will be excluded if the correction equals or exceeds 450 msec for males and 470 msec for females for 2 or more of the 3 ECGs conducted. If only 1 ECG has a corrected QTcF of equal to or greater than 450 msec for males or 470 msec for females and it is not reproduced at either of the other 2 assessments, the subject meets the inclusion criteria. Only if results are exclusionary at screening will a repeat ECG be performed prior to the baseline visit; the results must be available and inclusionary prior to randomization. All subsequent ECG assessments require a single ECG recording.

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

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

8.7.5 Suicidality Monitoring

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

Suicidality will be monitored during the trial using the C-SSRS.[24] The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide related thoughts and behaviors during the assessment period. The interview includes

definitions and suggested questions to solicit the type of information needed to determine if a suicide related thought or behavior has occurred.

The C-SSRS has a "Baseline/Screening" version, which will be completed at the screening visit and a "Since Last Visit" version that will be completed at all subsequent assessments as shown in Table 1.3-1. There are required items to be completed, potential additional items if there is a positive response to a required item, and items for suicide/suicide behavior present during the interview. The C-SSRS uses dichotomous scales (ie, yes or no), Likert scales, and text or narrative to further describe the thoughts or behaviors.

8.7.6 Other Safety Variables

8.7.6.1 Study Medication Withdrawal Questionnaire

The SMWQ is a questionnaire to assess withdrawal symptoms that will be completed at the time points shown in the Schedule of Assessments (Table 1.3-1). The SMWQ is a modification of the Amphetamine Withdrawal Questionnaire in which the terms "amphetamines and methamphetamine" are replaced with the term "the study medication."[25,26,27]

8.7.6.2 Hamilton Anxiety Rating Scale

The HAM-A should be administered by an experienced clinician at the timepoints shown in the schedule of assessments (Table 1.3-1).[28] The HAM-A consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a 5-point scale, ranging from 0 = not present to 4 = severe.

8.7.6.3 Montgomery-Asberg Depression Rating Scale

The MADRS is a clinician-rated assessment of the subject's severity of depression.[29] The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts. Each item is scored in a range of 0 to 6 points, with higher scores indicating increased depressive symptoms.

8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at

screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of double-blind treatment. In more detail, TEAEs are all AEs which started after the start of double-blind IMP treatment; or if the event was continuous from baseline and was worsening, serious, IMP related, or resulted in death, discontinuation, interruption, or reduction of IMP.

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

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

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

Adverse Events of Special Interest (AESIs): A noteworthy event for the particular product/IMP or class of products that a sponsor may wish to monitor carefully. All newly acquired skin eruptions that are non-traumatic are considered AESIs (see Section 8.8.5) and are to be reported as IREs.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Any AESIs (see Section 8.8.5)
- Potential serious hepatotoxicity (see Section 8.8.6).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. This includes pregnancy of the subject or the partner of the subject. Pregnancy will only be documented on the AE eCRF if the pregnancy occurs in a female subject and there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of laboratory tests for each individual subject as they become available. This review will be documented by the investigator's dated signature on the laboratory report. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant (ie, clinically significant) by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated in the eCRF. The severity of an adverse experience is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

Protocol 405-201-00056

8.8.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRF provided by the sponsor. Adverse event collection will begin after a subject signs the ICF, and will continue until the subject's last scheduled contact unless the AE must be followed further (see Section 8.8.9). All AEs must be reported after subject informed consent has been obtained, including screening failures due to AEs, irrespective of IMP administration.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition. In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 8.8.3. Special attention should be paid to recording hospitalization and concomitant medications.

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

8.8.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, after he/she or site personnel become aware of any IRE (SAE, AE related to occupational exposure, AESI, potential serious hepatotoxicity, or confirmed pregnancy by telephone, fax, or e-mail to the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE eCRF). Patient confidentiality must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding Safety Information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.8.9.2

8.8.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.8.5 Adverse Events of Special Interest

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

Refer to the separate Rash/Skin Eruption AESI Workup Instructions for complete details, including reporting forms, on extra measures that must be performed to characterize any skin AESI of a newly acquired skin eruption that is non-traumatic.

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

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

An Abuse Potential Monitoring Process (APMP) will be in place and will be shared with each site. A key objective of the 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, MHIs must be reported, and AEs related to abuse potential and AEs involving MHIs must be reported as an ESAM with detailed narratives.

Investigators and site staff at each trial site will be trained on reporting potentially abuse related AEs (eg, recording a description of the event in the subject's own words in the source documents as well as the eCRF, in addition to the clinical term, and to be aware that a subject's report may encompass more than one event and that these should be recorded separately). The investigators will be provided with examples of potentially abuse-related AEs, and trained on how to handle such events (eg, additional monitoring). While the investigators will be provided with examples of AE terms as a guide during trial conduct, the analysis of potentially abuse-related AEs will be based on a search of all Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, all verbatim terms, and any open text fields within the AE data to identify text strings suggestive of abuse potential, in line with the 2017 FDA guidance (Assessment of Abuse Potential of Drugs).[30] Refer to the separate APMP documentation for complete details on MHIs and ESAMs, including documenting and reporting procedures, examples of potentially abuse related AE terms that meet the criteria for ESAM reporting, and guidance for the training of investigators and trial site staff.

8.8.7 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in 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 in the eCRF.

8.8.8 Procedure for Breaking the Blind

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

8.8.9 Follow-up of Adverse Events

8.8.9.1 Follow-up of Nonserious Adverse Events

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

8.8.9.2 Follow-up of Immediately Reportable Events

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

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eCRF page and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a subject's last

scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eCRF page and the IRE form, according to the appropriate reporting procedures described in Section 8.8.3.

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

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

Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.

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

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

Any new IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor according to the procedures outlined in Section 8.8.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.9 Treatment of Overdose

For treatment of overdose, refer to the IB.[15]

Protocol 405-201-00056

8.10 Subject Assessment Recording

8.10.1 Diagnostic Criteria for Binge Eating Disorder

The subject's DSM-5[7] diagnosis of BED, based on the clinical interview and medical/psychiatric history and confirmed by the SCID-5-CT, should be documented in eSource.

8.10.2 Structured Clinical Interview for DSM-5

The SCID-5-CT is a primary diagnostic measure that will be utilized to establish the presence of binge eating disorder in adults.

8.11 Other Assessments

Not applicable.

9 Statistical Considerations

9.1 Sample Size

Assuming a treatment difference of 1.1 points with a standard deviation of 1.7 in the mean change from baseline in binge eating days per week at Weeks 7-8 in either centanafadine dose group (high dose centanafadine or low dose centanafadine) compared to the placebo group (effect size = 0.65), a sample size of 114 evaluable subjects (38 in each treatment arm) will yield at least 80% power to detect the treatment effects at a 2-tailed significance level of 0.05. Approximately 126 subjects will be randomized to ensure 114 evaluable subjects in the study. The power and sample size were obtained using the PASS 14 (2015) statistical computing software.

9.2 Datasets for Analysis

The following datasets are defined for this trial:

- Randomized Analysis Set: comprises all subjects who were randomized in the double-blind treatment period. Subjects are considered randomized when they are assigned a treatment group at the baseline visit.
- Safety Analysis Set: comprises those randomized subjects in the double-blind treatment period who receive at least 1 dose of double-blind IMP. Subjects will only be excluded from this population if there is documented evidence (ie, numbers of drug dispensed are equal to numbers of drug returned, or no IMP dispensed at all) that the subject did not take IMP. If a subject is dispensed IMP and is lost to follow-up, he/she will be considered exposed.

- Efficacy Analysis Set: comprises all subjects in the Safety Analysis Set who have a baseline value and at least 1 valid post-randomization efficacy evaluation in the double-blind treatment period.

The core dataset for all efficacy analyses is the Efficacy Analysis Set. In order to handle missing data and restrictions imposed by different types of analyses (eg, change from baseline analysis), datasets derived from Efficacy Analysis Set will be used for the efficacy analysis.

9.3 Handling of Missing Data for Primary and Key Secondary Endpoint Analysis

The mixed-effect model repeated measures (MMRM) assumes data are missing at random (MAR), which is a reasonable assumption in longitudinal clinical trials in the binge eating disorder population. However, the possibility of "missing not at random" (MNAR) data can never be ruled out. [redacted] CCI [redacted] In addition, adjustment for missing diary data related to the primary efficacy endpoint will be specified in the SAP.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

9.4.1.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the change from baseline in binge eating days per week at Weeks 7-8, having binge eating day defined as a day with at least one binge eating episode. The primary estimand defining the treatment effect of interest in the trial uses

the hypothetical strategy specified in the draft ICH E9 (R1) Addendum.[37] In the hypothetical strategy, the event of withdrawing IMP is considered missing at random (MAR), and the primary endpoint of the trial could be considered as a combination of the responses of on-treatment completers at Week 8 and the imputation of the endpoint to Week 8 following the trend in each treatment group using the MMRM method for subjects who withdraw IMP during the trial. All data collected during the trial treatment period will be used for statistical analysis.

The comparison between the centanafadine groups and the placebo group will be tested at a significance level of 0.05 (2-sided) in a fixed sequence testing of 1) high dose centanafadine versus placebo, and 2) low dose centanafadine versus placebo, in which Test 2) won't be performed unless Test 1) is statistically significant.

The primary efficacy analysis will be performed by fitting an MMRM analysis with an unstructured variance covariance structure, in which change from baseline in binge eating days per week at the scheduled visits will be the dependent variable based on the OC data set. The model will include fixed effect terms for treatment, trial center, visit week, and an interaction term of treatment by visit week. The model will also include the interaction term of baseline values of binge eating days per week by visit week as covariates. The level of visit in the MMRM will include Week 1, Week 2, Week 3, Week 4, Week 6, and Week 8. The primary comparison between centanafadine groups and the placebo group at Weeks 7-8 will be estimated as the difference between Least Squares means utilizing the computing software SAS procedure PROC MIXED. If there is a convergence problem with the unstructured variance covariance matrix of the MMRM model, the following structures other than unstructured will be used in order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry and the first (co)variance structure converging to the best fit will be used as the primary analysis. If a structured covariance has to be used, the "sandwich" estimator of the standard error of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix. Details of this analysis will be provided in the SAP.

Within MMRM analysis, baseline is defined as the last available measurement prior to the first dose of IMP in the double-blind treatment period and small centers will be pooled as needed. The linear model assumptions will also be checked. Details will be provided in the SAP.

Protocol 405-201-00056

CCI

[redacted]

CCI

[redacted]

9.4.1.3 Key Secondary Efficacy Endpoint Analysis

The key secondary endpoint of change from baseline in CGI-S score at Week 8 will be analyzed using MMRM, similar to primary efficacy endpoint.

9.4.1.4 Other Efficacy Endpoint Analysis

Changes from baseline in Y-BOCS-BE score, PGI-S score, and SF-36v2 PCS and MCS scores will be analyzed using MMRM similar to primary efficacy endpoint. CGI-C score and PGI-C score will be analyzed using Cochran-Mantel-Haenszel (CMH) method based on raw mean score statistics with trial center as controlling factor. Proportion of subjects with four-week cessation from binging at Week 8/ET will be evaluated by the CMH method controlling for trial center. Change from baseline in EDE-Q7 global score will be

analyzed using analysis of covariance including treatment group, trial center as fixed factors and baseline as covariate. The other efficacy variables will be evaluated at a nominal 0.05 level (2-sided) without adjusting for multiplicity.

9.4.1.5 Control of Experiment-wise Type 1 Error

To control the overall experiment-wise type I error at the 0.05 level, a fixed sequence testing approach will be applied. The statistical test will be performed in the following order:

1) Change from baseline to Weeks 7-8 in binge eating days per week between high dose centanafadine and placebo;
2) Change from baseline to Weeks 7-8 in binge eating days per week between low dose centanafadine and placebo;
3) Change from baseline to Week 8 in CGI-S score between high dose centanafadine and placebo;
4) Change from baseline to Week 8 in CGI-S score between low dose centanafadine and placebo.

The test for the subsequent hypothesis will be performed only if the test for the previous hypothesis is statistically significant.

9.4.1.6 Other Efficacy Endpoint Analysis

Not applicable.

9.4.2 Safety Analysis

9.4.2.1 Adverse Events

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

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

9.4.2.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements will be provided. In addition, potentially clinically significant laboratory

results will be identified using criteria prospectively defined in the SAP and will be summarized. Change from baseline in fasting triglycerides and total cholesterol at Week 8/ET will be analyzed using analysis of covariance including treatment group, trial center as fixed factors and baseline as covariate.

9.4.2.3 Physical Examination and Vital Signs Data

By-subject listings will be provided for physical examination findings. Summary statistics for changes from baseline in vital signs will be provided. Potentially clinically significant results in vital signs and body weight will also be summarized. In addition, change from baseline in body weight and percentage of change from baseline in body weight will be analyzed using MMRM.

9.4.2.4 Electrocardiogram Data

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

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

- QTcF is the length of the QT interval corrected for heart rate by the Fredericia formula: $QTcF = QT / (RR)^{0.33}$
- QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN = QT / (RR)^{0.37}$

In addition, potentially clinically significant ECG results will be identified using criteria prospectively defined in the SAP and will be summarized.

9.4.2.5 Other Safety Data

Change from baseline in HAM-A total score, MADRS total score, medication withdrawal symptoms assessed by SMWQ, and suicidality monitored during the trial using the C-SSRS at the scheduled visit(s) will be summarized by treatment group in descriptive statistics. Details of the analysis will be included in the SAP.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height, and BMI for the randomized subjects will be summarized using descriptive

statistics (frequency, mean, median, SD, maximum, minimum, and percentage when applicable).

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

9.4.3.2 Pharmacokinetic Analysis

Sparse PK samples will be evaluated to confirm compliance with dosing. Concentrations will be listed in the bioanalytical report.

9.4.3.3 Pharmacodynamic Analysis

No PD analysis is planned.

9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

No PK/PD analysis is planned.

9.4.3.5 Pharmacogenomic Analysis

No PGx analysis is planned.

CCI [redacted]

CCI [redacted].

9.5 Interim Analysis and Adaptive Design

Not applicable.

9.5.1 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

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

10.1.1 Ethics and Responsibility

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

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

10.1.2 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The informed consent form (ICF) will be approved by the same IRB that approves this protocol.

Each ICF will comply with the ICH (International Council for Harmonisation) GCP Guidelines, and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF used in the trial before submission to the IRB. In support of the site's standard process for administering informed consent, this trial will also allow for eICF as a tool within applicable regions and trial sites. The eICF utilizes the IRB-approved site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, trial sites will have subjects review and sign the eICF prior to starting any trial procedures; however, if local regulations do not allow for use of the electronic format, subjects may continue in the trial utilizing the standard paper and wet ink signature process.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and

documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

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

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

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

CCI [redacted]

10.1.3 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel

(or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

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

10.1.4 Quality Control and Quality Assurance

10.1.4.1 Monitoring

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

10.1.4.2 Auditing

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

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

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor or designee at the earliest possible time by telephone or via e-mail. The investigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the

subject's continuation in the trial. This decision will be documented by the investigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation.

10.1.6 Records Management

10.1.6.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, logs, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

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

10.1.6.2 Data Collection

During each subject's visit to the site, an investigator or their designee participating in the trial will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed, including dosing and IMP compliance;
- The signature (or initials) and date of the investigator (or designee) who made an entry in the medical record.

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

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

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

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

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

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

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

10.1.6.3 File Management at the Trial Site

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

10.1.6.4 Records Retention at the Trial Site

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

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

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

10.1.6.5 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND

4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

Protocol 405-201-00056

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Hematology:	Serum Chemistry:
Hemoglobin	Alkaline phosphatase
Hematocrit	Alanine aminotransferase
Mean corpuscular hemoglobin concentration	Aspartate aminotransferase
Mean corpuscular volume	Bicarbonate
Neutrophils	Bilirubin, total
RBC	Urea nitrogen
WBC (with differential)	Calcium
Platelets	Chloride
MCH	Cholesterol (total)
RDW	CPK
RBC morphology	Creatinine
	Gamma glutamyl transferase
Urinalysis:	Glucose
Appearance	Lactate dehydrogenase
Color	Potassium
Blood	Protein, total
Glucose	Sodium
Microscopic analysis, WBC/RBC counts per high powered field	Triglycerides
	Uric acid
pH	
Protein	Additional Tests:
Specific gravity	HbA1c (at screening only)
	Alcohol test (via urine, blood, or breathalyzer)
Urine drug screen:	Urine pregnancy for all subjects of CBP (a serum test will be confirmatory for positive urine pregnancy)
Amphetamines	
Barbiturates	
Opiates	
Benzodiazepines	Coagulation Parameters:
Cocaine	PT
THC	aPTT
Methadone	INR
Phencyclidine	

aPTT = activated partial thromboplastin time; CPK = creatine phosphokinase; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; PT = prothrombin time; RBC = red blood cell count; RDW = red cell distribution width; THC = tetrahydrocannabinol; WBC = white blood cell count.

Protocol 405-201-00056

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Subjects of CBP are subjects whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months). Subjects of nonchildbearing potential do not meet definition of CBP.

For males and subjects of CBP, or their partners, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remains abstinent) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP for female subjects, and 30 days after the last dose of IMP for male subjects and their partners who are of CBP. Unless the subject is sterile (ie, who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months or subjects who have had a bilateral orchiectomy) or remains abstinent during the trial and for 30 days after the last dose of IMP for female subjects, and 30 days after the last dose of IMP for male subjects and their partners who are of CBP, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, birth control implant, birth control depot injection, birth control patch, condom with spermicide, sponge with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide]. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the eCRF. Subjects must also agree not to donate sperm from trial screening through 30 days/weeks/months after the last dose of IMP.

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

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

Protocol 405-201-00056

Before trial enrollment, males and subjects of CBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine or serum pregnancy test for human chorionic gonadotropin (hCG) will be performed the time points described in the schedule of assessments (Table 1.3-1) on all subjects of CBP. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all subjects of CBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects must be instructed to contact the investigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 30 days after the last dose of IMP for 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 the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

Protocol required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

10.4 Appendix 10: Protocol Amendments

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

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

CCI

CCI

CCI

11 References

1 Hudson J, Hiripi E, Pope Jr HG, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007;61(3):348-358.

2 Santomauro DF, Melen S, Mitchison D, Vos T, Whiteford H, Ferrari AJ. The hidden burden of eating disorders: an extension of estimates from the Global Burden of Disease Study 2019. Lancet Psychiatry Actions. 2021;8(4):320-328.

3 McElroy SL. Pharmacologic treatments for binge-eating disorder. J Clin Psychiatry. 2017;78 Suppl 1:14-19.

4 VYVANSE (lisdexamfetamine dimesylate) US Prescribing Information. Shire US Inc.; Lexington, MA; January 2017.

5 Cortese S, Bernardina BD, Mouren MC. Attention-deficit/hyperactivity disorder (ADHD) and binge eating. Nutr Rev. 2007;65(9):404-411.

6 Seymour KE, Reinblatt SP, Benson L, Carnell S. Overlapping neurobehavioral circuits in ADHD, obesity, and binge eating: evidence from neuroimaging research. CNS Spectr. 2015;20(4):401-411.

7 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th Edition, 2013. Available from: https://www.psychiatry.org/psychiatrists/practice/dsm.

8 CCI [redacted]

9 Kessler RM, Hutson PH, Herman BK, Potenza MN. The neurobiological basis of binge-eating disorder. Neurosci Biobehav Rev. 2016;63:223-238.

10 Renasci. Microdialysis experiment in freely moving rats measuring DA in the nucleus accumbens: effects of TTX infusion on extracellular levels. Study No. RS1775, 2019.

11 Renasci. Evaluation of the discriminative properties of centanafadine and reference comparator drugs, methylphenidate, phentermine, bupropion and modafinil, in rats trained to discriminate d-amphetamine from saline. Study No. RS1777.

12 Renasci. Investigation of the reinforcing potential of centanafadine in an intravenous self administration procedure in cocaine maintained rats. Study No. RS1778.

13 Renasci. Determination of the potential of centanafadine to induce pharmacological tolerance and physical dependence on withdrawal in male sprague dawley rats. Study No. RS1779.

14 Renasci. Determination of the potential of centanafadine to induce pharmacological tolerance and physical dependence on withdrawal in female sprague dawley rats. Study No. RS1780.

15 Otsuka Pharmaceutical Development and Commercialization. Centanafadine (EB-1020) Investigator's Brochure, Edition 10. Otsuka Report, issued 22 Dec 2020.

16 Fairburn CG, Beglin SJ. Assessment of eating disorders: interview or self-report questionnaire? International Journal of Eating Disorders. 1994;16(4):363-70.

[17] Grilo CM, Crosby RD, Peterson CB, Masheb RM, White MA, et al. Factor structure of the eating disorder examination interview in patients with binge-eating disorder. Obesity. 2010;8:977-981.

[18] Grilo CM, Crosby RD, White MA. Spanish-language Eating Disorder Examination interview: Factor structure in Latino/as. Eating Behaviors. 2012;13:410-413.

[19] Grilo CM, Reas DL, Hopwood CJ, Crosby RD. Factor structure and construct validity of the eating disorder examination-questionnaire in college students: Further support for a modified brief version. Int J Eat Disord. 2015;48:284-289.

[20] Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.

[21] Ware J, Kosinski M, Bjorner J, Turner-Bowker D, Gandek B, Maruish M. Development. User's Manual for the SF-36v2® Health Survey. Lincoln (RI): QualityMetric Incorporated; 2007.

[22] Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry. 1989;46:1006-1011.

[23] Yee K, Serrano D, Kando J, and McElroy SL. A psychometric analysis and revalidation of the Yale-Brown Obsessive Compulsive Scale modifed for Binge Eating in adults with binge eating disorder. Quality of Life Research. 2019;28:3385-3394.

[24] Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035-104.

[25] Srisurapanont M, Jarusuraisin N, Jittiwutikan J. Amphetamine withdrawal: I. Reliability, validity and factor structure of a measure. Aust N Z J Psychiatry. 1999;33(1):89-93.

[26] Hendricks EJ, Srisurapanont M, Schmidt SL, Haggard M, Souter S, Mitchell CL, et al. Addiction potential of phentermine prescribed during long-term treatment of obesity. Int J Obes (Lond). 2014;38(2):292-298.

[27] McGregor C, Srisurapanont M, Jittiwutikarn J, Laobhripatr S, Wongtan T, White JM. The nature, time course and severity of methamphetamine withdrawal. Addiction. 2005;100(9):1320-1329.

[28] Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32:50–55.

[29] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-389.

[30] U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research. Assessment of Abuse Potential of Drugs. Guidance for Industry. Jan 2017.

[31] Diggle P, Kenward MG. Informative drop-out in longitudinal data analysis. Applied Statistics. 1994;43:49-93.

[32] Little RJA. Pattern-mixture models for multivariate incomplete data. J Am Stat Assoc. 1993;88:125-134.

[33] Little RJA. Modeling the drop-out mechanism in repeated measures studies. J Am Stat Assoc. 1995;90:1112-1121.

[34] Hedeker D, Gibbons RD. Application of random effects pattern-mixture models for missing data in longitudinal studies. Psychological Methods. 1997;2(1):64-78.

[35] Ali MW, Siddiqui O. Multiple imputation compared with some informative dropout procedures in the estimation and comparison of rates of change in longitudinal clinical trials with dropouts. J Biopharmaceutical Stats. 2000;10(2):165-181.

[36] Wu MC, Bailey KR. Estimation and comparison of changes in the presence of informative right censoring: conditional linear model. Biometrics. 1989;45(3):939-955.

[37] ICH Harmonised Guideline Estimands and Sensitivity Analysis in Clinical Trials E9(R1), 16 June 2017.

Protocol 405-201-00056

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, centanafadine, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where centanafadine will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

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

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

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: 405-201-00056 Protocol Amendment 2

Document Number: 1000135319

Document Version: 4.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Clinical Approval	24-Jan-2022 19:09:41
PPD	Biostatistics Approval	24-Jan-2022 19:08:14
PPD	Clinical Approval	24-Jan-2022 22:58:55